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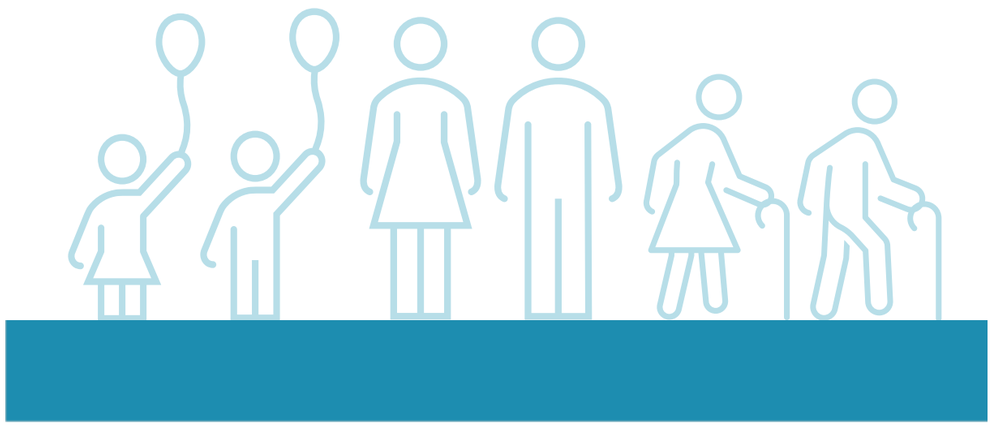

Wannee KANTASIRIPITAK

MODEL-INFORMED PRECISION DOSING OF INFLIXIMAB TO IMPROVE OUTCOMES OF INDIVIDUAL PATIENTS WITH INFLAMMATORY BOWEL DISEASES

February 2023

KU LEUVEN

DOCTORAL SCHOOL of BIOMEDICAL SCIENCES

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Dissertation presented in partial fulfillment of the requirements for the degree of Doctor in Pharmaceutical Sciences

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Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Pharmaceutical Sciences

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# Word of Thanks

When I was little, I always dreamt to go studying abroad. At the time, it seemed to be just a daydream and I forgot about it. Thanks to my former colleagues at the first workplace (GPO), their passions reignited my dream. Now that I am about to graduate with the highest education degree from one of the best universities in Europe. It is hard for me to put into words how grateful I am for all the help and support, the inspiring people that I crossed paths with, and all the small events and decisions that have led me to this point.

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# Summary

**Background** For over two decades, the 5 mg/kg weight-based dosing of infliximab was approved for inducing and maintaining remission in all patients with moderate-to-severe inflammatory bowel disease (IBD). Infliximab not only controls IBD symptoms but also modifies the disease course, enables long-lasting remission, and prevents long-term disability from structural damage. However, several issues with infliximab treatment still exist such as treatment failure (such as primary nonresponse, and loss of response due to immunogenicity), underdosing of infliximab in children, and lack of safety data in real-world populations, especially in elderly patients. With well-established relationships between infliximab concentration and treatment outcomes, dose optimisation based on infliximab and antibodies to infliximab concentrations (i.e., therapeutic drug monitoring [TDM]) has been attempted. However, TDM is not capable of quantifying variability in the pharmacokinetics (PK) of infliximab, which is considered high. Model-based TDM – also known as model-informed precision dosing (MIPD) – has been advocated as a promising dosing strategy for infliximab treatment. MIPD can quantify the PK of infliximab and adjust dosing based on simulations to ensure adequate exposure associated with treatment outcomes. MIPD employs drug-specific population PK (popPK) models, patient-specific covariates, measured drug concentrations, a target exposure, and a Bayesian forecasting software tool to predict optimal doses for individual patients.

**Aims** In this doctoral research work, we aimed to contribute to the therapeutic drug monitoring cycle regarding (i) identifying concentration targets in children and elderly (*Part II. Special populations*), and (ii) developing MIPD strategies for guiding dose optimisation of infliximab in patients with IBD (*Part I. Model-informed precision dosing and Part II. Special populations*).

**Methods** The concentration targets during induction treatment for both children and elderly patients were identified using a logistic regression Markov exposure-response model (***chapters III, IV***). In addition, relationships between infliximab exposure and safety events were investigated in elderly patients using repeated time-to-event models (***chapter V***). Single-model and multi-model approaches for MIPD were compared in terms of their predictive performances in *a priori* prediction (based solely on covariate data), and a maximum *a posteriori* prediction (based on covariate and concentration data) (***chapters II, III***). Requirements of MIPD software tools were identified by experts in the field of precision dosing and the performance of currently available MIPD software tools was evaluated against the requirements (***chapter I***). The selected model approaches were implemented into the TDMx software tool (***chapters II, III***).

**Results** For paediatric patients with IBD, an infliximab target concentration at week 12 of 7.5 mg/L was associated with the envisioned 64% rate of deep remission (i.e., combined

clinical and endoscopic remission). To attain the identified target, the earliest infliximab dose optimisation guided by MIPD is recommended at week 6 (by providing only the trough concentration at week 6). For adult patients with IBD, an infliximab trough concentration at week 14 of 15.6 mg/L was the best related to a 50% probability of attaining post-induction endoscopic remission. The same infliximab trough concentration at week 14 could also be targeted in elderly patients with IBD, regardless of the patient's age. Infliximab exposure during induction treatment was not found to be a risk factor for (serious) adverse events.

In general, multi-model approaches had systematically better predictive performance than single-model approaches regardless of the number of provided concentration data. *A priori* prediction was inaccurate and imprecise, while maximum *a posteriori* prediction with at least one previous concentration greatly improved the predictive performance and was robust to lacking and misspecification of covariate data.

The available MIPD software tools had unique features but well fulfilled the requirements. In collaboration with TDMx software tool, we developed two MIPD modules for infliximab dosing of adult and paediatric patients with IBD. Currently, the developed software tool is being utilised to guide infliximab dosage de-escalation in the prospective MODIFI study (NCT04982172).

**Conclusion** The aims of this doctoral research work were fulfilled. Moreover, this doctoral research work facilitated the initiation of a prospective clinical trial and implementation of MIPD of infliximab in the treatment of patients with IBD.

# List of abbreviations

| | |
|---|---|
| ACE | affinity capture elution |
| AE | adverse event |
| AIC | Akaike information criterion |
| ARTG | The Australian Register of Therapeutic Goods |
| ATI | antibodies to infliximab |
| AUC | area under the curve |
| AUROC | area under the receiver operating characteristic curve |
| CD | Crohn's disease |
| CDAI | Crohn's disease activity index |
| CI | confidence interval |
| CL | clearance |
| CRP | C-reactive protein |
| EC | Ethics Committee |
| EHR | electronic health record |
| ELISA | enzyme-linked immunosorbent assay |
| EM | expectation maximisation |
| ESR | erythrocyte sedimentation rate |
| EU GDPR | European Union General Data Protection Regulation |
| Fab | antigen-binding fragment |
| FcRn | neonatal Fc receptor |
| FcγR | Fc gamma receptor |
| FDA | United States Food and Drug Administration |
| FO | first order |
| FOCE-I | first-order conditional estimation with interaction |
| GUI | graphical user interface |
| HBI | Harvey-Bradshaw index |
| HMSA | high-pressure liquid chromatography-based homogeneous mobility shift assay |
| IBD | inflammatory bowel disease |
| Ig | immunoglobulin |
| IQR | interquartile range |
| KWS | clinical workstation |
| MAA | model averaging algorithm |
| MAP | maximum *a posteriori* prediction |
| MeSH | medical subject heading |
| MIPD | model-informed precision dosing |
| MLE | maximum likelihood estimate |
| MSA | model selection algorithm |
| NPDE | normalised prediction distribution error |
| NS | not significant |
| OFV | objective function value |
| PAGE | Population Approach Group in Europe |
| PBPK | physiologically-based pharmacokinetic |
| PCDAI | paediatric Crohn's disease activity index |
| pcVPC | prediction-corrected visual predictive check |

| | |
|---|---|
| PD | pharmacodynamics |
| PIBD | paediatric inflammatory bowel disease |
| PK | pharmacokinetics |
| popPK | population pharmacokinetics |
| popPK-PD | population pharmacokinetic-pharmacodynamic |
| PRO2 | two-item patient-reported outcome |
| PUCAI | paediatric ulcerative colitis activity index |
| Q | intercompartmental clearance |
| rBias | relative bias |
| ROC | receiver operating characteristic |
| rRMSE | relative root means square error |
| RTTE | repeated time-to-event |
| SAE | severe adverse event |
| SD | standard deviation |
| SES-CD | simple endoscopic score for Crohn's disease |
| SIR | sampling importance resampling |
| SSE | sum of squared error |
| STRIDE | Selecting Therapeutic Targets in Inflammatory Bowel Disease |
| Th | T-helper |
| TC | trough concentration |
| TDM | therapeutic drug monitoring |
| TNF-α | tumour necrosis factor-α |
| TNFR | receptor of TNF-α |
| UC | ulcerative colitis |
| Vc | volume of distribution in the central compartment |
| Vd | volume of distribution |
| Vp | volume of distribution in the peripheral compartment |
| VPC | visual predictive check |
| W | weight |
| w | week |
| %CV | percent coefficient of variation |

# Introduction

Parts of the introduction are published as

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The introduction section is divided into three parts: disease, patients, and drug (**Figure 1**).

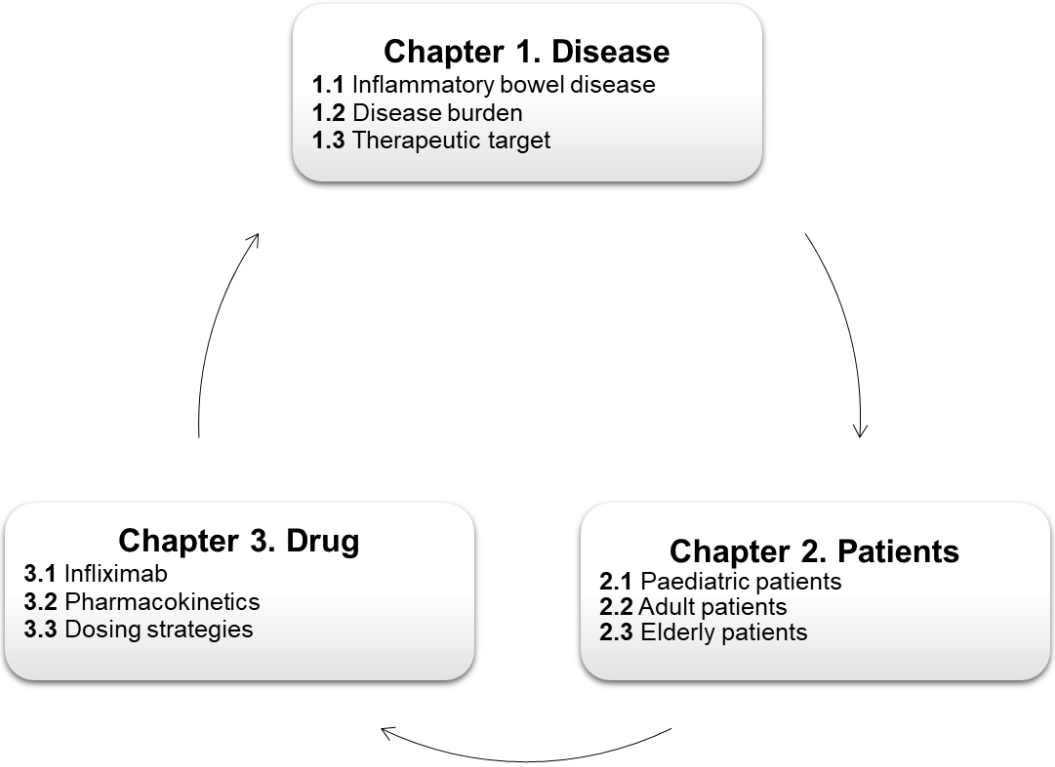


***Figure 1.*** *Schematic overview of the introduction section.*

# Chapter 1. Disease

## 1.1 Inflammatory bowel diseases

### 1.1.1 Diagnosis

Inflammatory bowel diseases (IBD) are a spectrum of diseases with Crohn's disease (CD) and ulcerative colitis (UC) as the major types. The onset of IBD ranges from early childhood to after the age of 60. Up to 25% of IBD cases start in early childhood or adolescence, whereas 10% – 15% of IBD patients are diagnosed after the age of 60.[2] The peak age of onset is in the third and fourth decades of life.[3] IBD is characterised by chronic and relapsing inflammation of the gastrointestinal tract.[4,5] CD typically shows segmental, asymmetrical, and transmural inflammation which can affect all segments of the gastrointestinal tract, whereas UC shows continuous involvement of the mucosal and submucosal layers of the rectum, extending to proximal segments of the colon.[4,5] The diagnosis of IBD is based on a combination of characteristics including history, physical examination, biochemical laboratory results, and endoscopic findings (**Table 1**).[6] UC usually presents with bloody diarrhoea and is diagnosed by colonoscopy and histological findings whereas the typical clinical representations of patients with CD are abdominal pain, chronic diarrhoea, weight loss, and fatigue.[4,5]

***Table 1.*** *Comparison of diagnosis for ulcerative colitis and Crohn's disease.*

| Characteristics | Ulcerative colitis | Crohn's disease |
|---|---|---|
| *History* | | |
| Location | Starts in the rectum and extends to proximal segments of the colon | Anywhere in GI tract |
| Abdominal pain | Uncommon | Common |
| Rectal bleeding | ++ | + |
| Non-gastrointestinal symptoms | Uncommon | Common |
| Fatigue | ++ | +++ |
| Weight loss | + | +++ |
| *Physical examination* | | |
| Fever | + | +++ |
| Abdominal tenderness | + | +++ |
| *Laboratory* | | |
| Anaemia | ++ | +++ |
| Elevated CRP and/or ESR | + | +++ |
| ASCA | - | ++ |
| pANCA | +++ | + |
| *Endoscopy findings* | | |
| Rectal involvement | +++ | +/- |
| Continuous mucosal involvement | +++ | + |

*ASCA, anti-Saccharomyces cerevisiae; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; pANCA: perinuclear anti-neutrophil cytoplasmic antibody; +, degree of prevalence; - not prevalent. Table reproduced with permission from the journal that published Sairenji et al.[6]*

### 1.1.2 Pathogenesis

IBD is an immune-mediated disease that arises due to a dysregulation of the immune response. The dysregulation is caused by complex interactions between genetic predisposition, exposures to surrounding environmental factors (e.g., smoking, diet, and oral contraceptives), alteration of gut microbiota composition, alteration in the immune response of host, and alteration in mucosal barrier function (**Figure 2**).[7,8] Currently, the divergence in molecular mechanisms (e.g., intestinal permeability, inflammation, and wound healing process) of underlying pathologies between IBD types is increasingly recognised due to T-helper (Th) 1 or Th2 mediated response in CD, and UC, respectively.[9]

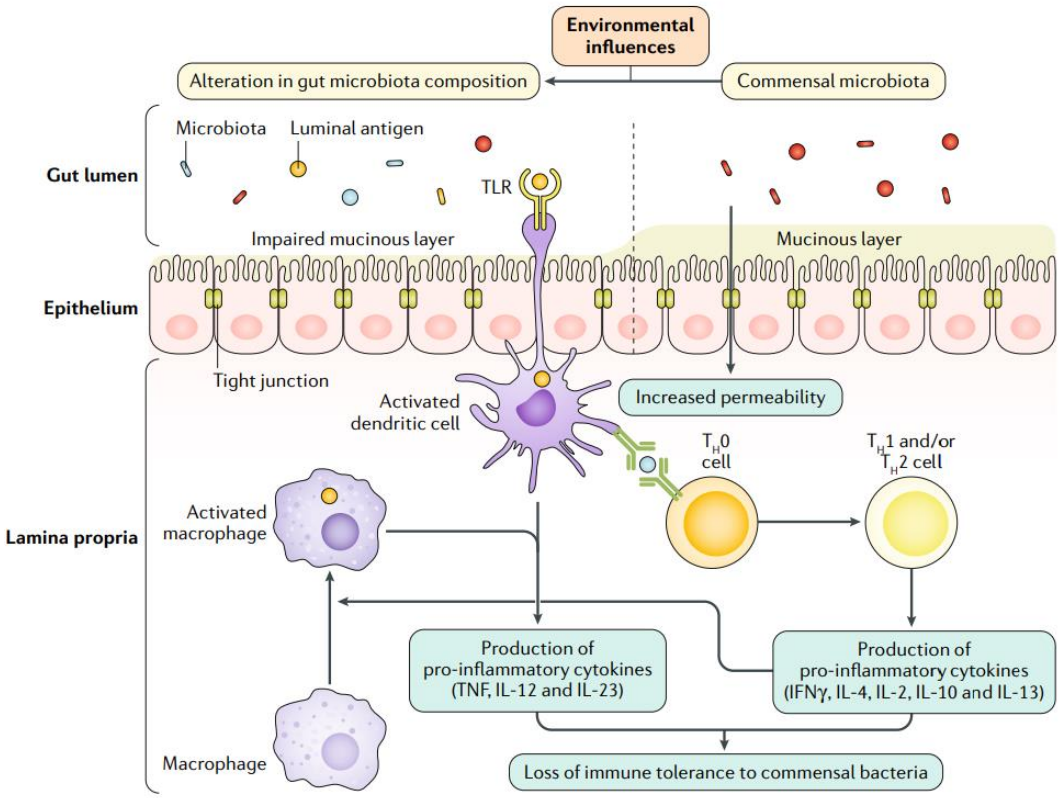


***Figure 2.*** *The pathophysiology of inflammatory bowel disease is related to an inappropriate host immune response to commensal bacteria in genetically susceptible individuals. Dendritic cells and macrophages are antigen-presenting cells involved in the activation of T cells and the production of pro-inflammatory cytokines. Dendritic cells are activated through the recognition of luminal antigens by Toll-like receptors (TLRs) and are in turn necessary for the activation of naive T cells. Macrophages can also serve as antigen-presenting cells once stimulated by interferon-gamma (IFNγ), which is secreted by T cells. Activated macrophages and dendritic cells also produce pro-inflammatory cytokines, including tumour necrosis factor (TNF), interleukin 12 (IL-12) and interleukin 23 (IL-23). The result of this pro-inflammatory cytokine cascade is a loss of immune tolerance to commensal bacteria and the production of pro-inflammatory cytokines by activated T cells. $T_H$, T helper. Figure reproduced with permission from the journal that published Khalili et al.*[8]

There is growing evidence that there are potential differences in host-gene-microbial interactions, disease characteristics, and family history of IBD across the age spectrum (**Figure 3**).[2]

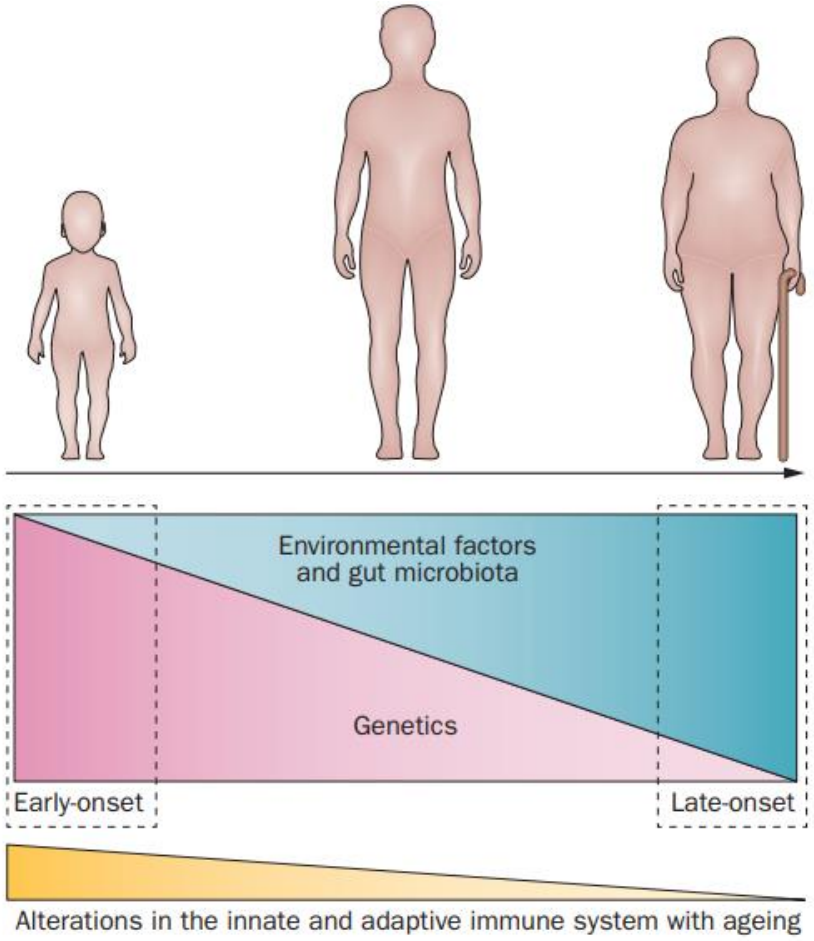


***Figure 3.*** *Differences in the respective contributions of genetics and environmental factors and gut microbiota composition, and host immune system according to the age of onset in inflammatory bowel disease (IBD). Figure reproduced with permission from the journal that published Ruel et al.*[2]

### 1.1.3 Treatment and management

IBD is not curable. Therefore, treatment goals of IBD are to minimise symptoms, improve quality of life, and minimise progression and complications of the diseases.[6] Despite similar diagnostic considerations for patients with UC and CD, treatment of these diseases differs greatly.

The UC management primarily aims to induce and maintain remission (defined as resolution of symptoms and endoscopic healing) with long-term goals that include prevention of disability, colectomy, and colorectal cancer.[5] For patients with UC, the selection of medications (e.g., drug choice and route of administration) are based on severity of disease (e.g., mild, moderate, or severe) and the degree of colonic involvement.[6] The most commonly uses UC severity indices are the Mayo score and the Ulcerative Colitis Endoscopic Index of Severity which include the endoscopy subscore.[10,11] Endoscopy is crucial in disease severity assessment since endoscopic healing is associated with improved remission rates, decreased risk of colectomy, and limited corticosteroid use.[12] Treatment options include 5-aminosalicylates, corticosteroids, immunomodulators, and biological drugs.[5] A rapid step-up approach is recommended based on disease severity and treatment response, while early use of biological drugs should be considered in patients with acute severe UC and steroid-dependent UC.[5] Medications can be continued or added once remission is induced to further maintain the remission.[12] Colectomy can be required for medically refractory disease.[5] Moreover, the patients are at risk of colorectal cancer, screening colonoscopy should be done 8 to 10 years after initial diagnosis.[6]

The CD management aims for deep and long-lasting remission, preventing complications (e.g., surgery and disease progression), bowel damage, and disability.[4] For patients with CD, assessment of disease activity, disease severity, and prognostic factors for the complications are crucial for guiding therapeutic options.[4] Disease activity refers to the assessment of symptoms, and objective assessment of disease activity (such as endoscopy, cross-sectional imaging, and biomarkers [C-reactive protein; CRP and faecal calprotectin]) at a given timepoint.[13] On the other hand, disease severity is used to assess an overall disease course including the cumulative complications and surgical resections, the disability produced by disease, and the inflammatory burden of disease.[14] Similar to patients with UC, a rapid step-up approach is recommended.[4] However, the approach failed to change the course of disease as evidenced by high rate of surgery.[4] Therefore, a top-down approach might be considered in patients with CD who have poor prognostic factors, severe disease, or complicated disease.[15]

## 1.2 Disease burden

In the 21st century, IBD has become a global disease with rapidly rising incidence rates in newly industrialised countries (e.g., South America, eastern Europe, Asia, and Africa) and increasing prevalence in western countries because of improved survival.[16] The rise of earlier onset IBD (i.e., paediatric IBD [PIBD]) means longer disease duration and potentially more complex disease over a patient's lifespan, leading to challenges in managing IBD in an ageing population (**Figure 4**).[17,18] Healthcare systems are under pressure to proactively plan for the problems of an ageing population with comorbid diseases and a prolonged disease course as well as an increase in the number of patients with IBD.

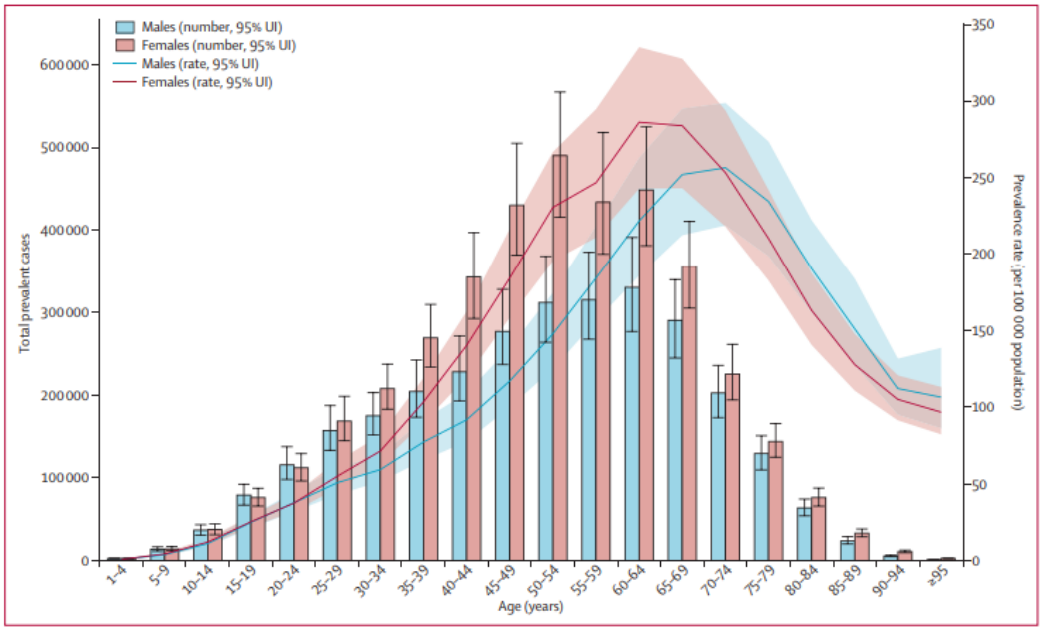


***Figure 4.*** *Age patterns by sex in 2017 of the total number of prevalent cases and age-specific prevalence rate of inflammatory bowel diseases at the global level. Figure reproduced with permission from the journal that published Global Burden of Disease 2017 Inflammatory Bowel Disease Collaborators.*[17]

IBD is a chronic and lifelong disease that causes a significant burden on the patients' quality of life. IBD is manifested by not only intestinal symptoms (e.g., abdominal pain, diarrhoea, loss of appetite, and bloody stools) but also extra-intestinal symptoms (e.g., fatigue, painful joints, lower back pain, and insomnia).[19] These symptoms persist throughout life and cause IBD to have a substantial impact on the well-being of patients. As a result, IBD imposes a growing burden on physiological function, public health systems, and socio-economic productivity (e.g., absenteeism and healthcare costs).[20–22]

These burdens highlight the need for research into the prevention and treatment of IBD and innovations in health-care systems to manage these complex and costly diseases.

## 1.3 Therapeutic target

Over the past ten years, IBD management has been evolving according to a *"treat-to-target"* paradigm from symptom control to endoscopic healing and patient-centric approaches.[23–25] An updated Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) guidelines suggested treatment targets in both adult and paediatric patients.[26] Also, quality of life and avoidance of disability were identified as formal targets for IBD management for the first time. The STRIDE-II consensus established a timeline for targets of IBD management from disease control to disease modification (**Figure 5**).[23] IBD management should focus on achieving clinical remission, biomarker normalisation, and endoscopic healing in the short term, to rapidly make the patient return to a normal life while avoiding disease complications, surgery, and hospitalisations in the medium to long term.

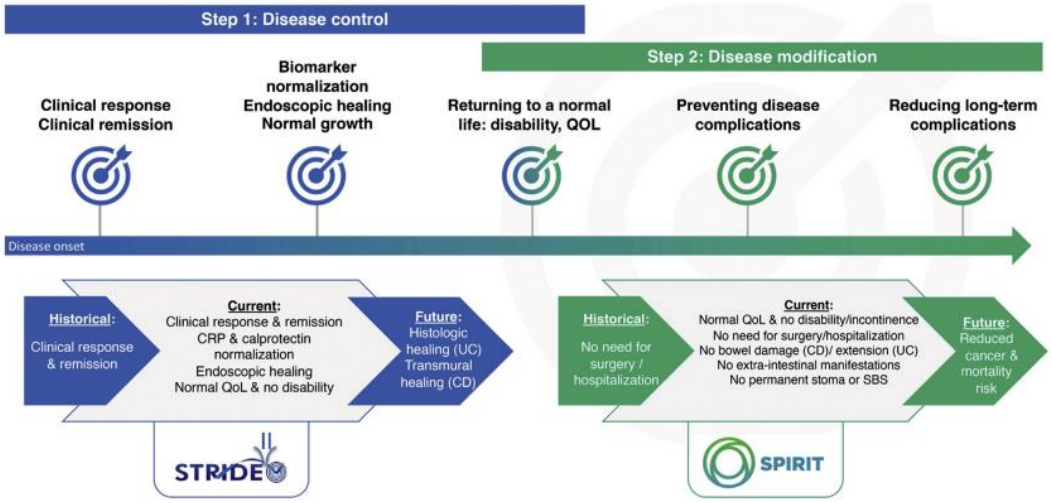


***Figure 5.*** *Summary of evolving short-term and long-term treatment targets in inflammatory bowel diseases. CD, Crohn's disease; CRP, C-reactive protein; QoL, quality of life; SBS, short bowel syndrome; UC, ulcerative colitis. Figure reproduced with permission from the journal that published Le Berre et al.*[23]

However, it is yet unknown if early treatment using the treat-to-target approach impacts the natural course of IBD, necessitating the need for prospective disease-modification trials. The targets of these trials were established by the SPIRIT consensus to evaluate the long-term effects of early treatment.[27] The targets in treating IBD may continue to change according to emerging evidence regarding the risk-benefit ratio of aiming for deeper healing, including histological and transmural healing.

# Chapter 2. Patients

## 2.1 Paediatric patients

PIBD is associated with more extensive disease, higher disease activity, and a more complicated course than adult-onset IBD.[28] In addition, particularly important complications of IBD in children and adolescent patients are impaired growth, delayed puberty, and low bone mineral and density.[29] The key management strategy of PIBD is to attain sustained control of intestinal inflammation and monitor for potential disease complications and side effects of treatments.[30] Various practical guidelines and society consensus statements on the management of paediatric CD[31] and UC[32,33] are available. However, the evidence on the management of PIBD in children is less extensive than in adults. Prior to 2000, the cornerstone of PIBD treatment was 5-aminosalicylates and corticosteroids. Currently, the range of treatment options has expanded to immunomodulators and biologics. To date, only two biologics have been approved for PIBD (namely infliximab and adalimumab).[34] Many treatment options that are available for adult patients (e.g., filgotinib, tofacitinib, ustekinumab, vedolizumab), are indeed not available for children yet. Considering the limited treatment options, optimisation of biologics is recommended in PIBD management guidelines (**Figure 6**).[31,32] Moreover, there is increasing evidence that the treatment plan for a paediatric patient should be individualised and consider factors such as age, disease location, disease behaviour, presence of growth delay, potential side effects of medications, and quality of life.[31,32]

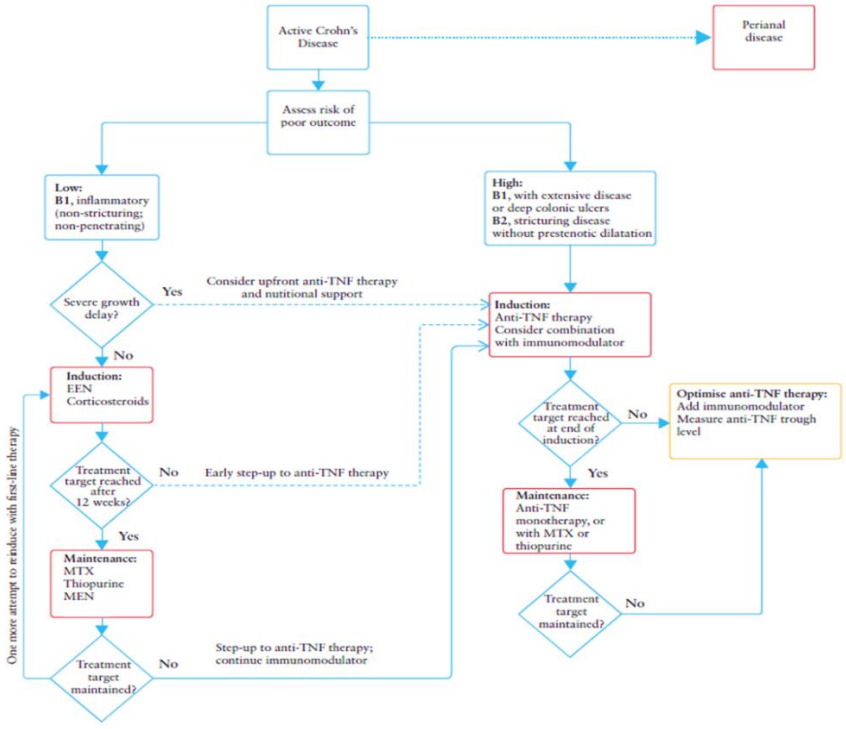


***Figure 6.*** *Example of a flowchart for medical management in paediatric luminal Crohn's disease. Figure reproduced with permission from the journal that published Van Rheenen et al.*[31]

## 2.2 Adult patients

A treat-to-target approach has gained momentum in disease management for adult patients with IBD.[25,26] The approach focuses on minimising disease activity at an early stage of IBD, controlling symptoms, limiting progression, improving long-term outcomes, and altering the natural course of the disease.[35] It is becoming increasingly obvious that IBD frequently recurs after treatment strategies aimed solely at controlling symptoms without the healing of inflammatory lesions.[36] However, the approach is a collaborative approach between patient and clinician. The approach entails identifying an appropriate therapeutic target, selecting initial treatment according to the risk of disease progression, measuring baseline characteristics of the disease, monitoring progress, and optimising treatment to reach the desired outcome (**Figure 7**).[36] To date, evidence of its potential benefits is required for implementing the approach in routine practice.

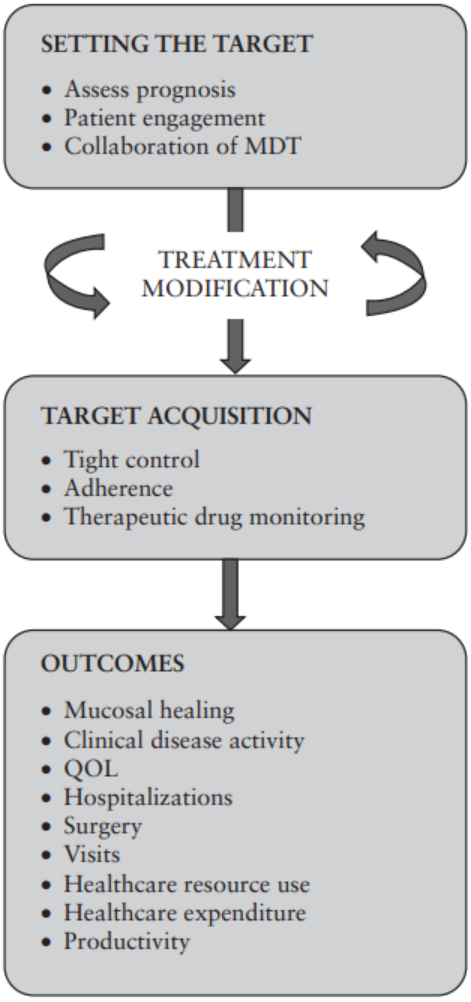


***Figure 7.*** *An overview of factors supporting the implementation of the treat-to-target approach. MDT, multidisciplinary team; QOL, quality of life. Figure reproduced with permission the journal that published Colombel et al.*[36]

## 2.3 Elderly patients

Elderly patients with IBD can be divided into two groups: older-onset IBD (i.e., an elderly patient with onset of IBD at an old age) and younger-onset IBD (i.e., an elderly patient with disease onset at a younger age).[37] Age of disease onset may be associated with differences in the disease phenotype and biological evolution of the disease.[2] Older-onset IBD (defined as an individual diagnosed at a late age e.g., after the age of 50) generally present with less complicated diseases than younger-onset IBD, particularly for CD.[38] However, a difference in the biological evolution of older-onset IBD compared with younger-onset IBD is still inconclusive, leading to challenges in selecting appropriate treatments for this population.[38]

To date, no consensus guidelines exist to direct the management within the elderly IBD population. The medical managements are generally similar to the younger IBD patients.[39] However, several unique challenges should be considered in the therapeutic management of elderly patients with IBD especially coexisting comorbidities and functional limitations (**Figure 8**).[40]

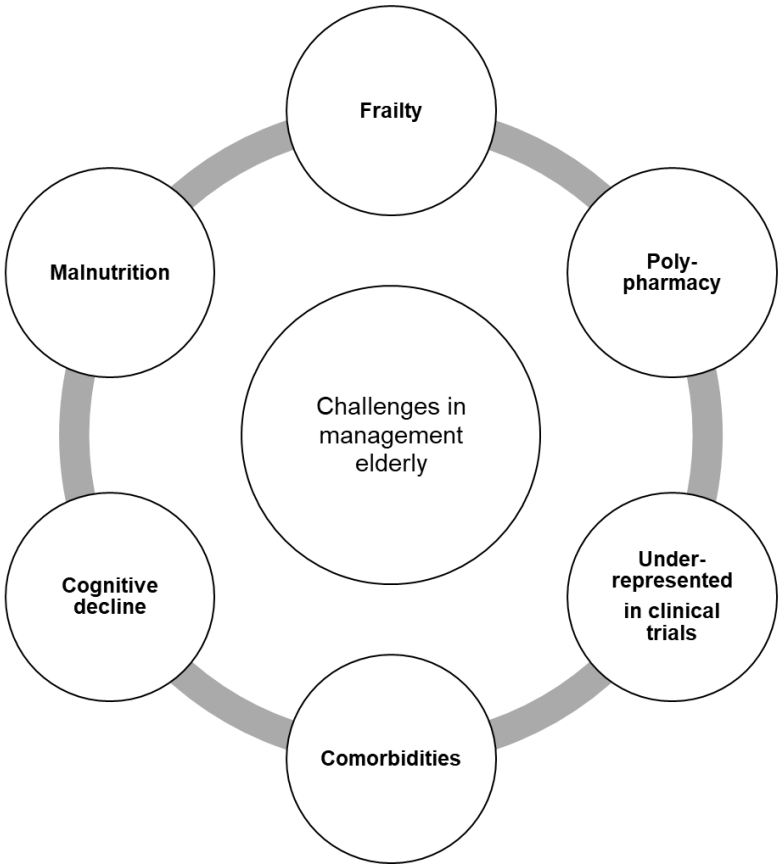


***Figure 8.*** *Challenges in the therapeutic management of elderly patient with IBD. Figure adapted from Tran et al.*[40]

# Chapter 3. Drug

## 3.1 Infliximab

To date, the mainstay of medical management of IBD is based on 5-aminosalicylates, corticosteroids, immunomodulators (e.g., thiopurines, methotrexate, calcineurin inhibitors), biological drugs, and small molecules.[41,42] Most of the conventional treatments control symptoms of IBD through pharmacotherapy, while biological drugs not only control symptoms but can modify the disease course, enable long-standing remission, and prevent long-term disability from structural damage.[43]

For over two decades, infliximab (Remicade®, Janssen Biotech, Inc. Horsham, PA, USA) was approved for IBD treatment in both adult and paediatric patients based on clinical development programs.[44] Infliximab is an established treatment for inducing and maintaining remission in patients with moderate-to-severe IBD above the age of six.[44] The package label lists weight-based dosing of 5 mg/kg intravenous infusions at weeks 0, 2, and 6 (induction treatment) and every eight weeks thereafter (maintenance treatment) (**Figure 9**).[45] In June 2013, the first biosimilar of intravenous infusion infliximab CT-P13 (Inflectra®, Hospira, UK) was approved by the European Medicine Agency for all indications of the originator product.[46] Recently, a novel subcutaneous formulation of infliximab CT-P13 has become available.[47] Patients with IBD start with 5 mg/kg intravenous infusion at weeks 0 and 2, then switch to 120 mg subcutaneous infliximab CT-P13 every other week from week 6 onwards.[47]

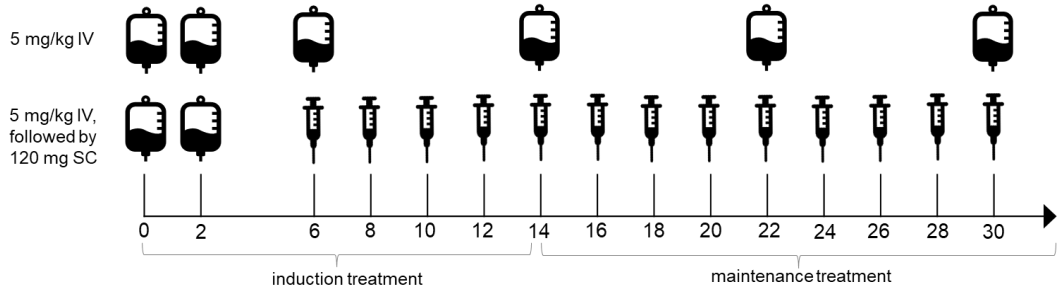


***Figure 9.*** *The approved dosing regimen of intravenous (IV) infusion of infliximab and subcutaneous (SC) formulation of infliximab CT-P13 for patients with inflammatory bowel diseases.*

### 3.1.1 Mechanism of action

Tumour necrosis factor-alpha (TNF-α) is a potent proinflammatory cytokine that plays a role in the dysregulation of the mucosal immune response.[48] An increased expression of TNF-α drives the underlying body's inflammatory response.[49] In patients with IBD, the level of TNF-α in the intestinal mucosa is elevated.[50] Therefore, through inhibition of TNF-α, this chronic inflammation can be controlled, and the disease can be successfully treated.

There are two receptors of TNF-α (i.e., TNFRI and TNFRII) with distinct intracellular signalling pathways. TNFRI mainly binds to the soluble form of TNF-α, whereas TNFRII binds to the transmembrane form of TNF-α.[51] TNFRI signalling pathways drive not only the acute phase response but also cellular behaviour such as cell migration and proliferation, and cell death in a highly context-dependent manner. In contrast, TNFRII plays a protective role in the intestinal mucosa.[52] This suggests that inhibitors of TNF-α may have multiple mechanisms besides neutralising the biological activity of the soluble form.

Infliximab is a chimeric immunoglobulin G1 (IgG) monoclonal antibody (mAb) that targets both soluble and transmembrane forms of TNF-α (**Figure 10A**).[51] In addition to the neutralisation of soluble TNF-α, two more alternative mechanisms of action have been proposed to involve in a resolution of inflammation and mucosal healing: i) the induction of lamina propria T cell apoptosis, and ii) induction of M2-type wound-healing macrophages (**Figure 10B and C**).[51]

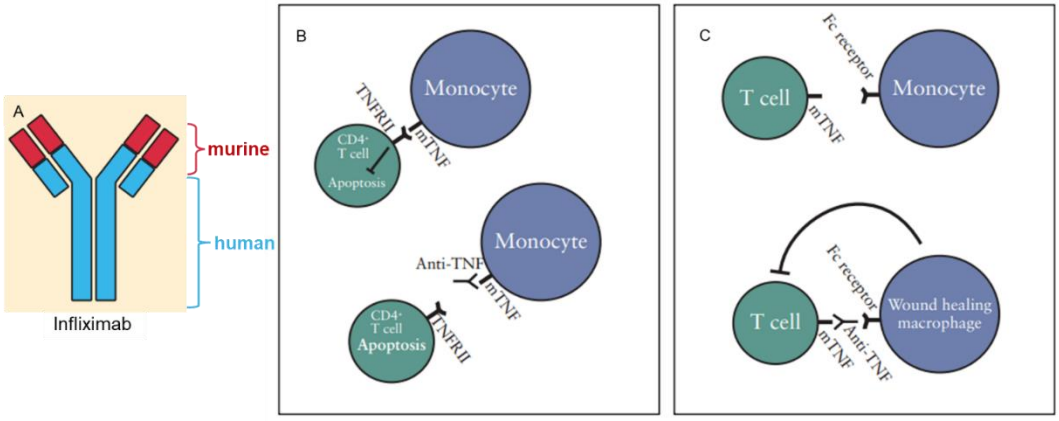


***Figure 10 A.*** *Schematic representation of infliximab. Two of the major alternative mechanisms of action of anti-tumour necrosis factor (anti-TNF), including* ***B.*** *induction of T cell apoptosis,* ***C.*** *triggering monocytes differentiation to an M2-like alternative or wound-healing macrophage through Fc region of anti-TNF. Figures reproduced with permission from the journal that published Levin et al.*[51]

### 3.1.2 Efficacy

However, up to 40% of patients with IBD do not respond to induction treatment (primary non-response), and around 23 – 46% of the patients lose response after one year of treatment (secondary non-response).[53] In general, treatment failures are caused by either insufficient dosing (i.e., pharmacokinetics [PK] failure) or mechanistic failure (i.e., pharmacodynamics [PD] failure).[54] PK failure could be due to several reasons, for instance, high inflammatory burden, increased clearance of infliximab, presence of antibodies to infliximab, and insufficient dosing concerning the disease state of the patient (e.g., patients with acute severe UC).[55] The former cause of failure can be overcome by infliximab dose escalation, while the latter requires switching to new agents that target different inflammatory mediators.[41,42] The inflammations in these patients are mainly driven by TNF-independent pathways.[56]

### 3.1.3 Safety

TNF-α is also a crucial mediator for tissue repair, immune modulation, and homeostasis.[57] Inhibition of TNF-α was expected to be associated with an increase in infections and malignancy over long-term use.[44] According to data on the file of Janssen, there was a higher rate of infections including serious infections in patients treated with Remicade than with placebo (21.0% versus 11.0% for infections and 2.4% versus 1.8% for serious infections, respectively).[44] However, incidences of malignancies (including lymphomas) were too infrequent to assess any possible association with infliximab use.[44] Similarly, the long-term post-marketing surveillance (TREAT™ Registry) observed an increased risk of serious infections with infliximab treatment, but no significant association between malignancy and infliximab treatment was observed after the mean length of 5.2 years follow-up time.[58,59] Also, as an exogenous protein, infliximab also raised concerns regarding immunogenicity, allergic/hypersensitivity reactions, and infusion reactions. In general, infliximab is considered a safe treatment. However, fully defining the safety profile of infliximab is still ongoing, specifically in the real-world setting and in special populations that are more vulnerable.[44]

### 3.1.4 Immunogenicity

Immunogenicity is the potential for an antigen to induce an immune response. Infliximab is structurally comprised of 75% human and 25% murine sequences.[60] Therefore, it could potentially trigger a host immune response and induce the occurrence of immunogenicity, leading to loss of response and treatment failure.[61] Antibodies to infliximab can directly interfere with the biological activity by preventing infliximab and TNF-α binding through the antigen-binding fragment (Fab) of infliximab (i.e., neutralising antibodies). Antibodies to

infliximab can also bind to different parts of infliximab and subsequently facilitate drug elimination (i.e., non-neutralising antibodies).[62]

The incidence of antibodies to infliximab is approximately 20% in both young adult and paediatric patients with IBD receiving infliximab for the treatment.[63,64] Also, the rate of infusion reactions is similar between adult and paediatric patients.[65] Around 75% of IBD patients treated with infliximab developed antibodies to infliximab by week 22 of treatment and 90% of the patients developed antibodies to infliximab within the first 12 months.[66]

Several factors can contribute to the formation of antibodies to infliximab such as the structure and mechanism of action of the biological drugs, manufacturing process, clinical use of a drug (e.g., route of administration and dosing regimen), and factors intrinsic to a patient (e.g., age, genetic predisposition, comedication, prior drug use).[67]

There is a dynamic relationship between immunogenicity and serum drug concentrations (i.e., immunogenicity leads to low serum concentrations of drug and the low serum levels lead to an increased probability in the formation of antidrug antibodies).[68] Regarding this, several managements of infliximab treatment have been proposed to sustain the initial clinical benefit of infliximab treatment and to reduce antibody formation including a high-dose induction regimen, an induction regimen followed by maintenance treatment, maintaining target levels of infliximab, testing for antibodies to infliximab, and co-administration with immunomodulators.[69–71]

Several methods are available to determine antibodies to infliximab titres. Early-developed test methods (i.e., drug-sensitive assays) are susceptible to infliximab interference and detect free antibodies to infliximab such as enzyme-linked immunosorbent assay (ELISA).[72] Subsequent advances in the test methods (i.e., drug-tolerant assays) become increasingly resistant to interference by infliximab (e.g., the high-pressure liquid chromatography-based homogeneous mobility shift assay; HMSA).[73] The drug-tolerant assays can quantify not only free antibodies to infliximab but also infliximab-bound antibodies (i.e., total antibodies to infliximab). However, the specific clinical risk of infliximab-bound antibodies has not yet been identified.[74] Therefore, drug-sensitive assays are currently the most used method for quantifying antibodies to infliximab in clinical practice.

### 3.1.5 Use in special populations

In paediatric patients with IBD, infliximab is indicated when the conventional treatment is not successful (e.g., steroid dependency, failure of corticosteroids, exclusive enteral nutrition, or failure of conventional immunomodulators). There is rising evidence that early treatment with biologicals (such as anti-TNF-α therapy) is superior to early immunomodulators. Also currently, infliximab is recommended for inducing remission in new-onset patients with high risk for a complicated disease course.[31] However, a step-up approach is still commonly used in most European paediatric centres due to restricted regulations. An eight-week maintenance dosing regimen was proven to have clinical benefits in children with CD and UC.[75,76] However, higher induction doses (up to 10 mg/kg), shorter dosing intervals, or both, are required to reach target serum trough concentrations, particularly in children with a bodyweight <30 kg, extensive disease, and low serum albumin.[77] Similar to adult patients, infliximab treatment failure can be related to insufficient serum drug concentration resulting from inadequate dosing and the formation of antibodies to infliximab.[78] Therefore, an early proactive therapeutic drug monitoring (TDM) of serum drug concentrations and antibody formation has been recommended in infliximab treatment for paediatric patients.[31–33]

Evidence on the effectiveness of infliximab treatment in elderly patients compared to younger adult patients is currently contradictory.[79,80] More safety data are required on the use of infliximab in elderly patients. The development of infections and malignancy are common concerns in treating elderly patients with biological drugs. Patients with IBD older than 60 years treated with infliximab had a higher rate of severe infections compared with younger patients or patients of the same age who were not treated with infliximab.[80,81] An increased malignancy rate was reported in the elderly patients treated with infliximab.[80] Infliximab is contraindicated in patients with heart failure (NYHA class III and IV) and must be used with caution in patients with a history of malignancy, especially lymphoma.[82] Furthermore, a prolonged combination of immunosuppressive agents should be avoided because of the increased risk of infectious and neoplastic complications.[83]

## 3.2 Pharmacokinetics

### 3.2.1 Pharmacokinetics

Infliximab is administered intravenously, which allows immediate distribution into the bloodstream with 100% bioavailability. The distribution of infliximab is mainly restricted to the central compartment and extracellular spaces due to its high molecular weight (~149.1 kDa) and hydrophilicity.[84] For large, polar substances such as infliximab, convective transport is a primary mechanism responsible for the transport of antibodies from blood fluid to interstitial fluids of tissue.[85] The rate of extravasation by convective transport is determined by the rates of fluid movement from blood to tissue and by the sieving effect of paracellular pores in the vascular endothelium.[85] However, in-tissue distribution can be limited due to tight binding to the immobile target (i.e., transmembrane TNF-α) near the site of antibody extravasation.[86] At steady state, the volume of distribution of infliximab ranges from 4.5 L to 6 L which is approximately equal to intravascular fluid volume of the extracellular compartment (0.11 L/kg).[87] Infliximab is cleared from circulation primarily via catabolism (i.e., protein turnover). Catabolism depends on rates of extracellular degradation via proteolysis mediated by Fc gamma receptors (FcγRs), and rates of recycling through interaction with the Brambell or neonatal Fc receptor (FcRn).[85] The median half-life of infliximab is approximately 14 [IQR 10.4 – 17.8] days.[55,84]

The PK of infliximab can differ between young paediatric patients and adults due to differences in drug disposition mechanisms (**Figure 11**).[88] It is generally known that the tissue water content of young patients is relatively higher than that of older children and adults.[89] Therefore, the volume of distribution of infliximab would be expected to be higher when normalised for kilograms of bodyweight. In general, catabolism seems to be substantially higher in young patients compared to adults.[90] However, with less presence of endogenous IgG, FcRn is more effective at recycling infliximab, leading to a lower clearance in this age range.[88] Further clinical evidence is still needed to ascertain whether the effects of paediatric age on these mAb elimination-related processes cancel out or result in differences in mAb elimination.[88] Recently, a paediatric physiologically-based pharmacokinetic (PBPK) model combined with population approaches has been developed to provide mechanistic insight into age-dependent changes (e.g., in bodyweight, organ weight, and organ blood flow rate) on the PK of infliximab.[91]

In elderly patients with IBD, the PK of infliximab can be impaired due to age-dependent changes in body composition. The volume of distribution of infliximab can be altered by the age-related increase in body fat and reduction in total body water, lean muscle mass, and hypoproteinaemia resulting in higher infliximab exposure.[92]

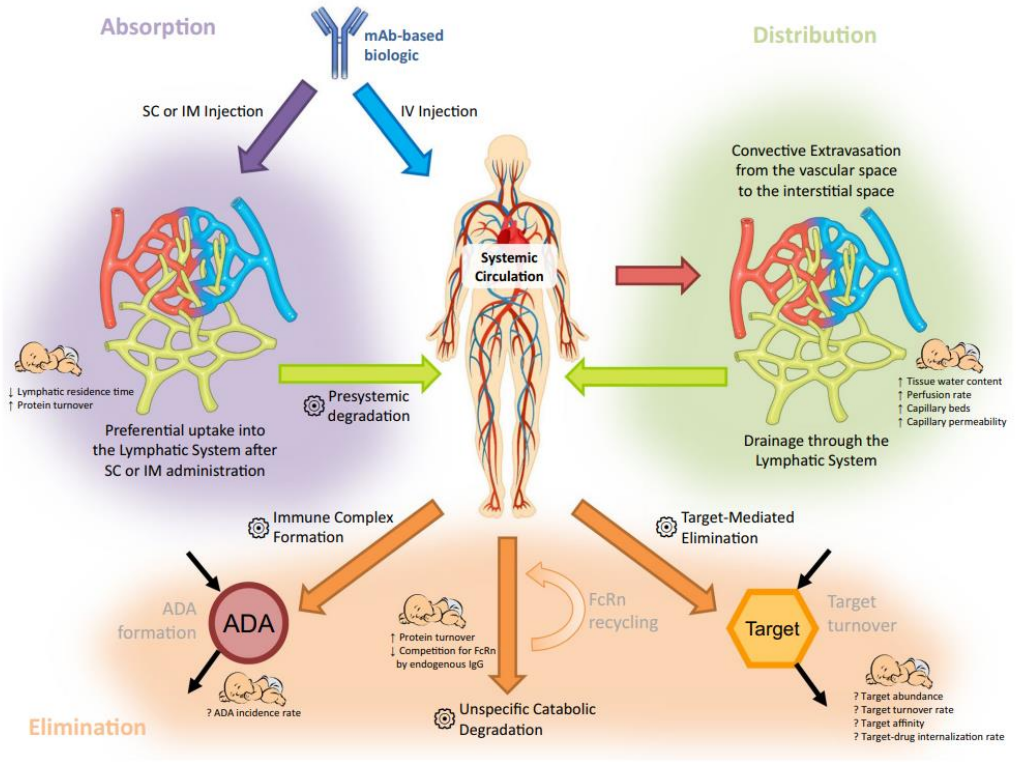


***Figure 11.*** *Summary of the major pharmacokinetic processes in young paediatric patients. The gear symbol indicates drug disposition mechanisms. ADA anti-drug antibody, FcRn neonatal Fc receptor, Ig immunoglobulin, IM intramuscular, IV intravenous, mAb monoclonal antibody, SC subcutaneous. Figure reproduced with permission from the journal that published Temrikar et al.*[88]

Several factors could potentially affect the PK of infliximab in both adults and children with IBD (**Figure 12**).[55,77,93]

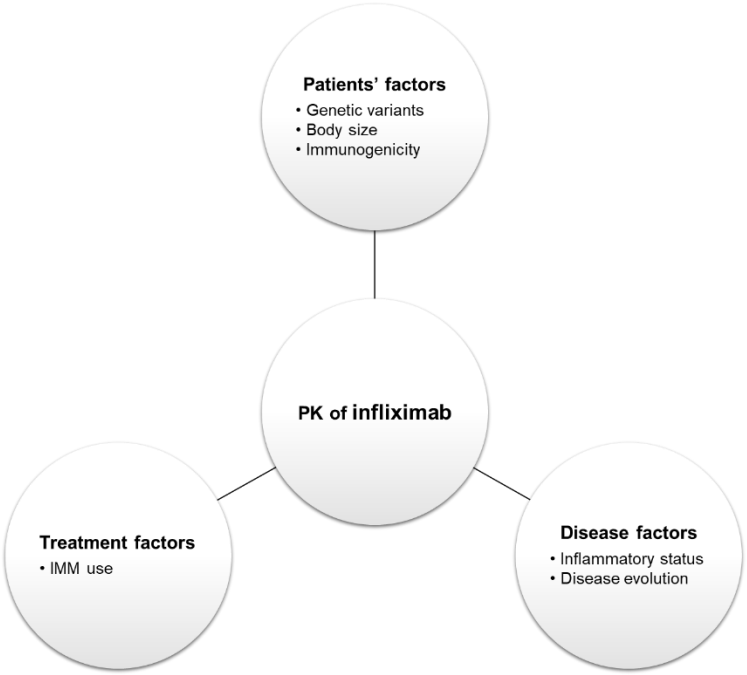


***Figure 12.*** *Factors that affect pharmacokinetics (PK) of infliximab. IMM, immunomodulators.*

*(i) Patients' factors*

- A genetic variation in FcRn affects serum infliximab concentrations since the decrease in FcRn expression results in increased clearance (CL) and decreased the systemic exposure of infliximab.[94]
- Body size affects differences in the distribution and elimination of therapeutic mAbs.[95]
- The formation of antibodies to infliximab is associated with accelerated clearance of infliximab due to the rapid elimination of the complex between infliximab and antibodies to infliximab.

*(ii) Disease factors*

- Catabolism of infliximab is upregulated in a high inflammatory status as shown by the associations between infliximab clearance and concentrations of indirect markers for inflammation (such as baseline TNF-α, serum albumin, and CRP).[55] A high level of TNF-α in gut mucosa may require a greater amount of infliximab to neutralise excess TNF-α resulting in lower serum infliximab concentrations.[96] The endogenous catabolic rate for albumin is highly correlated with the catabolic turnover of IgG.[93] Thus, increased protein turnover, as indicated by hypoalbuminemia, results in increased catabolic degradation of IgG molecules and increased CL, and reduced systemic exposure of therapeutically administered mAbs.[93] Hypoalbuminemia also indicates loss of serum protein through leakage in the gastrointestinal tract (i.e., protein-losing enteropathy).[97,98] An increase in serum concentration of CRP has also been associated with increased infliximab clearance.[99]
- Clearance of mAb may vary over time because of disease evolution.[93] A linear increase in CL with time was reported in IBD patients who underwent infliximab dose de-escalation.[100] The magnitude of the increase was approximately 13 – 14% from baseline after one year of treatment.[101]

*(iii) Treatment factors*

- Concomitant use of immunomodulatory drugs in patients receiving infliximab treatment resulted in a lower incidence of antibodies to infliximab.[102]

A serum infliximab concentration-time profile is characterised by a high peak-to-trough ratio because of the relatively large intravenous dose and long infusion interval (i.e., eight-week infusion interval) (**Figure 13**).[99,103] The profile is biphasic, with a distribution and an elimination phase (on a log scale of the y-axis). During repeated infusions of infliximab (every 4 – 8 weeks), no accumulation was observed, and serum concentrations and the area under the serum infliximab concentration-time curve increased proportionately to the infused dose indicating linear PK.[84] Also, it has been demonstrated that serum infliximab concentration-time data in patients with IBD vary greatly over time both within and between individual patients.[99,103]

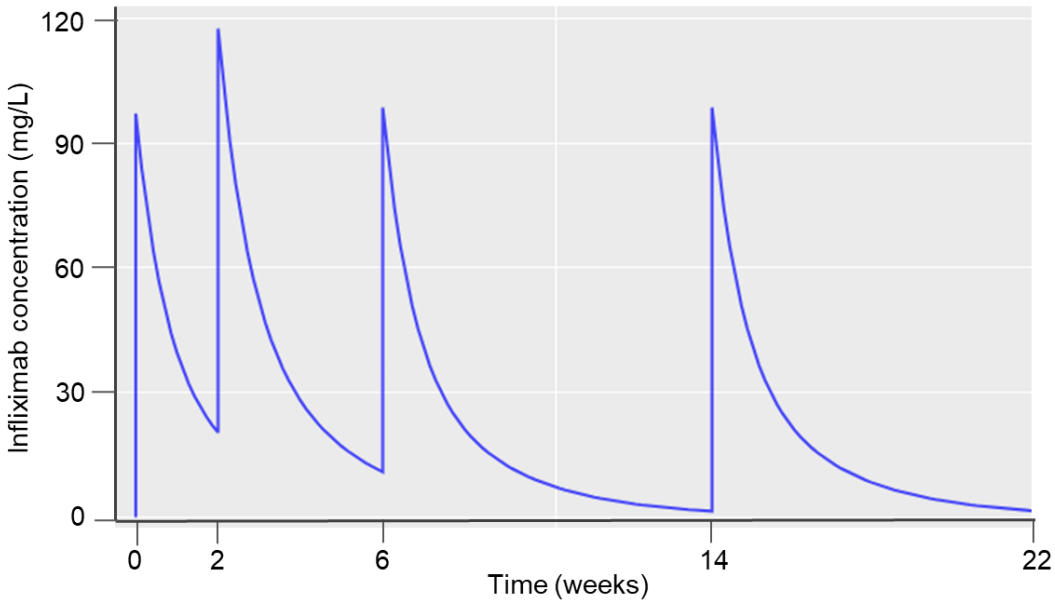


***Figure 13.*** *The simulated serum infliximab concentration-time profile following the approved weight-based dosing regimen (5 mg/kg) from week 0 to week 22 using the model of Fasanmade et al. (combined paediatric and adult populations) available in our developed https://tdmx.shinyapps.io/Infliximab_paediatric/. An 18-year-old male with CD, serum albumin 41 g/L, without immunomodulator, and no antibodies to infliximab. The simulation was performed without unexplained between-subject variability.*

### 3.2.2 Population pharmacokinetics

Population PK (popPK) pharmacometrics analyses have been utilised in drug development to identify and quantify drug disposition characteristics, sources of PK variability within study populations (such as within-subject or between-subject variability), and the impact of covariates on systemic drug exposure and their potential implications for clinical dosing.[95]

The disposition characteristics of infliximab in patients with IBD were well described with a two-compartment model with zero-order infusion and linear elimination (**Figure 14**).[99,103] In patients with IBD, the estimated CL of infliximab ranged from 0.23 – 0.41 L/day, which is relatively close to the estimated CL of endogenous IgG of 0.21 L/day.[95] Population estimates of the volumes of distribution ($V_d$) in the central ($V_c$) and peripheral ($V_p$) compartments are typically small, with median values of 3.3 (range, 2.28 – 4.0) L and 1.4 (range, 1.23 – 4.13) L, respectively, reflecting the limited ability of infliximab to leave the vascular space.

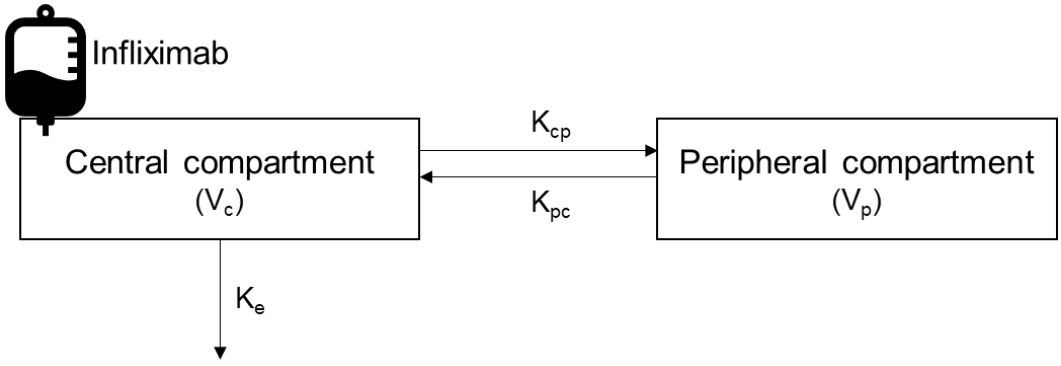


***Figure 14.*** *Schematic of a representative structural pharmacokinetic model of infliximab. $V_c$, the volume of distribution in the central compartment; $V_p$, the volume of distribution in the peripheral compartment; $K_e$, elimination rate constant calculated by clearance/$V_c$; $K_{cp}$, distribution rate constant from central to peripheral compartment calculated by intercompartmental clearance/$V_c$; $K_{pc}$, distribution rate constant from central to peripheral compartment calculated by intercompartmental clearance/$V_p$.*

Infliximab is characterised by large PK variability between subjects, with coefficients of variation of 37.7% for CL and 22.1% for $V_c$.[55] However, information is limited regarding the between-subject variability in other distribution-related parameters, such as $V_p$ and intercompartmental clearance (Q). Covariates that have been identified to account for a part of the observed variabilities in CL are the presence of antidrug antibodies, the use of concomitant immunomodulators, the degree of systemic inflammation, the serum albumin concentration, and bodyweight.[104]

### 3.2.3 Dose-Exposure-Response Relationship

The administration of the standard infliximab dosing regimen was demonstrated to be effective.[105,106] However, treatment responses greatly differ among individual patients.[55] In adult patients with IBD, serum infliximab concentrations during induction and maintenance treatment are associated with clinical remission, endoscopic improvement, endoscopic remission, and need for surgery.[105–107] Similar to the adult patients, a positive relationship was noted between the serum infliximab concentrations and the treatment outcomes in children with IBD.[108–110] Inadequate infliximab exposure as measured by serum infliximab trough concentrations is associated with loss of response to infliximab treatment.[55]

A bi-directional relationship between PK and PD is common for mAbs used in IBD (**Figure 15**).[1] Given the exposure-response relationship, patients with higher CL of infliximab will have lower drug exposure and are subsequently at higher risk of not attaining or losing therapeutic response (i.e., *exposure drives response*). The higher CL of infliximab is associated with high bodyweight, low serum albumin, the degree of systemic inflammation, and the presence of antibodies to infliximab.[55] On the other hand, high disease activity can impair the intestinal barrier function resulting in faecal loss of protein, including infliximab.[98] The loss of infliximab lowers drug exposure (i.e., *response drives exposure*).

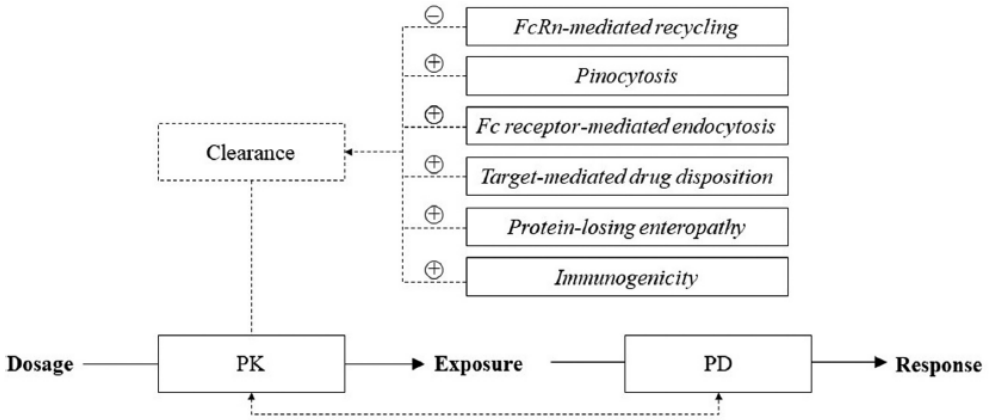


***Figure 15.*** *A schematic diagram illustrating the concept of a bi-directional relationship between pharmacokinetics (PK) and pharmacodynamics (PD) of monoclonal antibodies. Underlying mechanisms of the clearance of monoclonal antibodies are indicated. The dashed arrow between PK) and PD denotes the bidirectional relation between both. FcRn, neonatal Fc receptor. Figure reproduced with permission from the journal that published Kantasiripitak et al.*[1]

## 3.3 Dosing strategies

The bodyweight is the most common size-based dosing approach for mAbs.[88] The 5 mg/kg weight-based dosing of infliximab was approved for all patients with IBD above the age of six.[45] However, the weight-based dosing may not be optimal across a wide age range due to the nonlinearity relationship between bodyweight and CL of mAb.[95] As a consequence, the linear relationship between dose and bodyweight may not result in adequate exposure levels in all patients. Patients with a low bodyweight are particularly at risk for underexposure and may require a higher dose than the standard dosing regimen.[77] The paediatric patients with IBD who receive a 5 mg/kg dose have substantially lower exposure (25 – 40%) than the adults.[111]

In general, the absence or loss of response to infliximab could also be caused by the extensive PK variability of infliximab in patients with IBD.[55] Therefore, the *'one size fits all'* theory may not apply to all patients with IBD receiving infliximab. To manage patients treated with infliximab, alternative dosing strategies have been proposed such as TDM in conjunction with flowchart-guided dosing and model-based TDM (i.e., model-informed precision dosing [MIPD]) (**Figure 16**).[112,113] TDM is a clinical decision-making tool that enables dosage regimen adjustments based on clinical and laboratory measurements, typically drug blood concentrations, to reach drug exposure that is associated with the treatment outcomes. Therefore, two fundamental requirements for performing TDM are i) the accessibility of assays to measure the drug concentration and ii) the availability of therapeutic target concentrations associated with clinical effectiveness or with drug-related toxicity.[114]

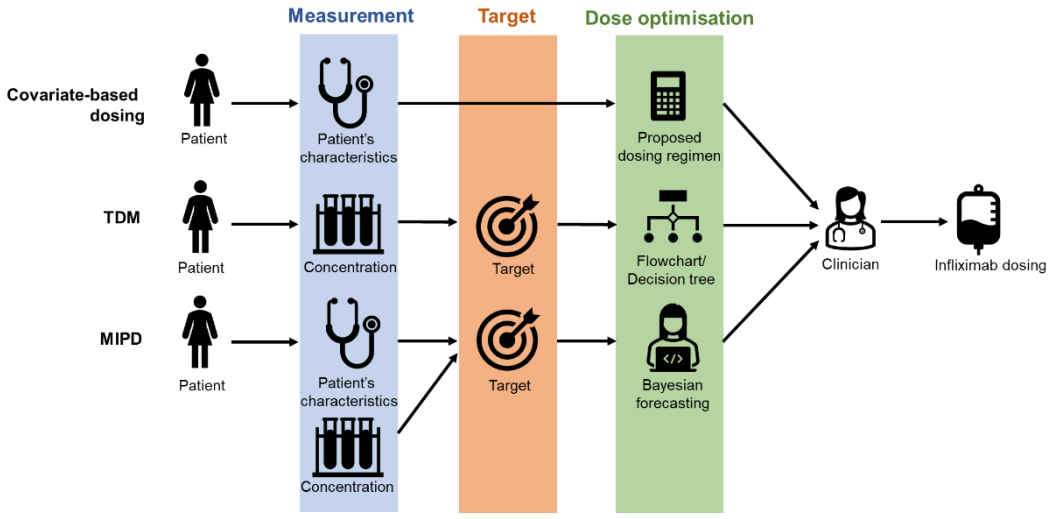


***Figure 16.*** *A comparison of the workflows of covariate-based dosing, therapeutic drug monitoring (TDM), and model-informed precision dosing (MIPD).*

### 3.3.1 Therapeutic drug monitoring

Over the years, TDM has been introduced as a dose optimisation strategy for infliximab treatment in patients with IBD. TDM of infliximab can be performed in the absence (proactive TDM) of signs of active disease to maintain a therapeutic concentration and treatment outcomes, or in the presence (reactive TDM) of signs of active disease to direct further treatment.[115] The concepts related to TDM, including target attainment from different routes of administration, dose optimisation, and impacts of antidrug antibodies on serum drug concentrations are illustrated in **Figure 17**.[116]

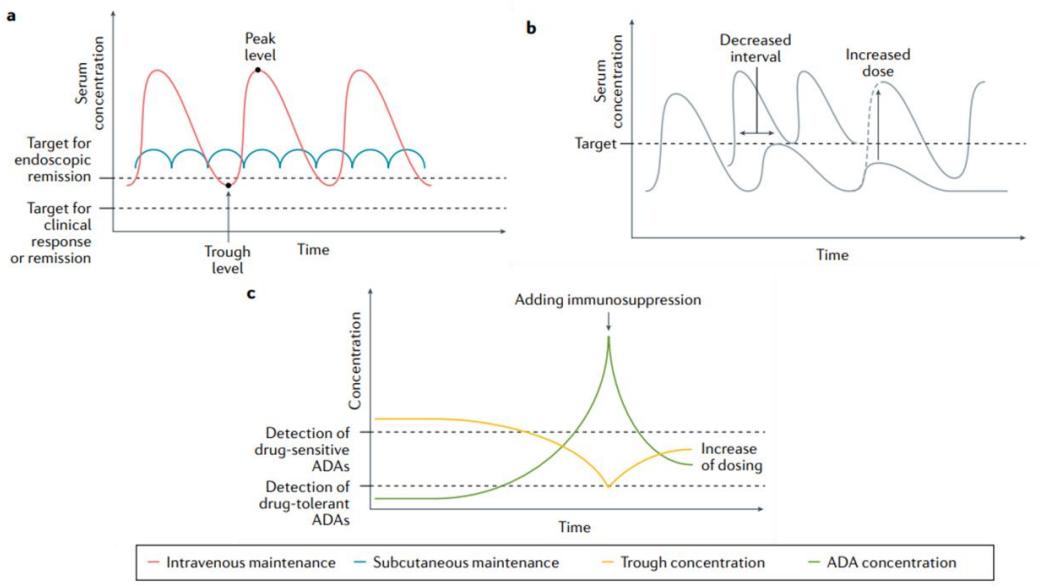


***Figure 17.*** *Concepts related to therapeutic drug monitoring in inflammatory bowel disease. a) Typical serum concentrations with intravenous (red) and subcutaneous (blue) administration of biologic therapy for inflammatory bowel disease concerning target concentrations for clinical versus endoscopic remission. b) Dose optimisation options in case of subtherapeutic serum concentrations: the decreased interval between dosing versus increased dose. c) Immunogenicity and the response of antidrug antibodies (ADAs) detected with drug-tolerant versus drug-sensitive assays, including the effect of adding immunosuppression and/or a dose increase. Serum drug concentrations and concentrations of ADAs are illustrated in yellow and green, respectively. Figure reproduced with permission from the journal that published Argollo et al.*[116]

TDM of infliximab is done by measuring serum infliximab concentrations and antibodies to infliximab to guide individual dose adjustment, aiming at a serum concentration target that is associated with the desired treatment outcome (**Figure 18**).[117] The recommended targets of serum infliximab concentrations for patients with IBD based on empirical data are summarised in **Table 2**. To note, TDM implies a relationship between the drug concentration and outcome. The combined use of both measurements allows the identification of underlying PK and PD-related reasons for treatment failure.[44] It enables the identification of patients who might benefit from dose adjustment versus those who need to switch to another drug within or outside the class.

A TDM flowchart/decision tree is a relatively simple tool for guiding clinical decision-making. However, the potential advantage of TDM could be undermined due to large variability in PK of infliximab and complex relationships between covariates and infliximab PK that makes it challenging to hit the exposure target quickly and precisely.[115]

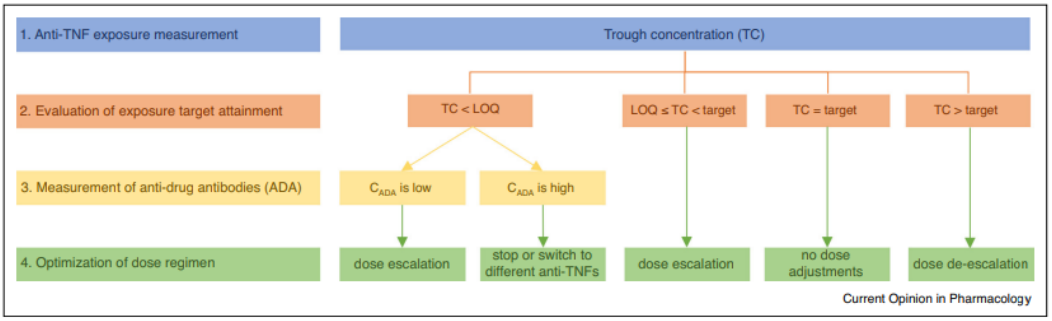


***Figure 18.*** *A generic 'analogous' therapeutic drug monitoring flowchart/decision tree. The cut-off between low and high concentrations of anti-drug antibodies can depend on the assay to assay. Dose escalation is achieved through interval shortening and/or dose increase. Dose de-escalation is achieved through interval extension and/or dose decrease. ADA, anti-drug antibody; anti-TNF, anti-tumour necrosis factor; CADA, the concentration of anti-drug antibodies; LOQ, the limit of quantification; TC, trough concentration. Figure reproduced with permission from the journal that published Wang et al.****[117]***

***Table 2.*** *The recommended targets of serum infliximab concentrations for patients with IBD are based on empirical data.*

| Time point (week) | Paediatric patients[31,109,118] | Adult patients[115] | Elderly patients |
|---|---|---|---|
| | Target serum infliximab concentration (mg/L)[a] | | |
| 2 | ≥25 | 20 – 25 | NA |
| 6 | ≥15 | 10 – 15 | NA |
| 14 | ≥5 | 3 – 7 | NA |
| Maintenance | ≥5 | 3 – 7 | NA |

[a]*The higher serum drug concentration thresholds of the range are typically needed for achieving more stringent therapeutic outcomes, such as mucosal healing, and in patients with a more complicated IBD phenotype, such as fistulising CD or acute severe UC. NA, not available. Table adapted from Vermeire et al.****[115]***

In adult patients with IBD, there is no clear clinical benefit in favour of a proactive or reactive TDM approach from the available prospective evidence. Reactive TDM significantly reduced treatment costs without improving clinical efficacy compared to routine infliximab dose escalation in CD patients who lost response during maintenance treatment.***[119]*** Similarly, the clinical benefit of proactive TDM could also not be addressed in adult patients with IBD during induction (NOR-DRUM A[120]) and maintenance infliximab treatment (TAXIT[121], TAILORIX[122]). The recently published NOR-DRUM B demonstrated that proactive TDM during maintenance treatment with infliximab was more effective in sustaining disease control in immune-mediated inflammatory diseases than treatment without TDM.***[123]*** However, the results must be interpreted with caution due to open-label design and lack of objective measures of disease activity.[124]

To date, the available controlled evidence does not support TDM approaches in routine strategies to monitor and optimise infliximab treatment in adult patients with IBD.[125] The current American Gastroenterological Association (AGA) guideline for IBD conditionally recommends the use of TDM during maintenance therapy in response to suboptimal disease control based on very-low-quality evidence.[112] Therefore, TDM may at least be used to guide dose optimisation in IBD treatment (e.g., escalation of infliximab treatment, the introduction of an immunomodulator, or another biologic drug).

Contrary to adult patients with IBD, the current guidelines for the medical management of paediatric patients with IBD recommend both early proactive TDM and reactive TDM regardless of the lack of prospective evidence.[31–33] Currently, a value of TDM has been justified in children based on a well-established positive association between higher serum trough concentrations and better treatment outcomes.[108–110] There is mounting evidence that treatment outcomes and serum drug and antidrug antibody concentrations are inversely correlated; therefore, several studies have recommended assessing these levels to improve the management of IBD.[126]

The potential benefit of TDM is more important in paediatric patients with IBD due to limited treatment options and underdosing of infliximab in patients with low bodyweight.[34,127] The first proactive TDM is recommended just before the fourth infusion (i.e., 14 weeks after the first dose) in paediatric patients with CD treated with infliximab. An earlier first proactive TDM may be recommended at the second or third infusion in patients at risk for accelerated infliximab CL during induction, such as children <30 kg, those with extensive disease, those with low serum albumin, and those on infliximab monotherapy.[31] The reactive TDM is recommended to guide treatment change over empirically escalating the infliximab dose or switching to other treatments.[31,32]

### 3.3.2 Model-informed precision dosing

Model-informed TDM or MIPD has been proposed as an alternative dosing approach to quantify the PK of infliximab in individual patients and adjust dosing based on simulations to ensure adequate exposure associated with treatment outcomes (i.e., target exposure).[117] MIPD employs drug-specific popPK models, patient-specific covariates, measured drug concentrations, a target exposure, and a Bayesian forecasting software tool to predict optimal doses for individual patients. As opposed to covariate-based dosing or analogous TDM algorithms that typically consider one or two covariates, MIPD employing popPK can consider several covariates (*a priori*) and/or measured drug concentrations (*a posteriori*) at the same time, which allows more information in predicting individual PK parameters.[128]

The basis of MIPD is a popPK model. PopPK is the study of PK at the population level that evaluated data from all individuals in a population simultaneously using nonlinear mixed effects modelling.[129] The word “nonlinear” refers to the nonlinear relationship between the dependent variable (e.g., serum drug concentration) and the model parameters and independent variable(s).[129] The term “mixed-effects” refer to the parameterisation: parameters that do not vary between individuals are called fixed-effect parameters (i.e., structural model and covariate model), while parameters that vary across individuals are called random-effect parameters (statistical model).[129] The common goal of nonlinear mixed-effect methods (first-order; FO and expectation maximisation; EM) is to determine the set of fixed-effect parameters that best fit the population data and account for all possible values of individual parameters via the random-effect parameters.[130] Fixed-effects parameters take a single value that represents the population typical value of the parameter. Random-effects parameters represent the variance of distribution of unexplained variabilities. Modelling of a parametric distribution requires three components of the distribution, including (i) a distribution shape (e.g., symmetric), (ii) a value of central tendency (e.g., mean of 0), and (iii) a variance.

The parameter estimation is based on minimising an objective function value (OFV), often using maximum likelihood estimation. The OFV is minus twice the log of the likelihood and provides an overall summary of how close the model predictions (i.e., a set of model parameters) describe the observed data (maximum likelihood = lowest OFV = the best fit to the data).[129] In addition to OFV, other model evaluation tools are used during popPK model development including graphical evaluations (e.g., goodness-of-fit plots), simulation-based methods (e.g., visual predictive check; VPC), and the precision of parameter estimates (e.g., bootstrap).[131–133]

Components of popPK model are as follows (**Figure 19**):

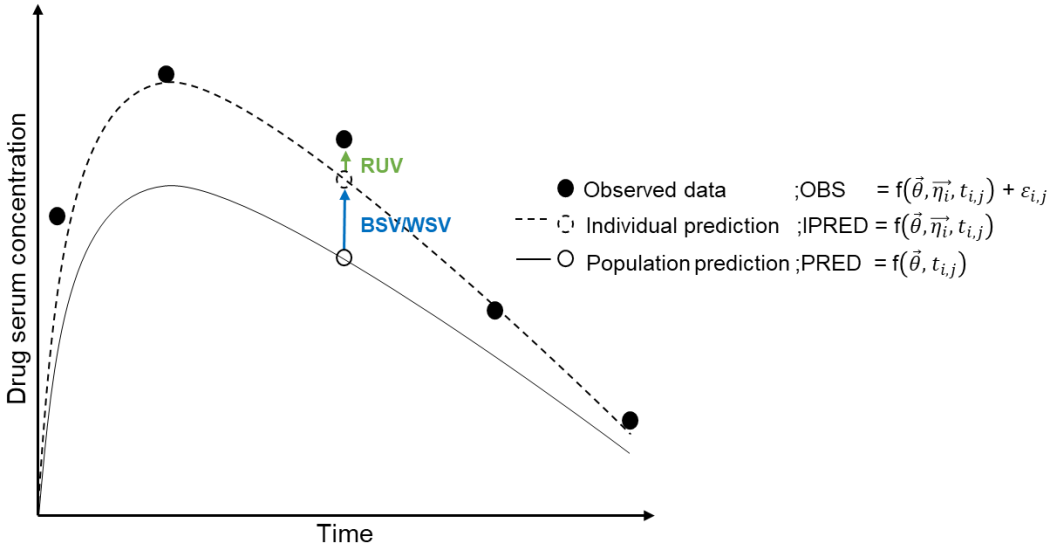


***Figure 19.*** *Summary representation of population pharmacokinetic model. BSV, between-subject variability; RUV, residual unexplained variability; WSV, within-subject variability. f(·) represents the nonlinear functions of the independent variables including vector of fix-effect parameters of population ($\vec{\boldsymbol{\theta}}$), vector of random effect parameters of individual i ($\vec{\boldsymbol{\eta}_i}$), and time of individual i at timepoint j. $\boldsymbol{\varepsilon_{i,j}}$ represents the residual variability for individual i at time point j.*

(i) ***Structural models*** describe the typical drug serum concentration-time profile within the population. The models represent structural elements in a PK model such as CL or $V_d$.

$$CL = \theta_1 \qquad \textit{Equation 1}$$

$$V_d = \theta_2 \qquad \textit{Equation 2}$$

(ii) ***Statistical models*** account for unexplained variabilities around the structural model (Level 1; e.g., between-subject or within-subject variability) and the differences between the individually predicted serum drug concentrations and observed concentrations (Level 2; e.g., residual unexplained variability). The level 2 variability may arise due to assay variability, errors in sample time collection and model misspecification.[129] Selection of function for statistical models is based on the type of evaluated data.[129]

- For level 1 random-effect parameters (between-subject variability), each subject has a unique vector containing the individual subject estimates of the parameters termed as eta ($\eta$) vector ($\eta_{i,n}$; *i* for individual, *n* for index of the element in the vector). The standard deviation of the $\eta_{i,n}$ values and the variance ($\omega_n^2$) can be obtained by combining eta vectors from all subjects. PK parameters are positive values with right-skewed. Therefore, log-normal distributions of PK parameters are often assumed and can be described using a log-normal function of $\eta$ as follows:

$$CL = \theta_1 \times e^{\eta_{i,1}} \quad \textit{Equation 3}$$

$$V_d = \theta_2 \times e^{\eta_{i,2}} \quad \textit{Equation 4}$$

where $\theta_1$, $\theta_2$ are the population values of CL and $V_d$, respectively. $\eta_{i,1}$, $\eta_{i,2}$ are the deviations from the population values of CL and $V_d$ for the individual *i*, respectively. The different variances and covariances of $\eta$ are collected into an omega matrix ($\Omega$) as follow:

$$\Omega = \begin{matrix} variance\ of\ CL\ (\omega_{1,1}^2) & covariance\ of\ CL\ and\ V_d \\ covariance\ of\ CL\ and\ V_d & variance\ of\ V_d\ (\omega_{2,2}^2) \end{matrix} \quad \textit{Equation 5}$$

To note, variance terms should be included on the parameters that are expected to gain information from the covariates. Without including the variance term, a PK parameter equates to a population typical value (i.e., complete shrinkage) and consequently restricts the covariate evaluation to the incorporation of allometric or maturation models.[129]

- For level 1 random-effects parameters (within-subject variability), individual PK parameters could change along the treatment phase (e.g., induction, and maintenance phase). The within-subject variability can be handled by incorporating as a component of between-subject variability as the following example:

$$CL = \theta_1 \times e^{\eta_{i,1} + WSV} \quad \textit{Equation 6}$$

It is important to note that a large extent of within-subject variability could undermine the benefit of dose adjustment based on previous measured drug concentrations (i.e., *a posteriori* prediction).[134]

- For level 2 random-effect parameters, each observation has the magnitude of unexplained differences between the observed and predicted values of the dependent variable (e.g., serum drug concentration). The standard deviation and variance of the magnitude of differences are termed as $\varepsilon$ and $\sigma^2$, respectively, and collected into a sigma matrix ($\Sigma$). The statistical model with level 2 random-effects parameters (e.g., additive error function) can be expressed as follows:

$$Y_{i,j} = f(\vec{\theta}, \overrightarrow{\eta_i}, t_{i,j}) + \varepsilon_{i,j} \quad \textit{Equation 7}$$

where Y represents the dependent variable (e.g., serum drug concentration) in an individual *i* at time point *j* as the nonlinear function of the independent variables including vector of fixed-effects parameters of population ($\vec{\theta}$), vector of random effect parameters of individual *i* ($\overrightarrow{\eta_i}$), and time of individual *i* at time point *j*. $\varepsilon_{i,j}$ represent the residual variability for individual *i* at time point *j*, accounting for the unexplained differences between the observed and model-predicted values.

(iii) ***Covariate models*** explain the relationship between the PK parameters and patient-specific covariates (e.g., bodyweight and disease activity markers). Identification of covariates that can explain between-subject variability in PK parameters is important in popPK model development. Various methods were developed for covariate model building such as generalised additive models, forward addition/backward deletion, and full random effect models.[135–137] Parameterisation of the covariate models is based on the covariate data type (e.g., continuous [bodyweight], discrete [IBD type]).

A Bayesian method is generally used in a Bayesian forecasting software tool. The method allows updating prior information (a popPK model) using new data (patient data). Essentially, the prior dominates in estimating the updated model parameters when the amount of new data is limited. Whereas when the amount of new data is increased, the prior is mostly ignored (**Figure 20**).[138] This type of parameter estimation is called maximum *a posteriori* estimation. An updating of model parameters using maximum a *posteriori* estimation is called "Bayes updating". Using the updated parameters to predict concentrations or doses is generally called "Bayes forecasting". The Bayesian method using a popPK model as prior information allows better inferring of PK parameters from a population of patients rather than from one individual.[138] The Bayesian method was first introduced in the seminal publication by Sheiner and Beal to individualise drug dosage by estimating PK parameters.[139]

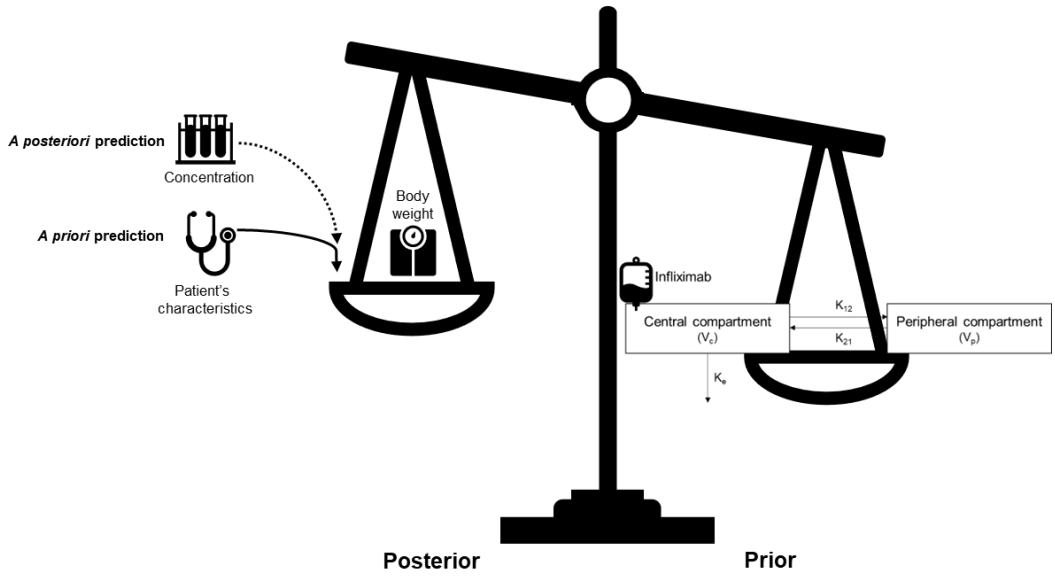


***Figure 20.*** *Balancing the prior and posterior data. In the absence of any individual data, the predictions of a population pharmacokinetic model can be weighted in favour of the prior using the Bayes approach. The model predictions for an individual shift toward an individual prediction based on the quantity of individual data available (posterior). Figure adapted from Mould et al.*[138]

During MIPD, the popPK model serves as a Bayesian prior and is needed for forecasting PK parameters.[138] The popPK model can be updated to *a posterior* model of an individual patient by taking into account the covariates or characteristics of the patient that explain variation in PK parameters (probabilistic dosing or *a priori* prediction) and by taking into account previous measurements of that patient's drug concentrations (Bayesian forecasting or *a posteriori* prediction). The individual PK parameters are estimated (empiric Bayes estimates) based on patient characteristics and drug concentration data and then used to forecast the subsequent dose needed for that patient to reach a predetermined exposure target.[115]

MIPD is often perceived as a complicated and time-consuming task.[140] To overcome these obstacles, MIPD software tools have been developed to support clinical decision-making on therapeutic individualisation.[138,141] MIPD software tools contain a popPK model and optimisation algorithm that allow inference from input data (covariate[s] and concentration[s]) and evaluate a dosing regimen that maximises the chance to meet the prespecified target.[138,141]

MIPD could potentially overcome several issues of infliximab treatment in patients with IBD such as large between-subject variability in the PK of infliximab, underdosing of infliximab in paediatric patients, and loss of response due to PK failure.[138] The potential of implementing MIPD of infliximab in patients with IBD has been demonstrated not only in retrospective studies[142,143] but also in prospective studies[144,145]. The first prospective study in the multicentre randomised trial (the PRECISION trial; NCT02453776) showed that using MIPD guiding infliximab maintenance treatment significantly reduced the incidence of loss of response (clinical remission) in comparison to standard infliximab dosing.[144] Also, the second prospective intervention study in a real-world IBD setting demonstrated the benefits of applying MIPD in infliximab dose optimisation during induction treatment.[145] The benefits of applying MIPD included a significantly lower chance of infliximab discontinuation and incidence of antibodies to infliximab, and improvement of clinical outcomes after one year of treatment. Due to the acknowledged benefits of MIPD in treating patients with IBD, great efforts are currently being made to improve components of MIPD.[146]

# Objectives

For over 20 years, infliximab has been approved for the treatment of patients with IBD. However, there are several concerns regarding the suitability of standard infliximab dosing in patients with IBD:

i) Approximately one-third of the **adult patients** do not respond to standard induction therapy, and up to half of the patients with a good initial response will lose response over time under standard maintenance therapy.[147]

ii) The use of the labelled weight-based dosing of infliximab in **paediatric patients** has been associated with a high rate of subtherapeutic serum trough concentrations during induction treatment.[118]

iii) The relationship between infliximab exposure and efficacy and safety outcomes remains to be elucidated in **elderly patients**.[148]

We hypothesise that implementing **MIPD** could substantially improve outcomes of infliximab treatment in patients with IBD.

This doctoral research work aimed to contribute to the therapeutic drug monitoring cycle regarding target and dose optimisation as follows (**Figure 21**):

**Part I. Model-informed precision dosing**

*Objective:* To develop and prospectively implement MIPD strategies for guiding infliximab dosage regimen de-escalation in adult patients with IBD.

**Part II. Special populations**

*Objective:* To retrospectively evaluate dose-exposure-response relationships and *in silico* explore dose optimisation opportunities of infliximab during induction treatment in paediatric and elderly IBD population subgroups.

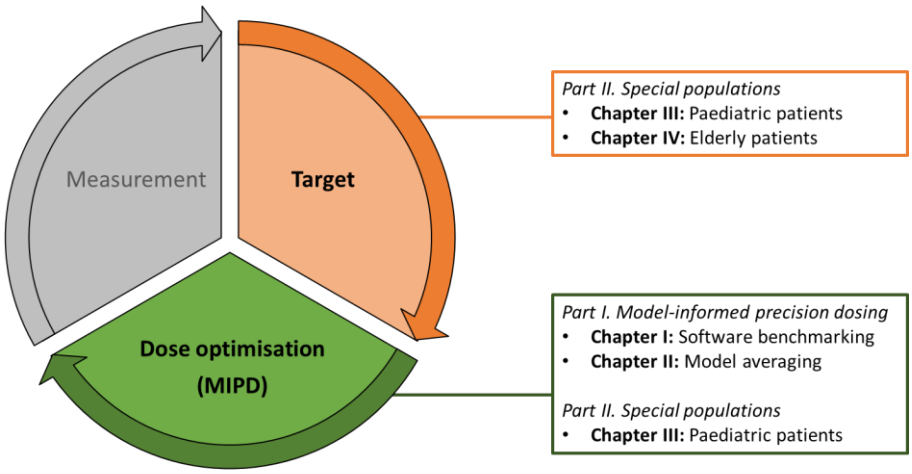


***Figure 21.*** *Contribution of research chapters to the therapeutic drug monitoring cycle.*

# Research chapters

# Part I. Model-informed precision dosing

# Software Tools for Model-Informed Precision Dosing: How Well do They Satisfy the Needs?

This chapter is published as

**Wannee Kantasiripitak**, Ruth Van Daele, Matthias Gijsen, Marc Ferrante, Isabel Spriet, Erwin Dreesen. Software Tools for Model-Informed Precision Dosing: How Well do They Satisfy the Needs? Front. Pharmacol. 2020; 11:620. Article reproduced with permission from the journal that published Kantasiripitak *et al*.[149]

## Abstract

Model-informed precision dosing (MIPD) software tools are used to optimise dosage regimens in individual patients, aiming to achieve drug exposure targets associated with desirable clinical outcomes. Over the last few decades, numerous MIPD software tools have been developed. However, they have still not been widely integrated into clinical practice. This study focuses on identifying the requirements for and evaluating the performance of the currently available MIPD software tools. First, a total of 22 experts in the field of precision dosing completed a web survey to assess the importance (from 0; do not agree at all, to 10; completely agree) of 103 pre-established software tool criteria organised in eight categories: user-friendliness and utilisation, user support, computational aspects, population models, quality and validation, output generation, privacy and data security, and cost). Category mean ±pooled standard deviation importance scores ranged from 7.2 ± 2.1 (user-friendliness and utilisation) to 8.5 ± 1.8 (privacy and data security). The relative importance score of each criterion within a category was used as a weighting factor in the subsequent evaluation of the software tools. Ten software tools were identified through literature and internet searches: four software tools were provided by companies (DoseMeRx, InsightRX Nova, MwPharm++, and PrecisePK) and six were provided by non-company owners (AutoKinetics, BestDose, ID-ODS, NextDose, TDMx, and Tucuxi). All software tools performed well in all categories, although there were differences in terms of in-built software features, user interface design, the number of drug modules and populations, user support, quality control, and cost. The choice for a certain software tool should be made based on these differences and personal preferences. However, there are still improvements to be made in terms of electronic health record integration, standardisation of software and model validation strategies, and prospective evidence for the software tools' clinical and cost benefits.

## Introduction

"First, do no harm" is a fundamental dictum in pharmacotherapy. Nevertheless, we may want to raise the bar and aim for optimal efficacy with minimal toxicity in all patients. Although this may seem evident, therapeutic failure and toxicity are still very frequent in clinical practice. The standard label-recommended dosing regimens may not be effective and safe in all patients due to large interpatient variability in exposure and response. To improve drug treatment outcomes and avoid adverse drug reactions in individual patients, a precision dosing approach has been proposed, which aims at the precise attainment of predefined drug exposure targets.[150] The precision dosing approach is justified when pharmacokinetic (PK) variability exceeds the limits of a safe and effective range of drug exposure.[151] Since inter- and intra-patient PK variability can be quantified and taken into account by employing population PK models, such models can be used to predict the optimal dose of a drug in an individual patient.[152] This model-based approach has been referred to as model-informed precision dosing (MIPD) in recent publications.[140,153]

MIPD involves the application of mathematical and statistical algorithms using simultaneous integration of patient covariates (i.e., *a priori* prediction) and individual drug concentration measurements (i.e., *a posteriori* prediction or Bayesian forecasting). Therefore, MIPD is often perceived as a complicated and time-consuming task. To overcome these obstacles, these models have been implemented in software tools to support clinical decision-making on therapeutic individualisation. The first computer-based algorithms for dose prediction were introduced half a century ago.[154–157] However, fifty years later, apart from some isolated local efforts[158,159], MIPD has not been widely implemented in routine clinical practice.

Barriers that hampered MIPD software tools from being widely implemented in health care include little published evidence of large-scale utility and impact of these software tools, lack of user-friendliness, lack of technical expertise at the practice site, and cumbersome validation of the software tools in clinical settings.[140] To ensure wider integration of MIPD software tools in routine clinical use, the software tool functionalities should align with the requirements of the end-users (i.e., healthcare professionals).[140] In the past few years, MIPD has gained renewed attention as a result of the increasing awareness that one dose does not fit the needs of all patients, especially in special populations, such as frail elderly patients, pediatric patients, patients with renal or hepatic impairment and critically ill patients.[160,161] This renewed attention is evidenced by the publication of opinion papers, the scheduling of various dedicated conference sessions (ASCPT, PAGE, ACoP, and ACCP), the creation of a special interest group within ISoP ("Applied Clinical Pharmacometrics") and most importantly the release of new MIPD software tools.[141]

Hence, an evaluation of the current status of MIPD software tools and a comparison with previous conclusions on this topic are needed. Therefore, we aimed to (i) identify requirements that MIPD software tools should comply with based on experts' opinions, and (ii) compare performances of the currently available MIPD software tools based on these requirements. This information can assist healthcare professionals in selecting the software tool that fits best their specific needs.

## Methods

### *Search strategy and selection criteria*

MIPD software tools were identified through searching PubMed, Google, Google Scholar, Web of Science, and the Population Approach Group in Europe (PAGE) website until February 2020 by using the following Medical Subject Headings (MeSH) terms and free text variations of these terms: “software”, “software tool”, “dosing software”, “dashboard”, “precision dosing”, “model-informed precision dosing”, “model-based precision dosing”, “therapeutic drug monitoring”, “target concentration intervention”, “adaptive feedback control”, “concentration control”, and “Bayesian”. These terms were combined with Boolean logical operators “and” and “or”. Reference lists were hand-searched for other relevant literature. The MIPD software tools identified through these searches had to meet the following selection criteria: (i) the software is available and actively updated, (ii) the software has a graphical user interface (GUI), (iii) the software is capable of Bayesian forecasting, (iv) the software supports more than one drug module, and (v) the software provider accepts participation in this study.

### *Establishing evaluation criteria*

The criteria used to benchmark the MIPD software tools were defined based on a literature review and the experts’ opinions. These evaluation criteria were grouped into eight categories related to (i) user-friendliness and utilisation, (ii) user support, (iii) computational aspects, (iv) population models, (v) quality and validation, (vi) output generation, (vii) privacy and data security, and (viii) cost. For criteria with binary classification (yes/no), a score of either 0 or 1 was assigned with 1 indicating the best performance. For ordered categorical criteria with <10 categories, a score of 0 to 1 with stepsize 1/(*n*-1) was assigned with the highest score indicating the best performance. For continuous criteria (i.e., ordered categorical with ≥10 categories), a score ranging from 0 (for the lowest performance) to 1 (for the highest performance) with stepsize 0.1 was assigned. NA was assigned when not applicable.

### *Experts’ opinion*

Clinicians, pharmacists, and pharmacometricians active in the field of precision dosing were invited to participate in a web survey that queried the level of importance of each of the established evaluation criteria that were used to evaluate the software tools. The criteria were scored on a scale from 0 to 10, with 0 indicating “I do not agree at all that this criterion is important” and 10 indicating “I completely agree that this criterion is important”. There was also an “undecided” option for every question indicating “I think that my level of knowledge is not sufficient to evaluate this criterion”. Moreover, experts could suggest additional criteria regarding each category. The scores representing the levels of

importance were then used as weighting factors in the benchmarking to calculate the final score for each evaluation criterion.

***Software tool evaluation***

The selected MIPD software tools were independently evaluated by four authors (WK, RVD, MG, and ED) using the established evaluation criteria. Benchmarking scores were calculated based on an evaluation grid consisting of the scoring definitions and the possible scores of each criterion. Standalone versions of the software tools were evaluated. The evaluations were performed on one desktop and three laptop computers with 64-bit operating system Windows 10 Enterprise. The web-based software tools were accessed through the Google Chrome web browser. Next to the evaluation by the authors, some criteria were evaluated based on the software provider's answers in a web survey. A web survey was filled out by all of the software providers. This web survey consisted of two parts. The first part of the survey queried the descriptive characteristics of the MIPD software tool. The second part queried features of the MIPD software tool over the eight aforementioned categories. To facilitate the benchmarking, a maximum one-hour online introduction was allowed upon request of the software providers to obtain more information. Also, the benchmarking scores of the criteria that were evaluated based on the software provider's answers were cross-checked by the providers to allow a double-control and confirmation.

***Data analysis***

Data were imported in R (version 3.6.1; R Foundation for Statistical Computing, R Core Team, Vienna, Austria) for data wrangling, visualisation, and statistical analyses. Graphics were generated using the ggplot2 package in RStudio (version 1.2.5001; R Studio, Inc., RStudio Team, Boston, MA, USA). Descriptive statistics were stated as percentages for discrete variables and as mean ±standard deviation (SD) or median [minimum-maximum] for continuous variables The scores of the experts' opinions on the importance of each criterion were summarised by category using the within-category mean and the pooled within-category standard deviation ($S_{pooled}$;

$$S_{pooled} = \sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2+\cdots+(n_k-1)s_k^2}{n_1+n_2+\cdots+n_k-k}} \qquad \textit{Equation 8}$$

with *s* the standard deviation of each criterion, *n* the number of responses in each criterion, and *k* the number of criteria within the category).

The average scores of the experts' opinions on the importance of each criterion were used to compute the weighting factors. The relative weighting factor $w_{rel}$ for criterion *i* was calculated by dividing the average score assigned to this criterion $w_i$ by the sum of the average scores of all criteria in that category *k*;

$$w_{rel,i} = \frac{w_i}{\sum_{i=1}^{k} w_i} \qquad \textit{Equation 9}$$

to normalise the sum of the relative weighting factors in each category to 1. The relative weighting factor for each criterion was multiplied by the benchmarking score given to that criterion, to obtain importance-weighted benchmarking scores. The importance-weighted benchmarking scores were summed by category and compared between the MIPD software tools. In addition, a ranking of the MIPD software tools was established by summing the importance-weighted benchmarking scores to obtain an overall performance score for each evaluated MIPD software tool.

## Results

### *Included software tools*

Twenty-eight MIPD software tools were identified, of which ten were included in this study (**Figure 22**). Two software providers (iDose and RxKinetics) did not accept participation in our study. The provider of iDose declined participation due to an ongoing update. For RxKinetics, we did not receive a response from the provider. Descriptive characteristics of the included MIPD software tools are presented in

**Table** 3. The earliest release year amongst the included software tools was 2012 (NextDose). Four out of ten software tools are provided by software companies (DoseMeRx, InsightRX Nova, MwPharm++, and PrecisePK). The others are non-company providers (AutoKinetics, BestDose, ID-ODS, NextDose, TDMx and Tucuxi). Seven out of ten software tools serve both research and clinical purposes. While BestDose only serves a research purpose, ID-ODS and Tucuxi only serve a clinical purpose. All the evaluated software tools have a web-based version available, except MwPharm++ and Tucuxi. All the evaluated software tools have a standalone version except AutoKinetics.

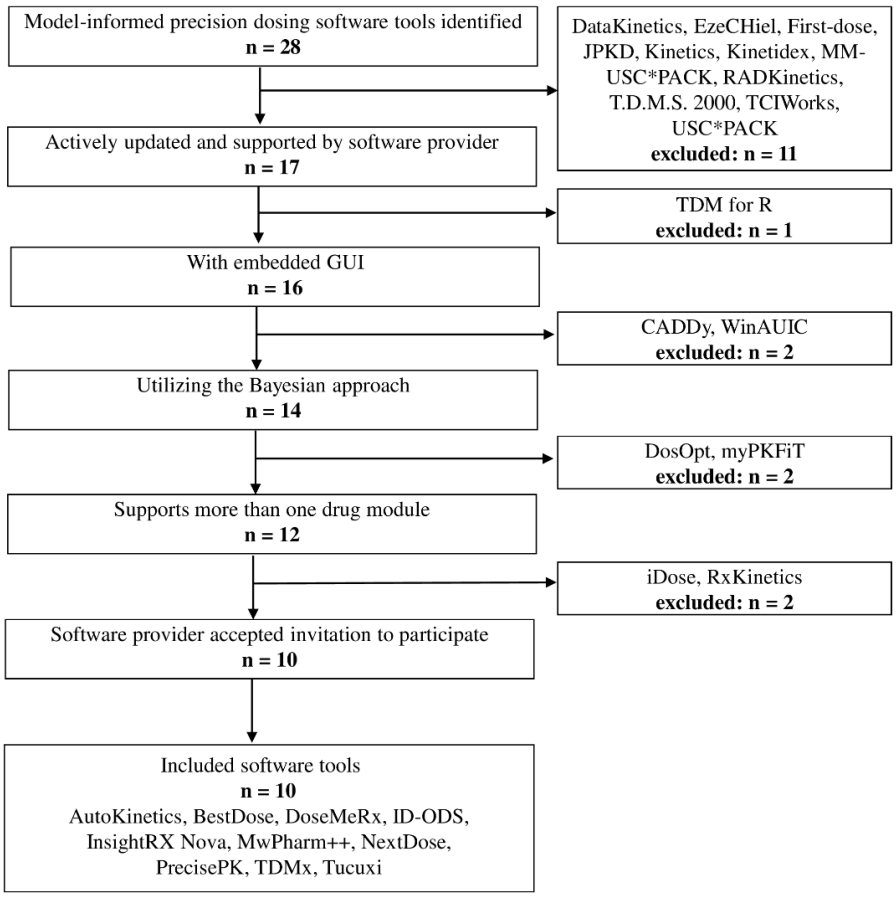


***Figure 22.*** *Flowchart of the included and excluded model-informed precision dosing software tools. GUI, graphical user interface.*

***Table 3.*** *Descriptive characteristics of the model-informed precision dosing software tools.*

| | AutoKinetics<br>**AutoKinetics** | BestDose<br>**BestDose** | DoseMeRx<br>**DoseMeRx** | ID-ODS<br>**ID-ODS** | Insight RX<br>**InsightRX Nova** | MEDIWARE<br>**MwPharm++** | NextDose<br>**NextDose** | PrecisePK<br>**PrecisePK** | TDMx<br>**TDMx** | TUCUXI<br>**Tucuxi** |
|---|---|---|---|---|---|---|---|---|---|---|
| *Founder* | Paul Elbers<br>Rob Bosman | Roger Jelliffe | Robert McLeay | Andras Farkas<br>Gergely Daroczi | Sirj Goswami<br>Ron Keizer<br>Ranvir Mangat | Johannes H. Proost<br>Cees Neef<br>Jiří Potůček<br>Nieko Punt | Sam Holford<br>Nick Holford | Philip Anderson<br>Anjum Gupta | Sebastian Wicha | Yann Thoma |
| *CEO* | NA | NA | Charles Cornish | NA | Sirj Goswami | Jiří Potůček | NA | Anjum Gupta | NA | NA |
| *Company/ Institution* | Departments of Intensive Care Medicine of Amsterdam UMC, location VUmc and OLVG Oost Hospital | Laboratory of Applied Pharmacokinetics and Bioinformatics, Children's Hospital Los Angeles | DoseMe (Tabula Rasa HealthCare Company) | Optimum Dosing Strategies | Insight Rx Inc. | Mediware a.s. | University of Auckland | Healthware Inc. | Institute of Pharmacy, University of Hamburg | School of Engineering and Management Vaud (HEIG-VD) |
| *Location of company/ Institution* | Amsterdam, The Netherlands | Los Angeles, California, USA | Moorestown, New Jersey, USA | Bloomingdale, New Jersey, USA | San Francisco, California, USA | Groningen, The Netherlands / Prague, Czech Republic | Auckland, New Zealand | San Diego, California, USA | Hamburg, Germany | Yverdon-les-Bains, Switzerland |
| *Previous version names* | - | MM-USC*PACK | - | - | InsightRX Software | MwPharm DOS, MwPharm 4.0 | - | T.D.M.S. | - | - |
| *Release date of the first version* | 1 August 2018 (desktop)<br>1 March 2018 (web-based) | 1 October 2018 | 11 July 2014 | 23 August 2013 (web-based)<br>23 August 2013 (mobile application) | 1 June 2015 | 1 January 2015 (desktop) | 1 April 2012 | 1 January 1986 (desktop)<br>11 November 2019 (web-based) | 1 January 2015 | 1 June 2017 |
| *Reviewed version* | Web-based version 1.2.0 | Web-based version 0.2.0 | Web-based version 2.11.13 | Web-based version 2.9.1-20191010.d4baf19 | Web-based version 1.16.1 | Desktop version 1.7.5 | Web-based version 1.6.0 | Web-based 19.07.26 | Web-based version Beta | Desktop version Gui Git revision: 60435e8ee, Tucucore Git revision: 33280802 |
| *Computer language of source code* | Asp.net and vb.net | Fortran, R | Perl, R, python | Ionic, R | R, JavaScript | C# | Javascript, PHP, MySQL, NM-TRAN | C++, PHP<br>Web App: JSX, C++ | R/C++ | C++ |
| *Software version (Compatible Platform or mobile application name or website)* | Desktop (Windows), Web-based | Desktop (Windows), Web-based (bestdoserx.com/) | Web-based (app.doseme-rx.com), Android and iOS (DoseMe) | Web-based (app.id-ods.org), Android (ID-ODS Adult), iOS (app.id-ods.org) | Web-based (pk.insight-rx.com) | Desktop (Windows), Web-based, Android, iOS (mwpharm.online) | Web-based (nextdose.org) | Desktop (Windows, Mac), Web-based (app.precisepk.com/login) | Web-based (tdmx.eu/Launch-TDMx/) | Desktop (Windows, Mac, Linux) |
| *Website* | autokinetics.eu | lapk.org/bestdose.php | doseme-rx.com | optimum-dosing-strategies.org/id-ods/ | insight-rx.com | mediware.cz | nextdose.org | precisepk.com | tdmx.eu/ | tucuxi.ch |
| *Purpose of use* | research and clinical | research | research and clinical | clinical | research and clinical | research and clinical | research and clinical | research and clinical | research and clinical | clinical |

*NA, not applicable because not a company.

***Expert's opinion***

A total of 22 out of 63 (35%) contacted experts (seven clinicians, six pharmacists, and nine pharmacometricians) have completed the survey. Fifteen of them indicated being involved in precision dosing programs at least weekly, mostly in the domain of antimicrobials and monoclonal antibodies (**Figure 23**). The mean ±pooled SD of the importance levels ranged from 7.15 ±2.11 (user-friendliness and utilisation) to 8.54 ±1.80 (privacy and data security) as illustrated in **Figure 24**. The six criteria evaluated as most important, with an average score above nine, were (i) the software should be able to propose *a priori* and *a posteriori* dosing regimens, (ii) the software should provide models developed in relevant populations, (iii) suitable diagnostic tools and/or methods should be used in model selection before implementing a model in the software, (iv) the model qualification should be performed for 'fit for purpose' before software, (v) the dosing recommendation from the software should be straightforward and easy to understand, and (vi) software should comply with the European Union General Data Protection Regulation (EU GDPR) or equivalent. The least important criterion, with an average score below five, was the pharmaceutical industry should have been involved in software development. Moreover, experts did not suggest additional evaluation criteria in addition to the already established ones.

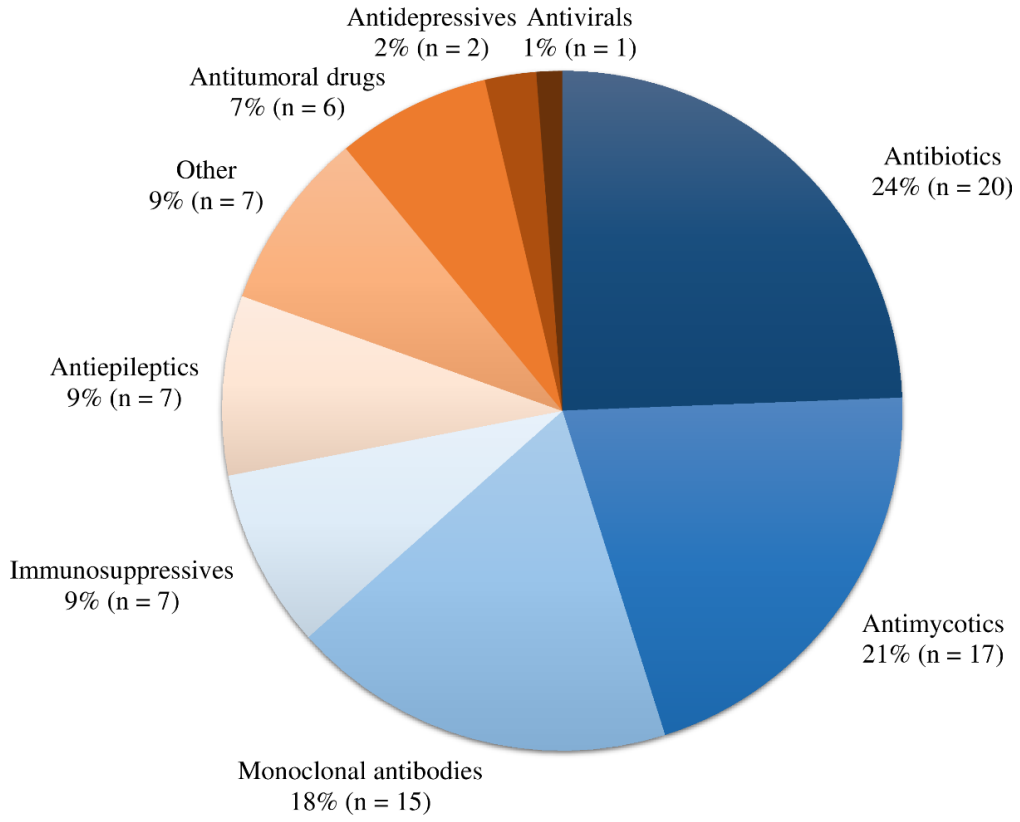


***Figure 23.*** *Overview of drug classes involved in precision dosing programs of the participating experts.*

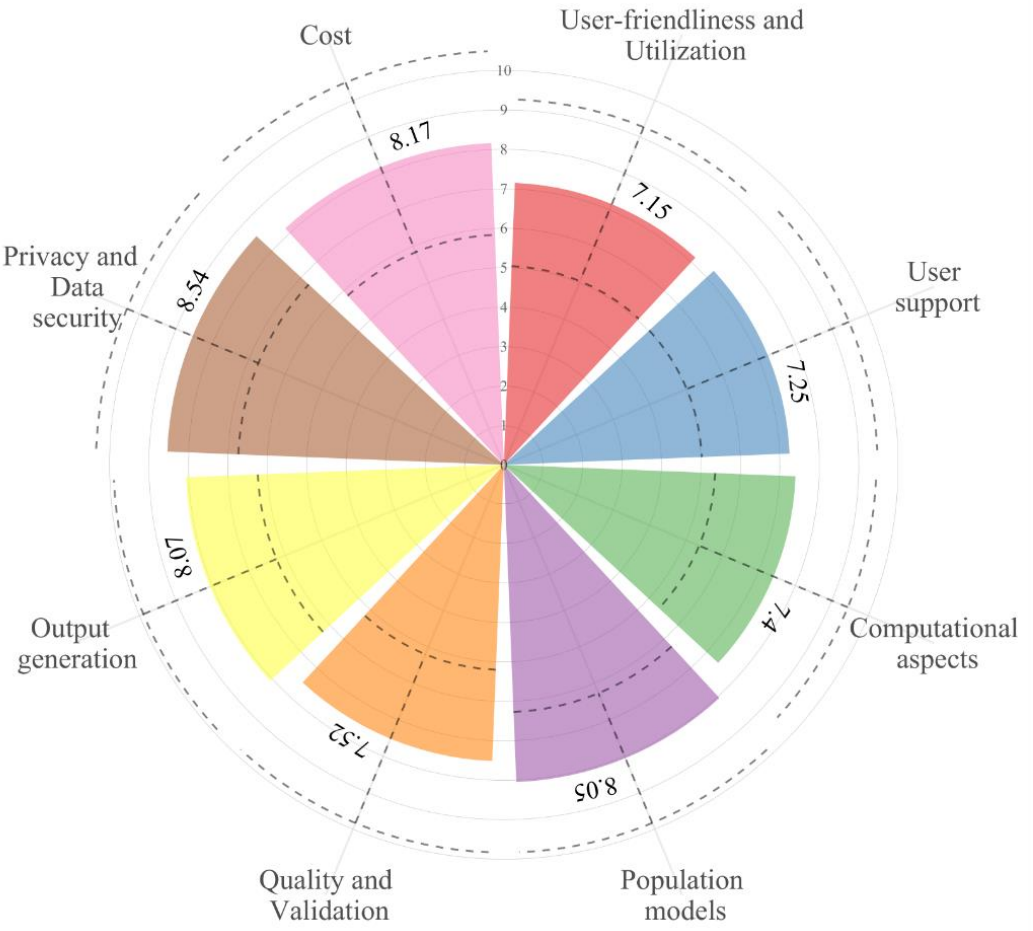


***Figure 24.*** *The overall mean (±1 pooled standard deviation; dashed lines) of importance levels of the considered criteria in the eight categories.*

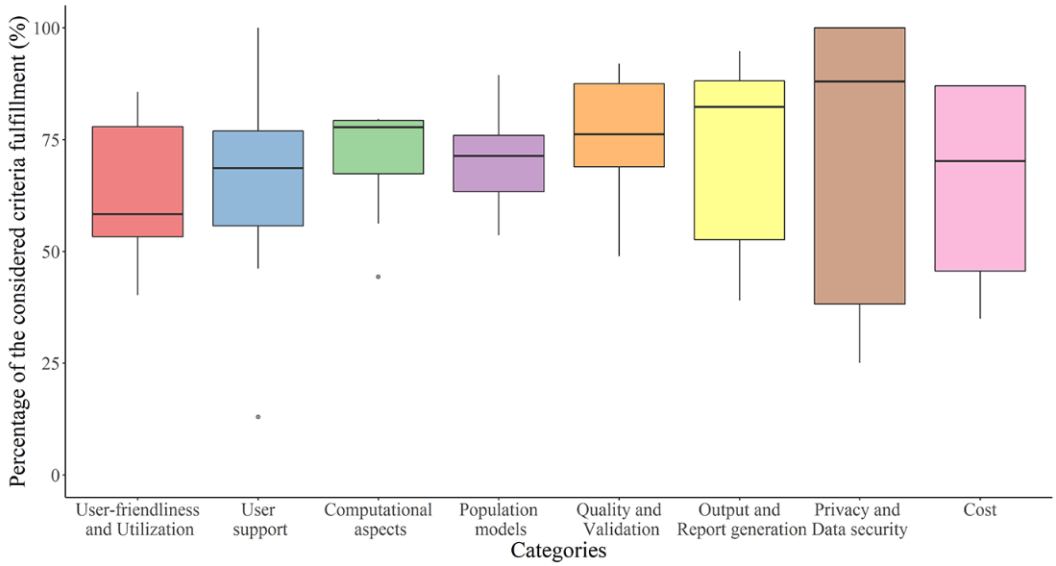


***Figure 25.*** *Tukey boxplot representing fulfillment of the considered criteria by the ten evaluated software tools in each category.*

***Benchmarking***

The distribution of percentage of fulfilled requirements by category is reported in **Figure 25**. The overall performance of each software tool and percentage of the fulfilled requirements in each category are illustrated for every evaluated software tool in **Figure 26**.

*User-friendliness and utilisation*

The evaluated software tools fulfilled user-friendliness and utilisation criteria for 58% [40%–86%]. MwPharm++ (86%), DoseMeRx (84%), and InsightRX Nova (81%) fulfilled the considered criteria the most.

Software tools differed most in terms of easiness in manual data entry and the capability of electronic health record (EHR) integration. Most software tools are available as web-based software apart from Tucuxi which is only available as desktop software. The desktop software can be downloaded via the software websites. For TDMx, users can freely access its web-based software tools without registration required. Six software tools can be integrated into the EHR (AutoKinetics, DoseMeRx, InsightRX Nova, MwPharm++, PrecisePK, and Tucuxi). The installation of EHR-integrated version may require technical support. In addition, ID-ODS is currently in the process of integrating its software tools with the EHR. All software tools with input data storage capability provide database search by patient name, patient identification, drug name, or date. The benchmarking score of easiness in manual data entry criterion was highest in DoseMeRx, InsightRX Nova and PrecisePK. These software tools provide structured layouts and toolbox widgets that assist users in entering data. In addition, they scored the highest on global visual appeal.

*User support*

The evaluated software tools fulfilled the user support criteria for 69% [13%–100%]. InsightRX Nova (100%), PrecisePK (86%), and ID-ODS (78%) fulfilled the considered criteria the most.

Differences between software tools are mostly explained by the type of user support services and the availability of an online discussion forum for the software users. Most of the software providers offer both on-site and online user training, except NextDose and Tucuxi. All software tools provide support documentation to the user, except Tucuxi and BestDose. In addition to the user manuals, 24/7 user support as a helpdesk (AutoKinetics), a call support (PrecisePK), and web support services and live chat (DoseMeRx and InsightRx Nova) are provided to the users. InsightRX Nova and BestDose also host a discussion forum for online support.


***Figure 26.*** *Fulfillment of the considered criteria in the eight categories by each of the evaluated software tools. Numbers in parentheses are percentage of the overall performance scores. Software tools are ranked in order of decreasing the overall performance scores (highest score panel A, lowest score panel J). Black solid circles in each category represent the median fulfillment (%) of the considered criteria by the ten evaluated software tools. *Manual data entry not possible. †A report cannot be generated. ‡The data privacy method in data collection cannot be evaluated since no data are collected in the software. §Database encoding cannot be evaluated since no data are stored in the software. |An individual license is not available. An institution license is not available.*

*Computational aspects*

The evaluated software tools fulfilled the computational aspects criteria for 78% [44%–80%]. MwPharm++ (80%), DoseMeRx (79%), InsightRX Nova (79%), PrecisePK (79%), and ID-ODS (79%) fulfilled the considered criteria the most. All software tools require a maximum of four gigabytes of random-access memory for running the software (common in computers these days). Only MwPharm++ requires .NET Framework 4.0 to run the software. None of the web-based software tools can access previous versions, except for AutoKinetics. However, lists of changes and bug fixes between versions have been documented for all web-based software tools except Autokinetics and TDMx. Although Tucuxi is a desktop software, its previous versions are not accessible and there are no changes documented. None of the software tools provides their source code to the user, except for AutoKinetics which will share part of its source code publicly after completing a clinical trial. All the software tools provide error or warning messages to the users when unusual results are obtained. Moreover, structured data can be imported into all company-provided software tools, ID-ODS, and Tucuxi.

*Population models*

The evaluated software tools fulfilled the criteria related to population models for 71% [54%–89%]. MwPharm++ (89%), InsightRX Nova (83%), and PrecisePK (77%) were the three software tools that fulfilled the considered criteria the most. Differences between software tools are mostly explained by the number of included drugs and population models. The number of drugs covered by a software tool varies from five in AutoKinetics, BestDose, and TDMx to more than 180 in MwPharm++. Antibiotics are included in all of the evaluated software tools. The two most included antibiotics are vancomycin (9/10 software tools, excluding TDMx) and gentamicin (8/10 software tools, excluding AutoKinetics and BestDose). Three software tools only support antibiotics (AutoKinetics, ID-ODS, TDMx). However, monoclonal antibodies, for which there is an emerging interest in precision dosing[114], have only been included in two of the evaluated software tools (infliximab in MwPharm++ and InsightRX Nova, adalimumab in InsightRX Nova).

In addition to various drug classes, company software tools provide more extensive populations (e.g., neonates, children, adults, specific disease conditions, and ethnicity) in comparison with non-company-owned software tools. Automated population model selection based on the patient's input data is activated in DoseMeRx, ID-ODS, InsightRX Nova, and PrecisePK. Published models have been selected in standardised ways before implementing in the software tools except for Tucuxi. However, the model selection procedures differ between software tools (e.g., published model from the peer-review journal, demographics of study participants, graphical or numerical goodness of fit, and simulation diagnostics). Models with inter-occasion variability are incorporated into five software tools (InsightRX Nova, MwPharm++, NextDose, PrecisePK, and Tucuxi). Users are allowed to define models and model parameter values in four software tools (MwPharm++, PrecisePK, Tucuxi, and TDMx). Model refinements with data collected from

the intended clinical use are also possible for all the company software tools, AutoKinetics, and ID-ODS.

All of the software tools are capable of proposing *a priori* and *a posteriori* dosing regimens and also of handling non-steady states and irregular situations. Therapeutic target values are prespecified in eight software tools, except BestDose and PrecisePK. Users can also define their target values in all software tools excluding AutoKinetics. The probability of target attainment is calculated and reported in five software tools (BestDose, ID-ODS, InsightRX Nova, MwPharm++, and TDMx). However, the user cannot define the desired probability of target attainment in any software. Concentration simulation with a specified dosing regimen is possible in all software tools except AutoKinetics. Also, the optimal sampling time point module is available in three software tools (BestDose, MwPharm++, and TDMx).

*Quality and validation*

The evaluated software tools fulfilled the quality and validation criteria for 76% [49%–92%]. DoseMeRx (92%), MwPharm++ (91%), and InsightRX Nova (90%), and were three software tools that fulfilled most of the considered criteria.

A multidisciplinary team has been involved in all software developments (healthcare professionals, academic researchers, and computer experts). Only InsightRX Nova has involved the pharmaceutical industry in its development team. Seven software tools, except for BestDose, MwPharm++, and PrecisePK, verified their optimisation algorithm against well-established mathematical software tools: NONMEM (AutoKinetics, InsightRx Nova, TDMx, and Tucuxi), R (AutoKinetics), Matlab (ID-ODS), and GNU Scientific Library (DoseMeRx). All EHR-integrated software tools validate the data exchange between software tools and the EHR, except for Tucuxi. All software tools are validated in the clinical setting in which they are intended to be deployed, except for NextDose and Tucuxi. Moreover, the software performance is continuously monitored once deployed in the clinical setting for all the company software tools, AutoKinetics, and NextDose.

In addition to software validation, model qualification has been performed by most evaluated software tools excluding Tucuxi. The selected models have been qualified for ‘fit for purpose’ (i.e., *a priori* and *a posteriori* predictive performance) by using various diagnostic tools such as visual predictive checks and forecasting imprecision and bias. The model qualifications have been done by using not only external datasets but also historical data drawn from records of the clinical setting in which the software is intended to be used. A scientific publication of the implemented models is referred to in all software tools except for BestDose. To date, two software tools are CE-marked and registered as medical devices in Europe (i.e., DoseMeRx and MwPharm++). In addition, DoseMeRx is registered as a medical device in Australia.

*Output generation*

The evaluated software tools fulfilled the output generation criteria for 82% [39%–95%]. Tucuxi (95%), PrecisePK (90%), InsightRX Nova (88%), DoseMeRx (88%), and NextDose (88%) were the four software tools that fulfilled the most considered criteria. Differences between software tools are mostly explained by formats of recommended dosing regimen and report and capability of report generation.

A recommended dosing regimen is the primary output of MIPD software tools. PrecisePK, NextDose, and InsightRX Nova scored highest regarding a straightforward and easy to understand recommended dosing regimen. In contrast with other software tools, InsightRX Nova only outputs a dosing regimen table instead of a recommended dosing regimen. Their users can select the best dosing regimen based on the output table. Users can also customise the recommended dosing regimen (e.g., dosing interval) from most of the software tools except AutoKinetics and ID-ODS. In addition to the recommended dosing regimen, all software tools report individual PK parameters and generate a PK plot.

Seven software tools can generate reports except for AutoKinetics, BestDose, and the benchmarked versions of TDMx. All the reports are customisable and can be converted to PDF format. Reports from InsightRX Nova, PrecisePK, and DoseMeRx scored the highest regarding readability.

*Privacy and data security*

The evaluated software tools fulfilled the privacy and data security criteria for 88% [25%–100%]. The software tools provided by software companies and AutoKinetics fulfilled all the considered criteria (100%). Software tools differ mostly in terms of compliance to privacy policies and data security. All software tools except BestDose and ID-ODS informed that their software tools comply with European Union General Data Protection Regulation (EU GDPR) or equivalents. DoseMeRx and MwPharm++, two certified software-based medical devices, have also clarified terms about data storage and management in their privacy policy to their users. Three of six software tools (DoseMeRx, InsightRX Nova, and PrecisePK) that are capable of data collection for model refinement comply with the Health Insurance Portability and Accountability Act (HIPAA) legislation. For the other three software tools (AutoKinetics, ID-ODS, and MwPharm++), either data anonymisation or informed consent have been used in the data collection. For software tools with data storage capability, the databases are either encrypted or password-protected excluding the databases of BestDose. Also, multiple user accommodations with a personal login and secured password are possible in all software tools except the benchmarked versions of TDMx and Tucuxi.

*Cost*

Four of the six non-company-owned providers offer their software tools free of charge (ID-ODS, NextDose, TDMx, and Tucuxi). The other two non-company-owned providers charge their users for maintenance and support contracts (AutoKinetics) and software development and software hosting (BestDose). For company-provided software tools, their cost plans are flexible and customisable. Maintenance and support costs are covered in their license fees. Moreover, the costs of all the software tools can vary depending on the organisation (e.g., based on the number of users, type [i.e., academic, enterprise]) and desired functionalities (e.g., integration, cloud storage). Five software tools have performed a cost-effectiveness analysis of the software-based treatment in comparison with standard treatment (i.e., AutoKinetics [part of the current ongoing trial[162]], BestDose[163], DoseMeRx [as white papers], InsightRX Nova [as a white paper], and MwPharm++ [trial ongoing]).

## Discussion

This study is the first to comparatively evaluate the performances of MIPD software tools that are currently available worldwide since the benchmarking study by Fuchs *et al.* in 2013, based on both selection and evaluation criteria. During the past seven years, we found that notable efforts have been put into the development of user-friendly, high-quality and highly secured MIPD software tools. Nevertheless, the ten evaluated software tools were widely different in terms of in-built software features, user interface design, number of drug modules and populations, user support, quality control, and cost. Furthermore, there is still a demand for EHR integration, standardisation of software and model validation strategies, and prospective evidence for the software tools' clinical and cost benefits.

There were substantial differences between the MIPD software tools evaluated in our study in comparison to those evaluated in two previous landmark studies in terms of (i) included software tools, (ii) type of software application, and (iii) improvement in user-friendliness and data storage capability. In 1993, Buffington *et al.* published a review of 13 "clinical PK software programs" that were commercially available in the United States.[164] They concluded that the reviewed software programs can assist in the analysis of plasma drug concentration data for medications that warrant therapeutic drug monitoring. Twenty years later, Fuchs *et al.* published a benchmarking study of 12 "therapeutic drug monitoring software tools".[165] Only four included software tools were from previous studies by Buffington *et al.* They concluded that a simple, flexible, and user-friendly MIPD software tool with capabilities of data storage and EHR integration is still in demand. All the software tools reviewed by the two previous studies were desktop software, while eight software tools included in our study are web-based software. Web-based software can be run from any web browser with an internet connection regardless of the operating system, instead of requiring local installation. Web-based software also allows users to always access the most recent version of the software. We observed an evolution towards intuitive, easy-to-use, customisable software tools, and providers offering extensive user support and training. These findings are in agreement with a recently published study evaluating the user-friendliness of three software tools.[166] Moreover, eight evaluated software tools are capable to store data with data security management.

The capability to integrate into EHRs facilitates MIPD software tool utilisation.[167,168] The integrated software tool can then automatically retrieve all required data available in the hospital's health records and send back the output. There is a significant increase in the number of software tools with EHR integration capability from only one out of twelve software tools in Fuchs *et al*. study (MwPharm) to six out of ten software tools in our study. Moreover, all six EHR-integrated software tools comply with privacy regulations (i.e., EU GDPR or equivalent and HIPAA). However, differences in EHR and clinical workflow remain challenges for wide integration of MIPD software tools in routine clinical practice.

Most of the evaluated software tool providers pay attention to not only the quality of the software tool itself but also to the quality of population models implemented in these tools. It is important to implement the most appropriate model for a specific patient/population that can predict a recommended dosing regimen precisely and with the lowest risk of bias. The models can be selected from either literature, be newly developed using data obtained from the intended population[169], or be a meta-model in the case of well-studied drugs with a large number of published models[170,171]. The selected models should qualify for 'fit for purpose' predictive performances (i.e., *a priori* prediction and *a posteriori* prediction). Model qualifications for MIPD have been done by using an external dataset[172], multiple external datasets[173] and case-specific dataset[174]. However, specific model diagnostic tools for model qualification, that allow standardised evaluation, are still lacking.[141] The qualified model might be undermined by user-defined model features that are allowed in some of the evaluated MIPD software tools. Therefore, such features should be restricted to an experienced user. Moreover, the quality of data collected from the intended clinical use for model refinement should be taken into consideration.

The quality system regulations for MIPD software tools in Europe and Australia differ from those in the United States. The European Commission and the Australian Register of Therapeutic Goods (ARTG) define software that provides information to be used in making decisions for treatment as a 'medical device'.[175,176] Conversely, the United States Food and Drug Administration (FDA) classifies clinical decision support software regarding the software's recommendation.[177] Software that provides consistent recommendations with FDA-required labelling is considered as a 'non-device clinical decision support software, while there is still no regulation for software that recommends an off-label dosing regimen. Regarding user training requirements, EU medical device regulation requires both initial and ongoing training for software users (European Commission, 2017). To date, the only Bayesian software that has been registered in the United States is myPKFiT (Takeda Pharmaceutical Company Limited, Lexington, MA) for the precision dosing of factor VIII in the management of haemophilia A.[178] The myPKFiT software was co-developed by the pharmaceutical industry during drug development so that its suggested dose is consistent with the prescribing information. Moreover, it is a milestone software tool that has been widely adopted into routine clinical practice as a companion tool for drug prescribing.[179]

Until today, MIPD software tools have not been widely integrated into routine clinical practice. Various factors have withheld the software tools from wider integration.[140,153,180] Firstly, evidence for its clinical and economic benefit generated from prospective randomised controlled trials is still lacking. To date, clinical trials to prospectively access clinical and cost-saving impacts of the evaluated MIPD software tools have not been widely conducted [e.g., a desktop version of BestDose[163], the benchmarked version of TDMx[181], and the ongoing trial of AutoKinetics[162]]. However, both finished studies reported superior clinical benefits from utilising the MIPD software tools. Secondly, the actual implementation of MIPD into clinical workflow is likely to be more complex (e.g., additional clinical visits for blood sampling, availability of rapid sample measurement, and flexibility of available drug

dose).[114,179,182] To facilitate a wider integration of MIPD software tools into clinical practice, a group of patients, drug characteristics, and diseases that are highly impacted by MIPD should be clearly defined so that resource allocation and evidence of clinical utility grow more rapidly.[183] Moreover, interdisciplinary collaborations between software providers, software purchasers (e.g., hospital executives), clinical end-users (e.g., clinicians, clinical pharmacists, and pharmacometricians), and regulators require to fulfil all sectors' need for the MIPD software tool in practice.

In addition to the MIPD module, DoseMeRx and InsightRX Nova also offer broader functions to their users. DoseMeRx offers DoseMe Crunch as a big data mining tool for data analysis, while InsightRX Nova offers additional innovative modules in its platform framework for continuous learning such as specialised analytic dashboards and human-assisted artificial intelligence. Moreover, recently, InsightRX Nova has partnered up with BestDose to incorporate BestDose's non-parametric optimisation algorithms and its models into the InsightRX Nova platform.[184]

The focus of our study was not to recommend the best software tools, but rather to provide information about the features of currently available MIPD software tools. Although ranking software tools based on their benchmarking scores is an objective evaluation criterion and represents a sensible way of evaluating the "overall performance" of a software tool, this approach has several limitations. First, a better quantitative performance (fulfilling more benchmarking criteria) does not necessarily imply a better qualitative performance. For example, the more drug modules are available, the higher the benchmarking score assigned to the software tool. However, a potential end-user may only be interested in one or a few specific drug modules. Also, the software providers that perform model validation before integration into the software tool receive a higher benchmarking score. However, model validation procedures are not standardised and may differ in quality. Second, the specific needs of a certain end-user are not necessarily fulfilled by the software tool with the best overall performance. An MIPD software tool that fulfilled more of the considered criteria may have been assigned a higher benchmarking score, but this does not necessarily mean that the software tool is the 'best' for every end-user. Therefore, the overall performance scores may not be the best guide for selecting an MIPD software tool that needs to fit a specific clinical setting and end-users' needs. Instead of a software tool ranking, it was our ambition to give an overview of all features, providing tailored guidance to the reader when selecting a software tool.

This study has some limitations. First, we only evaluated one version and type of software application of each software tool. It may be that functions are not available in other versions and vice versa. Second, the AutoKinetics software was evaluated based on a one-hour web meeting with the providers because the software is only available as the EHR-integrated version. Third, some of the evaluation criteria could not be tested by the researchers, for example, the capability of EHR integration, model qualification and model selection procedures before implementing models into the software, and verification of the

software optimisation algorithm. For those criteria we relied on the available information on their websites, the information in previous literature, filled-out answers by the software providers, a one-hour online introduction with the software providers (DoseMeRx, PrecisePK, InsightRX Nova, and AutoKinetics), and email responses from the providers. Fourth, as opposed to Fuchs *et al.*, we did not test software tools with real clinical precision dosing cases. Nevertheless, most of the currently proposed minimum quality standard considerations for pharmacokinetic calculators for drug dose individualisation were included in our evaluation grid.[185] This was evidenced by the fact that the experts did not suggest any additional evaluation criteria in this study. Moreover, in comparison with the previous benchmarking study by Fuchs *et al.*, this study included a higher number of experts (22 as opposed to 15 in the study by Fuchs *et al.*). We consulted pharmacometricians instead of computer engineers in the field of precision dosing. Moreover, the software tool was evaluated by four researchers (two pharmacists and two pharmacometricians) instead of one pharmacist in the study by Fuchs *et al.* Based on our findings, we believed that future work should focus on the standardisation of software validation, model selection, and model validation in MIPD software tool development. While today these strategies widely differ between software tools, harmonisation of these processes will allow a better comparison between different MIPD initiatives and will hopefully unambiguously demonstrate its clinical value. Joint efforts from software providers, academic researchers, and regulators are therefore required to stimulate this standardisation and facilitate a wider integration of MIPD software tools into clinical practice.

To conclude, this study provides important insight into the comparative performance of currently available MIPD software tools and their requirements. All software tools in our study performed well in all the evaluated categories. With these overall positive results, it is anticipated that wider implementation of these software tools will increase routine clinical practice. However, the establishment of a MIPD-centred healthcare workflow requires not only a state-of-the-art software tool but also other crucial components such as point-of-care assays and flexibility of drug dose and label.

# Multi-model averaging improves the performance of model-guided infliximab dosing in patients with inflammatory bowel diseases

This chapter is published as

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## Abstract

Infliximab dosage de-escalation without prior knowledge of drug concentrations may put patients at risk for underexposure and trigger the loss of response. A single-model approach for model-informed precision dosing during infliximab maintenance therapy has proven its clinical benefit in patients with inflammatory bowel diseases. We evaluated the predictive performances of two multi-model approaches, a model selection algorithm and a model averaging algorithm, using 18 published population pharmacokinetic models of infliximab for guiding dosage de-escalation. Data from 54 patients with Crohn's disease and ulcerative colitis who underwent infliximab dosage de-escalation after an earlier escalation was used. *A priori* prediction (based solely on covariate data) and maximum *a posteriori* prediction (based on covariate data and trough concentrations) were compared using accuracy and precision metrics and the classification accuracy at the trough concentration target of 5.0 mg/L. *A priori* prediction was inaccurate and imprecise, with the lowest classification accuracies irrespective of the approach (median 59%, interquartile range 59%-63%). Using maximum *a posteriori* prediction, the model averaging algorithm had systematically better predictive performance than the model selection algorithm or the single-model approach with any model, regardless of the number of concentration data. Only a single trough concentration (preferably at the point of care) sufficed for accurate and precise prediction. Predictive performance of both single- and multi-model approaches was robust to the lack of covariate data. Model averaging using four models demonstrated similar predictive performance with a five-fold shorter computation time. This model averaging algorithm was implemented in the TDMx software tool to guide infliximab dosage de-escalation in the forthcoming prospective MODIFI study (NCT04982172).

## Introduction

For over two decades, infliximab, an anti-tumour necrosis factor-alpha monoclonal antibody, has been approved for the treatment of several chronic immune-mediated diseases, including inflammatory bowel disease (IBD) ulcerative colitis (UC) and Crohn's disease (CD).[4,5] The package label lists 5 mg/kg intravenous infusions at weeks 0, 2, and 6 (induction therapy) and every eight weeks thereafter (maintenance therapy). However, approximately 20% to 40% of adult patients do not respond to standard induction therapy and up to half of the patients with a good initial response will lose response over time.[44,147]

Underexposure to infliximab is a common cause of loss of response in patients with IBD.[107] To boost infliximab trough concentrations (TCs) and subsequently regain the response, empirical dosage regimen escalations (i.e., shortening the dosing interval and/or increasing the dose) are widely practised.[187] However, long-term maintenance of the escalated dosage regimen has financial, practical, and potential safety implications and is therefore not warranted.[188–190] Accordingly, many centres have attempted to de-escalate the infliximab dosing (i.e., extending the dosing interval and/or decreasing the dose) in patients who maintained response on an escalated infliximab dosage regimen.

Empirical de-escalation of infliximab dosing could put patients at risk for underexposure and trigger again the loss of response due to extensive interindividual pharmacokinetic (PK) variability.[191] Model-informed precision dosing (MIPD) has been proposed to ensure adequate exposure and maintained response compared to traditional therapeutic drug monitoring (TDM).[192] MIPD employs drug-specific population PK (popPK) models, patient-specific monitoring data, and a Bayesian forecasting software tool to predict optimal doses for individual patients.[149] Selecting the most suitable popPK model is challenging, especially when many models are available, as is the case for infliximab.[172,193] A single-model approach could potentially result in inappropriate dose recommendations, leading to suboptimal treatment outcomes or jeopardising patients' safety. A multi-model selection algorithm (MSA) and a multi-model averaging algorithm (MAA) have previously been proposed by Uster *et al*.[193] to guarantee fit-for-purpose predictive performances during vancomycin MIPD.[193] The multi-model algorithms automate the MIPD procedure for selecting the prediction of either the best model (MSA) or the combination of models (MAA).

This study aimed to compare the predictive performance of published popPK models and multi-model selection and averaging approaches for guiding infliximab dosage regimen de-escalation to ensure the attainment of a prespecified TC target.

## Methods

### *Clinical data*

Adult patients with IBD who underwent infliximab dosage regimen de-escalation at the University Hospitals Leuven (Leuven, Belgium) between February 2017 and June 2020 were included. Dosage regimen de-escalation was defined as extending the dosing interval (with or without changing the dose) and/or decreasing the dose (with or without changing the dosing interval). The study was approved by the Ethics Committee (EC) Research UZ / KU Leuven (S63206). Serum samples were available from the CCare Biobank. All included patients have given written informed consent (B322201213950/S53684).

Patients with four consecutive trough samples, three before dosage regimen de-escalation (times $T_{-2}$, $T_{-1}$, and $T_0$) and one after de-escalation ($T_{+1}$) were eligible for inclusion (**Figure 27**). TCs were measured using the apDia Infliximab ELISA (apDia, Turnhout, Belgium), with a lower limit of quantification of 0.3 mg/L.[194] Patients with IBD type unclassified, with an ileal anal pouch anastomosis, with an ostomy, and who received infliximab prophylactically were excluded.

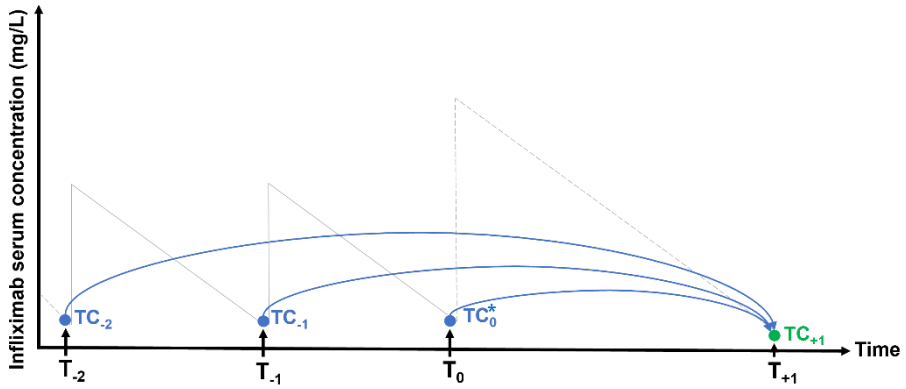



***Figure 27.*** *Study diagram of the prediction of the infliximab trough concentration (TC) at relative time +1 ($TC_{+1}$). In addition to covariate data, Bayesian forecasting was performed using one to three consecutive previously measured infliximab trough concentrations: $TC_{-2}$, $TC_{-1}$, and $TC_0$. T, time; TCs, trough concentrations. *rapid assay needed to obtain $TC_0$ for prospective implementation in model-informed precision dosing.*

Sex, age, IBD type (UC or CD), disease duration, previous IBD surgery, previous biological use, and duration of infliximab treatment were recorded right before dosage regimen de-escalation (at $T_0$) and were handled as time-invariant throughout the study follow-up. Body weight, fat-free mass, serum albumin, C-reactive protein, faecal calprotectin, infliximab dose, concomitant medications use (i.e., systemic corticosteroids or the immunomodulator azathioprine), Partial Mayo score for patients with UC, and Crohn's Disease Activity Index (CDAI) and Harvey-Bradshaw Index (HBI) for patients with CD were handled as time-varying throughout the study follow-up. Single imputation with the last observation carried forward was used for handling missing covariate data.

### *Candidate models*

A systematic literature search of PubMed from January 1996 until June 2021 was performed to identify published popPK models of infliximab in adult patients with IBD. The query was (infliximab) AND (model) AND (population) AND (pharmacokinetics). Articles were screened in full text for eligibility.

### *Single-model evaluations*

The fit of the data to the candidate models was visually inspected with goodness-of-fit plots (measured versus individual predicted concentrations). Also, simulation-based evaluations were performed, including prediction-corrected visual predictive checks (VPCs) and normalised prediction distribution errors (NPDEs). A normal distribution of NPDEs $\mathcal{N}(0,1)$ was tested using a Wilcoxon signed-rank test (to compare the median of the NPDE to zero), a Fisher variance test (to compare the variance of the NPDE to one), and a Shapiro-Wilk test (to compare the distribution of the NPDE to a normal distribution). An adjusted *p*-value of all three tests (a global test) was calculated to identify the best predictive model.[195]

### *Multi-model approaches*

Two multi-model approaches were evaluated using all candidate models jointly; an MSA and an MAA.[193] The multi-model approaches used all of the candidate models simultaneously for predicting the infliximab concentration at $T_{+1}$. The prediction of the MSA was the prediction of the candidate model with the highest weight, whereas the prediction of the MAA was an ensemble of weighted predictions of all candidate models (**Figure 28**). For each individual, predictions of the multi-model approaches were based on the weights (W) calculated from the maximum likelihood estimate (MLE) of each candidate model *i* in relation to the sum of MLEs of all *n* candidate models:

$$W_{MLE_i} = \frac{MLE_i}{\sum_1^n MLE_n} = \frac{e^{(-0.5 \times OFV_i)}}{\sum_1^n e^{(-0.5 \times OFV_n)}} \qquad \textit{Equation 10}$$

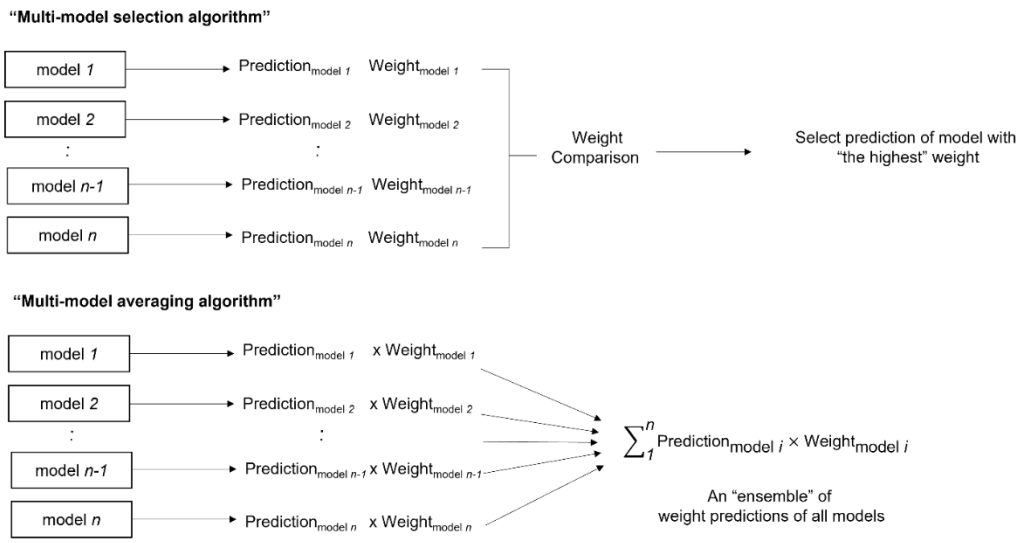



***Figure 28.*** *Flowcharts illustrate workflows of multi-model selection and multi-model averaging algorithms.*

***Predictive performance evaluations***

The predictive performance was evaluated from the differences between the predicted and the measured TC at $T_{+1}$ ($TC_{+1}$) in two prediction modalities: *a priori* prediction (using only the patients' covariates) and maximum *a posteriori* prediction (MAP; including at least one previous TC in addition to covariates). Three *a posteriori* prediction settings were compared: prediction with one ($TC_0$, $TC_{-1}$, or $TC_{-2}$), two ($TC_0$ and $TC_{-1}$, $TC_0$ and $TC_{-2}$, or $TC_{-1}$ and $TC_{-2}$), and three ($TC_0$, $TC_{-1}$, and $TC_{-2}$) previous TCs. The retrospective predictive performance of the models/algorithms was also evaluated by including the measured $TC_{+1}$ in the *a posteriori* prediction in addition to the three previous TCs.

The model-predicted versus measured $TC_{+1}$ in the different single-/multi-model approaches, prediction modalities, and evaluation settings were compared by calculating the relative bias (rBias) and the relative root mean square error (rRMSE) to determine accuracy and precision, respectively.

$$rBias = \frac{1}{n} \times \sum_1^i \left( \frac{TC_{+1,predicted,i} - TC_{+1,measured,i}}{TC_{+1,measured,i}} \right) \times 100\% \quad \textit{Equation 11}$$

$$rRMSE = \sqrt{\frac{1}{n} \times \sum_1^i \left( \frac{\left(TC_{+1,predicted,i} - TC_{+1,measured,i}\right)^2}{TC_{+1,measured,i}^{\ 2}} \right)} \times 100\% \quad \textit{Equation 12}$$

with *n* representing the total number of patients, and *i* each patient. An rBias between ±20% with a 95% confidence interval (CI) including zero was deemed clinically acceptable.[193] No rRMSE threshold for clinical acceptability was prespecified. Lower rRMSE values indicated more precise predictions.

***Robustness analysis and software implementation***

A robustness analysis was performed to reduce the number of popPK models without losing the predictive performance of the multi-model approach algorithms.[193] The average computation time was compared between the multi-model approaches using all versus only the subset of models. The subset of models was implemented in the TDMx software tool.[196] The performance of TDMx was cross-validated against NONMEM.

***Bland-Altman analysis, classification accuracy, and sensitivity analysis***

The MSA and MAA with the subset of models were evaluated using predictive performance metrics, Bland-Altman analysis[197], classification accuracy, and sensitivity analysis. The Bland-Altman plot was used to assess the agreement between the predicted and measured $TC_{+1}$ across the range of measured $TC_{+1}$. The predicted and measured $TC_{+1}$ were classified at the prespecified target TC of 5.0 mg/L.[198] The classification accuracy was calculated as

$$Classification\ accuracy\ = \frac{TN + TP}{n} \times 100\% \qquad \textit{Equation 13}$$

with TN and TP representing the numbers of true negative (predicted and measured $TC_{+1}$ ≥5.0 mg/L) and true positive (predicted and measured $TC_{+1}$ <5.0 mg/L) predictions, respectively, and *n* representing the total number of predictions. To note, outside the TDM context, a positive test result indicates the least desirable scenario which demands a clinical/pharmaceutical intervention. In the same way, we defined a positive TDM test result as a subtherapeutic concentration measurement ($TC_{+1}$ <5.0 mg/L), warranting a dose optimisation. A $TC_{+1}$ ≥5.0 mg/L was thus defined as a negative test result, not needing any dose optimisation. Consequently, a true or a false result was designated based on the correctness of the prediction with respect to the cutoff. The sensitivity of the predicted $TC_{+1}$ to missing covariate data was evaluated using single imputation with the median value around which the covariate is centred in the model. McNemar's tests were performed to evaluate differences in classification performance between the MAA and the subset of models, or the MSA.

***Software***

All models were coded in NONMEM (v7.5; Icon plc, Gaithersburg, MD, USA). Predictions were performed using NONMEM with a GNU Fortran 95 compiler. Data were analysed in R (v4.0.3; R Foundation for Statistical Computing, R Core Team, Vienna, Austria) with the RStudio integrated development environment (v1.2.5001; RStudio, Inc., Boston, MA, USA).

## Results

### *Clinical data*

Data were available from 54 patients with IBD (38 [70%] patients with CD and 16 [30%] patients with UC; **Table 4**). The majority of these patients (61%, 33/54) received 5 mg/kg infliximab every six weeks before changing the dosage regimen to 7.5 mg/kg infliximab every eight weeks. The median [interquartile range; IQR] of the measured $TC_0$ and $TC_{+1}$ were 7.0 [ 5.3-9.4] mg/L and 5.0 [3.8-6.7] mg/L, respectively. Only 52% (28/54) of patients had $TC_{+1}$ above or equal to 5.0 mg/L.

***Table 4.*** *Patients' characteristics (N=54).*

| **Parameter** | |
|---|---|
| *Demographics and disease history* | |
| Sex, female, n (%) | 22 (41) |
| Age, years, median [IQR] | 44 [34 – 56] |
| Body weight, kg, median [IQR] | 81 [69 – 93], NA=2 |
| Body length, cm, median [IQR] | 174 [168 – 180] |
| Body mass index, kg/m$^2$, median [IQR] | 25.7 [23.9 – 28.9], NA=2 |
| Fat-free mass, kg, median [IQR] | 57.7 [48.6 – 64.3], NA=2 |
| IBD type, UC:CD, n (%) | 16:38 (30:70) |
| Age at diagnosis, years, median [IQR] | 24 [20 – 34], NA=3 |
| Disease duration, years, median [IQR] | 14 [10 – 20], NA=3 |
| Previous IBD surgery, yes, n (%) | 18 (33) |
| Previous biological used, yes, n (%) | 10 (19) |
| Duration of infliximab treatment, years, median [IQR] | 8 [4 – 11] |
| *Biological characteristics* | |
| Serum albumin, g/L, median [IQR] | 44 [43 – 45] |
| C-reactive protein, mg/L, median [IQR] | 2 [1 – 4] |
| Faecal calprotectin, mg/kg, median [IQR] | 68.5 [37.8 – 224.5], NA=50 |
| *Clinical characteristics* | |
| *For UC patients* | |
| Partial Mayo score, 0:1, n (%) | 7:1 (88:12), NA=46 |
| *For CD patients* | |
| Crohn's disease activity index, median [IQR] | 41 [13 – 108], NA=19 |
| Harvey-Bradshaw Index, median [IQR] | 0 [0 – 2.8], NA=16 |
| *Systemic concomitant medication used* | |
| Corticosteroids, n (%) | 1 (2) |
| Immunomodulators (i.e., azathioprine), n (%) | 3 (6) |
| 5-aminosalicylate acid, n (%) | 3 (6) |
| *De-escalation characteristics* | |
| Type of de-escalation, n (%) | |
| - both infusion interval extension and dose increase | 48 (89) |
| - only infusion interval extension | 5 (9) |
| - only dose reduction | 1 (2) |
| Combination treatment, n (%) | 7 (13) |

CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; n, number; NA, data not available (If NA not mentioned in the table, there were no missing data); UC, ulcerative colitis.

### *Candidate models*

Eighteen popPK models were identified. They differed in structure, covariates, and parameter estimates, as well as population, dosing schedules, and sampling schemes that they were based on (**Table 5**). Half of the models (50%, 9/18) were developed on data from mixed UC and CD populations. The majority of the models (67%, 12/18) were two-compartment models. Antibodies to infliximab, serum albumin, and body weight were the most frequently identified covariates on clearance. Body weight was the most commonly identified covariate on volumes of distribution.

***Table 5.*** *Overview of the 18 candidate infliximab population pharmacokinetic models.*

| Model | N | IBD type | Treatment phase | Sampling times | Number of compartments |
|---|---|---|---|---|---|
| Aubourg[199] | 133 | CD | induction, maintenance | peak, trough | 2 |
| Brandse_2016[200] | 20 | UC | induction | peak, trough intermediate | 2 |
| Brandse_2017[201] | 332 | UC, CD | induction, maintenance | peak, trough intermediate | 2 |
| Buurman[202] | 42 | UC, CD | induction, maintenance | trough | 2 |
| Dotan[111] | 54 | UC, CD, UI | induction, maintenance | peak, trough intermediate | 2 |
| Dreesen_2019[203] | 204 | UC | induction | trough | 1 |
| Dreesen_2021[204] | 116 | CD | induction, maintenance | trough, intermediate | 2 |
| Edlund[205] | 68 | CD | maintenance | trough, intermediate | 2 |
| Fasanmade_2009[99] | 482 | UC | induction, maintenance | peak, trough intermediate | 2 |
| Fasanmade_2011[103] | 692 | CD | induction, maintenance | peak, trough intermediate | 2 |
| Grisic[206] | 121 | UC, CD, UI | maintenance | trough, intermediate | 2 |
| Matsuoka[207] | 121 | CD | maintenance | trough | 1 |
| Passot[208] | 79 | UC, CD | induction, maintenance | trough | 1 |
| Petitcollin[100] | 91 | UC, CD | maintenance | trough | 1 |
| Ternant_2008[209] | 33 | UC, CD | induction, maintenance | peak, trough intermediate | 2 |
| Ternant_2015[210] | 111 | CD | maintenance | trough, intermediate | 1 |
| Ternant_2018[211] | 50 | UC, CD | induction, maintenance | trough | 1 |
| Xu[212] | 788 | UC, CD | NS | NS | 2 |

CD, Crohn's disease; IBD, inflammatory bowel diseases; N, number of patients; NS, not specified; UC, ulcerative colitis; UI, undetermined inflammatory bowel disease type.

***Single-model evaluations***

Each patient contributed the same number of consecutive trough concentration samples (i.e., four). The individual predicted concentrations of each model were in good agreement with their measured concentrations except for the Edlund model predictions that showed a spread deviating from the identity line (**Appendix A**). The VPCs of the models differed markedly (**Appendix B**). The Buurman model displayed the best alignment of predicted and measured concentrations. In line with the VPC results, the Buurman model was identified as the best predictive model regarding the distribution of the NPDEs (**Appendix C and D**).

***Multi-model approaches***

Using the MSA in the *a posteriori* prediction modality, the Buurman model was selected for 36% [32%-40%] of the patients, followed by the Ternant_2008 model (25% [16%-34%] of patients) and the Dotan model (22% [22%-24%] of patients). Using the MAA in the *a posteriori* prediction modality with one previous TC, all models had nearly equal weights. By adding more previous TCs, some models started dominating the *a posteriori* predictions of the MAA.

***Predictive performances evaluations***

*A priori* prediction of the $TC_{+1}$ was clinically unacceptable with both single- and the multi-model approaches (rBias -75% to +483%, rRMSE 58% to 629%; **Figure 29**), except for the prediction with the Edlund model (rBias +16%; 95% CI -5% to +36%, rRMSE 77%).

Providing one previous TC ($TC_0$, $TC_{-1}$, or $TC_{-2}$) greatly improved the predictive performance (rBias -27% to +38%, rRMSE 28% to 69%; **Figure 29**). Providing more than one previous TC improved the predictive performances only marginally. Compared with the single-model approach, the predictive performances of multi-model approaches were less sensitive to the number of provided TCs for MAP. MAA performed systematically better than MSA both in terms of accuracy and precision. MAA provided more precise predictions than MSA in all *a posteriori* prediction settings (one previous TC: rRMSE 33% to 41% for the MAA versus rRMSE 50% to 57% for the MSA; three previous TCs: rRMSE 30% for MAA versus rRMSE 46% for MSA; **Figure 29**).

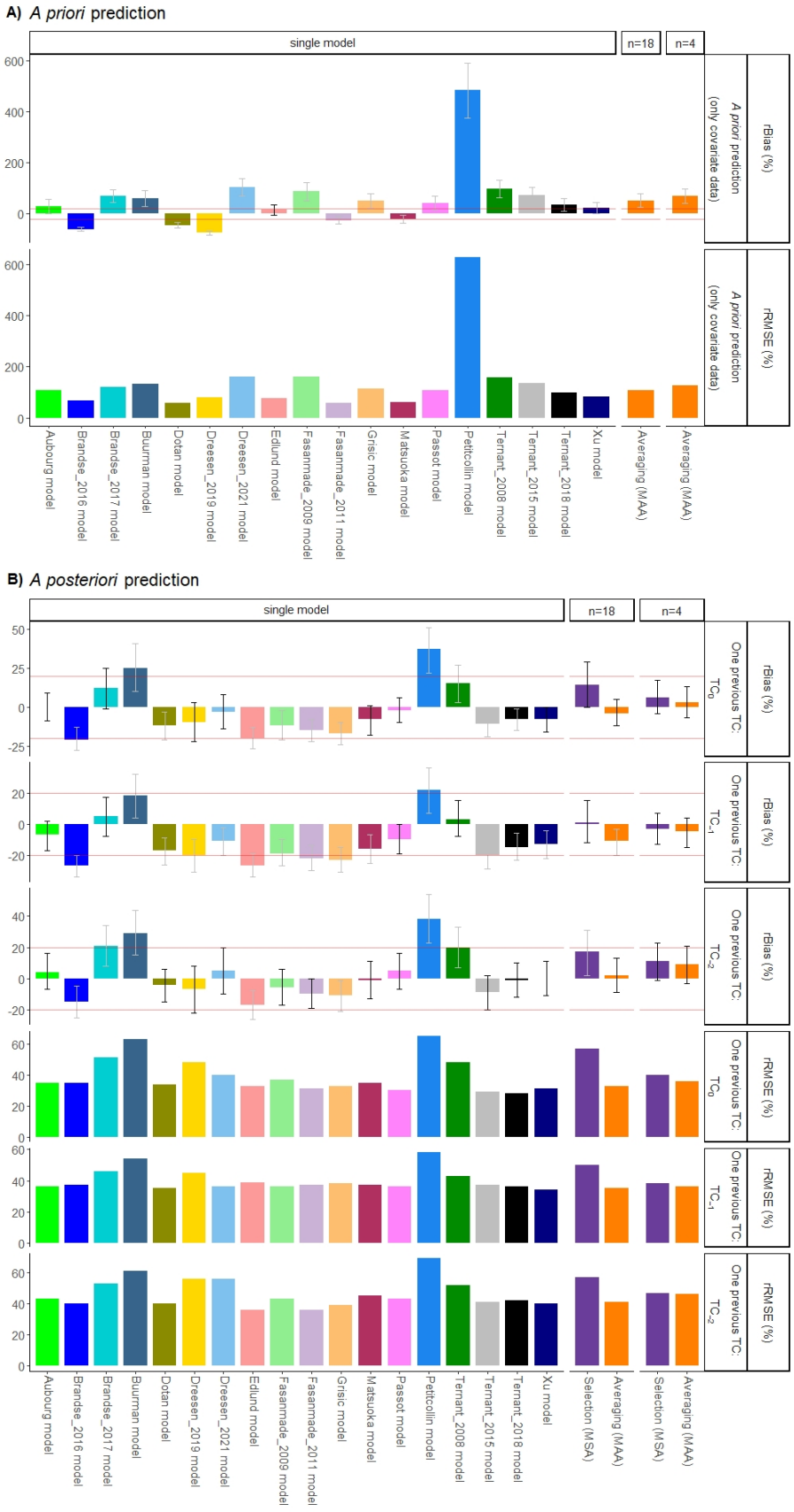



***Figure 29.*** *The predictive performance of 18 single candidate population pharmacokinetic models versus the multi-model approaches using all 18 models versus the four models for predicting the infliximab trough concentration (TC) at time +1 ($TC_{+1}$). (A) a priori prediction (with only covariate data); (B) a posteriori prediction settings using covariate data and one previous TC ($TC_0$, $TC_{-1}$, or $TC_{-2}$). Whiskers indicate the 95% confidence interval (CI) of the relative bias calculated via the standard error (black whiskers indicate 95% CIs including 0). Horizontal red lines indicate ±20% range of the relative that is deemed clinically acceptable. rBias, relative bias; rRMSE, relative root mean square error. Note: Model weights during a priori prediction are equal (1/number of models), precluding a model selection procedure in this setting.*

***Robustness analysis and software implementation***

Four candidate models were selected considering their overall predictive performance metrics in the *a posteriori* prediction settings (Aubourg model, Dreesen_2021 model, Passot model; all with a negative rBias), and the best model with positive rBias (Ternant_2008 model). The predictive performances of the multi-model approaches with only the four models were in good agreement with the multi-model approaches including all models (**Figure 29**). In addition, by providing at minimum one previous TC, the predictive performances of both multi-model approaches were clinically acceptable even when only three or two instead of four models were used (rBias -4% to +2%; **Appendix E**).

The average computation time of the multi-model approaches using only the four models decreased five-fold from the multi-model approaches using all 18 models (average 0.115 seconds versus 0.576 seconds per patient).

An infliximab module was added to TDMx (https://tdmx.shinyapps.io/infliximab/). Results of the objective function values and model averaging predictions using TDMx were in good agreement with NONMEM (*a posteriori* prediction setting with $TC_{-1}$) (**Appendix F and G**).

***Bland-Altman analysis, classification accuracy, and sensitivity analysis***

The tendency of prediction bias across the measured concentration range from 3.0 mg/L to 10.0 mg/L was the least by providing only $TC_0$ in Bayesian forecasting (**Figure 30**).

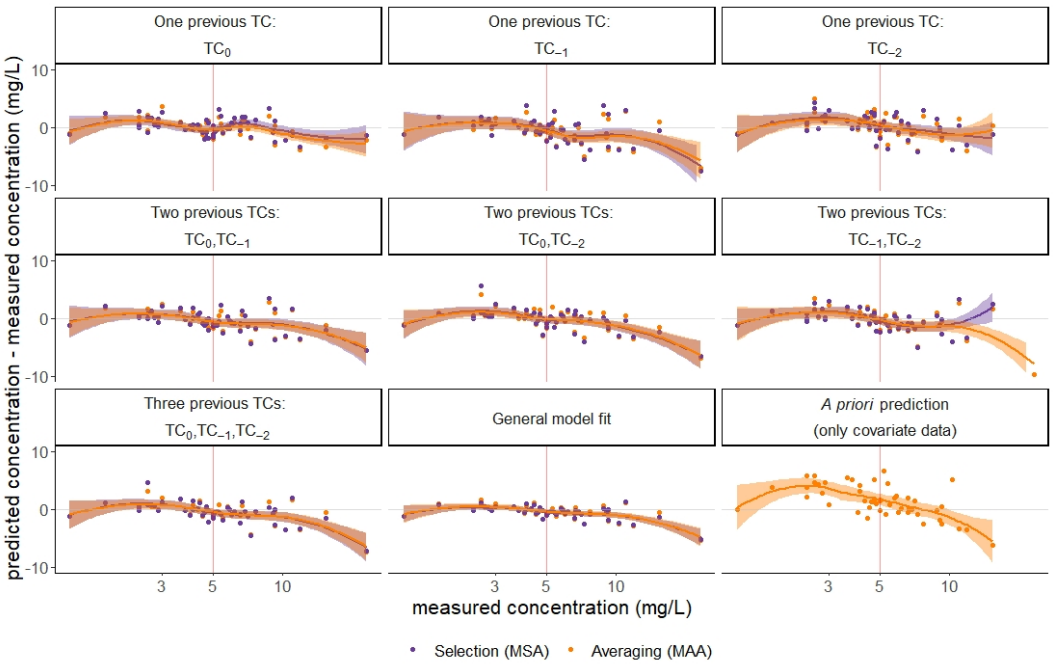



***Figure 30.*** *Bland-Altman plots showing the agreement between the measured infliximab concentrations and the predicted infliximab concentrations across the range of measured infliximab concentrations in various prediction settings using the model averaging algorithm (MAA; orange) and the model selection algorithm (MSA; purple). The vertical red line indicates the 5.0 mg/L trough concentration target. The solid line with the shaded area represents a locally weighted smoother with its 95% confidence interval based on the data (MAA in orange and MSA in purple).*

*A priori* predictions of both single and multi-model approaches had the lowest classification accuracy (median 59%, IQR 59%-63%) and the highest percentage of falsely predicting the $TC_{+1}$ ≥5.0 mg/L (false negative rate median 35%, IQR 30%-37%; **Figure 31**). In comparison with *a priori* prediction, providing at least one previous TC significantly improved not only the classification accuracy (median 72%, IQR 71%-76%; $p<0.05$) but also significantly decreased the false negative prediction rate (median 8%, IQR 6%-15%; $p<0.05$). *A posteriori* prediction with the $TC_0$ resulted in a significantly higher classification accuracy than with the $TC_{-1}$ or the $TC_{-2}$ ($p$ <0.01). Also, the availability of the $TC_0$ significantly lowered the chance of falsely predicting the $TC_{+1}$ <5.0 mg/L in comparison with only providing the $TC_{-1}$ ($p$ = 0.004). Providing more than one previous TC did not improve the classification accuracy metrics (**Figure 31**). However, the classification performances of the MAA were not significantly different from the MSA and the other single models ($p$ >0.10), except for *a posteriori* predictions using the Ternant_2008 model with the $TC_{-1}$ ($p$ = 0.023) (**Figure 31**).

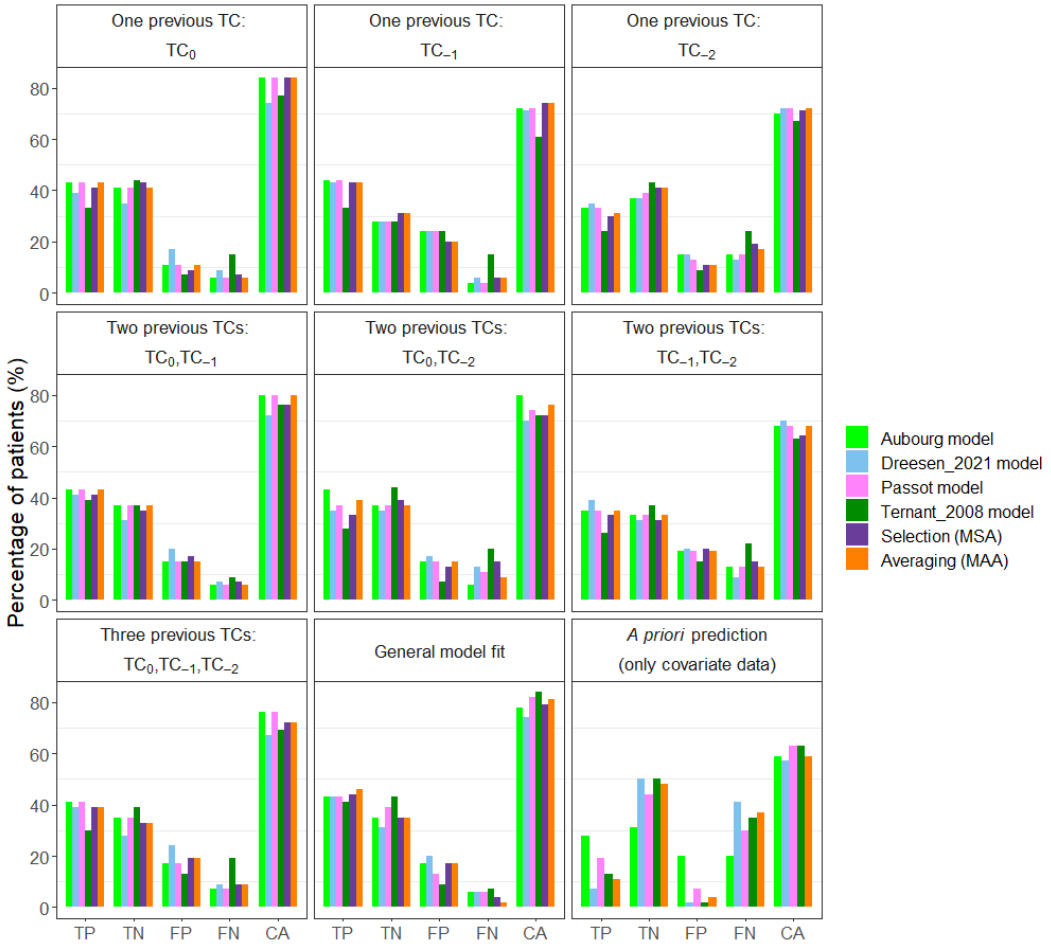



***Figure 31.*** *The percentage of patients (N=54) in four classes based on the predicted and measured $TC_{+1}$ according to the prespecified trough concentration target of 5.0 mg/L in various prediction settings: (i) True positive (TP): both measured and predicted <5.0 mg/L; (ii) True negative (TN): both measured and predicted ≥5.0 mg/L; (iii) False positive (FP): measured ≥5.0 mg/L, but predicted <5.0 mg/L; (iv) False negative (FN): measured <5.0 mg/L, but predicted ≥5.0 mg/L. (v) Classification accuracy (CA): the number of correct predictions (TP and TN) divided by the total number of predictions (n=54). TC, trough concentration.*

The predictive performance of the single-model approach with any model was maintained when applying median covariate imputation (**Figure 32**). Also, there was no change of accuracy and precision of predictive performances for multi-model approaches in the *a priori* setting (MAA: rBias +68%, rRMSE 125% for true value versus rBias +66%, rRMSE 125% for imputed value), and the *a posteriori* setting (MAA: rBias -5%, rRMSE 36% for both true value and imputed value; MSA: rBias -3%, rRMSE 38% for true value versus rBias -1%, rRMSE 39% for imputed value).

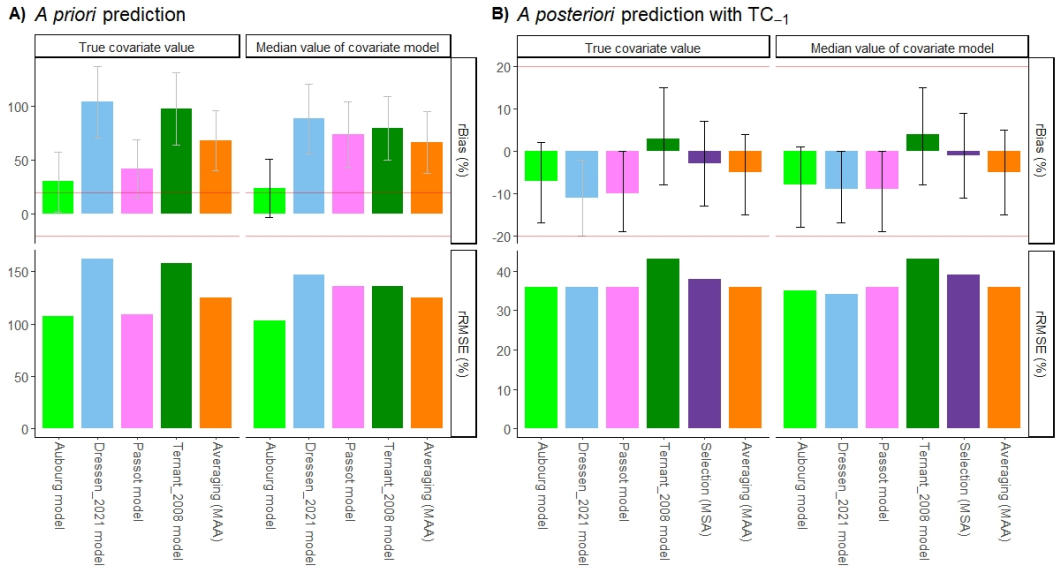



***Figure 32.*** *Comparison of the predictive performance between scenarios with and without covariate data available. The scenario of missing covariate information used a single imputation strategy with the median covariate value around which the covariate effect was centred in the respective model. (A) a priori prediction (with only covariate data); (B) a posteriori prediction settings using covariate data and one previous TC ($TC_{-1}$). Whiskers indicate the 95% confidence interval (CI) of the relative bias calculated via the standard error (black whiskers indicate 95% CIs including 0). Horizontal red lines indicate ±20% range of the relative that is deemed clinically acceptable. rBias, relative bias; rRMSE, relative root mean square error.*

## Discussion

The selection of a popPK model for guiding individualised dose optimisation is a crucial step in MIPD. For infliximab, 18 popPK models have been developed to describe the PK characteristics of adult patients with IBD. To date, the benefits of MIPD with a single infliximab model in patients with IBD have been evidenced both retrospectively[213] and prospectively[144]. However, alternative approaches that integrate multiple popPK models have not been investigated for infliximab. In our study, we found that an MAA resulted in the most accurate and precise *a posteriori* predictions, regardless of the number of TCs provided, as compared to a single model approach. *A priori* prediction using covariate data alone resulted in biased and imprecise predictions with either single or multi-model approaches. The predictive performance of both single- and multi-model approaches was robust to the lack of covariate data.

PK variability of infliximab is challenging for traditional flowchart-guided TDM. No significant clinical benefits were shown for proactive TDM during infliximab induction therapy in patients with immune-mediated inflammatory diseases (i.e., NOR-DRUM A[214]). During infliximab maintenance therapy, the clinical benefit of proactive TDM could also not be addressed in patients with IBD (i.e., TAXIT[121], TAILORIX[122]), yet it was addressed in a mixed population of patients with immune-mediated inflammatory diseases (i.e., NOR-DRUM B[123]). Recently, the PRECISION[144] trial using a single-model approach implemented in a Bayesian dashboard for infliximab dosing showed significant clinical benefit over label dosing during maintenance therapy. Due to the acknowledged benefits of MIPD in personalised medicine[141,192], great efforts are being made to improve components of MIPD such as methods for the selection of models[193,215] and methods for the estimation of parameters[216,217]. In this study, we investigated alternative approaches allowing the incorporation of multiple popPK models simultaneously for MIPD. The MSA and MAA could provide more flexibility in PK parameter estimation and potentially increase generalisability to unseen data compared to MIPD using a single-model approach. In agreement with findings from Uster *et al.* using vancomycin as a case study, the multi-model approaches had better predictive performance than any single-model approach.[193] Furthermore, we found that the MAA outperformed the MSA and single-model approaches since the MAA systematically resulted in more precise predictions.

The predictive performance of infliximab popPK models was previously externally evaluated in patients with inflammatory diseases[218], including patients with IBD[219,220]. In the studies of Santacana *et al.*[219] and Schräpel *et al.*[220], the two models developed by Fasanmade *et al.*[99,103] (using data from the phase 3 trials) demonstrated the best predictive performance in patients with IBD. In our study, both Fasanmade models gave inaccurate *a posteriori* predictions in most of the evaluated settings. In addition, these two models were not selected for any of the patients in the MSA. The differences in predictive performances of candidate models between studies could potentially be caused by differences in the approaches used to assess the model's predictive performance

(e.g., provided measured concentration for MAP, the estimation of empirical Bayes PK parameter approach, predictive performance metrics). The observed differences emphasise the importance of site-specific external validation prior to clinical implementation. In our study, we evaluated predictive performance of candidate models for predicting trough concentrations. Infliximab clearance is the PK parameter that mainly drives the trough concentration. Our case is different from for example vancomycin, where the exposure target is an area under the curve, which is driven by all popPK parameters. Therefore, as expected, we did not observe any difference in the predictive performance of one- and two-compartment models (data not shown). Although we reduced the number of models participating in the multi-model approach to gain computation time without losing predictive performance, this action may not be as innocent as it appears and may show to be a sacrifice in a more extensive external validation/application. Therefore, external validation with all identified 18 models may be suggested prior to using our developed software in other settings.

In our study, we used a comprehensive set of model qualification tools, ranging from closeness of study population and goodness-of-fit plots over predictive performance and classification accuracy assessments to Bland-Altman analysis and sensitivity analysis. Nevertheless, to control the inherent risks associated with PK prediction as much as possible, a wider set of diagnostic tools for model qualification for MIPD may still be needed.[141] Apparent contradictory findings between model qualification tools are common. A model that conforms to various model evaluation standards may not perform well in the prediction evaluations. For example, the Edlund model fitted the data worst, but it was the only model with clinically acceptable *a priori* predictions. Furthermore, while the Petitcollin model was developed using data from a clinical setting closest to the one that we are studying, the Buurman model was the best model based on VPC and NPDE. Nevertheless, both models did not perform well in *a priori* and *a posteriori* predictions. The *a priori* prediction is a population prediction based solely on covariate data, while VPC and NDPE take into account both covariate and concentration in the evaluations. Therefore, *a priori* prediction performance may not be indicated via VPC and NDPE. The complementary use of a comprehensive set of model qualification tools should be considered during model selection. Also, standard goodness-of-fit evaluations are not appropriate for evaluating the suitability and predictive performance of models for MIPD. Yet, since the multi-model approaches rely on the calculation of model weights based on a goodness-of-fit measure, the standard model evaluation toolkit should not just yet be discarded, and the relation between the descriptive and predictive ability of models requires further investigation.

A single TC suffices to allow accurate and precise MIPD. Based on our findings, the acceptable timeframe of TC monitoring to predict the TC+1 accurately was TC from previously consecutive dosing that was not further than three dosing intervals before dosage regimen de-escalation. Due to interoccasion variability, an “old” concentration may have lost the ability to predict future exposure. Therefore, the predictive performance of MIPD using trough concentrations from the later time points may require further

investigation. Moreover, providing only one TC adequately informs about PK parameters and subsequently makes the covariate data relatively unimportant for the predictive performance. Median imputation of missing covariate data is, therefore, a safe strategy. This finding is intuitive, knowing that covariates generally only explain a small part of the interindividual variability (up to 6% for clearance[99,103]), while Bayesian forecasting can identify the remaining, often high "unexplained" interindividual variability (median of 32.7% [IQR 28.0-36.0%] on clearance[99,103]).

Theoretically, utilising point-of-care testing may improve the clinical and economic benefits of MIPD. In this study, we found that a single most recent TC (at $T_0$) resulted in the highest classification accuracy with not only a low chance of falsely predicting the $TC_{+1}$ ≥5.0 mg/L (i.e., risk of losing therapeutic response) but also a low chance of falsely predicting the $TC_{+1}$ <5.0 mg/L (i.e., risk of unnecessary dose escalation). However, a recently published prospective study using a rapid assay during traditional flowchart-guided proactive TDM (i.e., a decision-making flowchart designed to maintain infliximab concentration within the desirable therapeutic range) could not show clinical benefits in patients with IBD during infliximab maintenance therapy.[221] Nevertheless, a rapid assay may show its full potential when used in combination with an MIPD software tool. Yet, a prospective evaluation is warranted.

An MIPD approach could potentially improve the treatment efficacy in patients undergoing dosage regimen de-escalation. Petitcollin *et al.* reported that the clearance of infliximab in these patients was not only a factor in patient selection but also a predictor for disease relapse after treatment de-escalation.[100] Also, the infliximab clearance gradually increased over time in association with body weight variations. Therefore, the MAA as implemented in the TDMx Bayesian forecasting software tool will be used to guide infliximab dosing in the forthcoming prospective MODIFI study (NCT04982172). In the MODIFI study, we aim to deliver proof-of-concept of the superiority of MIPD over empirical dosage regimen de-escalation. The primary endpoint is the proportion of patients maintaining steroid-free, combined clinical and biological remission during one year after the start of infliximab de-escalation.

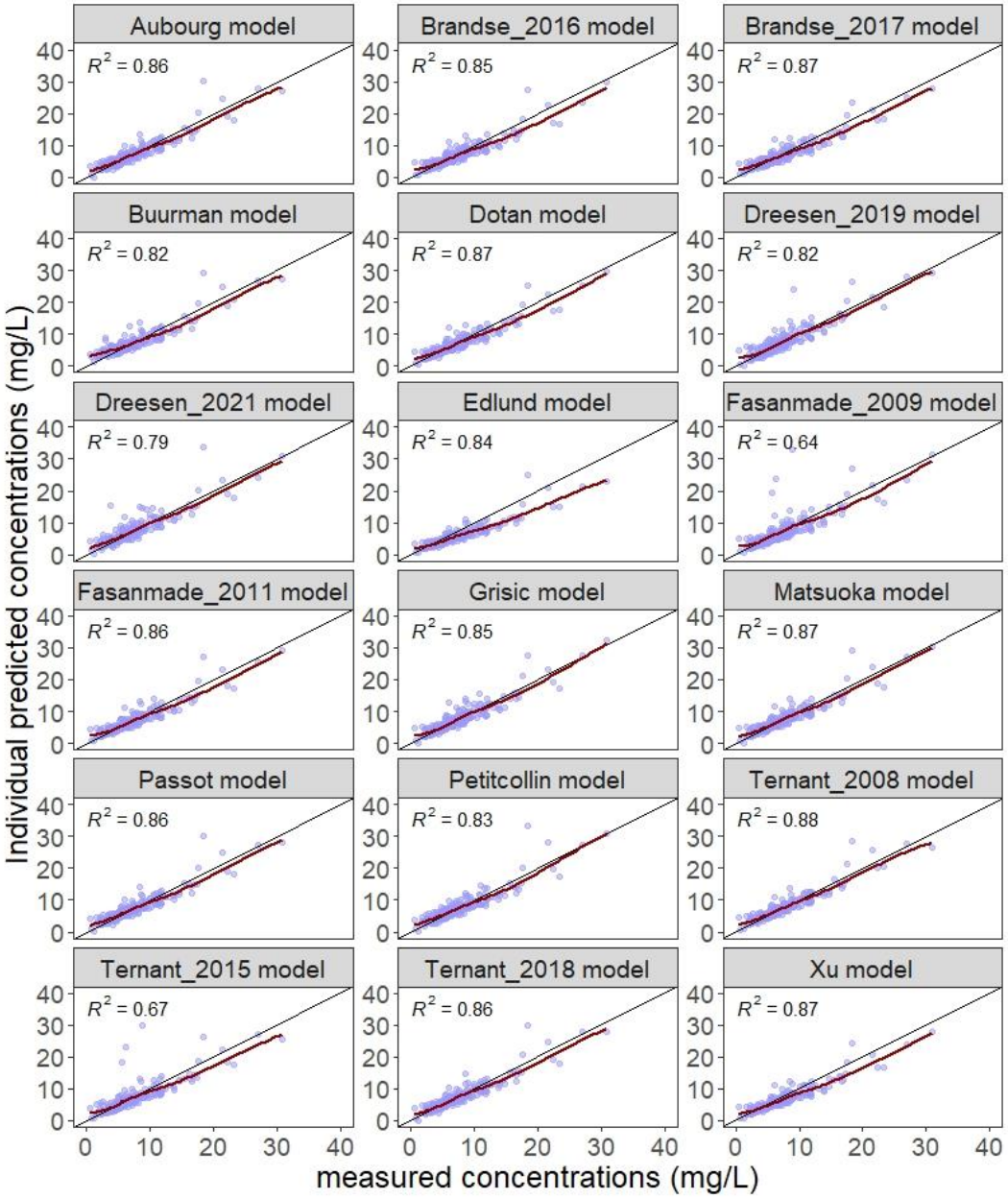
This study had several strengths. First, we evaluated the predictive performance of multi-model approaches for MIPD in a very different context (i.e., biological drug, chronic disease) from Uster *et al.* (i.e., vancomycin, infectious diseases)[193]. Second, additional analysis tools (i.e., Bland-Altman analysis and classification accuracy) for evaluating the fit-for-purpose of popPK models for use in MIPD were introduced. Currently, there is no well-established target of classification accuracy for MIPD approach. To the best of our knowledge, classification accuracy has only been included for model predictive performance evaluation for infliximab in Schräpel *et al.*[220] Therefore, defining clinical relevance of these additional analysis tools still requires further investigation to facilitate the translation and appropriate use of the MIPD approaches in clinical care. Third, we also

scrutinised the importance of utilising point-of-care testing and the availability of covariate data on predictive performances.

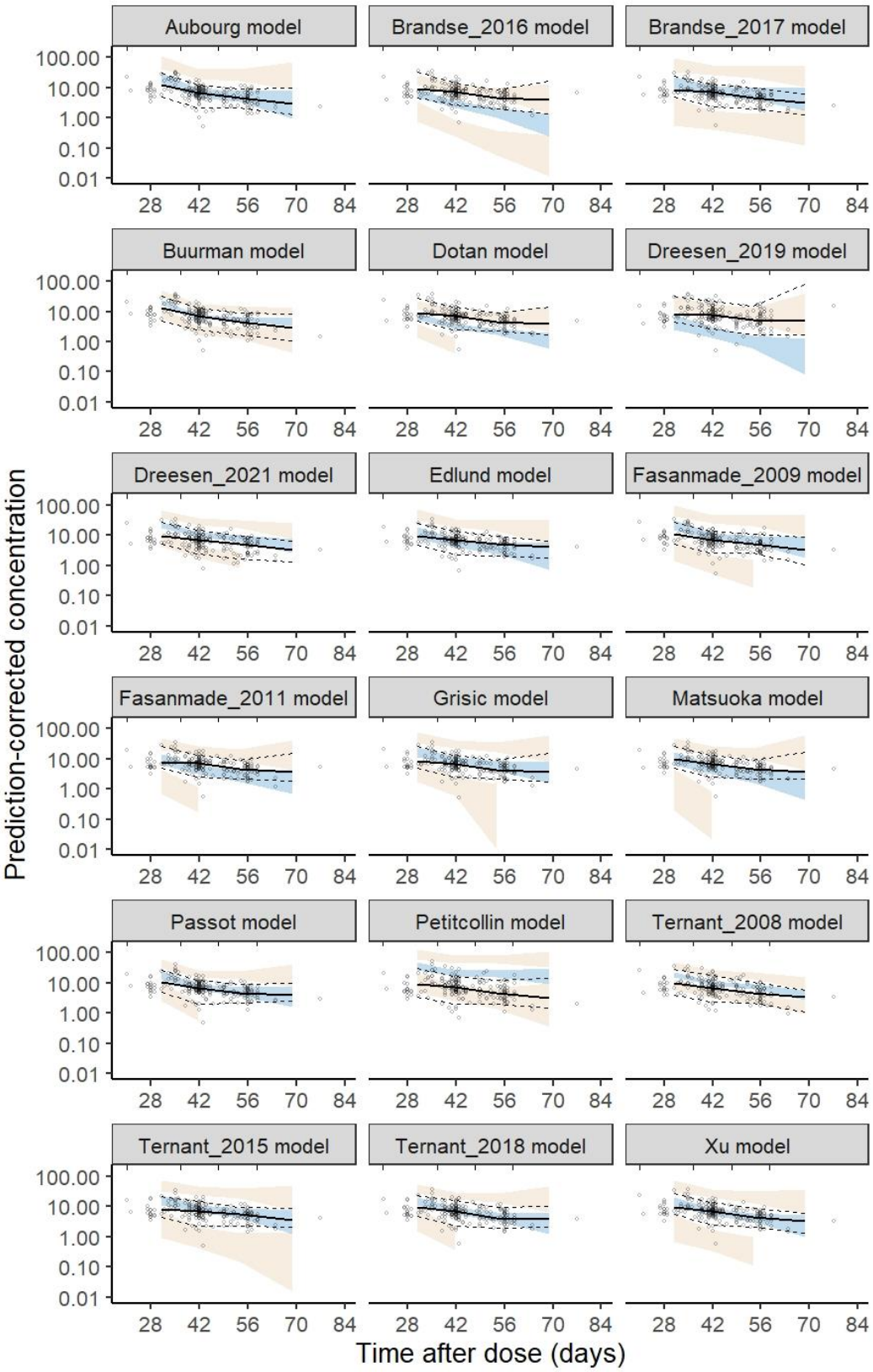
Still, our study had some limitations. First, incomplete reporting of information on error models, median values for centring covariate effects, and variance-covariance matrices limited the reproducibility of the published popPK models. Therefore, assumptions had to be made for the missing information. In recent years, the importance of an "Open" approach to science and the accessibility to mathematical models has become well-recognised as a crucial step in maintaining reproducibility, rigour, and integrity in published pharmacometrics models.[222] Second, a limited number of patient data from a single clinical centre was used in this analysis. This study was an exploratory study and so was not powered to obtain statistical significance. Therefore, the interpretation of our results should be done with care and we recognise the importance of continued validation of our MIPD algorithm in patients with IBD in other clinical centres.[223] Also, the need for centre-specific external validation of our algorithm will be required before broader clinical implementation. The differences between clinical centres include the level of health care (e.g., primary care, secondary care, and tertiary care), bioanalysis method, clinical workflows, etc. To allow us and others to do so, we provide the weblink to the MIPD tool in this paper. Third, due to the retrospective nature of our study, a potential selection bias cannot be ruled out. We only collect data from patients who have given written informed consent for collecting their data and serum samples. Therefore, future prospective confirmation of our findings will be needed. Lastly, the generalisability of our work beyond the studied clinical context will require further investigation to rule out potential bias. We studied the value of model-informed precision dosing specifically for guiding dose de-escalation, but the value of our work may be of interest in other clinical scenarios as well (e.g., dose intensification, proactive therapeutic drug monitoring, and reactive therapeutic drug monitoring). Also, concentration data used in this analysis were measured using only one commercially available assay. Therefore, external validations with larger and different cohorts in other clinical centres using other bioanalysis assays are needed to confirm the generalisability of our work.

To conclude, we developed a robust and precise MAA for guiding infliximab MIPD using a single recently measured TC. The algorithm is implemented in the freely available TDMx software tool and will be evaluated in the prospective MODIFI study (NCT04982172).

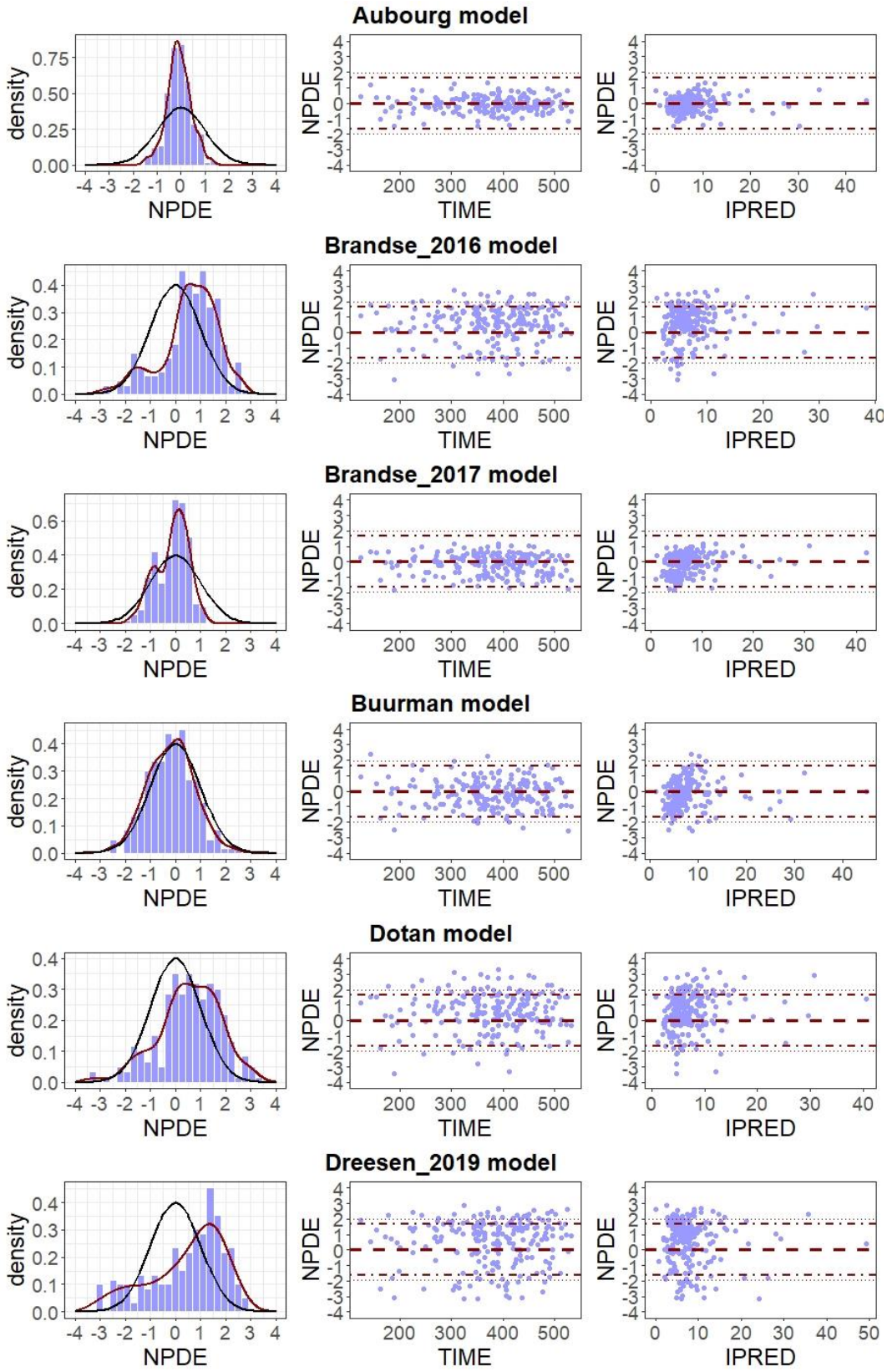
# Appendix



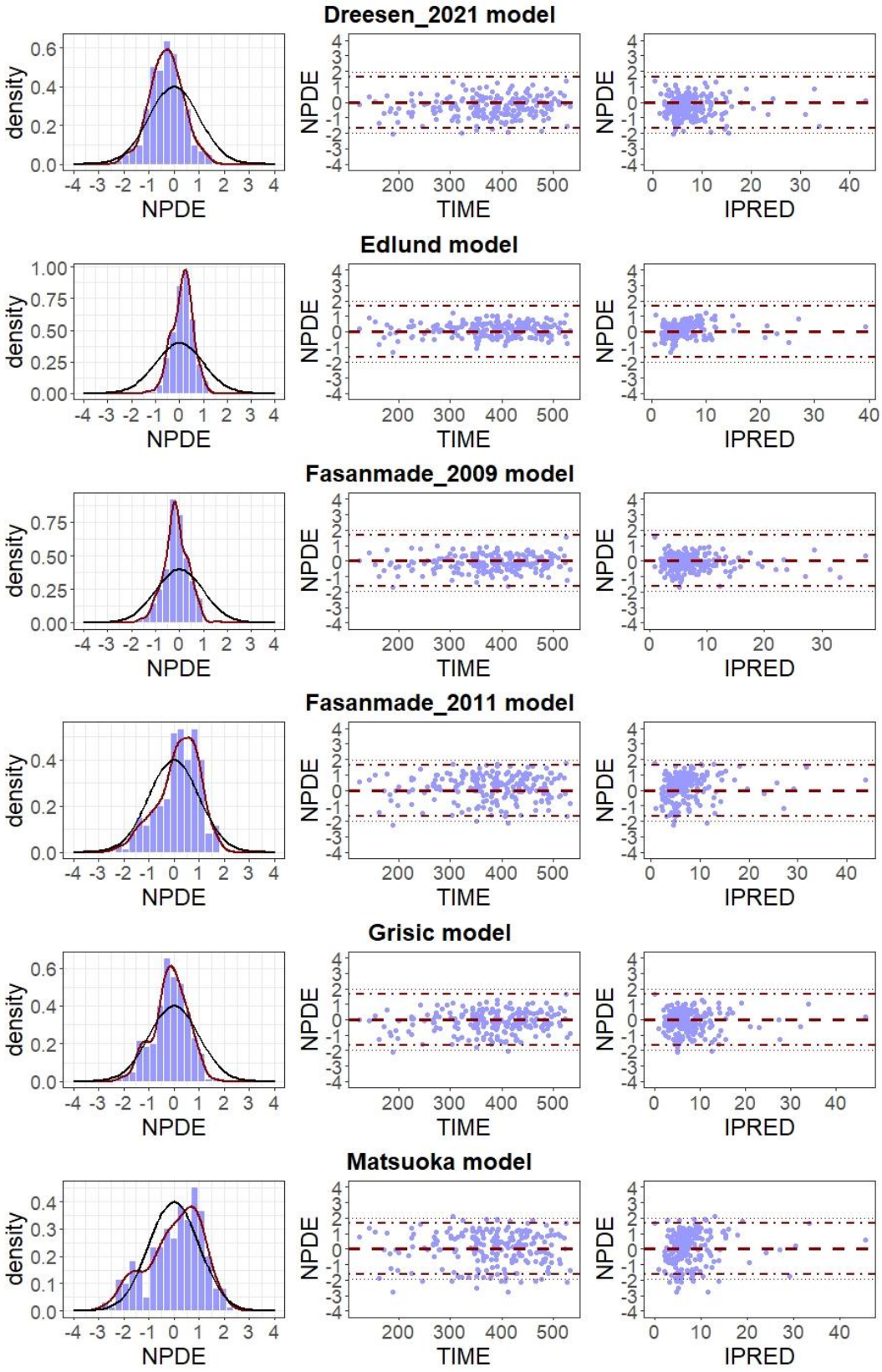

***Appendix A.*** *Goodness-of-fit plots showing measured concentrations versus individual predicted concentrations. The solid black diagonal line is a line of identity. The solid red line is a locally weighted smoother.*



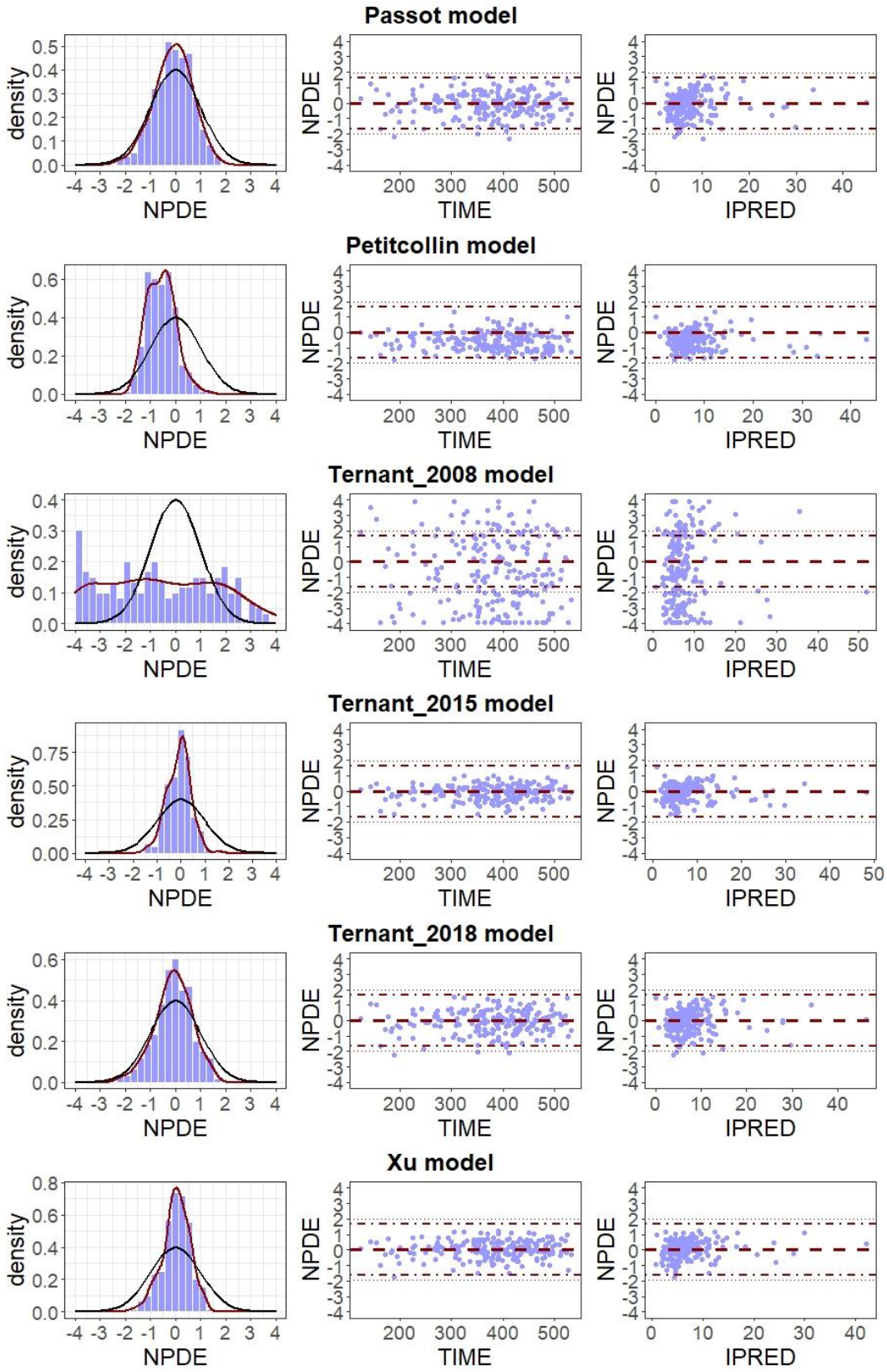

***Appendix B.*** *Prediction-corrected visual predictive checks of the a priori prediction-corrected infliximab concentration (in log scale) versus time after dose (days) in 54 patients for each of the 18 candidate models. Solid lines indicate the median of the data and dashed lines the 5$^{th}$ and 95$^{th}$ percentile of the data. The shaded areas indicate the 90% confidence intervals of the respective prediction obtained from the models. The vertical dashes at the top of each plot indicate the binning intervals.*




***Appendix C*** (1/3). Plots illustrating normalised prediction distribution errors (NPDE) and a goodness-of-fit plot of the 18 candidate models. *The first plot*: Histogram and density (solid red line) of the distribution of NPDE overlayed with theoretical $\mathcal{N}(0,1)$ distribution (solid black line). *The second plot*: Scatterplot of NPDE versus Time (days). *The third plot*: Scatterplot of NPDE versus individual predicted concentrations (IPRED). The dashed horizontal lines are the null line (NPDE = 0). The dot-dashed horizontal lines indicate the 90% range (NPDE = -1.645, 1.645). The dotted lines indicate the 95% range (NPDE = -1.96, 1.96). ESAMPLE was set at 10,000.




***Appendix C*** (2/3). Plots illustrating normalised prediction distribution errors (NPDE) and a goodness-of-fit plot of the 18 candidate models. *The first plot*: Histogram and density (solid red line) of the distribution of NPDE overlayed with theoretical $\mathcal{N}(0,1)$ distribution (solid black line). *The second plot*: Scatterplot of NPDE versus Time (days). *The third plot*: Scatterplot of NPDE versus individual predicted concentrations (IPRED). The dashed horizontal lines are the null line (NPDE = 0). The dot-dashed horizontal lines indicate the 90% range (NPDE = -1.645, 1.645). The dotted lines indicate the 95% range (NPDE = -1.96, 1.96). ESAMPLE was set at 10,000.

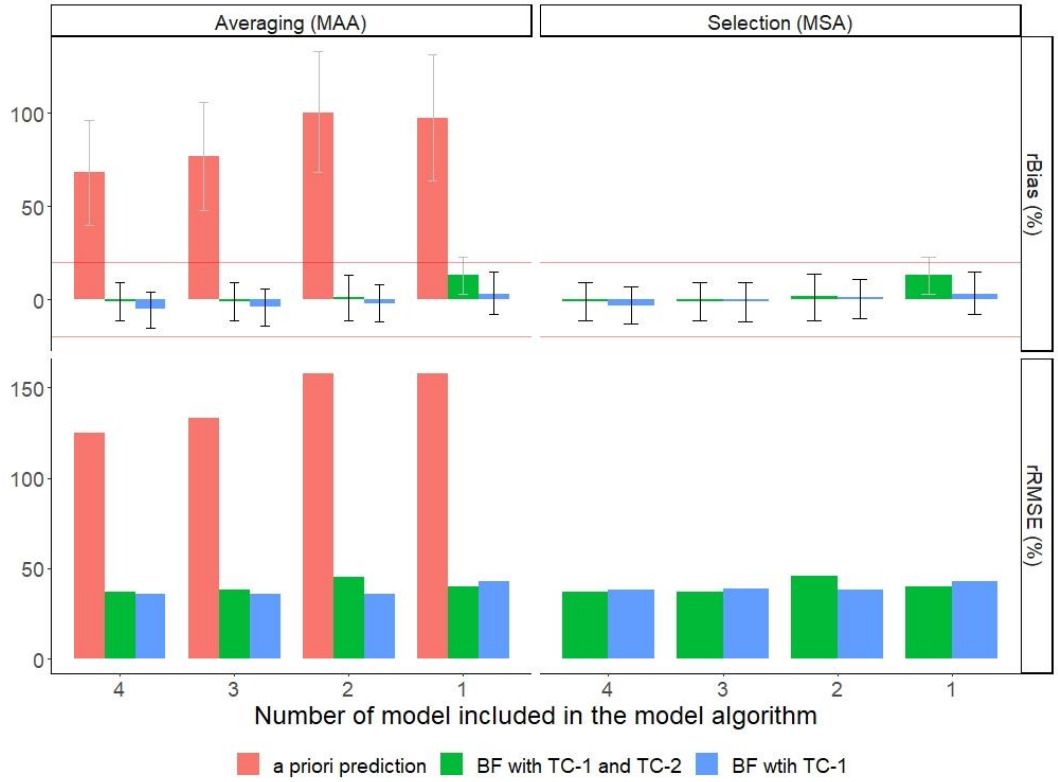



***Appendix C*** (3/3). Plots illustrating normalised prediction distribution errors (NPDE) and a goodness-of-fit plot of the 18 candidate models. *The first plot*: Histogram and density (solid red line) of the distribution of NPDE overlayed with theoretical $\mathcal{N}(0,1)$ distribution (solid black line). *The second plot*: Scatterplot of NPDE versus Time (days). *The third plot*: Scatterplot of NPDE versus individual predicted concentrations (IPRED). The dashed horizontal lines are the null line (NPDE = 0). The dot-dashed horizontal lines indicate the 90% range (NPDE = -1.645, 1.645). The dotted lines indicate the 95% range (NPDE = -1.96, 1.96). ESAMPLE was set at 10,000.

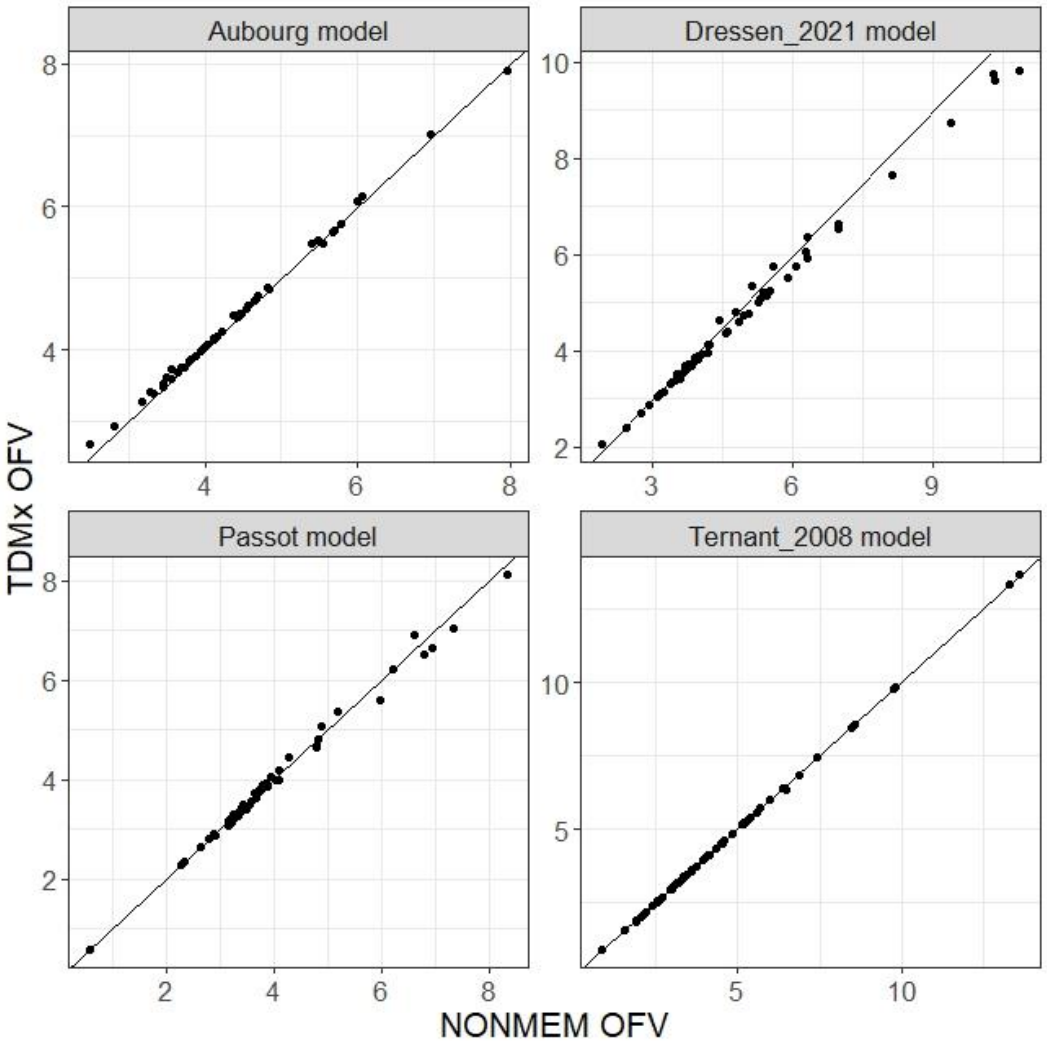
***Appendix D.*** *Statistical tests for evaluating normality of the normalised prediction distribution errors (NPDE) of the 18 candidate models.*

| Model | Wilcoxon test[1] | Fisher test[2] | Shapiro-Wilks test[3] | Global test[4] | Ranking[5] |
|---|---|---|---|---|---|
| Aubourg | 0.082 (*) | <0.0001 | 1 (.) | <0.0001 | 14 |
| Brandse_2016 | <0.0001 | 0.018 (**) | <0.0001 | <0.0001 | 7 |
| Brandse_2017 | 0.184 (.) | <0.0001 | 0.0005 | <0.0001 | 10 |
| Buurman | 0.019 (**) | 0.204 (.) | 1 (.) | 0.019 (**) | 1 |
| Dotan | <0.0001 | <0.0001 | 0.030 (**) | <0.0001 | 6 |
| Dreesen_2019 | <0.0001 | 0 | <0.0001 | 0 | 17 |
| Dreesen_2021 | <0.0001 | <0.0001 | 1 | <0.0001 | 9 |
| Edlund | <0.0001 | <0.0001 | 0.571 (.) | <0.0001 | 16 |
| Fasanmade_2009 | 0.001 | <0.0001 | 1 (.) | <0.0001 | 13 |
| Fasanmade_2011 | 0.001 | 0.001 | 0.0002 | 0.0002 | 2 |
| Grisic | 0.037 (**) | <0.0001 | 0.202 (.) | <0.0001 | 8 |
| Matsuoka | 0.689 (.) | 0.405 (.) | 0.0001 | 0.0001 | 3 |
| Passot | 0.521 (.) | <0.0001 | 1 (.) | <0.0001 | 4 |
| Petitcollin | <0.0001 | <0.0001 | 0.214(.) | <0.0001 | 12 |
| Ternant_2008 | 0.001 (***) | 0 | <0.0001 | 0 | 18 |
| Ternant_2015 | 0.110 (.) | <0.0001 | 0.695 (.) | <0.0001 | 15 |
| Ternant_2018 | 0.720 (.) | <0.0001 | 0.641 (.) | <0.0001 | 5 |
| Xu | 0.524 (.) | <0.0001 | 0.080 (*) | <0.0001 | 11 |

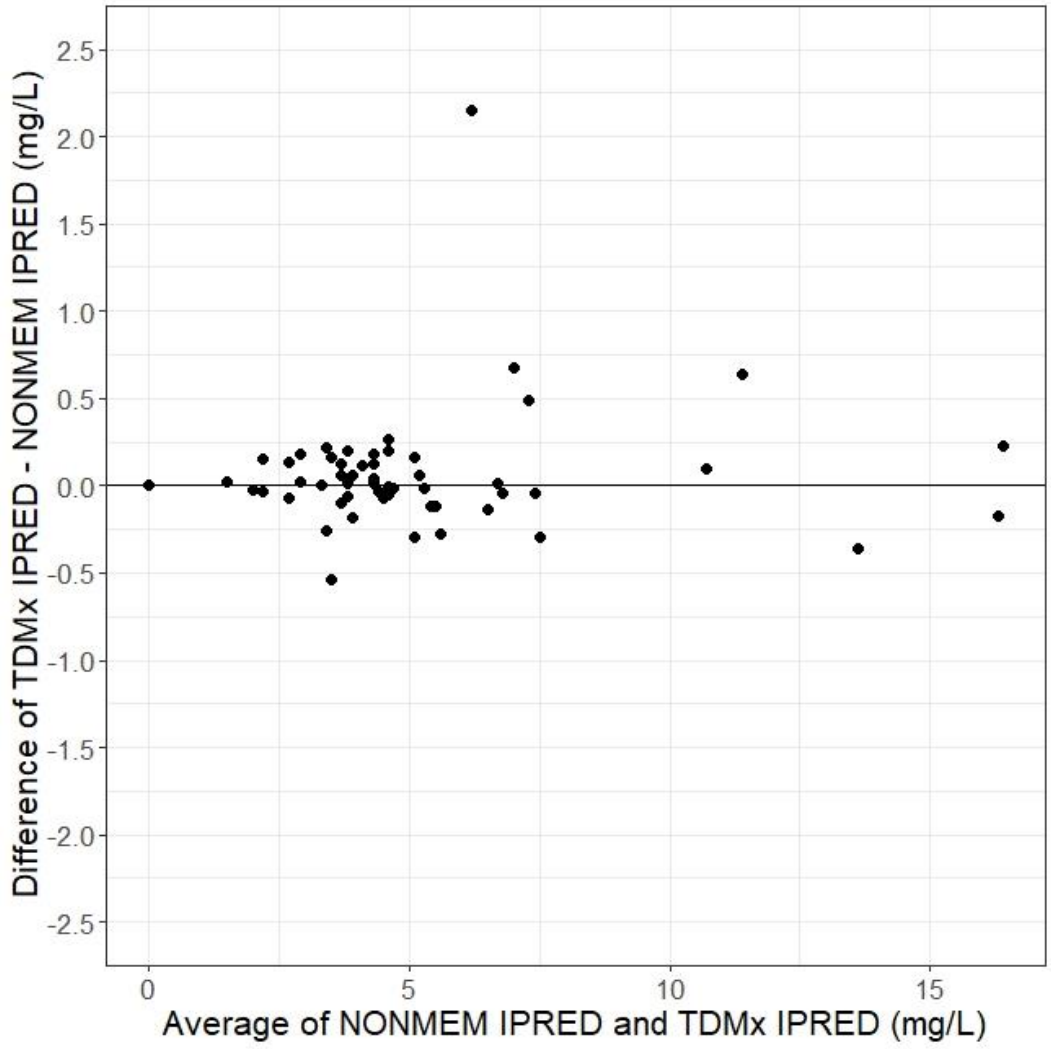
[1] Wilcoxon test compared the mean of the NPDE to 0.
[2] Fisher test compared the variance of the NPDE to 1.
[3] Shapiro-Wilks test compared the NPDE to the normal distribution.
[4] *P*-value of the global test was equal to the minimum of the adjusted *p*-values. The adjusted *p*-values are the raw *p*-value of the three individual tests multiplied by 3.
[5] Ranking based on the *p*-value of the global test (highest value to lowest value).
'.' >0.1; '*' >0.05; '**' >0.01; '***' >0.001, Significant levels indicate that the NPDEs are different from $\mathcal{N}(0,1)$ distribution for the specified tests.




***Appendix E.*** *Robustness of the model averaging algorithm (MAA; left) and the model selection algorithm (MSA; right) displayed through the relative root mean square error (rRMSE) and relative bias (rBias). The successively excluded models (according to the predictive performance metrics in various settings) are: Passot model, Aubourg model, Dreesen_2021 model, and Ternant_2008 model (from left to right). Three evaluated settings are a priori prediction using the patient covariates only; Bayesian forecasting (BF) using infliximab concentrations from one previous trough concentration ($TC_{-1}$), and two previous trough concentrations ($TC_{-1}$ and $TC_{-2}$). Whiskers cover the 95% confidence interval of the rBias calculated via the standard error.*




***Appendix F.*** Comparison of individual objective function values (OFV) of the four selected models using NONMEM or MIPD software 'TDMx' for *a posteriori* prediction of $TC_{+1}$ with one previous trough concentration ($TC_{-1}$). Each black circle represents the OFV of each patient. The diagonal line represents the identity line.




***Appendix G.*** *Bland-Altman plots showing the agreement between the predicted infliximab concentrations of the model averaging algorithm obtained from NONMEM and the TDMx software for a posteriori prediction of the* $TC_{+1}$ *with one previous trough concentration (*$TC_{-1}$*) across the range of the averaged predicted concentrations from both software tools.*

# Part II. Special populations

# A Model-Based Tool for Guiding Infliximab Induction Dosing to Maximise Long-Term Deep Remission in Children with Inflammatory Bowel Diseases

This chapter is based on

**Wannee Kantasiripitak**, Sebastian G. Wicha, Debby Thomas, Ilse Hoffman, Marc Ferrante, Séverine Vermeire, Karen van Hoeve, Erwin Dreesen. A model-based tool for guiding infliximab induction dosing to maximise long-term deep remission in children with inflammatory bowel diseases. [manuscript resubmitted]

## Abstract

**Background and aims** Adequate infliximab concentrations during induction treatment are predictive for deep remission (corticosteroid-free clinical and endoscopic remission) at six months in children with inflammatory bowel disease (IBD). Under standard infliximab induction dosing, children often have low infliximab trough concentrations. Model-informed precision dosing (MIPD) (i.e., model-based therapeutic drug monitoring) is advocated as a promising infliximab dosing strategy. We aimed to develop and validate an MIPD framework for guiding paediatric infliximab induction treatment.

**Methods** Data from 31 children with IBD (4 – 18 years) receiving standard infliximab induction dosing (5mg/kg at week [w]0, w2, and w6) were repurposed. Eight paediatric population pharmacokinetic models were evaluated. Modelling and simulation were used to identify exposure targets, an optimal sampling strategy, and develop a multi-model prediction algorithm for implementation into an MIPD software tool. A role for infliximab clearance monitoring was evaluated.

**Results** A 7.5mg/L infliximab concentration target at w12 was associated with 64% probability of deep remission at six months. With standard dosing, less than 80% of simulated children <40kg attained this target. The w12 target was most accurately and precisely achieved by implementing MIPD at w6 using the w6 infliximab concentration (rapid assay required). The multi-model algorithm outperformed single models when optimising the w6 dose based on both w2 and w4 concentrations. MIPD using only the w2 concentration resulted in biased and imprecise predictions. Infliximab clearances at w6 and w12 were predictive for deep remission.

**Conclusions** A freely available, multi-model MIPD tool facilitates infliximab induction dosing and improves deep remission rates in children with IBD.

## Introduction

Infliximab was the first licensed anti-tumour necrosis factor agent approved for use in children with Crohn's disease (CD) and ulcerative colitis (UC).[45] As for adults with inflammatory bowel disease (IBD), children generally receive 5 mg/kg weight-based infusions at weeks 0, 2, and 6 (induction) and every six to eight weeks thereafter (maintenance) according to the label.[45] Dosing of infliximab in children aged 6 to 17 years was approved based on two landmark phase 3 trials.[224,225] However, patients with a low bodyweight (including children) may be underdosed as evidenced by a population pharmacokinetic (popPK) analysis of one of these trials (**Figure 33**).[103] Currently, there is no recommendation on appropriate dosing schemes of infliximab in children to overcome the underdosing issue.

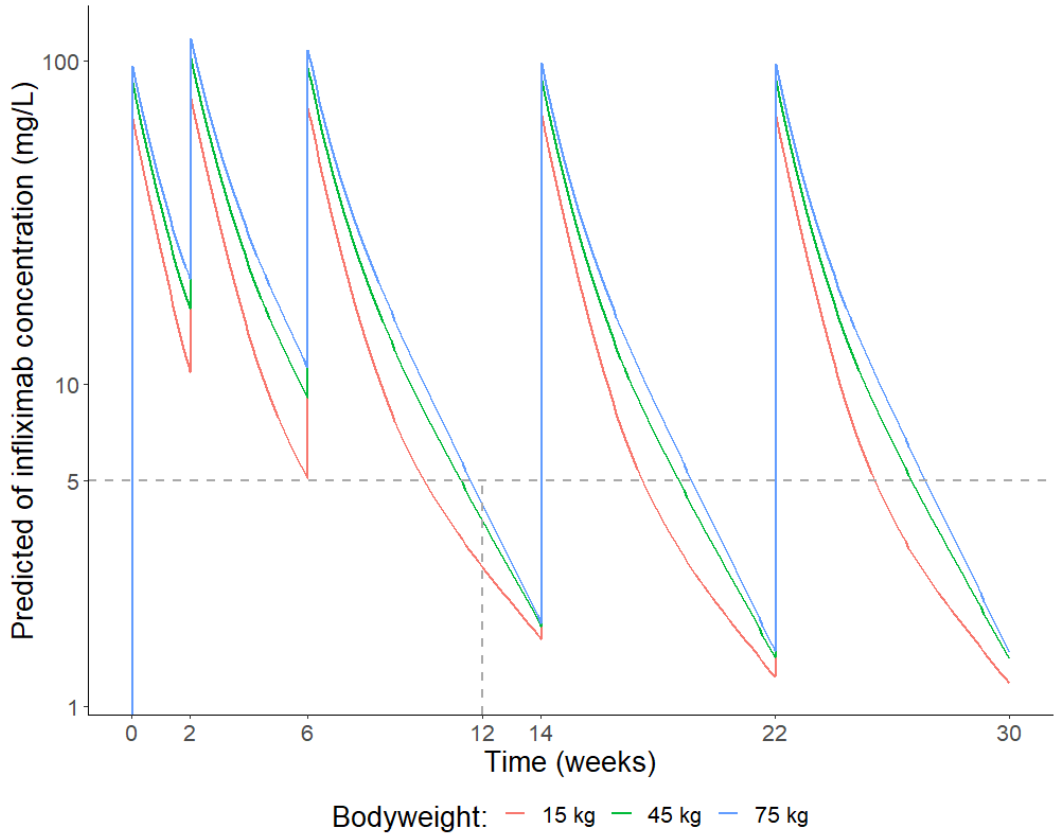



***Figure 33.*** *The simulated effect of bodyweight on the infliximab concentration-time profiles following the approved weight-based dosing regimen (5 mg/kg) from week 0 to week 30 using the model of Fasanmade et al. (combined paediatric and adult population model)4. Median and range of bodyweights observed in our UZ Leuven study cohort7 were simulated (15 kg [red line], 45 kg [green line], and 75 kg [blue line]). All other patient characteristics were set to median values of the model (serum albumin 41 g/L, without immunomodulator, and no antibodies to infliximab). Grey horizontal and vertical dashed lines indicate the previously proposed target concentration of 5.0 mg/L at week 12.7 Simulations were performed without inter-patient variability.*

Adequate infliximab concentrations during induction therapy in children with IBD have been shown to predict persistent long-term clinical and endoscopic remission.[108,226] van Hoeve *et al*. recently proposed a 5.0 mg/L target concentration at week 12.[110] The popPK simulations in **Figure 33** predict that most children do not reach this target under label dosing, which has unfortunately been confirmed by real-world observations.[108] Therefore, therapeutic drug monitoring (TDM) has been advocated to optimise infliximab induction dosing, whereby optimal concentration targets associated with desirable treatment outcomes can be better engaged.[32,118,227,228]

Conflicting reports on the clinical benefits of TDM in adult patients with IBD should not temper expectations in paediatric patients.[120–122] Assa *et al*. demonstrated that proactive TDM of adalimumab is superior to reactive TDM, resulting in higher sustained remission rates.[229] Recently, the PRECISION trial showed the benefit of utilising model-based TDM – also known as model-informed precision dosing (MIPD) – of infliximab in adult patients.[144] The success of MIPD in adult patients raises the question of whether this approach would also benefit children with IBD.

Moreover, we postulate that MIPD is preferable over TDM in the paediatric IBD setting since it provides better control of drug exposure, which is desirable, particularly in this vulnerable patient population.[77,230] MIPD involves the application of drug-specific popPK models using simultaneous integration of patient covariates (i.e., *a priori* prediction) and individual drug concentration measurements (i.e., *a posteriori prediction* or Bayesian forecasting). These models are implemented in software tools to predict optimal doses for individual patients.[149]

In this study, we aimed to develop and validate an MIPD framework to maximise the success of paediatric infliximab induction dosing by leveraging real-world data from a clinical trial. Also, we developed an MIPD software tool to inform decisions regarding optimal infliximab dosing hosted by TDMx.[196] Our tool is publicly available for stakeholders seeking to integrate innovative tools into their decision-making to improve the care of children with IBD.

## Methods

### *Clinical data*

Individual-level data of 31 patients on standard infliximab dosing (5 mg/kg at weeks 0, 2, and 6) from a prospective paediatric study[110] were repurposed for developing and validating an MIPD software tool. In this study, children aged 4 to 18 years with IBD started their first infliximab treatment for active luminal disease between May 2017 and May 2019. For a detailed description of the study cohort, we refer to the work by van Hoeve *et al*.[110] In brief, patients received standard infliximab induction treatment of 5 mg/kg infusions at weeks 0, 2, and 6. Infliximab concentrations were measured at peak (two hours after stop of the infusions), mid-dose (at weeks 1 and 4), and trough (right before the infusions at weeks 2, 6, and 12). To note, maintenance treatment started at week 12 instead of week 14 (the standard induction schedule) in all patients to decrease the risk of underexposure at the fourth infusion.[108,118] Infliximab concentrations were measured using the RIDASCREEN® IFX Monitoring enzyme-linked immunosorbent assay (apDia, Turnhout, Belgium) with a lower limit of quantification of 0.3 mg/L. Antibodies to infliximab (ATI) were only quantified in samples with an undetectable infliximab concentration using an in-house developed drug-sensitive anti-infliximab bridging assay (limit of quantification at 5.0 mg/L MA-IFX10F9 equivalents).[231]

Patient characteristics (age, sex, bodyweight, and IBD type), clinical disease activity (paediatric Crohn's disease activity index [PCDAI] for CD[232] or paediatric ulcerative colitis activity index [PUCAI] for UC[233]), standard laboratory tests (including serum albumin, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], complete blood count, and iron panel), and co-medications were collected at every visit. Missing covariate data were handled using single imputation with the last observation carried forward, representing a feasible working strategy for handling missing data in real-world practice. Single imputation with the last observation carried forward was used for the three patients with missing week 1 and/or week 4 data.

Active luminal disease at baseline was proven with endoscopic activity indices (simple endoscopic score for Crohn's disease [SES-CD] >3 for CD and Mayo endoscopic subscore ≥2 for UC).[13,234–236] Treatment success was assessed as deep remission, defined as combined systemic corticosteroid-free clinical remission (PCDAI or PUCAI of <10)[237,238] and endoscopic remission (SES-CD <3 or Mayo endoscopic subscore of 0)[13,26,234–236] six months after the start of infliximab treatment. All endoscopies were re-evaluated at 24 ±2 weeks. Endoscopies were performed by two paediatric gastroenterologists (IH and KVH) who were blinded to the PK results at the time of the endoscopy.

***Exposure target identification***

The predictive ability of a range of measured exposure metrics for the probability of attaining deep remission was investigated. These exposure metrics included the measured infliximab concentrations and the areas under the individually measured infliximab concentration-time curves (AUCs). The AUCs were calculated using noncompartmental analysis (*ubiquity* R package[239]) with peak and trough samples (both taken at the scheduled infusion visits), either with or without the mid-cycle samples.

The predictive ability was assessed using (i) the Wilcoxon rank-sum test for univariable analysis of unpaired continuous variables ($p \leq 0.05$), (ii) logistic regression Markov models with an Emax function to describe the relationship between the exposure metrics and the probability of attaining deep remission ($p \leq 0.05$; objective function values [OFV] drops ≥3.84 from base model), and (iii) receiver operating characteristic (ROC) analysis to assess classification performance (95% confidence interval [CI] of the area under the ROC curve [AUROC] computed by Delong's method not including 0.5). A higher median of AUROC was considered a better classification performance. Then, exposure targets with an optimal probability of deep remission were identified based on the developed model and subsequently used as exposure targets for MIPD. The probability of deep remission was calculated as

$$Probability\ of\ deep\ remission\ = E_{max} \times \frac{infliximab\ exposure\ metric}{infliximab\ exposure\ metric + EX_{50}}$$ *Equation 14*

with $E_{max}$ and $EX_{50}$ representing the maximum probability of attaining the deep remission and the estimated values of an infliximab exposure metric (concentration or AUC) corresponding to a 50% probability of attaining the deep remission, respectively. Odd's ratios and their 95% CI for attaining deep remission when these exposure targets were met were calculated (*epitools* R package[240]). If the 95%CI includes 1 meaning that reaching the target was not associated with attaining deep remission.

***PopPK model identification and evaluation***

A literature review was conducted in PubMed from January 1996 until January 2022 to identify popPK models describing the infliximab PK in paediatric patients with IBD. The query was (infliximab) AND (model) AND (pharmacokinetics) AND (inflammatory bowel disease) AND ((children) OR (paediatric)). Articles were screened in full text for eligibility.

The infliximab concentration-time profile of a typical patient in this study cohort was simulated with the identified models. Furthermore, the fit of the data to the identified models was visually inspected with goodness-of-fit plots (measured concentration versus predicted concentration and conditional weighted residuals versus time after dose).[131] Also, simulation-based evaluations were performed, including prediction-corrected visual predictive check (pcVPC) and normalised prediction distribution errors (NPDE).[195]

***Simulations***

A dataset containing 2,000 virtual children was generated. The virtual patients included 500 females with CD, 500 females with UC, 500 males with CD, and 500 males with UC. Each group of 500 patients was divided into ten subgroups of 50 patients with assigned bodyweight from 10 kg to 100 kg with an increment of 10 kg. Other biomarkers (including serum albumin, CRP, and ESR) were sampled from the variance-covariance matrix at each time point (weeks 0, 1, 2, 4, 6, and 12) as observed in our UZ Leuven study cohort[110] using multivariate normal distributions with bounds of the study dataset minimum and maximum values for each covariate (*dmutate* R package[241]). The impact of ATI was investigated. All identified popPK models were used for simulation and the predictions of models were averaged. Simulation scenarios included weight-based dosing regimens during induction treatment (at weeks 0, 2, 6): 5 mg/kg, 7.5 mg/kg, and 10 mg/kg infliximab with or without the use of immunomodulators. The probability of attaining the identified exposure target was compared between the different dosing regimens.

***MIPD approaches***

A single-model approach and two multi-model approaches using the models jointly (a model selection algorithm [MSA] and a model averaging algorithm [MAA], as previously described[193,242]) were evaluated. Predictions of multi-model approaches using different weighting schemes based on the OFV, the adjusted Akaike information criterion (AIC), and the sum of squared errors (SSEs), all obtained from Bayesian-estimated, individual concentration-time data, were compared.[193] Prediction using the MSA was based on the model with the highest weight, while prediction using the MAA was based on an ensemble of weighted predictions of all models. *A priori* and maximum *a posteriori* (MAP) predictions using both model approaches were compared regarding accuracy and precision of the predicted exposure metrics. For MAP prediction, the predictive performance of different sampling time points was also evaluated.

Relative bias (rBias) and relative root mean square error (rRMSE) were used to determine the bias and imprecision of the model-predicted versus measured infliximab concentrations, respectively. Clinical acceptability was defined as an rBias between ±20% with a 95% CI including zero.[193] No rRMSE acceptability threshold was prespecified (lower rRMSE indicated more precise predictions). The classification accuracy at the identified exposure targets was compared between the model approaches. A sensitivity analysis was performed to assess the impact of misspecification of the immunogenicity status.

### *Monitoring markers and their ability to predict treatment outcome*

The model-predicted exposure metrics (concentrations and AUCs), the estimated infliximab clearance, and observed biomarkers were evaluated as potential therapeutic monitoring markers. The differences in AUROC between the potential markers and the identified target were compared using Delong's method ($p \leq 0.05$). The model-predicted AUCs were calculated from predicted concentration-time profiles using the popPK models. Infliximab clearance was estimated using MAP prediction with the popPK models. The model-predicted exposure metrics and the model-estimated clearances of all models were averaged. Biomarkers included CRP, ESR, serum albumin, and the CRP/albumin ratio.[243]

### *Software implementation*

The popPK models were implemented in the TDMx software tool.[196] Performance of the paediatric infliximab module was cross-validated against NONMEM. The module can be used to obtain the estimated clearance and predicted exposure metrics, thus facilitating drug monitoring and MIPD in paediatric patients with IBD.

### *Software*

Predictions and simulations were performed using NONMEM (v7.5; Icon plc, Gaithersburg, MD, USA) with a GNU Fortran 95 compiler. All models were coded in NONMEM. Data were analysed in R (v4.0.3; R Foundation for Statistical Computing, R Core Team, Vienna, Austria) with the RStudio integrated development environment (v1.2.5001; RStudio, Inc., Boston, MA, USA).

### *Ethical statement*

The original study was approved by the Ethics Committee Research UZ/KU Leuven (S59870, April 10, 2017). All included patients and their parents provided written informed consent before inclusion.

## Results

### *Clinical data*

Patients' characteristics at the start of infliximab treatment are summarised in **Table 6**. Two patients below the age of six received off-label infliximab therapy, and their bodyweight was below the range reported in the landmark phase 3 trial.[224] A total of 251 infliximab concentrations were available with a median of eight samples per patient (range 6 to 10 samples per patient). One patient had undetectable infliximab concentrations (<0.3 mg/L) at weeks 6 and 12 but had no measurable ATI. At six months after start of the infliximab treatment, 58% (18/31) of the patients achieved deep remission.

### *Exposure target identification*

Measured infliximab concentrations at weeks 4, 6, and 12, and the $AUC_{w6\text{-}w12}$ were positively associated with deep remission at month 6 (**Table 7**). The measured infliximab concentration at week 12 was the best predictor and classifier for deep remission. An infliximab concentration at week 12 of 4.3 mg/L corresponded to a 50% probability of attaining deep remission. Based on the developed exposure-response model, the previously identified infliximab target concentration at week 12 of 5.0 mg/L[110] was associated with only a 54% probability of attaining deep remission. Therefore, a higher infliximab target at week 12 of 7.5 mg/L was now identified as a target associated with a more clinically relevant 64% probability of attaining deep remission (**Figure 34**). An infliximab concentration of 35.2 mg/L at week 4 and 13.5 mg/L at week 6 were also associated with a 64% probability of attaining deep remission, as was an $AUC_{w6\text{-}w12}$ of 1,685 mg×day/L. Patients who attained the identified target at weeks 4 and 12 were 6.1 (95%CI 1.2 – 31.2) and 8.6 (95%CI 1.5 – 51.2) times more likely to attain deep remission at six months, respectively. Whereas 95% CIs of odd ratios for patients who attained the identified target at week 6 and $AUC_{w6\text{-}w12}$ included 1: 4.0 (95%CI 0.9 – 18.8) and 8.8 (95%CI 0.9 – 83.4) times, respectively.

***Table 6.*** *Patients characteristics at the start of infliximab treatment (N=31).*

| **Characteristics** | |
|---|---|
| *Demographics* | |
| Sex, female, n (%) | 20 (65) |
| Age, years, median [range] | 14.0 [4.0 – 18.0] |
| Age at diagnosis, years, median [range] | 12.2 [3.5 – 16.5] |
| Bodyweight, kg, median [range] | 44 [15 – 76] |
| IBD type, CD:UC, n (%) | 20:11 (65:35) |
| *Biological characteristics* | |
| Serum albumin, g/L, median [IQR] | 43.0 [39.0 – 45.2] |
| CRP, mg/L, median [IQR] | 2.6 [0.6 – 6.0] |
| ESR, mm/h, median [IQR] | 15.0 [10.0 – 31.5] |
| *Paris classification*[244] | |
| *For CD patients* | |
| Age at diagnosis, A1a: A1b, n (%) | 6:14 (30:70) |
| Disease location, L1:L2:L3, n (%) | 7:6:7 (35:30:35) |
| Upper GI involvement, L4a: L4b, n (%) | 10:0 (50:0) |
| Disease behavior, B1:B2:B3, n (%) | 18:2:0 (90:10:0) |
| Perianal disease modifier, n (%) | 4 (20) |
| Growth, G0: G1, n (%) | 16:4 (80:20) |
| *For UC patients* | |
| Disease extent, E1:E2:E3:E4, n (%) | 0:5:0:6 (0:45:0:55) |
| Disease severity, S0:S1, n (%) | 9:2 (82:18) |
| *Disease activity score* | |
| *For CD patients* | |
| PCDAI, median [IQR] | 27.5 [20.0 – 30.6] |
| SES-CD, median [IQR], n (%)<br>with isolated ileal disease<br>without isolate ileal disease | <br>6 [4 – 8], 7 (35)<br>18 [11 – 20], 13 (65) |
| *For UC patients* | |
| PUCAI, median [IQR] | 50.0 [ 32.5 – 52.5] |
| Mayo endoscopic subscore, 2:3, n (%) | 7:4 (64:36) |
| *Systemic concomitant medication used* | |
| Corticosteroids, n (%) | 10 (32) |
| Immunomodulators, n (%) | 27 (87) |

CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal tract; IBD, inflammatory bowel disease; IQR, interquartile range; n, number; PCDAI, paediatric Crohn's disease activity index; PUCAI, paediatric ulcerative colitis activity index; SES-CD, simple endoscopic score for Crohn's disease; UC, ulcerative colitis.

***Table 7.*** *Infliximab exposure metrics associated with probability of attaining deep remission.*

| Infliximab exposure metrics | ΔOFV (*p*-value[a]) | Estimate of $EX_{50}$[b] (%RSE) | Bootstrap [95%CI][c] |
|---|---|---|---|
| *Measured infliximab concentrations* | | | |
| at week 4 | -5.498 (<0.05) | 19.8 mg/L (37%) | 19.7 [9.15 – 39.6] mg/L |
| at week 6 | -6.672 (<0.01) | 7.6 mg/L (40%) | 7.4 [3.3 – 15.3] mg/L |
| at week 12 | -9.304 (<0.01) | 4.3 mg/L (35%) | 4.2 [1.9 – 8.9] mg/L |
| *AUC* | | | |
| from week 6 to week 12 | -3.998 (<0.05) | 948 (mg×day/L) (35%) | 958 [432 – 1,836] (mg/L*day) |

AUC, areas under the infliximab concentration-time curve using noncompartmental analysis with all samples; CI, confidence interval; RSE, relative standard error; ΔOFV, the difference in the objective function value from the baseline model.
[a] *p*-value of the Chi-square distribution with 1 degree of freedom.
[b] Estimated values of infliximab exposure metric (concentration or AUC) corresponding to a 50% probability of attaining the deep remission.
[c] A total of 1,000 (100%) successfully minimised runs were used to calculate the median values of the parameter estimates and the 2.5th and 97.5th percentiles, defined by the lower and upper limits, respectively, of the 95% confidence interval for the final model parameter estimates.

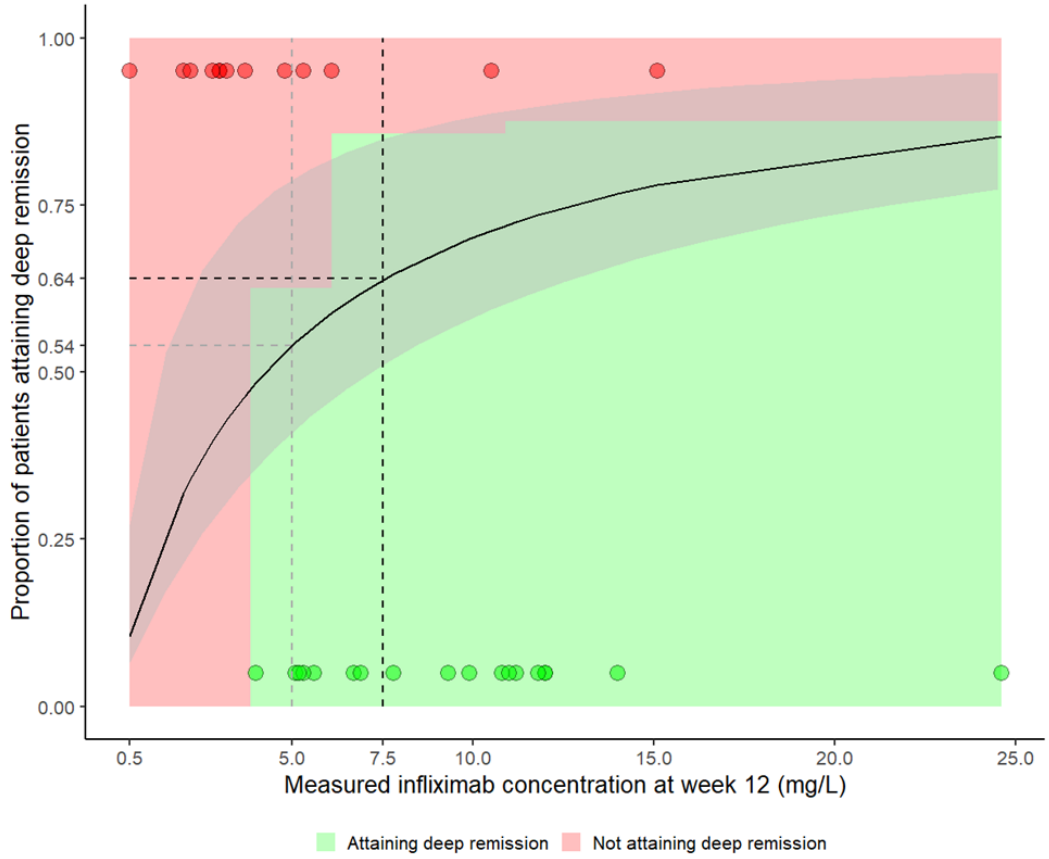



***Figure 34.*** *The goodness-of-fit plot of the logistic regression Markov exposure-response model. Observed (tiles) proportion of patients attaining (green) and not attaining (red) deep remission and predicted (solid black line) proportion of patients attaining deep remission as a function of the measured infliximab concentration at week 12 with a symmetric 95% confidence interval (grey shaded area). The grey horizontal and vertical dashed lines indicate the previously proposed infliximab target concentration at week 12 of 5.0 mg/L7 corresponding to a 54% probability of attaining deep remission. The black horizontal and vertical dashed lines indicate the newly identified infliximab target concentration at week 12 of 7.5 mg/L corresponding to a 64% probability of attaining deep remission. Circular shapes represent children attaining (green) and not attaining (red) deep remission.*

***Population pharmacokinetic model identification and evaluation***

Eight popPK models were identified (

**Table** 8). Four models were developed based solely on data from paediatric patients, while the other four were developed to describe data from combined paediatric and adult patients. Four models were developed based on data from patients with CD only and the other four were developed based on mixed UC and CD populations. Six were two-compartment models, while two were one-compartment models. Except for the Petitcollin model[245], all models identified bodyweight on both clearance and volume of distribution parameters. In addition to bodyweight, also IBD type, sex, albumin, ATI, and ESR were identified as covariates on clearance in one or more models.

The predicted infliximab concentration-time profiles of a typical patient differed noticeably between one- and two-compartment models, while the predicted profile differed marginally between IBD types using the Passot model[208] (**Figure 35**). Both one-compartment models (Passot model[208] and Petitcollin model[245]) underpredicted peak concentrations, while their predictions for trough concentrations were acceptable compared to those of the two-compartment models. Both Fasanmade models[103] (one based on paediatric data only and one based on combined adult and paediatric data) were identified as the popPK models with the highest predictive performance.

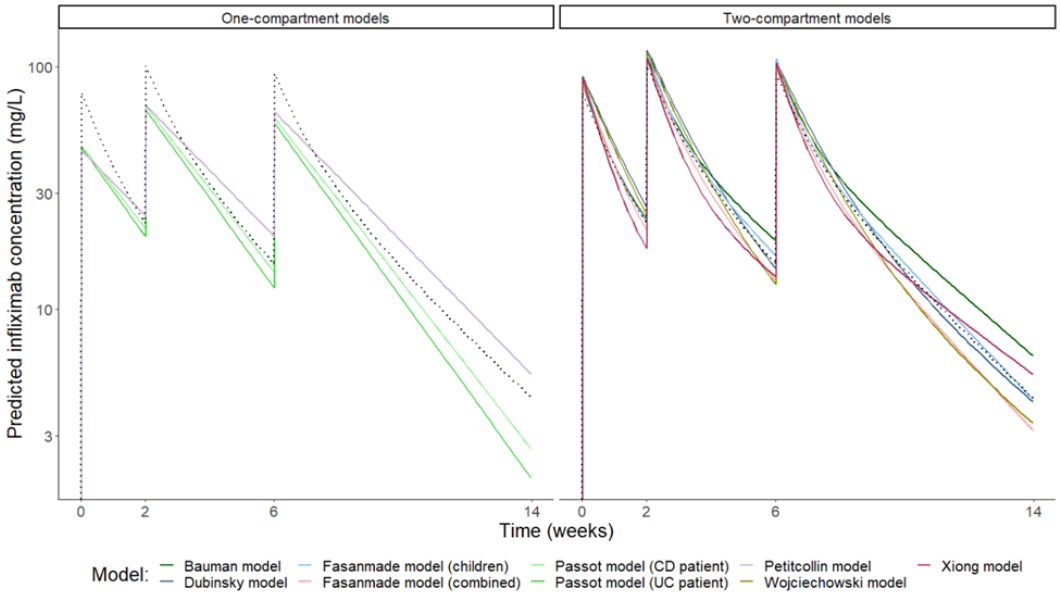



***Figure 35.*** *The predicted infliximab concentration (on log scale) versus time (day) of a typical patient in this study cohort (female patient, 14 years, bodyweight 44 kg, serum albumin 43.0 g/L, C-reactive protein 2.6 mg/L, erythrocyte sedimentation rate 15 mm/h, no antibodies to infliximab, receiving the label infliximab induction treatment combined with an immunomodulator). The one-compartment and two-compartment models are shown on the left (n=2) and on the right (n=6), respectively. Dotted lines represent the average of the predicted profiles from all models. Simulations were performed without inter-patient variability. CD, Crohn's disease; UC, ulcerative colitis.*

***Table 8.*** *Published population pharmacokinetic models describing the infliximab pharmacokinetics in paediatric patients with inflammatory bowel diseases.*

| Model | N | Population | IBD type | Treatment phase | Sampling time | Comp. | Covariate | Variable type of ATI | ATI Assay method |
|---|---|---|---|---|---|---|---|---|---|
| Bauman[246]* | 135 | children | CD, UC | maintenance | trough | 2 | CL: (+)WGT, (-)ALB, (+)ATI, (+)ESR<br>Vc: (+)WGT<br>Vp: (+)WGT<br>Q: (+)WGT | Dichotomous | Drug-tolerant |
| Dubinsky[247] | NS | children | CD, UC | NS | NS | 2 | CL: (+)WGT, (-)ALB, ATI (yes > no)<br>Vc: (+)WGT<br>Vp: (+)WGT<br>Q: (+)WGT | Dichotomous | Drug-sensitive |
| Fasanmade[103] | 112 | children | CD | induction, maintenance | peak, intermediate, trough | 2 | CL: (-)WGT,<br>(-)ALB<br>Vc: (-)WGT<br>Vp: (-)WGT | Not included | Drug-sensitive |
| Fasanmade[103] | 692 | children + adults | CD | induction, maintenance | peak, intermediate, trough | 2 | CL: (-)WGT, (-)ALB, ATI (yes > no),<br>IMM(use < no)<br>Vc: (-)WGT<br>Vp: (-)WGT | Dichotomous | Drug-sensitive |
| Passot[208] | 218 | children + adults<br>(≤15years, n=11) | inflammatory diseases<br>(CD, n=63<br>UC, n=16) | induction, maintenance | trough | 1 | CL: (+)WGT, IBD (UC > CD),<br>Sex (male > female)<br>Vc: (+)WGT, Age (at 15years cutoff),<br>IBD (UC > CD),<br>sex (male > female) | Not included<br>*Patients with ATI were not included in the analysis. | NS |
| Petitcollin[245] | 20 | children | CD | induction, maintenance | trough | 1 | CL: (-)ALB,<br>(+)risk of ATI | Risk function of time | Drug-sensitive |
| Wojciechowski[212] | 788 | children + adults<br>(<17years,<br>n=305) | inflammatory diseases<br>(CD, n=112<br>UC, n=543) | NS | NS | 2 | CL: (+)WGT, (-)ALB, ATI (yes > no)<br>Vc: (+)WGT<br>Vp: (+)WGT<br>Q: (+)WGT | Dichotomous | Different assay methods used |
| Xiong[248]* | 78 | children + young adults;<22 years | CD | induction, maintenance | peak, intermediate, trough | 2 | CL: (+)WGT, (-)ALB, (+)ATI,<br>(+)ESR, (+)nCD64<br>Vc: (+)WGT<br>Vp: (+)WGT<br>Q: (+)WGT | Continuous<br>LOQ (22 ng/mL)<br>ATI+ (> 22 ng/mL) | Drug-tolerant |

* Bauman model and Xiong model were used as normal models. Their error models were assumed to be proportional error models (i.e., exponent of reported additive error). ALB, serum albumin; CD, Crohn's disease; CL, clearance; Comp., number of compartments; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel diseases; IMM, immunomodulator use; LOQ, limit of quantification; N, number of patients; NS, not specified; nD64, neutrophil CD64 activity ratio; Q, inter-compartmental clearance; UC, ulcerative colitis; Vc, volume of distribution of the central compartment; Vp, volume of distribution of the peripheral compartment; WGT, bodyweight; +, positive association between continuous covariate and pharmacokinetic parameter; -, negative association between continuous covariate and pharmacokinetic parameter.

***Simulations***

With the label dose of 5 mg/kg, none of the virtual children with bodyweight 10 kg (approximate age of 1 year[249]) attained the identified target (**Figure 36**). Also, children with a bodyweight of 20 kg and 30 kg had probabilities of target attainment below 50% and below 80%, respectively. Children with bodyweight 40 kg and heavier (approximate age of 14 years and above[249]) had probabilities of target attainment above 80%.

Virtual children with a bodyweight of 10 kg reached a probability of target attainment above 80% after receiving 10 mg/kg infliximab. Children with bodyweight 20 kg and heavier reached probabilities of target attainment above 80% after receiving 7.5 mg/kg infliximab. Immunomodulator combo therapy only subtly improved the probability of target attainment.

The presence of ATI lowered the probability of target attainment considerably, particularly after receiving 5 mg/kg infliximab (**Figure 36**).

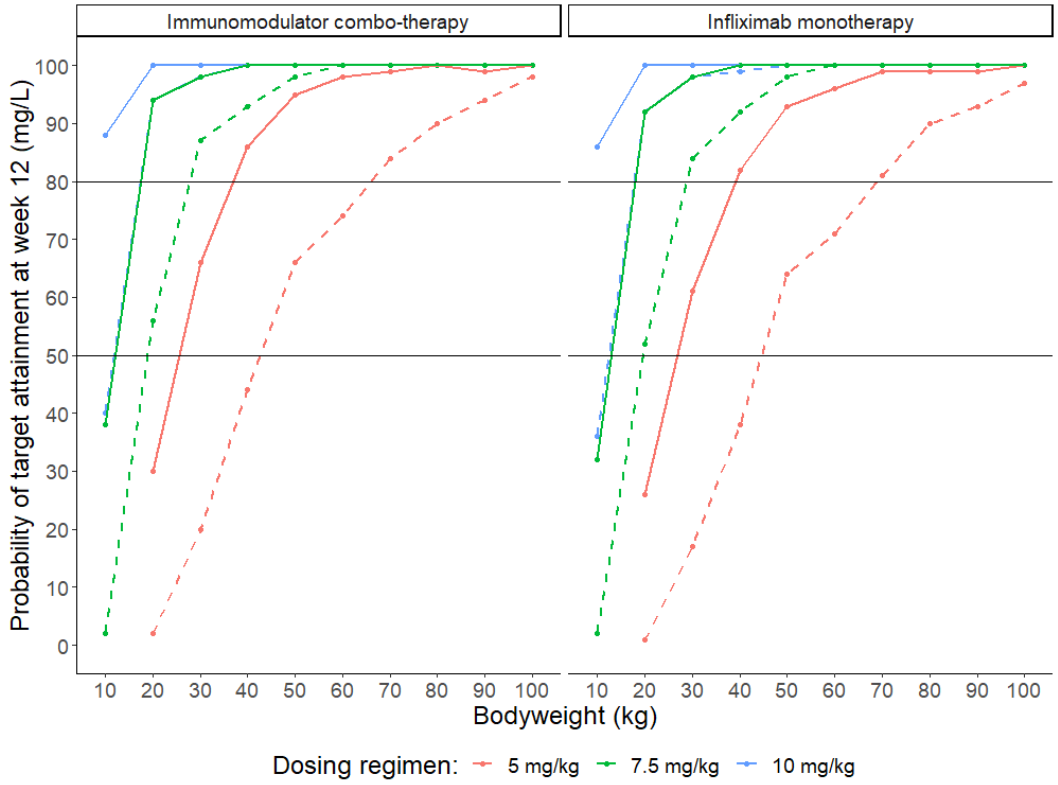



***Figure 36.*** *The probability of attaining the identified infliximab target concentration of 7.5 mg/L at week 12 after receiving 5 mg/kg (red), 7.5 mg/kg (green), and 10 mg/kg (blue) infliximab at weeks 0, 2 and 6 with or without the use of an immunomodulator. Immunogenicity status as absence and presence are presented with solid lines and dashed lines, respectively. Each dot represents the probability of target attainment based on 1000 virtual paediatric patients with IBD in the absence of antibodies to infliximab. Black horizontal lines reference 50% and 80% target attainment at week 12. Simulations were performed with inter-patient variability.*

### *MIPD approaches*

The performance metrics of the multi-model approaches using SSEs were better than the other weighting schemes. Therefore, SSEs were used in the following analyses (**Figure 37**).

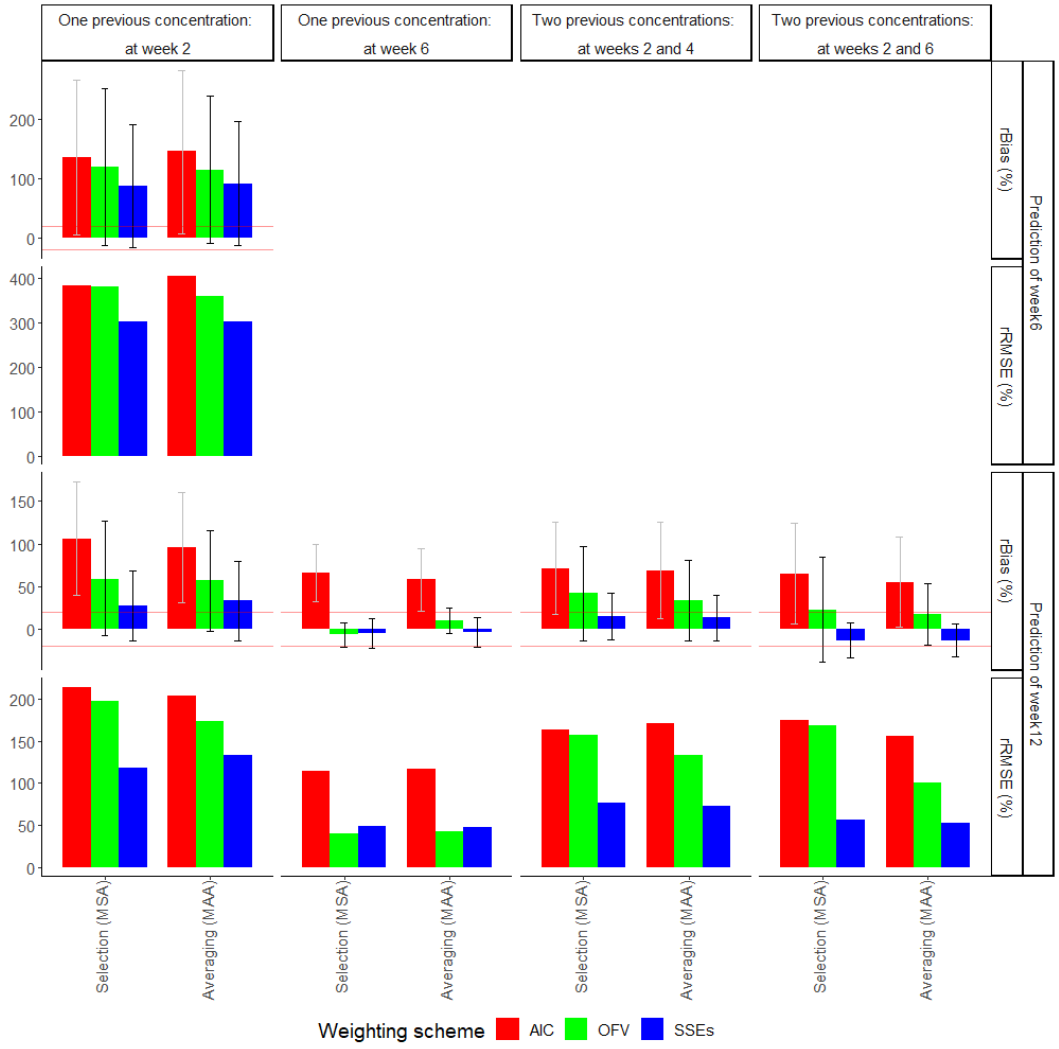



***Figure 37.****The predictive performances of the multi-model approaches using three different weighting schemes: an adjusted Akaike information criterion (AIC; red), objective function values (OFV; green), and the squared prediction errors (SSEs; blue). Whiskers indicate the 95% confidence interval (CI) of the relative bias calculated via the standard error (black whiskers indicate 95% CIs including 0). Horizontal red lines indicate ±20% range of the relative that is deemed clinically acceptable. MAA, model averaging algorithm; MSA, model selection algorithm; rBias, relative bias; rRMSE, relative root mean square error.*

The accuracy of the predicted week 6 infliximab trough concentration based on covariates (*a priori* prediction) or the trough concentration (MAP prediction) at week 2 was clinically unacceptable (**Figure 38**). The accuracy of the predicted week 12 infliximab concentration based on week 6 covariates was also highly biased and imprecise (rBias +31% to +175%, rRMSE 120% to 272%). MAP prediction using the trough concentration at week 6 resulted in a clinically acceptable prediction of the week 12 concentration. With an rBias of -4%, the MAA numerically outperformed the MSA (rBias -5%) and the single-model approach with any model (five out of eight had a clinically acceptable accuracy: rBias -18% to -6%). However, the rRMSEs remained high for all approaches (39% to 61%). Predicting the week 12 concentration not only using the week 6 but also the week 2 trough concentration reduced the predictive performances. Providing only the trough concentration at week 2 resulted in clinically acceptable predictions of the week 12 concentration using a single-model approach based on the Fasanmade model (combined)[103] and the Wojciechowski model[212]. Providing an additional intermediate concentration at week 4 to the trough concentration at week 2 improved predictions of the week 12 concentration using all single- and multi-model approaches. Across all the evaluated settings, the predictive performance of multi-model approaches was more consistent than that of the single-model approaches. Also, both multi-approaches performed equally well with the MAPs. The predictive performance of the MIPD model averaging algorithm was robust to misspecification of the patient's immunogenicity status.

To predict the trough concentration at week 12, MAPs providing the trough concentration at week 6 had significantly higher classification accuracy than without the trough concentration at week 6 (providing trough concentrations at weeks 2 and 4) (median 87 [interquartile range; IQR 82-90] % versus 76 [71-79] %, $p = 0.020$). However, their chances of a falsely predicted infliximab concentration at week 12 ≥7.5 mg/L (i.e., risk of loss of response) were not significantly different (MAPs providing week 6 concentration: median 7 [IQR 7-7] % versus week 2 and 4 concentrations: 13 [10-13] %, $p = 0.160$).

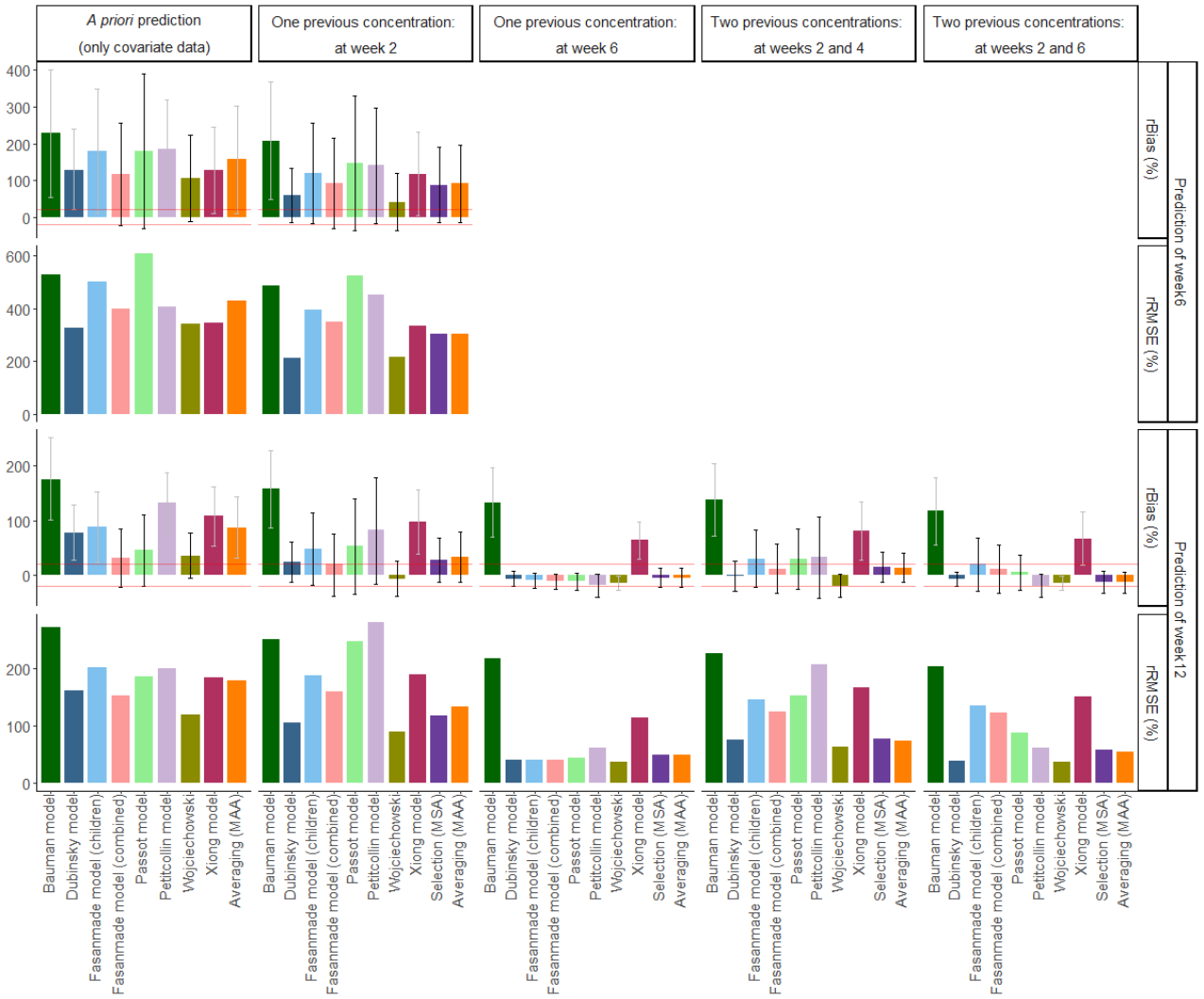



***Figure 38.*** *The predictive performance of eight single population pharmacokinetic models versus the multi-model approaches using all eight models for predicting the infliximab concentration at week 6 (top) and week 12 (bottom). Evaluated settings included a priori prediction (with only covariate data) and maximum a posteriori (MAP) prediction using covariate data and one previous concentration (at week 2, or week 6) or two previous concentrations (at weeks 2 and 4, or weeks 2 and 6). Whiskers indicate the 95% confidence interval (CI) of the relative bias calculated via the standard error (black whiskers indicate 95% CIs including 0). Horizontal red lines indicate the ±20% range of the relative bias that is deemed clinically acceptable. rBias, relative bias; rRMSE, relative root mean square error. Note: Model weights during a priori prediction are equal (1/number of models), precluding a model selection procedure in this setting.*

***Monitoring markers and their ability to predict treatment outcome***

As for the measured exposure metrics, also the multi-model averaged predicted infliximab concentrations at weeks 4, 6, and 12, and the $AUC_{w6\text{-}w12}$ were predictive for deep remission. The multi-model averaged estimates of the infliximab clearance at weeks 6 and 12 were significantly lower in patients who attained deep remission in comparison with patients who did not attain deep remission (week 6: median 0.202 [IQR 0.160-0.259] L/day versus 0.269 [0.244-0.315] L/day, $p$ = 0.020; week 12: 0.215 [0.158-0.240] L/day versus 0.243 [0.227-0.301] L/day, $p$ = 0.022). The AUROCs of multi-model averaged predicted exposure metrics and estimated clearances were not significantly different from the AUROC of the measured infliximab concentration at week 12 in classifying deep remission (**Figure 39**). None of the observed biomarkers (CRP, ESR, serum albumin, and the CRP/albumin ratio) was predictive for deep remission.

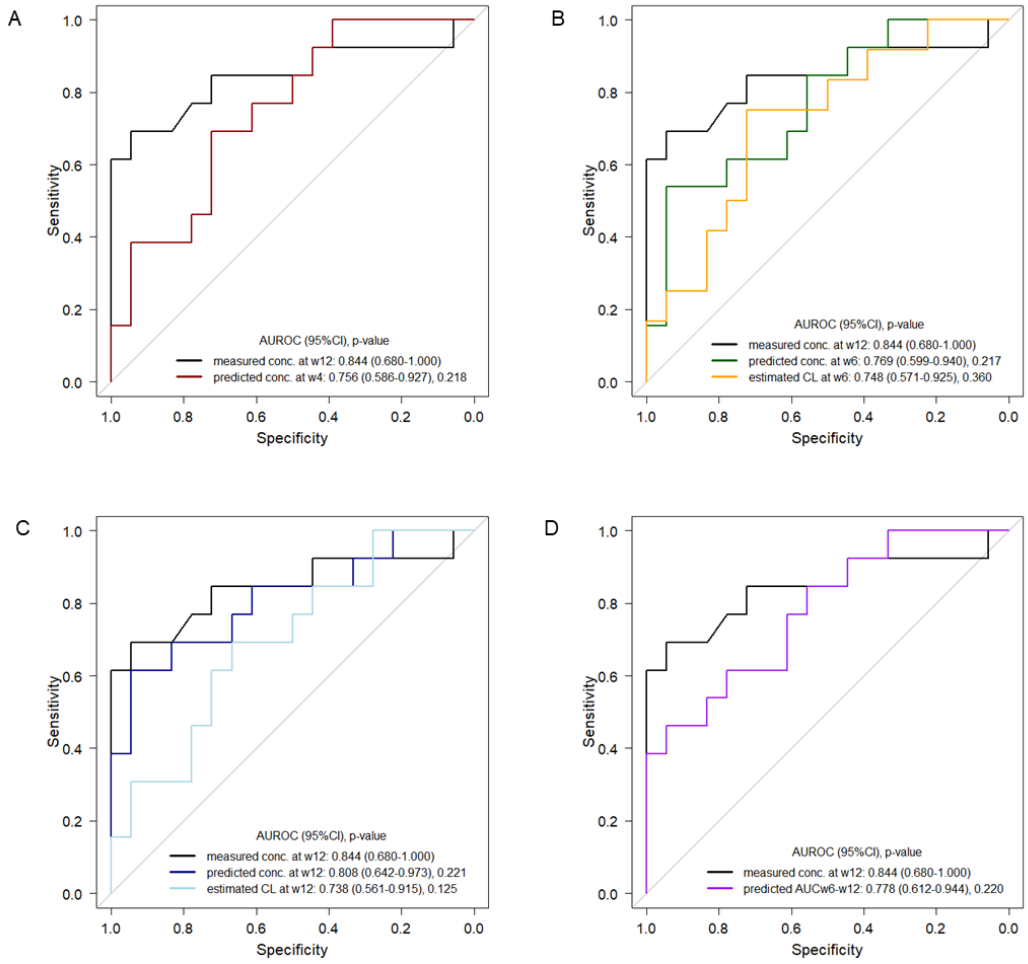



***Figure 39.*** *The receiver operating characteristic (ROC) curves representing the predictive performance of the model-predicted exposure metrics and/or the estimated infliximab clearance at week 4 (A), at week 6 (B), at week 12 (C), and from week 6 to week 12 (D) in comparison to the measured infliximab concentration at week 12 (black solid line). Gray diagonal lines represent the ROC curve of a random classifier. AUC, areas under the infliximab concentration-time curve; AUROC, area under the ROC curve; CI, confidence interval; CL, clearance; conc., concentration; w, week.*

***Software implementation***

Results of the model predictions using TDMx were in good agreement with NONMEM (MAP of the concentration at week 12 providing the trough concentration at week 6) (**Figure 40**). Infliximab module was added to TDMx: https://tdmx.shinyapps.io/Infliximab_paediatric/.

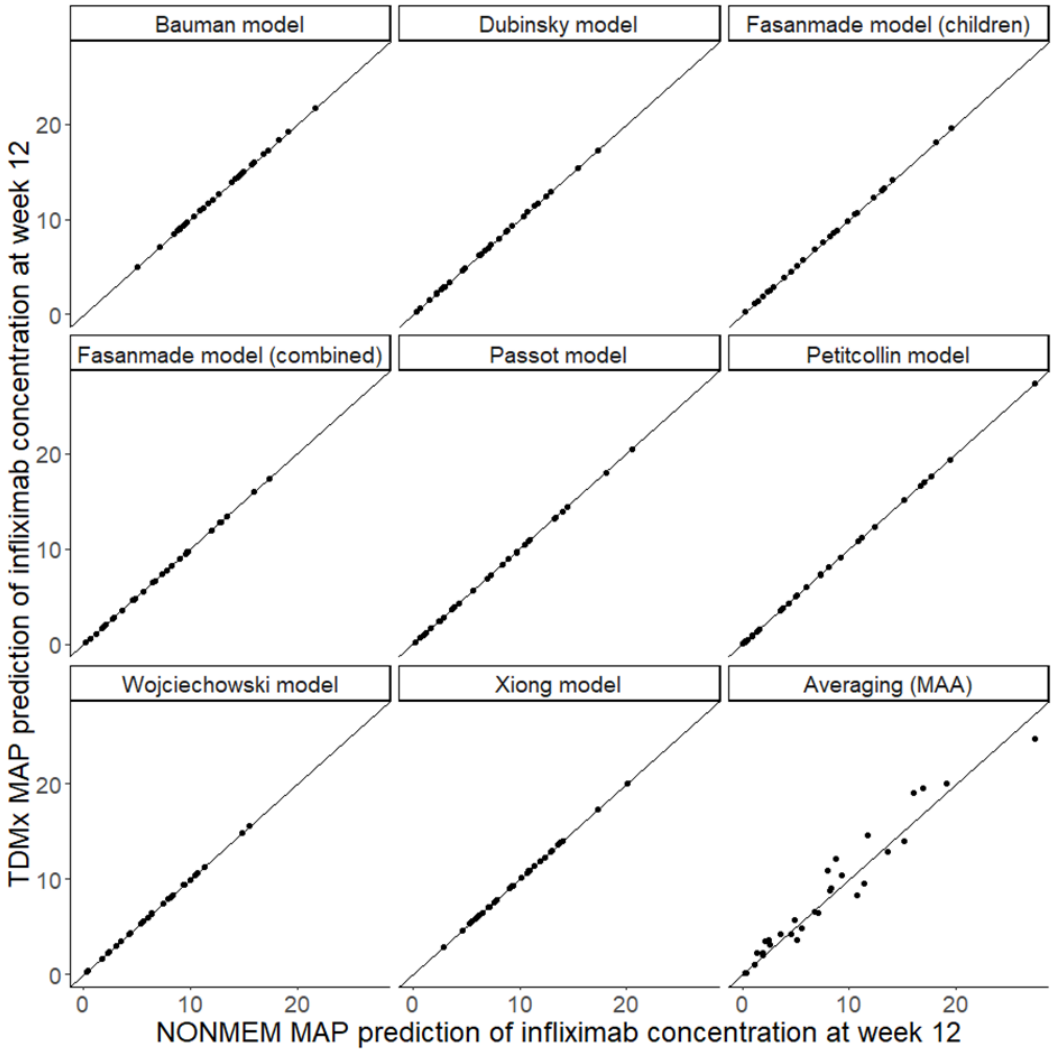



***Figure 40.*** *Comparison of maximum a posteriori (MAP) predictions of infliximab concentrations at week 12 (providing the trough concentration at week 6) from the eight population pharmacokinetic models and the model-averaging algorithm (MAA) using NONMEM (gold standard) and our TDMx software tool for MIPD. Each black circle represents the MAP prediction of a single patient (N=30). The diagonal line represents the identity line. Differences in MAP predictions between NONMEM and TDMx in the MAA scenario are due to small numerical differences in SSE that resulted in magnified differences in the individual model weight.*

## Discussion

Weight-based infliximab dosing of 5 mg/kg according to the label impedes adequate exposure in a significant proportion of children with IBD. MIPD has been advocated as the most promising strategy to guide dosing decisions. A recent real-world study reported the benefits of MIPD during induction treatment to minimise development of ATI and maintain effective infliximab monotherapy.[145] To allow stakeholders to investigate the merit of MIPD in these vulnerable patients, we have developed and validated an MIPD framework for guiding infliximab induction treatment in children with IBD.

The MIPD framework includes an exposure target with an optimised probability of deep remission, a sampling strategy with optimal prediction accuracy, a multi-model approach with improved accuracy, and a freely available MIPD software tool. The infliximab concentration at week 12 was identified as the best predictor of deep remission at six months. Instead of the previously reported target concentration of 5.0 mg/L[110], we propose a week 12 target of 7.5 mg/L, which is associated with an improved probability of attaining deep remission. With standard 5 mg/kg dosing, less than 80% of the simulated children with bodyweight below 40 kg (approximate age of 12 years and above[249]) attained the identified target. Our simulations showed that target attainment was compromised in patients with lower body weight. To increase the chance of target attainment at the specific moment of week 12, dose optimisation at week 6 using MIPD with only the trough concentration at week 6 was recommended. A rapid assay would be required to adjust the dose.[250] The week 2 infliximab concentration is still too close to the week 0 infusion (less than 1.5× the infliximab half-life) and is therefore not informative for the individual patient's clearance. At the start of infliximab treatment, all patients have high disease activity and infliximab clearance. Therefore, the clearance at the start of treatment is not predictive of treatment outcomes. Over the treatment course, some patients who attain remission have lower infliximab clearance than those who do not. Consequently, the predicted week 12 concentration is biased. We, therefore, recommend not to sample at week 2. Besides infliximab concentrations, also the estimated infliximab clearances at weeks 6 and 12 were found to predict deep remission and thus may be of interest to monitor in routine practice. A prospective confirmatory study is awaited. Our MIPD software tool allows early adoption of precision dosing and clearance monitoring during infliximab treatment in children with IBD.

Previous studies relied on ROC curve analysis to identify infliximab concentration cutoffs with optimal discriminatory performance. Since these cutoffs are not necessarily good target concentrations, we developed a logistic regression Markov exposure-response model to guide the identification of an infliximab concentration target based on the probability/rate of attaining deep remission that is deemed clinically realistic and acceptable. Our 7.5 mg/L infliximab target concentration at week 12 closely aligns with the identified target concentration of 7.0 mg/L at week 14 from the PANTS study.[251] On the one hand, this is because we raised the bar in terms of the envisioned deep remission rate

(64%). On the other hand, our considered treatment outcome was combined clinical and endoscopic remission, which requires higher infliximab concentrations as compared to clinical remission.[252] Unfortunately, evaluations of higher concentration targets and associated remission rates are not supported by our data. High-dose infliximab data are needed to identify the maximum remission rate achievable through exposure optimisation. Mechanistic failure rates are roughly estimated at 20 – 30%[253], meaning that 70 – 80% remission rates may be within reach with further dose escalations.

Xiong *et al*. recently identified a cumulative infliximab exposure AUC target throughout induction treatment ($AUC_{w0\text{-}w14}$) of 3,306 mg×day/L for surgery-free week 52 biochemical remission in children with CD.[248] We could not identify the $AUC_{w0\text{-}w14}$ target but instead found that the $AUC_{w6\text{-}w12}$ was identified to be associated with probability of deep remission. However, the $AUC_{w6\text{-}w12}$ was less predictive for deep remission than the concentration at week 12. Therefore, our study does not support the need for measuring infliximab peak concentrations for AUC calculation. Instead, we propose an MIPD approach with minimal sampling (only at week 6). A rapid assay is needed to allow adjustment of the week 6 dose guided by our MIPD software tool to accurately achieve the week 12 target concentration. In line with findings in the adult patients (TAILORIX)[204], CRP and serum albumin were not identified as biomarkers with any relevant clinical predictive value. Therefore, we conclude that concentration monitoring is more relevant than biomarker monitoring in children with IBD. However, a lack of statistical power may explain why we were not able to identify predictivity of the biomarkers for deep remission. Also, faecal calprotectin (a more disease-specific marker) was not measured in our study cohort.

The weight-based infliximab dosing regimen practised in adults is not deemed appropriate for children.[77,143] Adult-to-paediatric extrapolation requires a consensus of the typical PK parameters in children as compared to adults. In contrast to small molecules, therapeutic proteins have nonlinear relationships between bodyweight and not only clearance (for small molecules) but also volume of distribution.[254,255] For infliximab, the first popPK analysis in children with IBD reported a comparable clearance (in mL/kg/day) and a higher peripheral volume of distribution (in L/kg) in comparison to adults.[103] Also, infliximab has a high degree of between-patient variability in PK. Therefore, MIPD may be utilised to predict the PK of infliximab in children and translate these predictions into one/more suggested dosing regimens with an optimal probability of attaining a clinically relevant target.[256]

The concept of clearance monitoring was recently introduced into the field of IBD by Petitcollin *et al*.[245,257] The infliximab clearance is an intrinsic patient characteristic, independent of the dosing regimen. It is a valuable predictor during dose optimisation when exposure is manipulated and thus loses its predictive ability for the outcome.[1] Also, the current European Crohn's and Colitis Organisation/European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines recommend infliximab clearance as a marker for the need for early proactive TDM.[227] Patients at risk for accelerated infliximab clearance during induction therapy were identified as children with a bodyweight <30 kg,

those with extensive disease, and those with low serum albumin.[118] In our study cohort, the role of clearance monitoring was also identified during the induction treatment of infliximab. However, its clinical and economic benefits still need to be confirmed.

Immunogenicity is known to be a major driver of infliximab PK. This we demonstrated in our weight-based dosing simulations, where the need for stratified dosing based on the patient's immunogenicity status was confirmed; Patients with ATI require higher infliximab dosing to attain the trough concentration target. However, the vast array of assay methods to quantify ATI, and the variety of implementation strategies across population PK models undermines the generalisability of our weight-based dosing recommendations for ATI-positive patients. Therefore, we also investigated MIPD (Bayesian forecasting) based on TDM samples. We found that the accuracy of MIPD is robust to misspecification of the patient's immunogenicity status. In other words, the availability of a single infliximab trough concentration can compensate for missing or incorrect information on the patient's immunogenicity status. This can be intuitively explained by the fact that the impact of ATI on the infliximab clearance is reflected in the infliximab concentration, meaning that these infliximab concentrations are a necessary and sufficient source of information to accurately account for the impact of immunogenicity, thereby making the use of an ATI assay in MIPD redundant. So, we conclude that MIPD is the preferred dosing strategy over stratified dosing, certainly when no ATI assay is available.

Strengths of our study include (i) the use of a dataset with rich PK sampling, (ii) the infliximab exposure target which is based on an evidence-based, fully parametric, predictive exposure-response model with minimal assumptions, (iii) the need for minimal PK sampling with a commercially available rapid assay, (iv) the robust MIPD qualification strategy not relying on a single popPK model but using a multi-model approach to reduce the burdensome fit-for-purpose assessment of individual models, (v) the used models built on both UC and CD cohorts in one tool which allows wide applicability across disease types. Regardless of differences in PK between patients with UC and CD, the algorithm can handle this by automatically adjusting the weights based on the individual patient's goodness-of-fit to the available TDM data. The more suitable models become stronger drivers of the predictions and dose recommendations, and (vi) a freely available interactive MIPD software tool that handles complex calculations resulting in accurate dose recommendations.

There are limitations in our study. First, the sample size was relatively small. However, our cohort was not that small in relation to the 60 children with UC included in the registrational phase 3 trial (NCT00336492)[225]. Nevertheless, confirmation of the predictive performance of our exposure-response model and the MIPD algorithm in a validation dataset with a more diverse patient population that received a wider variety of dosing regimens would be valuable. To allow others to do so, we included all model codes in a Supplementary file. Second, SES-CD scoring was handled identically for all patients with CD, irrespective of disease location. However, patients with ileum-dominant and isolated colonic CD are

different in their probability of response to therapy, which highlights the need for separate endoscopic indices.[258] Third, only one probability of target attainment was selected to illustrate our methodology. However, we provided the formula so that readers can calculate a target for their chosen probability of target attainment. Fourth, in our study, anti-drug antibodies were quantified using a drug-sensitive assay. None of the patients had measurable anti-drug antibodies. Anti-drug antibodies may have been detected with a drug-tolerant assay. However, we decided to not use a drug-tolerant assay because they did not find their way into routine clinical practice (yet). Offering an MIPD tool that requires the use of a drug-tolerant assay would be less widely applicable. Certain questions about immunogenicity are still pending and require further investigation, but in our research, we focus on working with data that are widely available in routine clinical care, and not with research tools that are not (yet) available. Lastly, only dose change (and not interval change) was performed in the simulation study because the scenario was closest to the intervention performed in our own centre. However, user can perform any simulation they want (dose changes, interval changes) with the online tool we provide.

In conclusion, the success rate of infliximab induction therapy in children could be improved by measuring the infliximab concentration at week 6 using a rapid assay and adjusting the infliximab dose on the same day using our MIPD software tool, aiming for a 7.5 mg/L infliximab concentration at week 12. The infliximab clearance may be monitored as well by sampling again at week 12 or 14. Our MIPD software tool is freely available for stakeholders seeking to perform an innovative prospective clinic trial aiming at improved paediatric IBD care.

# The Effect of Aging on Infliximab Exposure and Response in Patients with Inflammatory Bowel Diseases

This chapter is published as

**Wannee Kantasiripitak**, Bram Verstockt, Dahham Alsoud, Triana Lobatón, Debby Thomas, Ann Gils, Séverine Vermeire, Marc Ferrante, Erwin Dreesen. The Effect of Aging on Infliximab Exposure and Response in Patients with Inflammatory Bowel Diseases. Br J Clin Pharmacol. 2021; 87:3776–3789. Article reproduced with permission from the journal that published Kantasiripitak *et al*.[259]

## Abstract

**Background & Aims** Controversies regarding infliximab treatment in elderly patients with inflammatory bowel diseases remain. We evaluated the effect of the patient's age on infliximab exposure, efficacy, and safety.

**Methods** Retrospective case-control data of patients receiving infliximab induction treatment were analysed. A population pharmacokinetic model was developed to estimate individual pharmacokinetic parameters. A logistic regression model was used to investigate the effect of exposure on endoscopic remission. Repeated time-to-event models were developed to describe the hazard of safety events over time.

**Results** A total of 104 patients (46 elderly; ≥65 years) were included. A two-compartment population pharmacokinetic model with linear elimination adequately described the data. Infliximab clearance decreased with older age, higher serum albumin, lower fat-free mass, lower C-reactive protein, and absence of immunogenicity. Yet, infliximab exposure was not significantly different between the elderly and non-elderly. Regardless of age, an infliximab trough concentration at week 14 of 15.6 mg/L was associated with a 50% probability of attaining endoscopic remission between week 6 and week 22. Infliximab exposure during induction treatment was not a risk factor for (serious) adverse events. The hazard of serious adverse events and malignancy increased by 2% and 7%, respectively, with an increasing year of age. Concomitant immunomodulator use increased the hazard of infection by 958%, regardless of age.

**Conclusions** Elderly patients attained infliximab exposure and endoscopic remission similarly to non-elderly patients. Therefore, the same infliximab trough concentration target can be used in therapeutic drug monitoring. The hazards of serious adverse events and malignancy increased with age, but not with infliximab exposure.

## Introduction

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic and incurable inflammatory diseases of the gastrointestinal tract.[260] The burden of IBD is rising globally as a result of a substantial increase in their prevalence.[261] The prevalence continues to rise due to increasing rates of diagnosis, population ageing, and extended longevity. In 2017, the global peak prevalence rate of IBD occurred at 60-64 years of age in females and 70 – 74 years of age in males.[17] In addition, elderly patients, variably defined as patients older than 60 or 65 years, represent 10%-30% of all patients with IBD and 10%-15% of new diagnoses.[37,262] Consequently, the increasing number of elderly patients with IBD raises concerns about the efficacy and safety of the approved treatments.

For over two decades, biological drugs have revolutionised the management of IBD due to their efficacy and impact on the disease course.[263] The prototypic biological drug approved for IBD treatment is the anti-tumour necrosis factor-α (TNF-α) monoclonal antibody infliximab. In addition to clinical outcomes, infliximab is effective in inducing endoscopic remission in patients with IBD.[264] Endoscopic remission has emerged as an important treatment goal to lower the risk of surgery and hospitalisations and the need for systemic steroids.[25] Although therapeutic management of elderly patients with IBD mostly conforms with their younger counterparts, infliximab is less likely to be prescribed in the elderly.[265,266]

To date, the efficacy and safety of infliximab treatment in elderly patients with IBD remain controversial. The main reason is a lack of evidence due to the under-representation of elderly patients in clinical trials, leading to an unmatched trend with the real-world IBD population.[267,268] Therefore, more real-world data are needed on infliximab treatment in the elderly. Concerns about suboptimal effectiveness and increased risks of infection, malignancy, and mortality that are associated with infliximab exposure in the elderly population are still under debate.[269] Although numerous studies show an association between infliximab exposure and effectiveness outcomes (not safety outcomes) in adult patients with IBD, this cannot be extrapolated to elderly patients due to potential confounding factors.[270,271]

Currently, the relationship between infliximab dose, exposure, effectiveness and safety outcomes in elderly patients with IBD have not been studied. Therefore, data regarding pharmacokinetic properties and the exposure-response relationship of infliximab in this population are needed. The present study aimed (i) to assess relationships between infliximab exposure and efficacy, as well as safety, in the elderly, and (ii) to evaluate the effect of age on infliximab exposure, efficacy, and safety of infliximab treatment.

## Methods

### *Study population*

Patients initiating infliximab treatment between March 2000 and July 2016 were obtained from an observational retrospective case-control study[79] and a single-centre database search at the University Hospitals Leuven, Belgium. All patients included in the analysis had given written consent to participate in the Institutional Review Board-approved IBD Biobank (B322201213950/S53684), whereby serum, biopsies, and clinical characteristics are collected prospectively on serial and pre-defined time points.

Patients with a confirmed diagnosis of IBD receiving infliximab treatment with weight-based dosing at weeks 0, 2, 6, and 14 were screened. Patients with at least one serum sample with detectable infliximab within the first 14 weeks of treatment (induction) were eligible for inclusion. Patients with unclassified IBD, pouchitis, and pyoderma gangrenosum without luminal disease were excluded.

The study population was divided into a non-elderly (age below 65 years) and elderly (age 65 or older) subgroup regarding the age at initiation of infliximab treatment.[272] Elderly-onset IBD were defined as a disease onset at the age of 60 years or older and adult-onset IBD were defined as a disease onset at the age below 60 years.[265]

### *Covariate data*

Time-invariant covariates (at the start of infliximab treatment) were age, being elderly, age at diagnosis, elderly-onset IBD, sex, IBD type (UC or CD), disease duration, disease location, disease extent, disease behaviour, previous IBD surgery, Charlson Comorbidity Index (patients with no comorbidity were defined as the Charlson Comorbidity Index equal to 0), and smoking status.[273,274]

Time-varying covariates (throughout the infliximab treatment) were body weight, body mass index, fat-free mass[275], serum albumin, C-reactive protein (CRP), concomitant medication (systemic corticosteroids and/or immunomodulators), and antibodies to infliximab (ATI).

Missing time-invariant covariates were imputed using multivariable multiple imputations by chained equations assuming data to be missing completely at random. Missing time-varying covariates were imputed using univariable single imputation within the patient. For individuals with a missing time-varying covariate at all time points, imputation with the median of the available covariate data of other patients per time point was used.

***Dosing and sampling scheme***

Infliximab was administered intravenously with weight-based dosing at weeks 0, 2, 6, and 14. Serum samples were collected at trough (i.e., right before the infliximab infusion at weeks 2, 6, and 14). Samples were stored at -20°C.[276]

***Analytical methods***

Infliximab serum concentrations were measured using an in-house developed and clinically validated direct enzyme-linked immunosorbent assay (ELISA), with lower limit of quantification 0.3 mg/L.[194] The lower limit of quantification was defined as the lowest concentration that could be accurately measured with a coefficient of variation ≤25%.[277] All samples with an infliximab concentration below 5.0 mg/L were measured for ATI with a drug-tolerant affinity capture elution (ACE) assay with lower limit of quantification of 70 µg/L MA-IFX10F9 equivalents (recovery of 98% and coefficient of variation of 13%).[231]

***Efficacy evaluation***

Patients that underwent lower endoscopy at baseline (within 20 weeks before the first infliximab infusion) and after two to four induction doses (between week 6 and week 22 of treatment) were included in the efficacy evaluation.

For patients with UC, endoscopic remission was defined as going from baseline Mayo endoscopic subscore 2 (moderate disease) or 3 (severe disease) to post-induction subscore 0 (inactive disease). Endoscopic improvement was defined as going from baseline Mayo endoscopic subscore 2 or 3 to post-induction subscore 0 or 1.[278]

For patients with CD, endoscopic remission was defined as the complete disappearance of ulcerations. Endoscopic improvement was defined as a clear endoscopic improvement but with ulceration still present.[279]

***Safety evaluation***

Adverse events (AEs) included no required hospital admission events such as mild infections, acute hypersensitive reactions, dermatological side effects, and others.

Severe adverse events (SAEs) included hospital admission due to infections (serious infections), malignancies, IBD-related surgery, IBD-related hospitalisations, side effects, and death.

Safety data were collected until two years after initiating infliximab treatment or until censoring due to infliximab discontinuation. The safety events were considered related to infliximab treatment when occurring within three months after the recorded day of infliximab treatment stop.

***Population pharmacokinetic model***

Different structural models were fitted to the infliximab pharmacokinetic data. Infliximab concentrations below the limit of quantification were accounted for using the M3 method.[280] First-order conditional estimation with interaction (FOCE-I) using the Laplacian method was used for parameter estimation with differential equation solver ADVAN6. All structural model parameters were assumed log-normally distributed. Two levels of random effects were estimated: interindividual variability and residual variability.

Relationships between pharmacokinetic parameters and covariates were considered in the covariate model. Pharmacokinetic parameters with an eta-shrinkage ≤20% were deemed acceptable for covariate testing.[281] Covariate effects were evaluated using stepwise covariate modelling with forward selection ($\alpha = 0.050$) and backward elimination ($\alpha = 0.010$). Continuous covariate values were centralised around the median population value and both power and exponential functions were tested.

***Exposure-response model***

Population pharmacokinetic and exposure-response modelling was performed sequentially. Empirical Bayes estimates of individual pharmacokinetic parameters were used to calculate individual infliximab exposure metrics (trough concentrations and cumulative areas under the infliximab concentration-time curve). The relationships between the infliximab exposure metrics and the individual observed endoscopic outcomes were assessed.

A logistic regression Emax model was developed to characterise the probability of attaining endoscopic outcomes. The first order (FO) method was used to approximate the likelihood of pooled data. Infliximab exposure metrics and other patient covariates were evaluated to affect remission and improvement probabilities.

***Repeated time-to-event model***

A parametric repeated time-to-event (RTTE) model was developed with FOCE-I using the Laplacian method and differential equation solver ADVAN6.[282] A constant hazard (exponential) model, a Weibull distribution hazard model, and a Gompertz distribution hazard model were evaluated. Censoring was set at two years after initiating infliximab treatment or three months after infliximab discontinuation. Interindividual variability on the hazard was estimated to describe how much the probable number of safety events varied between individuals. Subsequently, a stimulatory effect of infliximab exposure metrics was tested as an Emax function on the baseline hazard. Other potential covariates were univariately evaluated as significant risk factors on the probability of safety events.

***Model evaluation***

The most parsimonious model was selected based on model fit evaluations using standard goodness-of-fit diagnostics, the convergence of the minimisation criteria, the condition number of the model, physiological plausibility, and precision of the parameter estimates. Significance was identified as a ≥3.84-point drop in objective function value (OFV; $p \leq .050$, 1 degree of freedom). Visual predictive checks (VPCs) of the population pharmacokinetic and exposure-response models were performed with 1000 simulated replicates based on the selected models. Performance of the RTTE model was evaluated by a Kaplan-Meier VPC. Confidence intervals of parameter estimates were derived using sampling importance resampling (SIR).[283]

***Software***

Data were analysed in R (v3.6.1; R Foundation for Statistical Computing, R Core Team, Vienna, Austria) with the RStudio integrated development environment (v1.2.5001; RStudio, Inc., Boston, MA, USA). All nonlinear mixed-effects modelling and simulation were performed using NONMEM (v7.4; Icon plc, Gaithersburg, MD, USA) with a GNU Fortran 95 compiler and the Perl-speaks-NONMEM (PsN; v4.9.0) toolkit on the interface software Pirana (v2.9.9; Certara, Inc., Princeton, NJ, USA).

***Statistical analyses***

Descriptive statistics were stated as percentages for discrete variables and as median [interquartile range; IQR] for continuous variables. A complete case analysis was implemented to deal with missing endoscopy data. The Fisher exact test was used to analyse discrete variables. The Wilcoxon signed-rank test was used for paired measurements. Unpaired data were analysed with the Wilcoxon rank-sum test. The Jonckheere-Terpstra test was used to compare the trends of median values of time-varying covariates. Diagnostic performance was assessed with receiver operating characteristic curve (ROC) analysis. A therapeutic threshold value was selected using the Youden *J* statistic.[284] A two-sided P value ≤.050 denoted statistical significance. The *rateratio* function of the fmsb R package was used to calculate the incidence rate ratio and its 95% confidence intervals based on approximation.[285]

## Results

***Patient characteristics***

The study cohort included data from 104 patients (**Table 9**). Of these, 46 (44%) were elderly. Elderly patients had significantly lower body weight, fat-free mass, and serum albumin at baseline in comparison with the non-elderly patients. Throughout the study, serum albumin had a significantly increasing trend in both elderly and non-elderly patients ($p$ = 0.002 and $p$ <0.0001, respectively), while CRP had a significantly decreasing trend in both patient groups ($p$ = 0.0003 and $p$ <0.0001, respectively). The proportion of patients with ATI was not significantly different between elderly and non-elderly patients (13% versus 14%; $p$ =1.00).

***Population pharmacokinetic analysis***

*Base model*

Infliximab serum concentrations were obtained from 272 peripheral venepuncture samples (**Table 9**). Six samples (2%) had an infliximab serum concentration below the limit of quantification. Observed infliximab trough concentrations at weeks 2, 6, and 14 of the elderly were not significantly different from the non-elderly, as demonstrated in **Figure 41** ($p$ = 0.900, $p$ = 0.757, $p$ = 0.121, respectively). Our two-compartment model with linear elimination and interindividual variability on clearance (CL) and volume of distribution in the peripheral compartment ($V_p$) described the data better than a one-compartment model with linear elimination and interindividual variability on CL and volume of distribution in the central compartment ($V_c$) (Akaike information criterion 1324.6 points versus 1385.2 points, respectively) (**Table 10**). Residual variability was best described using a combined additive and proportional error model.

***Table 9.*** *Patient characteristics.*

| Parameter | <65 years | ≥65 years | Pooled | P value |
|---|---|---|---|---|
| Number of patients, n (%) | 58 (56) | 46 (44) | 104 | |
| *Baseline demographics* | | | | |
| Sex, female, n (%) | 27 (47) | 27 (59) | 54 (52) | 0.241 |
| Age, years, median [IQR] | 38 [28-52] | 69 [67-74] | 62 [38-68] | **<0.0001** |
| Body weight, kg, median [IQR] | 72 [62-80] | 64 [59-74] | 66 [60-78] | **0.033** |
| Body length, cm, median [IQR] | 172 [164-178], NA=3 | 164 [157-170], NA=3 | 168 [61-176], NA=6 | **0.0003** |
| Body mass index, kg/m$^2$, median [IQR] | 24.1 [21.0-27.4], NA=3 | 24.8 [21.9-27.6], NA=3 | 24.4 [21.4-27.6], NA=6 | 0.574 |
| Fat-free mass, kg, median [IQR] | 49.8 [40.4-60.0], NA=3 | 41.9 [38.5-51.0], NA=3 | 46.4 [39.7-58.1], NA=6 | **0.023** |
| IBD type, UC:CD, n (%) | 43:15 (74:26) | 22:24 (48:52) | 65:39 (62:38) | **0.008** |
| Age at diagnosis, years, median [IQR] | 29 [23-38] | 60 [48-69] | 41 [27-60] | **<0.0001** |
| Onset of disease, elderly-onset IBD, n (%) | 4 (7) | 24 (52) | 28 (27) | **<0.0001** |
| Disease duration, years, median [IQR] | 5 [2-12] | 9 [2-21] | 6 [2-18] | 0.133 |
| CD location[a], n (%) | | | | |
| Ileal disease (L1) | 6 (40) | 10 (42) | 16 (41) | 0.413 |
| Colonic disease (L2) | 2 (13) | 7 (29) | 9 (23) | |
| Ileocolonic disease (L3) | 7 (47) | 7 (29) | 14 (36) | |
| Upper gastrointestinal involvement (L4) | 0 (0) | 0 (0) | 0 (0) | |
| CD behavior[a], n (%) | | | | |
| Inflammatory (B1) | 4 (27) | 4 (17) | 8 (21) | 0.922 |
| Stricturing (B2) | 2 (13) | 6 (25) | 8 (21) | |
| Penetrating (B3) | 2 (13) | 3 (12) | 5 (13) | |
| Inflammatory + perianal disease (B1p) | 3 (20) | 4 (17) | 7 (18) | |
| Stricturing + perianal disease (B2p) | 4 (27) | 7 (29) | 11 (28) | |
| UC extension[a], n (%) | | | | |
| Proctitis (E1) | 1 (2) | 2 (9) | 3 (5) | 0.414 |
| Left-sided colitis (E2) | 17 (40) | 9 (41) | 26 (40) | |
| Extensive colitis (E3) | 25 (58) | 11 (50) | 36 (55) | |
| Extraintestinal manifestations, yes, n (%) | 14 (24) | 6 (13) | 20 (19) | 0.211 |
| Previous IBD surgery, yes, n (%) | 8 (14) | 18 (39) | 26 (25) | **0.006** |
| Charlson Comorbidity Index, >0, n (%) | 19 (33) | 31 (67) | 50 (48) | **0.001** |
| Active smoker, n (%) | 9 (16) | 3 (7) | 12 (12) | 0.219 |
| *Serology at baseline* | | | | |
| Serum albumin, g/L, median [IQR] | 42 [39-43], NA=21 | 38 [31-41], NA=1 | 40 [35-42], NA=22 | **0.0007** |
| C-reactive protein, mg/L, median [IQR] | 6 [3-24], NA=0 | 11 [4-23], NA=1 | 8 [3-23], NA=1 | 0.673 |
| *Concomitant medication* | | | | |
| Systemic corticosteroids, n (%) | 17 (29) | 12 (26) | 29 (28) | 0.827 |
| Immunomodulators, n (%) | 28 (48) | 12 (26) | 40 (38) | **0.026** |
| Systemic corticosteroids and immunomodulator, n (%) | 9 (16) | 3 (7) | 12 (12) | 0.219 |
| *Dosing during induction* | | | | |
| Infliximab dose, 5:10:combination of 5,10, mg/kg, n (%) | 49:7:2 (84:12:3) | 40:2:4 (87:4:9) | 89:9:6 (86:9:6) | 0.222 |
| Number of doses, 1:2:3:4, n (%) | 0:4:53:1 (0:7:91:2) | 0:6:39:1 (0:13:85:2) | 0:10:92:2 (0:10:88:2) | 0.514 |
| *Sampling* | | | | |
| Samples available, n (%) | 160 (59) | 112 (41) | 272 | |
| Samples per patient, 1:2:3 samples, n (%) | 4:6:48 (7:10:83) | 7:12:27 (15:26:59) | 11:18:75 (11:17:72) | **0.022** |
| Samples with undetectable infliximab, n (%) | 3 (2) | 3 (3) | 6 (2) | 0.693 |
| Samples with undetectable infliximab and with antibodies to infliximab, n (%) | 2 (67) | 3 (100) | 5 (83) | 1.00 |
| Samples with antibodies to infliximab, n (%) | 8 (5) | 8 (7) | 16 (6) | 0.602 |
| Patients with antibodies to infliximab, n (%) | 8 (14) | 6 (13) | 14 (13) | 1.00 |
| *Endoscopy* | | | | |
| Number of patients with endoscopic data, n (%) | 37 (64) | 20 (43) | 57 (55) | |
| IBD type of patients, UC:CD, n (%) | 37:0 (100:0) | 15:5 (75:25) | 52:5 (91:8) | **0.004** |
| Time of the baseline endoscopy, days, median [IQR] | -7 [-8, -1] | -6 [-28, -3] | -7 [-9, -1] | 0.375 |
| Time of the post-endoscopy, days, median [IQR] | 59 [56, 93] | 81 [56, 102] | 62 [56, 97] | 0.131 |
| Baseline Mayo endoscopic subscore, 2:3, n (%) | 21:16 (57:43) | 6:9 (40:60) | 27:25 (52:48) | 0.362 |
| Post-induction Mayo endoscopic subscore, 0:1:2:3, n (%) | 9:13:9:6 (24:35:24:16) | 2:3:4:6 (13:20:27:40) | 11:16:13:12 (21:31:25:23) | 0.299 |
| Patients with CD with presence of ulceration at baseline, n (%) | - | 5 (100) | 5 (100) | - |
| Patients with CD with endoscopic remission: endoscopic improvement: no improvement at postinduction lower endoscopy, n (%) | - | 3:1:1 (60:20:20) | 3:1:1 (60:20:20) | - |

[a] Following Montreal classification. [b] The Fisher exact test was used for the analysis of discrete variables. The Wilcoxon rank sum test was used for the analysis of continuous variables. A two-sided P value ≤.050 denoted statistical significance (bold entry). CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; n, number; NA, data not available (If NA not mentioned in the table, there was no missing data); UC, ulcerative colitis.

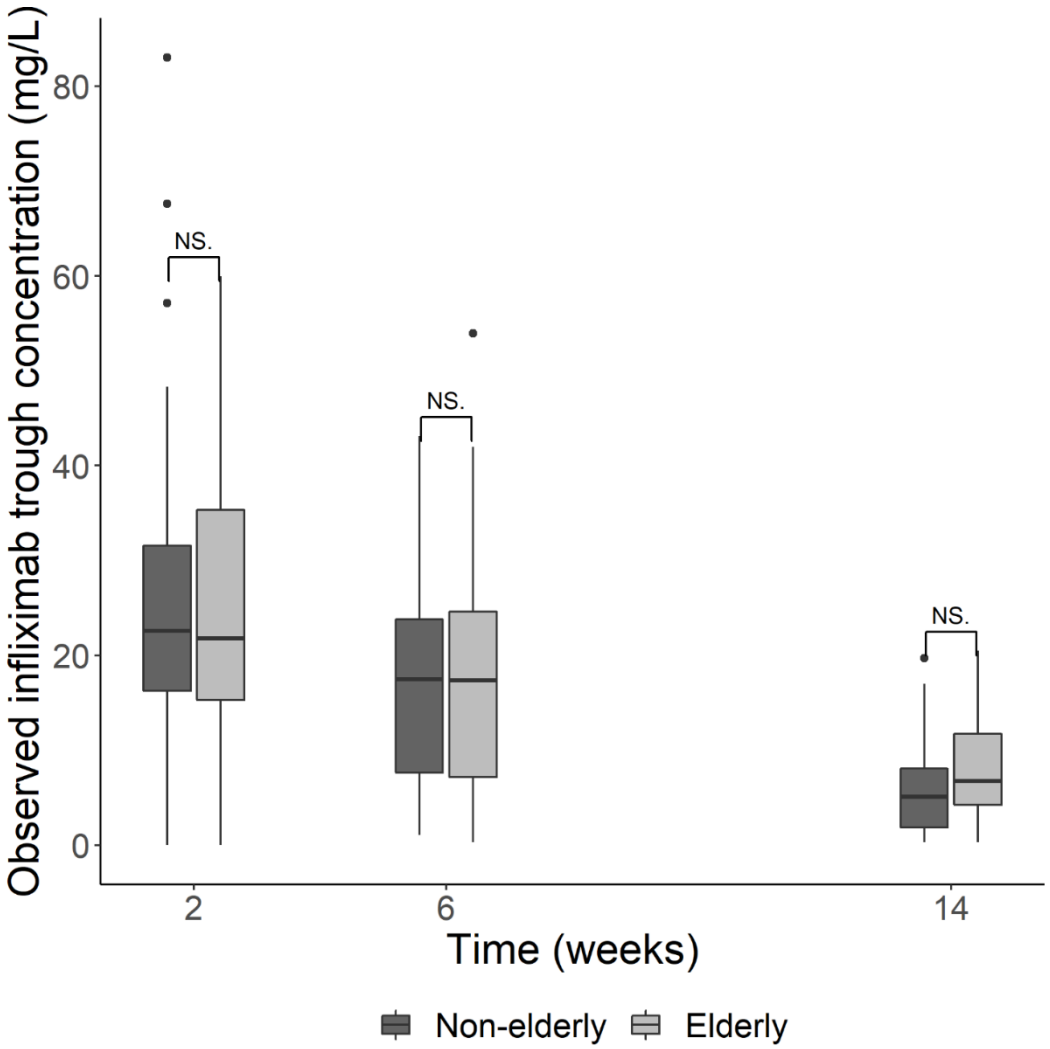



***Figure 41.*** *Comparison of observed infliximab trough concentrations during induction treatment (at weeks 2, 6, and 14) between elderly patients (age 65 or older) and non-elderly patients (age below 65 years). Tukey boxplots, Wilcoxon rank sum test. NS: not significant.*

***Table 10.*** *Base and final model parameter estimates.*

| **Parameter** | **Estimate (%RSE) [%shrinkage]** | **Estimate (%RSE) [%shrinkage]** | **SIR estimate[a] [95% CI]** |
|---|---|---|---|
| *Pharmacokinetic model* | Base model (OFV = 1308.553) | Final model (OFV = 1238.646) | |
| CL (L/day) | 0.334 (5.1) | 0.278 (5.3) | 0.283 [0.258-0.309] |
| Age on CL | - | -0.0054 (34.7) | -0.0050 [-0.0087 to -0.0013] |
| Baseline fat free mass on CL | - | 0.0121 (24.4) | 0.0123 [0.0063-0.0186] |
| Antibodies to infliximab on CL | - | 0.404 (35.9) | 0.414 [0.191-0.679] |
| Albumin on CL | - | -0.0392 (15.8) | -0.0387 [-0.0514 to -0.0267] |
| C-reactive protein on CL | - | 0.0029 (26.3) | 0.0030 [0.0011-0.0051] |
| $V_c$ (L) | 5.26 (7.7) | 5.03 (9.0) | 5.17 [4.55-5.88] |
| Q (L/day) | 0.0628 (12.2) | 0.0597 (13.0) | 0.0543 [0.0447-0.0671] |
| $V_p$ (L) | 3.33 (18.5) | 3.04 (24.7) | 2.74 [1.88-3.85] |
| IIV on CL (%CV) | 42.2 (9.2) [7] | 29.6 (17.0) [9] | 30.1 [25.5-34.4] |
| IIV on $V_p$ (%CV) | 86.3 (14.1) [67] | 81.5 (32.8) [67] | 80.8 [60.5-105.2] |
| Additive RUV (mg/L) | 1.38 (14.2) [19] | 1.24 (19.5) [20] | 1.18 [0.83-1.68] |
| Proportional RUV (%) | 0.263 (4.5) [19] | 0.269 (6.3) [20] | 0.270 [0.235-0.310] |

[a] Sampling importance resampling estimation (10000 final samples and a resample size of 1000) was used to calculate the median values of the parameter estimates and the 2.5th and 97.5th percentiles, defined by the lower and upper limits, respectively, of the 95% confidence interval for the final model parameter estimates. CI: confidence interval; CL: clearance; CV: coefficient of variation; IIV: interindividual variability; OFV: objective function value; Q: intercompartmental clearance; RSE: relative standard error; RUV: residual unexplained variability; SIR: sampling importance resampling; $V_c$: volume of distribution in the central compartment; $V_p$: volume of distribution in the peripheral compartment.

*Covariate analysis and final model*

Parameter-covariate relationships were only tested on clearance (eta-shrinkage 7%). Three time-invariant covariates (age and fat-free mass) and two time-varying covariates (serum albumin, CRP, and ATI) were withheld in the final model to explain interindividual variability in clearance. The infliximab clearance of patient *i* at time *j* ($CL_{i,j}$) was estimated in the final model from the following equation:

$$CL_{i,j} = 0.278 \times e^{-0.0054\times(AGE_i - 62)} \times e^{0.0121\times(FFM_i - 46.4)} \times e^{-0.0392\times(ALB_{i,j} - 41.21)} \times e^{0.0029\times(CRP_{i,j} - 4)} \times \left(1 + 0.404 \times ATI_{i,j}\right) \times e^{\eta_i} \quad \textit{Equation 15}$$

Where $\eta_i$ represents the deviation of the clearance of patient *i* from the typical population value, and ATI can be 0 or 1 indicating the absence or presence of ATI at some point during induction treatment, respectively. Infliximab clearance increased with increasing fat-free mass, increasing CRP, decreasing age, decreasing serum albumin, and the presence of ATI. The five included covariates explained 12.6% of the interindividual variability in infliximab clearance. Still, 29.6% of the variability remained unexplained. The prediction-corrected VPC plot shows a good agreement between model simulations and observed data (**Figure 42**).

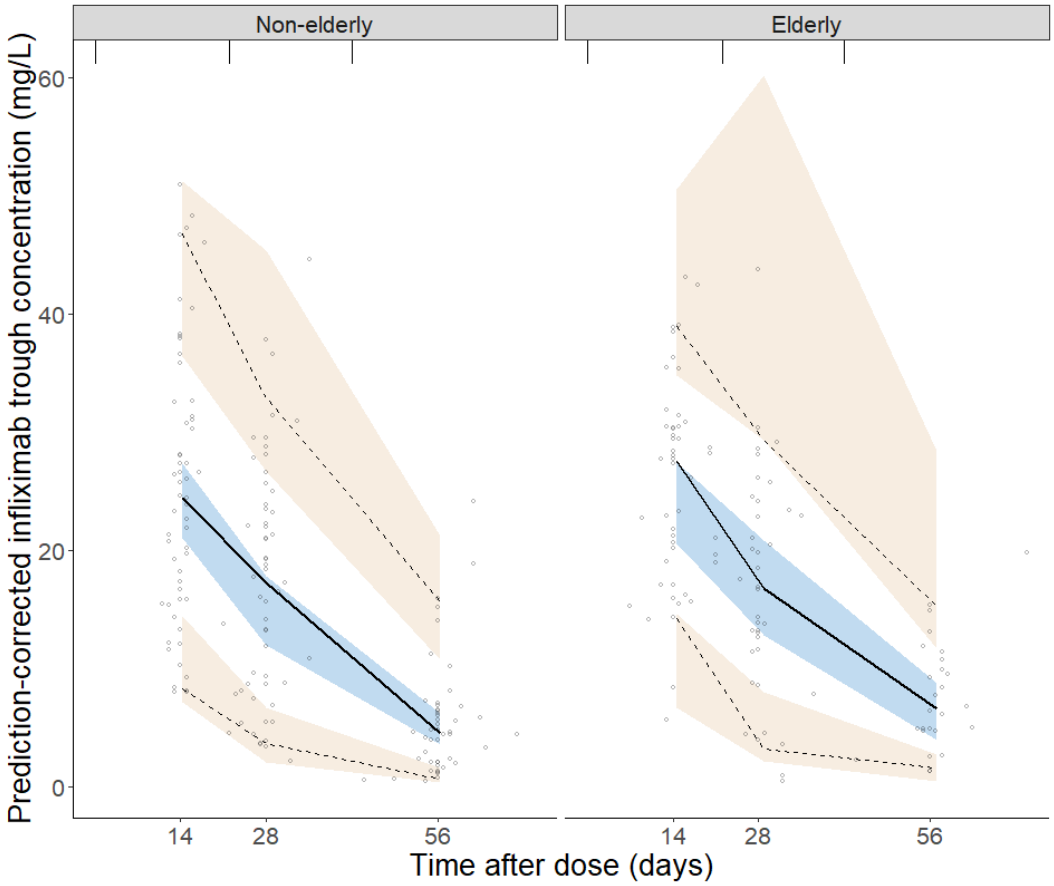



***Figure 42.*** *The prediction-corrected visual predictive check of the final population pharmacokinetics model stratified patients into elderly patient (age 65 or older) and non-elderly patient (age below 65 years). The observed infliximab concentrations are represented by black open circles. The solid black line is the median of the observed data. The dashed black lines are the 2.5th and 97.5th percentile of the observed data. The red and blue shaded areas indicate the 90% prediction intervals of the median and 2.5th and 97.5th percentile, respectively, of the simulated data (n = 1000).*

### *Exposure-response analysis*

A total of 57 patients (55%) underwent both baseline and post-induction lower endoscopies (**Table 9**). Of these patients, 14 (25%) attained endoscopic remission. The proportion of patients attaining endoscopic remission was not significantly different between elderly and non-elderly patients (25%, 5/20 versus 24%, 9/37; $p$ = 1.000). Endoscopic improvement was achieved in 31 patients (54%, 31/57) and no significant difference was observed between elderly and non-elderly patients (45%, 9/20 versus 59%, 22/37; $p$ = 0.405). The predicted infliximab trough concentration at week 14 of treatment was significantly higher in patients who attained endoscopic remission ($p$ = 0.025). A predicted infliximab trough concentration at week 14 was also the best marker of the probability of attaining endoscopic remission (lowest OFV) (**Table 11, Figure 43**). The value of Emax was estimated at 0.999 and was therefore fixed at 1. An infliximab trough concentration of 15.6 mg/L at week 14 corresponded to a 50% probability of attaining endoscopic remission ($E_{50}$) (95% confidence interval 8.6-31.1 mg/L). None of the covariates, including age and being elderly, were found to significantly affect the probability of attaining any of the endoscopic outcomes. Contrary to endoscopic remission, endoscopic improvement was not associated with infliximab exposure (data not shown).

The area under the ROC curve (AUROC) of the predicted infliximab trough concentration at week 14 as a marker for endoscopic remission was 0.699 (95% confidence interval 0.523 – 0.876). An infliximab trough concentration at week 14 of 8.6 mg/L was identified as a supposedly optimal therapeutic threshold (0.57 sensitivity, 0.81 specificity, 0.85 negative predictive value, and 0.50 positive predictive value).

***Table 11.*** *Infliximab exposure metrics and endoscopic remission models and their parameter estimates.*

| **Infliximab exposure-related metrics** | **OFV (ΔOFV)** | **Estimate of $E_{50}$[a] (%RSE)** |
|---|---|---|
| No effect of infliximab (baseline model) | 63.551 | 0.246<br>(23.2) |
| Infliximab trough concentration at week 14 (mg/L) | 58.320<br>**(-5.231*)** | 15.6<br>(32.9) |
| Cumulative area under the infliximab concentration-time curve up to the time of the post-induction lower endoscopy (mg/L·day) | 61.583<br>(-1.968) | 9140<br>(31.3) |
| Cumulative area under the infliximab concentration-time curve up to week 14 (mg/L·day) | 62.234<br>(-1.317) | 10200<br>(31.5) |
| Cumulative dose until the time of the post-induction lower endoscopy (mg) | 66.864<br>(3.313) | 3930<br>(32.6) |
| Infliximab concentration at the time of the post-induction lower endoscopy (mg/L) | 77.713<br>(14.162) | 64.9<br>(40.7) |

OFV: objective function value; ΔOFV: the difference in the objective function value from the baseline model; RSE: relative standard error. [a] Estimated values of infliximab exposure-related metrics corresponding to a 50% probability of attaining the endoscopic remission. * P ≤.050, 1 degree of freedom.

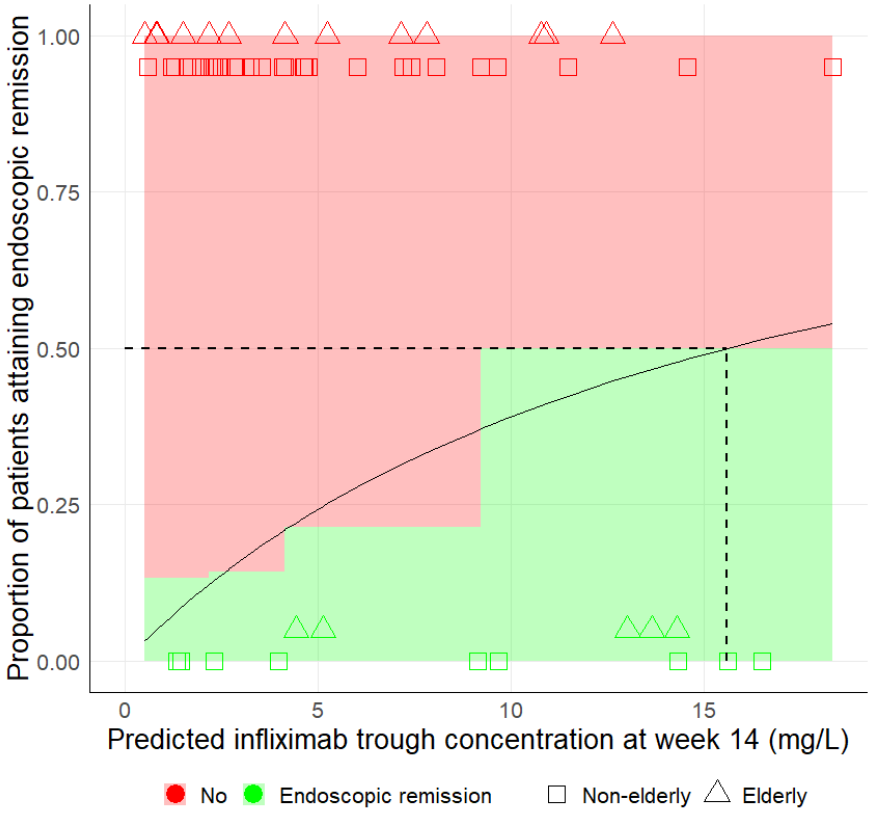



***Figure 43.*** *The goodness-of-fit plot of the logistic regression exposure–response model. Observed (tiles) proportion of patients attaining endoscopic remission (green) and not attaining endoscopic remission (red) and predicted (solid black line) proportion of patients attaining endoscopic remission as a function of the predicted infliximab trough concentration at week 14. The dashed lines indicate an infliximab trough concentration at week 14 of 15.6 mg/L corresponding to a 50% probability of attaining endoscopic remission. Triangular and square shapes represent elderly and non-elderly patients, respectively, attaining (green) and not attaining (red) endoscopic remission.*

### *Safety analysis*

*Safety data*

A total of 58 safety events were documented in 41/104 patients (39%, 19/41 occurred in elderly patients). Of the 58 safety events, 41 events (71%) were SAEs. The incidence rate of SAEs in the elderly compared with the non-elderly patients was significantly higher (incidence rate ratio 1.85, 95% confidence interval 1.00-3.41; $p$ = 0.046) as presented in **Table 12**. The proportion of patients who discontinued infliximab after induction treatment was significantly higher in the elderly than in the non-elderly (47%, 18/38 versus 20%, 11/54; $p$ = 0.011). Of the 18 elderly patients, five patients discontinued the treatment due to safety events (28%).

***Table 12.*** *Incidence rate ratio of safety events in elderly patients (age 65 or older) compared with non-elderly patients (age below 65 years).*

| | **<65 years (*n*=22)** | | **≥65 years (*n*=19)** | | **Pooled (*N*=41)** | | | |
|---|---|---|---|---|---|---|---|---|
| **Follow-up years**[a] | 83 | | 52 | | 135 | | **IRR**[b] **[95%CI]** | ***P* value**[c] |
| | n (%) | IR/100 py | n (%) | IR/100 py | n (%) | IR/100 py | | |
| *Type of AEs* | | | | | | | | |
| Total AEs | 12 | 14.5 | 5 | 9.6 | 17 | 12.6 | 0.6 [0.23, 1.89] | 0.440 |
| Mild infection | 7 (58) | 8.4 | 1 (20) | 1.9 | 8 (47) | 5.9 | 0.23 [0.03, 1.85] | 0.131 |
| Acute hypersensitive reactions | 3 (25) | 3.6 | - | - | 3 (18) | 2.2 | - | 0.170 |
| Dermatological side effects | 1 (8) | 1.2 | 1 (20) | 1.9 | 2 (12) | 1.5 | 1.60 [0.10, 25.52] | 0.740 |
| Other[d] | 1 (8) | 1.2 | 3 (60) | 5.8 | 4 (24) | 3.0 | 4.79 [0.50, 46.03] | 0.134 |
| *Type of SAEs* | | | | | | | | |
| Total SAEs | 19 | 22.9 | 22 | 42.3 | 41 | 30.4 | 1.85 [1.00, 3.41] | **0.046** |
| IBD-related hospitalisations | 9 (47) | 10.8 | 7 (32) | 13.5 | 16 (39) | 11.9 | 1.24 [0.46, 3.33] | 0.667 |
| IBD-related surgery | 4 (21) | 4.8 | 4 (18) | 7.7 | 8 (20) | 5.9 | 1.60 [0.40, 6.38] | 0.505 |
| Serious infection | 3 (16) | 3.6 | 3 (14) | 5.8 | 6 (15) | 4.4 | 1.60 [0.32, 7.91] | 0.563 |
| Malignancy | 1 (5) | 1.2 | 3 (14) | 5.8 | 4 (10) | 3.0 | 4.79 [0.50, 46.03] | 0.134 |
| Death[e] | - | - | 3 (14) | 5.8 | 3 (7) | 2.2 | - | **0.029** |
| Other[f] | 2 (11) | 2.4 | 2 (9) | 3.9 | 4 (10) | 3.0 | 1.60 [0.22, 11.33] | 0.637 |

AEs, adverse events; CI, confidence interval; IBD, inflammatory bowel disease; IQR, interquartile range; IR, incidence rate; IRR, incidence rate ratio; n, number; py, patient-years; SAEs, severe adverse events

[a] Follow-up years was defined as summation of follow-up time of all the patients from initiating of infliximab treatment until two years or until three months after infliximab discontinuation (in case of patients who discontinued first infliximab treatment before two years follow-up).

[b] Incidence rate (events per 100 patient-years) of different safety events in age group ≥ 65 years compared with age group < 65 years, expressed as incidence rate ratios.

[c] The significant probability of the result of null-hypothesis (incidence rate ratio equals to 1) was tested.

[d] Others included arthralgia and myalgia, IBD-associated arthropathy, anti-TNF-α induced neuropathy, and alopecia.

[e] Causes of the death incidences were cardiac congestive failure, ischaemic heart failure, and post-operative complications.

[f] Others included hospital admissions that were not related to inflammatory bowel disease.

*Repeated time-to-event analysis*

RTTE models were developed to describe infection, malignancy, combined infection and/or malignancy, and overall SAEs events over time. The median time of censoring was at 470 [225-730] days. Constant hazard baseline models were ample to describe infection, malignancy, and combined infection/malignancy events over time, while the overall SAEs over time were best described with a Weibull distribution hazard model (**Table 13**). The interindividual variability was estimated to be 160.3 %CV (percent coefficient of variation) in the hazard of combined events between patients and 107.2 %CV in the hazard of overall SAEs events between patients. Concomitant immunomodulator use was identified as a statistically significant risk factor for an infection event (ΔOFV = -13.384, $p$ <0.001) and a combined infection/malignancy event (ΔOFV = -5.078, $p$ <0.050). In case of concomitant immunomodulator use, the hazard of infection and combined infection/malignancy increased by 958% and 448% from the infliximab monotherapy, respectively. Age was a statistically significant risk factor for a malignancy event (ΔOFV = -4.855, $p$ <0.050) and an SAE (ΔOFV = -5.397, $p$ <0.050). The hazard of SAEs and malignancy increased by 2% and 7%, respectively, with an increasing year of age. None of the infliximab exposure metrics were found to be significant risk factors for the studied events (drop in OFV of less than 3.84 points).

***Table 13.*** *Parameter estimates of the final repeated time-to-event models for all infection, malignancy, and combined all infection and malignancy incidences.*

| Parameter | Estimate (%RSE) [%shrinkage] | Estimate (%RSE) [%shrinkage] | Median SIR[e] [95% CI] |
|---|---|---|---|
| *Infection event*[a] | Base model (OFV = 256.749) | Final model (OFV = 243.365) | |
| λ (1/day) | 0.00028 (27.5) | 0.00007 (71.2) | 0.00007 [0.00001-0.00020] |
| $\beta_{IMM}$ | - | 2.26 (33.8) | 2.21 [0.95-3.75] |
| *Malignancy event*[b] | Base model (OFV = 83.379) | Final model (OFV = 78.933) | |
| λ (1/day) | 0.00008 (49.7) | 0.00008 (52.4) | 0.00007 [0.00002-0.00018] |
| $\beta_{Age}$ | - | 0.0723 (35.3) | 0.0690 [0.0070-0.1469] |
| *Combined infection/ malignancy event*[c] | Base model (OFV = 313.784) | Final model (OFV = 308.706) | |
| λ (1/day) | 0.00011 (84.9) | 0.00006 (70.3) | 0.00006 [0.00001-0.00022] |
| IIV on λ (%CV) | 184.4 (36.6) [51] | 160.3 (41.6) [55] | 176.1 [45.9-307.8] |
| $\beta_{IMM}$ | - | 1.5 (36.7) | 1.4 [0.2-2.8] |
| *Overall SAEst*[d] | Base model (OFV = 640.016) | Final model (OFV = 634.619) | |
| λ (1/day) | 0.00026 (46.4) | 0.00036 (42.9) | 0.00035 [0.00013-0.00075] |
| γ (1/day) | 0.727 (12.3) | 0.734 (12.5) | 0.751 [0.540-0.985] |
| IIV on λ (%CV) | 117.9 (25.2) [46] | 107.2 (25.8) [49] | 117.5 [44.3-182.4] |
| $\beta_{Age}$ | - | 0.0266 (46.2) | 0.0275 [0.0068-0.0524] |

$\beta_{Age}$: proportional hazard covariate per year of age, scaled to age 62 years; $\beta_{IMM}$: proportional hazard covariate on baseline hazard for concomitant immunomodulators used relative to no used; CI: confidence interval; CV: coefficient of variation; γ: shape parameter of the Weibull distribution; IIV: interindividual variability; λ: baseline hazard; OFV: objective function value; RSE: relative standard error; SAEs, severe adverse events; SIR: sampling importance resampling.

[a] The hazard of the final model for all infection events was given by $h(t)=\lambda \cdot e^{\beta_{IMM} \cdot IMM}$, where IMM = 1 for concomitant immunomodulators used, and IMM = 0 for no concomitant immunomodulators used.

[b] The hazard of the final model for malignancy event was given by $h(t)=\lambda \cdot e^{\beta_{Age} \cdot (Age-62)}$, where age = patient's age in a year.

[c] The hazard of the final model for combined all infection and malignancy events was given by $h(t)=\lambda \cdot e^{\beta_{IMM} \cdot IMM} \cdot e^{\eta}$, where IMM = 1 for concomitant immunomodulators used, and IMM = 0 for no concomitant immunomodulators used η is a random effect describing a log-normal distribution of the hazard in the population.

[d] The hazard of the final model for overall SAEs event was given by $h(t)=\lambda\gamma(\lambda t)^{\gamma-1} \cdot e^{\beta_{Age} \cdot (Age-62)} \cdot e^{\eta}$, where age = patient's age in years, η is a random effect describing a log-normal distribution of the hazard in the population.

[e] Sampling importance resampling estimation (10000 final samples and a resample size of 1000) was used to calculate the median values of the parameter estimates and the 2.5th and 97.5th percentiles, defined by the lower and upper limits, respectively, of the 95% confidence interval for the final model parameter estimates.

Distributions of the infliximab exposure metrics in patients with each safety event are shown in **Figure 44**. The final models adequately described the observed Kaplan-Meier survival for the first, second, and third events over time (**Figure 45**).

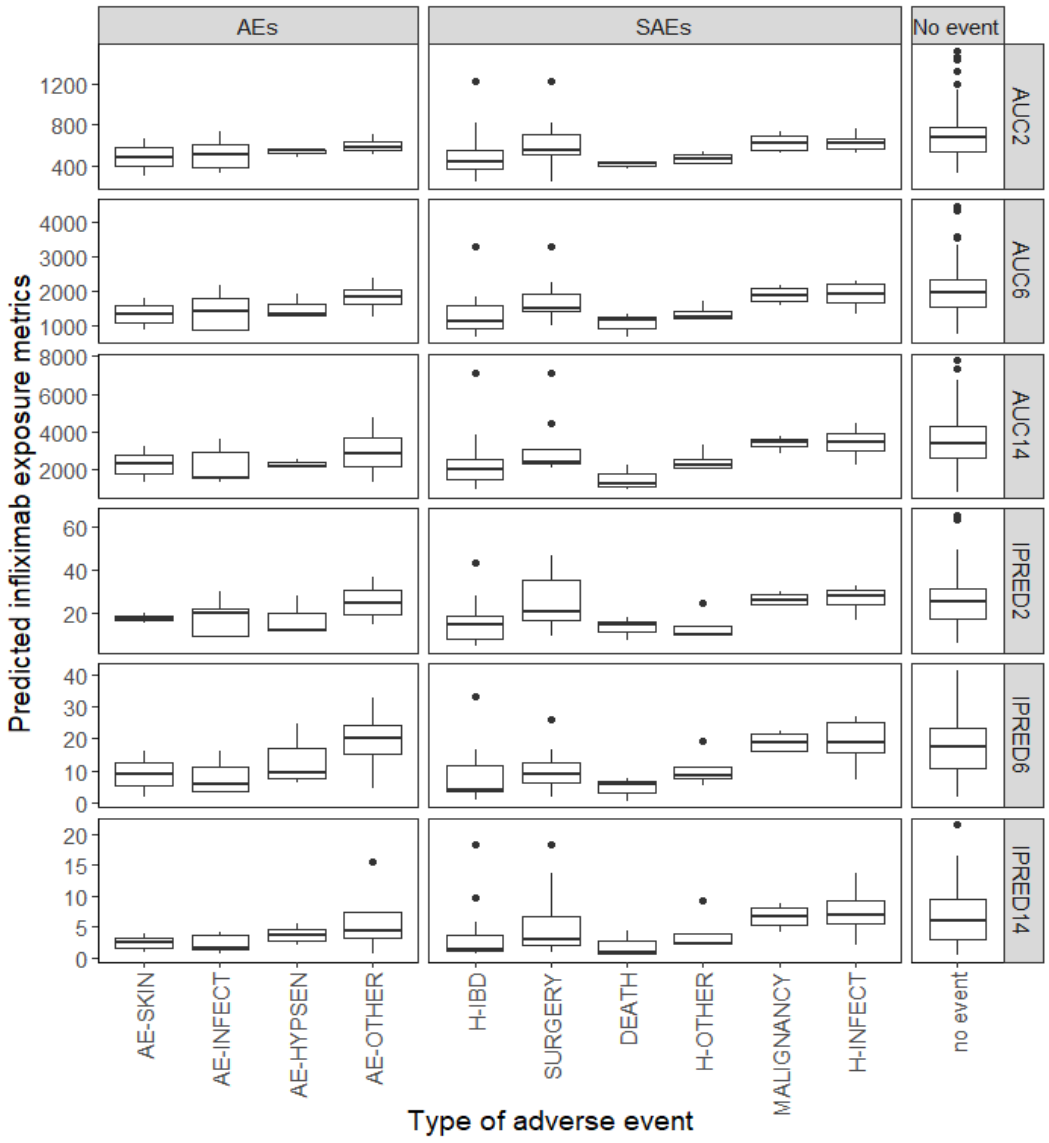



***Figure 44.*** *Distribution of predicted infliximab exposure metrics in patients with and without incidence of safety event. Predicted infliximab exposure metrics are cumulative areas under the infliximab concentration-time curve up to weeks 2 (AUC2), 6 (AUC6), 14 (AUC14), and infliximab trough concentrations at weeks 2 (IPRED2), 6 (IPRED6), 14 (IPRED14). Safety events are divided into adverse events (AEs) and severe adverse event (SAEs). AE-HYPSEN: acute hypersensitive reactions, AE-INFECT: mild infection, AE-SKIN: dermatological side effect, AE-OTHER: others adverse events included arthralgia and myalgia, arthropathy, neuropathy, and alopecia, DEATH: death, H-IBD: inflammatory bowel disease-related hospitalisation, H-INFECT: serious infection, H-OTHER: hospital admissions that were not related to inflammatory bowel disease, MALIGNANCY: malignancy, SURGERY: inflammatory bowel disease-related surgery.*

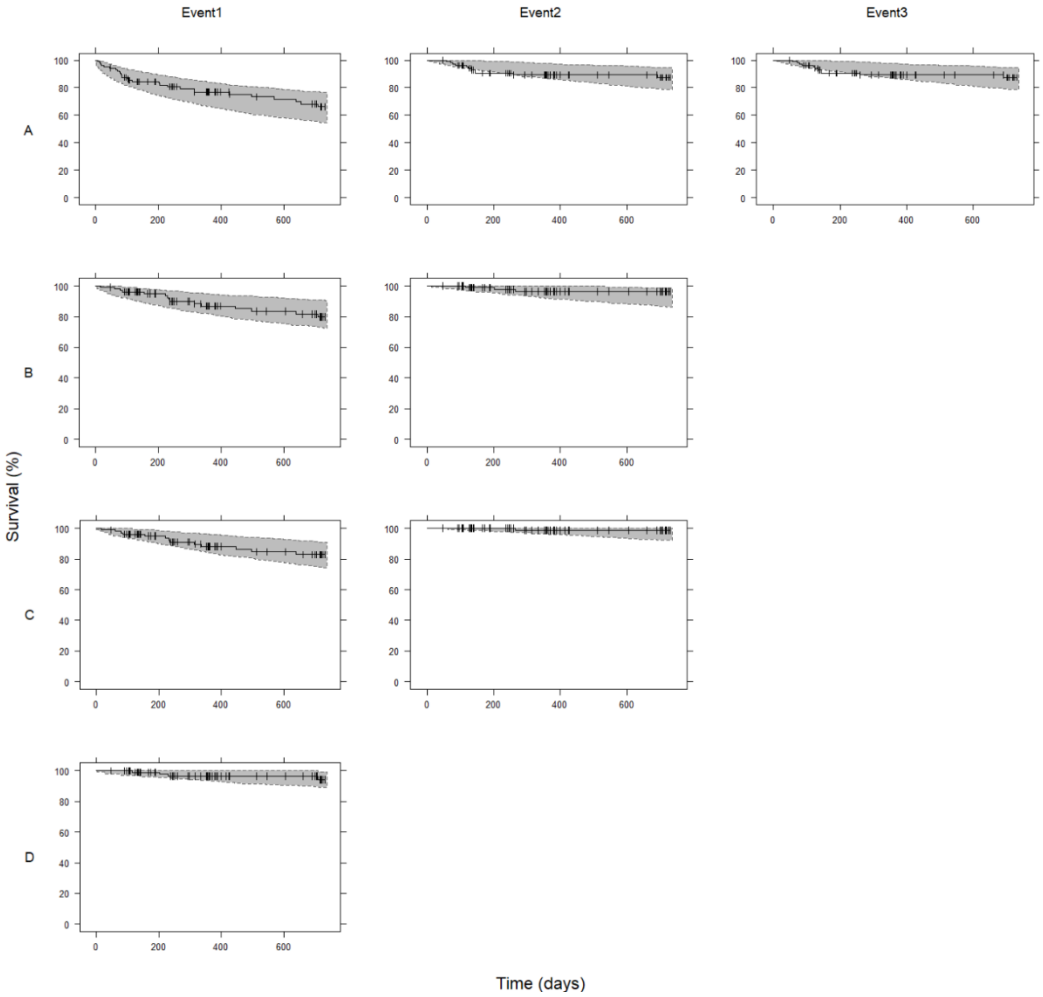



***Figure 45.*** *The visual predictive check of the final repeated time-to-event models for first to third safety events: overall severe adverse event (A), combined infection/malignancy event (B), infection event (C), and malignancy event (D). The solid lines represent the median of the observed data and shaded areas represent the 95% confidence intervals of the predicted data based on 1,000 simulations. The vertical lines mark that a patient was censored before the first to third safety events occurred.*

## Discussion

This study is the first to provide insight into infliximab exposure during induction treatment of elderly patients with IBD in comparison with their younger counterparts. We also investigated the effects of age, infliximab exposure and other potential confounders on endoscopic outcomes and AEs. We found no significant difference in infliximab exposure and endoscopic remission between elderly and non-elderly patients. Infliximab exposure during induction treatment was not found to be a significant risk factor for any safety event. However, age was an independent predictor for higher infliximab exposure, SAEs and malignancy, while combined immunomodulator use increased the hazard of acquiring an infection drastically.

In agreement with previous studies, the efficacy of infliximab treatment in elderly patients with IBD did not differ from that in younger adult patients.[265,286] Furthermore, our findings confirm age as a risk factor for SAE[287] and malignancy[286], and concomitant immunomodulator use as a risk factor for acquiring infections.[288] We also found a higher discontinuation rate after induction treatment in elderly patients, which is also consistent with previous studies.[286,289]

Our findings differed from those of the previous studies in terms of the incidence of ATI in elderly patients. A previous study observed a significantly higher proportion of elderly patients with ATI.[290] Other studies reported that concomitant immunomodulator use reduced the presence of ATI.[291,292] However, in our study, the proportion of patients with ATI was not significantly different between elderly receiving concomitant immunomodulators as compared to elderly receiving infliximab monotherapy (0%, 0/12 versus 18%, 6/34; $p$ = 0.317). The contradictory finding may, however, be due to inadequate study power.

There is a large interindividual variability in the pharmacokinetics of infliximab. While the estimated pharmacokinetic parameter values agree with those reported in previous pharmacokinetic studies of infliximab[201,202], these estimates are however atypical. The intercompartmental clearance is low, likely due to the sparse sampling scheme, and the central volume of distribution is larger than the plasma volume. Consequently, the distribution and elimination half-lives of 8.8 days and 45.8 days, respectively, are physiologically atypical. Therefore, comparison with two-compartment models built on rich sampling should be done with care.[99,103,293] Still, irrespective of the lack of physiological plausibility of the parameter values, our model fitted the data well and the estimated area under the curve is a valid summary metric of exposure, even though it does not necessarily reflect the actual area under the curve as would be observed with rich sampling. In the present study, the clearance of infliximab was estimated to vary over time due to time-varying serum albumin, CRP, and ATI. The result corroborated with the finding of previous studies that the clearance of infliximab is time-dependent due to immunogenicity and a changing disease activity upon the induction treatment. In addition, baseline age and

baseline fat-free mass were found to explain interindividual variability in infliximab clearance. Two studies evaluated the effect of age on infliximab pharmacokinetics.[103,208] One of these studies, a retrospective analysis of data from two phase III clinical trials, reported that age was not found to influence infliximab pharmacokinetics in the tested age range (6 – 76 years) of patients with CD.[103] The other study found a higher volume of distribution in paediatric patients with CD than in adults.[208] On the contrary, our study was able to define the effect of age on infliximab clearance, most likely due to the wider age range in our study population (16 – 91 years). However, age, together with the other covariates in our final model, accounted for only 12.6% of the interindividual variability, leaving 29.6% unexplained. Therefore, the age effect on clearance does not translate into an effect on the infliximab trough concentrations. The effect of fat-free mass on infliximab pharmacokinetics was previously reported.[203] In general, the distribution of monoclonal antibodies is restricted to the blood plasma and extracellular fluids because of their high molecular weight and hydrophilicity.[294] Therefore, the total body volume of distribution of infliximab may be better correlated to fat-free mass than body weight.

The optimal exposure of infliximab that is required to have the highest probability of attaining endoscopic remission has not been widely agreed upon. The cumulative area under the infliximab concentration-time curve until the endoscopic evaluation of 3752 mg/L*day at week 12 was predicted to associate with 70% of patients attaining endoscopic remission.[203] Contrary to this previous finding, we identified an infliximab trough concentration at week 14 of 15.6 mg/L to be best related with a 50% probability of attaining post-induction endoscopic remission. Age and being elderly were not found to drive the probability of attaining endoscopic remission. Therefore, this same threshold concentration may be targeted in the early optimisation of infliximab treatment, regardless of patients' age.

Uncertainty exists concerning the relationship between infliximab exposure and the risk of (S)AEs. A previous study reported that infliximab concentrations above 15.0 mg/L were not associated with a higher frequency of infections.[295] In contrast, higher cumulative exposure to infliximab during maintenance treatment was recently reported to be significantly associated with a 2-fold increase in the risk of infection in patients with IBD.[296] In our study, we observed higher infliximab exposure during induction treatment in patients with serious infections and malignancies. However, infliximab exposure during induction treatment was not found to be a significant risk factor for the (S)AEs. The result should be interpreted with caution since the lack of a statistically significant difference may be due to either a true lack of effect or an inadequate study power. Also, safety events with no significant difference in incidence rate between elderly and non-elderly patients ($p$ >0.050) had wide 95% confidence intervals of incidence rate ratios. The wide confidence intervals indicated the absence of evidence for differences, thus larger sample size is needed to draw the conclusions.

Our study had several limitations. First, data were obtained retrospectively, which may have led to several potential sources of bias, including a treatment selection bias and a reporter bias for minor AEs. Second, some data, such as endoscopic outcome data and safety events, were missing due to the nature of retrospective data collection. Third, the sample size of the study was relatively small in comparison to phase III clinical trials of infliximab treatment in patients with IBD (ACT1, ACT2, and ACCENT I), leading to large relative standard errors for parameter estimates in the exposure-response and repeated time-to-event models. Due to the sparse sampling scheme, physiological interpretation of the pharmacokinetic parameters should be done with care. Still, our model fitted the data well and the estimated area under the curve is a valid summary metric of exposure. Fourth, the use of exponential functions instead of power functions for describing the covariate effects precludes inter-publication comparison. Last, the chronological age may not be sufficient to represent the biological age of elderly patients. Thus, a frailty index should also be considered in future studies.[297] A clinical distinction must be made between the fit and frail elderly. Furthermore, we believe that the fit elderly should be allowed to participate in randomised controlled trial studies. According to the increasing trend of the ageing IBD population, well-conducted prospective studies are needed to further assess the efficacy and long-term safety profile of biological treatments in this population.

The statistically significant effect of age on the infliximab clearance did not translate into different infliximab trough concentrations between elderly and non-elderly patients. This can be explained by the large remaining unexplained interindividual variability and the compensatory effects of changing body composition (fat-free mass) and disease activity (serum albumin). As a consequence, the large remaining unexplained variability in infliximab pharmacokinetics during induction treatment warrants early dose optimisation based on therapeutic drug monitoring, irrespective of patient age.[298,299] Furthermore, the same infliximab trough levels can be targeted to attain endoscopic remission, disregarding patients' age. Age is pronounced as a risk factor for SAE and malignancy. Also, combined immunomodulator use accelerated the hazard of infection in comparison to infliximab monotherapy. Infliximab exposure during induction treatment was not found to be a significant risk factor for (S)AE. Still, future studies are needed to ensure our findings.

# General discussion and perspectives

Parts of the general discussion are published as

**Wannee Kantasiripitak***, Zhigang Wang*, Isabel Spriet, Marc Ferrante, Erwin Dreesen. Recent advances in clearance monitoring of monoclonal antibodies in patients with inflammatory bowel diseases. Expert Rev Clin Pharmacol. 2021 Dec;14(12):1455-1466. *These authors contributed equally to this work. Article reproduced with permission from the journal that published Kantasiripitak *et al*.[1]

# General discussion

A growing body of evidence refutes the 'one size fits all' theory of infliximab treatment in patients with inflammatory bowel diseases (IBD).[77,95] More than a decade ago, the concept of personalised medicine has been introduced to infliximab treatment, providing therapeutic recommendations for individual patients using tools such as therapeutic drug monitoring (TDM) and model-based TDM (i.e., model-informed precision dosing [MIPD]).[115] However, TDM-guided infliximab dosing based on an analogous flowchart proved to be too simple for attaining a target exposure (i.e., TAXIT, TAILORIX).[121,122] On the contrary, MIPD can quantify variabilities in pharmacokinetics (PK), support optimal dose selection, and enable personalised medicine.[300] Although the obvious potential of MIPD has been acknowledged, great efforts are still required in prospectively confirming its value and facilitating its implementation into clinical practice.[153] Several key challenges need to be addressed regarding (i) definition and terminology, (ii) understanding the value of MIPD, (iii) scientific aspects, (iv) practical aspects, and (v) drug development and regulatory aspects (**Figure 46**).[146] In this doctoral research work, we focused on addressing challenges regarding scientific aspects such as the suitability of a drug for precision dosing, the availability of target associated with therapeutic outcome, the underlying methodology for MIPD, underlying models of MIPD, translation of scientific findings into user-friendly MIPD software tools, prospective evidence for benefits of MIPD, and guidelines on how to implement MIPD.

We identified four knowledge gaps regarding scientific aspects that could hinder the implementation of MIPD of infliximab treatment in patients with IBD. First, there is no consensus on exposure targets during infliximab induction treatment, particularly in special populations such as children and the elderly. Second, the selection of the most accurate population PK (popPK) model for MIPD remains challenging. Third, there is still a need for an open-source MIPD software tool specifically for the MIPD of infliximab for patients with IBD. Lastly, a prospective study comparing the benefits of MIPD over weight-based dosing is still awaited.

We followed Sheiner's "learn and confirm" cycle in our research[301], starting with learning from former experience (retrospective studies), followed by confirming what has been learned (prospective studies). The learn-confirm cycle highlights the importance of science-based study design and applying scientific tools for planning studies and analysing data. The goal of the learning step is to learn from a selected group of patients to get a better insight into the outcomes of interest. Whereas the goal of the confirming step is to demonstrate in a large and representative patient population to confirm a finding from the learning step. In principle, the results of one study provide the basis for the design of the next study. This sequential approach of scientific development could result in more thorough evaluation, more rapid approval, and less expensive studies.[301] Moreover, we

contributed to not only a theoretical aspect (What is the target?) but also a practical aspect (How to reach the target?) of MIPD.

In this doctoral research work, we (i) identified the serum concentration target during infliximab induction treatment for special populations, (ii) established an MIPD framework of infliximab, and (iii) developed two MIPD modules for infliximab dosing of patients with IBD implemented in TDMx software tool. With these contributions, we facilitate the initiation of a prospective clinical trial and the implementation of MIPD of infliximab in the treatment of patients with IBD. The positioning of this doctoral research work within the scientific field is illustrated in **Figure 47**.

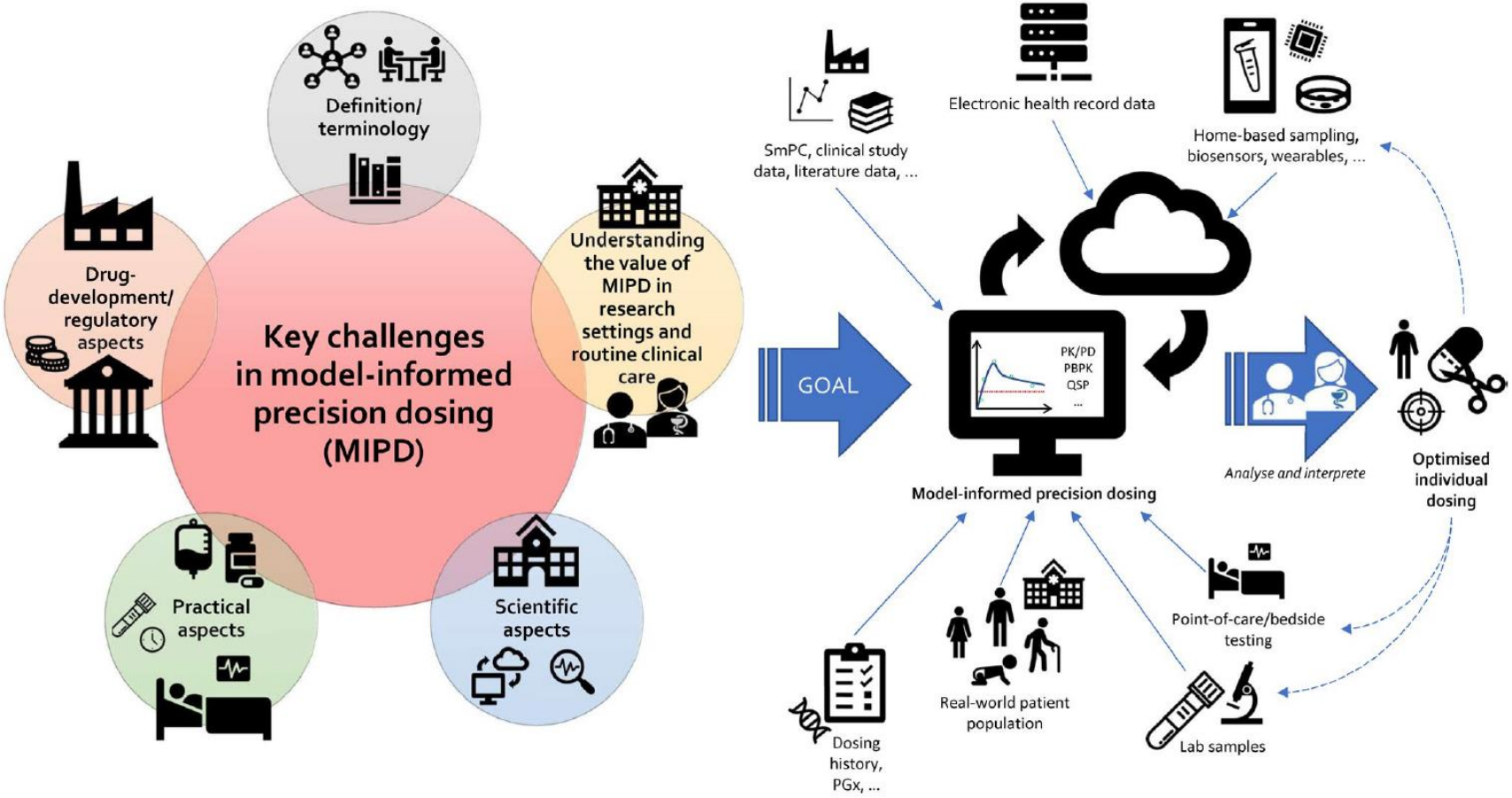



***Figure 46.*** *Key challenges and future perspectives for model-informed precision dosing (MIPD). PBPK, physiologically based pharmacokinetics; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; QSP, quantitative systems pharmacology; SmPC, summary of product characteristics. Figure reproduced with permission from the journal that published Kluwe et al.*[146]

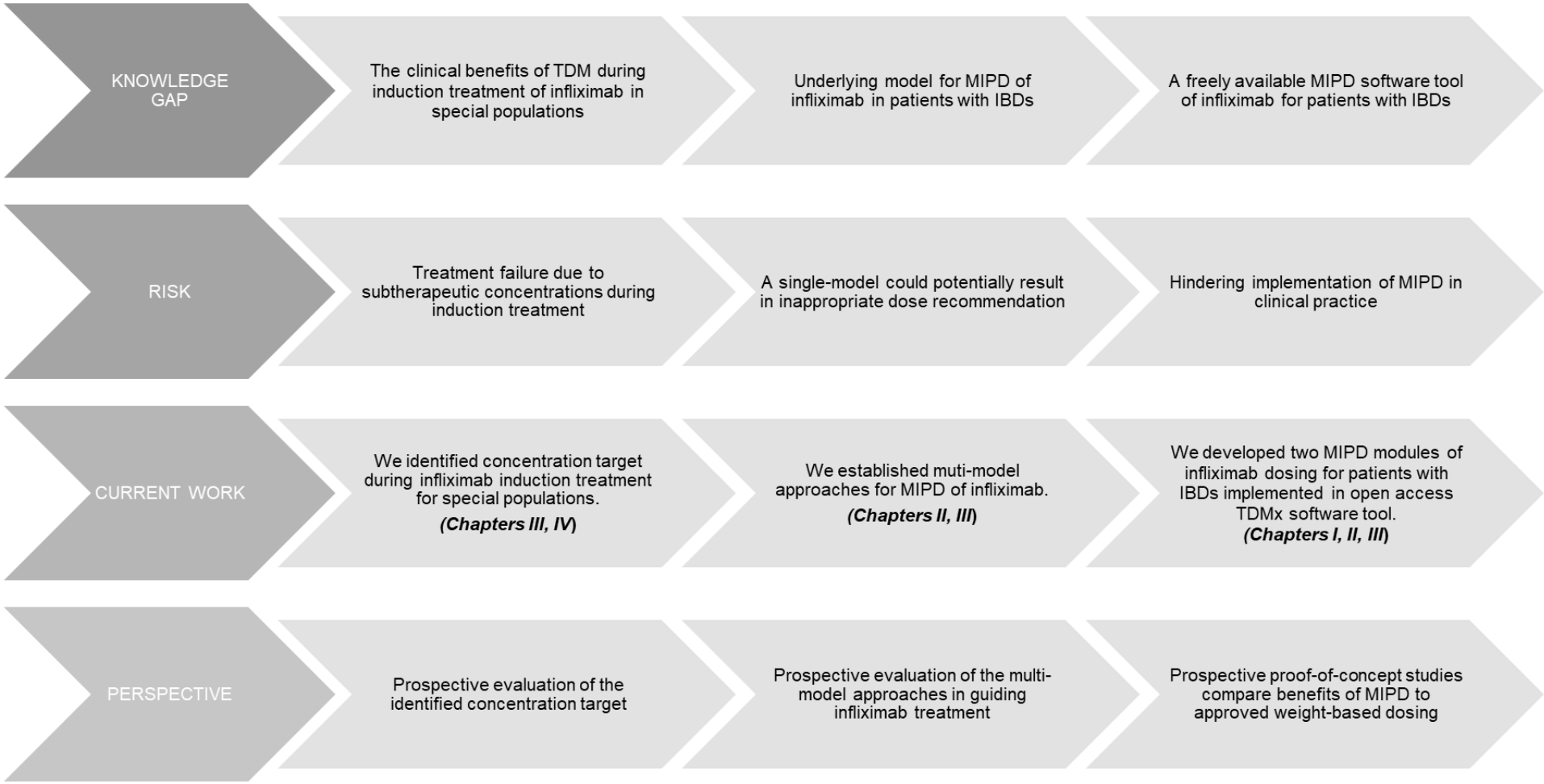



***Figure 47.*** *Schematic overview of this doctoral research work's position in a broader scientific context. IBD, inflammatory bowel diseases; MIPD, model-informed precision dosing; TDM, therapeutic drug monitoring.*

## Infliximab exposure targets in special populations

A clearly defined group of patients who have an actual benefit from personalised medicine is crucial for broader clinical use.[183] TDM is important in certain special populations who are prone to (i) have efficacy and safety issues to usual dosing regimens, (ii) be excluded from the clinical trials conducted to approve dosing regimen (e.g., at the extremes of age, with multiple co-morbidities on polypharmacy, frail elderly), and (iii) express atypical PK as the result of physiological, environmental, disease, or genetic causes (e.g., patient with acute severe ulcerative colitis [UC], patient with postoperative Crohn's disease [CD]).[302] In these patients, retrospective data from real-world settings have been utilised to explore the value of TDM.

The infliximab exposure targets have been previously identified based on receiver operating characteristic (ROC) analysis.[118,251,303] ROC analysis identifies serum infliximab concentration cutoffs with optimal discriminatory performance.[304] In this doctoral research work (***chapters III, IV***), we developed logistic regression Markov exposure-response models to guide the identification of serum infliximab concentration targets based on the probability/rate of attaining treatment outcomes for paediatric and elderly patients with IBD. For paediatric patients, we identified a target of serum infliximab concentration at week 12 of 7.5 mg/L, which was associated with a 64% rate of deep remission (i.e., combined clinical and endoscopic remission). For adult patients, we identified an infliximab trough concentration at week 14 of 15.6 mg/L to be best related to a 50% probability of attaining post-induction endoscopic remission. The same infliximab trough concentration at week 14 could be targeted in elderly patients with IBD. However, further evidence regarding differences in the exposure-response relationships and target of serum infliximab concentrations among IBD population subgroups could be obtained either by developing a model for pooled data from all populations or using an adult model as a prior and then estimating different exposure-response parameters for the other population subgroups. With this regard, a consensus on treatment response among all populations may be needed. Moreover, the elderly study was a relatively small exploratory study in comparison to the confirmatory phase III clinical trials of infliximab treatment in patients with IBD (ACT1, ACT2, and ACCENT I). Therefore, a multicentre individual patient data meta-analysis (IPDMA) should be performed to repeat our analysis. The identified optimal therapeutic target should be validated in a prospective randomised controlled trial. The validated therapeutic target will facilitate a wide use of TDM during induction treatment.

To date, there is still conflicting evidence regarding the relationship between infliximab exposure and adverse events.[295,296] Moreover, the full safety profile of infliximab is still to be established.[44]

## Early dose optimisation

Previously, prospective TDM trials focused on adult patients with IBD undergoing infliximab maintenance treatment (TAXIT and TAILORIX).[121,122] Recent data suggest a clinical utility for TDM during infliximab induction treatment.[303] The early dose optimisation could improve both short- and long-term outcomes by preventing the primary nonresponse caused by PK failure (i.e., inadequate serum infliximab concentration).[303] Moreover, the early TDM of infliximab has been recommended in the current treatment guideline for paediatric patients with IBD.[31,32]

The early phase of treatment is crucial, particularly in patients with active disease.[31] These patients typically have a significant inflammatory burden indicated by elevated C-reactive protein (CRP), decreased serum albumin, and drug loss in stool. The inflammatory burden results in higher drug clearance and subsequently lower serum drug concentrations.[305] These actively sick patients would likely benefit most from early dose optimisation.

In this doctoral research work (***chapter III***), we established a framework for infliximab dose optimisation guided by MIPD during induction treatment. We found that the earliest infliximab dose optimisation guided by MIPD is recommended at week 6 (by providing only the trough concentration at week 6) to attain the identified serum concentration target at week 12. The rapid assay at the point-of-care is required to quantify trough concentration at week 6. The currently available point-of-care assays allow an optimisation of drug dosage based on real-time PK information by reduction of the analysis time to 15 to 20 minutes.[115] The week 2 serum infliximab concentration should not be used to inform dose optimisation since week 2 is still too close to the week 0 infusion (less than 1.5x the infliximab half-life). Therefore, the trough concentration at week 2 is not informative for the individual patient's clearance.

We found that *a priori* prediction (based solely on covariate data) was inaccurate and imprecise, while maximum *a posteriori* prediction (MAP; based on covariate data and trough concentration) was accurate and precise. In general, covariates only account for a small portion of the between-subject variability (up to 6% for clearance[99,103]), while Bayesian forecasting can identify the remaining, often high "unexplained" between-subject variability (median of 32.7% [interquartile range 28.0 – 36.0%] on clearance[99,103]). Moreover, maximum *a posteriori* prediction was robust to lacking and misspecification of covariate data. These findings could make MIPD more affordable, considering only a single previous trough concentration (preferably at the point-of-care) sufficed for accurate dose optimisation.

## Selection of model for model-informed precision dosing

For infliximab, the first approved biological drug for the treatment of adult patients with IBD, there are more than 20 popPK models developed for this patient population.[242] The majority of these models was developed to describe the time course of drug exposure in patients and to identify sources of variability in exposure. The purposes of the development were not to predict PK parameters for use in MIPD.[129] Therefore, a selection of these developed popPK models for MIPD becomes more challenging.

An MIPD guided by a single popPK model of infliximab showed benefits in both retrospective and prospective studies of patients with IBD.[144,213] However, a single popPK model may not provide a suitable prediction of the concentration-time profile due to possible differences in patient population, narrow range of covariate data, limitation of the study design, or patients with specific PK parameters.[193] Considering these limitations, a compilation of developed popPK models from the same drug-disease system has been proposed as an alternative approach for the model selection.[146,193]

In this doctoral research work (***chapters II, III***), we established the value of multi-model approaches for guiding intravenous infliximab induction and maintenance dosing in patients with IBD. The multi-model approaches include model selection algorithm (MSA) and model averaging algorithm (MAA).[193,306] The compiled results from the population pharmacokinetic models could be used to construct informative priors for Bayesian data analysis or to construct parameter uncertainty distributions to simulate PK data. We found that predictive performances of the multi-model approaches were more robust to concentration data provided for MAP than the single-model approach, regardless of the number of provided concentration data.

There are more emerging attempts to improve the predictive performance of MIPD in terms of (i) alternative approach to pooling of popPK models (e.g., a continuous learning approach[215,307,308]), (ii) methodologies for MIPD (e.g., flattened priors[217], Bayesian data assimilation methods[309]), (iii) alternative models for MIPD (e.g., a popPK-pharmacodynamic [popPK-PD] model[192], physiologically based pharmacokinetic [PBPK] model [310]).

In addition to the pooling of published popPK models, a continuous learning approach has been proposed as another methodology for MIPD. For continuous learning, a published model is initially used in MIPD and then the parameters of the model are updated with available data. The updating of parameters can be done by using published model parameters as an informative prior or without a prior (i.e., refit entirely to newly collected data).[308] This approach allows for capturing patients' characteristics and clinical practice (e.g., dosing, co-medications, sampling assays) at each specific site where the MIPD will be implemented.[308]

To enable MIPD, MAP-based estimation is typically used to estimate PK parameters by combining patient-specific data with prior knowledge from drug-specific models. The published popPK model is used to provide prior knowledge of the drug PK parameter in the general population. However, the PK parameters of a certain individual patient may not be well described by the published model. Flattening of priors coupled with the machine learning approach was proposed to identify the weight of the model priors relative to the observed data of the patient.[217] The hybrid Bayesian PK approaches and machine learning leverage the predictive performance while maintaining the mechanistic insight and interpretability of PK models.[217] Furthermore, the MAP-based estimation provides only a point estimate without associated uncertainties leading to relevant risks associated with dosing regimen selection.[311] Bayesian data assimilation methods have been proposed to overcome the limitation by allowing a comprehensive uncertainty quantification by approximating the full posterior distribution.[309] Quantifying associated uncertainties could enable reliable, efficient, and more informed decision support.

Next to popPK, popPK-PD modelling and simulation has been identified as an alternative approach for MIPD.[192] The popPK-PD model describes a dose-exposure-response relationship. Through this relationship, a certain probability of target attainment (i.e., response) can be converted to its corresponding PK target (i.e., exposure). Then, a dose required to attain the corresponding PK target can be indicated via PKPD simulations.[204] With this approach, treatment response can be directly considered in dose optimisation. Another promising approach for MIPD is a PBPK model, a mechanistic-based model. PBPK for MIPD can be applied by creating virtual twins for each individual to mimic real patients.[310] Virtual twins are generated in a population-based PBPK platform. Recently, the PBPK model presented an adequate predictive performance and could be useful for the MIPD of gentamicin in neonates.[312] The developed PBPK model was evaluated for its performance in predicting drug concentrations and PK parameters of neonates. However, there are still some uncertainties regarding the possibility of PBPK-based MIPD for precise dosage decisions, which necessitates the attention of a group of interested parties (e.g., healthcare providers, industry, academia, regulators, etc.).[310]

Ultimately, it is critical to consider how MIPD could be improved from these innovative methodologies. The goal is not to find the best approach but to explore their complementarity for MIPD.[146]

## Model-informed precision dosing software tools of infliximab

MIPD approach is being increasingly used to improve TDM. To fulfil this demand, several MIPD software tools and R packages have been developed.[313–315] To date, biological drug modules are available in two MIPD software tools provided by software companies MwPharm++ and InsightRX Nova. Recently, InsightRX Nova has launched extensive monoclonal antibody modules for the treatment of patients with IBD.[316] Innovation has been sparked by the crowded market for MIPD software tools. However, a freely available MIPD software tool that provides biological drug modules remains uncommon.

In this doctoral research work (***chapters I, II, III***), we collaborated with TDMx, an academic initiative MIPD software tool, led by Professor Sebastian Wicha from the University of Hamburg.[196] We developed MIPD modules for infliximab dosing of adult and paediatric patients with IBD implemented in the freely available TDMx software tool (**Figure 48**). The software tool provides both single models and multi-model algorithms for dose optimisation. Open access to the MIPD software tool could facilitate the initiation of future clinical studies and wider use of MIPD in clinical practice.


https://tdmx.shinyapps.io/infliximab/ https://tdmx.shinyapps.io/Infliximab_paediatric/

***Figure 48.*** *MIPD modules for infliximab dosing of patients with IBD implemented in TDMx software tool.*

There are still improvements to be made to our developed software tool. First, our software tool is not integrated into the electronic health records of the University Hospitals Leuven (UZ Leuven). The electronic health record integration would automatically input data into the software tool; therefore, it could minimise human error from manual data entry and workload at routine practice.[300,317] Currently, at KU Leuven, another MIPD software tool is in the development process using internal KU Leuven funding (C3). This software tool is integrated into the clinical workstation (KWS) which is a connected electronic health record of all healthcare institutions in Belgium. The software tool will facilitate future prospective clinical studies and the wider use of MIPD in clinical practice. Second, there are still concerns regarding the generalisability of our developed TDMx infliximab for adult patients since only four single models of infliximab were implemented into the software based on their predictive performances. However, our developed software tools are freely available which allow other users to validate the tools in their clinical centres. Lastly, the probability of target attainment cannot be obtained from the MAA. Future research is needed to develop an MAA that also accounts for uncertainty in predictions.

The wider implementation of the MIPD software tool requires not only state-of-the-art software tools but also the other crucial components around it for instance an establishment of MIPD-centred healthcare workflow, multistakeholder collaborations, a point-of-care assay, and flexibility of drug dose and label.[146,300,318,319]

## Prospective evidence for clinical and cost benefits

To date, evidence of large-scale clinical utility and cost-benefit is sparse which impedes a wider integration of TDM and model-based TDM in routine practice.[146,300] Moreover, earlier landmark prospective studies could not support evidence for TDM benefits (TAXIT, TAILORIX, and NOR-DRUM A for infliximab; SERENE-UC and SERENE-CD for adalimumab).[120–122,320,321] However, a lack of benefit of TDM is still inconclusive.

To justify the utility of TDM, several components should be considered in designing future prospective studies. Firstly, the design of TDM studies could be informed by clinical trial simulations using pharmacometrics models developed on large datasets.[192] Secondly, the benefit of TDM should be evaluated at the individual level instead of the population level. Only relevant patient subgroups that need TDM should be included in the study (e.g., patients prone to underexposure with inadequate response to approved dosing regimens, and patients who require higher serum infliximab concentrations [with acute severe UC, and patients with fistulising CD]).[322–324] Moreover, adaptive enrichment designs may be considered to adaptively update the eligibility criteria by restricting entry to patients likely to benefit from the treatment.[325] This can improve the effectiveness of the trial, particularly if just a small percentage of patients respond well to the treatment. Thirdly, point-of-care testing should be utilised to allow dose optimisation based on real-time PK information. Recently, a pilot study of ultra-proactive TDM incorporating infliximab point-of-care testing showed the feasibility and effectiveness of the dose optimisation approach in patients with IBD.[221] Lastly, MIPD algorithms should be implemented to quantify the PK variability of infliximab instead of a simple analogous flowchart.[192]

With the distinct promise of MIPD in treating patients with IBD, great efforts are put into proving its benefit. The clinical utilities of MIPD in infliximab treatment have already been shown in prospective trials in both paediatric and adult patients with IBD.[144,145] Moreover, there is active collaboration between centres to set up a prospective study (OPTIMIZE trial) to gather sufficiently powered evidence in favour of MIPD. The trial is investigating the utility of proactive TDM combined with MIPD from the start of infliximab induction treatment in adolescent and adult patients with CD.[326]

In this doctoral research work (***chapters II, III***), we developed MIPD software tools that could facilitate the initiation of a prospective clinical trial in patients with IBD. We have rolled out a monocentric, two-arm, non-randomised, non-blinded, historically controlled, interventional trial at UZ Leuven since February 2022. The two study arms include (i) a historical control group (REFINED study, S63206; N=30) and,
(ii) an interventional group (MODIFI, S64521, NCT04982172; N=30, 10/30 patients are currently enrolled in the study).

We aim to deliver proof-of-concept of the superiority of model-informed infliximab dose de-escalation for maintaining steroid-free, combined clinical and biological remission (i.e., treatment outcome) during one year after the start of infliximab dose de-escalation in comparison with standard dose de-escalation practice as performed in the control group (**Figure 49**). Clinical remission is defined as a two-item patient-reported outcome (PRO2) ≤1 for patients with UC and ≤8 for patients with CD, and biological remission is defined as C-reactive protein <5 mg/L and faecal calprotectin <250 mg/kg.[327,328] All patients were in corticosteroid-free combined clinical and biological remission at inclusion ($T_0$). Dose optimisation aims at ≥80% probability of reaching the 5.0 mg/L infliximab trough concentration target.[112]

The socio-economic aspects and quality of life are also included as secondary endpoints. The cost-effectiveness ratio will be compared between the two study arms one year after $T_0$. The cost-effectiveness ratio is defined as an additional cost per unit of effectiveness (i.e., treatment outcome and quality-adjusted life years).[329,330]

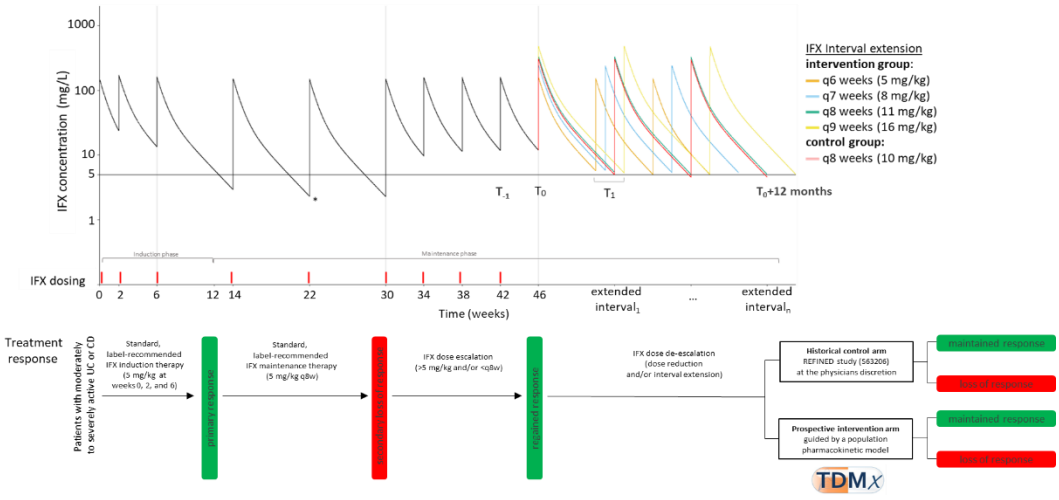



***Figure 49.*** *Overview of the study design aligned with a simulated serum infliximab concentration-time profile for a patient with body weight 70 kg, albumin 50 g/L, and absence of antibodies to infliximab (based on the population pharmacokinetic model as described in the study by Dotan et al.[293]). CD: Crohn's disease, IFX: infliximab, qxw: every x weeks, UC: ulcerative colitis.*

An example of a virtual patient was used to illustrate dose optimisation guided by the TDMx software tool in the interventional group:

The patient previously underwent infliximab dose escalation (5 mg/kg every six weeks). At $T_0$ (03/11/2022), patients received an optimised dose to extend the dosing interval to eight weeks (29/12/2022). Infliximab dose was optimised at $T_0$ by targeting ≥80% probability of reaching the trough concentration target of 5.0 mg/L eight weeks later. Dose optimisation was performed using MSA and MAA using the sum of squared errors (SSEs) as a weighting scheme.

The patient's data are as follows:

(i) *Patient characteristics at $T_0$*: female patient with CD, bodyweight 60 kg, serum albumin 42 g/L, faecal calprotectin 50 mg/kg, no antibodies to infliximab.

(ii) *Previous serum concentration data before $T_0$*: trough concentration at $T_{0-1}$ (22/09/2022) of 7.5 mg/L and intermediate serum concentration (three weeks before $T_0$; 13/10/2022) of 20 mg/L.

The MSA selected the Ternant_2008 model[209] based on the highest weight. The estimated PK parameters of this virtual patient were in line with the PK parameters of a typical patient in the Ternant_2008 model (**Table 14**).

***Table 14.*** *Estimated pharmacokinetic parameters of the virtual patient in comparison to the typical patient of Ternant_2008 model.*

| Pharmacokinetic parameter | Typical value | Estimate value |
|---|---|---|
| CL (L/day) | 0.288 | 0.237 |
| $V_c$ (L) | 1.1 | 2.68 |
| Q (L/day) | 0.130 | 0.131 |
| $V_p$ (L) | 1.9 | 1.66 |

CL: clearance; Q: intercompartmental clearance; $V_c$: volume of distribution in the central compartment; $V_p$: volume of distribution in the peripheral compartment.

For MSA, the recommended dose was 400 mg (6.7 mg/kg) of infliximab on 03/11/2022 to reach a 95.2% probability of target attainment on 29/12/2022 (**Figure 50**). For MAA, the recommended dose was 390 mg (6.5 mg/kg) of infliximab with no simulated probability of target attainment (**Figure 51**). According to the study protocol, we aim for ≥80% probability of target attainment; therefore, the MAA cannot be used to provide dose recommendations.

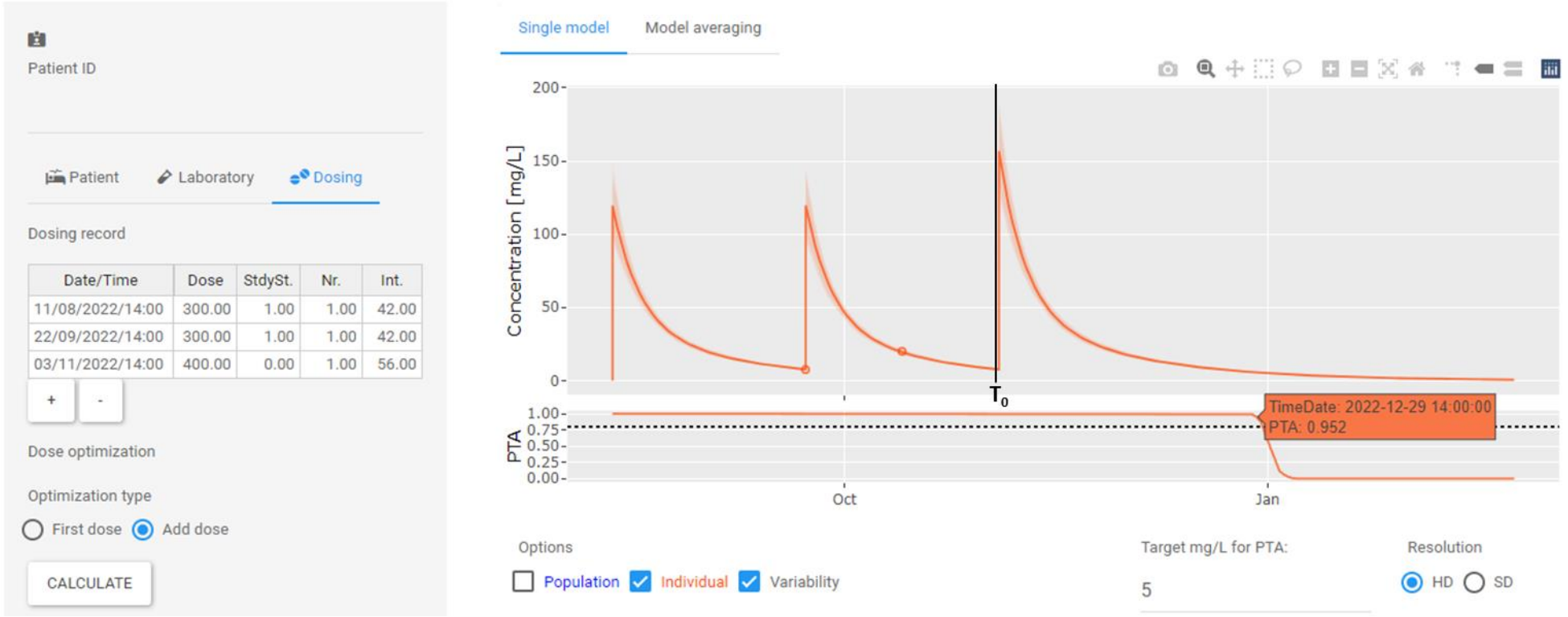



***Figure 50.*** *Screen capture of TDMx using the model selection algorithm for dose optimisation. The individual serum concentration-time profile is illustrated with the solid orange line. The uncertainty of the estimated profile is illustrated with the orange shaded area. The uncertainty was derived from 250 simulations from the posterior distribution including between-subject and residual unexplained variability. The 80% probability of target attainment is indicated with a horizontal dashed line in the PTA-time plot. PTA, probability of target attainment. $T_0$, at the start of dose de-escalation.*

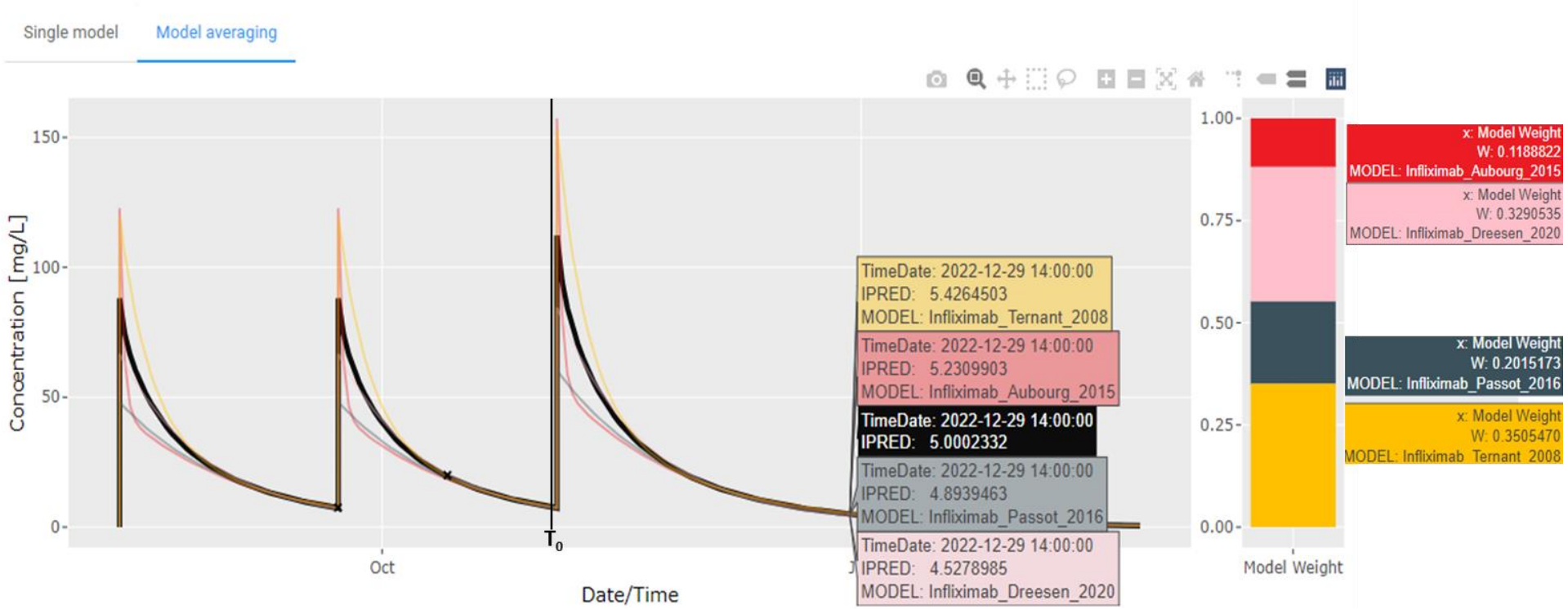



***Figure 51.*** *Screen capture of TDMx using the model averaging algorithm for dose optimisation. The individual serum concentration-time profiles are illustrated with a red line for the Aubourg model[199], a pink line for the Dreesen_2021 model[204], a grey line for the Passot model[208], and an orange line for the Ternant_2008 model[209]. A weighted average prediction of the individual concentration-time profile is illustrated with a black line. IPRED, individual predicted serum concentration; T0, at the start of dose de-escalation; W, weight.*

## Clearance monitoring

TDM of infliximab-guided dose optimisation is based on measuring serum infliximab concentrations. The serum infliximab concentrations result from the interplay between dosage regimen (extrinsic factor) and PK (intrinsic factor), and the dosage regimen confounds the relative contribution of the PK. Recently, clearance of monoclonal antibodies has been suggested to serve as a monitoring marker for IBD treatment.[101] Clearance is a primary PK parameter that provides insights not only into intrinsic drug elimination but also into disease activity (e.g., through leaky gut). Monitoring clearance of monoclonal antibodies over time using a Bayesian forecasting software tool allows a better insight into the immunogenicity and disease status of patients with IBD. Also, clearance monitoring may outperform exposure-guided monitoring in identifying changes in PK and PD during dose adaptations (**Figure 52**).

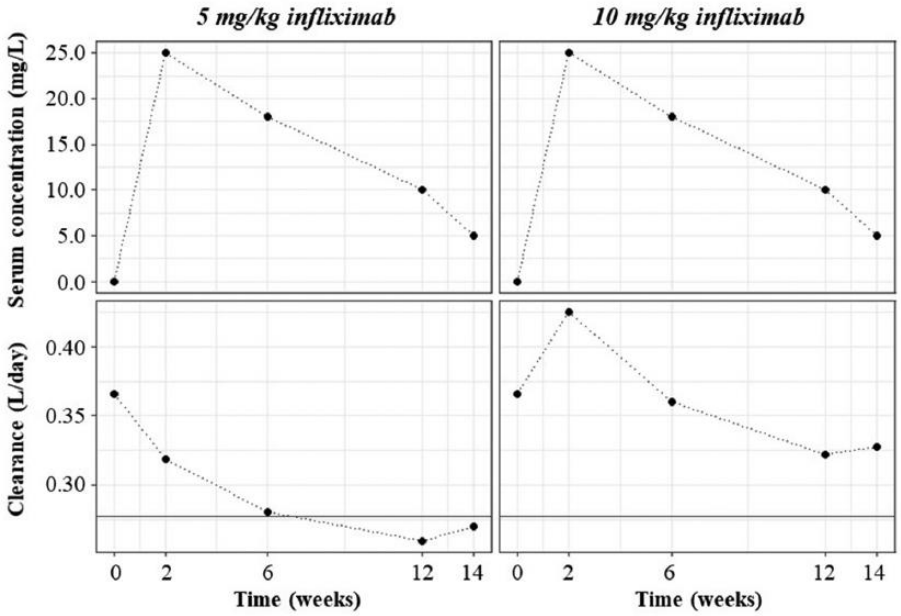



***Figure 52.*** *The time courses of observed serum concentrations and estimated clearances of infliximab in two virtual patients with identical covariate constellations, one receiving 5 mg/kg infliximab, the other receiving 10mg/kg infliximab. The green line in the clearance panels indicates the typical infliximab clearance in the population (0.277 L/day). NONMEM (version 7.5; Icon plc, Gaithersburg, MD, USA) was used for Bayesian forecasting. Figure reproduced with permission from the journal that published Kantasiripitak et al.*[1]

To date, the value of clearance monitoring has been identified in two IBD settings: (i) as a predictor for the need for colectomy during induction treatment in patients with acute severe UC[331], and (ii) as a predictor for the relapse risk in stable patients who undergo treatment de-escalation[257].

We believe that clearance monitoring will be utilised for broader purposes: (i) for PK monitoring (i.e., during precision dosing and early detection of immunogenicity) and (ii) for PD monitoring (i.e., for monitoring disease activity and predicting treatment outcome. These insightful understandings could potentially improve the efficacy, safety, and cost-effectiveness of monoclonal antibody treatments. However, before becoming a tool for precision medicine, the clinical value of clearance monitoring awaits to be confirmed.

# Strengths and limitations

There are some general limitations as well as strengths to this doctoral research work. Firstly, the retrospective nature of these research works (***chapters II, IV***) may have led to potential bias (e.g., selection bias, reporting bias) and these research works may not have sufficient statistical power. Therefore, the interpretation of our results should be done with care and future prospective confirmation of our findings will be needed. Nevertheless, it is important to explore retrospectively collected data to gain more insights and generate hypotheses. Also, developed models based on these studies allow a model-based design of the prospective confirmatory study. Secondly, the sample size of this research work (***chapter IV***) may be considered relatively small in comparison to phase III clinical trials of infliximab treatment in patients with IBD. Essentially, this research work focused on subgroups of vulnerable patients in real-world practice that are normally underrepresented in the clinical trials conducted by the pharmaceutical industry. Small samples sizes are therefore intrinsic to this research, demanding analysis using powerful pharmacometrics tools. Thirdly, incomplete reporting information on published pharmacometrics models limited the reproducibility of the published popPK models. Therefore, assumptions had to be made about the missing information in these research works (***chapters II, III***). In recent years, the importance of an "Open" approach to science and the accessibility to mathematical models has become well-recognised as a crucial step in maintaining reproducibility, rigour, and integrity in published pharmacometrics models.[222] Lastly, data from a single clinical centre was used in evaluations of MIPD algorithms implemented in software tools (***chapters II, III***). Therefore, centre-specific external validation of our algorithm will be required before broader clinical implementation in other clinical centres. The differences between clinical centres include the level of health care (e.g., primary care, secondary care, and tertiary care), bioanalysis method, clinical workflows, etc.

# Conclusions

There is a potential clinical benefit of utilising MIPD during the induction treatment of infliximab in paediatric and elderly patients with IBD. Infliximab exposure during induction treatment was not found to be a risk factor for (serious) adverse events, while concomitant immunomodulator use increased the hazard of infection, regardless of age.

The identified serum infliximab concentration targets together with the developed MIPD modules could facilitate the initiation of a prospective clinical trial and implementation of MIPD of infliximab in the treatment of patients with IBD. The identified target in the adult can also be used in TDM of the elderly. During the induction treatment, the earliest infliximab dose optimisation guided by MIPD is recommended at week 6.

In general, multi-model approaches had systematically better predictive performance than single-model approaches regardless of the number of provided concentration data. *A priori* prediction was inaccurate and imprecise, while maximum *a posteriori* prediction with at least one previous concentration greatly improved the predictive performance and was robust to lacking and misspecification of covariate data.

# References


1. Kantasiripitak W., Wang Z., Spriet I., Ferrante M., Dreesen E. Recent advancements in clearance monitoring of monoclonal antibodies in patients with inflammatory bowel diseases. Expert Rev Clin Pharmacol 2022. Doi: 10.1080/17512433.2021.2028619.

2. Ruel J., Ruane D., Mehandru S., Gower-Rousseau C., Colombel J-F. IBD across the age spectrum: is it the same disease? Nat Rev Gastroenterol Hepatol 2014;11(2):88–98. Doi: 10.1038/nrgastro.2013.240.

3. Cosnes J., Gower-Rousseau C., Seksik P., Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 2011;140(6):1785–94. Doi: 10.1053/j.gastro.2011.01.055.

4. Torres J., Mehandru S., Colombel J-F., Peyrin-Biroulet L. Crohn's disease. The Lancet 2017;389(10080):1741–55. Doi: 10.1016/S0140-6736(16)31711-1.

5. Ungaro R., Mehandru S., Allen PB., Peyrin-Biroulet L., Colombel J-F. Ulcerative colitis. Lancet 2017;389(10080):1756–70. Doi: 10.1016/S0140-6736(16)32126-2.

6. Sairenji T., Collins KL., Evans DV. An Update on Inflammatory Bowel Disease. Prim Care 2017;44(4):673–92. Doi: 10.1016/j.pop.2017.07.010.

7. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nature Reviews Gastroenterology and Hepatology 2015;12(4):205–17. Doi: 10.1038/nrgastro.2015.34.

8. Khalili H., Chan SSM., Lochhead P., Ananthakrishnan AN., Hart AR., Chan AT. The role of diet in the aetiopathogenesis of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2018;15(9):525–35. Doi: 10.1038/s41575-018-0022-9.

9. Ruiz Castro PA., Yepiskoposyan H., Gubian S., Calvino-Martin F., Kogel U., Renggli K., et al. Systems biology approach highlights mechanistic differences between Crohn's disease and ulcerative colitis. Sci Rep 2021;11(1):11519. Doi: 10.1038/s41598-021-91124-3.

10. Travis SPL., Schnell D., Krzeski P., Abreu MT., Altman DG., Colombel J-F., et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut 2012;61(4):535–42. Doi: 10.1136/gutjnl-2011-300486.

11. Dignass A., Eliakim R., Magro F., Maaser C., Chowers Y., Geboes K., et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis 2012;6(10):965–90. Doi: 10.1016/j.crohns.2012.09.003.

12. Shah SC., Colombel JF., Sands BE., Narula N. Systematic review with meta-analysis: Mucosal healing is associated with improved long-term outcomes in Crohn's disease. Alimentary Pharmacology and Therapeutics 2016;43(3):317–33. Doi: 10.1111/apt.13475.

13. Vuitton L., Marteau P., Sandborn WJ., Levesque BG., Feagan B., Vermeire S., et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. Gut 2016;65(9):1447–55. Doi: 10.1136/gutjnl-2015-309903.

14. Siegel CA., Whitman CB., Spiegel BMR., Feagan B., Sands B., Loftus EV., et al. Development of an index to define overall disease severity in IBD. Gut 2018;67(2):244–54. Doi: 10.1136/gutjnl-2016-312648.

15. Peyrin-Biroulet L., Fiorino G., Buisson A., Danese S. First-line therapy in adult Crohn's disease: who should receive anti-TNF agents? Nature Reviews Gastroenterology & Hepatology 2013;10(6):345–51. Doi: 10.1038/nrgastro.2013.31.

16. Ng SC., Shi HY., Hamidi N., Underwood FE., Tang W., Benchimol EI., et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet (London, England) 2018;390(10114):2769–78. Doi: 10.1016/S0140-6736(17)32448-0.

17. GBD 2017 Inflammatory Bowel Disease Collaborators The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5(1):17–30. Doi: 10.1016/S2468-1253(19)30333-4.

18. Roberts SE., Thorne K., Thapar N., Broekaert I., Benninga MA., Dolinsek J., et al. A Systematic Review and Meta-analysis of Paediatric Inflammatory Bowel Disease Incidence and Prevalence Across Europe. J Crohns Colitis 2020;14(8):1119–48. Doi: 10.1093/ecco-jcc/jjaa037.

19. Perler BK., Ungaro R., Baird G., Mallette M., Bright R., Shah S., et al. Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. BMC Gastroenterol 2019;19(1):47. Doi: 10.1186/s12876-019-0963-7.

20. Jairath V., Feagan BG. Global burden of inflammatory bowel disease. Lancet Gastroenterol Hepatol 2020;5(1):2–3. Doi: 10.1016/S2468-1253(19)30358-9.

21. Malmborg P., Everhov ÅH., Söderling J., Ludvigsson JF., Bruze G., Olén O. Earnings during adulthood in patients with childhood-onset inflammatory bowel disease: a nationwide population-based cohort study. Aliment Pharmacol Ther 2022;56(6):1007–17. Doi: 10.1111/apt.17148.

22. Freckmann M., Seipp A., Laass MW., Koletzko S., Claßen M., Ballauff A., et al. School-related experience and performance with inflammatory bowel disease: results from a cross-sectional survey in 675 children and their parents. BMJ Open Gastroenterol 2018;5(1):e000236. Doi: 10.1136/bmjgast-2018-000236.

23. Le Berre C., Ricciuto A., Peyrin-Biroulet L., Turner D. Evolving Short- and Long-Term Goals of Management of Inflammatory Bowel Diseases: Getting It Right, Making It Last. Gastroenterology 2022;162(5):1424–38. Doi: 10.1053/j.gastro.2021.09.076.

24. Sudhakar P., Wellens J., Verstockt B., Ferrante M., Sabino J., Vermeire S. Holistic healthcare in inflammatory bowel disease: time for patient-centric approaches? Gut 2022:gutjnl-2022-328221. Doi: 10.1136/gutjnl-2022-328221.

25. Peyrin-Biroulet L., Sandborn W., Sands BE., Reinisch W., Bemelman W., Bryant RV., et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol 2015;110(9):1324–38. Doi: 10.1038/ajg.2015.233.

26. Turner D., Ricciuto A., Lewis A., D'Amico F., Dhaliwal J., Griffiths AM., et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology 2021;160(5):1570–83. Doi: 10.1053/j.gastro.2020.12.031.

27. Le Berre C., Peyrin-Biroulet L., SPIRIT-IOIBD study group Selecting End Points for Disease-Modification Trials in Inflammatory Bowel Disease: the SPIRIT Consensus From the IOIBD. Gastroenterology 2021;160(5):1452-1460.e21. Doi: 10.1053/j.gastro.2020.10.065.

28. Pigneur B., Seksik P., Viola S., Viala J., Beaugerie L., Girardet J-P., et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis 2010;16(6):953–61. Doi: 10.1002/ibd.21152.

29. Jin H-Y., Lim J-S., Lee Y., Choi Y., Oh S-H., Kim K-M., et al. Growth, puberty, and bone health in children and adolescents with inflammatory bowel disease. BMC Pediatr 2021;21(1):35. Doi: 10.1186/s12887-021-02496-4.

30. Oliveira SB., Monteiro IM. Diagnosis and management of inflammatory bowel disease in children. BMJ 2017;357:j2083. Doi: 10.1136/bmj.j2083.

31. van Rheenen PF., Aloi M., Assa A., Bronsky J., Escher JC., Fagerberg UL., et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. Journal of Crohn's and Colitis 2021;15(2):171–94. Doi: 10.1093/ecco-jcc/jjaa161.

32. Turner D., Ruemmele FM., Orlanski-Meyer E., Griffiths AM., de Carpi JM., Bronsky J., et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;67(2):257–91. Doi: 10.1097/MPG.0000000000002035.

33. Turner D., Ruemmele FM., Orlanski-Meyer E., Griffiths AM., de Carpi JM., Bronsky J., et al. Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis-An Evidence-based Consensus Guideline From the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;67(2):292–310. Doi: 10.1097/MPG.0000000000002036.

34. Croft NM., de Ridder L., Griffiths AM., Hyams JS., Ruemmele FM., Turner D., et al. Paediatric inflammatory bowel disease: a multi-stakeholder perspective to improve development of drugs for children and adolescents. J Crohns Colitis 2022:jjac135. Doi: 10.1093/ecco-jcc/jjac135.

35. Colombel JF., Narula N., Peyrin-Biroulet L. Management Strategies to Improve Outcomes of Patients With Inflammatory Bowel Diseases. Gastroenterology 2017;152(2):351-361.e5. Doi: 10.1053/j.gastro.2016.09.046.

36. Colombel J-F., D'haens G., Lee W-J., Petersson J., Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. Journal of Crohn's and Colitis 2020;14(2):254–66. Doi: 10.1093/ecco-jcc/jjz131.

37. Gisbert JP., Chaparro M. Systematic review with meta-analysis: inflammatory bowel disease in the elderly. Aliment Pharmacol Ther 2014;39(5):459–77. Doi: 10.1111/apt.12616.

38. Ananthakrishnan AN., Shi HY., Tang W., Law CCY., Sung JJY., Chan FKL., et al. Systematic Review and Meta-analysis: Phenotype and Clinical Outcomes of Older-onset Inflammatory Bowel Disease. J Crohns Colitis 2016;10(10):1224–36. Doi: 10.1093/ecco-jcc/jjw054.

39. Hruz P., Juillerat P., Kullak-Ublick G-A., Schoepfer AM., Mantzaris GJ., Rogler G., et al. Management of the Elderly Inflammatory Bowel Disease Patient. Digestion 2020;101 Suppl 1:105–19. Doi: 10.1159/000503099.

40. Tran V., Limketkai BN., Sauk JS. IBD in the Elderly: Management Challenges and Therapeutic Considerations. Curr Gastroenterol Rep 2019;21(11):60. Doi: 10.1007/s11894-019-0720-7.

41. Harbord M., Eliakim R., Bettenworth D., Karmiris K., Katsanos K., Kopylov U., et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis 2017;11(7):769–84. Doi: 10.1093/ecco-jcc/jjx009.

42. Gomollón F., Dignass A., Annese V., Tilg H., Van Assche G., Lindsay JO., et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis 2017;11(1):3–25. Doi: 10.1093/ecco-jcc/jjw168.

43. Cai Z., Wang S., Li J. Treatment of Inflammatory Bowel Disease: A Comprehensive Review. Front Med (Lausanne) 2021;8:765474. Doi: 10.3389/fmed.2021.765474.

44. Melsheimer R., Geldhof A., Apaolaza I., Schaible T. Remicade® (infliximab): 20 years of contributions to science and medicine. Biologics 2019;13:139–78. Doi: 10.2147/BTT.S207246.

45. Janssen Biologics B.V. Remicade : EPAR - Product Information 2021.

46. Gecse KB., Lovász BD., Farkas K., Banai J., Bene L., Gasztonyi B., et al. Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort. J Crohns Colitis 2016;10(2):133–40. Doi: 10.1093/ecco-jcc/jjv220.

47. Schreiber S., Ben-Horin S., Leszczyszyn J., Dudkowiak R., Lahat A., Gawdis-Wojnarska B., et al. Randomized Controlled Trial: Subcutaneous vs Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease. Gastroenterology 2021;160(7):2340–53. Doi: 10.1053/j.gastro.2021.02.068.

48. Xavier RJ., Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007;448(7152):427–34. Doi: 10.1038/nature06005.

49. Zelová H., Hošek J. TNF-α signalling and inflammation: interactions between old acquaintances. Inflamm Res 2013;62(7):641–51. Doi: 10.1007/s00011-013-0633-0.

50. Stallmach A., Giese T., Schmidt C., Ludwig B., Mueller-Molaian I., Meuer SC. Cytokine/chemokine transcript profiles reflect mucosal inflammation in Crohn's disease. Int J Colorectal Dis 2004;19(4):308–15. Doi: 10.1007/s00384-003-0554-4.

51. Levin AD., Wildenberg ME., van den Brink GR. Mechanism of Action of Anti-TNF Therapy in Inflammatory Bowel Disease. J Crohns Colitis 2016;10(8):989–97. Doi: 10.1093/ecco-jcc/jjw053.

52. Dubé PE., Punit S., Polk DB. Redeeming an old foe: protective as well as pathophysiological roles for tumor necrosis factor in inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol 2015;308(3):G161-170. Doi: 10.1152/ajpgi.00142.2014.

53. Ben-Horin S., Kopylov U., Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmunity Reviews 2014;13(1):24–30. Doi: 10.1016/j.autrev.2013.06.002.

54. Desroches M., Louis G., Gleizes A., Krzysiek R., Emilie D. Treatment failure with antagonists of TNF-α: mechanisms and implications for the care of patients. Eur Cytokine Netw 2010;21(4):226–31. Doi: 10.1684/ecn.2010.0212.

55. Hemperly A., Vande Casteele N. Clinical Pharmacokinetics and Pharmacodynamics of Infliximab in the Treatment of Inflammatory Bowel Disease. Clin Pharmacokinet 2018;57(8):929–42. Doi: 10.1007/s40262-017-0627-0.

56. Chowers Y., Sturm A., Sans M., Papadakis K., Gazouli M., Harbord M., et al. Report of the ECCO workshop on anti-TNF therapy failures in inflammatory bowel diseases: biological roles and effects of TNF and TNF antagonists. J Crohns Colitis 2010;4(4):367–76. Doi: 10.1016/j.crohns.2010.05.011.

57. Yang S., Wang J., Brand DD., Zheng SG. Role of TNF-TNF Receptor 2 Signal in Regulatory T Cells and Its Therapeutic Implications. Front Immunol 2018;9:784. Doi: 10.3389/fimmu.2018.00784.

58. Lichtenstein GR., Feagan BG., Cohen RD., Salzberg BA., Diamond RH., Langholff W., et al. Drug therapies and the risk of malignancy in crohn's disease: Results from the TREATTM registry. American Journal of Gastroenterology 2014;109(2):212–23. Doi: 10.1038/ajg.2013.441.

59. Lichtenstein GR., Feagan BG., Cohen RD., Salzberg BA., Diamond RH., Price S., et al. Serious Infection and Mortality in Patients With Crohn's Disease: More Than 5 Years of Follow-Up in the TREATTM Registry. The American Journal of Gastroenterology 2012;107(9):1409–22. Doi: 10.1038/ajg.2012.218.

60. Knight DM., Trinh H., Le J., Siegel S., Shealy D., McDonough M., et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Molecular Immunology 1993;30(16):1443–53. Doi: 10.1016/0161-5890(93)90106-L.

61. Purcell RT., Lockey RF. Immunologic responses to therapeutic biologic agents. J Investig Allergol Clin Immunol 2008;18(5):335–42.

62. Bendtzen K. Immunogenicity of anti-TNF-α biotherapies: II. Clinical relevance of methods used for anti-drug antibody detection. Frontiers in Immunology 2015;6(APR):1–5. Doi: 10.3389/fimmu.2015.00109.

63. O'Meara S., Nanda KS., Moss AC. Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: A systematic review and meta-analysis. Inflammatory Bowel Diseases 2014;20(1):1–6. Doi: 10.1097/01.MIB.0000436951.80898.6d.

64. Zitomersky NL., Atkinson BJ., Fournier K., Mitchell PD., Stern JB., Butler MC., et al. Antibodies to infliximab are associated with lower infliximab levels and increased likelihood of surgery in pediatric IBD. Inflammatory Bowel Diseases 2015;21(2):307–14. Doi: 10.1097/MIB.0000000000000284.

65. Lichtenstein L., Ron Y., Kivity S., Ben-Horin S., Israeli E., Fraser GM., et al. Infliximab-Related Infusion Reactions: Systematic Review. J Crohns Colitis 2015;9(9):806–15. Doi: 10.1093/ecco-jcc/jjv096.

66. Ungar B., Chowers Y., Yavzori M., Picard O., Fudim E., Har-Noy O., et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut 2014;63(8):1258–64. Doi: 10.1136/gutjnl-2013-305259.

67. Krishna M., Nadler SG. Immunogenicity to Biotherapeutics - The Role of Anti-drug Immune Complexes. Front Immunol 2016;7:21. Doi: 10.3389/fimmu.2016.00021.

68. Baert F., Noman M., Vermeire S., Van Assche G., D' Haens G., Carbonez A., et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348(7):601–8. Doi: 10.1056/NEJMoa020888.

69. Hanauer SB., Wagner CL., Bala M., Mayer L., Travers S., Diamond RH., et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clinical Gastroenterology and Hepatology 2004;2(7):542–53. Doi: 10.1016/S1542-3565(04)00238-1.

70. Vermeire S., Gils A., Accossato P., Lula S., Marren A. Immunogenicity of biologics in inflammatory bowel disease. Therapeutic Advances in Gastroenterology 2018;11(2s):1756283X17750355-1756283X17750355. Doi: 10.1177/1756283X17750355.

71. Steenholdt C., Bendtzen K., Brynskov J., Ainsworth MA. Optimizing Treatment with TNF Inhibitors in Inflammatory Bowel Disease by Monitoring Drug Levels and Antidrug Antibodies. Inflammatory Bowel Diseases 2016;22(8):1999–2015. Doi: 10.1097/MIB.0000000000000772.

72. Bortlik M., Duricova D., Malickova K., Machkova N., Bouzkova E., Hrdlicka L., et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. J Crohns Colitis 2013;7(9):736–43. Doi: 10.1016/j.crohns.2012.10.019.

73. Wang SL., Ohrmund L., Hauenstein S., Salbato J., Reddy R., Monk P., et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. Journal of Immunological Methods 2012;382(1–2):177–88. Doi: 10.1016/j.jim.2012.06.002.

74. Marini JC., Sendecki J., Cornillie F., Popp JW., Black S., Blank M., et al. Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade®. The AAPS Journal 2017;19(1):161–71. Doi: 10.1208/s12248-016-9981-3.

75. Hyams J., Crandall W., Kugathasan S., Griffiths A., Olson A., Johanns J., et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007;132(3):863–73; quiz 1165–6. Doi: 10.1053/j.gastro.2006.12.003.

76. Hyams J., Damaraju L., Blank M., Johanns J., Guzzo C., Winter HS., et al. Induction and Maintenance Therapy With Infliximab for Children With Moderate to Severe Ulcerative Colitis. Clinical Gastroenterology and Hepatology 2012;10(4):391–9. Doi: 10.1016/j.cgh.2011.11.026.

77. Winter DA., Joosse ME., de Wildt SN., Taminiau J., de Ridder L., Escher JC. Pharmacokinetics, Pharmacodynamics and Immunogenicity of Infliximab in Paediatric Inflammatory Bowel Disease; a Systematic Review and Revised Dosing Considerations. Journal of Pediatric Gastroenterology and Nutrition 2020. Doi: 10.1097/MPG.0000000000002631.

78. Afif W., Loftus EV., Faubion WA., Kane SV., Bruining DH., Hanson KA., et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. American Journal of Gastroenterology 2010;105(5):1133–9. Doi: 10.1038/ajg.2010.9.

79. Lobatón T., Ferrante M., Rutgeerts P., Ballet V., Van Assche G., Vermeire S. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. Aliment Pharmacol Ther 2015;42(4):441–51. Doi: 10.1111/apt.13294.

80. Cottone M., Kohn A., Daperno M., Armuzzi A., Guidi L., D'Inca R., et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9(1):30–5. Doi: 10.1016/j.cgh.2010.09.026.

81. Borren NZ., Ananthakrishnan AN. Safety of Biologic Therapy in Older Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2019;17(9):1736-1743.e4. Doi: 10.1016/j.cgh.2018.12.032.

82. Sinagra E., Perricone G., Romano C., Cottone M. Heart failure and anti tumor necrosis factor-alpha in systemic chronic inflammatory diseases. Eur J Intern Med 2013;24(5):385–92. Doi: 10.1016/j.ejim.2012.12.015.

83. Stallmach A., Hagel S., Gharbi A., Settmacher U., Hartmann M., Schmidt C., et al. Medical and surgical therapy of inflammatory bowel disease in the elderly - prospects and complications. J Crohns Colitis 2011;5(3):177–88. Doi: 10.1016/j.crohns.2011.02.001.

84. Klotz U., Teml A., Schwab M. Clinical pharmacokinetics and use of infliximab. Clinical Pharmacokinetics 2007;46(8):645–60. Doi: 10.2165/00003088-200746080-00002.

85. Wang W., Wang EQ., Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2008;84(5):548–58. Doi: 10.1038/clpt.2008.170.

86. Shi S. Biologics: An Update and Challenge of Their Pharmacokinetics. Current Drug Metabolism 2014;15(3):271–90. Doi: 10.2174/1389200215030140412212905.

87. Mould DR., Green B. Pharmacokinetics and pharmacodynamics of monoclonal antibodies: Concepts and lessons for drug development. BioDrugs 2010;24(1):23–39. Doi: 10.2165/11530560-000000000-00000.

88. Temrikar ZH., Suryawanshi S., Meibohm B. Pharmacokinetics and Clinical Pharmacology of Monoclonal Antibodies in Pediatric Patients. Paediatr Drugs 2020;22(2):199–216. Doi: 10.1007/s40272-020-00382-7.

89. Kearns GL., Abdel-Rahman SM., Alander SW., Blowey DL., Leeder JS., Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349(12):1157–67. Doi: 10.1056/NEJMra035092.

90. Beaufrère B. Protein turnover in low-birth-weight (LBW) infants. Acta Paediatr Suppl 1994;405:86–92. Doi: 10.1111/j.1651-2227.1994.tb13404.x.

91. Chang HP., Shakhnovich V., Frymoyer A., Funk RS., Becker ML., Park KT., et al. A population physiologically-based pharmacokinetic model to characterize antibody disposition in pediatrics and evaluation of the model using infliximab. Br J Clin Pharmacol 2022;88(1):290–302. Doi: 10.1111/bcp.14963.

92. Butter M., Weiler S., Biedermann L., Scharl M., Rogler G., Bischoff-Ferrari HA., et al. Clinical manifestations, pathophysiology, treatment and outcome of inflammatory bowel diseases in older people. Maturitas 2018;110:71–8. Doi: 10.1016/j.maturitas.2018.01.015.

93. Ryman JT., Meibohm B. Pharmacokinetics of Monoclonal Antibodies. CPT Pharmacometrics Syst Pharmacol 2017;6(9):576–88. Doi: 10.1002/psp4.12224.

94. Billiet T., Dreesen E., Cleynen I., Wollants W-JJ., Ferrante M., Van Assche G., et al. A Genetic Variation in the Neonatal Fc-Receptor Affects Anti-TNF Drug Concentrations in Inflammatory Bowel Disease. American Journal of Gastroenterology 2016;111(10):1438–45. Doi: 10.1038/ajg.2016.306.

95. Dirks NL., Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clinical Pharmacokinetics 2010;49(10):633–59. Doi: 10.2165/11535960-000000000-00000.

96. Olsen T., Goll R., Cui G., Christiansen I., Florholmen J. TNF-alpha gene expression in colorectal mucosa as a predictor of remission after induction therapy with infliximab in ulcerative colitis. Cytokine 2009;46(2):222–7. Doi: 10.1016/j.cyto.2009.02.001.

97. Ungaro R., Babyatsky MW., Zhu H., Freed JS. Protein-losing enteropathy in ulcerative colitis. Case Rep Gastroenterol 2012;6(1):177–82. Doi: 10.1159/000338191.

98. Brandse JF., van den Brink GR., Wildenberg ME., van der Kleij D., Rispens T., Jansen JM., et al. Loss of Infliximab Into Feces Is Associated With Lack of Response to Therapy in Patients With Severe Ulcerative Colitis. Gastroenterology 2015;149(2):350-355.e2. Doi: 10.1053/j.gastro.2015.04.016.

99. Fasanmade AA., Adedokun OJ., Ford J., Hernandez D., Johanns J., Hu C., et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol 2009;65(12):1211–28. Doi: 10.1007/s00228-009-0718-4.

100. Petitcollin A., Brochard C., Siproudhis L., Tron C., Verdier M-C., Lemaitre F., et al. Pharmacokinetic Parameters of Infliximab Influence the Rate of Relapse After De-Escalation in Adults With Inflammatory Bowel Diseases. Clin Pharmacol Ther 2019;106(3):605–15. Doi: 10.1002/cpt.1429.

101. Petitcollin A., Bensalem A., Verdier M-C., Tron C., Lemaitre F., Paintaud G., et al. Modelling of the Time-Varying Pharmacokinetics of Therapeutic Monoclonal Antibodies: A Literature Review. Clin Pharmacokinet 2020;59(1):37–49. Doi: 10.1007/s40262-019-00816-7.

102. Colombel JF., Sandborn WJ., Reinisch W., Mantzaris GJ., Kornbluth A., Rachmilewitz D., et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. New England Journal of Medicine 2010;362(15):1383–95. Doi: 10.1056/NEJMoa0904492.

103. Fasanmade AA., Adedokun OJ., Blank M., Zhou H., Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 2011;33(7):946–64. Doi: 10.1016/j.clinthera.2011.06.002.

104. Ordás I., Mould DR., Feagan BG., Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther 2012;91(4):635–46. Doi: 10.1038/clpt.2011.328.

105. Maser EA., Villela R., Silverberg MS., Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol 2006;4(10):1248–54. Doi: 10.1016/j.cgh.2006.06.025.

106. Adedokun OJ., Sandborn WJ., Feagan BG., Rutgeerts P., Xu Z., Marano CW., et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology 2014;147(6):1296-1307.e5. Doi: 10.1053/j.gastro.2014.08.035.

107. Seow CH., Newman A., Irwin SP., Steinhart AH., Silverberg MS., Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut 2010;59(1):49–54. Doi: 10.1136/gut.2009.183095.

108. van Hoeve K., Dreesen E., Hoffman I., Van Assche G., Ferrante M., Gils A., et al. Adequate Infliximab Exposure During Induction Predicts Remission in Paediatric Patients With Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2019;68(6):847–53. Doi: 10.1097/MPG.0000000000002265.

109. van Hoeve K., Dreesen E., Hoffman I., Van Assche G., Ferrante M., Gils A., et al. Higher Infliximab Trough Levels Are Associated With Better Outcome in Paediatric Patients With Inflammatory Bowel Disease. J Crohns Colitis 2018;12(11):1316–25. Doi: 10.1093/ecco-jcc/jjy111.

110. van Hoeve K., Seyed Tabib NS., Dreesen E., Tops S., Hoffman I., Gils A., et al. Infliximab Concentrations during Induction Are Predictive for Endoscopic Remission in Pediatric Patients with Inflammatory Bowel Disease under Combination Therapy. J Pediatr 2022;240:150-157.e4. Doi: 10.1016/j.jpeds.2021.08.079.

111. Dotan I., Ron Y., Yanai H., Becker S., Fishman S., Yahav L., et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. Inflamm Bowel Dis 2014;20(12):2247–59. Doi: 10.1097/MIB.0000000000000212.

112. Vande Casteele N., Herfarth H., Katz J., Falck-Ytter Y., Singh S. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. Gastroenterology 2017;153(3):835-857.e6. Doi: 10.1053/j.gastro.2017.07.031.

113. Primas C., Reinisch W., Panetta JC., Eser A., Mould DR., Dervieux T. Model Informed Precision Dosing Tool Forecasts Trough Infliximab and Associates with Disease Status and Tumor Necrosis Factor-Alpha Levels of Inflammatory Bowel Diseases. J Clin Med 2022;11(12):3316. Doi: 10.3390/jcm11123316.

114. Dreesen E., Bossuyt P., Mulleman D., Gils A., Pascual-Salcedo D. Practical recommendations for the use of therapeutic drug monitoring of biopharmaceuticals in inflammatory diseases. Clin Pharmacol 2017;9:101–11. Doi: 10.2147/CPAA.S138414.

115. Vermeire S., Dreesen E., Papamichael K., Dubinsky MC. How, When, and for Whom Should We Perform Therapeutic Drug Monitoring? Clinical Gastroenterology and Hepatology 2020;18(6):1291–9. Doi: 10.1016/j.cgh.2019.09.041.

116. Argollo M., Kotze PG., Kakkadasam P., D'Haens G. Optimizing biologic therapy in IBD: how essential is therapeutic drug monitoring? Nature Reviews Gastroenterology and Hepatology 2020;17(11):702–10. Doi: 10.1038/s41575-020-0352-2.

117. Wang Z., Dreesen E. Therapeutic drug monitoring of anti-tumor necrosis factor agents: lessons learned and remaining issues. Curr Opin Pharmacol 2020;55:53–9. Doi: 10.1016/j.coph.2020.09.007.

118. Clarkston K., Tsai Y-T., Jackson K., Rosen MJ., Denson LA., Minar P. Development of Infliximab Target Concentrations During Induction in Pediatric Crohn Disease Patients. J Pediatr Gastroenterol Nutr 2019;69(1):68–74. Doi: 10.1097/MPG.0000000000002304.

119. Steenholdt C., Brynskov J., Thomsen OØ., Munck LK., Fallingborg J., Christensen LA., et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut 2014;63(6):919–27. Doi: 10.1136/gutjnl-2013-305279.

120. Syversen SW., Goll GL., Jørgensen KK., Sandanger Ø., Sexton J., Olsen IC., et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Infliximab Induction on Disease Remission in Patients With Chronic Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA 2021;325(17):1744–54. Doi: 10.1001/jama.2021.4172.

121. Vande Casteele N., Ferrante M., Van Assche G., Ballet V., Compernolle G., Van Steen K., et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148(7):1320-1329.e3. Doi: 10.1053/j.gastro.2015.02.031.

122. D'Haens G., Vermeire S., Lambrecht G., Baert F., Bossuyt P., Pariente B., et al. Increasing Infliximab Dose Based on Symptoms, Biomarkers, and Serum Drug Concentrations Does Not Increase Clinical, Endoscopic, and Corticosteroid-Free Remission in Patients With Active Luminal Crohn's Disease. Gastroenterology 2018;154(5):1343-1351.e1. Doi: 10.1053/j.gastro.2018.01.004.

123. Syversen SW., Jørgensen KK., Goll GL., Brun MK., Sandanger Ø., Bjørlykke KH., et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA 2021;326(23):2375–84. Doi: 10.1001/jama.2021.21316.

124. Syversen SW., Jahnsen J., Haavardsholm EA. Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy and Control of Immune-Mediated Inflammatory Diseases-Reply. JAMA 2022;327(15):1506–7. Doi: 10.1001/jama.2022.2938.

125. Torres J., Bonovas S., Doherty G., Kucharzik T., Gisbert JP., Raine T., et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis 2020;14(1):4–22. Doi: 10.1093/ecco-jcc/jjz180.

126. van Hoeve K., Hoffman I., Vermeire S. Therapeutic drug monitoring of anti-TNF therapy in children with inflammatory bowel disease. Expert Opin Drug Saf 2018;17(2):185–96. Doi: 10.1080/14740338.2018.1413090.

127. Frymoyer A., Piester TL., Park KT. Infliximab Dosing Strategies and Predicted Trough Exposure in Children With Crohn Disease. J Pediatr Gastroenterol Nutr 2016;62(5):723–7. Doi: 10.1097/MPG.0000000000001123.

128. Wicha SG., Märtson AG., Nielsen EI., Koch BCP., Friberg LE., Alffenaar JW., et al. From Therapeutic Drug Monitoring to Model-Informed Precision Dosing for Antibiotics. Clinical Pharmacology and Therapeutics 2021;109(4):928–41. Doi: 10.1002/cpt.2202.

129. Mould DR., Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development—Part 2: Introduction to Pharmacokinetic Modeling Methods. CPT: Pharmacometrics & Systems Pharmacology 2013;2(4):e38–e38. Doi: 10.1038/psp.2013.14.

130. Bauer RJ. NONMEM Tutorial Part II: Estimation Methods and Advanced Examples. CPT: Pharmacometrics and Systems Pharmacology 2019;8(8):538–56. Doi: 10.1002/psp4.12422.

131. Hooker AC., Staatz CE., Karlsson MO. Conditional weighted residuals (CWRES): A model diagnostic for the FOCE method. Pharmaceutical Research 2007;24(12):2187–97. Doi: 10.1007/s11095-007-9361-x.

132. Yafune A., Ishiguro M. Bootstrap approach for constructing confidence intervals for population pharmacokinetic parameters. I: A use of bootstrap standard error. Statistics in Medicine 1999;18(5):581–99. Doi: 10.1002/(SICI)1097-0258(19990315)18:5<581::AID-SIM47>3.0.CO;2-1.

133. Bergstrand M., Hooker AC., Wallin JE., Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. The AAPS Journal 2011;13(2):143–51. Doi: 10.1208/s12248-011-9255-z.

134. Abrantes JA., Jönsson S., Karlsson MO., Nielsen EI. Handling interoccasion variability in model-based dose individualization using therapeutic drug monitoring data. Br J Clin Pharmacol 2019;85(6):1326–36. Doi: 10.1111/bcp.13901.

135. Mandema JW., Verotta D., Sheiner LB. Building population pharmacokinetic--pharmacodynamic models. I. Models for covariate effects. J Pharmacokinet Biopharm 1992;20(5):511–28. Doi: 10.1007/BF01061469.

136. Jonsson EN., Karlsson MO. Automated covariate model building within NONMEM. Pharm Res 1998;15(9):1463–8. Doi: 10.1023/a:1011970125687.

137. Yngman G., Bjugård Nyberg H., Nyberg J., Jonsson EN., Karlsson MO. An introduction to the full random effects model. CPT Pharmacometrics Syst Pharmacol 2022;11(2):149–60. Doi: 10.1002/psp4.12741.

138. Mould DR., D'Haens G., Upton RN. Clinical Decision Support Tools: The Evolution of a Revolution. Clin Pharmacol Ther 2016;99(4):405–18. Doi: 10.1002/cpt.334.

139. Sheiner LB., Beal SL. Bayesian individualization of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. J Pharm Sci 1982;71(12):1344–8. Doi: 10.1002/jps.2600711209.

140. Darwich AS., Ogungbenro K., Vinks AA., Powell JR., Reny J-L., Marsousi N., et al. Why has model-informed precision dosing not yet become common clinical reality? lessons from the past and a roadmap for the future. Clin Pharmacol Ther 2017;101(5):646–56. Doi: 10.1002/cpt.659.

141. Keizer RJ., Ter Heine R., Frymoyer A., Lesko LJ., Mangat R., Goswami S. Model-Informed Precision Dosing at the Bedside: Scientific Challenges and Opportunities. CPT Pharmacometrics Syst Pharmacol 2018;7(12):785–7. Doi: 10.1002/psp4.12353.

142. Eser A., Primas C., Reinisch S., Vogelsang H., Novacek G., Mould DR., et al. Prediction of Individual Serum Infliximab Concentrations in Inflammatory Bowel Disease by a Bayesian Dashboard System. Journal of Clinical Pharmacology 2018;58(6):790–802. Doi: 10.1002/jcph.1069.

143. Dubinsky MC., Phan BL., Singh N., Rabizadeh S., Mould DR. Pharmacokinetic Dashboard-Recommended Dosing Is Different than Standard of Care Dosing in Infliximab-Treated Pediatric IBD Patients. AAPS J 2017;19(1):215–22. Doi: 10.1208/s12248-016-9994-y.

144. Strik AS., Löwenberg M., Mould DR., Berends SE., Ponsioen CI., van den Brande JMH., et al. Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. Scand J Gastroenterol 2021;56(2):145–54. Doi: 10.1080/00365521.2020.1856405.

145. Dubinsky MC., Mendiolaza ML., Phan BL., Moran HR., Tse SS., Mould DR. Dashboard-Driven Accelerated Infliximab Induction Dosing Increases Infliximab Durability and Reduces Immunogenicity. Inflamm Bowel Dis 2022:izab285. Doi: 10.1093/ibd/izab285.

146. Kluwe F., Michelet R., Mueller-Schoell A., Maier C., Klopp-Schulze L., van Dyk M., et al. Perspectives on Model-Informed Precision Dosing in the Digital Health Era: Challenges, Opportunities, and Recommendations. Clin Pharmacol Ther 2021;109(1):29–36. Doi: 10.1002/cpt.2049.

147. Ben-Horin S., Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther 2011;33(9):987–95. Doi: 10.1111/j.1365-2036.2011.04612.x.

148. Löwenberg M. Anti-TNF Agents in Elderly IBD Patients: Cause for Concern? J Crohns Colitis 2020;14(7):881–2. Doi: 10.1093/ecco-jcc/jjaa025.

149. Kantasiripitak W., Van Daele R., Gijsen M., Ferrante M., Spriet I., Dreesen E. Software Tools for Model-Informed Precision Dosing: How Well Do They Satisfy the Needs? Front Pharmacol 2020;11:620. Doi: 10.3389/fphar.2020.00620.

150. Polasek TM., Kirkpatrick CMJ., Rostami-Hodjegan A. Precision dosing to avoid adverse drug reactions. Ther Adv Drug Saf 2019;10:2042098619894147. Doi: 10.1177/2042098619894147.

151. Holford NHG., Buclin T. Safe and effective variability-a criterion for dose individualization. Ther Drug Monit 2012;34(5):565–8. Doi: 10.1097/FTD.0b013e31826aabc3.

152. Polasek TM., Shakib S., Rostami-Hodjegan A. Precision dosing in clinical medicine: present and future. Expert Rev Clin Pharmacol 2018;11(8):743–6. Doi: 10.1080/17512433.2018.1501271.

153. Polasek TM., Rostami-Hodjegan A., Yim D-S., Jamei M., Lee H., Kimko H., et al. What Does it Take to Make Model-Informed Precision Dosing Common Practice? Report from the 1st Asian Symposium on Precision Dosing. AAPS J 2019;21(2):17. Doi: 10.1208/s12248-018-0286-6.

154. Jelliffe RW. Administration of digoxin. Dis Chest 1969;56(1):56–60. Doi: 10.1378/chest.56.1.56.

155. Sheiner LB. Computer-aided long-term anticoagulation therapy. Comput Biomed Res 1969;2(6):507–18. Doi: 10.1016/0010-4809(69)90030-5.

156. Jelliffe RW., Buell J., Kalaba R. Reducation of digitalis toxicity by computer-assisted glycoside dosage regimens. Ann Intern Med 1972;77(6):891–906. Doi: 10.7326/0003-4819-77-6-891.

157. Sheiner LB., Rosenberg B., Melmon KL. Modelling of individual pharmacokinetics for computer-aided drug dosage. Comput Biomed Res 1972;5(5):411–59. Doi: 10.1016/0010-4809(72)90051-1.

158. Barrett JS. Paediatric models in motion: requirements for model-based decision support at the bedside. Br J Clin Pharmacol 2015;79(1):85–96. Doi: 10.1111/bcp.12287.

159. Van der Zanden TM., De Wildt SN., Liem Y., Offringa M., De Hoog M., Dutch Paediatric Pharmacotherapy Expertise Network NKFK (Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen) Developing a paediatric drug formulary for the Netherlands. Arch Dis Child 2017;102(4):357–61. Doi: 10.1136/archdischild-2016-311674.

160. Kohn MS., Sun J., Knoop S., Shabo A., Carmeli B., Sow D., et al. IBM's Health Analytics and Clinical Decision Support. Yearb Med Inform 2014;9:154–62. Doi: 10.15265/IY-2014-0002.

161. Collins FS., Varmus H. A New Initiative on Precision Medicine. New England Journal of Medicine 2015;372(9):793–5. Doi: 10.1056/NEJMp1500523.

162. Roggeveen LF., Fleuren LM., Guo T., Thoral P., de Grooth HJ., Swart EL., et al. Right Dose Right Now: bedside data-driven personalized antibiotic dosing in severe sepsis and septic shock - rationale and design of a multicenter randomized controlled superiority trial. Trials 2019;20(1):745. Doi: 10.1186/s13063-019-3911-5.

163. Neely MN., Kato L., Youn G., Kraler L., Bayard D., van Guilder M., et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. Antimicrob Agents Chemother 2018;62(2). Doi: 10.1128/AAC.02042-17.

164. Buffington DE., Lampasona V., Chandler MH. Computers in pharmacokinetics. Choosing software for clinical decision making. Clin Pharmacokinet 1993;25(3):205–16. Doi: 10.2165/00003088-199325030-00004.

165. Fuchs A., Csajka C., Thoma Y., Buclin T., Widmer N. Benchmarking therapeutic drug monitoring software: a review of available computer tools. Clin Pharmacokinet 2013;52(1):9–22. Doi: 10.1007/s40262-012-0020-y.

166. Kumar A., Burgard M., Stacey S. An evaluation of the user-friendliness of Bayesian forecasting programs in a clinical setting. - PubMed - NCBI. Br J Clin Pharmacol 2019;85(10):2436–41. Doi: 10.1111/bcp.14066.

167. Neely M. Scalpels not hammers: The way forward for precision drug prescription. Clinical Pharmacology & Therapeutics 2017;101(3):368–72. Doi: 10.1002/cpt.593.

168. Vinks AA., Peck RW., Neely M., Mould DR. Development and Implementation of Electronic Health Record-Integrated Model-Informed Clinical Decision Support Tools for the Precision Dosing of Drugs. Clin Pharmacol Ther 2019. Doi: 10.1002/cpt.1679.

169. Germovsek E., Kent A., Metsvaht T., Lutsar I., Klein N., Turner MA., et al. Development and Evaluation of a Gentamicin Pharmacokinetic Model That Facilitates Opportunistic Gentamicin Therapeutic Drug Monitoring in Neonates and Infants. Antimicrob Agents Chemother 2016;60(8):4869–77. Doi: 10.1128/AAC.00577-16.

170. Knøsgaard KR., Foster DJR., Kreilgaard M., Sverrisdóttir E., Upton RN., van den Anker JN. Pharmacokinetic models of morphine and its metabolites in neonates:: Systematic comparisons of models from the literature, and development of a new meta-model. Eur J Pharm Sci 2016;92:117–30. Doi: 10.1016/j.ejps.2016.06.026.

171. Claisse G., Zufferey PJ., Trone JC., Maillard N., Delavenne X., Laporte S., et al. Predicting the dose of vancomycin in ICU patients receiving different types of RRT therapy: a model-based meta-analytic approach. Br J Clin Pharmacol 2019;85(6):1215–26. Doi: 10.1111/bcp.13904.

172. Broeker A., Nardecchia M., Klinker KP., Derendorf H., Day RO., Marriott DJ., et al. Towards precision dosing of vancomycin: a systematic evaluation of pharmacometric models for Bayesian forecasting. Clin Microbiol Infect 2019. Doi: 10.1016/j.cmi.2019.02.029.

173. Guo T., van Hest RM., Roggeveen LF., Fleuren LM., Thoral PJ., Bosman RJ., et al. External Evaluation of Population Pharmacokinetic Models of Vancomycin in Large Cohorts of Intensive Care Unit Patients. Antimicrob Agents Chemother 2019;63(5). Doi: 10.1128/AAC.02543-18.

174. Dhaese SAM., Farkas A., Colin P., Lipman J., Stove V., Verstraete AG., et al. Population pharmacokinetics and evaluation of the predictive performance of pharmacokinetic models in critically ill patients receiving continuous infusion meropenem: a comparison of eight pharmacokinetic models. J Antimicrob Chemother 2019;74(2):432–41. Doi: 10.1093/jac/dky434.

175. European Commission. REGULATION (EU) 2017/ 745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=OJ:L:2017:117:FULL&from=EN. Accessed February 2, 2020.

176. Australian Register of Therapeutic Goods. Consultation: Regulation of software, including Software as a Medical Device (SaMD). Available at: https://www.tga.gov.au/sites/default/files/consultation-regulation-software-including-software-medical-device-samd.pdf. Accessed February 2, 2020.

177. U.S. Food and Drug Administration. Clinical Decision Support Software. Draft Guidance for Industry and Food and Drug Administration Staff. U.S. Food and Drug Administration. Available at: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-decision-support-software. Accessed December 16, 2019.

178. Álvarez-Román MT., Fernandez-Bello I., de la Corte-Rodríguez H., Hernández-Moreno AL., Martín-Salces M., Butta-Coll N., et al. Experience of tailoring prophylaxis using factor VIII pharmacokinetic parameters estimated with myPKFiT® in patients with severe haemophilia A without inhibitors. Haemophilia 2017;23(1):e50–4. Doi: 10.1111/hae.13141.

179. Polasek TM., Rayner CR., Peck RW., Rowland A., Kimko H., Rostami-Hodjegan A. Toward Dynamic Prescribing Information: Codevelopment of Companion Model-Informed Precision Dosing Tools in Drug Development. Clin Pharmacol Drug Dev 2019;8(4):418–25. Doi: 10.1002/cpdd.638.

180. Wright DFB., Martin JH., Cremers S. Spotlight Commentary: Model-informed precision dosing must demonstrate improved patient outcomes. Br J Clin Pharmacol 2019. Doi: 10.1111/bcp.14050.

181. Olbrisch K., Kisch T., Thern J., Kramme E., Rupp J., Graf T., et al. After standard dosage of piperacillin plasma concentrations of drug are subtherapeutic in burn patients. Naunyn Schmiedebergs Arch Pharmacol 2019;392(2):229–41. Doi: 10.1007/s00210-018-1573-6.

182. Strik AS., Wang Y-MC., Ruff LE., Yashar W., Messmer BT., Mould DR. Individualized Dosing of Therapeutic Monoclonal Antibodies-a Changing Treatment Paradigm? AAPS J 2018;20(6):99. Doi: 10.1208/s12248-018-0257-y.

183. Polasek TM., Shakib S., Rostami-Hodjegan A. Precision medicine technology hype or reality? The example of computer-guided dosing. F1000Res 2019;8:1709. Doi: 10.12688/f1000research.20489.1.

184. InsightRX. InsightRX and Children's Hospital Los Angeles (CHLA) to Partner on Precision Dosing. Available at: https://www.prnewswire.com/news-releases/insightrx-and-childrens-hospital-los-angeles-chla-to-partner-on-precision-dosing-300810186.html. Accessed December 15, 2019.

185. Janković SM. A Critique of Pharmacokinetic Calculators for Drug Dosing Individualization. Eur J Drug Metab Pharmacokinet 2019. Doi: 10.1007/s13318-019-00589-1.

186. Kantasiripitak W., Outtier A., Wicha SG., Kensert A., Wang Z., Sabino J., et al. Multi-model averaging improves the performance of model-guided infliximab dosing in patients with inflammatory bowel diseases. CPT Pharmacometrics Syst Pharmacol 2022;11(8):1045–59. Doi: 10.1002/psp4.12813.

187. Einarson TR., Bereza BG., Ying Lee X., Lelli F. Dose escalation of biologics in Crohn's disease: critical review of observational studies. Curr Med Res Opin 2017;33(8):1433–49. Doi: 10.1080/03007995.2017.1335001.

188. Bodger K. Cost effectiveness of treatments for inflammatory bowel disease. Pharmacoeconomics 2011;29(5):387–401. Doi: 10.2165/11584820-000000000-00000.

189. Williams CJM., Peyrin-Biroulet L., Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-α therapy in inflammatory bowel disease. Aliment Pharmacol Ther 2014;39(5):447–58. Doi: 10.1111/apt.12624.

190. Ford AC., Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol 2013;108(8):1268–76. Doi: 10.1038/ajg.2013.138.

191. Lucidarme C., Petitcollin A., Brochard C., Siproudhis L., Dewitte M., Landemaine A., et al. Predictors of relapse following infliximab de-escalation in patients with inflammatory bowel disease: the value of a strategy based on therapeutic drug monitoring. Aliment Pharmacol Ther 2019;49(2):147–54. Doi: 10.1111/apt.15046.

192. Wang Z., Dreesen E. Therapeutic drug monitoring of anti-tumor necrosis factor agents: lessons learned and remaining issues. Current Opinion in Pharmacology 2020;55:53–9. Doi: 10.1016/j.coph.2020.09.007.

193. Uster DW., Stocker SL., Carland JE., Brett J., Marriott DJE., Day RO., et al. A Model Averaging/Selection Approach Improves the Predictive Performance of Model-Informed Precision Dosing: Vancomycin as a Case Study. Clin Pharmacol Ther 2021;109(1):175–83. Doi: 10.1002/cpt.2065.

194. Vande Casteele N., Buurman DJ., Sturkenboom MGG., Kleibeuker JH., Vermeire S., Rispens T., et al. Detection of infliximab levels and anti-infliximab antibodies: a comparison of three different assays. Aliment Pharmacol Ther 2012;36(8):765–71. Doi: 10.1111/apt.12030.

195. Brendel K., Comets E., Laffont C., Laveille C., Mentré F. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. Pharm Res 2006;23(9):2036–49. Doi: 10.1007/s11095-006-9067-5.

196. Wicha SG., Kees MG., Solms A., Minichmayr IK., Kratzer A., Kloft C. TDMx: a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. Int J Antimicrob Agents 2015;45(4):442–4. Doi: 10.1016/j.ijantimicag.2014.12.010.

197. Altman DG., Bland JM. Measurement in Medicine: The Analysis of Method Comparison Studies. Journal of the Royal Statistical Society: Series D (The Statistician) 1983;32(3):307–17. Doi: 10.2307/2987937.

198. Feuerstein JD., Nguyen GC., Kupfer SS., Falck-Ytter Y., Singh S., American Gastroenterological Association Institute Clinical Guidelines Committee American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017;153(3):827–34. Doi: 10.1053/j.gastro.2017.07.032.

199. Aubourg A., Picon L., Lecomte T., Bejan-Angoulvant T., Paintaud G., Ternant D. A robust estimation of infliximab pharmacokinetic parameters in Crohn's disease. Eur J Clin Pharmacol 2015;71(12):1541–2. Doi: 10.1007/s00228-015-1942-8.

200. Brandse JF., Mathôt RA., van der Kleij D., Rispens T., Ashruf Y., Jansen JM., et al. Pharmacokinetic Features and Presence of Antidrug Antibodies Associate With Response to Infliximab Induction Therapy in Patients With Moderate to Severe Ulcerative Colitis. Clin Gastroenterol Hepatol 2016;14(2):251-258.e1-2. Doi: 10.1016/j.cgh.2015.10.029.

201. Brandse JF., Mould D., Smeekes O., Ashruf Y., Kuin S., Strik A., et al. A Real-life Population Pharmacokinetic Study Reveals Factors Associated with Clearance and Immunogenicity of Infliximab in Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23(4):650–60. Doi: 10.1097/MIB.0000000000001043.

202. Buurman DJ., Maurer JM., Keizer RJ., Kosterink JGW., Dijkstra G. Population pharmacokinetics of infliximab in patients with inflammatory bowel disease: potential implications for dosing in clinical practice. Aliment Pharmacol Ther 2015;42(5):529–39. Doi: 10.1111/apt.13299.

203. Dreesen E., Faelens R., Van Assche G., Ferrante M., Vermeire S., Gils A., et al. Optimising infliximab induction dosing for patients with ulcerative colitis. Br J Clin Pharmacol 2019. Doi: 10.1111/bcp.13859.

204. Dreesen E., Berends S., Laharie D., D'Haens G., Vermeire S., Gils A., et al. Modelling of the relationship between infliximab exposure, faecal calprotectin and endoscopic remission in patients with Crohn's disease. Br J Clin Pharmacol 2021;87(1):106–18. Doi: 10.1111/bcp.14364.

205. Edlund H., Steenholdt C., Ainsworth MA., Goebgen E., Brynskov J., Thomsen OØ., et al. Magnitude of Increased Infliximab Clearance Imposed by Anti-infliximab Antibodies in Crohn's Disease Is Determined by Their Concentration. AAPS J 2017;19(1):223–33. Doi: 10.1208/s12248-016-9989-8.

206. Grisic A-M., Eser A., Huisinga W., Reinisch W., Kloft C. Quantitative relationship between infliximab exposure and inhibition of C-reactive protein synthesis to support inflammatory bowel disease management. Br J Clin Pharmacol 2021;87(5):2374–84. Doi: 10.1111/bcp.14648.

207. Matsuoka K., Hamada S., Shimizu M., Nanki K., Mizuno S., Kiyohara H., et al. Factors contributing to the systemic clearance of infliximab with long-term administration in Japanese patients with Crohn's disease: Analysis using population pharmacokinetics. Int J Clin Pharmacol Ther 2020;58(2):89–102. Doi: 10.5414/CP203569.

208. Passot C., Mulleman D., Bejan-Angoulvant T., Aubourg A., Willot S., Lecomte T., et al. The underlying inflammatory chronic disease influences infliximab pharmacokinetics. MAbs 2016;8(7):1407–16. Doi: 10.1080/19420862.2016.1216741.

209. Ternant D., Aubourg A., Magdelaine-Beuzelin C., Degenne D., Watier H., Picon L., et al. Infliximab pharmacokinetics in inflammatory bowel disease patients. Ther Drug Monit 2008;30(4):523–9. Doi: 10.1097/FTD.0b013e318180e300.

210. Ternant D., Berkane Z., Picon L., Gouilleux-Gruart V., Colombel J-F., Allez M., et al. Assessment of the Influence of Inflammation and FCGR3A Genotype on Infliximab Pharmacokinetics and Time to Relapse in Patients with Crohn's Disease. Clin Pharmacokinet 2015;54(5):551–62. Doi: 10.1007/s40262-014-0225-3.

211. Ternant D., Passot C., Aubourg A., Goupille P., Desvignes C., Picon L., et al. Model-Based Therapeutic Drug Monitoring of Infliximab Using a Single Serum Trough Concentration. Clin Pharmacokinet 2018;57(9):1173–84. Doi: 10.1007/s40262-017-0621-6.

212. Wojciechowski J., Upton RN., Mould DR., Wiese MD., Foster DJR. Infliximab Maintenance Dosing in Inflammatory Bowel Disease: an Example for In Silico Assessment of Adaptive Dosing Strategies. AAPS J 2017;19(4):1136–47. Doi: 10.1208/s12248-017-0082-8.

213. Faelens R., Wang Z., Bouillon T., Declerck P., Ferrante M., Vermeire S., et al. Model-Informed Precision Dosing during Infliximab Induction Therapy Reduces Variability in Exposure and Endoscopic Improvement between Patients with Ulcerative Colitis. Pharmaceutics 2021;13(10):1623. Doi: 10.3390/pharmaceutics13101623.

214. Syversen SW., Goll GL., Jørgensen KK., Sandanger Ø., Sexton J., Olsen IC., et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Infliximab Induction on Disease Remission in Patients With Chronic Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA 2021;325(17):1744–54. Doi: 10.1001/jama.2021.4172.

215. Maier C., de Wiljes J., Hartung N., Kloft C., Huisinga W. A continued learning approach for model-informed precision dosing: updating models in clinical practice. CPT Pharmacometrics Syst Pharmacol 2021. Doi: 10.1002/psp4.12745.

216. Maier C., Hartung N., Kloft C., Huisinga W., de Wiljes J. Reinforcement learning and Bayesian data assimilation for model-informed precision dosing in oncology. CPT Pharmacometrics Syst Pharmacol 2021;10(3):241–54. Doi: 10.1002/psp4.12588.

217. Hughes JH., Keizer RJ. A hybrid machine learning/pharmacokinetic approach outperforms maximum a posteriori Bayesian estimation by selectively flattening model priors. CPT Pharmacometrics Syst Pharmacol 2021;10(10):1150–60. Doi: 10.1002/psp4.12684.

218. Konecki C., Feliu C., Cazaubon Y., Giusti D., Tonye-Libyh M., Brixi H., et al. External Evaluation of Population Pharmacokinetic Models and Bayes-Based Dosing of Infliximab. Pharmaceutics 2021;13(8):1191. Doi: 10.3390/pharmaceutics13081191.

219. Santacana E., Rodríguez-Alonso L., Padullés A., Guardiola J., Rodríguez-Moranta F., Serra K., et al. External Evaluation of Population Pharmacokinetic Models of Infliximab in Patients With Inflammatory Bowel Disease. Ther Drug Monit 2018;40(1):120–9. Doi: 10.1097/FTD.0000000000000476.

220. Schräpel C., Kovar L., Selzer D., Hofmann U., Tran F., Reinisch W., et al. External Model Performance Evaluation of Twelve Infliximab Population Pharmacokinetic Models in Patients with Inflammatory Bowel Disease. Pharmaceutics 2021;13(9):1368. Doi: 10.3390/pharmaceutics13091368.

221. Bossuyt P., Pouillon L., Claeys S., D'Haens S., Hoefkens E., Strubbe B., et al. Ultra-proactive therapeutic drug monitoring of infliximab based on point-of-care-testing in inflammatory bowel disease: results of a pragmatic trial. J Crohns Colitis 2021:jjab127. Doi: 10.1093/ecco-jcc/jjab127.

222. Rowland Yeo K., Hennig S., Krishnaswami S., Strydom N., Ayyar VS., French J., et al. CPT: Pharmacometrics & Systems Pharmacology - Inception, Maturation, and Future Vision. CPT Pharmacometrics Syst Pharmacol 2021;10(7):649–57. Doi: 10.1002/psp4.12680.

223. Keizer R. Experiences in applied clinical pharmacometrics: challenges, recommendations, and research opportunities. n.d. p. PAGE 27 (2018).

224. Hyams J., Crandall W., Kugathasan S., Griffiths A., Olson A., Johanns J., et al. Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-Severe Crohn's Disease in Children. Gastroenterology 2007;132(3):863–73. Doi: 10.1053/j.gastro.2006.12.003.

225. Adedokun OJ., Xu Z., Padgett L., Blank M., Johanns J., Griffiths A., et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. Inflamm Bowel Dis 2013;19(13):2753–62. Doi: 10.1097/01.MIB.0000435438.84365.f7.

226. Singh N., Rosenthal CJ., Melmed GY., Mirocha J., Farrior S., Callejas S., et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2014;20(10):1708–13. Doi: 10.1097/MIB.0000000000000137.

227. van Rheenen PF., Aloi M., Assa A., Bronsky J., Escher JC., Fagerberg UL., et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. J Crohns Colitis 2020:jjaa161. Doi: 10.1093/ecco-jcc/jjaa161.

228. Singh N., Dubinsky MC. Therapeutic Drug Monitoring in Children and Young Adults With Inflammatory Bowel Disease: A Practical Approach. Gastroenterology & Hepatology 2015;11(1):48–55.

229. Assa A., Matar M., Turner D., Broide E., Weiss B., Ledder O., et al. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. Gastroenterology 2019;157(4):985-996.e2. Doi: 10.1053/j.gastro.2019.06.003.

230. Lega S., Bramuzzo M., Dubinsky MC. Therapeutic Drug Monitoring in Pediatric IBD: Current Application and Future Perspectives. Curr Med Chem 2018;25(24):2840–54. Doi: 10.2174/0929867324666170911163021.

231. Van Stappen T., Billiet T., Vande Casteele N., Compernolle G., Brouwers E., Vermeire S., et al. An Optimized Anti-infliximab Bridging Enzyme-linked Immunosorbent Assay for Harmonization of Anti-infliximab Antibody Titers in Patients with Inflammatory Bowel Diseases. Inflamm Bowel Dis 2015;21(9):2172–7. Doi: 10.1097/MIB.0000000000000434.

232. Hyams JS., Ferry GD., Mandel FS., Gryboski JD., Kibort PM., Kirschner BS., et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 1991;12(4):439–47.

233. Turner D., Otley AR., Mack D., Hyams J., de Bruijne J., Uusoue K., et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology 2007;133(2):423–32. Doi: 10.1053/j.gastro.2007.05.029.

234. Daperno M., D'Haens G., Van Assche G., Baert F., Bulois P., Maunoury V., et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60(4):505–12. Doi: 10.1016/s0016-5107(04)01878-4.

235. Vuitton L., Peyrin-Biroulet L., Colombel JF., Pariente B., Pineton de Chambrun G., Walsh AJ., et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. Aliment Pharmacol Ther 2017;45(6):801–13. Doi: 10.1111/apt.13948.

236. Sandborn WJ., Ghosh S., Panes J., Vranic I., Su C., Rousell S., et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367(7):616–24. Doi: 10.1056/NEJMoa1112168.

237. Turner D., Griffiths AM., Walters TD., Seah T., Markowitz J., Pfefferkorn M., et al. Appraisal of the pediatric Crohn's disease activity index on four prospectively collected datasets: recommended cutoff values and clinimetric properties. Am J Gastroenterol 2010;105(9):2085–92. Doi: 10.1038/ajg.2010.143.

238. Turner D., Hyams J., Markowitz J., Lerer T., Mack DR., Evans J., et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). Inflamm Bowel Dis 2009;15(8):1218–23. Doi: 10.1002/ibd.20867.

239. ubiquity: PKPD, PBPK, and Systems Pharmacology Modeling Tools. R package version 2.0.0. n.d.

240. epitools: Tools for training and practicing epidemiologists including methods for twoway and multi-way contingency tables. R package version 0.5-10.1 n.d.

241. dmutate: Mutate Data Frames with Random Variates. R package version 0.1.3. n.d.

242. Kantasiripitak W., Outtier A., Wicha SG., Kensert A., Wang Z., Sabino J., et al. Multi-model averaging improves the performance of model-guided infliximab dosing in patients with inflammatory bowel diseases. CPT Pharmacometrics Syst Pharmacol 2022. Doi: 10.1002/psp4.12813.

243. Gibson DJ., Hartery K., Doherty J., Nolan J., Keegan D., Byrne K., et al. CRP/Albumin Ratio: An Early Predictor of Steroid Responsiveness in Acute Severe Ulcerative Colitis. J Clin Gastroenterol 2018;52(6):e48–52. Doi: 10.1097/MCG.0000000000000884.

244. Levine A., Griffiths A., Markowitz J., Wilson DC., Turner D., Russell RK., et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17(6):1314–21. Doi: 10.1002/ibd.21493.

245. Petitcollin A., Leuret O., Tron C., Lemaitre F., Verdier M-C., Paintaud G., et al. Modeling Immunization To Infliximab in Children With Crohn's Disease Using Population Pharmacokinetics: A Pilot Study. Inflamm Bowel Dis 2018;24(8):1745–54. Doi: 10.1093/ibd/izy129.

246. Bauman LE., Xiong Y., Mizuno T., Minar P., Fukuda T., Dong M., et al. Improved Population Pharmacokinetic Model for Predicting Optimized Infliximab Exposure in Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis 2020;26(3):429–39. Doi: 10.1093/ibd/izz143.

247. Dubinsky MC., Phan BL., Singh N., Rabizadeh S., Mould DR. Pharmacokinetic Dashboard-Recommended Dosing Is Different than Standard of Care Dosing in Infliximab-Treated Pediatric IBD Patients. The AAPS Journal 2017;19(1):215–22. Doi: 10.1208/s12248-016-9994-y.

248. Xiong Y., Mizuno T., Colman R., Hyams J., Noe JD., Boyle B., et al. Real-World Infliximab Pharmacokinetic Study Informs an Electronic Health Record-Embedded Dashboard to Guide Precision Dosing in Children with Crohn's Disease. Clin Pharmacol Ther 2021;109(6):1639–47. Doi: 10.1002/cpt.2148.

249. Growth charts Flanders 2004. Available at: https://www.vub.be/groeicurven/english.html. Accessed May 17, 2022.

250. Curci D., Lucafò M., Cifù A., Bramuzzo M., Martelossi S., Favretto D., et al. Determination of Serum Infliximab Concentration by Point-of-care Devices in Children With Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2019;69(4):474–9. Doi: 10.1097/MPG.0000000000002410.

251. Kennedy NA., Heap GA., Green HD., Hamilton B., Bewshea C., Walker GJ., et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4(5):341–53. Doi: 10.1016/S2468-1253(19)30012-3.

252. Papamichael K., Rakowsky S., Rivera C., Cheifetz AS., Osterman MT. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn's disease. Inflammatory Bowel Diseases 2018;24(10):2266–71. Doi: 10.1093/ibd/izy132.

253. Fine S., Papamichael K., Cheifetz AS. Etiology and Management of Lack or Loss of Response to Anti-Tumor Necrosis Factor Therapy in Patients With Inflammatory Bowel Disease. Gastroenterol Hepatol (N Y) 2019;15(12):656–65.

254. Malik PRV., Temrikar ZH., Chelle P., Edginton AN., Meibohm B. Pediatric Dose Selection for Therapeutic Proteins. J Clin Pharmacol 2021;61 Suppl 1:S193–206. Doi: 10.1002/jcph.1829.

255. Xu Y., Langevin BA., Zhou H., Xu Z. Model-Aided Adults-to-Children Pharmacokinetic Extrapolation and Empirical Body Size-Based Dosing Exploration for Therapeutic Monoclonal Antibodies-Is Allometry a Reasonable Choice? J Clin Pharmacol 2020;60(12):1573–84. Doi: 10.1002/jcph.1677.

256. Barrett JS., Barrett RF., Vinks AA. Status Toward the Implementation of Precision Dosing in Children. J Clin Pharmacol 2021;61 Suppl 1:S36–51. Doi: 10.1002/jcph.1830.

257. Petitcollin A., Brochard C., Siproudhis L., Tron C., Verdier M-C., Lemaitre F., et al. Pharmacokinetic parameters of infliximab influence the rate of relapse after de-escalation in adults with inflammatory bowel diseases. Clin Pharmacol Ther 2019. Doi: 10.1002/cpt.1429.

258. Dulai PS., Singh S., Vande Casteele N., Boland BS., Rivera-Nieves J., Ernst PB., et al. Should We Divide Crohn's Disease Into Ileum-Dominant and Isolated Colonic Diseases? Clin Gastroenterol Hepatol 2019;17(13):2634–43. Doi: 10.1016/j.cgh.2019.04.040.

259. Kantasiripitak W., Verstockt B., Alsoud D., Lobatón T., Thomas D., Gils A., et al. The Effect of Aging on Infliximab Exposure and Response in Patients with Inflammatory Bowel Diseases. British Journal of Clinical Pharmacology 2021:0–2. Doi: 10.1111/bcp.14785.

260. Baumgart DC., Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 2007;369(9573):1627–40. Doi: 10.1016/S0140-6736(07)60750-8.

261. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015;12(12):720–7. Doi: 10.1038/nrgastro.2015.150.

262. Taleban S., Colombel J-F., Mohler MJ., Fain MJ. Inflammatory bowel disease and the elderly: a review. J Crohns Colitis 2015;9(6):507–15. Doi: 10.1093/ecco-jcc/jjv059.

263. Papamichael K., Lin S., Moore M., Papaioannou G., Sattler L., Cheifetz AS. Infliximab in inflammatory bowel disease. Ther Adv Chronic Dis 2019;10:2040622319838443. Doi: 10.1177/2040622319838443.

264. Cholapranee A., Hazlewood GS., Kaplan GG., Peyrin-Biroulet L., Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Aliment Pharmacol Ther 2017;45(10):1291–302. Doi: 10.1111/apt.14030.

265. Sturm A., Maaser C., Mendall M., Karagiannis D., Karatzas P., Ipenburg N., et al. European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly. J Crohns Colitis 2017;11(3):263–73. Doi: 10.1093/ecco-jcc/jjw188.

266. Charpentier C., Salleron J., Savoye G., Fumery M., Merle V., Laberenne J-E., et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. Gut 2014;63(3):423–32. Doi: 10.1136/gutjnl-2012-303864.

267. Ruiter R., Burggraaf J., Rissmann R. Under-representation of elderly in clinical trials: An analysis of the initial approval documents in the Food and Drug Administration database. Br J Clin Pharmacol 2019;85(4):838–44. Doi: 10.1111/bcp.13876.

268. Johnson C., Barnes EL., Zhang X., Long MD. Trends and Characteristics of Clinical Trials Participation for Inflammatory Bowel Disease in the United States: A Report From IBD Partners. Crohns Colitis 360 2020;2(2):otaa023. Doi: 10.1093/crocol/otaa023.

269. Löwenberg M. Anti-TNF Agents in Elderly IBD Patients: Cause for Concern? J Crohns Colitis 2020;14(7):881–2. Doi: 10.1093/ecco-jcc/jjaa025.

270. Papamichael K., Cheifetz AS. Letter: infliximab concentrations during induction therapy-one size does not fit all. Aliment Pharmacol Ther 2018;47(9):1334–5. Doi: 10.1111/apt.14616.

271. Kim M., Katz S., Green J. Drug Management in the Elderly IBD Patient. Curr Treat Options Gastroenterol 2015;13(1):90–104. Doi: 10.1007/s11938-014-0039-2.

272. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2019;67(4):674–94. Doi: 10.1111/jgs.15767.

273. Silverberg MS., Satsangi J., Ahmad T., Arnott IDR., Bernstein CN., Brant SR., et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 Suppl A:5A-36A. Doi: 10.1155/2005/269076.

274. Charlson M., Szatrowski TP., Peterson J., Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47(11):1245–51. Doi: 10.1016/0895-4356(94)90129-5.

275. Janmahasatian S., Duffull SB., Ash S., Ward LC., Byrne NM., Green B. Quantification of lean bodyweight. Clin Pharmacokinet 2005;44(10):1051–65. Doi: 10.2165/00003088-200544100-00004.

276. Gislefoss RE., Grimsrud TK., Mørkrid L. Stability of selected serum proteins after long-term storage in the Janus Serum Bank. Clin Chem Lab Med 2009;47(5):596–603. Doi: 10.1515/CCLM.2009.121.

277. Van Stappen T., Brouwers E., Tops S., Geukens N., Vermeire S., Declerck PJ., et al. Generation of a Highly Specific Monoclonal Anti-Infliximab Antibody for Harmonization of TNF-Coated Infliximab Assays. Ther Drug Monit 2015;37(4):479–85. Doi: 10.1097/FTD.0000000000000162.

278. Dulai PS., Singh S., Jairath V., Ma C., Narula N., Vande Casteele N., et al. Prevalence of endoscopic improvement and remission according to patient-reported outcomes in ulcerative colitis. Aliment Pharmacol Ther 2020;51(4):435–45. Doi: 10.1111/apt.15577.

279. Schnitzler F., Fidder H., Ferrante M., Noman M., Arijs I., Van Assche G., et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15(9):1295–301. Doi: 10.1002/ibd.20927.

280. Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 2001;28(5):481–504. Doi: 10.1023/a:1012299115260.

281. Savic RM., Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J 2009;11(3):558–69. Doi: 10.1208/s12248-009-9133-0.

282. Karlsson KE., Plan EL., Karlsson MO. Performance of three estimation methods in repeated time-to-event modeling. AAPS J 2011;13(1):83–91. Doi: 10.1208/s12248-010-9248-3.

283. Dosne A-G., Bergstrand M., Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. J Pharmacokinet Pharmacodyn 2017;44(6):509–20. Doi: 10.1007/s10928-017-9542-0.

284. Robin X., Turck N., Hainard A., Tiberti N., Lisacek F., Sanchez J-C., et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011;12:77. Doi: 10.1186/1471-2105-12-77.

285. Nakazawa M. fmsb: Functions for Medical Statistics Book with some Demographic Data. R package version 0.7.0. 2019.

286. Desai A., Zator ZA., de Silva P., Nguyen DD., Korzenik J., Yajnik V., et al. Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19(2):309–15. Doi: 10.1002/ibd.23026.

287. Cheng D., Cushing KC., Cai T., Ananthakrishnan AN. Safety and Efficacy of Tumor Necrosis Factor Antagonists in Older Patients With Ulcerative Colitis: Patient-Level Pooled Analysis of Data From Randomized Trials. Clin Gastroenterol Hepatol 2020. Doi: 10.1016/j.cgh.2020.04.070.

288. Khan N., Vallarino C., Lissoos T., Darr U., Luo M. Risk of Infection and Types of Infection Among Elderly Patients With Inflammatory Bowel Disease: A Retrospective Database Analysis. Inflamm Bowel Dis 2020;26(3):462–8. Doi: 10.1093/ibd/izz065.

289. de Jong ME., Smits LJT., van Ruijven B., den Broeder N., Russel MGVM., Römkens TEH., et al. Increased discontinuation rates of anti-TNF therapy in elderly inflammatory bowel disease patients. J Crohns Colitis 2020. Doi: 10.1093/ecco-jcc/jjaa012.

290. Paul S., Roblin X. Letter: immunogenicity of anti-TNF in elderly IBD patients. Aliment Pharmacol Ther 2019;50(3):336. Doi: 10.1111/apt.15312.

291. Lichtenstein GR., Diamond RH., Wagner CL., Fasanmade AA., Olson AD., Marano CW., et al. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. Aliment Pharmacol Ther 2009;30(3):210–26. Doi: 10.1111/j.1365-2036.2009.04027.x.

292. Ben-Horin S., Waterman M., Kopylov U., Yavzori M., Picard O., Fudim E., et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11(4):444–7. Doi: 10.1016/j.cgh.2012.10.020.

293. Dotan I., Ron Y., Yanai H., Becker S., Fishman S., Yahav L., et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. Inflamm Bowel Dis 2014;20(12):2247–59. Doi: 10.1097/MIB.0000000000000212.

294. Keizer RJ., Huitema ADR., Schellens JHM., Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49(8):493–507. Doi: 10.2165/11531280-000000000-00000.

295. Greener T., Kabakchiev B., Steinhart AH., Silverberg MS. Higher Infliximab Levels Are Not Associated With an Increase in Adverse Events in Inflammatory Bowel Disease. Inflamm Bowel Dis 2018;24(8):1808–14. Doi: 10.1093/ibd/izy066.

296. Landemaine A., Petitcollin A., Brochard C., Miard C., Dewitte M., Le Balc'h E., et al. Cumulative Exposure to Infliximab, But Not Trough Concentrations, Correlates With Rate of Infection. Clin Gastroenterol Hepatol 2020. Doi: 10.1016/j.cgh.2020.03.018.

297. Asscher VER., Lee-Kong FVY., Kort ED., van Deudekom FJ., Mooijaart SP., Maljaars PWJ. Systematic Review: Components of a Comprehensive Geriatric Assessment in Inflammatory Bowel Disease-A Potentially Promising but Often Neglected Risk Stratification. J Crohns Colitis 2019;13(11):1418–32. Doi: 10.1093/ecco-jcc/jjz082.

298. Kantasiripitak W., Van Daele R., Gijsen M., Ferrante M., Spriet I., Dreesen E. Software Tools for Model-Informed Precision Dosing: How Well Do They Satisfy the Needs? Front Pharmacol 2020;11:620. Doi: 10.3389/fphar.2020.00620.

299. Papamichael K., Cheifetz AS. Therapeutic drug monitoring in patients on biologics: lessons from gastroenterology. Curr Opin Rheumatol 2020;32(4):371–9. Doi: 10.1097/BOR.0000000000000713.

300. Darwich AS., Polasek TM., Aronson JK., Ogungbenro K., Wright DFB., Achour B., et al. Model-Informed Precision Dosing: Background, Requirements, Validation, Implementation, and Forward Trajectory of Individualizing Drug Therapy. Annu Rev Pharmacol Toxicol 2021;61:225–45. Doi: 10.1146/annurev-pharmtox-033020-113257.

301. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther 1997;61(3):275–91. Doi: 10.1016/S0009-9236(97)90160-0.

302. Walson PD. Therapeutic drug monitoring in special populations. Clin Chem 1998;44(2):415–9.

303. Papamichael K., Vande Casteele N., Ferrante M., Gils A., Cheifetz AS. Therapeutic Drug Monitoring During Induction of Anti-Tumor Necrosis Factor Therapy in Inflammatory Bowel Disease: Defining a Therapeutic Drug Window. Inflamm Bowel Dis 2017;23(9):1510–5. Doi: 10.1097/MIB.0000000000001231.

304. Florkowski CM. Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests. Clin Biochem Rev 2008;29 Suppl 1:S83-87.

305. Papamichael K., Gils A., Rutgeerts P., Levesque BG., Vermeire S., Sandborn WJ., et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. Inflamm Bowel Dis 2015;21(1):182–97. Doi: 10.1097/MIB.0000000000000202.

306. Aoki Y., Röshammar D., Hamrén B., Hooker AC. Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection. J Pharmacokinet Pharmacodyn 2017;44(6):581–97. Doi: 10.1007/s10928-017-9550-0.

307. Hughes JH., Tong DMH., Lucas SS., Faldasz JD., Goswami S., Keizer RJ. Continuous Learning in Model-Informed Precision Dosing: A Case Study in Pediatric Dosing of Vancomycin. Clin Pharmacol Ther 2021;109(1):233–42. Doi: 10.1002/cpt.2088.

308. Tong DMH., Hughes JH., Keizer RJ. Evaluating and Improving Neonatal Gentamicin Pharmacokinetic Models Using Aggregated Routine Clinical Care Data. Pharmaceutics 2022;14(10):2089. Doi: 10.3390/pharmaceutics14102089.

309. Maier C., Hartung N., de Wiljes J., Kloft C., Huisinga W. Bayesian Data Assimilation to Support Informed Decision Making in Individualized Chemotherapy. CPT Pharmacometrics Syst Pharmacol 2020;9(3):153–64. Doi: 10.1002/psp4.12492.

310. Polasek TM., Rostami-Hodjegan A. Virtual Twins: Understanding the Data Required for Model-Informed Precision Dosing. Clinical Pharmacology & Therapeutics 2020;0(0):cpt.1778-cpt.1778. Doi: 10.1002/cpt.1778.

311. Sheiner LB., Beal S., Rosenberg B., Marathe VV. Forecasting individual pharmacokinetics. Clinical Pharmacology and Therapeutics 1979;26(3):294–305. Doi: 10.1002/cpt1979263294.

312. Zazo H., Lagarejos E., Prado-Velasco M., Sánchez-Herrero S., Serna J., Rueda-Ferreiro A., et al. Physiologically-based pharmacokinetic modelling and dosing evaluation of gentamicin in neonates using PhysPK. Front Pharmacol 2022;13:977372. Doi: 10.3389/fphar.2022.977372.

313. Le Louedec F., Puisset F., Thomas F., Chatelut É., White-Koning M. Easy and reliable maximum a posteriori Bayesian estimation of pharmacokinetic parameters with the open-source R package mapbayr. CPT Pharmacometrics Syst Pharmacol 2021;10(10):1208–20. Doi: 10.1002/psp4.12689.

314. Leven C., Coste A., Mané C. Free and Open-Source Posologyr Software for Bayesian Dose Individualization: An Extensive Validation on Simulated Data. Pharmaceutics 2022;14(2):442. Doi: 10.3390/pharmaceutics14020442.

315. Smith NM., Chan A., Wilkinson LA., Chua HC., Nguyen TD., de Souza H., et al. Open-source maximum a posteriori-bayesian dosing AdDS to current therapeutic drug monitoring: Adapting to the era of individualized therapy. Pharmacotherapy 2021;41(11):953–63. Doi: 10.1002/phar.2631.

316. InsightRX Offers Precision Dosing Support for New Drug Categories. InsightRX. Available at: https://www.insight-rx.com/resource/insightrx-offers-precision-dosing-support-for-new-drug-categories/. Accessed November 3, 2022.

317. Alihodzic D., Broeker A., Baehr M., Kluge S., Langebrake C., Wicha SG. Impact of Inaccurate Documentation of Sampling and Infusion Time in Model-Informed Precision Dosing. Front Pharmacol 2020;11:172. Doi: 10.3389/fphar.2020.00172.

318. Neely M., Onufrak N., Scheetz MH., Avedissian S., Lakota E., Deitchman AN., et al. Supporting Precision Dosing in Drug Labeling. Clinical Pharmacology and Therapeutics 2021;109(1):37–41. Doi: 10.1002/cpt.2054.

319. Ca R., Mg W., Rp L., Km T., Dj G., B H., et al. Pharmacist-Driven Therapeutic Infliximab Monitoring at the Point Of Care Using Rapidly Assessed Drug Levels In Patients with Inflammatory Bowel Disease. Therapeutic Drug Monitoring 2022. Doi: 10.1097/FTD.0000000000001044.

320. D'Haens GR., Sandborn WJ., Loftus EV., Hanauer SB., Schreiber S., Peyrin-Biroulet L., et al. Higher vs Standard Adalimumab Induction Dosing Regimens and Two Maintenance Strategies: Randomized SERENE CD Trial Results. Gastroenterology 2022;162(7):1876–90. Doi: 10.1053/j.gastro.2022.01.044.

321. Panés J., Colombel J-F., D'Haens GR., Schreiber S., Panaccione R., Peyrin-Biroulet L., et al. Higher vs Standard Adalimumab Induction and Maintenance Dosing Regimens for Treatment of Ulcerative Colitis: SERENE UC Trial Results. Gastroenterology 2022;162(7):1891–910. Doi: 10.1053/j.gastro.2022.02.033.

322. Dreesen E. New Tools for Therapeutic Drug Monitoring: Making Big Things out of Small Pieces. J Crohns Colitis 2021:jjab137. Doi: 10.1093/ecco-jcc/jjab137.

323. Papamichael K., Vande Casteele N., Jeyarajah J., Jairath V., Osterman MT., Cheifetz AS. Higher Postinduction Infliximab Concentrations Are Associated With Improved Clinical Outcomes in Fistulizing Crohn's Disease: An ACCENT-II Post Hoc Analysis. Am J Gastroenterol 2021;116(5):1007–14. Doi: 10.14309/ajg.0000000000001111.

324. Beswick L., Rosella O., Rosella G., Headon B., Sparrow MP., Gibson PR., et al. Exploration of Predictive Biomarkers of Early Infliximab Response in Acute Severe Colitis: A Prospective Pilot Study. J Crohns Colitis 2018;12(3):289–97. Doi: 10.1093/ecco-jcc/jjx146.

325. Thall PF. Adaptive Enrichment Designs in Clinical Trials. Annu Rev Stat Appl 2021;8(1):393–411. Doi: 10.1146/annurev-statistics-040720-032818.

326. Papamichael K., Jairath V., Zou G., Cohen B., Ritter T., Sands B., et al. Proactive infliximab optimisation using a pharmacokinetic dashboard versus standard of care in patients with Crohn's disease: study protocol for a randomised, controlled, multicentre, open-label study (the OPTIMIZE trial). BMJ Open 2022;12(4):e057656. Doi: 10.1136/bmjopen-2021-057656.

327. Jairath V., Khanna R., Zou GY., Stitt L., Mosli M., Vandervoort MK., et al. Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. Aliment Pharmacol Ther 2015;42(10):1200–10. Doi: 10.1111/apt.13408.

328. Khanna R., Zou G., D'Haens G., Feagan BG., Sandborn WJ., Vandervoort MK., et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther 2015;41(1):77–86. Doi: 10.1111/apt.13001.

329. Jean L., Audrey M., Beauchemin C., Consortium OBOT iGenoMed. Economic Evaluations of Treatments for Inflammatory Bowel Diseases: A Literature Review. Can J Gastroenterol Hepatol 2018;2018:7439730. Doi: 10.1155/2018/7439730.

330. Negoescu DM., Enns EA., Swanhorst B., Baumgartner B., Campbell JP., Osterman MT., et al. Proactive Vs Reactive Therapeutic Drug Monitoring of Infliximab in Crohn's Disease: A Cost-Effectiveness Analysis in a Simulated Cohort. Inflamm Bowel Dis 2020;26(1):103–11. Doi: 10.1093/ibd/izz113.

331. Hindryckx P., Novak G., Vande Casteele N., Laukens D., Parker C., Shackelton LM., et al. Review article: dose optimisation of infliximab for acute severe ulcerative colitis. Aliment Pharmacol Ther 2017;45(5):617–30. Doi: 10.1111/apt.13913.

# Curriculum Vitae and publication list

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## Experience:

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## Honours and Grants:

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## Publications

### Publications as part of doctoral thesis:

**Wannee Kantasiripitak**, Sebastian G. Wicha, Debby Thomas, Ilse Hoffman, Marc Ferrante, Séverine Vermeire, Karen van Hoeve, Erwin Dreesen
A model-based tool for guiding infliximab induction dosing to maximise long-term deep remission in children with inflammatory bowel diseases
[manuscript resubmitted]

**Wannee Kantasiripitak**, An Outtier, Sebastian G. Wicha, Alexander Kensert, Zhigang Wang, João Sabino, Séverine Vermeire, Debby Thomas, Marc Ferrante, Erwin Dreesen
Multi-model averaging improves the performance of model-guided infliximab dosing in patients with inflammatory bowel diseases
CPT Pharmacometrics Syst Pharmacol. 2022;00:1–15 [PMID: 35706358]

**Wannee Kantasiripitak***, Zhigang Wang*, Isabel Spriet, Marc Ferrante, Erwin Dreesen
Recent advances in clearance monitoring of monoclonal antibodies in patients with inflammatory bowel diseases
Expert Rev Clin Pharmacol. 2021 Dec;14(12):1455-1466 [PMID: 35034509]
*These authors contributed equally to this work.

**Wannee Kantasiripitak**, Bram Verstockt, Dahham Alsoud, Triana Lobatón, Debby Thomas, Ann Gils, Séverine Vermeire, Marc Ferrante, Erwin Dreesen
The Effect of Aging on Infliximab Exposure and Response in Patients with Inflammatory Bowel Diseases
Br J Clin Pharmacol. 2021; 87:3776–3789 [PMID: 33604964]

**Wannee Kantasiripitak**, Ruth Van Daele, Matthias Gijsen, Marc Ferrante, Isabel Spriet, Erwin Dreesen
Software Tools for Model-Informed Precision Dosing: How Well do They Satisfy the Needs?
Front. Pharmacol. 2020; 11:620 [PMID: 32457619]

### Other publication:

Erwin Dreesen, **Wannee Kantasiripitak**, Iris Detrez, Sebastian Stefanović, Séverine Vermeire, Marc Ferrante, Thomas Bouillon, David Drobne, Ann Gils
A Population Pharmacokinetic and Exposure-Response Model of Golimumab for Targeting Endoscopic Remission in Patients With Ulcerative Colitis
Inflamm Bowel Dis. 2020; 26(4):570-580 [PMID: 31372650]

## Presentations at national and international conferences

**Wannee Kantasiripitak**, Karen van Hoeve, Sebastian G. Wicha, Debby Thomas, Ilse Hoffman, Marc Ferrante, Séverine Vermeire, Erwin Dreesen
Model-informed precision dosing during infliximab induction therapy to improve long-term deep remission rates in paediatric patients with inflammatory bowel diseases
Poster presentation (Abstr 10141), Population Approach Group in Europe (PAGE)
2022 – Ljubljana, Slovenia

Zhigang Wang, **Wannee Kantasiripitak**, Bram Verstockt, João Sabino, Marc Ferrante, Paul Declerck, Geert D'Haens, David Laharie, Séverine Vermeire, Erwin Dreesen
Higher clearance of therapeutic antibodies is associated with worse endoscopic outcomes in patients with Crohn's disease
Poster presentation (Abstr 9971), Population Approach Group in Europe (PAGE)
2022 – Ljubljana, Slovenia

Zhigang Wang, **Wannee Kantasiripitak**, Bram Verstockt, João Sabino, Marc Ferrante, Paul Declerck, Geert D'Haens, David Laharie, Séverine Vermeire, Erwin Dreesen
Infliximab and ustekinumab clearance during induction predicts post-induction endoscopic outcomes in patients with Crohn's Disease
Digital Poster presentation (DOP89), Congress of the European Crohn's and Colitis Organisation (ECCO)
2022 – virtual meeting

Zhigang Wang, **Wannee Kantasiripitak**, Bram Verstockt, João Sabino, Marc Ferrante, Paul Declerck, Geert D'Haens, David Laharie, Séverine Vermeire, Erwin Dreesen
Infliximab and ustekinumab clearance during induction predicts post-induction endoscopic outcomes in patients with Crohn's Disease
Oral presentation, World Conference of Pharmacometrics (WCOP)
2022 – virtual meeting

**Wannee Kantasiripitak**, An Outtier, Debby Thomas, João Sabino, Séverine Vermeire, Marc Ferrante, Erwin Dreesen
Predictors of sustained remission after infliximab de-escalation in patients with inflammatory bowel diseases
Poster presentation (P533), Congress of the European Crohn's and Colitis Organisation (ECCO)
2022 – virtual meeting

**Wannee Kantasiripitak**, An Outtier, Debby Thomas, Alexander Kensert, Zhigang Wang, João Sabino, Sebastian G. Wicha, Séverine Vermeire, Marc Ferrante, Erwin Dreesen
Precise and unbiased infliximab dosing in patients with inflammatory bowel diseases using a multi-model averaging approach
Poster presentation (P333), Congress of the European Crohn's and Colitis Organisation (ECCO)
2022 – virtual meeting

**Wannee Kantasiripitak**, An Outtier, Debby Thomas, João Sabino, Sebastian G. Wicha, Séverine Vermeire, Marc Ferrante, Erwin Dreesen
A multi-model averaging approach improves the performance of model-guided infliximab de-escalation in patients with inflammatory bowel diseases
Poster presentation (Abstr 9757), Population Approach Group in Europe (PAGE)
2021 – virtual meeting

**Wannee Kantasiripitak**, Karen van Hoeve, João Sabino, Séverine Vermeire, Ilse Hoffman, Paul Declerck, Debby Thomas, Marc Ferrante, Erwin Dreesen
Rational infliximab induction dosing to achieve long-term deep remission in children with Inflammatory Bowel Diseases
Poster presentation (P304), Congress of the European Crohn's and Colitis Organisation (ECCO)
2021 – virtual meeting

**Wannee Kantasiripitak**, Ron Mathôt, Bastiaan Oldenburg, Anthony Buisson, Marc Ferrante, David Laharie, Geert D'Haens, Séverine Vermeire, Erwin Dreesen
The value of endoscopic healing index monitoring for guiding infliximab dosing in patients with Crohn's disease
Poster presentation (P497), Congress of the European Crohn's and Colitis Organisation (ECCO)
2021 – virtual meeting

**Wannee Kantasiripitak**, Bram Verstockt, Dahham Alsoud, Triana Lobatón, Debby Thomas, Ann Gils, João Sabino, Séverine Vermeire, Marc Ferrante, Erwin Dreesen
The effect of aging on infliximab exposure and response in patients with inflammatory bowel diseases
Poster presentation (Su438), Digestive Disease Week (DDW)
2021 – virtual meeting

**Wannee Kantasiripitak**, Ron Mathôt, Thierry Dervieux, Anjali Jain, Marc Ferrante, David Laharie, Geert D'Haens, Séverine Vermeire, Erwin Dreesen
The value of combined serum infliximab and endoscopic healing index monitoring for guiding infliximab dosing in patients with Crohn's disease
Poster presentation (Su439), Digestive Disease Week (DDW)
2021 – virtual meeting

**Wannee Kantasiripitak**, Bram Verstockt, Triana Lobatón, Debby Thomas, Ann Gils, Séverine Vermeire, Marc Ferrante, Erwin Dreesen
The effect of age on infliximab pharmacokinetics in patients with inflammatory bowel disease
Poster presentation (P542), Congress of the European Crohn's and Colitis Organisation (ECCO).
2020 – Vienna, Austria

**Wannee Kantasiripitak**, Erwin Dreesen, Iris Detrez, Sebastian Stefanović, Séverine Vermeire, Marc Ferrante, Thomas Bouillon, David Drobne, Ann Gils
A population pharmacokinetic and exposure-response model of golimumab for targeting endoscopic remission in patients with ulcerative colitis
Poster presentation (Abstr 9103), Population Approach Group in Europe (PAGE)
2019 – Stockholm, Sweden

Erwin Dreesen, **Wannee Kantasiripitak**
Pharmacometric models to improve therapeutic drug monitoring of monoclonal antibodies in the treatment of inflammatory bowel diseases
Oral presentation, Pharmacometrics Network Benelux (PNB)
2019 – Niel, Belgium

**Wannee Kantasiripitak**, Erwin Dreesen, Iris Detrez, Sebastian Stefanović, Séverine Vermeire, Marc Ferrante, Thomas Bouillon, David Drobne, Ann Gils
A population pharmacokinetic model to improve mucosal healing upon golimumab induction therapy in patients with ulcerative colitis
Oral presentation, Belgian Week of Gastroenterology (BWGE)
2019 – Antwerp, Belgium

# Scientific acknowledgements, personal contribution, and conflicts of interest

# Scientific acknowledgements

**Chapter I:**

*Wannee Kantasiripitak*, *Ruth Van Daele, Matthias Gijsen, Isabel Spriet, and Erwin Dreesen* designed the research; *Wannee Kantasiripitak*, *Ruth Van Daele, Matthias Gijsen*, *and Erwin Dreesen* assembled the data and performed the research; *Wannee Kantasiripitak and Erwin Dreesen* analysed the data and wrote the manuscript; All authors revised the manuscript and approved the final version of the manuscript.

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**Chapter II:**

*Wannee Kantasiripitak* wrote the manuscript; *Wannee Kantasiripitak* and *Erwin Dreesen* designed the research; *Wannee Kantasiripitak, Sebastian G. Wicha, Alexander Kensert, Zhigang Wang, and Erwin Dreesen* performed the research; *Wannee Kantasiripitak* and *Erwin Dreesen* analysed the data; *An Outtier, Debby Thomas, João Sabino, Séverine Vermeire, and Marc Ferrante* provided data. All authors contributed to the review of the manuscript and approved the final version for submission.

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*Wannee Kantasiripitak and Erwin Dreesen* wrote the manuscript; *Wannee Kantasiripitak and Erwin Dreesen* designed the research study; *Wannee Kantasiripitak, Sebastian G. Wicha, and Erwin Dreesen* performed the research; *Wannee Kantasiripitak and Erwin Dreesen* analysed the data; *Debby Thomas, Ilse Hoffman, Marc Ferrante, Séverine Vermeire, and Karen van Hoeve* provided data. All authors contributed to the review of the manuscript and approved the final version for submission.

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**Chapter IV:**

*Wannee Kantasiripitak* wrote the manuscript; *Wannee Kantasiripitak* and *Erwin Dreesen* designed the research; *Wannee Kantasiripitak* performed the research; *Wannee Kantasiripitak* and *Erwin Dreesen* analysed the data; *Bram Verstockt, Dahham Alsoud,*

*Triana Lobatón, Debby Thomas, Ann Gils, Séverine Vermeire,* and *Marc Ferrante* provided data. All authors contributed to the review of the manuscript and approved the final version for submission.

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# Personal contribution

The author of this thesis manuscript fully contributed to the design of the studies, the generation and assembly of data, the analysis and interpretation of the data, and wrote the manuscripts.

## Conflicts of interest

*Alexander Kensert* declared no conflict of interest.

*An Outtier* declared no conflict of interest.

*Ann Gils* served as a speaker for Merck Sharp & Dohme, Janssen Biologicals, Pfizer, Takeda, Novartis, and AbbVie, and received Investigator-Initiated Research Grants from Pfizer and a national grant from Takeda. KU Leuven licensed anti- bodies for the infliximab, adalimumab, vedolizumab, golimumab, and ustekinumab ELISA to apDia and infliximab and adalimumab lateral flow assays to R-Biopharm.

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