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A time-to-event model relating infliximab trough concentrations to the risk of relapse after extending the infusion interval

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Background: Extending the infliximab infusion interval has been attempted in patients with Crohn's disease (CD) and ulcerative colitis (UC) who sustained treatment response following an earlier interval shortening. We aimed to identify predictors of sustained remission after infliximab interval extension.

Methods: Data from 30 adult patients (17 CD, 13 UC), who underwent infliximab interval extension following earlier interval shortening, were collected from a single-centre database search. All patients were in steroid-free clinical (two-item patient-reported outcome [PRO^2] ≤1 [UC] and ≤8 [CD]) and biological (C-reactive protein [CRP] <5 mg/L or faecal calprotectin [FC] <250 mg/kg) remission at interval extension. Time-to-relapse was modelled using a time-to-event (TTE) model with loss of steroid-free clinical and biological remission being the event of interest (NONMEM7.5). Various hazard functions were explored, and disease type, time-varying infliximab concentrations and infliximab clearance were investigated as predictors of the relapse hazard risk. The infliximab clearance was calculated using weighted averaging of the estimates of 18 population pharmacokinetics models.[1]

Results: In total, 37% of patients (n=11) remained relapse-free until one year after infliximab interval extension (Figure 1). A time-constant (exponential) hazard model proved best to describe the relapse data of patients with CD (Figure 2, Table 1). The Gompertz hazard model best described the data of patients with UC, with the relapse hazard risk increasing over time. Patients with CD had an overall higher relapse hazard risk than patients with UC. For patients with UC, the infliximab trough concentration was negatively related to the relapse hazard risk and was included in the model using a sigmoidal inhibitory E_{max} function. Also, in patients with UC, a higher infliximab clearance was associated with an increase in the relapse risk. The infliximab clearance was also a predictor of the relapse hazard risk, but its effect could not be precisely estimated.

Conclusion: Patients with CD had a higher relapse risk than patients with UC. Only in patients with UC, the hazard risk increased with time, but this risk was lower when the infliximab trough concentration increased. No exposure-response relationship was observed in patients

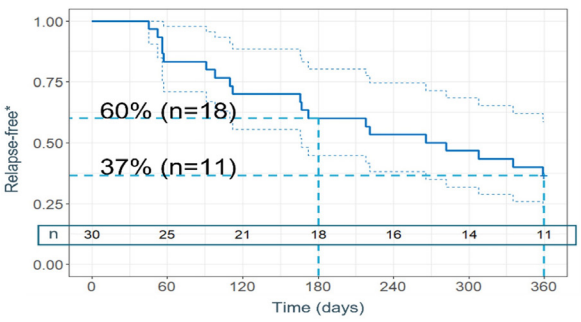

Figure 1. Kaplan–Meier curve of patients with sustained steroid-free clinical and biological remission after infliximab de-escalation. *Relapse-free defined as steroid-free combined clinical and biological remission

with CD. Results of this exploratory analysis should be interpreted with care and prospective confirmation is awaited (MODIFI study; NCT04982172).[2]

[1]Kantasiripitak W. et al. CPT PSP. 2022
[2]Sheiner LB. et al. CPT. 1997

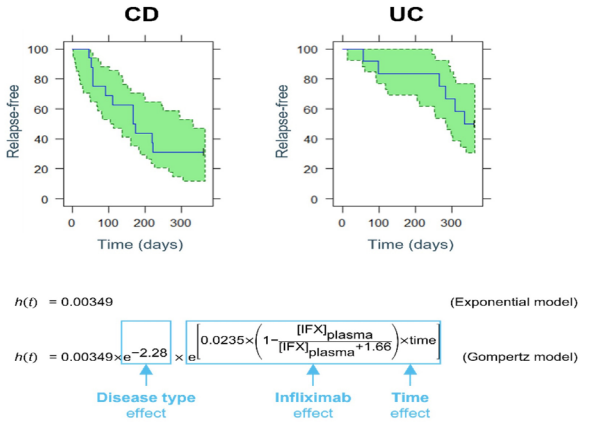

Figure 2. Kaplan–Meier curves and hazard functions of patients with CD and UC with sustained steroid-free clinical and biological remission after infliximab de-escalation.

Table 1. Parameter estimates for time-to-event model.

Model parameter	Estimate (%RSE)
Baseline hazard (λ)	0.00349 (28.9%)
IBD type on baseline	-2.28 (42%)
Shape parameter (γ) [UC only]	0.0235 (52.8%)
EC_{50} on shape [UC only]	1.66 (81.3%)