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Infliximab and prevention of colectomy in acute severe ulcerative colitis: an individual patient data meta-analysis

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Background: Infliximab (IFX) is used to treat patients with acute severe ulcerative colitis (ASUC) who fail to respond to intravenous corticosteroid therapy. Yet, a significant proportion of patients does not respond adequately and requires colectomy. Our aim was to explore baseline predictors of colectomy-free survival during IFX rescue therapy in patients with steroid-refractory ASUC.
Methods: We performed an individual patient data meta-analysis (IPDMA) with data retrospectively collected from hospitalised, corticosteroid-refractory patients diagnosed with ASUC (based on Truelove and Witts' criteria) who received IFX rescue therapy. Baseline characteristics including sex, smoking status, disease extent, disease duration, Mayo endoscopic subscore, serum albumin, C-reactive protein, haemoglobin, and white blood count were evaluated as predictors of colectomy-free survival at three and twelve months after start of IFX therapy. Data were analysed using R software (v4.2.0).
Results: Data were collected from six centres contributing a total of 140 patients (Table 1). Fifteen patients (10.7%) required colectomy within three months and another eight patients underwent colectomy by one year (total colectomy rate after one year 16.4%) (Figure 1). No baseline predictors of colectomy-free survival were identified (log-rank $P>0.05$). Patients who received intensified IFX induction therapy (n=64, >5 mg/kg), in contrast to patients on regular induction doses of 5 mg/kg at weeks 0-2-6 (n=49), did not have lower rates of colectomy. A total of 53 IFX serum trough concentrations (TC) were measured in 31 patients. The median IFX TC during weeks (w)1-2 of therapy was 13.5 mg/L (interquartile range [IQR] 9.3-16.3 mg/L), and 7.0 (IQR 1.9-12.0) mg/L during w3-6. Target attainment rates were 8.3% (1/12 patients) and 18.2% (2/11 patients), respectively, towards the previously reported IFX TC targets of 28.3 mg/L at w2 and 15.0 mg/L at w6 for achieving endoscopic remission at w12.[1] IFX TCs during induction were not significantly different between patients who received standard and intensified induction therapy.
Conclusion: Colectomy rates remain a significant burden of ASUC even for patients receiving IFX. In our interim IPDMA, we did not identify baseline predictors of colectomy-free survival. Poor target attainments of the previously established concentration targets demand dose optimisation. Pharmacometrics modelling of the IFX dose-exposure-biomarker/measure-response relationship within the spECTRUM consortium (DEFINE study) will facilitate dose-finding simulations to demonstrate the value of model-informed therapeutic drug monitoring.
References:
1. Papamichael *et al*. *Clin Gastroenterol Hepatol*. 2016.

Table 1. *Patients characteristics at the start of infliximab therapy*

Characteristics	Value
Number of patients	140
Demographics at baseline	
Sex, women, *n* (%)	79 (56.4)
Age at initiation of infliximab, years, median [IQR]	36.0 [27.0-48.5], NA=9
• ≥65 years, *n* (%)	9.0 (6.4)
• ≥75 years, *n* (%)	3.0 (2.1)
Height, cm, median [IQR]	167.0 [161.5-178.0], NA=101
Weight, kg, median [IQR]	64.5 [60.0-72.0], NA=28
Serology at baseline	
C-reactive protein, mg/L, median [IQR]	31.1 [8.4-70.9], NA=28
Serum albumin, g/L, median [IQR]	28.0 [19.0-35.0], NA=59
Haemoglobin, g/dL, median [IQR]	9.1 [1.1-12.5], NA=28
White blood count, g/L, median [IQR]	11.4 [8.14-14.55], NA=29
Disease characteristics at baseline	
Mayo endoscopic subscore, *n* (1:2:3:NA)	1 : 23 : 109 : 7
Disease duration, years, median [IQR]	3.0 (1.0-9.0), NA=9
Disease extent (Montreal), *n* (%)	
• Proctitis (E1)	8 (5.7)
• Left side colitis (E2)	30 (21.4)
• Extensive colitis (E3)	102 (72.9)
Medication history and smoking status at baseline	
Previous exposure to 5-aminosalicylic acid, *n* (%)	116 (82.9)
Previous exposure to immunomodulators, *n* (%)	46 (32.9)
Smoking status, *n* (%)	
• Active smoking	7 (5.0)
• Previous smoking	12 (8.6)
• Never smoking	48 (34.3)
• NA	73 (52.1)

IQR, inter-quartile range; NA, number of patients with mising information

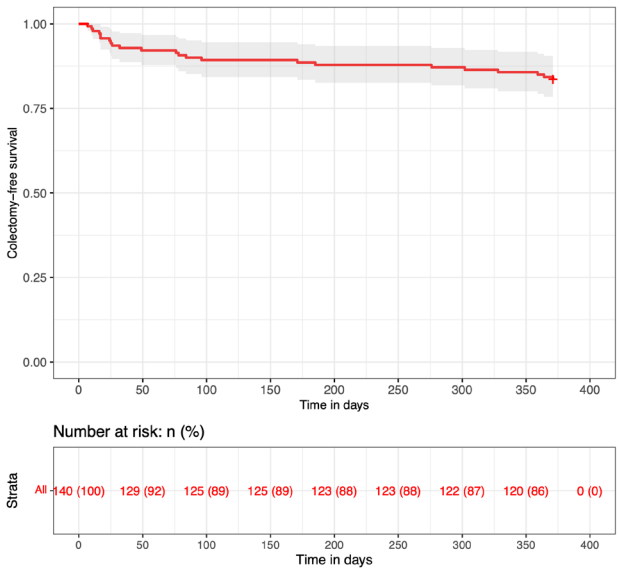

Figure 1. Colectomy-free survival during one-year after the start of infliximab therapy.