Cumulative exposure to infliximab during induction therapy predict remission in patients with Crohn's disease and ulcerative colitis

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Background

- Infliximab revolutionized the management of Crohn's disease (CD) and ulcerative colitis (UC) by reducing the need for hospitalization and surgeries.
- Not all patients with CD and UC enjoy the full benefits of infliximab. About 30% of patients does not respond to induction treatment and 50% loses response during the first year of maintenance treatment.
- The current clinical approach involves trough concentration (TC)-guided therapeutic drug monitoring (TDM) during maintenance treatment [1-2].
- We investigated the potential of using area under plasma concentration–time curves (AUCs) during induction treatment for predicting remission.

Objectives

- To investigate infliximab PK and exposure-response during induction therapy in patients with CD and UC.
- To compare the predictive performance of TCs and the AUCs for predicting remission at week 30.

Methods

- Adult patients with CD and UC received 5 mg/kg intravenous infliximab infusions at weeks 0, 2, 6, 14, 22, and 30.
- Infliximab serum concentrations were measured at 14 time points while clinical and biological data were collected at seven time points.
- A popPK model was developed using MonolixSuite (2023R1; Simulations Plus, California, USA).
- The developed model was used to estimate the AUCs and TCs during induction treatment (up to week 14).
- Logistic regression models were built to predict remission at week 30.

Results

Table 1. Patient characteristics at baseline (n=75)

Parameter	Value
Demographics	
Age (years), median [range]	39 [29–53]
Sex assigned at birth (female), n (%)	33 (44)
Bodyweight (kg), median [range]	70 [165–173]
Body mass index (kg/m^2), median [range]	23.5 [21.2–25.9]
Disease type	
CD, n (%)	41 (54.7)
UC, n (%)	34 (45.3)
Smoking status	
Current , n (%)	18 (24)
Former, n (%)	7 (9.3)
Never, n (%)	50 (66.7)
Clinical data	
Harvey-Bradshaw Index, median [range]	8 [6–10]
Partial Mayo score, median [range]	7 [6–8]
Laboratory data	
C-reactive protein (mg/L), median [range]	12.7 [3.1–22.6]
Fecal calprotectin (µg/g), median [range]	1117 [499–3286]
Serum albumin (mg/dL), median [range]	40.7 [38.3–44]

Table 2. PopPK parameter estimates

Parameter	Estimate	%RSE (%shrinkage)	Bootstrap Median (Confidence interval)
Typical values			
CL (L/day)	0.31	3.66 (1.03)	0.31 (0.29–0.33)
Albumin on CL	-1.13	25.9	-1.09 (-1.59–-0.73)
Body weight on CL	0.6	23.9	0.63 (0.25–0.97)
Anti-infliximab antibody on CL	0.32	0.21	0.13 (-0.13–0.81)
V1 (L)	2.97	2.73 (9.79)	2.95 (2.81–3.26)
Bodyweight on V1	0.58	18.9	0.63 (0.32–0.85)
Q (L/day)	0.33	12.9 (35.65)	0.4 (0.28–0.52)
V2 (L)	2.04	8.15 (9.39)	1.94 (1.55–2.41)
Interindividual variability (IIV)			
on CL	0.31	8.63	0.31 (0.27–0.35)
on V1	0.2	12.7	0.21 (0.15–0.25)
on Q	0.67	19.5	0.67 (0.42–0.99)
on V2	0.6	10.6	0.62 (0.46–0.89)
Corr between CL and V1	0.51	20.6	0.47 (0.17–0.71)
Corr between CL and V2	0.42	27.1	0.4 (0.18–0.63)
Corr between V1 and V2	0.68	15.2	0.6 (0.21–0.82)
Residual error model			
Additive error (µg/mL)	0.64	15.92	0.63 (0.21–1.06)
Proportional error	0.2	4.17	0.2 (0.17–0.24)

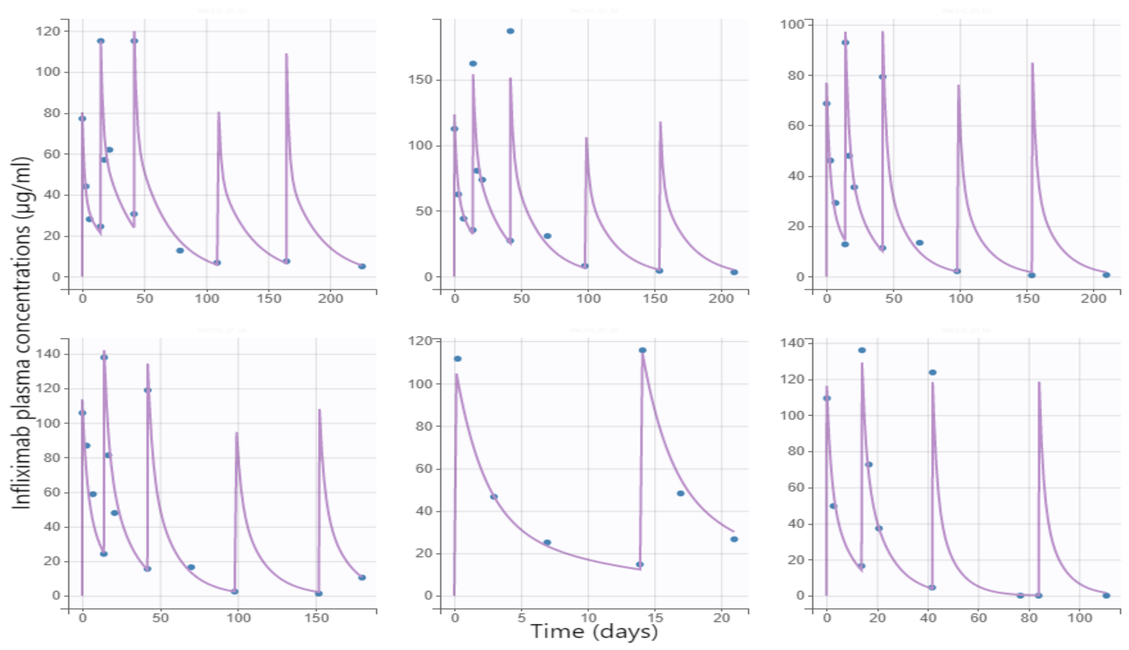

Figure 1. Individual fit of the popPK model (six randomly selected patients)

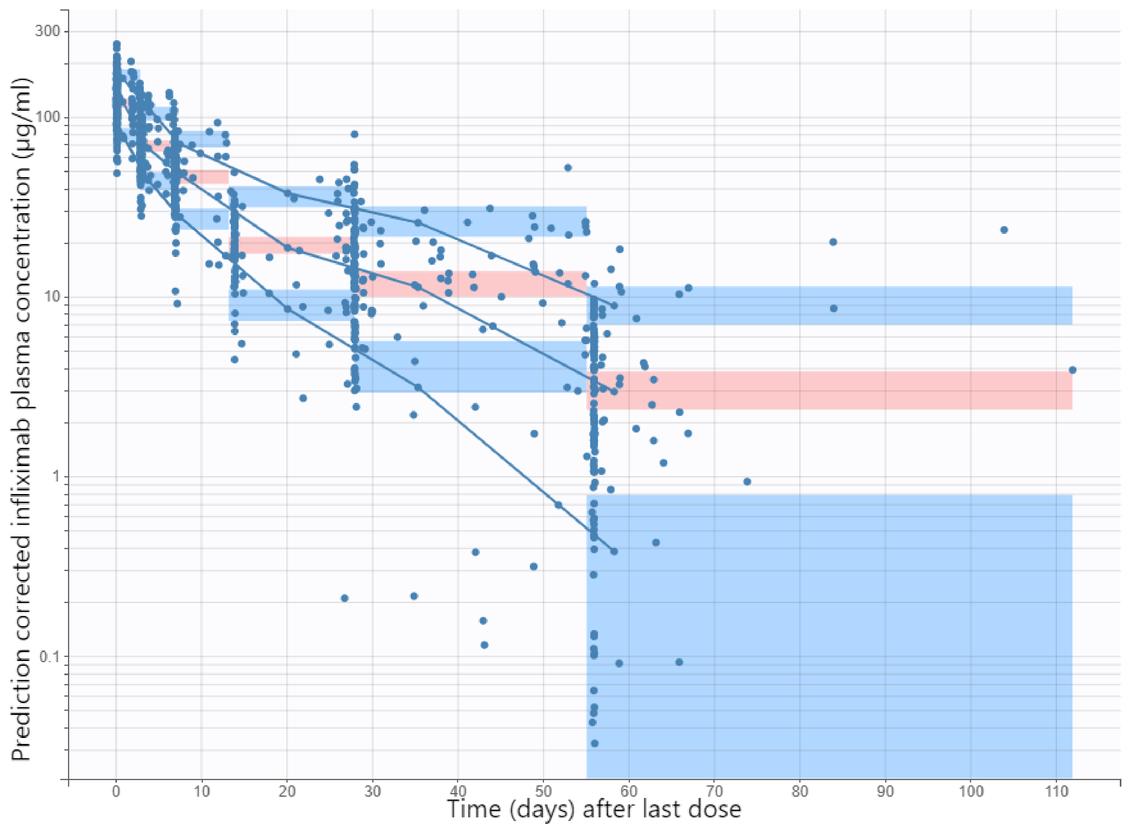

Figure 2. Prediction-corrected VPC of the popPK model.

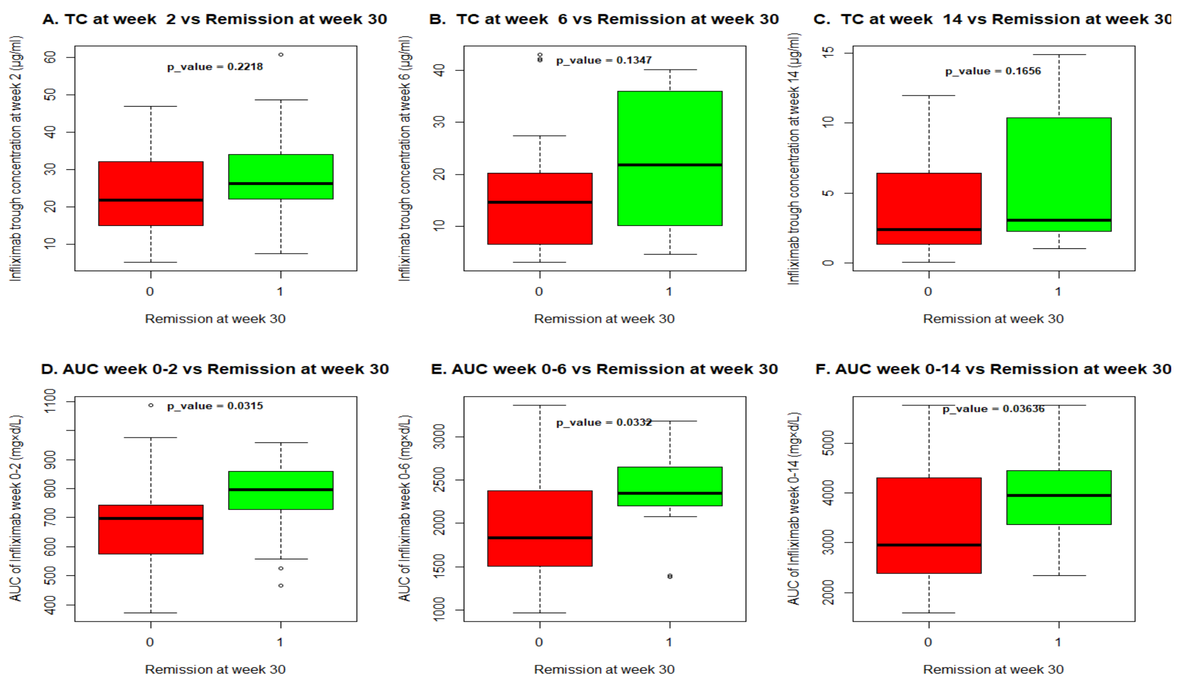

Figure 3. Comparison of TCs at weeks 2, 6, and 14 (panels A, B, C) and AUCs from weeks 0–2, 0–6, and 0–14 (panels D, E, F) between patients with and without remission at week 30.

Conclusion

- AUCs are better predictors for remission than TCs in patients with CD and UC.
- Therefore, a shift from TC-guided TDM to AUC-guided TDM may be considered.

References

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