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Estimation of precision and accuracy of five population pharmacokinetics models of infliximab in patients with inflammatory bowel diseases

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Background

Infliximab is a monoclonal antibody approved for the treatment of inflammatory disease. High interindividual variability in serum infliximab concentrations has been reported during treatment. The difference of dosing requirements for optimal efficacy imply that patients and/or disease characteristics may influence the PK of infliximab differently among patient populations. At this moment, the best approach to adjust the dose of infliximab is through a bayesian approach using a suitable pharmacokinetic model.

Objective

Our aim was to estimate the precision and accuracy of five pharmacokinetic models (PopPK) in patients with inflammatory bowel disease.

Methods

- **Design:** Retrospective observational study
- **Inclusion criteria:**
  - Patients older than 18 years old.
  - Patients with ulcerative colitis or Crohn's disease treated with infliximab since 2014 were included.
  - At least one trough blood samples for determining infliximab.
- The Infliximab concentrations were estimated (Individual prediction) from five models at the samples times through the empirical bayesian of estimates (EBEs) of the pharmacokinetic parameters.
- Data was stratified by indications:
  - Ulcerative Colitis (UC)
  - Crohn's disease (CD)
- Validation of predictive capacity:

Accuracy	Mean residual predictive error (MRPE)
Precision	Root mean square predictive error (RMSPE)

- PopPK models implemented in NONMEM

	Reference	Diagnostic	Age	Model
MOD_A	Fasanmade et al. 2009	Ulcerative colitis	18-81 years	BC
MOD_B	Fasanmade et al. 2011	Crohn's disease	6-76 years	BC
MOD_C	Buurman et al. 2015	Ulcerative colitis Crohn's disease	19–80 years	BC
MOD_D	Dotan et al. 2014	Ulcerative colitis Crohn's disease	20–70 years	BC
MOD_E	Brandse et al. 2017	Ulcerative colitis Crohn's disease	38.6 (13.9) years	BC

Results

Demographics	UC Group Mean (CI 95%)	CROHN Group Mean (CI 95%)
Patients (n)	58	101
Gender, male/female (%)	46/54	47/53
Age (years)	38 (33-43)	35 (30-41)
Infliximab / Biosimilar (%)	16/58 (28%)	35/101 (35%)
Weight (Kg)	72.11 (38.95-108.1)	75.27 (42.87-132.85)
Baseline albumine (mg/dL)	4.09 (2.55-4.8)	4.03 (2.76-4.84)
Immunosupressors (%)	41%	33%
Though concentration (n)	105	182
Trough Infliximab (mg/L)	3.16 (0.05-17.45)	3.35 (0.05-15.37)
ATI positive/total (%)	11/58 (19%)	18/101 (18%)

ATI: antibodies to infliximab

Table 1: Demographics summary of study population.

Accuracy	UC Group		CROHN'S Group	
Model	MRPE	CI 95%	MRPE	CI 95%
MOD_A	-7.73	-12.5; -2.9	-3.54	-5.1; -1.9
MOD_B	-7.95	-13.2; -2.6	-2.00	-3.01; -1.0
MOD_C	-28.87	-49.1; -8.5	-11.25	-14.8; -7.6
MOD_D	-0.88	-1.8; 0.09	0.11	-0.06; 0.28
MOD_E	-5.87	-9.0; -2.7	-2.70	-3.7; -1.6

Table 2: Accuracy of five models.

Precision	UC Group		CROHN'S Group	
Model	RMSPE	CI 95%	RMSPE	CI 95%
MOD_A	26.09	14.4; 37.7	11.52	6.8; 16.2
MOD_B	30.3	12.9; 47.6	7.20	4.4; 9.9
MOD_C	111.61	27.5; 195.6	26.20	15.6; 36.7
MOD_D	5.13	1.4; 8.8	1.21	0.85; 1.5
MOD_E	17.32	10.1; 24.6	7.42	5.1; 9.6

Table 3: Precision of five models with of parameters.

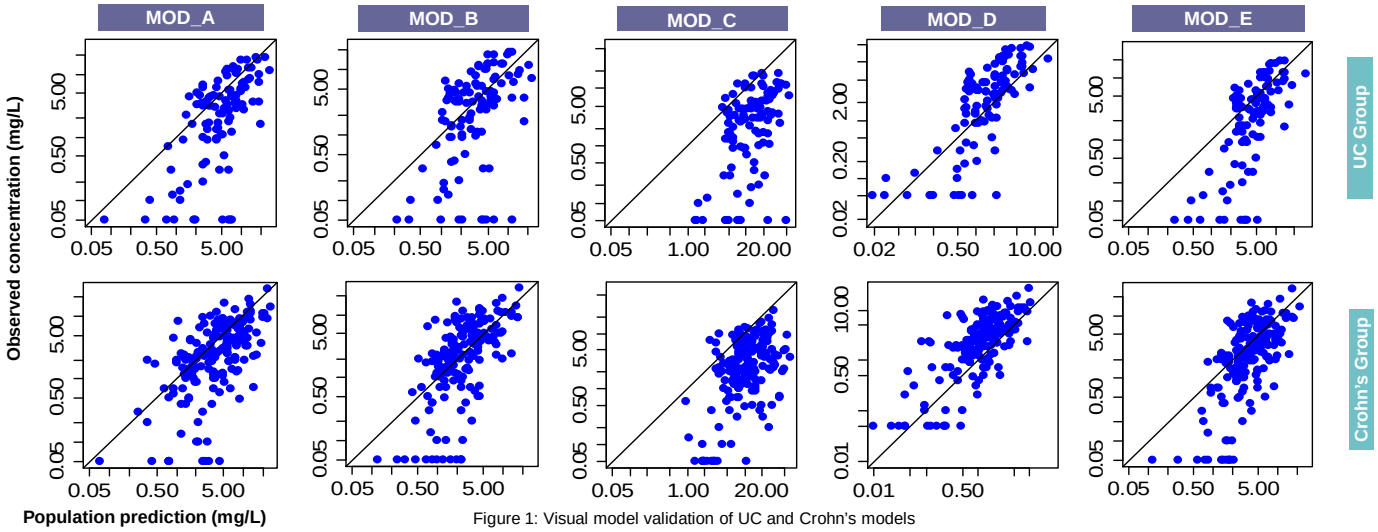

Figure 1: Visual model validation of UC and Crohn's models

Conclusions

- In our study, the bias from the population prediction concentration of all PopPK models except Mod_C have good bias (values close to zero), although the PopPK Model D (Dotan et al) is the only that statistically do not overestimate the infliximab concentration. These results are similar in UC and Crohn's group.
- In terms of precision, MOD_D also perform better than the rest of the model in both groups.
- To asses the predictive capacity of the five models analyzed to select the best model for using in a clinical setting, it would be necessary to calculate accuracy and precision of observed concentrations not used for the EBEs of the PK parameters.