A population pharmacokinetic model of adalimumab in a cohort of pediatric patients with inflammatory bowel disease: a preliminary analysis

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Background and Objective

Therapeutic drug monitoring (TDM) is useful to optimize adalimumab therapy in patients with inflammatory bowel disease (IBD).

The objective of this study was to design a preliminary population pharmacokinetic model (popPK) of adalimumab to evaluate covariates potentially responsible of the PK variability in pediatric patients with IBD.

Material and Methods

3-year retrospective, multicenter study (September 2016 to October 2019).

Study subject

- Children and adolescent (≤ 18 years) diagnosed of IBD.
- Non adherent patients were excluded from the study.

Data Collection

- Demographic.
- Clinical.
- Biochemical biomarkers: serum albumin, C-reactive protein (PCR) and fecal calprotectin.

TDM

- Adalimumab serum concentrations (ASC) and anti-adalimumab antibodies (AAA).
- ELISA technique.
- Pre-dose serum samples.

PopPK Analysis

- Non-linear mixed effects modelling NONMEM v 7.3
- Data visualization, including evaluation and representation of model in R version 3.3.1.

Results

Demographics

- ✓ 23 pediatric patients (10 women): 20 with Crohn disease and 3 with ulcerative colitis.
- ✓ Median (range): age 14.0 (5-18) years and weight 55.9 (20.4-80) Kg.
- ✓ Median (range) serum albumin: 4.0 (2.8-5.0) (g/dL).

TDM outcomes

- ✓ 75 ASC with a medium (range) of 10.72 (0.1-24.7) mcg/mL.
- ✓ Only one patient developed AAA.
- ✓ One-compartment with first order absorption and elimination.
- ✓ Among clinical variables analyzed, only albumin was significant on the apparent clearance (CL/F).
- ✓ Covariates analysis reduced the interindividual variability (IIV) associated with CL from 34.1% to 21.3%.

PopPK Model

$$CL/F\ (L/day) = 0.42 * (ALB/4)^{-2.32} * (WGT/56)^{0.75}$$

$$V/F\ (L) = 11.30 * (WGT/56)$$

$$Ka\ (day^{-1}) = 0.192$$ (From Sharma et al. 2015)

ALB: albumin (g/dL), CL/F: apparent clearance, WGT: weight, (Kg) Ka: Absortion rate constant, V/F: apparent volume of distribution.

Parameter (unit)	Estimate	RSE %	Shrinkage (%)
CL/F (L/day)	0.418	5	
ALB-CL/F (g/dL)	-2.32	9	
V/F (L)	11.3	16	
Ka (day^{-1})	0.192 (fixed)	-	-
IIV-CL (CV, %)	21.3	20	19
RUV (CV, %)	28.4	26	8

ALB: albumin, CL/F: apparent clearance; CV: coefficient of variation; IIVCL/F: interindividual variability on clearance; Ka: absorption rate constant; RSE: residual standard error; RUV: residual unexplained variability; V/F: apparent volume of distribution.

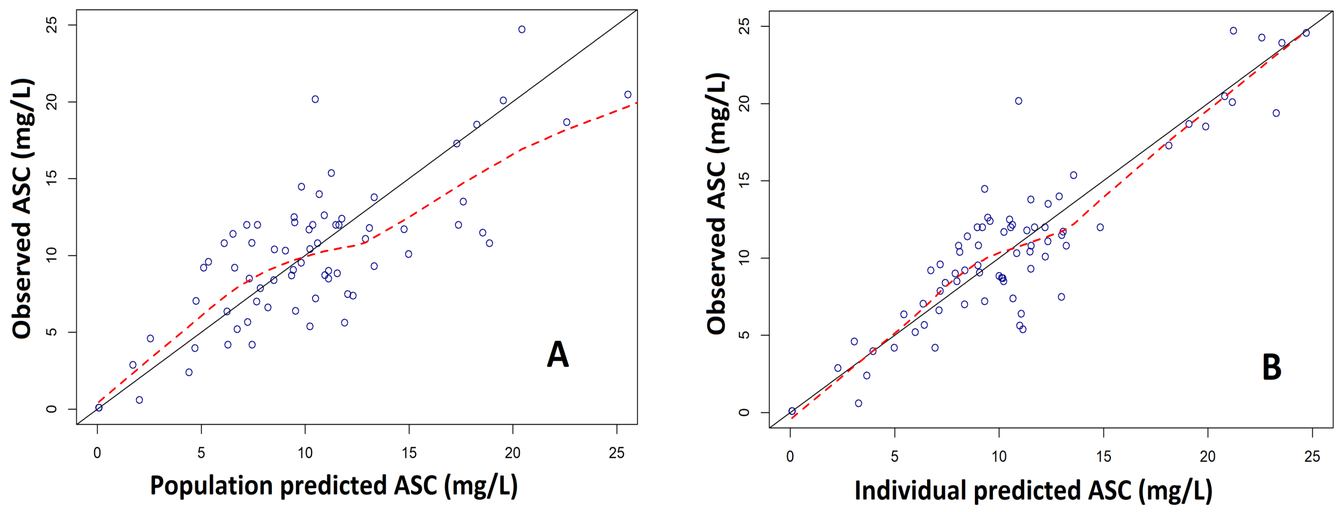

Figure 1. Goodness-of-fit plot of adalimumab concentrations with the final model. Population predictions (A) and Individual predictions (B) vs observed adalimumab serum concentrations. Black solid line: identity line; open circles: adalimumab serum concentrations observed; red dashed lines: locally weighted scatterplot smoothing (LOWESS).

Conclusions

Adalimumab popPK in pediatric patients with IBD was best described by a one-compartment model with first order absorption and elimination. WGT was included on the PK parameters following an allometric relationship. Albumin showed statistically significant differences on adalimumab CL/F explaining the 62.5% of its variability.

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