

Association of Adalimumab Clearance with Platelet Levels in Patients with Inflammatory Bowel Disease: A Nonlinear Mixed-Effects Modelling Approach



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Introduction

Adalimumab (ADM) is a biological drug approved for the treatment of moderately to severely active ulcerative colitis (UC), Crohn's disease (CD), and various other immune-mediated inflammatory diseases [1]. Numerous factors have been shown to accelerate adalimumab clearance (CL/F) in patients with inflammatory bowel disease (IBD), resulting in reduced drug levels [2]. This reduction may contribute to an elevated risk of suboptimal therapeutic response. Therapeutic drug monitoring (TDM) is usually applied reactively during the maintenance phase to optimise adalimumab therapy in these patients [3]. Identification of factors related to variability in drug levels is essential for effective implementation of TDM in clinical practice.

Objectives

The aim of this study was to develop a population pharmacokinetic (PK) model for adalimumab in adult IBD patients and to investigate factors associated with its CL/F.

Methods

Data were retrospectively collected from the medical records of 217 adult IBD patients treated at the Clinical Hospital Center "Zvezdara". Adalimumab was administered subcutaneously, including the induction phase (160 mg at week 0 followed by 80 mg at week 1 or 2) and the maintenance phase (40 mg every or every other week). Alongside adalimumab therapy characteristics, TDM (date and time of blood sampling and measured concentrations), co-therapy, demographic, clinical and available laboratory data were recorded. Levels of anti-adalimumab antibodies (ADA) were categorised as present or absent. Nonlinear mixed-effects modelling was performed for the PK model development and covariate analysis using NONMEM 7.5 software (ICON Development Solutions Inc., Dublin, Ireland). Parameters that could not be estimated with adequate certainty were either fixed to values derived from the literature or assigned informative priors to characterize their values and variability [4]. Evaluation of the final model was performed by internal validation technique.

Results - POPULATION CHARACTERISTICS

	UC (N=22)	CD (N=195)	Total (N=217)
SEX (female)	14 (63.6%)	99 (50.8%)	113 (52.1%)
AGE (years)*	38.64 ± 12.94	39.05 ± 11.91	39.01 ± 11.99
WT (kg)*	67.89 ± 1.68	68.11 ± 1.92	68.08 ± 1.89
BMI (kg/m²)*	23.21 ± 2.82	23.52 ± 4.28	23.49 ± 4.15
HGB (g/L)*	129.26 ± 13.98	136.58 ± 13.48	135.84 ± 13.68
SE (mm/h)*	12.81 ± 2.28	12.7 ± 4.27	12.71 ± 4.11
CRP (mg/L)*	5.27 ± 6.96	4.86 ± 6.68	4.91 ± 6.69
PLT (·10⁹/L)*	309.79 ± 48.62	284.55 ± 47.78	287.11 ± 48.36
ALB (g/L)*	42.40 ± 1.97	42.84 ± 1.41	42.80 ± 1.48
FCP (µg/g)*	393.59 ± 360.92	255.20 ± 252.34	269.23 ± 267.60

*Mean value ± SD

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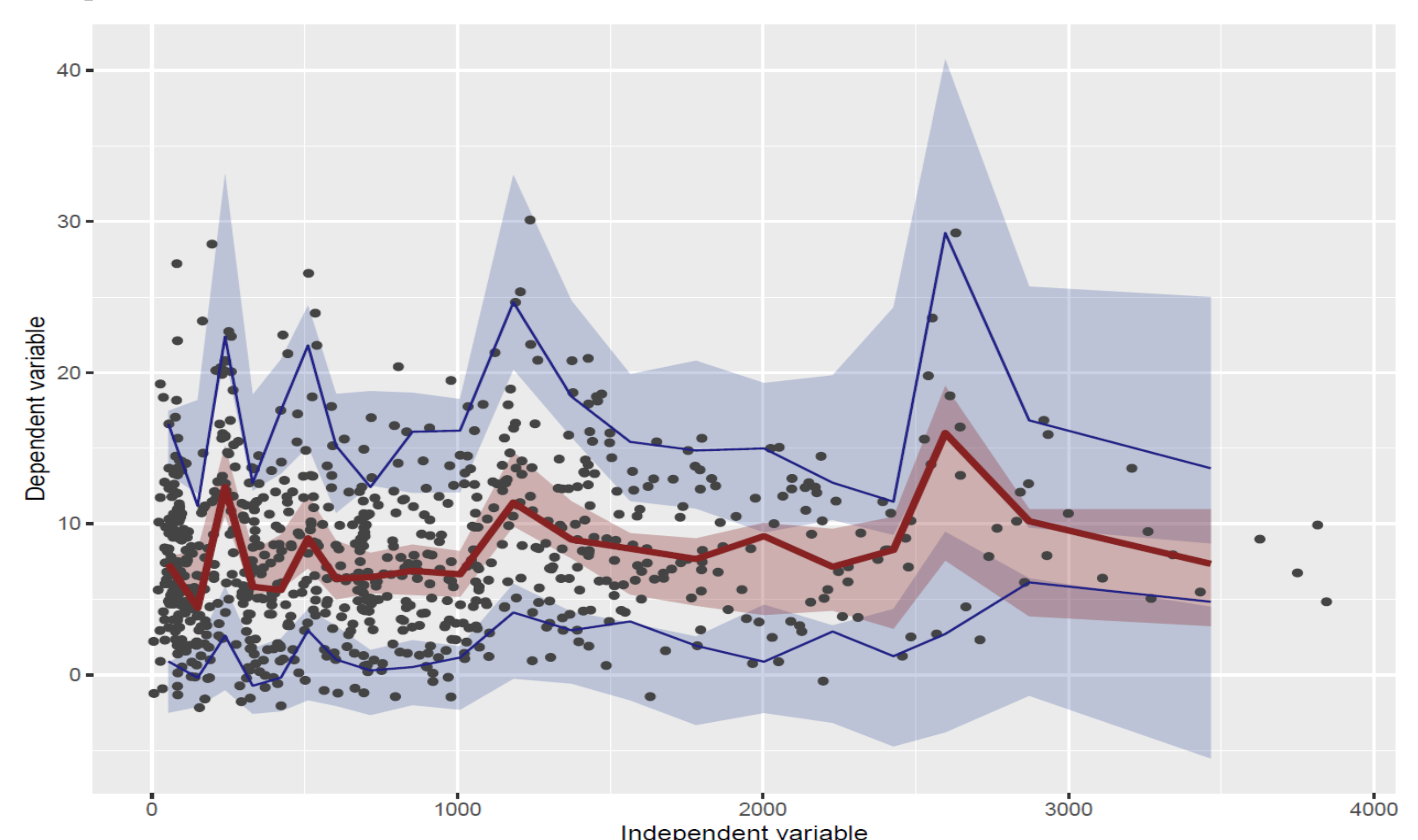
Results - MODEL

Data for modelling consisted of 832 trough adalimumab concentrations (8.661 ± 5.522 mg/L) obtained predominantly during the maintenance phase. Concentrations below the lower limit of quantification or above the upper limit of quantification were accounted for using the M3 method [5]. A one-compartment model using ADVAN2 TRANS2 subroutine with first-order absorption and elimination best described the data. Based on the literature data, the absorption rate constant was fixed at 0.15 1/day [6]. Informative priors were used for V/F and the effect of ADA based on the model developed by Ternant et al [6]. Among tested covariates, only influences of platelets (PLT) and diagnosis (DGN) on CL/F were statistically significant ($p < 0.01$). There were no significant impact of weight, body mass index, lean body weight, and faecal calprotectin.

Parameter	Final estimate	RSE	95%CI	Bootstrap median estimate	95%CI
Ka (1/day)	0.15 FIX	0%	0.15 - 0.15	0.15	0.15 - 0.15
V/F (L)	15 prior	6.9%	12.96 - 17.04	14.9	13.8-15.9
CL/F (L/day)	0.41	3.4%	0.383 - 0.437	0.408	0.383 - 0.442
CL-ADA	4.46 prior	27.6%	2.049 - 6.871	4.60	2.20 - 6.10
CL-PLT	0.00162	22.7%	0.001 - 0.002	0.00160	0.000751 - 0.00237
CL-DGN	0.613	36.4%	0.176 - 1.05	0.591	0.104 - 1.49
Wp	0.23	18.2%	0.148 - 0.312	0.233	0.111 - 0.306
Wa (mg/L)	3.8	6.1%	3.343 - 4.257	3.76	3.28 - 4.26

$$CL/F[L/day] = 0.41 \cdot (1 + 4.46 \cdot ADA) \cdot (1 + 0.613 \cdot DGN) \cdot (1 + 0.00162 \cdot (PLT - 285))$$

Inclusion of the covariates in the base model decreased inter-individual coefficient of variability for CL/F, and in the final model it was 36.95%. Acceptable model performances were confirmed by adequate diagnostic plots and internal validation.



Conclusion

The typical value of adalimumab CL/F in our study is comparable to previous reports [6,7]. This is the first population PK model to demonstrate a positive association between adalimumab CL/F and PLT levels in IBD patients. This finding may suggest that thrombocytosis reflects a higher inflammatory burden, potentially influencing adalimumab elimination, but on the other hand increased disease severity could result from increased elimination of the drug. Nevertheless, recognising factors associated with elevated CL/F may help identify individuals at greater risk of therapeutic failure or loss of response.

Acknowledgement: This research was supported by the Science Fund of the Republic of Serbia, grant no. 6777, project: Improving Clinical Outcomes with Precision Dosing in Patients with Inflammatory Bowel Disease Through Investigating Variability of Monoclonal Antibodies Based on Population Pharmacokinetic-Pharmacodynamic Modeling - optYmAb.