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Pharmacokinetics of adalimumab in Crohn's disease

David Ternant^{1,2} · Konstantinos Karmiris³ · Severine Vermeire³ · Céline Desvignes^{1,2} ·
Nicolas Azzopardi¹ · Theodora Bejan-Angoulvant^{1,4} · Gert van Assche³ ·
Gilles Paintaud^{1,2}

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Adalimumab, an anti-TNF- α monoclonal antibody, is approved for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, Crohn's disease (CD), and ulcerative colitis. The pharmacokinetics (PK) of adalimumab in RA patients was investigated using compartmental modeling [1, 2], but its characteristics in CD patients has never been reported. Patients may develop anti-adalimumab antibodies (AAA) which are responsible for a decrease in adalimumab serum concentration [3] and a loss of clinical response [4, 5, 3, 6, 7]. Antibodies towards another anti-TNF- α monoclonal antibody, infliximab, were shown to increase its clearance [8-11]. The quantitative influence of anti-adalimumab antibodies (AAA) on adalimumab clearance has not been reported yet. We report the first quantitative description of adalimumab pharmacokinetics in Crohn's disease patients.

This is a post hoc analysis of a prospective cohort of 65 patients, being part of a larger cohort, who participated in an observational study in the Inflammatory Bowel Disease unit of the University Hospital of Leuven and for whom at least four adalimumab concentrations were available. [3] Patients were treated subcutaneously either with 160/80 mg at weeks 0/2, or 80/40 mg as an induction phase. Following this phase, all patients were treated with 40-mg adalimumab every 2 weeks. Median follow-up was 20 months. Median [range] age and body weight were 37 years [17–61] and 68 kg [43–109], and 49 (75 %) were women. For 30 out of 65 patients, dosing regimen was increased to 40 mg every week. A total of 341 adalimumab serum concentrations were available. Anti-adalimumab antibodies were detected in nine patients. Adalimumab concentrations were measured using an ELISA technique derived from the one developed for infliximab, [12] and AAA were measured using a double-antigen ELISA based on their capture by adalimumab-coated plates. Adalimumab concentrations and AAA detection were performed in Tours University Hospital, France.

Adalimumab pharmacokinetics was studied by a population approach using MONOLIX 4.3.2 (Lixoft, Saclay, France). A one-compartment model with first-order absorption and elimination rates was used. Apparent volume of distribution (V/F), clearance (CL/F), and first-order absorption rate constant (k_a) were estimated. Interindividual and residual models were exponential and mixed additive-proportional, respectively. The presence of AAA was tested as a covariate on V/F and CL/F.

All parameters were estimated with satisfactory accuracy, and no obvious model misspecification was observed. Estimated typical parameters (relative standard error) were V/F = 13.5 L (10 %), CL/F = 0.42 L/day (9 %) and k_a = 0.15 day⁻¹. Interindividual standard deviations for V/F and CL/F (relative standard error) were

✉ David Ternant
david.ternant@univ-tours.fr

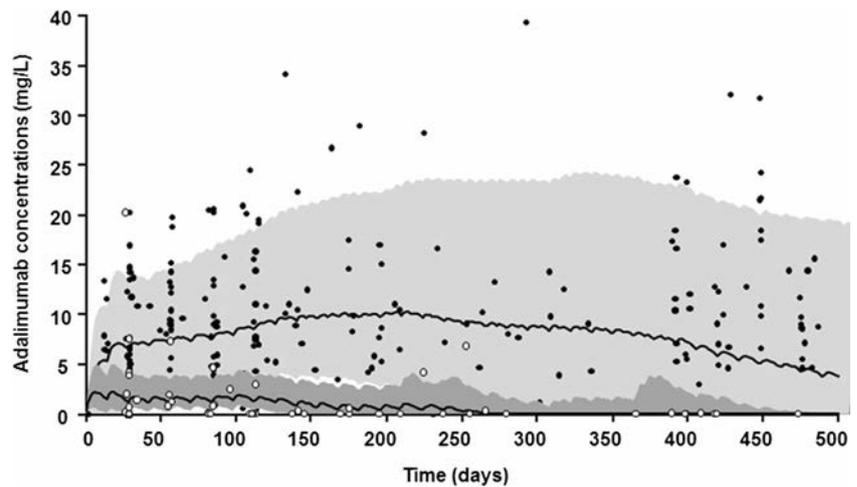
¹ Université François-Rabelais de Tours, CNRS, GICC UMR 7292, Tours, France

² CHRU de Tours, Laboratoire de Pharmacologie-Toxicologie, 2 boulevard Tonnellé, 37044 Tours Cedex, France

³ Department of Gastroenterology, University Hospital, Leuven, Belgium

⁴ CHRU de Tours, Service de Pharmacologie, Tours, France

Fig. 1 Visual predictive check for adalimumab pharmacokinetics in Crohn's disease patients. *Unfilled and solid circles* represent adalimumab concentrations in patients with and without anti-adalimumab antibodies (AAA), respectively. *Dark and light gray surfaces* represent 5–95 % prediction intervals for patients with and without AAA, respectively



$\omega_{V/F} = 48\%$ (19 %) and $\omega_{CL/V} = 65\%$ (10 %), respectively. Interindividual standard deviation for k_a could not be accurately estimated (shrinkage = 94 %) and was therefore fixed to 0. Additive and proportional (relative standard error) standard deviations were $\sigma_{add} = 1.8$ mg/L (8 %) and $\sigma_{prop} = 0.15$ (16 %), respectively. Apparent clearance was 5.5 times higher in presence of AAA (95 % confidence interval = [2.3–13.5], log-likelihood ratio test = 75.5, $p < 0.0001$). Elimination half-life in absence and in presence of AAA was 22 and 4.1 days, respectively (Fig. 1). Elimination half-life without AAA was similar to that reported for RA, 21 days [3].

Our study has some limitations. First, PK data were scarce. Second, the AAA assay was unable to detect them in the presence of adalimumab concentrations above 2 mg/L, which probably led to an underestimation of the proportion of immunized patients.

Overall, this study is the first to report a quantitative description of adalimumab PK in CD. We strongly believe that these results are a prerequisite for the design of future studies on the therapeutic drug monitoring of adalimumab in CD patients.

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Authors’ contribution D. Temant participated actively in execution of the study, analyzed and interpreted the data, and wrote the manuscript.

K. Karmiris, G. Van Assche, and S. Vermeire conceived the ideas and experimental design and participated actively in execution of the study.

C. Desvignes participated actively in execution of the study.

N. Azzopardi participated actively in execution of the study and to the analysis of the data.

T. Bejan-Angoulvant participated to the analysis of the data.

G. Paintaud participated to the conception of the ideas and experimental design, and participated actively in execution of the study, to the analysis and interpretation of the data, and to the writing of the manuscript.

Conflict of interest K. Karmiris reports personal fees from Abbvie and MSD outside the submitted work.

S. Vermeire reports grants and personal fees from UCB Pharma, Abbvie, Merck, and J&J and personal fees from Pfizer, Genentech/Roche, Takeda, Ferring, Celltrion, Mundipharma, Hospira, and Shire during the conduct of the study.

G. van Assche reports reports and Consultancy and/or honoraria from the following: Abbvie, Takeda, MSD, Janssen, and Falk. Research support to University of Leuven was from Abbvie.

G. Paintaud reports grants from Novartis, Roche Pharma, Genzyme, MSD, Servier, and Pfizer outside the submitted work.

D. Temant, C. Desvignes, N. Azzopardi, and T. Bejan-Angoulvant declare that they have no competing interest.

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