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LETTER TO THE EDITORS

A robust estimation of infliximab pharmacokinetic parameters in Crohn's disease

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Pharmacokinetic studies on infliximab, an anti-TNF-α monoclonal antibody, in Crohn's disease reported different pharmacokinetic (PK) parameters [1–4]. These discrepancies could be explained by (i) the inclusion of patients at distance of treatment initiation, (ii) the large intra-individual variability observed during long (>6 months) patient follow-up, or/and (iii) the inclusion of patients both with and without antibodies toward infliximab (ATI). We report here an analysis of infliximab pharmacokinetics in inflammatory bowel disease (IBD) patients that took into account these drawbacks.

This is an update of our previous study [3], and we retrospectively analyzed 133 patients treated by infliximab for IBD between 2006 and 2012 in Tours university hospital, in whom trough and peak infliximab concentrations were available during treatment initiation and ATI not detected during the first 6 months. These patients received 5 mg/kg infliximab at weeks 0, 2, 8, and 14. Median [range] body weight was 60 kg [41–120], and 79 (59 %) were women. Infliximab concentrations were measured using a validated ELISA technique [5].

Infliximab pharmacokinetics was described using a population approach (MONOLIX 4.3.2, Lixoft, Saclay, France). A two-compartment model was used. Central (V_1) and peripheral (V_2) volumes of distribution, and systemic (CL) and intercompartment clearances (Q) were estimated. Interindividual and residual models used were, respectively, exponential and mixed additive-proportional. Body weight (coded as a median-centered power function, β_{weight} being the power parameter for body weight) and gender were tested as covariates for V_1 and CL.

All parameters were estimated with satisfactory accuracy, and no obvious model misspecification was observed. Typical parameters (relative standard error) were V_1=2.6 L (4 %), CL=0.014 L/h (6 %), V_2=4.5 L (1 %), and Q=0.083 L/h (3 %). Interindividual standard deviations for V_1 and CL (relative standard error) were ω_{V1}=27 % (8 %) and ω_{CL}=47 % (7 %), respectively. Additive and proportional (relative standard error) standard deviations were σ_{add}=2.3 mg/L (16 %) and σ_{prop}=0.21 (6 %), respectively. Central volume of distribution (V_1) increased with body weight (β_{weight}=0.22, p=0.00013). Both V_1 and CL were higher in men than in women: typical V_1 was 3.2 L in men and 2.6 L in women, and typical CL was 0.019 L/h in men and 0.014 L/h in women. Distribution and elimination half-lives were $T½$-α=0.5 days and $T½$-β=16.1 days, respectively.

Compared to other PK studies of infliximab in IBD patients (Table 1), our $T½$-α estimate was similar to that reported by Fasanmade et al. (0.2 days [2]) but lower than that reported by others (approximately 3 days [1, 3, 6]). Of note, our $T½$-α estimate was similar to values reported in rheumatoid arthritis (0.3 days [7]) and ankylosing spondylitis (0.3 days [8, 9]).

Among PK studies of infliximab in IBD, this study is the first to analyze patients from their first infusion of infliximab, with a short follow-up of less than 6 months and after exclusion of ATI+ patients. Our study has nevertheless limitations. First, our data were scarce, consisting in trough and peak concentrations. Second, the ATI assay used for this cohort was unable to detect ATI in the presence of concentrations of infliximab >2 mg/L, which probably led to an underestimation of the proportion of immunized patients.

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Table 1 Summary of pharmacokinetic studies of infliximab in inflammatory bowel disease (IBD)

Study	Nb. Patients	PK model	New users of infliximab	Short follow-up (<6 months)	Exclusion of ATI+ patients	V_1 (L)	CL (L/day)	V_2 (L)	Q (L/day)	$T½–\alpha$ (days)	$T½–\beta$ (days)
Ternant et al. 2008	33	2 comp	No	No	No	3.1	0.012	2.4	0.0062	4.1	20.3
Fasanmade et al. 2009	482	2 comp	Yes	No	No	3.1	0.016	4.2	0.33	0.2	13.4
Fasanmade et al. 2011	692	2 comp	Yes	No	No	3.6	0.016	1.3	0.0061	3.5	11.5
Ternant et al. 2014	111	1 comp	No	Yes	Yes	5.8[a]	0.012	–	–	–	14.0
Dotan et al. 2014	54	2 comp	Not precised	No	No	2.4	0.016	1.4	0.0050	2.9	12.0
Present study	133	2 comp	Yes	Yes	Yes	2.6	0.014	4.5	0.083	0.5	15.7

1 comp one-compartment pharmacokinetic model, *2 comp* two-compartment pharmacokinetic model, V_1 central volume of distribution, *CL* systemic clearance, V_2 peripheral volume of distribution, Q intercompartmental clearance, $T½–\alpha$ distribution half-life, $T½–\beta$ elimination half-life

[a] Obtained using one-compartment model. Therefore, volume of distribution is at steady state, i.e., $V_{SS}=V_1+V_2$. Similarly, clearance is at steady state, i.e., $CL_{SS}=V_{SS}.\ \beta$, where β is elimination slope, i.e., $\beta=\ln(2)/T½\text{-}\beta$

Overall, our study is the first to describe infliximab pharmacokinetics at the time of treatment initiation, during the first 6 months of treatment, and in patient in whom ATI were not detected. It confirms the short distribution $T½$ of infliximab, in IBD patients as in other indications.

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Contribution of authors statement D. Aubourg analyzed and interpreted the data and wrote the manuscript; Dr. Picon participated actively in execution of the study; Dr. Lecomte participated in the execution of the study; Dr. Paintaud participated in the interpretation of the data in manuscript writing; Dr. Paintaud participated in the interpretation of the data in manuscript writing; Dr Ternant participated in the data analysis, interpretation, and in manuscript writing.

Conflict of interest Dr. Paintaud reports grants from Novartis, grants from Roche Pharma, grants from Genzyme, grants from MSD, grants from Servier, grants from Pfizer, outside the submitted work.

Dr. Aubourg, Dr Picon, Dr. Lecomte, Dr. Bejan-Angoulvant and Dr. Ternant declare that they have no conflict of interest.

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