


Increased Induction Infiximab Clearance Predicts Early Antidrug Antibody Detection

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Abstract

Treatment of patients with biologics such as infliximab may trigger development of antidrug antibodies, which are associated with faster drug clearance, reduced treatment efficacy, and increased risk of infusion-related reactions. The aim of this study was to identify predictors of baseline infliximab clearance and early antidrug antibody formation. Pharmacokinetic and pharmacokinetic/pharmacodynamic models for infliximab were developed using 21 178 observations from 859 patients from the PLANETRA (ClinicalTrials.gov identifier: NCT01217086) and PLANETAS (NCT01220518) studies in rheumatoid arthritis and ankylosing spondylitis, respectively, to address the specified aims. Infliximab pharmacokinetics were well described by a 2-compartment model with linear mean estimated baseline clearance of 0.26 L/day. Alongside increased body weight, serum C-reactive protein, and antidrug antibody concentrations and decreased serum albumin, elevated serum glucose levels predicted higher clearance. In patients with rheumatoid arthritis, baseline infliximab clearance and body weight were the only identified predictors of early antidrug antibody detection. The odds ratio for antidrug antibody detection for each 0.1 L/day increase in baseline infliximab clearance was 1.78 (95% confidence interval, 1.50–2.12); for each 10-kg increase in body weight, this was 1.19 (1.06–1.33). Here we describe increased serum glucose levels as a novel independent predictor of baseline infliximab clearance. Estimates of baseline infliximab clearance should be incorporated to guide dosing modifications and/or antidrug antibody prophylaxis in clinical practice.

Keywords

antidrug antibody, drug clearance, infliximab, pharmacokinetics

Tumor necrosis factor (TNF) plays a central role in the regulation of the inflammatory response in patients with rheumatoid arthritis, and therapies directed toward this cytokine have assumed a key role in the treatment of rheumatoid arthritis.¹ Infliximab is a chimeric human-murine monoclonal antibody that inhibits functional activity of TNF by binding to it with high affinity.² Infliximab (Remicade; Janssen Biotech Inc., Horsham, Pennsylvania) has well-established efficacy and is approved for the treatment of inflammatory-mediated immune disorders, namely, rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis.²

Antidrug antibodies (ADAs) may arise during treatment with biologic drugs such as infliximab. ADAs are associated with enhanced drug clearance and lower serum drug levels and, as a result, are also linked to reductions in efficacy.^{3,4} Development of ADAs also increases the likelihood of infusion-related reactions.^{5–7} Accordingly, regulatory guidance documents highlight the importance of assessing ADA formation during treatment with biologic drugs.^{8,9} The proportion of patients reported to develop ADAs during treatment varies by drug and ADA assay used, as well as between different inflammatory-mediated immune disorders.⁴

Better understanding of the risk factors for ADA formation—and the potential early identification, or

even prediction, of ADA development—offers an opportunity to reduce the incidence and impact of ADAs and thereby potentially improve the outcomes of infliximab therapy. Here we report retrospective population pharmacokinetic (PK) and PK/pharmacodynamic (PD) analyses of data collected from patients with

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rheumatoid arthritis and ankylosing spondylitis who were treated with infliximab or its biosimilar, CT-P13 (Inflectra; Remsima; CELLTRION Inc., Incheon, Republic of Korea), during 2 randomized, controlled trials (PLANETRA and PLANETAS).^{10,11} The specific objectives of these analyses were: (1) to develop a population PK model for infliximab and then identify whether certain patient-related factors, including ADA concentrations, were predictive of infliximab clearance; and (2) to develop a PK/PD model to identify potential early predictors of ADA formation during infliximab treatment.

Methods

Subjects

The PLANETRA and PLANETAS studies were approved by an institutional review board and performed according to the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent before enrollment.

Full details of the PLANETRA and PLANETAS studies have been published elsewhere.^{10,11} In brief, PLANETRA (ClinicalTrials.gov identifier: NCT01217086) was a randomized, double-blind, 2-arm, parallel-group phase 3 trial conducted at 100 centers across 19 countries in Europe, Asia, Latin America, and the Middle East.¹¹ Details of the study centers and IRBs are presented in Table S1. Eligible patients had a diagnosis of rheumatoid arthritis according to the revised American College of Rheumatology classification criteria for ≥ 1 year before screening and were naive to biologic ankylosing spondylitis therapy. Active disease was defined by the presence of ≥ 6 swollen joints, ≥ 6 tender joints, and at least 2 of the following: morning stiffness lasting ≥ 45 minutes, serum C-reactive protein (CRP) concentration > 2.0 mg/dL, and erythrocyte sedimentation rate > 28 mm/h despite methotrexate therapy for ≥ 3 months (stable dose of 12.5–25 mg/week for ≥ 4 weeks before screening).¹¹

PLANETAS (NCT01220518) was a randomized, double-blind, 2-arm, parallel-group phase 1 trial conducted at 46 centers across 10 countries in Europe, Asia, and Latin America.¹⁰ Details of the study centers and IRBs are presented in Table S1. Eligible patients had a diagnosis of ankylosing spondylitis according to the modified New York classification criteria for ≥ 3 months before screening, were naive to biologic rheumatoid arthritis therapy, and had a Bath Ankylosing Spondylitis Disease Activity Index score ≥ 4 (range, 0–10) and a visual analog scale score for spinal pain ≥ 4 (range, 0–10).¹⁰

Procedures

In PLANETRA, patients were randomly assigned 1:1 to receive a 2-hour intravenous infusion of 3 mg/kg infliximab or CT-P13 in weeks 0, 2, and 6 and then every 8 weeks up to week 54. Weekly methotrexate (12.5–25 mg/week, oral or parenteral dose) and folic acid (≥ 5 mg/week, oral dose) were coadministered.¹¹ In PLANETAS, patients were randomly assigned 1:1 to receive a 2-hour intravenous infusion of 5 mg/kg infliximab or CT-P13 at weeks 0, 2, and 6 and then every 8 weeks up to week 54. At the investigator's discretion, patients received an antihistamine (chlorpheniramine 2–4 mg or equivalent doses of other antihistamines) 30–60 minutes before infusion of study drug.¹⁰

PK data were obtained from the PLANETRA and PLANETAS studies and ADA data from the PLANETRA study only. In both studies, serum blood samples for PK analysis were obtained from patients immediately prior to study drug infusion, at the end of the infusion and 1 hour after the infusion at weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54. In the PK analyses reported here, serum concentration-time data from patients receiving infliximab or CT-P13 were pooled (and hereafter are referred to solely as “infliximab serum concentrations”) because no differences in PK between the 2 treatment groups were identified in PLANETAS or PLANETRA.^{10–13} Infliximab serum concentrations were measured using a flow-through immunoassay platform (Gyrolab xP, Gyros AB, Uppsala, Sweden).¹⁴ The lowest level of quantification for infliximab measurements was 500 ng/mL, and interassay precision and accuracy for CT-P13 and Remicade were confirmed as $\leq 14.4\%$ for coefficient of variation and within $\pm 9.7\%$ for difference from theoretical concentration, respectively. Samples for ADA analysis were obtained in weeks 0, 14, 30, and 54 of PLANETRA. ADAs to infliximab or CT-P13 were assessed in 5% patient serum using a validated bridging electrochemiluminescent immunoassay method involving the Meso Scale Discovery platform (MSD, Rockville, Maryland).¹⁰ This method involved both screening and confirmatory assays.¹⁵ In the screening assay, samples were acidified and then neutralized with biotinylated and SULFO-TAG-labeled drug so that any ADA present in the sample formed immune complexes with the labeled drug and during an incubation period, biotin-containing antibody bridges bound to streptavidin on the immunoassay plate. A reaction buffer was then added and the SULFO-TAG labels were electrochemically stimulated to emit light. The amount of luminescence was proportional to the amount of ADA in the sample. In the confirmatory assay, unlabeled drug was incubated with the sample and labeled drug. In this assay, unlabeled and labeled drug competed to bind to any ADAs in the sample. If ADAs were present, a reduction in

the luminescence signal occurred, confirming both the specificity of ADA and the positivity of the sample. The relative sensitivity of the ADA assay was 75 ng/mL in 100% human serum. Because ADA findings were similar for infliximab and CT-P13 in PLANETRA,^{11,13} PK/PD analyses reported here are based on pooled data from that study.

Population PK and PK/PD Modeling

Population PK and PK/PD models were generated in NONMEM version 7.3 (ICON Development Solutions, Dublin, Ireland) using the first-order condition estimation method without or with the LAPLACE INTERACTION NUMERICAL SLOW options, respectively. The PK model was a 2-compartment linear model fitted to all available infliximab serum concentration-time data obtained from both PLANETRA and PLANETAS. This model was parameterized in terms of clearance, intercompartmental clearance, and volumes of the central and peripheral compartments. All concentration-time data were modeled; observations below the limit of quantification were addressed using the M3 method.¹⁶ Standard model-building approaches were used, with covariates initially selected at $P < .05$ and retained on back-elimination at $P < .001$. The final model was subjected to visual predictive checks, nonparametric bootstrapping, and other model evaluations. This established the full PK model for infliximab in the complete database.

The second model was a PK/PD model developed to identify patient-related factors measurable at baseline and early in treatment that may be useful for identifying patients who subsequently develop ADAs. Because of the relatively low incidence of ADAs in infliximab-treated patients with ankylosing spondylitis, only data from the PLANETRA study were used to generate this model. The incidence of ADAs at any time postbaseline was modeled using logistic regression to describe the probability of developing ADAs. Initial individual estimated baseline clearance from the population PK model, along with additional selected potential baseline predictors of ADAs (body weight, albumin, patient sex, methotrexate dose, presence of immunosuppressants, and serum glucose), were tested and ranked using Fisher scoring.

Results

Population PK Model

Database. The original database contained 22 145 PK observations from a total of 860 patients with rheumatoid arthritis and ankylosing spondylitis who were enrolled in the PLANETRA and PLANETAS studies. Overall, 967 observations were removed from the database, of which 851 were predose observations.

In addition, 53 observations were removed as outliers because of high conditional weighted residuals, and 63 observations were removed because of a lack of information on concentration and treatment. An additional 2188 observation records were below the limit of quantification at some point during the studies. The final database contained 18 990 measurable observations and 2188 nonmeasurable observations from 859 patients (rheumatoid arthritis, $n = 602$; ankylosing spondylitis, $n = 257$).

Overall, baseline demographic characteristics were consistent between patients with rheumatoid arthritis enrolled in PLANETRA and patients with ankylosing spondylitis in PLANETAS (Tables 1 and 2). Patients with rheumatoid arthritis were slightly older than those with ankylosing spondylitis (mean age, 48.8 and 39.2 years, respectively). Baseline mean CRP levels were slightly higher in patients with ankylosing spondylitis compared with those patients with rheumatoid arthritis (213 and 183 nmol/L, respectively). ADAs were detected in the preinfusion serum of 3 patients.

Infliximab PK

Infliximab PK was well described by a 2-compartment model with linear clearance. First trough and maintenance levels are shown in Table S1. The parameters for this final model are summarized in Table 3. In this patient population, mean baseline infliximab clearance was 0.262 L/day. Goodness-of-fit plots and visual predictive checks for the final model are shown in Figures S1 and S2, respectively.

Predictors of Infliximab Clearance

Increased body weight, increased ADA concentrations, decreased serum albumin concentrations, and increased CRP or serum glucose concentrations were each predictive of higher baseline infliximab clearance (Figure 1). Over the range of body weight in the database (34–139 kg), baseline clearance ranged from 0.16 to 0.43 L/day. For ADA concentrations (0 – 2.097×10^7), albumin concentrations (22–59 g/L), and CRP concentrations (1–2927 nmol/L), baseline clearance range was 0.26–167.30, 0.32–0.23, and 0.24–0.31 L/day, respectively. For serum glucose concentration, baseline clearance ranged from 0.33 to 0.48 L/day. Baseline clearance was higher in patients with the highest serum glucose concentrations versus those with the lowest glucose concentrations (overall range of glucose concentrations, 3.16–28.6 mmol/L). Patient sex had only a weak impact such that women had a 7% lower baseline clearance than men. Concomitant immunosuppressant therapy, in the form of methotrexate, had little effect on baseline clearance (Figure 2). Unexplained variability in baseline infliximab clearance between patients, expressed as the coefficient of variation, was 28%.

Table 1. Continuous Baseline Demographics

| | PLANETRA (n = 602) | PLANETAS (n = 257) | Normal Laboratory Values for Examinations |
|------------------------------------|-----------------------|-----------------------|--|
| Age, years | | | |
| Mean (SD) | 48.8 (11.9) | 39.2 (11.4) | |
| Median (min, max) | 50 (18, 75) | 38 (18, 70) | |
| Weight, kg | | | |
| Mean (SD) | 70.3 (15.7) | 75.6 (14.8) | |
| Median (min, max) | 68.4 (36, 134) | 74.6 (45, 122) | |
| Body mass index, kg/m ² | | | |
| Mean (SD) | 26.4 (5.08) | 25.6 (4.19) | |
| Median (min, max) | 25.8 (13.9, 49.3) | 25.2 (17.5, 41.8) | |
| Body surface area, m ² | | | |
| Mean (SD) | 1.78 (0.225) | 1.89 (0.217) | |
| Median (min, max) | 1.76 (13.9, 49.3) | 1.89 (1.4, 2.5) | |
| ALT, IU/L | | | 0–35 |
| Mean (SD) | 21.4 (13.9) | 21.6 (13.1) | |
| Median (min, max) | 18 (0, 127) | 19 (4, 95) | |
| AST, IU/L | | | 0–35 |
| Mean (SD) | 20.3 (9.87) | 21 (8.33) | |
| Median (min, max) | 18 (0, 137) | 19 (5, 73) | |
| Albumin, g/L | | | 35–55 |
| Mean (SD) | 41.9 (3.84) | 44 (3.48) | |
| Median (min, max) | 42 (0, 58) | 45 (27, 54) | |
| Bilirubin, μmol/L | | | 5.1–20.5 (total) |
| Mean (SD) | 6.51 (3.51) | 6.51 (3.51) | |
| Median (min, max) | 5.6 (0, 36.8) | 5.6 (0, 36.8) | |
| CRP, nmol/L | | | |
| Mean (SD) | 183 (228) | 213 (275) | |
| Median (min, max) | 106 (0, 1980) | 126 (1, 1660) | |
| ADA concentration | | | |
| Mean (SD) | 2.23 (27.6) | 1.61 (20.5) | |
| Median (min, max) | 0 (0, 640) | 0 (0, 320) | |
| Glucose, mmol/L | | | 3.9–5.6 (fasting) |
| Mean (SD) | 5.32 (1.4) | 5.42 (2.1) | |
| Median (min, max) | 5.05 (3.2, 21.1) | 5.16 (3.5, 28.6) | |

ADA, antidrug antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; max, maximum; min, minimum; SD, standard deviation.

PK/PD Model (Predictors of ADA Formation)

Database. Overall, 398 patients developed ADAs during the 2 clinical studies (PLANETRA, n = 320 [53.2% of 602 patients]; PLANETAS, n = 78 [30.4% of 257 patients]); thus, the PK/PD model estimating the probability of ADA was built using data from the PLANETRA study (ie, from 614 patients with rheumatoid arthritis).

Predictors of ADA Formation

The model identified baseline infliximab clearance and body weight as the only significant predictors of ADA formation (both $P < .001$; Figure 3). Other investigated variables (serum albumin, patient sex, methotrexate dose, use of immunosuppressants, and serum glucose) did not predict ADA formation.

The odds ratio for ADA formation for each 0.1 L/day increase in baseline infliximab clearance was 1.78 (95% Wald-based confidence interval, 1.50–2.12); the corresponding figure for each 10-kg increase in body weight

was 1.19 (95% Wald-based confidence interval, 1.06–1.33). Mean baseline infliximab clearance for patients who became ADA-positive versus patients who did not develop ADAs during this study was 0.364 versus 0.264 L/day, respectively; the associated probabilities of seroconversion were 0.67 versus 0.49, respectively.

Discussion

In this analysis, we found that the PK profile of infliximab was well described by a 2-compartment model with linear clearance. Alongside well-described predictors of clearance, we found the serum glucose concentration to be predictive of fast infliximab clearance. Our study has also shown, for the first time conclusively, that body weight and baseline infliximab clearance are predictive for ADA formation. By longitudinally assessing the rate of baseline infliximab clearance in individual patients early during treatment with infliximab (including before ADAs were detectable), we were able to show

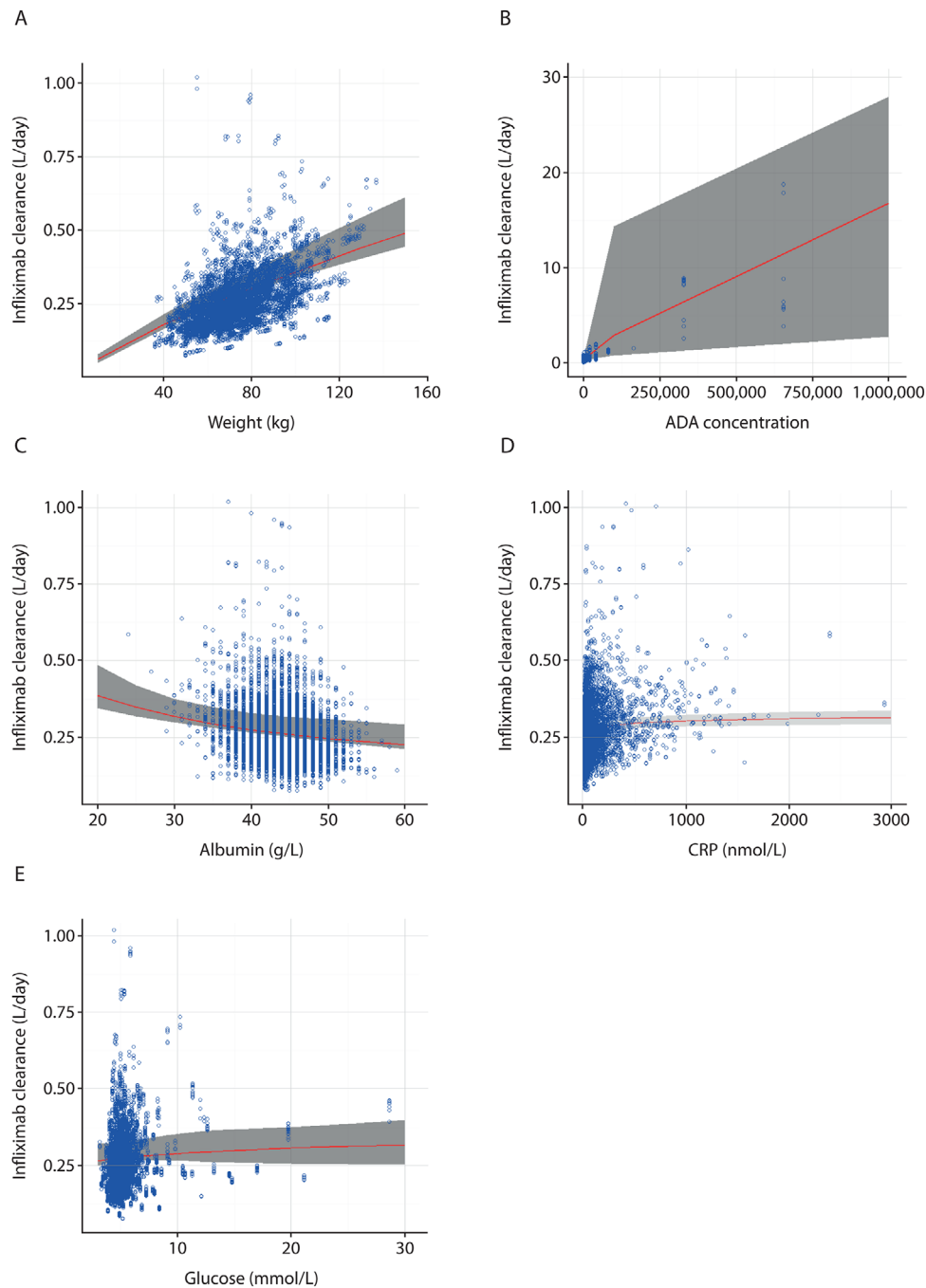


Figure 1. Effects of different patient factors on infliximab clearance: body weight (A), ADA concentration (B), albumin (C), CRP (D), and glucose (E). In all panels, the open blue circles represent the individual parameter values, the solid red line is the bootstrap median of the covariate effect, and the shaded gray area is the 90% bootstrap confidence interval of the covariate effect. ADA, antidrug antibody; CRP, C-reactive protein.

that rapid baseline clearance preceded and predicted the formation of ADAs. This novel finding strongly suggests that rapid baseline clearance of infliximab can act as a driver of ADA formation in patients treated with this anti-TNF therapy.

Calculated baseline infliximab clearance in patients with rheumatoid arthritis and ankylosing spondylitis in this analysis (0.262 L/day) was consistent with

published data for these 2 patient populations (0.26–0.27 L/day).¹⁴ We believe that our findings are also relevant to patients with inflammatory bowel disease (IBD), as most factors associated with increased infliximab clearance in our analysis (increased body weight, increased ADA, decreased albumin, and increased CRP) have also been found to be predictive of infliximab clearance in studies of patients with IBD.^{17–21} Of

Table 2. Categorical Baseline Demographics

| | PLANETRA (n = 602) | PLANETAS (n = 257) |
|---------------------|-----------------------|-----------------------|
| Sex | | |
| Male | 105 | 208 |
| Female | 497 | 49 |
| Race | | |
| White | 439 | 189 |
| Asian | 70 | 29 |
| Other | 93 | 39 |
| ADA grade | | |
| Negative | 580 | 248 |
| Positive | 3 | 3 |
| Unknown | 19 | 6 |
| NAb grade | | |
| Negative | 594 | 251 |
| Positive | 5 | 1 |
| Unknown | 3 | 5 |
| Treatment | | |
| Biosimilar (CT-P13) | 302 | 131 |
| Infliximab | 300 | 126 |
| Corticosteroid | | |
| No | 228 | 194 |
| Yes | 374 | 63 |
| Methotrexate | | |
| No | 6 | 256 |
| Yes | 596 | 1 |
| Budesonide | | |
| No | 600 | 257 |
| Yes | 2 | 0 |
| Azathioprine | | |
| No | 602 | 257 |
| Yes | 0 | 0 |
| Immunomodulators | | |
| No | 6 | 256 |
| Yes | 596 | 1 |
| Diabetes | | |
| No | 593 | 253 |
| Yes | 9 | 4 |

ADA, antidrug antibody; NAb, neutralizing antibody.

note, high baseline clearance has previously been shown to be associated with treatment failure in patients with ulcerative colitis.¹⁷ Interestingly, rapid clearance has also recently been linked to treatment outcomes; a retrospective analysis of 2 large randomized trials has demonstrated that rapid clearance was strongly linked to decreased overall survival in patients who received pembrolizumab for the treatment of melanoma and non-small cell lung cancer.²²

High glucose concentrations were also associated with more rapid baseline clearance of infliximab in our study: baseline clearance was approximately 15% higher in patients with the highest serum glucose concentrations than in those with the lowest glucose concentrations. This finding may reflect increased glycation of infliximab in the presence of high glucose concentrations,^{23,24} as there is evidence from animal studies that the vascular clearance of glycosylated

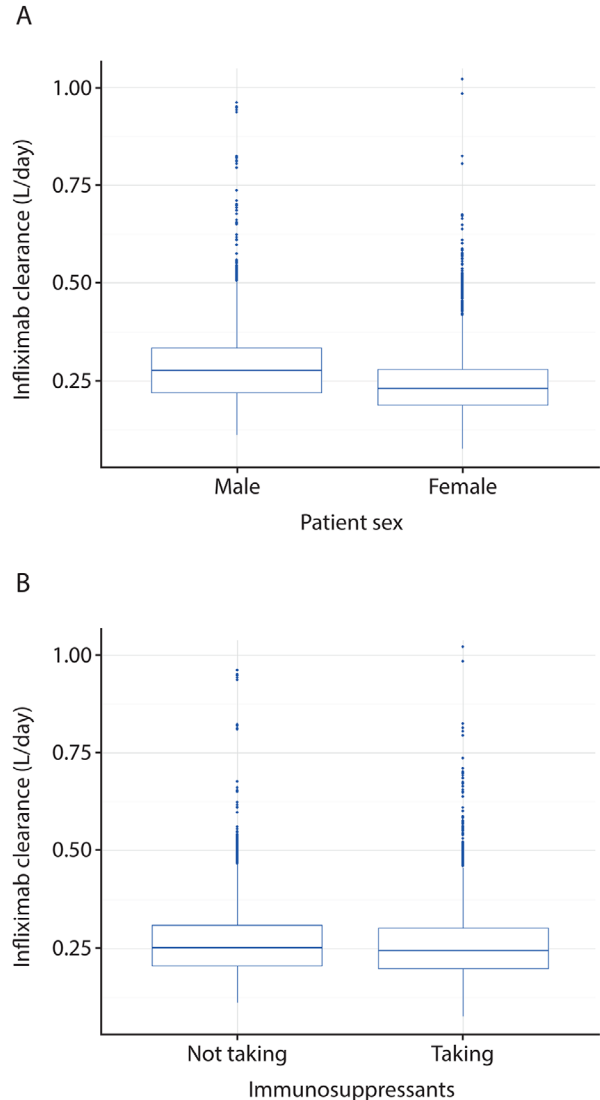


Figure 2. Effects of patient sex (A) and concomitant immunosuppressant therapy (B) on infliximab clearance. In these panels, the solid line in the middle represents the bootstrap median, the lower edge of the box is the lower 25th percentile, the upper edge of the box is the upper 75th percentile, the whiskers represent the lower 5th and upper 95th percentiles, and the symbols above the whisker are outliers.

immunoglobulin G is significantly faster than that of nonglycosylated antibodies.²⁴ Of note, diabetes (in addition to body weight, ADA, estimated creatinine clearance, patient sex, total albumin, and alkaline phosphatase) has been identified as a covariate of clearance for the interleukin-12- and interleukin-23-targeting monoclonal antibody ustekinumab in patients with psoriasis.²⁵ Increased clearance of infliximab in patients with high glucose levels might also be related to an increased inflammatory state in such patients that may drive TNF levels higher, resulting in greater target-mediated elimination of infliximab.

Table 3. Final Parameters for the Population Pharmacokinetic Model

| Parameter, Units | Typical Value | SE, % | Lower 2.5th Percentile | Bootstrap Median | Upper 97.5th Percentile |
|--|---------------|-------|------------------------|------------------|-------------------------|
| Baseline CL, L/day | 0.262 | 1.5 | 0.252 | 0.266 | 0.326 |
| V _c , L | 2.8 | 0.4 | 2.68 | 2.79 | 2.84 |
| Q, L/day | 0.0511 | 5.7 | 0.04063 | 0.0557 | 0.9389 |
| V _p , L | 0.868 | 3 | 0.7973 | 0.898 | 2.437 |
| Effect of weight on baseline CL | 0.726 | 5.8 | 0.5983 | 0.729 | 0.8537 |
| Effect of weight on V _c | 1 | Fixed | 1 | 1 | 1 |
| Effect of weight on Q | 0.75 | Fixed | 0.75 | 0.75 | 0.75 |
| Effect of weight on V _p | 1 | Fixed | 1 | 1 | 1 |
| Effect of albumin on baseline CL | -0.34 | 11.2 | -0.5031 | -0.32 | -0.1333 |
| Effect of ADA concentration on baseline CL | 0.304 | 10.3 | 0.02265 | 0.307 | 1.59 |
| Effect of glucose on baseline CL | 0.0709 | 27.6 | 0.02815 | 0.0725 | 0.173 |
| Effect of patient sex on baseline CL | -0.075 | 13.9 | -0.1187 | -0.0728 | -0.02763 |
| Effect of CRP on baseline CL | 0.0316 | 11.6 | 0.0152 | 0.029 | 0.04127 |
| Residual error, %CV | 0.449 | 0.5 | 42.33 | 44.8 | 47.47 |
| IIV baseline CL | 28 | 2.8 | 25.6 | 28.3 | 34.87 |

ADA, antidrug antibody; CL, clearance; CRP, C-reactive protein; CV, coefficient of variation; IIV, interindividual variability; Q, intercompartmental clearance; SE, standard error; V_c, volume of the central compartment; V_p, volume of the peripheral compartment.

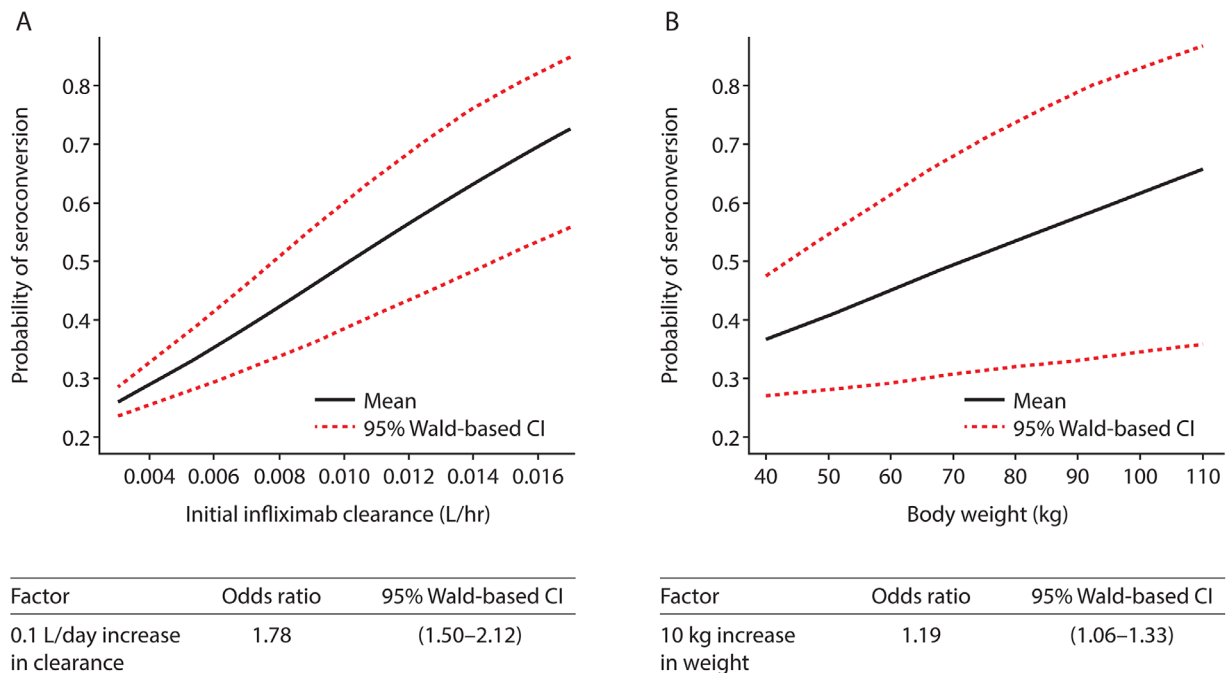


Figure 3. Effects of baseline infliximab clearance (A) and body weight (B) on the probability of ADA formation. ADA, antidrug antibody; CI, confidence interval.

In our analysis, concomitant immunosuppressant therapy had little effect on infliximab clearance. Although concomitant immunosuppressants have been shown to influence infliximab clearance in some studies,¹⁸ other studies have reported that concomitant immunosuppressants do not affect infliximab pharmacokinetics.^{26,27} This is in contrast with findings for adalimumab: mean steady-state adalimumab trough concentrations are increased by approximately 40% with concomitant methotrexate versus without

concomitant methotrexate in patients with rheumatoid arthritis.^{28,29} Several mechanisms have been proposed to explain how immunosuppressants can impact the clearance of anti-TNF therapies, including improving disease severity, preventing ADA formation and/or reducing ADA titers, and reducing the expression of the Fc- γ receptor responsible for immunoglobulin G clearance.^{30,31} The majority of patients received concomitant methotrexate throughout the PLANETRA study, and the sole use of this drug could explain

differences between studies if the effects of methotrexate and other immunosuppressants differ. Indeed, methotrexate has been shown to reduce Fc- γ receptor expression.³²

The potential clinical impact of ADAs, including a loss of response to treatment, is well known.³³ However, few studies have investigated which patient-related factors are predictive of ADA formation,²¹ especially in the early stages of treatment. In the analysis of data from the PLANETRA study reported here, we found that as body weight or baseline infliximab clearance increased in magnitude, the probability of ADA formation also increased. Although additional studies are required to elucidate the relationship between body weight and ADA formation, there are a couple of hypotheses that may help to explain our findings. The first is related to adipose tissue inflammation: in response to overnutrition, adipose tissue mounts an immune response by generating proinflammatory B-cell subsets that induce proinflammatory T cells, promote insulin resistance, and secrete pathogenic autoimmune antibodies.³⁴ As anti-TNF agents target adipose tissue inflammation as a bystander, adipose tissue could arise as a location of ADA formation. A second possible explanation relates to infliximab-TNF complexes: in mice, higher doses of infliximab were associated with higher infliximab-TNF complexes, which subsequently elicited formation of ADAs.³⁵ Although infliximab is dosed according to body weight, clearance is not linearly related to weight; as such, a similar process may have occurred in our study. With regard to the relationship between infliximab clearance and ADAs, other analyses have shown that low serum concentrations of TNF inhibitors are associated with the development of ADAs. Nevertheless, investigations to date have not been able to determine whether low serum concentrations are the cause or the consequence of ADA formation. Importantly, the innovative nature of our approach—assessing clearance as a dynamic variable from the first treatment infusion and before detection of ADAs—allowed us to show that ADA formation could be predicted by the magnitude of infliximab clearance measured from the start of treatment. Patients had a higher likelihood of developing ADAs if they had higher levels of infliximab clearance at treatment initiation (the odds ratio of ADA formation for each 0.1 L/day increase in infliximab clearance was 1.78).

It has been proposed that therapeutic drug monitoring may help to improve biological use for the treatment of patients with rheumatoid arthritis.³⁶ However, the implementation of therapeutic drug monitoring for immune-mediated inflammatory diseases is based on clinical experience and observational studies,³⁷ as prospective or randomized studies are lacking. In patients with IBD, clinical experience suggests that mea-

surement of drug levels can be used to guide treatment decisions.^{38–41} At present, however, proactive therapeutic drug monitoring is not widely recommended in current treatment guidelines. Findings from our study suggest that it may be useful to determine albumin and CRP before dosing to guide treatment decisions. In addition, we recommend that albumin should be checked regularly during therapy.

Concomitant treatment with immunosuppressants, particularly methotrexate, has previously been reported to be associated with reduced ADA formation during treatment with TNF inhibitors.⁷ In our analysis, neither methotrexate dose nor the absence of concomitant immunosuppressant therapy predicted the formation of ADAs in patients with rheumatoid arthritis participating in the PLANETRA study. However, it is important to note that only a small number of these patients ($n = 6$) did not receive concomitant methotrexate. Baseline albumin, glucose, and patient sex also did not predict ADA formation, although all factors contribute to individual clearance.

The strengths of this analysis include the large data set, which was derived from 2 large, randomized, controlled trials. It should be noted that the PK and ADA data used in this analysis arose from patients treated with either infliximab or the biosimilar CT-P13. In terms of PK, however, the primary end points of the PLANETAS study were area under the concentration-time curve and maximum serum concentration between weeks 22 and 30, and comparison of these end points between treatment groups showed that the PK profiles of infliximab and CT-P13 were statistically equivalent.¹⁰ Furthermore, no differences in the PK profiles of these 2 drugs were observed over the remainder of the PLANETAS study or throughout the PLANETRA study.^{11–13} The ADA profiles of infliximab and CT-P13 were also highly similar in these 2 randomized trials and were both measured using the same electrochemiluminescent immunoassay recommended by European and US regulatory authorities.⁴²

Conclusions

Our analyses identified body weight and baseline infliximab clearance as predictors for ADA formation in patients with rheumatoid arthritis treated with infliximab. Based on our findings, there is an urgent need for individualized approaches to treatment to be adopted in clinical practice, including early implementation of therapeutic drug monitoring to reduce the incidence and impact of ADAs in infliximab-treated patients.

Acknowledgments

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Conflicts of Interest

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Data-Sharing Statement

All available data are reported in the article and supplementary file.

Author Contributions

W.R. is the guarantor of this article. W.R. and D.R.M. were involved in the conception and design of the study. All authors were involved in the analysis and/or interpretation of data and drafting and revising the article for important intellectual content, and they have approved the final version of the article to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.