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Quantifying the Effect of Methotrexate on Adalimumab Response in Psoriasis by Pharmacokinetic–Pharmacodynamic Modeling

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Previously, we showed that the combination of methotrexate and adalimumab treatment leads to less antidrug antibody development. In this study, we quantify the pharmacokinetics/pharmacodynamics (PK/PD) of adalimumab and evaluate the influence of methotrexate cotreatment. A population PK–PD model was developed using prospective data from 59 patients with psoriasis (baseline PASI = 12.6) receiving adalimumab over 49 weeks. Typical PK and PD parameters and their corresponding interpatient variability were estimated. We performed a covariate analysis to assess whether interpatient variability could be explained by addition of methotrexate and other covariates. In total, 330 PASIs, 252 adalimumab serum concentrations, and 247 antidrug antibody titers were available. Presence of antidrug antibodies (adalimumab group = 46.7%, adalimumab + methotrexate group = 38.7%; $P = .031$) was correlated with increased adalimumab apparent clearance ($P < .001$). In the PD model, the use of concomitant methotrexate was borderline to significantly correlated with a decreased half-maximal inhibitory concentration (adalimumab concentration for which clinical response score is reduced by half; $P < .10$). On the basis of our PK–PD model, concomitant use of methotrexate indirectly increases adalimumab concentration, partially through less antidrug antibodies formation, which may result in better efficacy.

Keywords: Adalimumab, Antidrug antibodies, Methotrexate, PK-PD model, Psoriasis

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INTRODUCTION

Adalimumab (TNF inhibitor) is a beneficial treatment option for many patients with chronic plaque psoriasis. However, during the treatment with adalimumab, clinically relevant antidrug antibodies can be formed (Berends et al, 2018; Jullien et al, 2015; Menting et al, 2014; Xu et al, 2015). In rheumatoid arthritis, the (registered) concomitant treatment with methotrexate reduced antidrug antibody formation against adalimumab and improved its efficacy and drug survival (Krieckaert et al, 2012; Weinblatt et al, 2003; Weisman et al, 2003). This additional effect is also observed in a few smaller and uncontrolled studies with patients with psoriasis, where in contrast to rheumatoid arthritis, this combination treatment is off label (Jani et al, 2014; Philipp et al, 2012; van den Reek et al, 2013)

To investigate whether adalimumab treatment in patients with psoriasis can be optimized with the addition of methotrexate, the OPTIMAP study (OPTIMising Adalimumab treatment in Psoriasis with concomitant methotrexate) was performed (Busard et al, 2017; van der Kraaij et al, 2022). In this study, a trend toward better drug survival (although not significant) was found in the adalimumab + methotrexate–treated group than in the adalimumab-treated group in week 49 (74.2 vs 58.6%, respectively; $P = .15$). In the adalimumab + methotrexate–treated group, there was a trend toward a larger group of patients that achieved a 75%

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Abbreviations: CL/F, apparent clearance; IC_{50}, half-maximal inhibitory concentration; NONMEM, nonlinear mixed effects modeling; OFV, objective function value; PD, pharmacodynamics; PK, pharmacokinetics; V/F, apparent volume of distribution

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improvement of the PASI75 in week 49 (58.1 vs 36.7%; $P = .13$) than in the adalimumab monotherapy group.

With the use of conventional statistics, the results from the OPTIMAP trial were ambiguous; there was a trend toward better drug survival and better effectiveness, but significantly fewer patients showed antidrug antibodies in the combination group than in the monotherapy group (22.6 vs 60.0%; $P < .01$). It is unclear whether other patient characteristics than antidrug antibodies formation increase or decrease the effectiveness of adalimumab in psoriasis. Therefore, population pharmacokinetics (PK)–pharmacodynamics (PD) modeling was chosen as an alternative method to assess whether interindividual variability (the difference in parameters between subjects' clearance of adalimumab) could be explained by other specific patient characteristics and/or the addition of methotrexate. PK–PD population modeling is the field of research that studies the relationship between PK and PD of a drug and its interpatient variability.

PK is the process that describes what the body does to the drug by studying the absorption of a drug, its distribution into different tissues, metabolism, and elimination from the body. PK is often quantified in terms of volume of distribution (denoted as V) and clearance (denoted as CL) in the case of a drug with a known bioavailability (denoted as F). When bioavailability is unknown, the terms apparent volume of distribution (V/F) and apparent clearance (CL/F) are used, as is the case in our study (Sherwin et al, 2012).

PD is the process that describes what a drug does to the body, that is, the biological and physiological response. The relationships between concentration and effect can generally be described by an E_{max} model. The potency of inhibitors is specified with the half-maximal inhibitory concentration (IC_{50}): the concentration of the inhibitory compound required to inhibit a biological process (Marino et al, 2023). Background information on population PK–PD modeling can be found in the tutorials from Mould and Upton (2013, 2012) and Upton and Mould (2014).

In the literature, no models linking the PK of adalimumab combined with methotrexate to the PD of psoriasis were found, although a recent model studied the PK of adalimumab in psoriasis (Atalay et al, 2022). Patient characteristics, their influence on the PK of adalimumab, and any remaining unexplained variability between or within subjects might give insight into the differences between the adalimumab + methotrexate–treated group and the adalimumab-treated group in adalimumab drug level, antidrug antibodies titers, the concomitant use of methotrexate, and the relation to clinical response.

Therefore, we developed a population PK–PD model to quantify the relationship between dose, adalimumab concentration, and clinical response. It was investigated whether concomitant use of methotrexate and other patient characteristics changed the PK and/or PD parameters of adalimumab in patients with moderate-to-severe chronic plaque psoriasis.

RESULTS

Patients

Prospective data from 61 patients who participated in the OPTIMAP trial were available. After analysis of the raw data, 2 patients were excluded owing to missing data concerning the administration of adalimumab and other important covariates (n = 1) or absence of adalimumab serum levels (n = 1). The 59 remaining patients consisted of 43 males and 16 females. Their median age was 48 years, and their median body weight was 82 kg. Additional patient characteristics are listed in Table 1.

PK analysis

For the PK analysis, a total of 252 adalimumab trough concentrations and 247 antidrug antibody levels were available.

Table 1. Patient Characteristics

n = 59	Number (%) or Median (Interquartile Range)
Sex, male (%)	43 (72.9)
Age	48 (39–58)
Body weight (kg)	82 (70.3–93.8)
Length (m)	1.77 (1.70–1.84)
BMI	26.0 (22.6–29.4)
Number of trough measurements per patient (range)	4 (1–5)
Number of antidrug antibodies per patient (range)	4 (1–5)
Trough levels (n = 252)	5.89 (3.53–7.98)
Antidrug antibodies levels (n = 247[1]) (range)	<12–980 AU/ml
Baseline PASI	12.6 (10.2–15.0)
Allocated to concomitant methotrexate use (%)	29 (49.2)
Smoking (%)	25 (42.4)
Alcohol use (%)	39 (66.1)
Psoriatic arthritis diagnosis (%)	11 (18.6)
Previous biological therapy (%)	17 (28.8)
Previous Infliximab therapy (%)	2 (3.4)
Previous Etanercept therapy (%)	9 (15.3)
Previous Ustekinumab therapy (%)	4 (6.8)
Other biological therapy (%)	5 (8.5)
eGFR (<60/≥60)	5 (8.5)
Gamma-GT	29.5 (19.3–39.8)
ASAT	25 (20.5–29.5)
ALAT	27.5 (18.8–36.3)
Hb	9 (8.4–9.6)
Thrombocyte count	253 (215–291)
Leucocyte count	7.2 (6.3–8.2)
Investigator Global Assessment	3.0 (2.5–3.5)
Dermatology Life Quality Index	12.0 (6.8–17.3)
SKINDEX	50.0 (30.3–69.8)
Previous fumarate therapy (%)	34 (57.6)
Previous methotrexate therapy (%)	51 (86.4)
Previous ciclosporin therapy (%)	13 (22.0)
Previous acitretin therapy (%)	10 (16.9)
Previous UVA therapy (%)	7 (11.9)
Previous UVB therapy (%)	48 (81.4)
Previous coaltar therapy (%)	2 (3.4)
Previous other nonbiological therapy (%)	6 (10.2)

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; Gamma-GT, gamma-glutamyl transferase; Hb, hemoglobin; M, male.

[1]In the case of 5 missing measurements of the antidrug antibodies, the missing values were imputed with the median value; for a further explanation for missing data of other covariates, see Supplementary Text S1.

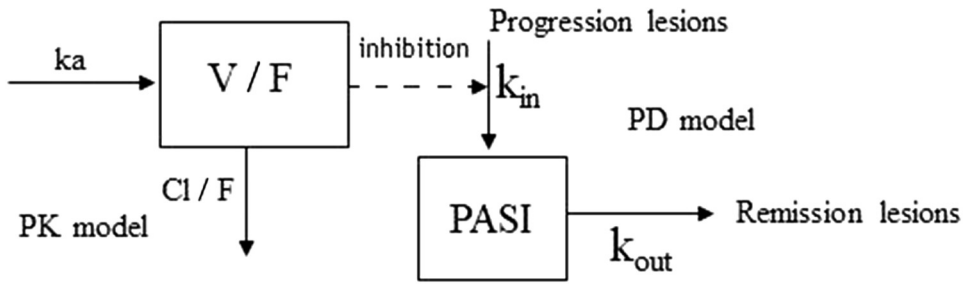

Figure 1. Pharmacokinetic and PK–PD models. Adalimumab pharmacokinetics was described using a 1-compartment model with depot with allometric scaling on V/F (1.0) and CL/F (0.75). The relationship between adalimumab concentrations and PASI was described using a turnover model. k_a denotes absorption rate, k_{in} denotes formation/progression of psoriatic lesions, and k_{out} denotes remission psoriatic lesions. CL/ F, apparent clearance; PK–PD, pharmacokinetic–pharmacodynamic; V/F, apparent volume of distribution.

Assumptions for the K_a (absorption rate) had to be made to build the model. A 1-compartment model with depot (Figure 1) with allometric scaling of V/F and CL/F using body weight achieved the best fit. The allometric exponents were 1 and 0.75 for V/F and CL/F, respectively. Interpatient variability of CL/F was 37%. Because only trough levels were available, interpatient variability could not be estimated for V/F. The best description of the residual error was achieved by the use of a proportional error model.

During the univariate covariate analysis, different covariates were added to the model. The fit of the model to the dataset only improved significantly ($P < .05$) when the covariates concomitant methotrexate use, historical use of acitretin, and antidrug antibodies were added. The covariates concomitant methotrexate use and historical use of acitretin were associated with lower CL/F (concomitant methotrexate use CL/F = 0.773 and historical use of acitretin CL/F = 0.665, as a fraction of original adalimumab clearance). The association between antidrug antibodies level and CL/F produced the largest improvement in model fit ($P < .001$). In a typical patient with an antidrug antibodies level of 30 AU/ml (lower limit of quantification), CL/F increased with a factor of ~4.1 compared with that in a patient without antidrug antibodies.

In the multivariate analysis, the covariates concomitant methotrexate use and historical use of acitretin were added to the model with antidrug antibodies but did not improve the PK model ($P > .05$). Inclusion of antidrug antibodies in the final PK model reduced the residual unexplained interpatient variability from 37 to 31.8% (Figures 1 and 2 and Supplementary Figures S1 and S2).

PD analysis

The individual posthoc PK parameter estimates, obtained from the developed PK model, were used as input for the PD model. For each patient, a baseline PASI was available, and

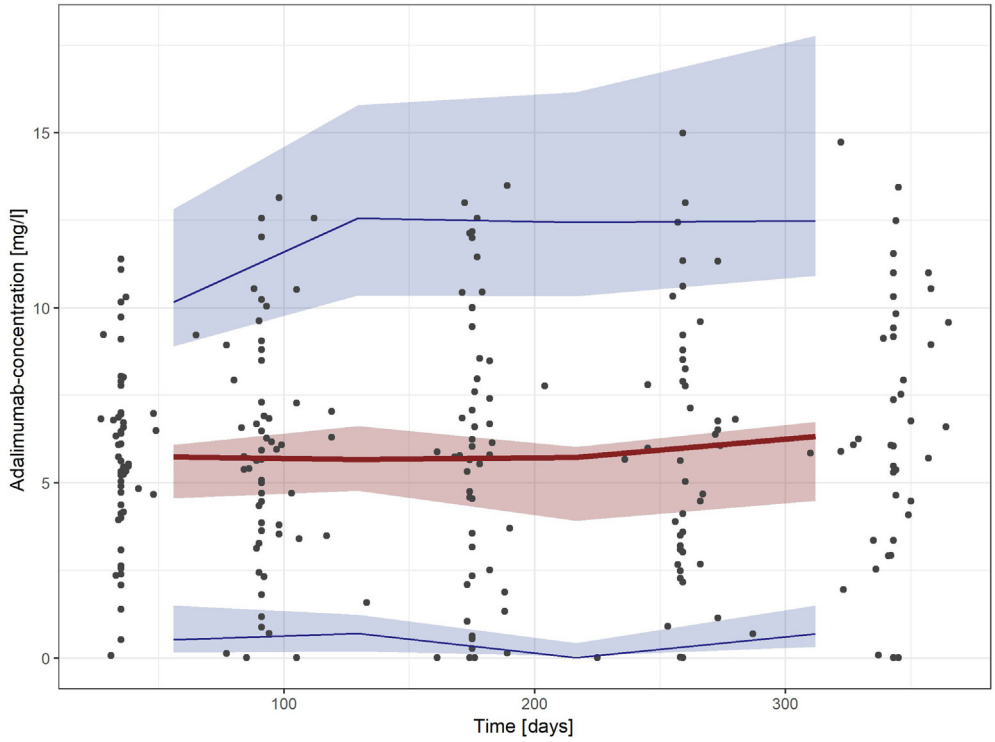

Figure 2. Visual predictive check of the final pharmacokinetic model of adalimumab concentrations. The red line represents the 50th percentile of observed data (median); the blue lines represent the 5th and 95th percentiles of the population model. Shaded areas depict the model-predicted 95% confidence intervals of the simulated percentiles.

261 PASIs were collected during the study visits. The relationship between serum concentration and PASIs was described by a turnover model (Figure 1), in which adalimumab inhibited the formation rate of psoriatic skin lesions (K_{in}) according to an E_{max} function. In the PD model, the parameter K_{out} represents the rate at which lesions went into remission. The PD model adequately described the time profile of PASI with an estimated IC_{50} (adalimumab concentration at half maximum inhibition) value of 1.19 mg/l and a K_{out} of 0.0314 1/day.

In this model, E_{max} could not be estimated and was fixed to unity, that is, 100% inhibition. Interpatient variability of IC_{50} was large with a value of 152.6% (Table 2). The residual error was described by a proportional error model. In the univariate analysis of covariates on the IC_{50}, a trend toward a relationship was seen for concomitant methotrexate use (1.85 fold decrease in IC_{50}, relative standard error = 30%), however with a change in objective function value (OFV) of −3.442; this led to a nonsignificant ($P = .06$) improvement of the model.

The goodness-of-fit plots between the predicted and observed PASIs were in agreement (Supplementary Figure S2). Furthermore, the visual predictive checks showed that the observed PASI values were well-centered around the predicted median of the adalimumab PASI PD model (Figure 3). The median values estimated in the bootstrap were in line with the parameters found in the final PD model (Table 3).

DISCUSSION

In this study, the relationship between adalimumab dose, concentration, and PASI was thoroughly investigated by application of an integrated PK–PD population model, using data from the OPTIMAP study (van der Kraaij et al, 2022). To our knowledge, no other PK–PD analyses in patients with psoriasis (Rodríguez-Fernández et al, 2022) investigating the PK of adalimumab combined with methotrexate and the clinical effect of this drug on PASIs are available. Comparable PK models for adalimumab have been assessed in patients with Crohn's disease (Berends et al, 2018; Kimura et al, 2018), hidradenitis suppurativa (Nader et al, 2017), and rheumatoid arthritis (Stepensky, 2012; Ternant et al, 2015; Weisman et al, 2003).

Table 2. Adalimumab Population Pharmacokinetic Parameters

Parameter	Final Model Values (RSE) (Shrinkage)	Bootstrap Median Value (95% CI)
K_a	0.28 (fixed)	n/a
V/F (l/82 kg)	14.7 (7%)	14.6 (12.7–17.2)
Exponent V/F	1 (fixed)	n/a
CL/F (l/day/82 kg)	0.365 (5%)	0.365 (0.332–0.400)
Exponent Cl	0.75 (fixed)	n/a
Effect (ADA) on CL/F	0.873 (4%)	0.872 (0.733–0.985)
Interindividual variability		
CL/F (untransformed)	0.101 (23%) (9%)	0.0986 (0.0585–0.147)
CL/F $\sqrt{(OMEGA^2)}$	31.8% (11%) (9%)	
Residual variability		
Proportional error (%)	33.2 (3%)	32.8 (26.4–39.4)

Abbreviations: ADA, antidrug antibody; CI, confidence interval; CL/F, apparent clearance, n/a, not applicable; RSE, relative standard error; V/F, apparent volume of distribution.

K_a denotes absorption rate. CL/F increased with a factor of ([ADA]/limit of detection/2).$^{0.873}$

Interpretation and clinical relevance: PK model and PD model

The CL/F (0.365 l/day/82 kg) and V/F (14.7 l/82 kg) found in our PK model can be compared with the CL/F (0.32 l/day/82 kg) and V/F (10.8 l/82 kg) in patients with rheumatoid arthritis (Ternant et al, 2015) and with the CL/F (0.32 l/day/82 kg) and V/F (4.07 l/82 kg) in patients with Crohn's disease (Berends et al, 2018). It appears that CL/F is similar in patients with different inflammatory diseases. However, V/F does differ in our model from that of patients with rheumatoid arthritis. This can be explained by a higher median body weight found in our dataset (l/82 kg) than in the dataset from Ternant et al (2015) and the use of allometric scaling. In the univariate covariate analysis, the fit of the PK model to the dataset improved significantly by the addition of the covariates antidrug antibodies formation, concomitant methotrexate use, and historical use of acitretin. Therefore, these covariates may have an influence on the CL/F of adalimumab.

In the univariate analysis in the study from Ternant et al (2015), additional significant covariates were sex and body weight. In our study, PK parameters were a priori scaled for body weight, as is common in PK–PD modeling (Anderson and Holford, 2008). Another discrepancy between our study and that of Ternant et al (2015) is the effect size of antidrug antibodies. However, in the dataset from Ternant et al (2015), no patients developed antidrug antibodies. They suggest that this might be a consequence of high concentrations of free adalimumab molecules that interfere with the detection of antidrug antibodies or due to adalimumab–antidrug antibodies complexes that increase adalimumab clearance.

When the covariate use of methotrexate and the covariate historical use of acitretin were added to the multivariate PK model containing antidrug antibodies as covariate, improvement of the model was no longer observed. This is due to the correlation between methotrexate use and the decreased risk of development of antidrug antibodies. However, the number of patients with a history of acitretin is unevenly distributed among the measurements with and without antidrug antibodies ($P < .05$). Therefore, the effect of acitretin in the univariate analysis is likely the result of a confounder. We do not think this finding has clinical implications for daily practice. From the PK analysis, it can be concluded that adalimumab CL/F is increased when antidrug antibodies are present. This result is comparable with those of rheumatology studies (Anderson, 2005; Wolbink et al, 2009), where concomitant use of methotrexate as prevention in antidrug antibodies formation is common practice (Krieckaert et al, 2012; l'Ami et al, 2017). The interpatient variability is quite large (152.6%), which suggests that with comparable

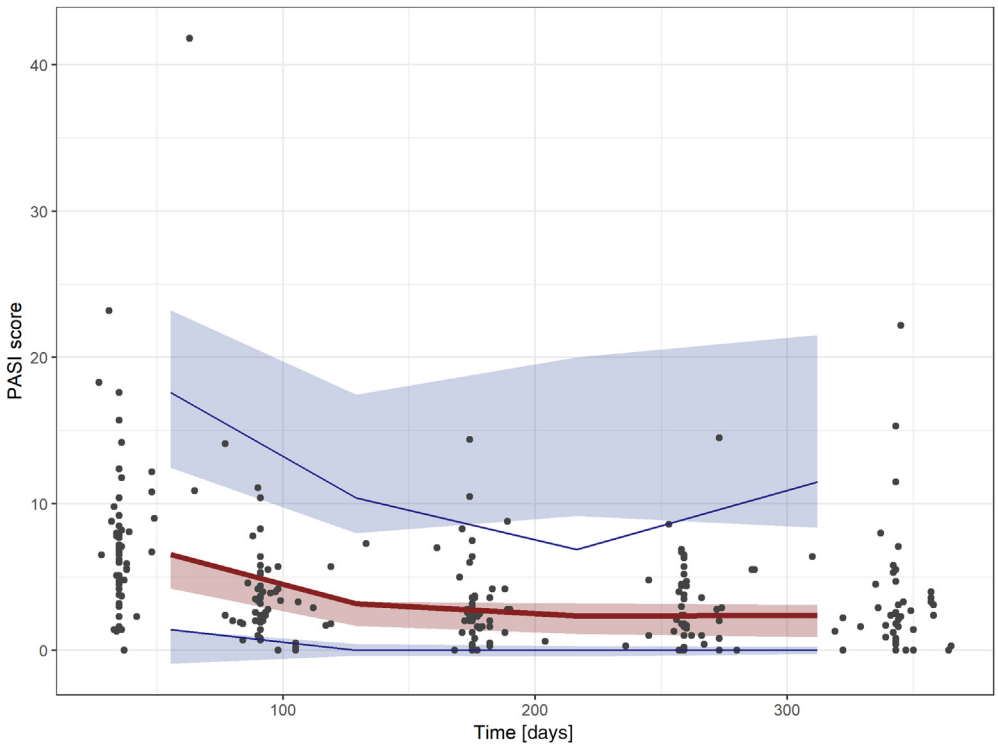

Figure 3. Visual predictive check of the final adalimumab—PASI pharmacodynamic model of observed PASI values. The red line represents the 50th percentile of observed data (median); the blue lines represent the 5th and 95th percentiles of the population model. Shaded areas depict the model-predicted 95% confidence intervals of the simulated percentiles.

concentrations, the PASI will vary significantly between patients. It is possible that a part of the interpatient variability in the response is due to variation in the scoring of the PASI by the investigators, but it also might indicate that individual measurements of adalimumab trough concentrations are not very suitable to assess efficacy in clinical practice. However, these findings should be interpreted cautiously owing to our small dataset. The observed interpatient variability value is comparable with the interpatient variability found in the PK/PD model of ustekinumab in psoriasis developed by Pan et al (2020). In the univariate analysis of the PD model, a trend toward a relationship between concomitant methotrexate use and IC_{50} was found. Although the majority of variability is likely explained by our PK model, a small part of the variability in PD might be explained by this relationship. This might indicate that patients who use concomitant methotrexate need lower adalimumab concentrations than patients who do not use concomitant methotrexate for the same response. No other covariates showed a relationship with the IC_{50}.

Table 3. ADL PASI Population Pharmacodynamic Parameters

Parameter	Final Model Values (RSE) (Shrinkage)	Bootstrap Median Value (95% CI)
K_{out} (1/day)	0.0314 (12%)	0.0316 (0.0228 −0.0366)
IC_{50} (mg/l)	1.19 (22%)	1.19 (0.77−1.69)
E_{max}	1 fixed	n/a
Interindividual variability		
IC_{50} (untransformed)	2.33 (34%) (7%)	2.34 (1.19−4.09)
IC_{50}	152.6% (17%) (7%)	
Residual variability		
Proportional error (%)	55.6% (8%)	54.7% (47.5−62.6)

Abbreviation: ADL, adalimumab; CI, confidence interval; IC_{50}, half-maximal inhibitory concentration; RSE, relative standard error.
K_{out} denotes elimination rate, IC_{50} denotes the concentration of ADL in which the clinical response score is reduced by half, and E_{max} denotes maximum effect.

We did not find comparable PK–PD models in the literature, in which the effect of concomitantly used methotrexate was assessed on PD parameters of adalimumab. From this PK–PD model, it can be concluded that there might be an extra clinical effect from this low-dose methotrexate on psoriatic skin. This could be a consequence of the immunomodulating effect of methotrexate itself or the synergetic effect of methotrexate due to less formation of antidrug antibodies (n = 24 in our dataset) (l'Ami et al, 2017) but also of the increased apoptosis of TNF-expressing cells through reverse signal transduction (Wang et al, 2020).

Results from the original randomized controlled trial and other PK–PD models

In the original OPTIMAP study, the adalimumab + methotrexate–treated group had a trend to a higher median (interquartile range) trough concentrations of 6.8 (5.5–9.2) versus 5.9 (3.5–8.8) mg/l ($P = .26$). This difference may be partially explained by the decrease of clearance when methotrexate is coadministered and development of antidrug antibodies is suppressed.

Strengths and limitations

A strength of the use of a statistical method such as nonlinear mixed effects modeling (NONMEM) is that it incorporates both fixed and random effects and is especially useful when

there are multiple measurements within subjects. Unlike other statistical methods, such as the 2-stage PK approach, datasets with relatively sparse data can be analyzed with NONMEM (Bauer, 2019). Another strength is the consequently collected randomized controlled trial data from a real-world setting, with a minimum of missing data. Therefore, our conclusions can be translated into daily practice.

A limitation of this study is the incomplete recruitment of the planned study population in the original OPTIMAP randomized controlled trial (van der Kraaij et al, 2022). Sixty-one patients from the planned 100 patients were included. As a result of this smaller study population, there is a decreased power in the covariate analysis, and that may have influenced our conclusions, especially on the effect of the weak covariates from our model. In addition, the sample size was calculated for the primary endpoint drug survival in the original OPTIMAP study and not for this PK–PD subanalysis. Finally, only adalimumab trough levels were available for PK analysis. However, owing to the long half-life of adalimumab, the estimation of V/F (14.7, relative standard error = 7%) was still resulting in values comparable with those of other publications (Ternant et al, 2015).

Future research

Future research should focus on the effect of methotrexate on the PK and PD of adalimumab in a larger population. The follow-up data of the original OPTIMAP randomized controlled trial (van der Kraaij et al, 2022) are recently analyzed until 3 years of treatment (van Huizen et al, 2023). PK–PD relationships quantified on the basis of those data can also be valuable for this model. Methotrexate serum levels and adalimumab serum levels at start and after week 1 and a trough level could be collected in future research as well. These data can further optimize the PK–PD model and diminish assumptions on methotrexate levels and absorption rates.

In this study, we show a significant effect of the concentration of antidrug antibodies on the clearance of adalimumab. In addition, we demonstrate a correlation between adalimumab concentrations and PASI scores through a mathematical formula. Besides, we observe a borderline to significant effect of methotrexate on the PD of adalimumab. On the basis of the prior knowledge that methotrexate can suppress the formation of antidrug antibodies, methotrexate might have a beneficial effect on the efficacy of adalimumab. Therefore, this drug might be considered in combination with adalimumab. However, our data should be interpreted cautiously, and the possible side effects of methotrexate should be taken into account.

MATERIALS AND METHODS

Patients

The data analyzed in the PK–PD analysis were from the OPTIMAP study (Busard et al, 2017; van der Kraaij et al, 2022), which was performed in 5 centers in the Netherlands and Belgium between 2014 and 2020. Written informed consent was obtained from all patients. The study was approved by the medical ethics committee of the Amsterdam University Medical Center. Please see our previous publications (Busard et al, 2017; van der Kraaij et al, 2022) for details involving the OPTIMAP study.

Sample analysis

The data used for this PK analysis were collected during the visits at screening; baseline; and weeks 5, 13, 25, 37, and 49. In our previous publication, we described more details on the analyses of antidrug antibodies adalimumab serum trough concentrations and antidrug antibodies at Sanquin Diagnostic Services (Amsterdam, The Netherlands) (Sanquin, 2021).

Available PK models

The literature was searched for suitable PK models, and multiple models were found (Berends et al, 2018; Kimura et al, 2018; Mazor et al, 2014; Nader et al, 2017; Stepensky, 2012; Ternant et al, 2015; Weisman et al, 2003; Zittan et al, 2016). The model of Ternant et al (2015) was chosen as the baseline model for the PK analysis because this population was comparable with our population. Ternant et al (2015) describe 30 patients with rheumatoid arthritis in their study and found a wide variation in PK and a concentration–effect relationship between their patients. The authors reported a higher adalimumab CL/F in men than in women and stated that adalimumab CL/F is influenced by body weight. Antidrug antibodies were not found in this study (Ternant et al, 2015).

Software and PK–PD model

To perform a PK–PD analysis of the obtained adalimumab and antidrug antibodies serum levels in relationship to the observed PASIs, the anonymized data of the OPTIMAP study were shared with the Department of Hospital Pharmacy and Clinical Pharmacology. For the PK–PD analysis, NONMEM (7.3 ICON Development Solutions) software was used. In NONMEM, mixed refers to the combination of fixed and randomized parameters (De Cock et al, 2011). In NONMEM, the PK and PD parameters can be estimated as well as their interpatient variability. In addition, residual variability is estimated. See Supplementary Text S1 for more details on the development of our PK–PD model and the involved equations. For an explanation of the terms used in this specific analysis and the process of PK(/PD) modeling, please refer to the reviews of Upton and Mould included in the references (Mould and Upton, 2012, 2013; Upton and Mould, 2014).

In a covariate analysis (univariate analysis $P < .05$ and multivariate analysis $P < .001$), it can be evaluated whether specific comedication or specific patient characteristics can explain this variability.

To explain interpatient variability of clearance correlations, the following PK covariates were investigated: the categorical covariates current methotrexate use, sex, presence of the comorbidity, psoriatic arthritis, smoking, alcohol, previous biologic drug, and previous nonbiologic drugs. The continuous covariates were age; disease duration; creatinine clearance; aspartate aminotransferase; alanine aminotransferase; gamma-glutamyl transferase; thrombocyte count; leucocyte count; and antidrug antibodies levels at weeks 5, 13, 25, 37, and 49. For the PD model, the categorical covariates current methotrexate use, sex, presence of the comorbidity psoriatic arthritis, smoking, alcohol, previous biologic drug, and previous nonbiologic drugs and the continuous covariates age, disease duration, creatinine clearance, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, thrombocyte count, and leucocyte count were tested for correlation with IC_{50}.

In a PK analysis, several compartment models, for example, 1 compartment and 2 compartment, were evaluated, with PK parameters expressed in terms of clearance and volume. Starting with a 1-compartment model, modifications to this model were investigated

using R (version 3.6.1), R-studio (version 1.2.1335), Perl-speaks-NONMEM (version 4.6.0), and Piraña (version 2.9.4).

The covariates were explored using a stepwise univariate forward addition (ΔOFV of 3.84 is statistically significant with a $P < .05$) and multivariate backward elimination procedure (ΔOFV of 7.88 is statistically with a $P < .001$). The covariate with the largest ΔOFV in the forward addition was added first to the multivariate analysis followed by the other covariates in descending order of the ΔOFV drop.

The individual posthoc PK parameter estimates of the final PK model were used as input for the turnover PD model. In the PD model, the inhibitory effect was quantified with an E_{max} function (inhibition = conc adalimumab × E_{max}/ IC_{50} + conc adalimumab). Interpatient variability was assessed on PD parameters. The adequacy of the PK–PD model was evaluated with goodness-of-fit plots by calculation of the standard errors of the estimates and the creation of visual predictive checks, which is common in PK–PD modeling (Mould and Upton, 2012, 2013; Upton and Mould, 2014).

The goodness-of-fit plots showed an acceptable agreement between the predicted and observed adalimumab concentration (Supplementary Figures S1 and S2). The precision of the parameters estimates and visual inspection of the diagnostic plots were evaluated with visual predictive checks. In visual predictive checks, the final version of the model and the PK parameters of adalimumab were simulated 200 times. These simulated data were summarized in a predicted range of concentration (eg, median, 5th percentile, and 95th percentile), overlayed with the observed data, and visually checked. Finally, a bootstrap using 1000 simulated datasets was used to assess the precision of the pharmacokinetic parameters and to calculate confidence intervals for the parameters. The 5th and 95th percentiles of the distribution of the parameters simulated in the bootstrap constitute the 90% confidence intervals. The individual posthoc PK parameter estimates of the final PK model were used as input for the PD model.

See Supplementary Text S1 for more information on the development of the PK and PD models, Tables 2 and 3 and Figure 1 for the final PK–PD model, and Supplementary Text S2 for the syntax of the final NONMEM model.

Data availability statement

The individual patient data that underlie the dataset for this PK–PD model are previously published online and can be found at https://doi.org/10.6084/m9.figshare.20026433, hosted at Figshare (van der Kraaij et al, 2022) (dataset first year - OPTIMAP. figshare). We can make the data available on a reasonable request. Data will be shared with researchers who provide a methodologically sound proposal after execution of a data-sharing agreement.

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CONFLICT OF INTEREST

AvH was involved as a subinvestigator in clinical trials for Abbvie, Lilly, LeoPharma, and UCB. AM was involved as a subinvestigator in clinical trials for Abbvie and Lilly. TR receives consultancy fees from Novartis and a research grant from Genmab. MvD has received grants from governmental research institutes Nederlandse Organisatie voor Wetenschappelijk Onderzoek and Zorg Onderzoek Nederland Medische Wetenschappen; received consulting fees or honorarium from Novartis, Abbvie, Pfizer, Leopharma, Sanofi, Lilly, Janssen, BMS, Almiral, Celgene, and Third Harmonic; and has received a grant and payment for lectures, including service on speakers bureaus from Novartis, Sanofi, and Janssen outside the submitted work. EP is an advisory board member, consultant, and speaker and/or received investigator-initiated grants from AbbVie, Boehringer Ingelheim, ChemoCentrix, InflaRx, Kymera, Leo Pharma, Janssen-Cilag, Novartis, Regeneron, and UCB. JL received unrestricted grants from AbbVie, Almirall, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, and UCB; served as a speaker for AbbVie, Almirall, Bristol-Myers Squibb, Janssen-Cilag, Pfizer, and UCB; and served as a consultant for AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, and UCB. All fees and grants were paid to the institutions UZ Gent and UGent (Ghent, Belgium). JvdR carried out clinical trials for AbbVie, Celgene, Almirall, and Janssen and has received speaking fees/attended advisory boards from AbbVie, Janssen, BMS, Almirall, LEO Pharma, Novartis, UCB, and Eli Lilly and reimbursement for attending or chairing a symposium from Janssen, Pfizer, Celgene, and AbbVie. All funding is not personal but goes to the independent research fund of the Department of Dermatology of Radboud University Medical Center (Nijmegen, The Netherlands). EdJ has received research grants from AbbVie, BMS, Janssen Pharmaceutica, Leo Pharma, Lilly, Novartis, and UCB for research on psoriasis; has acted as a consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis or eczema, including AbbVie, Boehringer-Ingelheim, Amgen, Almirall, Boehringer-Ingelheim, Celgene, Galapagos, Janssen Pharmaceutica, Lilly, Novartis, Leo Pharma, Sanofi, and UCB. All funding is not personal but goes to the institution. RM has received grants from governmental and societal research institutes such as Nederlandse Organisatie voor Wetenschappelijk Onderzoek and Zorg Onderzoek Nederland Medische Wetenschappen; Dutch Kidney Foundation and Innovation Fund; and unrestricted investigator research grants from Baxter/Baxalta/Shire/Takeda, Bayer, CSL Behring, Sobi, and CelltrionHC. He has served as an advisor for Bayer, CSL Behring, Merck Sharp & Dohme, and Baxter/Baxalta/Shire/Takeda. All grants and fees were paid to the institution. PS has received departmental independent research grants for TREAT NL registry, for which she is chief investigator, from pharma companies since December 2019 and is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of, for example, psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: AvH, PB, RM; Data Curation: AvH, PB, GvdK, AM, CB, SM, JvdR; Formal Analysis: PB; Investigation: AvH, PB; Methodology: PB, RM; Project Administration: AvH; Resources: RM, PS; Supervision: RM, PS; Validation: PB, RM; Visualization: AvH, PB; Writing – Original Draft Preparation: AvH, PB; Writing – Review and Editing: GvdK, AM, CB, SM, TR, AdV, MvD, EP, JL, JvdR, EdJ, RM, PS

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2023.10.022.

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SUPPLEMENTARY MATERIALS AND METHODS

Supplementary Text S1: Methods of the pharmacokinetics/pharmacodynamics model

Development of the population pharmacokinetic model. For this pharmacokinetics (PK)/pharmacodynamics (PD) analysis, a stepwise approach was used. First, a population PK model was developed using nonlinear mixed effects modeling subroutines ADVAN2, TRANS2, and the first-order estimation method with the interaction option (FOCE-I) with an absorption constant derived from the literature ($k_a = 0.28$). See Supplementary Text S2 for the nonlinear mixed effects modeling syntax. Adalimumab concentrations below the lower limit of quantification were replaced by lower limit of quantification/2 (M5 method) (Ahn et al, 2008). Allometric scaling of body weight to the median value found in the dataset (82 kg) was tested on clearance (apparent clearance [CL/F]) and the central volume of distribution (apparent volume of distribution [V/F]) and included in the structural model (Equation 1):

$$\theta_{pop\ PK} = \theta_{pk} \times \left(\frac{Bodyweight}{82}\right)^{\theta_{exp}} \quad (1)$$

In this equation, $\theta_{pop\ PK}$ refers to the typical population value for the PK parameters V/F and CL/F, which are dependent on body weight, where θ_{pk} is the PK value for an individual with a body weight of 82 kg. The θ_{exp} refers to an exponent that is fixed at 1 for the parameter V/F and 0.75 for CL/F.

Using Equation 2, the individual PK parameters were described as follows:

$$\theta_i = \theta_{pop\ PK} \times exp^{\eta i} \quad (2)$$

In Equation 2, $\theta_{pop\ PK}$ refers to the typical value of a PK parameter in the population, and ηi is the interindividual variability on the basis of a normal distribution with an estimated variance of ω2 and a mean of zero of the ith individual, resulting in the estimation of the individual PK parameter for this individual. In the PK analysis, an omega variance–covariance block matrix was used in the estimation of the PK parameters.

For the residual error model, a proportional error model (Equation 3), an additive error model (Equation 4), and a combined error model (a combination of Equations 3 and 4) were explored. In these models, Yij is the predicted adalimumab concentration for patient i at time point j.

The individual predicted concentration at time point j is $f(\theta,\eta i,x_{ij})$, and the residual error originating from a normal distribution with an estimated variance of σ2 and a mean of zero is defined as ε.

$$Y_{ij} = f(\theta,\eta_i,x_{ij}) \times (1+\varepsilon_{ij}) \quad (3)$$

$$Y_{ij} = f(\theta,\eta i,x_{ij}) + \varepsilon_{ij} \quad (4)$$

The final structural PK model was used to analyze the effect of covariates. Categorical covariates were modeled with an exponent with a flag variable with 0 for false and 1 for true (Equation 5). In the case of a continuous variable, a function was used where the covariate was divided by the median value to center it, and the exponent was estimated by nonlinear mixed effects modeling (Equation 6). If covariates varying over time were missing, the last observation was carried forward. If this last observation was not available, the median value was imputed. When a value below the limit of detection (LoD) (<12 AU/ml) for antidrug antibodies was determined; the value LoD/2 was imputed. For the interval between the LoD and the lower limit of quantification, the value (lower limit of quantification + LoD)/2 was imputed. In 5 cases of the 252 records with observations, the antidrug antibodies levels were missing. In those cases, the last observation carried forward resulted in an imputation of the median value of LoD/2. In case of missing values for other covariates, the median value was imputed for a missing baseline value (Supplementary Table S1), and the last observation was carried forward if measurements varying over time were missing (Supplementary Table S2).To analyze the influence of the impact of the missing covariate data on both the PK and PD models and the robustness of the used method of imputation for the missing covariate data, an approach proposed in a study by Irby et al (2021) for handling missing covariate data was used. In Figure 6 of their article, the options of a complete case (remove all missing cases) dataset or imputing to a reference value (as we did by imputing median value for missing baseline values) are recommended when <20% of covariate data in a dataset are missing. When a complete case approach for the current dataset was used in a reanalysis, the antidrug antibodies were the only covariate that remained significant. The imputing-to-a-reference-value method showed similar results. On the basis of the comparison with the other methods of imputation, the original dataset was used in the final analysis because this reflects common practice in population modeling:

$$\theta_{pop} = \theta_{pk} \times \left(\theta_1^{Flag1} \times \theta_2^{Flag2} \times \theta_3^{Flag3} \cdots\right) \quad (5)$$

$$\theta_{pop} = \theta_{pk} \times \left(\frac{Cov}{Cov_{median}}\right)^{\theta_{exp}} \quad (6)$$

Development of the population pharmacodynamic model. In the population PD modeling, the first-order estimation method with the interaction option (FOCE-I) and nonlinear mixed effects modeling subroutines ADVAN6 and TOL4 were used along with differential equations. To model the effect of adalimumab on the PASI scores, a turnover model was used along with individual PK estimates ($_iK_a$ [= 0.28], $_i$V/F, and $_i$CL/F). The absorption of adalimumab from the depot (adalimumab depot) is described by Equation 7, whereas changes in concentration of adalimumab in the central compartment (adalimumab) are described by Equation 8.

$$\frac{dADL\ depot}{dT} = -iKa * ADL_{depot} \quad (7)$$

$$\frac{dADL}{dT} = iKa * ADL_{depot} - iCl * (ADL/\ iVd) \quad (8)$$

The turnover model consists of a zero-order rate constant: the formation rate of psoriatic skin lesions (K_{in}), and a first-order rate at which lesions went into remission (K_{out}). The baseline PASI (denoted as BASE) measured at the beginning of the study can be defined as an equilibrium of K_{in} and K_{out} (Equation 9).

$$BASE = \frac{K_{in}}{K_{out}} \quad (9)$$

In Equation 10, the differential equation for the turnover model is displayed:

$$\frac{dPASI}{dT} = BASE \times K_{out} \times I - K_{out} \times PASI \quad (10)$$

In this equation, I is the inhibition as a function of the individual predicted adalimumab concentration.

$$I = 1 - \frac{Emax \times C^n}{IC_{50} + C^n} \quad (11)$$

In the equation described earlier, C is the adalimumab plasma concentration, and the slope is the change of effect per AU/ml adalimumab. The maximum effect is defined by the Emax, and the half-maximal inhibitory concentration (IC_{50}) is the concentration that produces 50% inhibition of the maximum effect. Finally, the hill coefficient is defined by n and determines the steepness of the sigmoidal concentration-effect curve. In the development of the structural model, the hill factor was fixed at 1, and the effect of fixing the hill factor was analyzed using a sensitivity analysis. The final step of the development of the structural model was the estimation of the interindividual variability for the PD parameters resulting in Equation 12.

$$\theta_i = \theta_{pop\ PD} \times exp^{\eta i} \quad (12)$$

The structural PD model was evaluated using objective function value, obtained estimated parameters, and the goodness-of-fit plots. The goodness-of-fit plots between the predicted and observed PASIs were in agreement (Supplementary Figure S2).

The final PK–PD model was evaluated using Visual-Predictive-Checks on the basis of 200 simulations and a bootstrap of 1000 to calculate confidence intervals for the PD parameters.

Supplementary Text S2: PK–PD model

;; PK-model

$PROBLEM PK one-comp + depot linear elim noCov

$INPUT ID TIME DV AMT MDV CMT EVID TAD ADABCATBIN ADABCATMUL ADABCONC LENGTHDIAG USEMTX GENDER LENGTH WEIGHT BMI AGEBASE SMOKING ALCOHOL PSADIAGNOSIS PREVBIOTHER PREVBIOTHERSORT00 PREVBIOTHERSORT01 PREVBIOTHERSORT02 PREVBIOTHERSORT03 PREVBIOTHERSORT04 PREVLENGTHTHER PREVNONBIOTHER01 PREVNONBIOTHER02 PREVNONBIOTHER03 PREVNONBIOTHER04 PREVNONBIOTHER05 PREVNONBIOTHER06 PREVNONBIOTHER07 PREVNONBIOTHER08 PREVNONBIOTHER00 EGFRLESSTHAN60 EGFRMORETHAN60 GAMMAGT ASAT ALAT KREAT HB TROMBO LEUKO; column names

$DATA dataset-pk.csv IGNORE=@; input datafile

$SUBROUTINE ADVAN2 TRANS2 ; 1-comp model SC bolus

$PK

V = THETA(4) * (WEIGHT/82) ** THETA(3) * EXP(ETA(1))

Ka = THETA(5)

TVCL = THETA(7) *(ADABCONC/6)**THETA(8)

CL = TVCL * (WEIGHT/82) ** THETA(6) * EXP(ETA(2))

S2 = V

$ERROR

IPRED = F

IRES = DV-IPRED

W = IPRED*THETA(1)+THETA(2)

IF (W.EQ.0) W = 1

IWRES = IRES/W

Y= IPRED+W*ERR(1)

; Initial estimates (lower boundary, initial) for typical parameters

$THETA

(0,0.2) ; prop err

(0.01 FIX) ; add err

(1.00 FIX) ; AMSc Vd

(0, 10.8) ; V1 [L]/F

0.28 FIX ; KA, abs c. {/day}

(0.75 FIX) ; AMSc Cl

(0, 0.32) ; CL [L/D]/F

(-1,0.01) ; F AB+

; Initial estimates between-subject variability variance

$OMEGA

0 FIX ; IIV V

0.1; IIV CL

; Residual variability

$SIGMA

1 FIX; Residual error proportional

; Estimation method

$ESTIMATION METHOD=1 INTER MAXEVAL=9999 NOABORT SIG=3 PRINT=1 POSTHOC

; Covariance step (standard errors)

$COVARIANCE MATRIX=S

; Output tables observed and predicted

$TABLE ID TIME TAD DV IPRED PRED MDV CWRES IWRES IRES W WRES VOLGNR3 NOAPPEND NOPRINT ONEHEADER FILE=sdtab; observed-predicted

$TABLE ID Ka V CL MDV ETA1 ETA2 VOLGNR3 NOPRINT NOAPPEND ONEHEADER FILE=patab ; parameters and covariates

$TABLE ID ADABCATBIN ADABCATMUL USEMTX GENDER SMOKING ALCOHOL PSADIAGNOSIS PREVBIOTHER PREVBIOTHERSORT01 PREVBIOTHERSORT02

```
PREVBIOTHERSORT03 PREVBIOTHERSORT04 PREVNONBIOTHER01 PREVNONBIOTHER02 PREVNONBIOTHER03 PREVNONBIOTHER04 PREVNONBIOTHER05 PREVNONBIOTHER06 PREVNONBIOTHER07 PREVNONBIOTHER08 PREVNONBIOTHER00 EGFRLESSTHAN60 EGFRMORETHAN60
  NOPRINT ONEHEADER FILE=catab
  $TABLE ID ADABCONC LENGTHDIAG LENGTH WEIGHT BMI AGEBASE PREVLENGTHTHER GAMMAGT ASAT ALAT KREAT HB TROMBO LEUKO
  NOPRINT ONEHEADER FILE=cotab
  ;; PD-model
  $PROBLEM PK-PD
  $INPUT ID TIME DV AMT MDV CMT EVID TAD IVD ICL PASIBASE ADABCATMUL ADABCONC LENGTHDIAG USEMTX GENDER LENGTH WEIGHT BMI AGEBASE SMOKING ALCOHOL PSADIAGNOSIS PREVBIOTHER PREVBIOTHERSORT00 PREVBIOTHERSORT01 PREVBIOTHERSORT02 PREVBIOTHERSORT03 PREVBIOTHERSORT04 PREVLENGTHTHER PREVNONBIOTHER01 PREVNONBIOTHER02 PREVNONBIOTHER03 PREVNONBIOTHER04 PREVNONBIOTHER05 PREVNONBIOTHER06 PREVNONBIOTHER07 PREVNONBIOTHER08 PREVNONBIOTHER00 EGFRLESSTHAN60 GAMMAGT ASAT ALAT HB TROMBO LEUKO
  $DATA dataset-pd.csv IGNORE=@; input datafile
  $SUBROUTINES ADVAN6 TOL=4
  $MODEL
  COMP=(ABS, DEFDOS)
  COMP=(CENT)
  COMP=(PASI, DEFOBS)
  $PK
  KA = 0.28
  CL = ICL
  V2 = IVD
  BASE = PASIBASE
  S2 = V2
  K12 = KA
  K20 = CL/V2
  TVKOUT = THETA(3)
  KOUT = TVKOUT
  TVEMAX = THETA(4)
  EMAX = TVEMAX
  TVIC50 = THETA(5)
  IC50 = TVIC50 * EXP(ETA(1))
  TVGAMMA = THETA(6)
  GAMMA = TVGAMMA
  KIN = BASE * KOUT
  F3 = BASE
  $DES
  DADT(1) = - K12 * A(1)
  DADT(2) = K12 * A(1) - K20 * A(2)
  CXC2 = A(2) / S2
  IF(CXC2.LE.0)CXC2=0.0000001
  INHIB = 1 - EMAX * CXC2**GAMMA / (IC50**GAMMA + CXC2**GAMMA)
  DADT(3) = BASE * KOUT * INHIB - KOUT * A(3)
  PASI = A(3)
  $ERROR
  IPRED = F
  IRES = DV-IPRED
  W = SQRT(THETA(1)**2*F*F+THETA(2)**2)
  IF (W.EQ.0) W = 1
  IWRES = IRES/W
  Y= IPRED+W*ERR(1)
  $THETA
  (0, 0.1) ;1 Prop
  (0.01) FIX ;2 Add (mg/L)
  (0, 0.0314) ;3 KOUT
  (1) FIX;4 EMAX
  (0, 0.14) ;5 IC50
  (1) FIX;6 GAMMA
  $OMEGA
  0.1 ;IIV IC50
  $SIGMA
  1 FIX
  $ESTIMATION SIG=3 MAXEVAL=9999 NOABORT PRINT=5 METHOD=1 INTER POSTHOC
  $COVARIANCE
  $TABLE ID TIME TAD CXC2 DV MDV EVID IPRED IWRES CWRES IRES W WRES ONEHEADER NOPRINT FILE=sdtab
  $TABLE ID KA CL V2 IC50 GAMMA EMAX KIN KOUT BASE PASIBASE ONEHEADER NOPRINT FILE=patab
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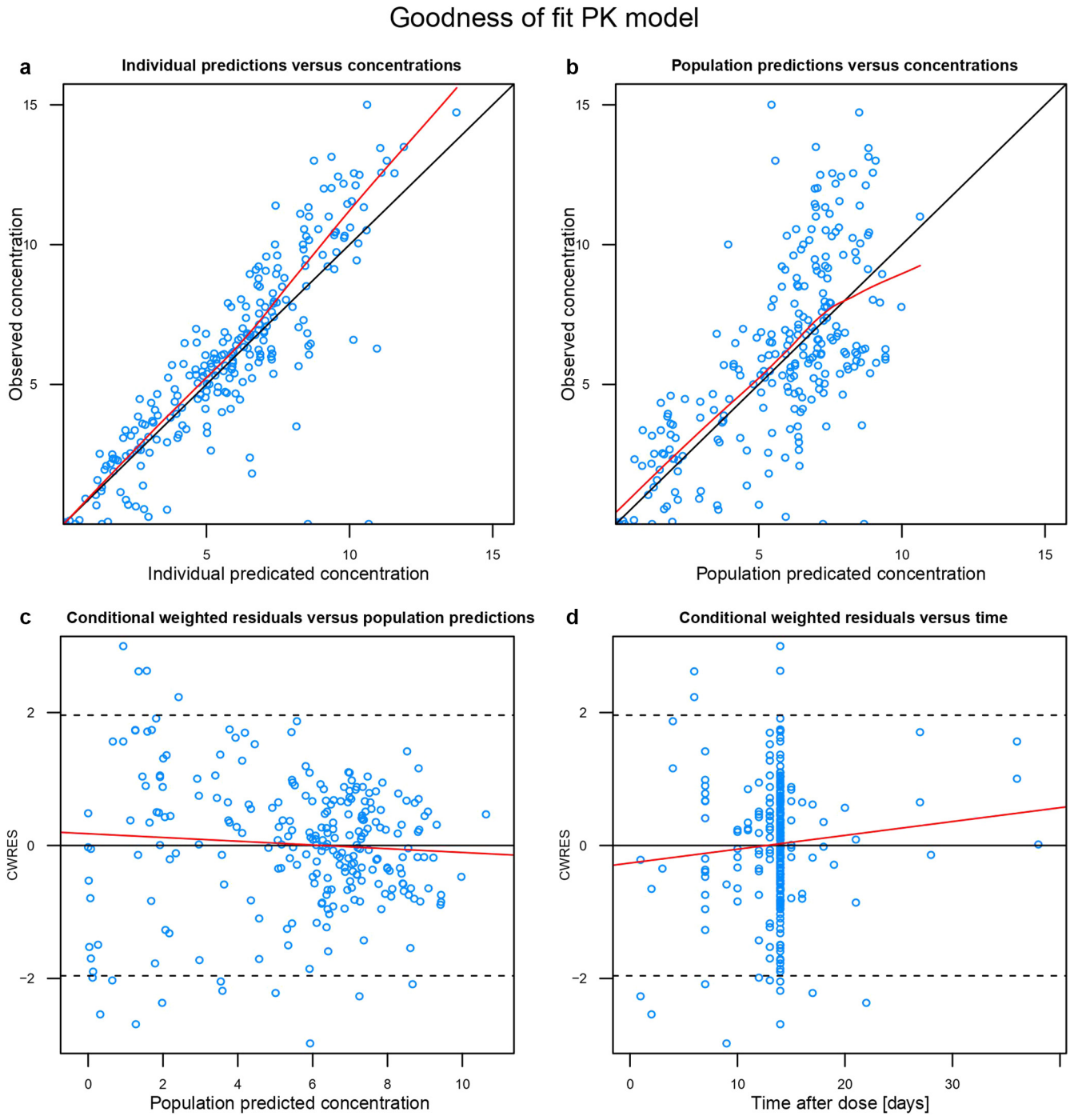
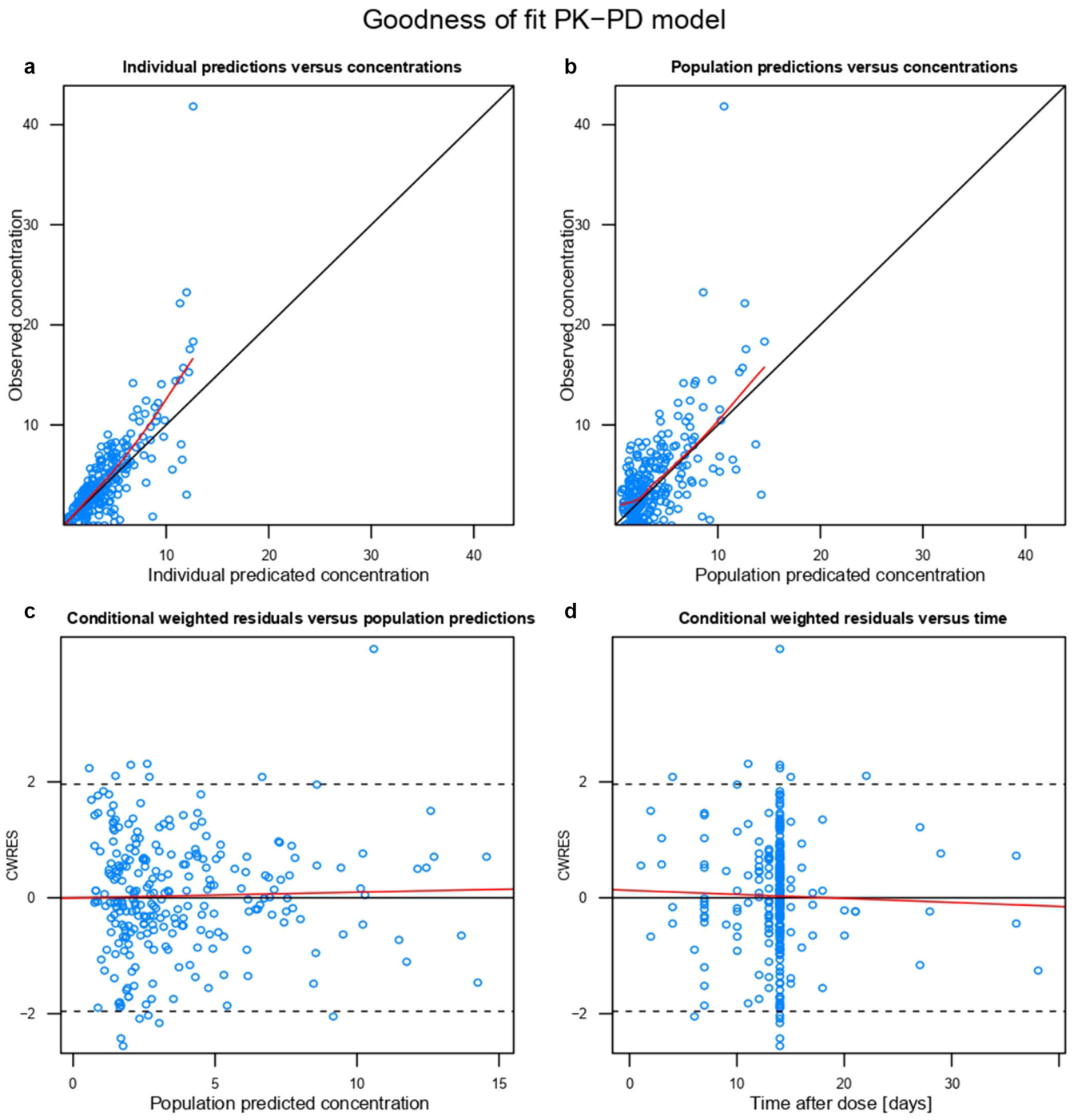
SUPPLEMENTARY REFERENCES

Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI [published correction appears in J Pharmacokinet Pharmacodyn 2010;37:305–8]. J Pharmacokinet Pharmacodyn 2008;35:401–21.

Irby DJ, Ibrahim ME, Dauki AM, Badawi MA, Illamola SM, Chen M, et al. Approaches to handling missing or "problematic" pharmacology data: pharmacokinetics. CPT Pharmacometrics Syst Pharmacol 2021;10:291–308.



Supplementary Figure S1. Goodness-of-fit plots of the PK model of adalimumab and population model of predicted concentration. (**a**) Individual predicted concentration (denoted as IPRED) versus observed concentration. (**b**) Population predicted (denoted as PRED) versus observed concentration. (**c**) PRED versus conditional weighted residuals (denoted as CWRES). (**d**) CWRES versus time after administration. The black solid line is the line of identity. The red line represents the local regression smooth line (LOESS smooth). LOESS, local regression smooth line; PK, pharmacokinetics.



Supplementary Figure S2. Goodness-of-fit plots of the PD model of adalimumab and population model of predicted concentration. (a) Individual predicted concentration (denoted as IPRED) versus observed concentration. (**b**) Population predicted (denoted as PRED) versus observed concentration. (**c**) PRED versus conditional weighted residuals (denoted as CWRES). (**d**) CWRES versus time after administration. The black line is the line of identity. The red line represents the local regression smooth line. PD, pharmacodynamics.

Supplementary Table S1. Covariates Other Than Antidrug Antibodies Missing at Baseline

Covariate	Number of Patients with Missing Covariate
Length of CPP diagnosis	1
eGFR	10
Alkaline phosphatase[1]	5
Gamma-GT	5
ASAT	5
ALAT	5
CRP[1]	13
Hb	6
Thrombocyte count	5
Leukocyte count	5
PIIINP[1]	57

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CPP, chronic plaque psoriasis; eGFR, estimated glomerular filtration rate; Gamma-GT, gamma-glutamyl transferase; Hb, hemoglobin; PD, pharmacodynamics; PIIINP, procollagen III N-terminal propeptide; PK, pharmacokinetics.

[1]These covariates were not included in the final analysis for our PK–PD model owing to the great number of missing data (it was no longer advised to routinely collect these laboratory values in the psoriasis national guideline).

Supplementary Table S2. Covariates Other Than Antidrug Antibodies Missing at Measurements Other Than Baseline

Covariate	Number of Patients with a Missing Covariate	Number of Missing Observations
eGFR	6	10
Alkaline phosphatase[1]	29	79
Gamma-GT	6	8
ASAT	13	16
ALAT	5	7
CRP[1]	20	40
Hb	6	12
Thrombocyte count	7	9
Leukocyte count	5	9
PIIINP[1]	58	215

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; Gamma-GT, gamma-glutamyl transferase; Hb, hemoglobin; PD, pharmacodynamics; PIIINP, procollagen III N-terminal propeptide; PK, pharmacokinetics.

[1]These covariates were not included in the final analysis for our PK–PD model owing to the great number of missing data (it was no longer advised to routinely collect these laboratory values in the psoriasis national guideline).