Early model-based precision-dosing at home to guide adalimumab therapy

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Abstract

1. Aims Underdosing of adalimumab can result in non-response and poor disease control. In this study we investigated the prediction of adalimumab levels with population pharmacokinetic model-based Bayesian forecasting early in therapy. This way underexposed non-responders can possibly be identified early to optimise disease control. 2. Methods A literature study was performed to identify adalimumab pharmacokinetic models. With data from a previous pharmacokinetic adalimumab study a model was evaluated retrospectively. In the prospective phase, a fit-for-purpose evaluation of the model was performed for rheumatologic and inflammatory bowel disease patients with peak, trough and control adalimumab samples obtained by a volumetric absorptive microsampling technique and administration data from an electronic needle container. Steady state adalimumab levels were predicted from peak and trough levels collected after the first adalimumab administration. Predictive performance was calculated with mean prediction error (MPE) and normalized root mean square error (RMSE). 3. Results An existing pharmacokinetic model was selected with external validation for the prospective phase. Thirty-six patients (22 rheumatologic and 14 IBD) were included in our study. After stratification for absence of anti-adalimumab antibodies, the calculated MPE was -2.6% and normalised RMSE 24.0%. Concordance between predicted and measured adalimumab serum levels falling within or outside the therapeutic window was 75%. Three patients (8.3%) developed detectable levels of anti-adalimumab antibodies. 4. Conclusion This prospective study demonstrates that adalimumab levels at steady state can be predicted from early samples. This concept enables early precision dosing at home to guide therapy.

Early model-based precision-dosing at home to guide adalimumab therapy

Running title: early prediction of adalimumab levels

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Ethical statements:

Data availability statement: raw data were generated at Máxima Medical Center and Radboud University Medical Center. Derived data supporting the findings of this study are available from the corresponding author [PK] on request.

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Ethics approval statement: the study was approved by the local ethics committee.

Patient consent statement: all patients provided written informed consent.

Clinical trial registration: the trial was registered in the Netherlands Trial Register with trial registry number NTR 7692 (www.trialregister.nl).

Keywords: adalimumab, model based precision dosing, Inflammatory bowel disease, rheumatology

Total word count excluding summary*:* 2144

- What is already known about this subject
- Capillary adalimumab sampling can be done at home
- Adalimumab treatment can be optimised with therapeutic drug monitoring
- Underdosing of adalimumab can lead to poor disease control and non-response
- What this study adds

- Steady state adalimumab concentrations can be predicted after a single dose
- Home capillary sampling and electronic needle container can be combined to monitor treatment at home
- MAP Bayesian forecasting can be used for precision dosing of adalimumab
- Abstract
- Aims

Underdosing of adalimumab can result in non-response and poor disease control. In this study we investigated the prediction of adalimumab levels with population pharmacokinetic model-based Bayesian forecasting early in therapy. This way underexposed non-responders can possibly be identified early to optimise disease control.

Methods

A literature study was performed to identify adalimumab pharmacokinetic models. With data from a previous pharmacokinetic adalimumab study a model was evaluated retrospectively. In the prospective phase, a fit-for-purpose evaluation of the model was performed for rheumatologic and inflammatory bowel disease patients with peak, trough and control adalimumab samples obtained by a volumetric absorptive microsampling technique and administration data from an electronic needle container. Steady state adalimumab levels were predicted from peak and trough levels collected after the first adalimumab administration. Predictive performance was calculated with mean prediction error (MPE) and normalized root mean square error (RMSE).

Results

An existing pharmacokinetic model was selected with external validation for the prospective phase. Thirty-six patients (22 rheumatologic and 14 IBD) were included in our study. After stratification for absence of anti-adalimumab antibodies, the calculated MPE was -2.6% and normalised RMSE 24.0%. Concordance between predicted and measured adalimumab serum levels falling within or outside the therapeutic window was 75%. Three patients (8.3%) developed detectable levels of anti-adalimumab antibodies.

Conclusion

This prospective study demonstrates that adalimumab levels at steady state can be predicted from early samples. This concept enables early precision dosing at home to guide therapy.

“Clinical trial registry number: Netherlands Trial Register, NTR 7692”

Keywords: model-based precision-dosing adalimumab

Introduction

Adalimumab is a fully human recombinant IgG1k monoclonal antibody against Tumor Necrosis Factor (TNF) alpha. It is approved for moderate to severe inflammatory bowel disease (IBD) and the rheumatic diseases rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (SpA) with poor response to conventional immunosuppressants. Adalimumab is administered subcutaneously. For RA, PsA and SpA the licensed dose is 40 mg every other week, without induction therapy. For IBD the licensed induction dose is either 80 mg followed by 40 mg after two weeks or 160 mg followed by 80 mg after two weeks, the latter induction scheme being used more frequently in clinical practice. The licensed maintenance dose is 40 mg every other week.

Up to 30% of patients with IBD do not respond to initial treatment with TNFα antagonists. It is important to differentiate between true primary non-responders (pharmacodynamic failure) and underexposed non-responders (pharmacokinetic failure), to intervene early in latter cases and adjust dosage to the individual patient. This serves patient satisfaction, disease control and drug expenses.

Target adalimumab trough-levels can range from 5-12 mg/L and therapeutic drug monitoring (TDM) can be performed in routine clinical practice, most often reactively during the maintenance phase of therapy. Population pharmacokinetic models have been developed and could theoretically be used for serum level

prediction at steady state and therefore early dosage prediction, but these models have not yet reached clinical practice.

In the current study, we investigated the feasibility of predicting adalimumab levels with population pharmacokinetic model-based Bayesian forecasting early in therapy. This can be used to identify underdosed non-responders as soon as possible to optimise disease control in clinical practice.

Materials and Methods

2.1 Population pharmacokinetic model selection

A 3-step-approach as described by *ter Heine et al* was used. For step 1, identification of models, a PubMed search for a population pharmacokinetic adalimumab model was performed and FDA registration data were evaluated. In step 2, an expert panel of pharmacometricians and clinical pharmacologists retrospectively evaluated the predictive performance of the pharmacokinetic models with data from a published study with IBD patients in Máxima Medical Center using Nonlinear Mixed Effects Modelling (NONMEM) version 7.4, executed through the Pirana workbench. Final model selection was based on Goodness of fit evaluation in line with best practice. Step 3 in this strategy is described below as the prospective observational cohort study.

2.2 Study design and population

This multicentre prospective observational cohort study aimed to collect data from 40 patients [?] 18 years with IBD or RA, SpA and PsA starting with adalimumab from March 2019 up to August 2020.

Patients were recruited from Rheumatology and Gastroenterology departments of Maxima Medical Center, Veldhoven/Eindhoven, the Netherlands and Gastroenterology department of Radboud University Medical Center (UMC), Nijmegen, the Netherlands. Adalimumab was dosed according to label and local clinical care pathways.

Pregnancy, known allergy for adalimumab or excipients and previous adalimumab use were exclusion criteria. For each drop-out a new patient was recruited. Patients weight, gender, date of birth and indication for treatment with adalimumab were collected.

The workflow is shown in figure 1.

2.3 Sampling

Sampling was done with a volumetric absorptive microsampling (VAMS) method. All patients were provided with 3 sampling sets for capillary blood microsampling at home. A sampling set consists of two 20 microliter Mitra^{TM} microsamplers (Neotyrex, Torrance, USA) and a BD microtainer 2 mm contact-activated lancet (BD, Dublin, Ireland). Patients were asked to perform capillary sampling at home 5 days, 13 days and 12 weeks after first adalimumab administration (Figure 1). Patients could receive sampling reminders for each sampling moment per email or text message on request. Samples were returned and stored under refrigerated conditions until analysis at Sanquin Diagnostic Services (Amsterdam, the Netherlands). Patients completed the trial upon returning the third sample.

2.4 Drug administration monitoring

All patients were required to use a an electronic needle container (HealthBeacon Injection Care Management System^{TM}, Health Beacon Ltd, Dublin, Ireland). Electronic needle containers were provided as part of standard care to all patients in this study. The electronic needle container is a device intended to monitor and improve compliance for patients on therapy with injectables. It reports the date and time a syringe is dropped in the device after use. The electronic needle container reports were automatically sent to Maxima Medical Center with secure mail.

2.5 Measurement of adalimumab and anti-adalimumab antibody concentrations

Mitra^{TM} tips processing.

Blood from Mitra^{TM} tips was eluted by overnight incubation in 0.5–1 ml PBS containing 0.05% Tween and 0.05% NaN_3 gently shaking at room temperature. Eluates were kept at 4*C until further measurements were performed as previously described.

Concentration measurements

Concentration measurements of adalimumab in patient samples were performed by a validated ELISAs at Sanquin Diagnostic Services (Amsterdam, the Netherlands). In short, TNFα is captured to the ELISA plate by a coating with mouse-anti-TNFα-antibody. Hereafter adalimumab derived from the patient samples is captured and detected by a biotin labelled anti-idiotype polyclonal antibody in combination with HPR coupled to streptavidin and TMB. The concentration of anti-adalimumab antibodies (ADA) was measured by radioimmunoassay. In short, antibodies from patient samples are captured by protein A sepharose and detected with radio-labelled $F(ab')_2$ fragment of adalimumab. Anti-adalimumab antibodies were only measured if adalimumab concentration (back-calculated to serum) was below 5 mg/L (cascade principle). The concentrations were back-calculated to serum concentrations by taking into account the exact volume of the absorbent Mitra^{TM} tip in combination with the volume of elution buffer and a fixed haematocrit value of 0.42. For all underfilled samples, for which the correction factor was unknown, the potassium concentration was measured in eluates of completely filled tips and in eluates of the underfilled tips of the same patient. The blood volume present in the eluate was calculated with these potassium concentrations and used for calculation of adalimumab concentration.

2.6 Fit-for-purpose evaluation and statistical analysis

The predictive performance of the selected models to predict the steady state adalimumab serum concentration at 12 weeks from the measurements at day 5 and day 13 was investigated. The adalimumab concentration measured in the eluate of the Mitra^{TM} tip performed at week 12 was considered the true serum level value and compared with the individual model-predicted value. The primary outcome of this analysis was a precise and accurate prediction defined as mean prediction error (MPE) and normalised root mean square error (RMSE) $< 25\%$. We defined normalized RMSE as RMSE divided by range (maximal dependent variable minus minimal dependent variable). Additionally, we calculated normalised RMSE defined as RMSE divided by average true values for all patients without detectable ADA. The 95% Confidence intervals (CI) are defined as 1.96 x standard error (SE) for MPE. Standard error for RMSE is defined as $\sqrt{1/2n}$ x normalised RMSE, where n represents the degrees of freedom.

The clinical applicability of early prediction of steady state adalimumab levels was evaluated by dividing all predictions into four classes: true positive (prediction and measured value within therapeutic range), true negative (prediction and measured value outside therapeutic range), false positive (prediction in therapeutic range, measured value outside therapeutic range), false negative (prediction outside therapeutic range, measured value in therapeutic range).

Secondary outcome of this analysis was fitting a new model to the collected pharmacokinetic data. The pharmacokinetic parameters were estimated with NONMEM version 7.4 (ICON plc, Dublin, Ireland) and PsN version 5.2.6. (https://github.com/UUPharmacometrics/PsN) Diagnostic plots were prepared in R (R Foundation for Statistical Computing, Vienna, Austria). Model predictive ability was assessed using the proseval tool in PsN.

2.7 Ethical considerations

The study was approved by the local ethics committee and all patients provided written informed consent. The trial was registered in the Netherlands Trial Register with trial registry number NTR 7692 (www.trialregister.nl).

Results

3.1 Population pharmacokinetic model selection

Based on the literature search and the external evaluation of existing models with our retrospective dataset, the model by Ternant *et al*was selected for use in this prospective analysis. Prediction corrected visual predictive check (VPC) used for the goodness of fit evaluation for this model is shown in figure 2. Other VPCs of the model as well as the model code are shown in the appendix.

3.2 Patients

A total of 56 patients were included in the trial. Drop-out rate in this trial was 20 patients (36%). Data of 36 patients were included in the prospective analysis. Inclusion was stopped at 36 patients because of the COVID pandemic. Twenty-two patients carried a diagnosis of rheumatic disease and 14 IBD. Baseline characteristics of patients included in the analysis are shown in table 1.

3.3 Fit-for-purpose evaluation

The predictive performance analysis resulted in an MPE of 294% (95% CI 261% to 326%) and a normalised RMSE of 80% (95% CI 61% to 99%). When stratified for absence of ADA, the MPE was-2.6% (95% CI -3.9% to -1.4%) and normalised RMSE 24.0% (95% CI 18.4% to 29.6%).

When calculating normalised RMSE defined as RMSE divided by average true values for patients without measured ADA, we found an RMSE of 42.5% (95% CI 37.5% to 47.6%)

Clinical applicability evaluation resulted in 75% true predictions. Full results from the clinical applicability evaluation are shown in table 2.

The results of parameter estimation based on the newly collected adalimumab levels and ADA titers collected in this study are shown in table 3.

3.3 Immunogenicity

Three patients in our cohort developed ADA at steady state 12 weeks after start of adalimumab therapy. None of these patients had received biologicals before and none of these patients were on combination therapy with other immunosuppressive drugs.

3.4 Feasibility at home

The combination of an electronic needle container and capillary blood microsampling enabled us to remotely monitor patient's medication treatment. Exclusion from the analysis was mostly caused by home sampling errors by a minority of patients resulting in samples unsuitable for concentration measurement. Other reasons were needle drop registration issues with health beacon occurred and some patients failed to provide a complete set of three samples. These issues should be addressed to increase feasibility at home.

Discussion

In this study we demonstrated the possibility of predicting steady state adalimumab concentrations, based on early single peak and trough levels only, resulting in a correct prediction (therapeutic – subtherapeutic) in the vast majority of cases without ADA. After stratification for ADA our primary outcome measures for bias and precision were met for patients without ADA. It should be noted that ADA development is not predictable in clinical practice. The application of MAP Bayesian forecasting early in therapy in combination with an electronic needle container and home capillary sampling is unique and enables us to fully remotely monitor the patient's medication treatment at home from pharmacokinetic point of view. Self-management can be of value for patients with chronic conditions on adalimumab treatment to reduce the number of visits to the clinic.

The foremost clinical implication of our study is the possibility of an early adalimumab dose optimisation for patients with predicted subtherapeutic levels. Since we did not measure clinical response, our prediction does not account for non-response due to other reasons.

This study shows that the population pharmacokinetic model selected (which is based on adalimumab concentrations measured in serum) could be used in combination with a VAMS method with capillary blood

for adalimumab sampling. This makes sampling more accessible for patients. This method has been compared to venepuncture for adalimumab and has been studied in IBD patients at home before with reliable results.

A drawback of the current VAMS technique is underfilling of the tips. In case of underfilling, it is a challenge to calculate the concentration that equals the serum concentration. For patients with at least one correctly filled sample, other underfilled samples were corrected for volume by potassium levels in both the correctly filled sample and the underfilled sample(s). Patients with potassium-corrected samples did not perform worse in our model then patients uncorrected samples, although this could not be statistically proven due to the small number of patients. For future research with home monitoring of anti-TNF serum concentrations, a more robust sampling method (e.g. wet blood collection with microsampling tubes) is recommended to avoid these sampling and correction issues.

We used an electronic needle container to collect data on timing of adalimumab administration. Unfortunately, the electronic needle container was not able to generate a report in all cases. Therefore, on a few occasions interpolations for the timing of adalimumab administration were necessary. We do not expect this will influence the outcome of our study since adalimumab has a long terminal elimination half-life and it concerned only a single administration in a series of administrations. For implementation of our adalimumab monitoring concept, other systems such as mobile health apps may be good alternatives.

Conclusion

In this study we have demonstrated prospectively that our model is fit-for-purpose for early prediction of adalimumab levels at steady state. This concept enables early precision dosing at home to guide therapy.

Acknowledgements: We thank Wil Adriaans, Louise Merry-Meier and Antoinette Piepenbrock-van Schooten for their efforts for the inclusion of patients in this trial.

Conflict of interest disclosure: the authors declare that there is no conflict of interest

Funding information: This study was funded by Máxima Medical Center

Data availability statement: raw data were generated at Máxima Medical Center and Radboud University Medical Center. Derived data supporting the findings of this study are available from the corresponding author [PK] on request.

References

Tables

Table 1:

Patient demographics at baseline

	N = 36
Crohn's disease (N, %)	8 (22%)
Ulcerative colitis (N, %)	6 (17%)
Rheumatoid arthritis (N, %)	11 (31%)
Ankylosing spondylitis (N, %)	4 (11%)
Psoriatic Arthritis (N, %)	7 (19%)
Male (N, %)	13 (36%)
Age (yr)	51.5 (42-58)
Weight (kg)	78 (64-89)

Categorical values are reported as count (percentage of total) Continuous values are reported as median values (interquartile range)

Table 2:

Concordance between predicted and measured adalimumab serum levels falling within or outside the therapeutic window (defined as 5 –12 mg/L)

	N = 36
True positive	21 (58%)
True negative	6 (17%)
False positive	4 (11%)
False negative	5 (14%)

true positive (prediction and measured value within therapeutic range), true negative (prediction and measured value outside therapeutic range), false positive (prediction in therapeutic range, measured value outside therapeutic range3), false negative (prediction outside therapeutic range, measured value in therapeutic range).

Table 3:

Model parameter estimates

Parameter	Value	Unit
CL/F	0.319	L/day (/70kg)
V/F	9.830	L(/70kg)
KA	0.376	/hr
AAA-CL	4.350	
IIV CL	46.400	%
IIV V	54.900	%
Proportional	0.145	%
Additive	0.617	mg/L

Figures

Figure 1.

Workflow

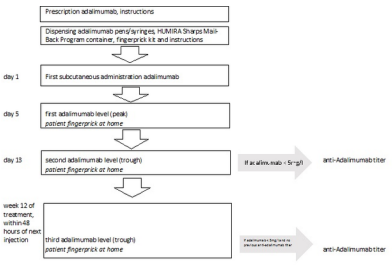

Figure 2.

Prediction-corrected visual predictive check (pc-VPC) for the model by Ternant et al. for the retrospective data. The shaded area's in this figure show the 95% of the 5th, 50th and 95th of data simulated from the model, calculated for each of the bins in the plot. The dashed lines indicate those same percentiles for the observed data. Dots indicate the observed adalimumab concentrations.

Hosted file

`image2.emf` available at https://authorea.com/users/430672/articles/713596-early-model-based-precision-dosing-at-home-to-guide-adalimumab-therapy

Appendices

Hosted file

`image3.emf` available at https://authorea.com/users/430672/articles/713596-early-model-based-precision-dosing-at-home-to-guide-adalimumab-therapy

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`image6.emf` available at https://authorea.com/users/430672/articles/713596-early-model-based-precision-dosing-at-home-to-guide-adalimumab-therapy

Model code:

$PROBLEM final model Adalimumab in adults (De Klaver et al.)

$INPUT ID TIME EVID MDV DV AMT RATE SEX AGE WT ATA

$DATA dataset.csv IGNORE=@

; TIME in hours

; WT: TBW in kg

; SEX: 0 = FEMALE, 1 = MALE

$SUBROUTINE ADVAN2 TRANS2 ; linear 1-cmt oral

$PK

; typical values

TVCL = (THETA(1)/24) * (WT/70)**0.75 * THETA(4)**ATA

TVV = THETA(2) * (WT/70)

TVKA = THETA(3)

KA = TVKA/24

; IIV

CL = TVCL * EXP(ETA(1))

V = TVV * EXP(ETA(2))

; scaling

S2=V

$ERROR

IPRED = F

Y = IPRED*(1+ERR(1)) + ERR(2)

$THETA

0.318775 ; 1 CL/F (L/day)

9.83155 ; 2 V/F (L)

0.375643 ; 3 KA (/day)

4.34751 ; 4 AAA˜CL

$OMEGA

0.215418 ; 1 IIV CL

0.301728 ; 2 IIV V

$SIGMA

0.0210676 ; 1 Proportional error

0.380199 ; 2 Additive error

$ESTIMATION METHOD=1 INTERACTION NOABORT MAXEVAL=9999 SIGDIG=3 PRINT=5

$COVARIANCE UNCOND

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3	
Introduction	Introduction	Introduction	Introduction	

Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	4,5
Methods	Methods	Methods	Methods
Study design	4	Present key elements of study design early in the paper	6-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7

		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9,10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9,10*
Bias	9	Describe any efforts to address potential sources of bias	6-10
Study size	10	Explain how the study size was arrived at	6,7

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-10	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9,10	
		(*b*) Describe any methods used to examine subgroups and interactions	N.A.	
		(*c*) Explain how missing data were addressed	N.A.	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N.A.	
		(*e*) Describe any sensitivity analyses	N.A.	
Results	Results	Results	Results	Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, table 1
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	Table 3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N.A.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	

		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*10-13*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	N.A.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.

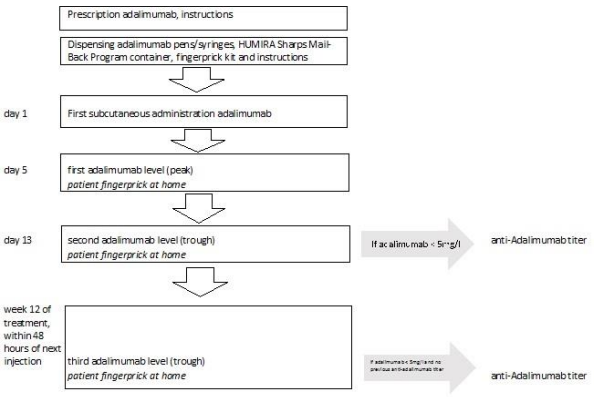
Continued on next page

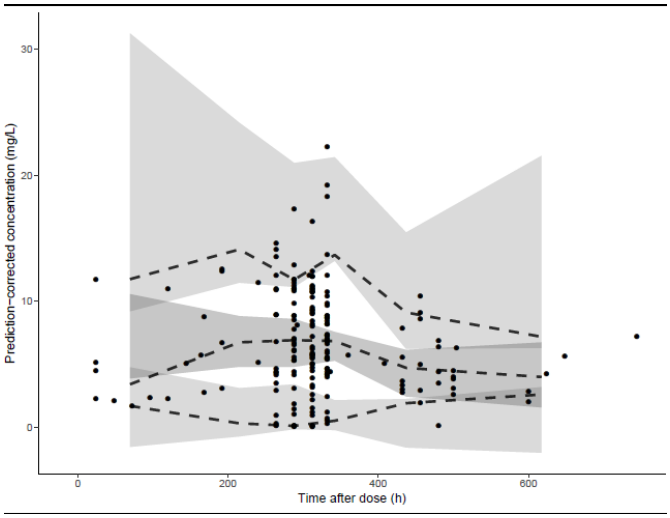
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensit
Discussion	Discussion	Discussion
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or in

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information	Other information	
Funding	22	Give the source of funding and the role of the funders for the present study and, i

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.-statement.org.





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False negative	5 (14%)

Parameter	Value	Unit
CL/F	0.319	L/day (/70kg)
V/F	9.830	L(/70kg)
KA	0.376	/hr
AAA-CL	4.350	
IIV CL	46.400	%
IIV V	54.900	%
Proportional	0.145	%
Additive	0.617	mg/L