Therapeutic drug monitoring in dermatology: the way towards dose optimization of secukinumab in chronic plaque psoriasis

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Summary

Background. Despite the favourable efficacy profile of secukinumab, clinicians encounter varying clinical responses among patients potentially associated with under- and overdosing. As biologics are expensive, their rational use is crucial and evident. Therapeutic drug monitoring could guide clinicians in making decisions about treatment modifications.

Aim. In this multicentre, prospective study, we aimed to develop and validate a secukinumab immunoassay and searched for the therapeutic window in patients with psoriasis.

Methods. We determined secukinumab concentrations at trough in sera from 78 patients with psoriasis at multiple timepoints (Weeks 12, 24, 36, 48 and 52; after Week 52, measurements could be taken at an additional three timepoints) during maintenance phase, using an in-house secukinumab immunoassay consisting of a combination of MA-SEC66A2 as capture antibody and MA-SEC67A9, conjugated to horseradish peroxidase, as detecting antibody. At each hospital visit, disease severity was assessed using the Psoriasis Area and Severity Index (PASI).

Results. After quantification, 121 serum samples were included for dose–response analysis. Based on a linear mixed-effects model, secukinumab trough concentrations were found to decrease with increasing body mass index (BMI). Based on receiver operating characteristic (ROC) analysis, we concluded that the minimal effective secukinumab threshold was 39.1 mg/L in steady state, and that this was associated with a 92.7% probability of having an optimal clinical response (PASI ≤ 2 or reduction in PASI of ≥ 90%).

Conclusions. Monitoring and targeting a secukinumab trough concentration of 39.1 mg/L may be a viable treatment option in suboptimal responders. In patients with higher BMI, weight-based dosing may be needed in order to prevent underdosing.

Introduction

Psoriasis is a chronic, multifactorial, immune-mediated inflammatory skin disease characterized by well-demarcated, raised, erythematous plaques with adherent silvery scales, and it is associated with a

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diminished quality of life, a number of comorbidities and even increased mortality.[1] Treatment strategies to achieve and maintain minimal disease activity are key for long-term management of the disease and its associated comorbidities.[2] Fortunately, new classes of biologics have revolutionized the treatment landscape of psoriasis, introducing a reduction in Psoriasis Area and Severity Index (PASI) by 90% (PASI90) as a realistic treatment goal.[3,4] Nevertheless, higher rates of nonresponse or loss of response to biologics are

reported from real-life clinical settings compared with randomized controlled trials.[5] In addition, biologics are expensive and impose a high burden on national healthcare expenditures, illustrating the importance of their rational and cost-effective use.[6,7]

Secukinumab, a fully human monoclonal antibody directed against interleukin (IL)-17A, has shown superior clinical efficacy compared with anti-tumour necrosis factor (TNF)-α inhibitors,[8] with rapid and sustained response and a favourable safety profile.[9,10] The current dosing scheme includes an initiation dose of 300 mg at Weeks 0, 1, 2, 3 and 4, and a fixed maintenance dose of 300 mg every 4 weeks thereafter.[11] However, this dosing regimen is based on a 'one dose fits all' principle and does not account for pharmacokinetics (PK) and pharmacodynamics (PD) variability among patients. In a subset of patients, this standard dosing scheme might lead to potential overdosing or underdosing, subsequently resulting in insufficient response (primary nonresponse) or loss of response (secondary nonresponse).[12–15] Huang et al. reported loss of efficacy of up to 18.9% after 24–32 weeks of secukinumab therapy.[16] In general, these various individual responses can be explained by differences in drug clearance, presence or absence of anti-drug antibodies or mechanistic failure.[17] Notably, although there are clinical concerns related to immunogenicity for TNF-α inhibitors, current research categorizes secukinumab as having low immunogenicity.[18] Nevertheless, these undesirable therapeutic outcomes have urged clinicians to explore trial-and-error off-label dose optimization, either by adjusting the dose or by altering the administration intervals.[19–21] In addition, alternative dose optimization strategies, such as a second induction phase of secukinumab, have been reported in patients with inadequate response.[22] In addition to concerns about loss of efficacy of secukinumab, a growing awareness is present that we might be overdosing patients that have an excellent clinical response, illustrated by several studies investigating the possibility of dose reduction, often by increasing the dosing interval, pausing therapy or even withdrawing the biologic.[23,24] These cases from everyday clinical practice highlight the compelling unmet medical need to guide physicians in their clinical decision-making about treatment modifications, eventually paving the way towards a more rational use of expensive biologics.

Therapeutic drug monitoring (TDM) could help tackle these issues. TDM refers to the clinical practice of measuring drug concentration (TC), ideally at trough, i.e. just before the next drug administration, to allow individual adjustment of the dosing regimen, striving for the lowest (overall) effective dose.[25] This would enable clinicians to tailor therapy at the individual level, avoiding waste of precious time and resources during trial-and-error dose optimization approaches. In our previous publication,[26] we analysed serum samples of 40 patients with moderate to severe psoriasis taken at a single timepoint during maintenance secukinumab therapy; in the current study, we expanded our cohort to 78 patients and 121 samples, and consequently we performed linear mixed effect modelling.

In this real-life longitudinal study, we further investigated the secukinumab dose–response relationship. We developed and validated an in-house sandwich-type ELISA and aimed to identify patient factors that influence secukinumab dose and clinical response.

Methods

The study was approved by the ethics committees of all participating sites and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from each patient for participation and publication of study results (B670201835652).

Study design and data collection

This was a multicentre, prospective study called BIOLOPTIM-SEC (NCT04080661) in patients with moderate to severe chronic plaque psoriasis at the Department of Dermatology of three Belgian centres. The study data were collected and managed using the REDCap (Research Electronic Data Capture) system, hosted at the University Hospital of Ghent.[27,28]

Participants and clinicopathological data

Patients were eligible for inclusion in the study if they were aged ≥ 18 years and had received secukinumab 300 mg (standard maintenance dosing) for the treatment of moderate to severe plaque psoriasis. Exclusion criteria were a predominance of a psoriasis type other than psoriasis vulgaris or treatment with secukinumab for a disease other than psoriasis.

All demographic and clinicopathological data, including age, sex, height, weight, body mass index (BMI), alcohol and/or tobacco use, psoriasis phenotype and onset, disease duration, previous psoriasis medication, comedication(s) and comorbidities, were obtained from the patients' medical record and discussed directly with the patients during the study visit.

Blood sampling

Blood samples were taken just before the next scheduled drug administration to determine the secukinumab TC. After an incubation time of maximum 24 h, all blood samples were centrifuged for 10 min at 252 g at room temperature (Model 5804; Eppendorf, Hamburg, Germany). Serum was prepared and preserved at a minimum of −20 °C for a median time of 59 days until analysis.[29]

Secukinumab trough concentrations

Development of secukinumab ELISA and measurement of patient serum samples. A panel of 10 monoclonal antibodies against secukinumab was generated, purified and conjugated to horseradish peroxidase (HRP) at KU Leuven, as described previously by Van Stappen et al.[30]

The monoclonal antibodies were pairwise tested for their suitability as capture and detecting antibody in an ELISA for determination of secukinumab concentrations.[31] In brief, 96-well plates were coated overnight with 100 μL MA-SEC66A2 [4 mg/mL in phosphate buffered saline (PBS)] at 4 °C, followed by blocking with 200 μL PBS containing 1% bovine serum albumin (BSA) for 2 h at room temperature. Samples were diluted 1 : 2000, 1 : 4000, 1 : 8000 and 1 : 16 000 in PTAE (PBS with 0.1% BSA, 0.002% Tween 80 and EDTA) buffer. For each diluted sample, 100 μL was applied to the plate and incubated for 2 h at room temperature on a plate shaker. The plates were then washed with PBS containing 0.008% Tween 80, and incubated for 2 h at room temperature with 100 μL of MA-SEC67A9–HRP in PBS containing 0.1% BSA and 0.002% Tween 80 for detection of bound secukinumab. Plates were then washed and developed using 0.4 g/L *o*-phenylenediamine and 0.003% H_2O_2 in citrate buffer (0.1 mol/L citric acid monohydrate with 0.2 mol/L disodium hydrogen phosphate dehydrate, pH 5.0) and the reaction was stopped after 30 min by adding 50 μL of 4 mol/L H_2SO_4. The absorbance was measured at 490 nm with an absorbance microplate reader (Model ELx808; BioTek Instruments Inc., Winooski, VT, USA) and the secukinumab dose–response curve was analysed by linear regression using GraphPad Prism (V.7.0; GraphPad Software, San Diego, CA, USA).

Validation of the secukinumab ELISA. After development of the secukinumab ELISA, the crossreactivity of the ELISA towards other biologics was determined by spiking infliximab, adalimumab, golimumab, etanercept, vedolizumab, ustekinumab, guselkumab, brodalumab, risankizumab or tildrakizumab at a concentration of 50 mg/L in PTAE buffer containing either no or 10 mg/L secukinumab. Thereafter, the secukinumab concentration was determined by interpolation from the secukinumab standard curve.

The assay limit of detection (LOD) was determined using a panel of 16 SEC-naive patient serum samples. The LOD was based on the mean optical density of a 1 : 100 dilution of the 16 secukinumab-naive serum samples plus three times the SD, and interpolated from the standard curve. The limit of quantification (LOQ) was defined as the lowest concentration that could be accurately measured in serum with a coefficient of variation (CV) of ≤ 20%.

The accuracy and imprecision of the assay was determined by preparing eight quality control samples in normal human serum (0.5, 1, 2.5, 5, 10, 25, 50 and 100 mg/L secukinumab) and measuring four repeats on one plate for the intra-assay variability and one repeat four times, each on a different day, for the interassay variability. The concentrations of the quality control samples were interpolated from a secukinumab concentration–response curve, which was calculated using linear regression. Acceptance criteria were defined as an accuracy of 80–120% and CV ≤ 20% for the intra-assay and interassay imprecision.

Clinical response

Disease activity was assessed using PASI, which is a composite evaluation instrument for psoriasis severity consisting of subscores for erythema, induration and scaling and the percentage of body surface area affected, scored from 0 to 72. The clinical response is the percentage of PASI reduction from baseline score, with optimal clinical response being ≥ 90% reduction in PASI (PASI90). Disease activity was assessed at the same time as blood sampling, i.e. at trough.

Dose–response modelling

Secukinumab dose. A linear mixed-effects model was used to describe the time course of secukinumab TCs during maintenance from Week 24 onwards. We used first-order conditional estimation with interaction for parameter estimation. Covariates affecting secukinumab TCs were investigated to yield the final model.

Clinical response. Factors affecting the clinical response were investigated by using generalized linear mixed-

effects models. Response models under three different definitions of optimal clinical response (PASI ≤ 2, PASI90 and PASI ≤ 2 or PASI90) were explored.

Covariate analysis. The continuous covariates included age, bodyweight, BMI, lean body mass, baseline PASI and disease duration. The categorical covariates included sex, maintenance dosing intervals (every 4 weeks or every month), previous exposure to biologics (yes/no) and smoking status. For the secukinumab TC model, covariates were tested in the base model with stepwise forward addition [α = 0.01, degrees of freedom (d.f.) = 1, decrease in objective function value (OFV) ≥ 6.64 points] followed by backward deletion (α = 0.001, d.f. = 1, increase in OFV ≥ 10.83 points).[32] For the response model, covariates were tested by comparing the Akaike information criteria (AIC) and the significant level (α = 5%) of parameter estimates between the covariate model and the base model.

Model evaluation. The most parsimonious model was selected based on comparisons using standard procedures, including the precision and physiological plausibility of parameter estimates, the OFV or AIC and goodness-of-fit plots. Bootstrapping was performed to obtain nonparametric estimates of uncertainty in parameter estimates (*n* = 2000 bootstrap runs).

Statistical analysis

Descriptive statistics were stated as frequencies and percentages for discrete variables and median and interquartile range (IQR) for continuous variables. Wilcoxon signed rank test was used for the analysis of paired measurements. Receiver operator characteristic (ROC) analysis was used to evaluate the diagnostic ability of the response models. The lower threshold of secukinumab TC at steady state was selected using the Youden *J* statistic.[33] The upper thresholds of the secukinumab therapeutic window at steady state were identified aiming at the 95th percentile of 99% predicted probability of optimal clinical response, standing no further clinical gain when increasing secukinumab TCs beyond the upper limit. For all statistical analyses, two-sided *P* < 0.05 was considered statistically significant.

Data were imported into R software (V4.0.3; R Foundation for Statistical Computing, R Core Team, Vienna, Austria) for data calculations (including the R packages data.table, dplyr and reshape2), generalized mixed effects modelling of the clinical response (glmer

package), ROC analysis (pROC package) and graphical evaluation (ggplot2 and xpose4 packages) in the RStudio integrated development environment (V1.3.1093; RStudio, Inc., Boston, MA, USA). Linear mixed-effects modelling of secukinumab TCs was performed using NONMEM (V7.4.4; Icon Development Solutions, Gaithersburg, MD, USA) with a GNU Fortran 95 compiler and the Perl-speaks-NONMEM (PsN; V4.9.0) toolkit on the interface software Pirana (V2.9.9; Certara, Inc., Princeton, NJ, USA).

Results

Patient selection and baseline demographics

The data of 78 adult patients with psoriasis were used for analysis. Baseline demographics and clinical characteristics are presented in Table 1. In brief, nearly two-thirds were men, and almost all participants (97.4%) were white with a median age of 48.5 years, median BMI of 28.4 kg/m², median disease duration of 18.0 years; approximately half (45.5%) of the patients were biologic-experienced. The median secukinumab treatment duration was 52.6 weeks and median baseline PASI was 11.0.

Secukinumab ELISA development and validation

After the pairwise testing of the 10 anti-secukinumab antibodies for their suitability to capture and detect secukinumab in our ELISA setup, MA-SEC66A2 was selected as capture antibody and MA-SEC67A9–HRP as detecting antibody. Using this combination, a linear secukinumab calibration curve, ranging from 0.3 to 25 ng/mL was obtained. Using a high concentration of 50 mg/L of infliximab, adalimumab, golimumab, etanercept, vedolizumab, ustekinumab, guselkumab, brodalumab, risankizumab or tildrakizumab in the assay, in the absence of secukinumab, revealed no values above the LOD. Furthermore, the presence of such a high concentration of these biologics did not interfere with the quantification of secukinumab, with a recovery of 88–117% of 10 mg/L secukinumab in the presence of 50 mg/L of any of these biologics. Based on the measurement of 16 secukinumab-naive serum samples, we determined the LOD at 0.16 mg/L and the LOQ at 0.5 mg/L secukinumab. The assay complied with the requirements for accuracy, with a mean accuracy of 109% (range 98–118%) and imprecision, with an intra-assay CV of 5% (range 2–9%) and an interassay CV of 11% (range 7–17%) for all quality control samples tested.

Table 1 Baseline characteristics of patients with psoriasis treated with secukinumab.

Parameter	Value
Patients, *n*	78
Demographics	
Ethnicity, *n* (%)	
White	76 (97.4)
Hispanic/Latino	2 (2.6)
M/F, *n* (%)	49 (62.8)/29 (37.2)
Age, years; median (IQR)	47.5 (37.0–60)
Weight, kg; median (IQR)	83.5 (74.4–94.2)
Length, cm; median (IQR)	174.0 (168.0–180.0)
BMI, kg/m^2; median (IQR)	27.3 (24.9–31.5)
Family history of psoriasis	
Positive	47 (60.3)
Negative	26 (33.3)
Unknown	3 (3.8)
Missing	2 (2.6)
Disease activity, median (IQR)	
Baseline PASI	11.0 (8.4–15.0)
Disease duration	17.0 (10.0–28.0)
Smoking status, *n* (%)	
Active smoking	20 (25.6)
Previous smoking	14 (17.9)
Never smoked	43 (55.1)
Comorbidities, *n* (%)	
None	16 (20.5)
Psoriatic arthritis	12 (15.4)
Metabolic syndrome/disorder(s)	18 (23.1)
Diabetes	5 (37.2)
Cardiovascular disorder(s)	29 (37.2)
Depression/mental health disorder(s)	8 (10.3)
Immune-mediated disorder(s)	17 (21.8)
Current/past malignancies	3 (3.8)
Musculoskeletal disorder(s)	3 (3.8)
Concomitant medication, *n* (%)	
None	30 (38.5)
Other immunosuppressive[a]	4 (5.1)
Antidiabetic	5 (6.4)
Antihypertensive	17 (21.8)
β-blocker	8 (10.3)
Antihyperlipidaemic agent	13 (16.7)
Antidepressant	1 (1.3)
Antiarrhythmic	1 (1.3)
Anticoagulant/antiaggregant	12 (15.4)
Antibiotic	3 (3.8)
Previous treatments	
Nonbiologic, *n* (%)	77 (98.7)
Methotrexate	71 (91.0)
Ciclosporin	60 (76.9)
Retinoids	29 (37.2)
Fumarates	0 (0.0)
Apremilast	10 (12.8)
Biologic, *n* (%)	35 (44.9)
Adalimumab	19 (24.4)
Etanercept	11 (14.1)
Infliximab	2 (2.6)
Ixekizumab	1 (1.3)
Ustekinumab	20 (25.6)

Table 1 continued

Parameter	Value
Brodalumab	3 (3.8)
Guselkumab	1 (1.3)

BMI, body mass index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index. [a]Apart from secukinumab.

Secukinumab dose slowly decreased over time and was affected by body mass index

Of the 78 patients, 14 patients were excluded from PK analyses due to a lack of serum samples at steady state (after Week 24 until Week 56), thus 121 secukinumab serum TCs from 64 patients were included in the PK analysis. A linear mixed-effects model with random intercepts was developed to describe the time course of the secukinumab TC between Weeks 24 and 54. Covariates such as age, sex, BMI, disease duration, smoking status and previous exposure to biologics were tested, and only BMI was identified as a significant covariate associated with secukinumab TC at steady state ($P < 0.01$), resulting in a decrease in interindividual variability (IIV) on secukinumab TC at Week 24 by 4.5% (Supplementary Table S1); however, the remaining IIV on the secukinumab TC was still large (26.5%). The parameters of the TC model are listed in Supplementary Table S2, and the plot of conditionally weighted residuals of the final TC model is presented in Supplementary Fig. S1.

The steady-state TC was found to decrease with time, with a decrease of 1.3 mg/L from Week 24 to Week 54 of treatment (Fig. 1). The median secukinumab steady-state TC was found to decrease from 39.1 to 30.6 mg/L as BMI increased from 27.1 to 37.1 kg/m^2. A typical patient, with a BMI of 27.1 kg/m^2, was estimated to have secukinumab TCs of 39.1 mg/L [6.6% relative standard error (RSE)] at Week 24. Equation 1 shows how secukinumab TCs of patient *i* at treatment timepoint *j* (TC$_{i,j}$) decreases with higher BMI:

$$[TC]_{i,j} = -0.034 \times (\text{treatment duration} - 24) + 39.1$$
$$\times (BMI_{i,j}/27.1)^{(-0.785)} \times e_j^\eta$$

$$(1)$$

At the population level (complete cohort), the decreasing rate of population secukinumab TC was 0.034 mg/L (53.5% RSE) per week and the population starting secukinumab TC at steady state was 39.1 mg/L (6.6% RSE). BMI$_{i,j}$ represents the BMI of individual

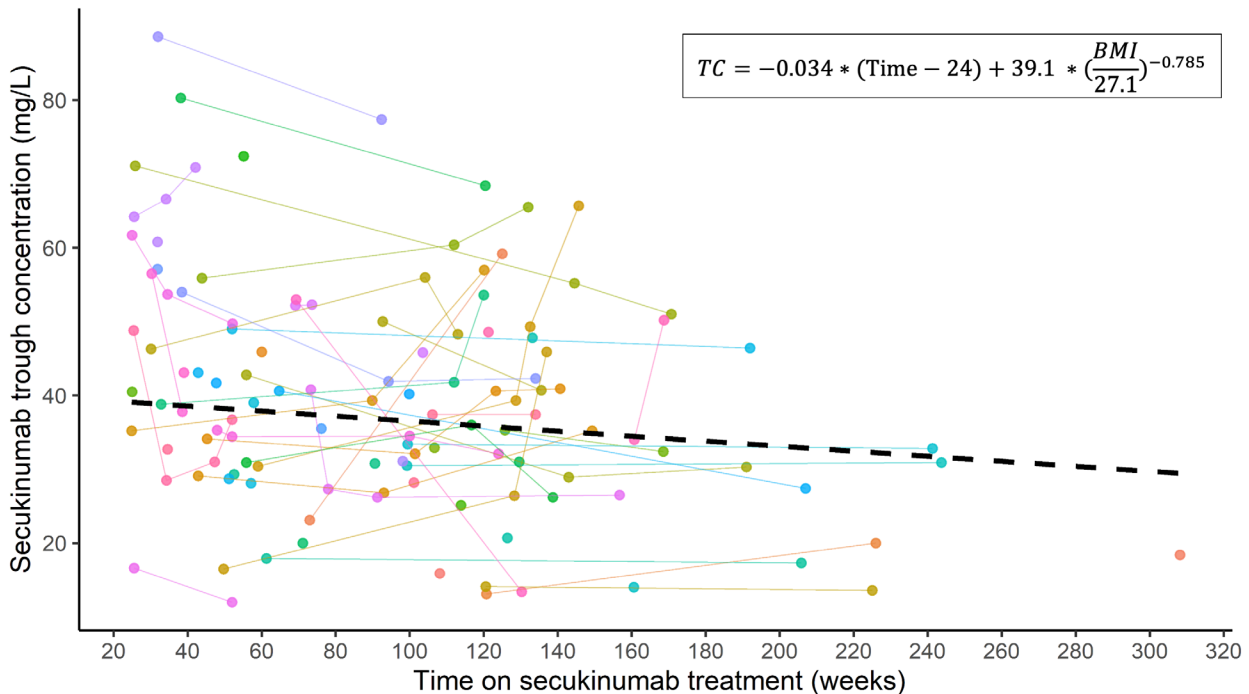$$TC = -0.034 * (Time - 24) + 39.1 * \left(\frac{BMI}{27.1}\right)^{-0.785}$$

Figure 1 Secukinumab TC in function of time on secukinumab treatment. The dots of the same colour represent the concentrations of the same individual. The black dashed line represents the mean TC time course of a typical patient (BMI 27.1 kg/m²). The mathematical equation of the mean TC time course of a typical patient is shown. BMI, body mass index; TC, trough concentration.

patient i at week j, and η_j represents the deviation of secukinumab TC of an individual patient i from the typical population secukinumab TC.

Trough concentration at steady state was the best predictor of clinical response to secukinumab

A generalized linear mixed-effects model was used to predict the probability of optimal clinical response, defined as (i) PASI ≤ 2 or PASI90; (ii) PASI ≤ 2; (iii) PASI90. The secukinumab TC was identified as the best and only covariate associated with the probability of obtaining an optimal clinical response, under all three definitions of optimal clinical response. Equation 2 shows how the probability of patient i being an optimal responder increases with higher secukinumab TC at steady state:

$$\text{Probability of optimal clinical response}_i = 1 - \frac{1}{1 + e^{\text{intercept}_i + \theta_{\text{slope}} \times \text{TC}_i}} \quad (2)$$

θ_{slope} represents the typical population slope factor describing the impact of secukinumab TC on the

probability of achieving optimal clinical response, intercept$_i$ represents the parameter intercept of patient i and TC$_i$ represents the TCs of individual patient i. The parameters of the final outcome models are listed in Supplementary Table S2. Goodness-of-fit plots of the developed outcome models are shown in Fig. 2.

In addition, a significant difference in secukinumab TC, baseline PASI and BMI was found between responders and nonresponders, independently of which definition of clinical response was taken into consideration (Fig. 3).

Defining a minimum effective secukinumab steady-state trough concentration that is associated with optimal response

For each of the three definitions of optimal response, the ROC analysis identified the same lower threshold target of secukinumab of 39.1 mg/L (Fig. 4, Table 2). The associated probabilities of being an optimal responder were 82.5% for PASI ≤ 2, 67.6% for PASI90 and 92.7% for PASI ≤ 2 or PASI90. Aiming at the 95th percentile of a 99% probability of optimal response, an upper limit of the therapeutic window of
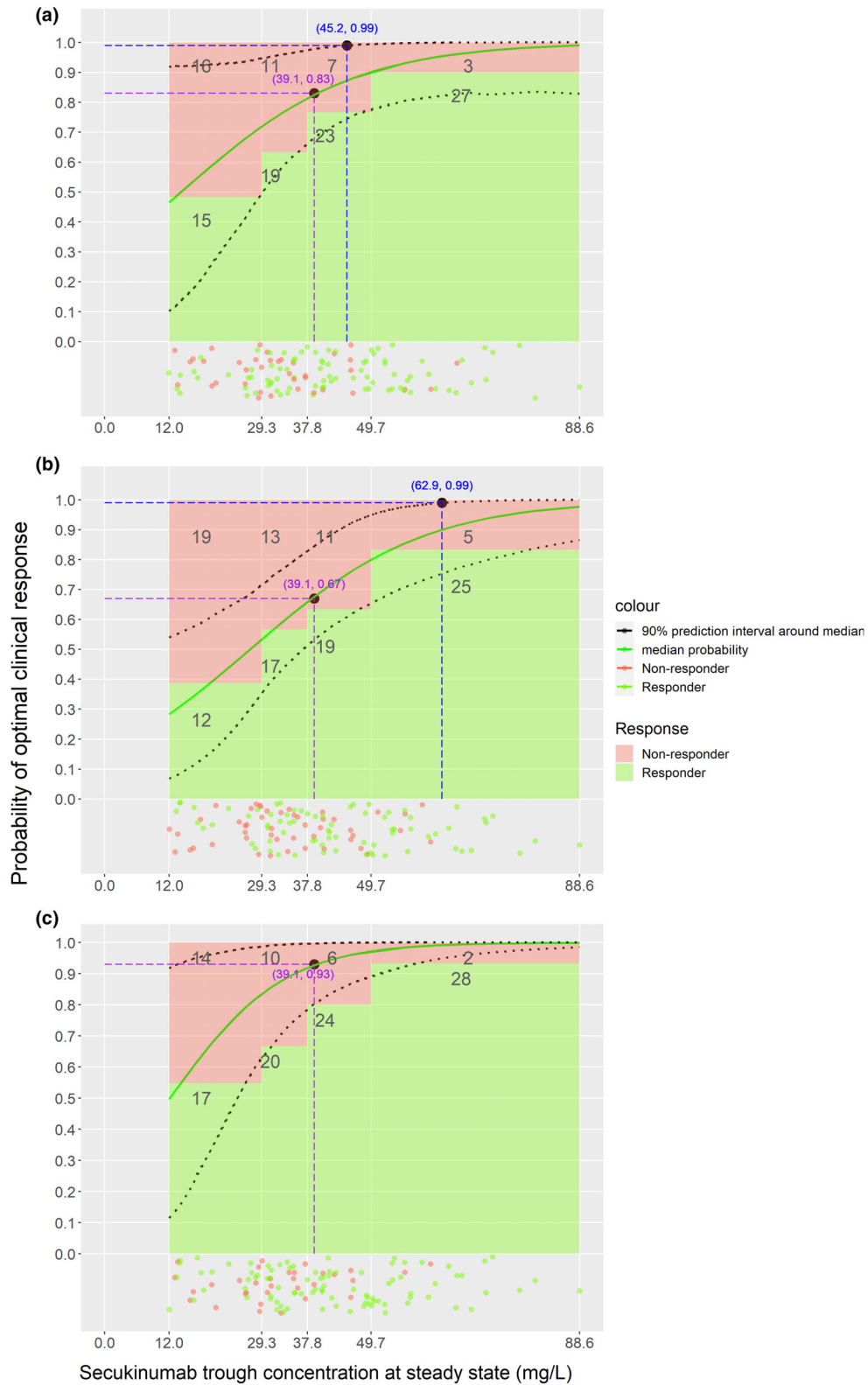
Figure 2 Goodness-of-fit plot of the response models. The probability of obtaining an optimal response [defined as (a) Psoriasis Area and Severity Index (PASI) ≤ 2, (b) 90% reduction in PASI compared with baseline or (c) PASI ≤ 2 or 90% reduction in PASI compared with baseline] is presented against the secukinumab trough concentrations (TCs). Patients achieving optimal (green dots) or suboptimal (red dots) response when having certain secukinumab TC at steady state are plotted. Observed and predicted fractions of patients achieving optimal response are presented by green tiles and lines, respectively; red tiles represent the observed fractions of patients not obtaining optimal response; black dashed lines represent the 90% prediction interval around the median prediction; grey numbers indicate the absolute number of patients in each quartile of secukinumab TC; purple coordinates represent the lower limit of the therapeutic window; blue coordinates represent the upper limit of the therapeutic window.

secukinumab TC during maintenance of 45.2 and 62.9 mg/L was identified when optimal response was defined by PASI ≤ 2 or PASI90, respectively. No upper target of secukinumab TC at steady state was identified when optimal response was defined by PASI ≤ 2 or PASI90, as the lower threshold target of 39.1 mg/L already hit the 99% probability at the 95th percentile of model prediction (Fig. 4).

Discussion

Real-life clinical cases of empirical dose adjustments of secukinumab and the lack of guidelines, highlight the existing unmet medical need to guide physicians in their clinical decision-making regarding treatment modifications.[34] TDM of biologics may pave the way towards personalized exposure-based dose optimization
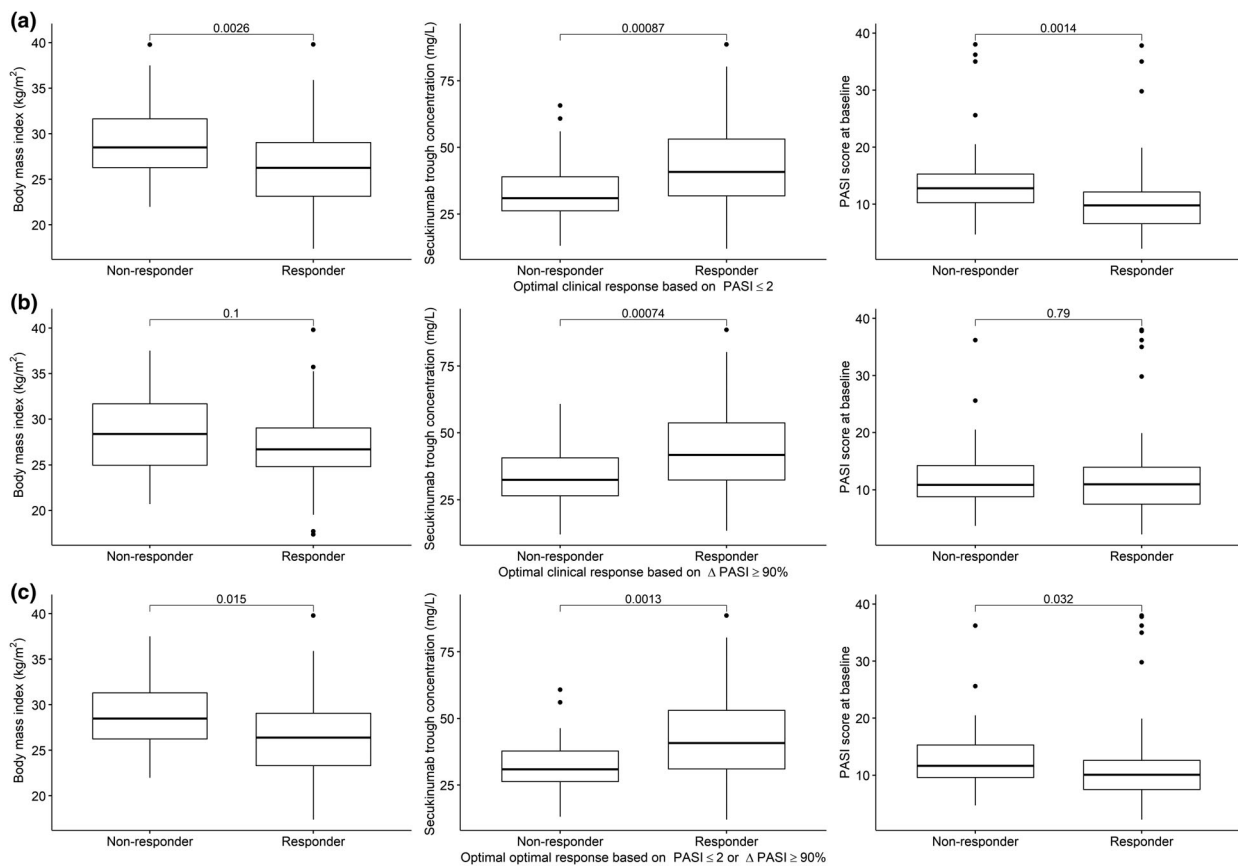

Figure 3 Wilcoxon test of body mass index, secukinumab trough concentration at steady state and Psoriasis Area and Severity Index (PASI) at baseline between optimal responder and nonoptimal responder. Three definitions of optimal response are presented: (a) PASI ≤ 2, (b) 90% reduction in PASI compared with baseline (ΔPASI ≥ 90%) or (c) PASI ≤ 2 or ΔPASI ≥ 90%. The data are plotted using Tukey boxplots.
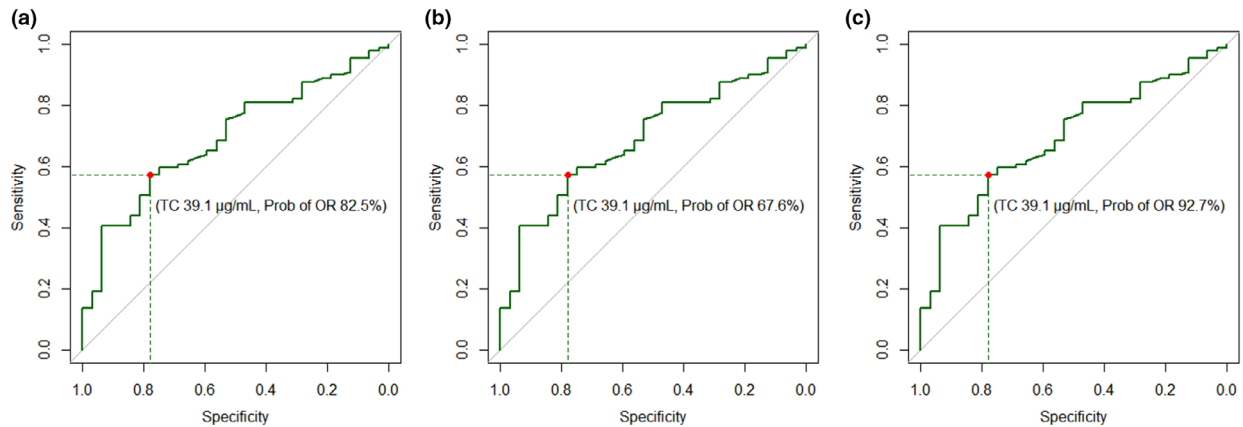
Figure 4 Receiver operator characteristic (ROC) analysis of the outcome models. The ROC curves at optimal response, defined as (a) Psoriasis Area and Severity Index (PASI) $\leq$ 2, (b) 90% reduction in PASI compared with baseline, or (c) PASI $\leq$ 2 or 90% reduction in PASI compared with baseline, are presented. The red dots are identified thresholds of the outcome models; the values between brackets are the associated secukinumab trough concentration (TC) for achieving the identified probability thresholds of optimal response (prob of OR). The area under the ROC curves is 0.69 (95% CI 0.59–0.79).

Table 2 Results from receiver operator characteristic analysis.

Definition of optimal response	Probability threshold of optimal response, %	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Associated SEC TC target, mg/L
PASI $\leq$ 2	82.5	57.3	78.1	87.9	39.7	39.1
PASI90	67.6	57.3	78.1	87.9	39.7	39.1
PASI $\leq$ 2 or PASI90	92.7	57.3	78.1	87.9	39.7	39.1

PASI, Psoriasis Area and Severity Index; PASI90, 90% reduction in PASI compared with baseline; SEC, secukinumab; TC, trough concentration.

and its relevance is driven by the presence of a dose–response relationship.[35,36] In the current study, we developed and validated an ELISA for secukinumab quantification, further characterized the secukinumab dose–response relationship and identified patient factors that affect secukinumab exposure and response.[26]

Looking at dose, the median secukinumab TC at steady state was 39.1 mg/L, which is in line with the mean steady-state TC reported by Bruin et al.[37] of approximately 44.5 mg/L of secukinumab at the 300 mg dose level. In addition, in our study, secukinumab steady-state TCs decreased slowly over time, in contrast to the report of Bruin et al., who found that secukinumab steady-state TCs remained stable for $\geq$ 5 years from initiation of treatment.[37] The clinical relevance of the statistically significant decrease in secukinumab steady-state TCs needs further investigation. As secukinumab exhibits minimal immunogenicity in patients with psoriasis, as described by Reich et al.,[18] exploring immunogenicity in this cohort could be of additional value, although this was out of the scope of our study. Furthermore, we observed a large

IIV in secukinumab TC, which was only partially explained by BMI, as secukinumab TC decreased with increasing BMI. Therefore, monitoring of secukinumab concentrations as well as weight-based secukinumab dosing may be warranted to prevent underexposure and subsequent suboptimal treatment response in patients with high BMI. In line with our results, the OPTIMISE trial recently assessed the efficacy and safety of different maintenance secukinumab dosing regimens, and reported that patients with a higher body weight ($\geq$ 90 kg) may benefit from dose intensification in maintenance phase (300 mg every 2 weeks).[38] Moreover, treatment stratification based on body weight is already applied for ustekinumab, an interleukin 12/23p40 inhibitor approved for the treatment of psoriasis, with patients receiving the drug subcutaneously at a dose of 45 mg if body weight is < 100 kg or 90 mg if body weight is $\geq$ 100 kg. Several studies in rheumatoid arthritis, ankylosing spondylitis and psoriasis arthritis have also established weight-based dose stratification of biologic drugs as an effective means of treatment optimization.[39,40]

Next, looking at response in our cohort, patients with higher secukinumab TCs at steady state had a higher probability of achieving optimal response. In line with this, a recent study[41] found an association between lower secukinumab exposure and a reduction in or even loss of response, suggesting that dose intensification may be needed. Besides dose intensification, continuation of the standard dosing regimen of secukinumab might be a clinically viable option before switching therapies, as supported by Augustin et al.,[42] who reported that half of their patients experiencing loss of response regained clinical response when secukinumab treatment was continued, mirroring the dynamic evolution of psoriasis. Similar results were obtained by Reich et al.,[41] who showed that continued secukinumab treatment resulted in regain of efficacy in some patients, suggesting a transient rather than a permanent loss of response. As a dose–response relationship of secukinumab was identified in our cohort, there is an evident possibility of defining therapeutic thresholds. We identified a minimal effective secukinumab concentration of 39.1 mg/L, which is higher than the previously reported threshold of 33.2 mg/L based on preliminary data of a smaller sample size.[26] In addition, this target was consistent across different definitions of response: (i) PASI ≤ 2 or PASI90, (ii) PASI ≤ 2, or (iii) PAS90. These findings suggest that, in cases of suboptimal response to secukinumab, targeting a secukinumab steady-state TC of 39.1 mg/L by altering the dose or changing the dose interval is warranted before considering discontinuation of the drug or switching to another therapy. Although currently not approved, higher dosing frequencies of up to 300 mg every 2 weeks have been explored in clinical trials. In the GAIN study, decreasing the secukinumab dosing interval showed a trend towards higher skin clearance rates in initial suboptimal responders (≥ PASI75 to < PASI90), potentially resulting from proportionally increased secukinumab serum concentrations.[42] Regarding real-life clinical cases, off-label secukinumab dose intensification has already led to clinically significant improvements without reporting any new or unexpected safety findings. This was the case in 14 out of 25 adult patients with psoriasis in a retrospective case study performed by Phung et al.[20] which was in line with the results of the case report of Beecker and Joo,[21] who described two cases demonstrating that dose escalation of secukinumab may be beneficial in selected patients with suboptimal response, particularly for those with high BMI.

Besides the lower threshold of 39.1 mg/L, upper targets of secukinumab TC at steady state of 45.2 and 62.9 mg/L were identified when optimal response was defined by PASI ≤ 2 and PASI90, respectively. Secukinumab TC above these thresholds will not lead to further benefit in clinical response. Several authors have indicated that dose tapering in patients with minimal disease activity and TC above the therapeutic range could prevent (long-term) overdosing, resulting in reduction in treatment costs and associated risks.[43,44] However, owing to the bidirectionality in the dose–response relationship (i.e. dose influences response, and response influences dose), the clinical applicability of the secukinumab threshold must be interpreted with caution as the intrinsic order of the relationship between dose, BMI and clinical response is still uncertain.[45]

Based on this secukinumab dose–response relationship, an intuitive and straightforward clinical algorithm needs to be developed before TDM can be implemented in clinical practice. When considering treatment modification, physicians need to take into account more than just drug dose. On the one hand, there may be concerns about the long-term safety and cost-effectiveness of dose escalation of biologics,[46] while on the other hand, there are questions about what impact dose reduction of biologics will have on the co-treatment of comorbidities, e.g. psoriatic arthritis and cardiometabolic parameters.[47–49] Therefore, a model-informed precision dosing software tool might facilitate the integration of personalized dosing into clinical practice.[47]

We have not addressed the optimal duration of the dose adjustments and the implications on the cost in a real-life setting here, and these require further research as has been done for dose-reduction strategies of anti-TNF inhibitors.[50] Another interesting point to highlight is the difference in using a therapeutic window compared with a target concentration as introduced here for secukinumab. A therapeutic window is better thought of as an acceptable range of concentrations associated with a desirable clinical response. Above the upper limit, an increase in drug dose will only lead to an increase in healthcare expenditures, with no or only minimal beneficial increase in treatment response. However, as biologics have not shown any risk of toxicity at higher concentrations, the therapeutic window can also be seen as a grey zone around the target concentration, for which clinicians are uncertain what treatment decisions need to be taken. Therefore, treating to a specific target concentration may be more straightforward.[51]

The key strengths of this study are the prospective design in a real-life clinical setting, the relatively

large sample size and the use of a validated secukinumab assay, Notably, the difference in serum concentration between the two available modes of administration for secukinumab (two 150-mg 1-mL prefilled syringes/pens or a single 300-mg 2-mL autoinjector) could not be investigated because at the time of sampling, the 300-mg autoinjector was not yet available in Belgium. This poses an interesting field of further investigation.

Conclusion

We have developed and validated an ELISA for secukinumab quantification and determined a steady-state target concentration of 39.1 mg/L for patients with psoriasis, thereby achieving two essential requirements for implementation of TDM in clinical practice. Moreover, we identified the upper targets of secukinumab TC at steady state of 45.2 and 62.9 mg/L when optimal response was defined by PASI $\leq$ 2 or PASI90 respectively. In addition, we found that dose stratification of secukinumab based on weight might be beneficial in a subset of patients to prevent underdosing.

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Conflicts of interest

JL has received grants scientific research grants (University of Ghent account) from Janssen, AbbVie and Pfizer; paid consultancies for scientific research (University of Ghent account) from AbbVie, Almirall, Argenx, BMS, Janssen Cilag, Pfizer, Leo Pharma, Novartis and UCB; and carried out clinical trials for Janssen-Cilag, Merck Serono, Amgen, Pfizer, AbbVie, Celgene, Regeneron and Novartis. LG has received paid speaker fees by UCB, AbbVie and R-Biopharm. ED has received consultancy fees from Argenx and Janssen. All fees were paid to the University of Ghent. The other authors have no conflicts of interest to declare. KU Leuven holds a licence agreement with apDia and R-Biopharm. The other authors have no conflicts of interest to disclose.

What's already known about this topic?

- Not all patients treated with secukinumab show optimal efficacy outcomes.
- TDM may be a valuable tool to guide clinical decision-making.

What does this study add?

- Monitoring secukinumab TCs during maintenance therapy can timely identify underdosed patients who may benefit from treatment optimization.
- In patients with higher BMI, weight-based dosing may be needed to prevent underdosing.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Figure S1 Conditional weighted residuals vs. population prediction plot of the pharmacokinetics model.

Supplementary Table S1 Univariate covariate analysis of the pharmacokinetics model.

Supplementary Table S2 Parameter estimates of the developed models.