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Conceptualization: EGY, RB; Data Curation: ABP; Formal Analysis: ABP; Funding Acquisition: EGY; Investigation: EDD, XP, HX, RB, EGY; Methodology: EGY, RB; Project Administration: YDE; Resources: EGY, YDE; Supervision: EGY; Validation: EBW, YDE, ESP, JGK, RB, EGY; Visualization: EDD, ABP, TS; Writing - Original Draft Preparation: EDD; Writing - Review and Editing: ABP, CD, TS, EBW, CM, CJ, JGK, EGY

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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.2019.04.008.

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Defining a Minimal Effective Serum Trough Concentration of Secukinumab in Psoriasis: A Step toward Personalized Therapy

Journal of Investigative Dermatology (2019) **139,** 2232–2235; doi:10.1016/j.jid.2019.04.012

TO THE EDITOR

The armamentarium of psoriasis treatments has been reinforced by the introduction of biologics that target IL-17A (European Medicines Agency, 2015; Frieder et al., 2018), and at present, achieving complete skin

Abbreviations: CI, confidence interval; C_{trough}, trough concentration; PASI, Psoriasis Area and Severity Index

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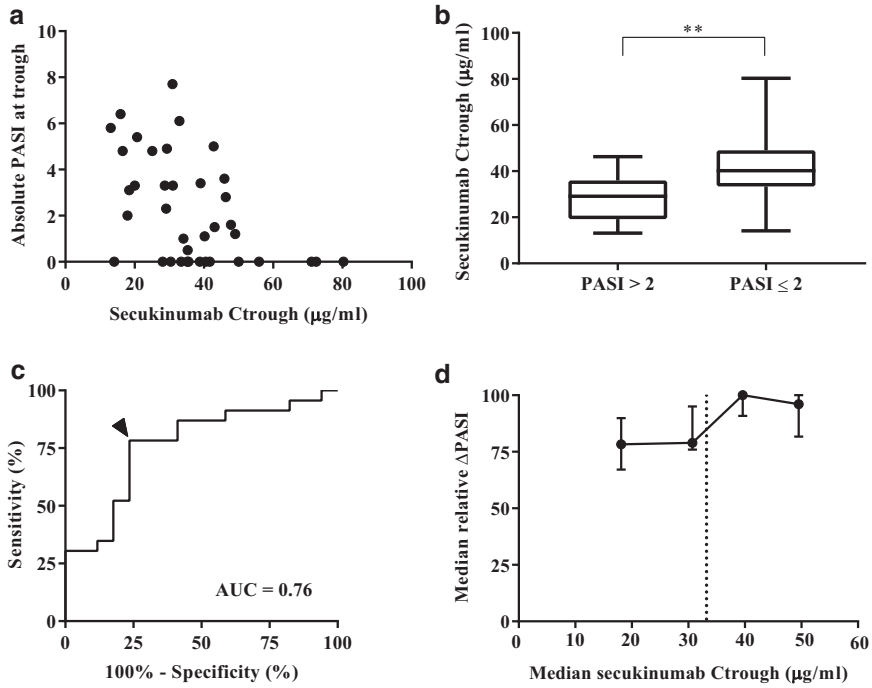
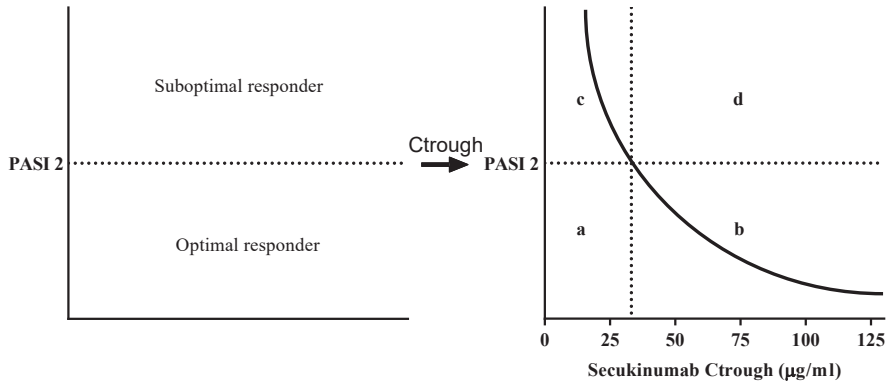


Figure 1. Comparison between secukinumab C_{trough} in optimal and suboptimal responders and visualization of a therapeutic window of secukinumab. (**a**) Correlation between C_{trough} and clinical response; Spearman rank test ($\rho = -0.442$; $P = 0.004$). (**b**) C_{trough} was compared between suboptimal (PASI > 2; n = 17) and optimal (PASI ≤ 2; n = 23) responders. (**c**) ROC analysis of secukinumab C_{trough}. Optimal cut-off point was selected by using the index of union (Unal, 2017). The minimal effective C_{trough} was set at 33.2 µg/ml. (**d**) Four equal-sized groups (n = 10) were formed based on ascending C_{trough} and correlated with the median ΔPASI per group. Each black dot represents the median C_{trough}, with correlating median ΔPASI for one group. Alongside each ΔPASI, the IQR is illustrated. The dashed vertical line represents the minimal effective secukinumab C_{trough} of 33.2 µg/ml. AUC, area under the curve; C_{trough}, trough concentration; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; ΔPASI, percentage of PASI improvement with baseline; ROC, receiver operating characteristic.

clearance has become a realistic goal. However, in clinical practice, physicians encounter various levels of responses, including insufficient response or loss of response with anti–IL-17A treatment. This has led to physicians exploring off-label intensification regimens through trial and error, either by increasing the dose or by shortening the administration intervals (Beecker and Joo, 2018; Phung et al., 2018). Thus, there is a current need to target the most optimal therapeutic response in an individual patient to use these highly effective and expensive drugs in a manner as cost-effective as possible. Therapeutic drug monitoring, in which dose adjustments are based on a definable relationship between measurable serum drug concentrations, often taken at trough (C_{trough}), and a clinical observable response can be used to reach this goal (Toro-Montecinos et al., 2019; Wilkinson et al., 2019). Nevertheless, to implement therapeutic drug monitoring, it is crucial to define the optimal therapeutic window for a given biologic in psoriasis (Hoseyni et al., 2018).

In this pilot study, we studied secukinumab, a fully human anti–IL-17A monoclonal antibody, $C_{troughs}$ in 40 patients with moderate to severe psoriasis, who administered secukinumab monthly during maintenance, using an in-house–developed, sandwich-type enzyme-linked immunosorbent assay. The medical ethics committee from the Ghent University Hospital, Belgium, approved this study (B670201835652), and written informed consent was obtained from all patients before any study procedure was performed. The Psoriasis Area and Severity Index (PASI) was assessed by a dermatologist before sample collection, and clinical response was established by comparing the percentage of PASI improvement



Before considering TDM, check adherence:

a + b) In optimal responders, there is no need to measure Ctrough
Recommendation: continue secukinumab therapy

c) Suboptimal responder with subtherapeutic Ctrough
Recommendation: dose escalation of secukinumab

d) Suboptimal responder with therapeutic Ctrough
Recommendation: switch to another biologic

Figure 2. Proposed monitoring algorithm for patients with psoriasis treated with secukinumab during maintenance phase. Before measuring C_{trough}, patient's adherence needs to be checked. If correct, the combination of clinical evaluation (PASI) and the minimal effective C_{trough} provide an algorithm to adequately monitor patients with psoriasis treated with secukinumab during maintenance phase (minimal 24 weeks). (**a, b**) In optimal responders, secukinumab treatment can be continued, but it is recommended to check C_{trough} when loss of response occurs. (**c**) In suboptimal responders with subtherapeutic C_{trough}, a dose escalation is recommended. (**d**) In suboptimal responders with therapeutic C_{trough}, it is recommended to switch to another biologic. The dashed horizontal and vertical line represent the absolute PASI 2 and C_{trough} threshold level (33.2 µg/ml), respectively. C_{trough}, trough concentration; PASI, Psoriasis Area and Severity Index; TDM, therapeutic drug monitoring.

with baseline (ΔPASI). Patients were classified as optimal responders (PASI $\leq$ 2) or suboptimal responders (PASI $>$ 2), as an absolute PASI cut-off of 2 is associated with the ΔPASI 90 response (Reich et al., 2018).

In our patient cohort (see Supplementary Table S1 online), we found a significant correlation between secukinumab C_{trough} and absolute PASI ($\rho = -0.442$; $P = 0.004$; Figure 1a) as well as between C_{trough} and relative ΔPASI ($\rho = 0.325$; $P = 0.041$). In addition, a significant difference in C_{trough} was observed between optimal responders and suboptimal responders ($P = 0.004$; Figure 1b), with a median C_{trough} of 40.2 μg/ml and 29.1 μg/ml, respectively. This correlation suggests a therapeutic window of secukinumab in patients with psoriasis.

Next, we sought the minimal effective threshold of the therapeutic window by using a receiver operator characteristic analysis and found a minimal effective maintenance secukinumab C_{trough} of 33.2 μg/ml with an area under the curve of 0.76 (95% confidence interval [CI] = 0.61−0.92; $P = 0.005$), sensitivity 78.3% (95% CI = 56.3−92.5), and specificity 76.5% (95% CI = 50.1−93.2), which was associated with a positive and negative predictive value of 0.82 (95% CI = 0.59−0.94) and 0.72 (95% CI = 0.46−0.89), respectively (Figure 1c) (Unal, 2017). This C_{trough} indicative of the minimal desirable effect implies that a secukinumab C_{trough} of 33.2 μg/ml can distinguish optimal responders (PASI $\leq$ 2) from suboptimal responders (PASI $>$ 2).

In addition, we created a concentration-effect curve to elucidate whether the C_{trough}, indicating the maximum clinical effect, could be determined. Although relative ΔPASI increased with increasing secukinumab C_{trough}, no plateau was observed, and thus, no upper C_{trough} threshold could be deduced in this cohort (Figure 1d).

To explore potential confounding factors of C_{trough} and/or clinical response, several correlations were tested. These results showed that obesity, active smoking, long treatment duration, and/or previous treatment with biologics were associated with lower secukinumab C_{trough}, which also resulted in lower clinical responses.

A limitation of our study is the small sample size that hampers a multivariate analysis. In addition, using the receiver operator characteristic analysis, the discrimination between optimal and suboptimal responders was only fair and may not be useful for clinical practice. Therefore, these findings need to be confirmed in a larger cohort as it is not unlikely that some patients may have an increased clearance of therapeutic antibodies or IgG in general.

Based on these results, we propose a treatment algorithm by combining clinical evaluation (PASI) and the minimal effective C_{trough} to adequately monitor patients with psoriasis who are treated with secukinumab during the maintenance phase (Figure 2). This algorithm highlights the potential added value of C_{trough} measurement in the clinic because it enables the physicians to make guided decisions instead of the current trial-and-error dose adaptations. In suboptimal responders with subtherapeutic C_{trough}, we suggest a dose escalation, which will inevitably lead to an increased cost. Nevertheless, measuring the secukinumab C_{trough} allows to select a priori those suboptimal responders in whom it is justified to dose escalate, defining an appropriate extra cost.

In summary and to our knowledge previously unreported, we describe a minimal effective secukinumab C_{trough} of 33.2 μg/ml and consequently unveil a potential role of therapeutic drug monitoring in patients with psoriasis who are treated with secukinumab. Our results suggest that patients with psoriasis with a suboptimal response and a C_{trough} below 33.2 μg/ml during the maintenance phase are potentially undertreated and could benefit from dose intensification.

Data availability statement

The data set related to this article can be found at https://osf.io/sbxpj/, hosted at Open Science Framework, and access can be obtained upon request.

CONFLICT OF INTEREST

JL has received grants from Janssen, AbbVie, and Pfizer; had paid consultancies from Pfizer, Novartis, AbbVie, Janssen-Cilag, and Leo Pharma; and carried out clinical trials for Janssen-Cilag, Merck Serono, Amgen, Pfizer, AbbVie, Celgene, Regeneron, and Novartis. AG served as a speaker for MSD, Janssen Biologicals, Abbvie, Pfizer, Takeda, and Novartis and as a consultant for UCB and Takeda, and KU Leuven—licensed (anti-) infliximab, (anti-) adalimumab, vedolizumab, golimumab and ustekinumab ELISA to apDia, and infliximab and adalimumab lateral flow to R-Biopharm AG. The remaining authors state no conflict of interest.

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Conceptualization: JL, LG, AG; Formal Analysis: RSo, EM, LG, RSp; Investigation: EM, RSo, NVdB, EB; Project Administration: RSo, LG; Resources: JL, AG, LT, SL; Supervision: AG, JL, LG; Validation: LG; Writing - Original Draft Preparation: RSo; Writing - Review and Editing: RSo, NVdB, LG, AG, JL

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SUPPLEMENTARY MATERIAL

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An Animal Model of Cutaneous Cyst Development Enables the Identification of Three Quantitative Trait Loci, Including the Homologue of a Human Locus (*TRICY1*)

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TO THE EDITOR

Epidermal cysts represent benign skin tumors that can arise in any location, but they are more frequent on the scalp, face, upper back, neck, and chest (Yang and Yang, 2009) as a result of traumatic inclusion of the epidermis in the dermis (Feng and Ma, 2015). Although most patients develop individual cysts, multiple lesions are observed in single cases (Yuksel and Tamer, 2016).

Cases of hereditary trichilemmal cysts originating from the hair follicle have been reported in the literature (Seidenari et al., 2013). Leppard et al. demonstrated in 1977 that trichilemmal cysts can have an autosomal dominant mode of inheritance (Leppard et al., 1977).

Using inbred Brown Norway (BN) rats susceptible to chemically induced cutaneous cyst development and resistant Long Evans (LE)/Stm rats (Supplementary Materials and Methods online), we were able to establish an animal model for genetic dissection of multiple cyst formation.

Low iodine diet–treated (LE × BN) F2 intercross rats of both orientations (n = 282) received a single injection of the alkylating carcinogen *N*-methyl-*N*-nitrosourea, originally applied for inducing thyroid neoplasia, into the tail vein at 50 days (Supplementary Materials and Methods), and a study on the genetic architecture of sex-dependent thyroid cancer development was performed simultaneously. BN rats treated with a low-iodine diet alone had been shown not to develop cutaneous cysts. At 260 days, animals were killed, followed by gross necropsy. The study was approved by the local administration's Ethical Committee on Experimental Animals (LANUV, Recklinghausen, Germany), in accordance with the national legislation. Histologic examination revealed different types of cysts that developed in the lower dermis and subcutis, with most cysts showing epidermal or, less frequently, trichilemmal keratinization of the epithelium or mixtures of these keratinization types. In a few cases, basophil granules in higher layers of the epithelium were reminiscent of a verrucous keratinization pattern (Figure 1a–f). Of the 142 male rats and 140 female rats, 117 (82%) and 63 (45%) presented cutaneous cysts, respectively. In addition, male rats tended to develop more cutaneous cysts per animal than female rats (Figure 1g, and Supplementary Table S1 online). The parental orientation of crosses [(LE × BN) vs. (BN × LE)] did not influence the development of cutaneous cysts (P = 0.28, Supplementary Table S1 online).

Because, in contrast to highly susceptible BN males, all BN females and most female F2 rats did not develop cutaneous cysts, quantitative trait locus interval mapping analysis was performed with 106 single-nucleotide polymorphisms (SNPs, average marker density 30 Mb) using DNA from 142 male F2 hybrids of both orientations (Supplementary Materials and Methods). Three quantitative trait loci linked to cyst numbers residing on chromosomes (Chrs) 1, 8, and 11 (*Ccd1*, *Ccd2,* and *Ccd3)* proved to surpass the genome-wide significance threshold (logarithm of the odds score, 3.74; see Figure 1h).

Figure 2a–c visualizes the strongest linkage between cutaneous cyst numbers per F2 male and genotype recorded for SNPs on Chrs 1, 8, and 11. Whereas F2 males with homozygous BN alleles for the SNP 213.36 Mb on Chr 1 located in the *Ccd1* locus and the SNP at 125.88 Mb in *Ccd2* on Chr 8 display comparatively high numbers of cysts per animal, heterozygous males show fewer cysts, and male F2 rats carrying homozygous LE alleles present the lowest numbers of cysts per animal (Figure 2a and b), suggesting an allele dose effect.

For the SNP 76.11 Mb in *Ccd3* on Chr 11, the situation is reversed, as homozygous LE alleles are associated with a higher number of cutaneous cysts, whereas heterozygous and

Abbreviations: BN, Brown Norway; Chr, chromosome; LE, Long Evans; SNP, single-nucleotide polymorphism

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Supplementary Table S1. Baseline Characteristics of Patients with Psoriasis Treated with Secukinumab

Characteristic	Total Patients (n = 40)
Age, y, median (IQR)	46.5 (36.3–53.0)
Male sex, n (%)	27 (67.5)
BMI, kg/m^2 (mean ± SD)	27.9 ± 3.8
Normal (<25), n (%)	8 (20.0)
Overweight (25–30), n (%)	21(52.5)
Obese (≥30), n (%)	11 (27.5)
Smoking, n (%)	
Current smoker	9 (22.5)
PsA, n (%)	6 (15.0)
Disease duration, y, median (IQR)	19.0 (12.0–31.0)
Treatment duration, wk, median (IQR)	55.9 (45.0–103.7)
PASI score before secukinumab treatment, median (IQR)	12.4 (10.3–18.5)
PASI score at trough, median (IQR)	1.4 (0.0–3.6)
Secukinumab C_{trough}, μg/ml, median (IQR)	34.6 (28.2–43.0)
Concomitant medication, n (%)	
No co-medication	23 (57.5)
Topical corticosteroids	15 (37.5)
Methotrexate	1 (2.5)
Methotrexate and topical corticosteroids	1 (2.5)
Previous biologic treatment, n (%)	21 (52.5)
Adalimumab	10 (25.0)
Ustekinumab	12 (30.0)
Etanercept	7 (17.5)
Ixekizumab	1 (2.5)
Brodalumab	2 (5.0)

Abbreviations: BMI, body mass index; C_{trough}, secukinumab serum trough concentration; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation; wk, week; y, year.