


Original Investigation

Developing a Therapeutic Range of Adalimumab Serum Concentrations in Management of Psoriasis

A Step Toward Personalized Treatment

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IMPORTANCE Adalimumab has proven to be effective in suppressing psoriasis disease activity and is administered in a standard dose.

OBJECTIVE To establish a therapeutic range for adalimumab trough levels in the treatment of plaque-type psoriasis, leading to a more personalized treatment.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, prospective, observational, daily practice cohort study conducted at an academic hospital with affiliated secondary care hospitals in Belgium (cohort 1) and 2 academic hospitals in the Netherlands (cohort 2). Both cohorts included adult patients treated with adalimumab for plaque-type psoriasis. Cohort 1 comprised 73 patients who were being treated with adalimumab for more than 24 weeks until 401 weeks. In cohort 2 (n = 62), serum samples were obtained between weeks 24 and 52 of treatment.

INTERVENTIONS Before the start of adalimumab therapy and at time of serum sampling, Psoriasis Area and Severity Index (PASI) scores were determined.

MAIN OUTCOMES AND MEASURES Adalimumab trough level and PASI score at the time of serum sampling to determine the receiver-operator characteristics analyses and concentration effect curve.

RESULTS By means of receiver-operator characteristics analyses with an area under the curve of 0.756 (SD, 0.046; 95% CI, 0.666-0.847) and a sensitivity of 78% and a specificity of 70%, 3.51 mg/L was established as the lower margin for the therapeutic range. By means of a concentration effect curve, 7 mg/L was established as the upper margin. One-third of patients had an adalimumab trough concentration exceeding 7 mg/L.

CONCLUSIONS AND RELEVANCE A therapeutic range of adalimumab trough levels of 3.51 mg/L to 7.00 mg/L, which corresponds to an optimal clinical effect, was identified. In one-third of patients, it was observed that trough concentrations exceeded the therapeutic window. Based on the established range, a therapeutic algorithm for adalimumab treatment for patients with psoriasis can be developed and validated in a prospective patient cohort. By identifying this range, a step has been taken toward a more rational use of biological therapy in psoriasis. Developing a therapeutic algorithm may lead to less overtreatment of patients and cost savings.

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During the past 2 decades, a more profound insight in the pathogenesis of psoriasis has led to the development biological treatments. These large protein molecules exert their function by targeting crucial immunologic mediators in the pathogenesis of psoriasis, such as tumor necrosis factor (TNF).¹

There are several biological treatments available for psoriasis. Adalimumab is a TNF-inhibitor that has proven to be highly effective in suppressing psoriasis disease activity, both in randomized clinical trials^{2,3} and daily practice.^{4,5} Aside from moderate to severe psoriasis, this biological agent is also a valuable treatment option for other immune-mediated inflammatory diseases (IMiDs) such as rheumatoid arthritis (RA) and Crohn disease. No relevant end-organ damage has yet been reported for TNF inhibitors.^{3,6} Adalimumab, like other biological agents, is isolated from mammalian cells by recombinant DNA technology.⁷ At present, all psoriatic patients are being treated with adalimumab according to a standardized dosing schedule. The European Medicines Agency and the US Food and Drug Administration approved adalimumab (40 mg) to be administered every other week from week 1 after an initial dose of 80 mg at week 0. With this fixed-dosing regimen, a wide variety in clinical response and adalimumab trough levels was observed in a daily practice cohort,⁸ with significantly higher serum drug concentrations in good-responding patients compared with nonresponders and moderate responders. Analogous to recent findings in RA, this possibly implies that a substantial part of psoriatic patients are under- or overtreated.⁹ Furthermore, some patients develop antidrug antibodies to adalimumab (ADAs), resulting in diminished adalimumab trough levels and reduced clinical response. Despite this extensive interindividual variation in pharmacokinetics, adalimumab serum levels and ADAs are not measured in daily practice and a therapeutic window of serum adalimumab trough concentrations has not yet been determined in psoriasis. In RA, such a range has been established,⁹ and personalized treatment by means of a therapeutic algorithm using trough levels has not only proven to be cost-effective,¹⁰ but quality-adjusted life-years were also gained through rational clinical decisions early in the treatment course.

Therefore, the main goal of this study was to establish a therapeutic range for adalimumab trough levels, corresponding with adequate clinical response. Determination of these values is necessary to compose a therapeutic algorithm for chronic plaque-type psoriasis, in which the dosing schedule can be adjusted according to serum trough levels of adalimumab and ADAs. A secondary objective of this study was to further detect and quantify ADAs and to correlate them with adalimumab trough levels and clinical response in a real-life setting in a larger cohort of patients with psoriasis.

Methods

Design

This multicenter cohort study consists of 135 patients. Ghent University Hospital (UZ Gent), in cooperation with affiliated dermatology clinics, collected samples from 73 patients, re-

cruitment started in January 2014 (cohort 1). The Academic Medical Center (AMC Hospital) in collaboration with Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, provided 62 suitable samples for this study from a previously described cohort (cohort 2).⁸ Approval was obtained from the medical ethics committees of all participating hospitals. All patients gave their written informed consent.

Patients and Samples

The study population included patients aged 18 years or older with chronic plaque-type psoriasis diagnosed by a dermatologist, who were being treated with subcutaneous adalimumab (40 mg) every other week for at least 24 weeks from week 1 after an initial dose of 80 mg at week 0. A minimum treatment duration of 24 weeks was chosen because in RA it has been shown that adalimumab steady-state concentration is reached after 24 weeks of treatment,¹¹ and in patients with psoriasis, ADAs (negatively impacting trough levels) mostly occur for the first time before 24 weeks of treatment.⁵ Cohort 1 consists of serum samples at random time points in treatment (after 24 weeks of treatment), whereas samples in cohort 2 were collected between 24 and 52 weeks of treatment. Patients who interrupted their treatment schedule during the 24 weeks prior to blood sampling were excluded. Samples of patients who were treated with adalimumab for any other inflammatory disease and later developed psoriasis were also excluded.

The blood samples, obtained within 24 hours before adalimumab administration, were each centrifuged during 10 minutes at 1500 rpm. Serum samples from cohort 1 were preserved at -80°, whereas cohort 2 samples were kept at -20°, until they were sent batchwise to the Laboratory for Monoclonal Therapeutics, Sanquin Diagnostic Services, Amsterdam, the Netherlands. Adalimumab trough concentrations were determined by means of enzyme-linked immunosorbent assay (ELISA). This assay is based on the principle that adalimumab is captured through its ability to bind TNF. Results were reported in milligrams per liter. Levels of ADAs were detected using a radioimmunoassay, which measures specific high avidity IgG antibodies against adalimumab by an antigen binding test. These results were converted into arbitrary units (AU) per milliliter, with a cutoff value set at 12 AU/mL. The radioimmunoassay does not detect ADAs bound to adalimumab and therefore may underestimate ADA formation.^{12,13} For this reason, samples were obtained at trough level. In December 2013, the procedure for measuring adalimumab trough levels was altered, with both methods showing a correlation 0.97.¹⁴ To obtain comparable data for both patient cohorts, sample results from cohort 2 were converted by means of a correction factor.

Clinical Response

Disease severity was measured by use of the Psoriasis Area and Severity Index (PASI) (the most extensively studied psoriasis clinical severity score and the most thoroughly validated¹⁵). In this way, clinical status was assessed by the treating dermatologist right before the start of adalimumab treatment (PASI baseline) and prior to serum sample collection (PASI sampling). In case patients switched to adalimumab therapy from a previous biological therapy without a washout period, the PASI before

this biological therapy was used as the PASI baseline to avoid unfair classification of patients as nonresponders. Percentage of PASI improvement compared with baseline (Δ PASI) represents clinical response. Patients were classified as nonresponders (Δ PASI <50.00), moderate responders (Δ PASI 50.00-74.99), or good responders (Δ PASI 75.00-100.00).¹⁶

Statistical Analyses

Adalimumab Trough Levels, ADAs, and Clinical Response

To perform statistical data analysis, SPSS Statistics 22 (IBM Corp) was used. For continuous variables, Shapiro-Wilk normality tests were performed. Correlation coefficients between adalimumab, ADA concentrations, and clinical response (Δ PASI) were calculated by means of the nonparametric Spearman rank test. For comparison of mean values between groups, the independent-samples *t* test, Mann-Whitney test, or χ^2 test was performed, as appropriate. For each test, the threshold for significance was set at $P < .05$.

Receiver-Operator Characteristics Analyses

To determine a representative cutoff value for adalimumab trough levels between the group of nonresponders and moderate responders and good responders, a receiver-operator characteristics curve was created. A trade-off was made between sensitivity and specificity to establish an adequate lower margin of the therapeutic adalimumab range.

Concentration Effect Curve

A concentration effect curve (CEC) was established to identify the upper margin of adequate adalimumab trough levels corresponding with maximal clinical efficacy. First, patients were stratified according to ascending adalimumab trough concentrations, with correlating Δ PASI scores. Data were then divided in equal-sized groups, each represented by a mean adalimumab trough level and a median Δ PASI score (with associated interquartile range). In this way, the interindividual variability between patients is reduced, and the relationship between adalimumab serum trough concentrations and clinical response is better represented.

Results

Patient Selection

In cohort 1, 82 patients were enrolled. Nine of them were excluded because adalimumab was not strictly administered every 2 weeks, resulting in 73 suitable samples. From the cohort previously described by Menting et al⁸ (cohort 2), 80 patients were enrolled, of which 18 were excluded because adalimumab was not administered every other week or because treatment was terminated prior to week 24. Thus, samples from 62 patients from cohort 2 were included.

Patient Characteristics

The total study population comprised 135 patients with a psoriasis (102 male [75.6%]), with a mean age of 45 years at the start of adalimumab treatment. Of the 135 patients enrolled in this study, 38 (28.8%) also had psoriatic arthritis. Only 11 patients

were concomitantly being treated with methotrexate (dose range, 7.5-20 mg/wk), 6 of whom were classified as good responders. After at least 24 weeks of treatment, 46 patients (34%) did not reach a 75% improvement in treatment response (measured using the PASI). Treatment duration in cohort 1 varied between 24 and 401 weeks, with a mean value of 157 weeks. The mean (SD) PASI score at the time of sampling was 2.4 (0.4). In cohort 2, samples were collected between 24 and 52 weeks of treatment, resulting in a mean treatment duration of 45 weeks. The mean (SD) PASI score at the time of sampling was 5.17 (0.75). Except for this significant discrepancy, there were no relevant methodological differences concerning data collection or significant differences at baseline between both study cohorts. A separate concentration effect curve was established to investigate whether treatment duration was of any influence on the upper margin of the therapeutic range. Both Belgium and the Netherlands apply similar reimbursement criteria for adalimumab; therefore, previous systemic psoriasis treatments are comparable between cohorts. No significant differences were observed between good responders vs nonresponders and moderate responders (Table).

Adalimumab Trough Levels

Adalimumab trough levels ranged from 0.00 to 16.38 mg/L, with a mean serum concentration of 5.02 mg/L. By means of a Spearman rank correlation coefficient ($\rho = 0.418$), a significantly positive but weak correlation between adalimumab serum trough levels and clinical response (Δ PASI) was shown ($P < .001$). With a mean adalimumab serum trough concentration of 2.99 mg/L in nonresponders and moderate responders compared with 6.07 mg/L in good responders, patients who did not reach Δ PASI 75.00 had significantly lower adalimumab trough levels compared with patients obtaining a 75% improvement in treatment response ($P < .001$) (Figure 1). Antidrug antibodies to adalimumab were detected in 31.9% of the study cohort, with a significantly higher percentage (56.5%) of antibody formation in the group of nonresponders and moderate responders vs good responders (19.1%) ($P < .001$) (eTable in the Supplement). Patients with a positive ADA titer had a significantly lower mean adalimumab trough concentration of 1.35 mg/L compared with patients with a negative ADA titer, who had a mean adalimumab level of 6.74 mg/L ($P < .001$). With a correlation coefficient of $\rho = -0.220$, a significantly negative but weak correlation between body mass index and adalimumab trough level was shown ($P = .01$). However, no significant correlation ($\rho = -0.079$) between BMI and clinical response was found ($P = .37$).

Receiver-Operator Characteristics Analyses

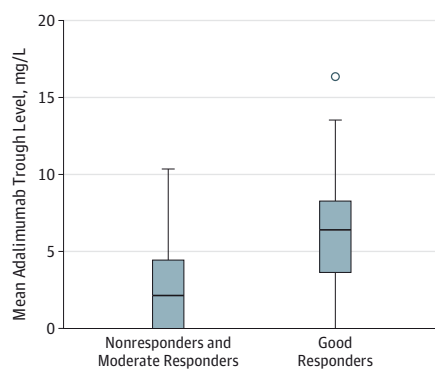
With an area under the curve of 0.756 (SD, 0.046; 95% CI, 0.666-0.847), these data demonstrate that determining the adalimumab serum trough level is a useful test to distinguish good responders from nonresponders and moderate responders ($P < .001$). The adalimumab cutoff value corresponding to the most optimal trade-off between sensitivity and specificity was 3.51 mg/L. With a sensitivity of 78% and a specificity of 70%, this demarcation point has a positive predictive value of 83% to obtain a 75% improvement in treatment response (Figure 2).

Table. Baseline Characteristics of 135 Patients Treated With Adalimumab for Plaque-Type Psoriasis

| Characteristic | Total Patients (N = 135) | Good Responders (n = 89) | Nonresponders and Moderate Responders (n = 46) |
|--|--------------------------|--------------------------|--|
| Age, mean (SD), y | 45 (11) | 46 (10) | 43 (12) |
| Male sex, No. (%) | 102 (75.6) | 69 (77.5) | 33 (71.7) |
| Disease duration, mean (SD), y | 24 (10) | 25 (9) | 23 (11) |
| Treatment duration, mean (SD), wk | 105 (89) | 127 (91) | 64 (67) |
| PASI baseline, mean (SD) | 15.5 (6.4) | 16.5 (6.1) | 13.4 (6.6) |
| BMI, mean (SD) | 28.4 (5.2) | 28.1 (5.0) | 28.8 (5.5) |
| PsA, No. (%) | 38 (28.8) | 25 (29.1) | 13 (28.3) |
| Concomitant methotrexate, No. (%) | 11 (8.3) | 6 (6.9) | 5 (10.9) |
| Previous biological treatment, No. (%) | 74 (55.2) | 39 (44.3) | 35 (76.1) |
| Etanercept | 71 (53) | 38 (43.2) | 33 (71.7) |
| Infliximab | 6 (4.5) | 3 (3.4) | 3 (6.5) |
| Efalizumab | 14 (10.4) | 5 (5.7) | 9 (19.6) |
| Adalimumab | 1 (0.7) | 1 (1.1) | 0 |
| Ustekinumab | 1 (0.7) | 1 (1.1) | 0 |

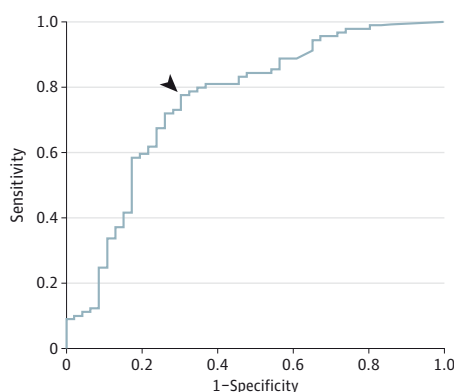
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis.

Figure 1. Mean Difference in Adalimumab Trough Level for Nonresponders and Moderate vs Good Responders



Boxes represent standard deviations; error bars, interquartile ranges; and the circle, an outlier that was included in the analyses.

Figure 2. Receiver-Operator Characteristics Analyses



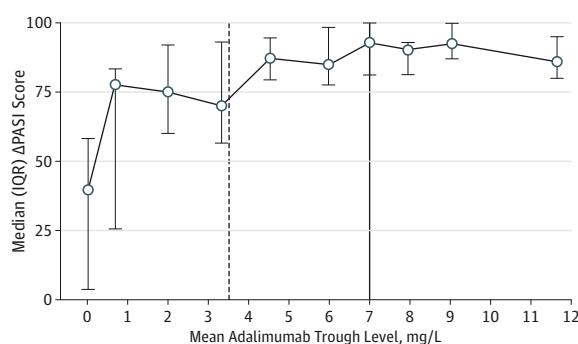
With an area under the curve of 0.756, determining the adalimumab serum trough level is a useful test to distinguish good responders from nonresponders and moderate responders. The adalimumab cutoff value corresponding with the most optimal trade-off between sensitivity and specificity is 3.51 mg/L (arrowhead).

Concentration Effect Curve

The CEC of the total study cohort contains 135 patients (Figure 3). To obtain this graphic result, all 135 patients were stratified in ascending order of their adalimumab trough concentrations, with correlating Δ PASI score. Consequently, patients were divided in 10 groups of 11, 13, 14, or 15 patients (1, 3, 5, and 1 groups, respectively). Each open circle represents the mean adalimumab concentration with correlating median Δ PASI score for 1 group. Alongside each Δ PASI score, the equivalent interquartile range is also depicted. As adalimumab trough levels increase, higher Δ PASI scores can be observed, with a maximal therapeutic response (Δ PASI 86.49) in the subgroup of patients with a mean trough level of 7 mg/L. Adalimumab concentrations exceeding 7 mg/L have no additional value to the therapeutic response.

The relationship between adalimumab trough levels and clinical response is shown separately for patients treated with adalimumab for more than 52 weeks (Figure 4A and B), and for 52 weeks or less (Figure 4A and C). Sixty patients were included for the CEC that included samples obtained at more than 52 weeks of treatment and were sorted according to ascending adalimumab levels with correlating Δ PASI scores. These data were stratified in 7 groups of 8 or 9 patients (3 and 4 groups, respectively). The same was done for the CEC that included 74 samples obtained at 52 weeks or less of treatment. These data were stratified in 9 groups of 7, 8, or 9 patients (1, 5, and 3 groups, respectively). Both CECs flattened around the same adalimumab trough concentration point of 7 mg/L. Therefore, it was considered appropriate to determine 1 adalimumab trough level range for both groups of patients with a treatment duration under and over 52 weeks (Figure 4A). These separate curves also depicted that serum levels up to 7 mg/L show a positive association with Δ PASI and that concentrations exceeding 7 mg/L had no further clinical value. One patient, from whom the treatment duration was unknown, could not be taken into account for the CEC curve of treatment more than 52 weeks or 52 weeks or less of treatment but was included in the analyses for the CEC of the total study cohort.

Figure 3. Concentration Effect Curve for Total Study Cohort



Adalimumab concentrations exceeding 7 mg/L (vertical line) had no additional value to the therapeutic response. The dashed vertical line represents the adalimumab cutoff value of 3.51 mg/L. Each open circle in the curve represents the mean adalimumab concentration, with correlating median Δ PASI score, for one group. Alongside each Δ PASI score, the equivalent interquartile range (IQR) is depicted.

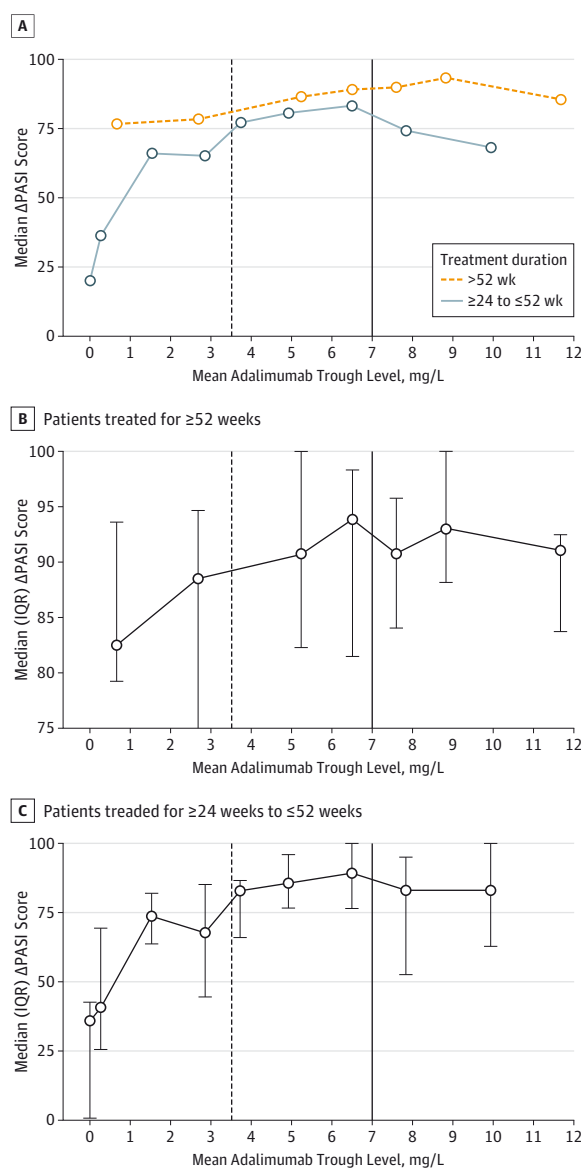
Discussion

Based on serum sample collection from 135 patients with psoriasis who were treated with adalimumab every other week for at least 24 consecutive weeks, a therapeutic range for adalimumab trough levels that corresponds with a good clinical response (Δ PASI 75.00) was defined (3.51–7.00 mg/L). With an area under the curve of 0.769, these data demonstrate that determining adalimumab serum trough level is a useful measurement to distinguish good responders from nonresponders to moderate responders. The lower margin was demarcated at 3.51 mg/L because this value correlated with the most optimal trade-off between sensitivity (78%) and specificity (70%).

Takahashi et al¹⁷ measured a mean adalimumab trough level of 7.62 μ g/mL in 32 patients with psoriasis who were treated according to the standard dosing schedule. A cutoff value for obtaining good clinical response (Δ PASI 75.00) was established at 7.84 μ g/mL. This cohort differs from our cohort in several ways. Our cohort consisted of 135 white patients with psoriasis patients vs 32 patients of Asian descent in the cohort described by Takahashi et al.¹⁷ The sample size of the latter cohort may be too limited to establish a cutoff in adalimumab trough level for obtaining good clinical response. Although Edson-Heredia et al¹⁸ stated that it is unlikely that race or ethnicity influence response rates of Δ PASI 75.00, we hypothesize that the mean body mass index, which according to Menter et al¹⁹ has a negative impact on adalimumab treatment response, is lower in the Japanese cohort compared with our cohort. Body mass index was not reported in the study by Takahashi et al.¹⁷

The upper margin of the therapeutic adalimumab range was determined by means of a CEC. By reducing intervariability between patients, an uncluttered image of the adalimumab clinical response correlation is generated. In the CEC curve of the total study cohort (Figure 3), as well as in both separate CEC curves according treatment duration subcategory

Figure 4. Concentration Effect Curves for Patients Treated for More Than 52 Weeks vs Patients Treated for 52 Weeks or Less



For patients treated for more than 52 weeks and patients treated for 24 weeks or more to 52 weeks or less, adalimumab concentrations exceeding 7 mg/L (solid vertical lines) had no additional value to the therapeutic response. A, Concentration effect curve for patients treated with adalimumab for more than 52 weeks and 24 weeks or more to 52 weeks or less. B, Concentration effect curve for patients treated with adalimumab for 52 weeks or more. C, Concentration effect curve for patients treated with adalimumab for 24 weeks or more to 52 weeks or less. The dashed vertical lines represent the adalimumab cutoff value of 3.51 mg/L. IQR indicates interquartile range.

(Figure 4), a deflection of the curve upward of 7 mg/L adalimumab can be observed. This trough level corresponded with a maximal improvement in treatment response (Δ PASI 86.46). Adalimumab levels exceeding 7 mg/L had no further beneficial effect on treatment response. In good responders, adalimumab trough concentrations up to 16.38 mg/L were observed, and 44 patients in this cohort (32.6%) had an adalimumab level

higher than 7 mg/L. In these patients, adalimumab dosing interval might be lengthened, leading to adalimumab trough concentrations within the therapeutic range without losing clinical efficacy and saving costs. Therefore, these data support the hypothesis that, with the current standard dosing regimen, an important percentage of patients with psoriasis are being over-treated. Besides trough concentrations above the upper margin, trough concentrations below the lower margin were also observed in good responders. In 20 patients, an adalimumab trough concentration below the lower margin of 3.51 mg/L was measured, and in 13 of these patients, trough concentration was even below half of the lower margin (1.75 mg/L). Because a meaningful clinical effect of these trough concentrations is not expected based up the therapeutic adalimumab range established herein, we hypothesize that disease activity in some of these patients is low. In these cases, one could envisage to stop adalimumab treatment under further careful clinical monitoring.

Pouw et al⁹ determined a therapeutic range of adalimumab (5.0–8.0 µg/mL), corresponding with good clinical response in RA. The proposed therapeutic window is higher than the range determined in our cohort. Psoriasis and RA are 2 different IMIDs, which might explain a difference in therapeutic values. The lower therapeutic adalimumab levels observed in patients with psoriasis might also be attributable to the fact that concomitant methotrexate use is not routine practice in dermatology. Concomitant methotrexate use, which leads to significantly higher functional adalimumab levels, is much more frequently practiced in patients with RA than in those with psoriasis and can be a possible explanation for the observation that lower adalimumab levels are measured in psoriasis than in RA.⁹ In our cohort, 11 patients were also treated with methotrexate, without a significant impact on adalimumab trough levels ($P = .92$). This is, however, not a meaningful observation because these numbers are very small, and it is hypothesized that methotrexate treatment should be initiated before the start of adalimumab treatment to exert its preventive effect on ADA formation. With this study we were able to confirm, at random time points in adalimumab treatment,

that serum adalimumab trough levels correlate with clinical response ($P < .001$). We also confirmed that patients positive for ADAs have significantly lower adalimumab trough levels ($P < .001$), and a worse clinical response status ($P < .001$). These results are consistent with those of Menting et al,⁸ from which serum samples were also included for cohort 2 presented herein). Thus, our data support the use of therapeutic drug monitoring in routine clinical practice.

This study has some limitations. As previously mentioned, only few patients were using concomitant methotrexate, and no subanalyses could be performed for this group of patients. Another limitation is that PASI baseline and the PASI at time of sampling were not always assessed by the same dermatologist, and interobserver variability might have been present. This study did not take into account other factors influencing response to treatment (genetic and nongenetic).²⁰ Furthermore, we want to emphasize that before using the therapeutic range developed in this study in daily practice, this study requires validation with a confirmation cohort. A therapeutic algorithm based on these data needs to be confirmed in a prospective patient cohort.

Conclusions

More rational use of biological therapy is a growing necessity in psoriasis, as in other IMIDs. On the one hand, dermatologists need guidelines to make informed decisions about an optimal (efficacious and safe) treatment regimen for an individual patient. On the other hand, increasing socioeconomic pressure aims to reduce the elevated costs of biological agents. In this study, we identified a therapeutic window of adalimumab trough levels (3.51–7.00 mg/L), which corresponds to an optimal clinical effect (Δ PASI 75.00). In one-third of patients it was observed that trough concentrations exceeded the therapeutic window. Based on the established range, a therapeutic algorithm for patients with psoriasis can be developed and validated in a prospective patient cohort.

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Author Contributions: Drs Menting and Coussens had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Menting and Coussens contributed equally to this work, and Drs Spuls and Lambert contributed equally to this work. *Study concept and design:* Menting, Coussens, de Jong, Spuls, Lambert. *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of the manuscript:* Menting, Coussens. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Menting, Coussens, Pouw, Temmerman. *Obtained funding:* Spuls, Lambert. *Administrative, technical, or material support:* Menting, Coussens, van den Reek, Temmerman, Boonen, Spuls. *Study supervision:* de Jong, Spuls, Lambert.

Conflict of Interest Disclosures: Dr Menting had carried out clinical trials for AbbVie, Pfizer, Amgen, and Novartis. Dr van den Reek has received speaking fees from AbbVie and had carried out clinical trials for AbbVie and Janssen. Dr Boonen had paid consultancies from Pfizer, AbbVie, Janssen, MSD and Leo Pharma and had carried out clinical trials for AbbVie. Dr de Jong has received speaking fees from AbbVie, MSD, Janssen, and Pfizer; has received grants from AbbVie, Pfizer, and Janssen; and had carried out clinical trials for AbbVie, MSD, Janssen, and Pfizer. Dr Spuls has received grants from Schering-Plough and LEO Pharma; had paid consultancies from Leo Pharma, AbbVie, and Novartis; and had carried out clinical trials for Leo Pharma, Janssen-Cilag, Almirall, Schering-Plough, Merck Serono, Amgen, Pfizer, Biogen Idec, Centocor, Roche, Eli Lilly, AbbVie, Celgene, Novartis, and Astellas. Dr Lambert has received grants from Janssen, AbbVie, and Pfizer; had paid consultancies from Pfizer, Novartis, AbbVie, Janssen Cilag, and Leo Pharma; and had

carried out clinical trials for Janssen-Cilag, Merck Serono, Amgen, Pfizer, AbbVie, Celgene, Regeneron and Novartis. No other disclosures are reported

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