Original Investigation

Extent and Consequences of Antibody Formation Against Adalimumab in Patients With Psoriasis One-Year Follow-up

Stef P. Menting, MD; Paula P. M. van Lümig, MD; Anna-Christa Q. de Vries, MD; Juul M. P. A. van den Reek, MD; Desiree van der Kleij, PhD; Elke M. G. J. de Jong, MD, PhD; Phyllis I. Spuls, MD, PhD; Lidian L. A. Lecluse, MD, PhD

IMPORTANCE In a previously reported cohort of 29 patients with plaque-type psoriasis followed up for 24 weeks, clinically relevant antidrug antibody (ADA) to adalimumab was frequently found. Long-term data were lacking. We now present the extension of this study: 80 patients followed up for 1 year.

OBJECTIVES To assess the extent of ADA and its clinical consequences after 24 weeks of adalimumab treatment for psoriasis in a cohort of 80 patients.

DESIGN, SETTING, AND PARTICIPANTS A multicenter cohort study, performed in the outpatient dermatology clinic of 2 academic hospitals, included 80 sequential patients receiving adalimumab therapy for plaque-type psoriasis and had a follow-up of 1 year. Outcome assessors were not aware of the presence of antibodies to adalimumab or the adalimumab serum concentration when assessing patients' Psoriasis Area and Severity Index (PASI), and personnel analyzing serum samples were blinded to patients' PASI.

INTERVENTIONS For 80 patients treated with adalimumab for psoriasis, disease severity (PASI) was assessed, blood samples were collected, and adalimumab and ADA concentrations was determined at baseline and at weeks 12, 24, and 52.

MAIN OUTCOMES AND MEASURES Patient PASI and adalimumab and ADA concentrations.

RESULTS Antidrug antibody formed in 49% of patients, before week 24 in 90% of them. Adalimumab and ADA concentrations, clinical response and ADA concentration, and adalimumab concentration and clinical response had correlations of −0.872, −0.606, and 0.519, respectively. The adalimumab dose interval was shortened because of lack of efficacy in 15 patients, 7 with and 8 without ADA; improvement in responder status occurred in 1 of 7 and 4 of 8, respectively.

CONCLUSIONS AND RELEVANCE Patients with no ADA formation in the first 24 weeks of treatment have little chance of it in the following 24 weeks. The presence of ADA is strongly correlated with adalimumab concentration and greatly influences clinical response. If ADA is present, dose interval shortening is less useful.

Published online December 18, 2013.

Copyright 2014 American Medical Association. All rights reserved.

Author Affiliations: Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands (Menting, de Vries, Spuls, Lecluse); Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands (van Lümig, van den Reek, de Jong); Laboratory for Monoclonal Therapeutics, Sanquin Diagnostic Services, Amsterdam, the Netherlands (van der Kleij).

Corresponding Author: Stef P. Menting, MD, Department of Dermatology, Academic Medical Center, Meibergdreef 9, 1105AZ, Amsterdam (s.p.menting@amc.uva.nl).
Adalimumab is a human monoclonal immunoglobulin G1 antibody and tumor necrosis factor antagonist that is a valuable treatment option for patients with moderate to severe psoriasis seen in clinical practice. As it has been shown for patients with Crohn disease and rheumatologic conditions, antibodies against adalimumab are associated with nonresponse and loss of initial response to adalimumab in a substantial proportion of patients. This effect has also been shown for patients with psoriasis. In a cohort study of 29 patients evaluated for up to 24 weeks of treatment, antidrug antibody (ADA) to adalimumab formed in 45%. This cohort has been extended to 80 patients (including the original 29), and here we present 1-year follow-up data. The purpose of this study is to assess whether ADAs develop, persist, or reduce after 24 weeks of adalimumab treatment and to determine the clinical consequences.

Methods

Detailed methods and study design have been reported elsewhere and have not changed. Briefly, approached for this prospective observational cohort study were all consecutive patients with psoriasis who were naïve to adalimumab and starting treatment with adalimumab for psoriasis at the Academic Medical Center, Amsterdam, and the Radboud University Nijmegen Medical Centre, Nijmegen (both in the Netherlands), between September 1, 2008, and July 12, 2012. The study was approved by the ethical committee of the participating hospitals and conducted according to Declaration of Helsinki principles. Patients gave written informed consent before initiation.

Certain baseline characteristics were collected. At the time of evaluation for this report, 80 patients were enrolled. Patients were treated with adalimumab according to the manufacturer’s recommendations, with an initial dose of 80 mg subcutaneously followed by 40 mg subcutaneously every other week, starting 1 week after the initial dose. Patients could be treated concomitantly with methotrexate from the start of the study. In patients with inadequate response to adalimumab, concomitant methotrexate could be started or the dose interval for adalimumab could be reduced to every 7 or 10 days (referred to hereafter as dose interval shortening). Treatment could be terminated because of nonresponse or adverse events. The reason for termination of treatment was registered. Decisions were made by the treating dermatologist and did not deviate from daily practice. The treating dermatologist was masked to the antibody status of the patient.

Disease severity was assessed by the treating physician at baseline and at weeks 12, 24, and 52 using the Psoriasis Area and Severity Index (PASI). Improvement was measured as the percentage of improvement compared with baseline PASI. Nonresponders were defined as patients achieving less than 50% improvement compared with baseline PASI, moderate responders as those achieving 50% to less than 75% improvement, and good responders as those achieving at least 75% improvement. In case patients switched to adalimumab therapy from a previous biologic therapy without a washout period, the PASI before this biologic therapy was used as the baseline PASI. This was done because otherwise these patients would seem to be nonresponders despite a good response to adalimumab therapy.

Blood samples were obtained before initiation of adalimumab treatment and at adalimumab serum trough levels at baseline and at weeks 12, 24, and 52 (just before administration of adalimumab). The adalimumab levels were measured by means of enzyme-linked immunosorbent assay, and the ADAs were detected with a radioimmunoassay (both performed at the Laboratory for Monoclonal Therapeutics, Sanquin Diagnostic Services). The radioimmunoassay does not detect ADA bound to adalimumab and might therefore underestimate ADA formation.

The antibody test results were considered positive when the antibody concentration exceeded 12 AU/mL. Concentrations between 12 and 100 AU/mL were considered low ADA titers and those above 100 AU/mL were considered high ADA titers. If no detectable ADAs were present (<12 AU/mL) this result was categorized as “no ADA.”

The methods of statistical analysis are explained in the earlier report. In addition, we used the Spearman rank test to calculate the correlation coefficients between the clinical response (expressed as ΔPASI), the level of antibodies against adalimumab, and the adalimumab trough level. To replace missing baseline PASI values, imputation of the mean was used. For missing visits, missing adalimumab levels, and missing antibody titers, the last observation carried forward method was used.

Results

Patient Characteristics

This cohort included 80 patients, 52 male and 28 female, with a mean age of 46 years (range, 24-73 years). The mean disease duration of psoriasis was 23 years (range, 7-51 years), and the mean PASI at baseline was 12 (range, 1.5-27). Three patients had low baseline PASI (1.5, 1.7, and 3.8) because they had to switch directly from efalizumab to adalimumab when efalizumab was withdrawn from the market. One patient had a baseline PASI of only 3 because she had switched from etanercept, to which her psoriasis responded but her arthritis did not. For these 4 patients, the baseline PASI from prior biologic therapy (9.6, 8.6, 18.8, and 11.7) was used as the baseline PASI for this study, as described in the Methods section.

Sixty-five percent of patients had a PASI of at least 10.0 (excluding the 4 patients just mentioned with replaced PASI values). Sixty-nine percent had used at least 4 previous systemic treatments for psoriasis; the most frequently used previous treatments were methotrexate and UV-B (in 95% and 94% of patients, respectively). The mean body mass index (calculated as weight in kilograms divided by height in meters squared) was 29.4, and 25% of patients had a diagnosis of psoriatic arthritis. See the Table for patient characteristics.
All patients reached the week 12 visit, at which point 38 patients (48%) were nonresponders, 16 (20%) were moderate responders, and 26 (32%) were good responders. Of 71 patients who reached the week 24 visit, 24 (30%) were nonresponders, 22 (28%) were moderate responders, and 25 (31%) were good responders. Of the 9 patients who stopped treatment between the week 12 and 24 visits, 5 discontinued treatment early because of nonresponse and 3 because of an adverse event (herpes zoster, pneumonia, and abscess formation in the adalimumab injection site). One patient stopped treatment because of nonresponse together with an adverse event (psoriasis palmoplantar). Fifty-nine patients (74%) reached the week 52 visit. Fifteen (19%) were nonresponders, 12 (15%) were moderate responders, and 32 were good responders (40%). Between the week 24 and 52 visits, 12 patients (15%) discontinued treatment; 3 were lost to follow-up, 8 stopped treatment with adalimumab because of nonresponse, and 1 stopped treatment because of nonresponse together with an adverse event. Termination of treatment for nonresponse occurred after a mean duration of 7.8 months. In total, 21 patients (26%) did not complete 1 year of treatment with adalimumab.

Clinical Response

All patients reached the week 12 visit, at which point 38 patients (48%) were nonresponders, 16 (20%) were moderate responders, and 26 (32%) were good responders. Of 71 patients who reached the week 24 visit, 24 (30%) were nonresponders, 22 (28%) were moderate responders, and 25 (31%) were good responders. Of the 9 patients who stopped treatment between the week 12 and 24 visits, 5 discontinued treatment early because of nonresponse and 3 because of an adverse event (herpes zoster, pneumonia, and abscess formation in the adalimumab injection site). One patient stopped treatment because of nonresponse together with an adverse event (psoriasis palmoplantar). Fifty-nine patients (74%) reached the week 52 visit. Fifteen (19%) were nonresponders, 12 (15%) were moderate responders, and 32 were good responders (40%). Between the week 24 and 52 visits, 12 patients (15%) discontinued treatment; 3 were lost to follow-up, 8 stopped treatment with adalimumab because of nonresponse, and 1 stopped treatment because of nonresponse together with an adverse event. Termination of treatment for nonresponse occurred after a mean duration of 7.8 months. In total, 21 patients (26%) did not complete 1 year of treatment with adalimumab.

Clinical Response and Adalimumab Trough Levels

At the study termination (at week 52 or the early termination [ET] visit), the adalimumab level varied significantly between nonresponders and moderate responders and between nonresponders and good responders. Of the 38 patients who were nonresponders at the week 12 visit, 18 and 9, respectively, remained nonresponders at weeks 24 and 52. Treatment was terminated early because of nonresponse in 6 nonresponders between weeks 12 and 24 and in 11 between weeks 24 and 52. Of the 26 patients who were good responders at the week 12 visit, 18 and 19, respectively, remained so at weeks 24 and 52. Treatment was terminated early (before week 52) in 6 good responders: in 1 because of an adverse event, in 3 because of loss of effectiveness over time, and in 2 because of loss to follow-up.
At week 12, the median adalimumab level in patients receiving adalimumab ranged from undetectable to 31 mg/L. Adalimumab trough levels varied significantly among patients with no, low, and high ADA, with a median (range) of 10.5 (2.0-29.2), 2.0 (0.1-6.5), and 0.0 (0.0-0.1) mg/L, respectively. Figure 2 shows different median adalimumab trough levels by ADA status and week. For weeks 12, 24, and 52, respectively, 9, 5, and 2 patients had no ADA, levels did vary significantly among patients with no, low, and high ADA, with a median (range) of 10.5 (2.0-29.2), 2.0 (0.1-6.5), and 0.0 (0.0-0.1) mg/L, respectively. Figure 2 shows different median adalimumab trough levels by ADA status and week. For weeks 12, 24, and 52, respectively, 9, 5, and 2 patients had no ADA, low ADA; and high ADA, high ADA.

Concentrations of Antibodies to Adalimumab

During 52 weeks of follow-up, ADAs were detected in 39 of 80 patients (49%). Antidrug antibody formation occurred for the first time before week 12 in 18 patients, between weeks 12 and 24 in 17, and between weeks 24 and 52 in 4. At the week 12 visit, 8 patients had a low ADA titer (13-34 AU/mL), 10 had a high ADA titer (195-7300 AU/mL), 53 had no ADA, and 9 had a missing value. In 16 of the 18 patients with ADA, the ADA titer at week 24 or ET had risen. At the week 24 visit, 20 patients had a low ADA titer (13-96 AU/mL), 9 had a high titer (1220-55700 AU/mL), 37 had no ADA, and 5 had a missing value. In 5 patients with ADA at week 24 (range, 14-35 AU/mL), ADA had disappeared at week 52 (no explanation found). In the remaining patients with ADA at week 24, ADA had increased or remained the same or patients had undergone ET. At the week 52 visit, 19 had a low ADA titer (13-96 AU/mL), 1 had a high ADA titer (6833 AU/mL), 37 had no ADA, and 2 had a missing value (Figure 2).

All 18 patients with ADA at week 12 had ADA at week 24 or underwent ET before week 24. All patients with low ADA titers continued to have low or high ADA titers at week 24. Of the 31 patients with ADA at the week 24 visit, 4 showed no ADA at week 52 (all had low ADA titers at week 24; range, 14-35 AU/mL). The remaining 27 patients still showed ADA at week 52 or underwent ET.

Adalimumab Trough Level and Antibodies to Adalimumab

Adalimumab trough level ranged from undetectable to 31 mg/L. At week 12, the median adalimumab level in patients receiving 40 mg of adalimumab every other week was 8 mg/L (range, 0-20). At weeks 24 and 52, the median (range) levels were 5 (0-31) and 7 (0-19) mg/L, respectively. Figure 2 shows different median adalimumab trough levels by ADA status and week. For weeks 12, 24, and 52, respectively, 9, 5, and 2 patients had no serum samples obtained. At week 52, in 5 patients it was not certain that serum samples were obtained at a trough level; these 5 measurements were excluded from analysis.

At termination of the study (week 52 or the ET visit), the adalimumab level did vary significantly among patients with no, low, and high ADA, with a median (range) of 10.5 (2.0-29.2), 2.0 (0.1-6.5), and 0.0 (0.0-0.1) mg/L, respectively (Figure 2). The Spearman rank correlation coefficient was calculated and showed a very strong negative correlation coefficient of −0.872 between adalimumab level and ADA concentration.

Adalimumab Dose Interval Shortening

Two patients had the dosing interval shortened at week 12, both because of nonresponse. One patient had no ADA and changed into a good responder. One patient was receiving oral prednisone for asthma together with a shortened dose interval. This patient had high ADA (474 AU/mL) at week 12 and changed into a moderate responder, with low ADA (25 AU/mL) at week 52. Seven patients had the dosing interval shortened between weeks 12 and 24, because of nonresponse in 5 and moderate response in 2. Three of the nonresponders had high ADA titers before dose interval shortening and remained nonresponders. Two patients without ADA before dose interval shortening improved in responder status, and 2 without ADA remained at the same level of responder status. Six patients had the dosing interval shortened between weeks 24 and 52, because of nonresponse and moderate response in 3 each. Three of the patients had ADA before dose interval shortening and did not improve responder status. Three of the patients had no ADA; responder status did not improve in 2 and did improve in 1 (Figure 3). There was no significant difference in adalimumab trough level between patients who underwent dose interval shortening and those who did not.
Concomitant Use of Methotrexate

Eight patients received concomitant methotrexate therapy from week 0. Among these 8 patients, (low) ADA developed in 3 (at weeks 12, 24, and 52). No methotrexate-treated patients had high ADA titers, and 5 had no ADA formation. Methotrexate dosage ranged from 2.5 to 20 mg/wk. Methotrexate therapy was initiated in 1 patient at week 12. Responder status improved in this patient who did not have ADA formation. At week 24, methotrexate therapy was initiated in 3 patients. Responder status improved in 2. In 1 of 2 patients who had ADA before concomitant methotrexate therapy, ADA titers went from high to low.

In 2 patients, the dose interval was shortened during the same time interval methotrexate was added. One patient remained a moderate responder, but ADA titers went from 2950 to 87 AU/mL; the other patient had no ADA and went from being a nonresponder to a good responder. There was no significant difference in adalimumab trough level between patients who were concomitantly treated with methotrexate and who were not.

Clinical Response and Concentrations of Antibodies to Adalimumab

Among the 32 good responders at the week 52 visit, 27 had no ADA, 5 had low ADA (range, 16-73 AU/mL), and none had high ADA. Among the 13 moderate responders, 7 had no ADA, 6 had low ADA (range, 13-96 AU/mL), and none had high ADA. Among the 14 nonresponders, 4 had no ADA, 9 had low ADA titers (range, 13-62 AU/mL), and 1 had a high ADA titer (68 333 AU/mL). In total, 14 patients underwent ET because of nonresponse, 5 between week 12 and 24 and 9 between week 24 and 52. Two of them had no ADA, 3 had low ADA, and 9 had high ADA. Figure 4 shows the responder status by ADA titer at the termination of the study (week 52 or ET visit, whichever came first). All patients with high ADA at week 12, 24, or 52 or ET were nonresponders at that time. Not all nonresponders had high ADA. At the termination of the study (at week 52 or ET visit, whichever came first), the ADA concentration varied significantly between nonresponders and moderate responders and between nonresponders and good responders (P < .05). There was no significant difference between moderate responders and good responders. The median (range) in AU/mL was 0 (0-73), 0 (0-31), and 39 (0-68333) for good, moderate, and nonresponders, respectively. The Spearman rank correlation coefficient was calculated and showed a moderately strong negative correlation coefficient of −0.606.

Discussion

The purpose of our study was to assess whether the extent of antibody formation against adalimumab in the treatment of psoriasis vulgaris increases, persists, or decreases after 24 weeks of adalimumab treatment and to determine the clinical consequences of such changes. In conclusion, our findings show that the biggest chance of first-time ADA development is in the first 24 weeks of treatment (35 vs 4 patients) and further support the notion that the presence of ADA is strongly correlated with adalimumab level (correlation coefficient, −0.872) and greatly influences clinical response (correlation coefficient, −0.606), also after 24 weeks of treatment. Dose interval shortening might be useful if no ADAs are present, but it seems less useful if they are present.

In the previous study, 13 of 29 patients (45%) had ADA formation,9 compared with 39 of 80 (49%) in the current study. In studies performed in patients with rheumatoid arthritis treated with adalimumab, these percentages are lower. Bartelds et al13 showed in a 3-year follow-up study that 28% of patients had ADA formation. Many patients (74%) in that study used concomitant methotrexate, but patients with ADA formation less often had concomitant MTX. Moreover, in other studies, the concomitant use of immunosuppressants reduces the frequency of antibody formation in response to biologic therapy,14,15 and a favorable effect of concomitant methotrexate on reducing antibody formation has been postulated. In a letter by Kriekckaert et al,16 it was reported that methotrexate seems to reduce ADA formation efficiently and in a dose-dependent manner.

Methotrexate treatment did not reduce ADA formation in our study; 3 of 8 patients (38%) who received methotrexate had (low) ADA. This might be due to the low dose of methotrexate used by these 3 patients (2.5, 10, and 10 mg/wk). The number of patients using concomitant methotrexate in our study was limited, so these data should be interpreted with caution. Of the patients in our cohort not receiving concomitant methotrexate, 50% (36 of 72 patients) had ADA formation. Bartelds et al13 found the same, with ADA formation in 50% of patients (35 of 70) not receiving concomitant methotrexate. Of their patients receiving concomitant methotrexate, only 20% (41 of 202) had ADA formation, which further supports the role of methotrexate in reducing immunogenicity, instead of, for example, disease (psoriasis)-related factors. The treatment dose of adalimumab is similar for psoriasis and rheumatoid arthritis. A
findings by Bartelds et al, in which 67% of patients had ADA formation for the first time before week 24. This is in line with the fact that ADA formation can lead to thromboembolic events or a type III hypersensitivity reaction, which has not been observed in this cohort.

In this study, we have also further endorsed the strong negative correlation between ADA formation and adalimumab serum trough levels, with a correlation coefficient of -0.872. The higher the ADA titer, the lower the adalimumab trough level. In a different study, it was shown that virtually all ADAs are neutralizing and that the ADAs are highly specific for adalimumab, forming small immune complexes, in this way neutralizing the drug. It has been suggested that ADA may lead to thromboembolic events or a type III hypersensitivity reaction, which has not been observed in this cohort.

The last observation carried forward method was used to replace missing values for adalimumab levels and antibody titers. This may have led to underestimation of ADA formation and overestimation of drug levels.

The antibody assay used in this study (a radioimmunoassay) is the same used in the studies by Bartelds et al and Krückeart et al but different from the bridging enzyme-linked immunosorbent assay used by Vermeire et al and Karmiris et al. The latter is more sensitive to drug interference and does not detect immunoglobulin G4 ADA, making comparison between these studies less reliable. The influence of methotrexate on ADA formation needs further research, as well as the influence of dose interval shortening in ADA-positive and ADA-negative patients.
invited commentary

PREVENTING AND DETECTING ANTIBODIES TO ANTI-TUMOR NECROSIS FACTOR AGENTS
GAPS IN PRACTICE OR IN EVIDENCE?

Kristina Callis Duffin, MD, MS

Although anti-tumor necrosis factor (TNF) agents are considered highly effective therapies for psoriasis, treatment failure is common. As highlighted in the study by Menting et al., primary failure is more frequent in the “real-world” setting compared with randomized clinical trials with adalimumab and is associated with formation of anti-drug antibodies (ADAs) and low serum drug levels. This article further highlights the high frequency of ADA formation (50%) in patients not receiving concomitant methotrexate. These issues raise 2 questions: (1) should adalimumab be prescribed with methotrexate at the outset and (2) should ADA and trough drug levels be drawn when patients fail to respond to adalimumab to aid in the decision to escalate dose or switch therapy?

There are no consensus guidelines that recommend methotrexate be routinely prescribed with adalimumab to prevent ADA formation and therefore prevent treatment failure. There have just not been enough data to support this when treat-