

Extent and Clinical Consequences of Antibody Formation Against Adalimumab in Patients With Plaque Psoriasis

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Objectives: To investigate the extent antibodies to adalimumab are formed in patients with plaque psoriasis and whether these antibodies have clinical consequences. Also, to examine the relationship between antibodies to adalimumab and adalimumab trough titers.

Design: Prospective observational cohort study.

Setting: Two Dutch dermatology departments in university hospitals.

Patients: All consecutive patients starting a regimen of adalimumab for chronic plaque psoriasis. Patients were screened and fulfilled the Dutch reimbursement criteria for adalimumab to treat psoriasis.

Intervention: Adalimumab treatment (per label).

Main Outcome Measures: The titer of antibodies to adalimumab, the adalimumab trough concentration, and the Psoriasis Area and Severity Index at weeks 12 and 24.

Results: Antibodies to adalimumab were detected in 13 of 29 patients (45%) during 24 weeks of treatment. Differences in response rates among patients with low, high, and no titers of antibodies to adalimumab were significant at weeks 12 and 24 ($P = .04$ and $P < .001$, respectively). The median adalimumab trough concentrations varied significantly among patients with low, high, and no titers of antibodies to adalimumab (1.30 [range, 0.01-5.50], 0.0 [range, 0.0-0.0], and 9.6 [range, 0.0-22.6] mg/L, respectively; $P < .001$). At week 24, the median adalimumab trough concentrations also differed significantly among good responders, moderate responders, and nonresponders (9.7 [range, 0.0-22.6], 8.9 [range, 3.2-12.6], and 0.0 [range, 0.0-13.3] mg/L, respectively; $P = .01$).

Conclusion: Antibodies to adalimumab are associated with lower serum adalimumab trough concentrations and with nonresponse or loss of response to adalimumab in patients with plaque psoriasis.

Arch Dermatol. 2010;146(2):127-132

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ANTIBODIES TO ADALIMUMAB have been associated with nonresponse or loss of initial response to adalimumab in a substantial portion of patients with rheumatoid arthritis or Crohn disease.¹⁻⁴ Adalimumab is a fully humanized monoclonal IgG1 antibody and tumor necrosis factor

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antagonist; its indication was extended for treatment of moderate to severe chronic plaque psoriasis in 2008. Treatment of psoriasis with adalimumab has shown promising results in phase 3 trials.^{5,6} Some patients with plaque psoriasis do not respond to adalimumab, or they no longer respond to adalimumab treatment despite initial good results. The mechanism of an-

tibody formation is assumed to have a role in these patients. Because adalimumab, with other biologic agents, represents the end of the therapeutic spectrum for treatment-resistant moderate to severe plaque psoriasis, it is important to identify factors that may impair the clinical response. Further research may then lead to treatment optimization.

The objectives of this study were to investigate the extent antibodies to adalimumab are formed in patients with plaque psoriasis and whether these antibodies have clinical consequences. Also, to examine the relationship between antibodies to adalimumab and adalimumab trough titers.

Therefore, we evaluated adalimumab trough concentration and concentration of antibodies to adalimumab relative to clinical response in a cohort of patients with plaque psoriasis and up to 24 weeks of adalimumab treatment.

Table. Clinical Characteristics of Patients at Baseline^a

Characteristic	Total Cohort (N=29)	Antibodies to Adalimumab	
		Patients With (n=13)	Patients Without (n=16)
Age, mean (SD), y	44 (11)	47 (13)	42 (10)
Male sex, No. (%)	20 (69)	8 (62)	12 (75)
Disease duration, mean, y	22	25	20
Psoriasis Area and Severity Index, mean	15.5	16.2	14.9
Body mass index ^b	29	30	28
Diagnosed as having psoriatic arthritis, No. (%)	5 (17)	3 (23)	2 (13)
Concomitant methotrexate, No. (%)	3 (10)	0	3 (19)
Previous systemic therapies, No. (%)			
Methotrexate	28 (97)	12 (92)	16 (100)
Cyclosporine	19 (66)	9 (69)	10 (63)
UV-B	27 (93)	12 (92)	15 (94)
Psoralen-UV-A	19 (66)	9 (69)	10 (63)
Etanercept	20 (69)	12 (92)	13 (81)
Infliximab	2 (7)	1 (8)	1 (6)
Efalizumab	8 (28)	5 (38)	3 (19)
Adalimumab	0	0	0
Mean No.	4.2	4.6	3.9

^aNo data differed significantly between patients with and without antibodies to adalimumab except for the proportion of patients previously treated with etanercept ($P=.02$). Last-observation-carried-forward method was used in 2 patients, if applicable.

^bCalculated as weight in kilograms divided by height in meters squared.

METHODS

PATIENTS

This prospective observational cohort study in the Netherlands consisted of all consecutive patients with plaque psoriasis starting a regimen of adalimumab at the Departments of Dermatology of the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Center in Nijmegen. Patients were treated with adalimumab (40 mg) every other week after an initial dose of 80 mg and a dose of 40 mg the week thereafter. In patients with an inadequate response as judged by the treating physician, the dosing interval of adalimumab could be reduced to once weekly. The study was approved by the medical ethics committees of both hospitals, and all patients gave written informed consent.

CLINICAL RESPONSE

Disease severity was assessed at baseline, at week 12, and at week 24 using the Psoriasis Area and Severity Index (PASI), which is the most commonly used outcome measure in trials of antipsoriatic agents.⁷ Response is measured as the percentage improvement on the PASI compared with baseline. Patients were classified as nonresponders (<50% improvement on the PASI compared with baseline), moderate responders ($\geq 50\%$ to <75% improvement), or good responders ($\geq 75\%$ improvement). The PASI assessment was performed before serum sample analysis.

MEASUREMENT OF ADALIMUMAB TROUGH CONCENTRATIONS

Blood was drawn at an adalimumab trough concentration (just before administration of adalimumab) 12 and 24 weeks after

initiation of treatment. The samples were frozen and analyzed when all sampling was completed. The laboratory had no access to clinical data at the time of analysis. Adalimumab trough concentrations were measured by enzyme-linked immunosorbent assay based on the principle that adalimumab is captured through its ability to bind tumor necrosis factor. Adalimumab trough concentrations were quantified as described previously.² Adalimumab binding was assessed by incubation with biotinylated rabbit IgG directed to the adalimumab idiotype. The detection limit of the assay is about 0.001 mg/L.

MEASUREMENT OF CONCENTRATIONS OF ANTIBODIES TO ADALIMUMAB

Concentrations of antibodies to adalimumab were measured using a radioimmunoassay. The assay measures specific high-avidity IgG antibodies to adalimumab by an antigen-binding test as described previously.² Because the presence of adalimumab interferes with the assay, concentrations of antibodies to adalimumab in patients with high concentrations of adalimumab are underestimated or undetectable. Therefore, blood was drawn at the adalimumab trough concentration. The antibody test was considered positive when the concentration of antibodies to adalimumab exceeded 12 arbitrary units (AU)/mL, which was previously shown² to be the mean + 6 SDs of the pretreatment values. In a previous study,² the serum concentrations of antibodies to adalimumab showed 2 clusters, which could be separated at a cutoff value of 100 AU/mL. In our cohort, the concentrations of antibodies to adalimumab also naturally formed 2 clusters; therefore, we used the same cutoff points for titers of antibodies to adalimumab. A concentration between 12 and 100 AU/mL was considered a low titer of antibodies to adalimumab, and a concentration above 100 AU/mL was considered a high titer of antibodies to adalimumab.

STATISTICAL ANALYSIS

For differences between groups, we used independent-samples t test, χ^2 test, Mann-Whitney test, or Kruskal-Wallis test, as appropriate. The threshold for significance was set at $P < .05$. To analyze clinical response in patients with and without antibodies to adalimumab after 24 weeks of treatment for patients who stopped treatment, we used the last-observation-carried-forward method.

RESULTS

PATIENT CHARACTERISTICS

Most patients in the cohort were male (69% [20 of 29]), with a mean age of 44 years (**Table**). The mean disease severity on the PASI at baseline was 15.5, and the mean disease duration was 22 years. One patient scored only 3 on the PASI at baseline because she had switched from etanercept, to which her plaque psoriasis responded, but her arthritis did not. Patients did not respond to a mean of 4.2 previous systemic therapies, including phototherapies. Among all patients, 17% (5 of 29) were also diagnosed as having psoriatic arthritis. At baseline, 1 patient used concomitant fumaric acid, 1 patient used concomitant acitretin, and 3 patients used concomitant methotrexate (mean dosage, 12 mg/wk). Most patients used concomitant topical therapies.

There were no significant differences between patients with and without antibodies to adalimumab in mean

age, proportion of male sex, PASI at baseline, body mass index, proportion of patients with psoriatic arthritis, or number of previous systemic therapies. The Table gives the patient characteristics of the cohort and for patients with and without antibodies to adalimumab.

CLINICAL RESPONSE

At week 12, 14 of 28 patients (50%) were moderate responders, 9 (32%) were good responders, and 6 (21%) had reached 90% improvement compared with baseline (data are missing for 1 patient). Twenty-seven of 29 patients were still receiving adalimumab at week 24. Two patients discontinued receiving adalimumab because of its ineffectiveness as decided by the treating dermatologist after 14 and 16 weeks. At week 24, 16 of 29 patients (55%) were moderate responders, 10 (34%) were good responders, and 4 (14%) had reached 90% improvement compared with baseline. At week 24, half of the nonresponders had reached 40% improvement compared with baseline.

Most patients who were good responders at week 12 (n=9) were still good responders at week 24 (n=7). Likewise, most of the nonresponders at week 12 (n=14) remained nonresponders at week 24 (n=8).

CONCENTRATIONS OF ANTIBODIES TO ADALIMUMAB

During 24 weeks of follow-up, antibodies to adalimumab were detected in 13 of 29 patients (45%). Seven patients had antibodies to adalimumab at week 12 and another 6 patients at week 24. At week 12, 2 of 25 patients (8%) had a low titer of antibodies to adalimumab (range, 13-21 AU/mL), and 5 (20%) had a high titer of antibodies to adalimumab (range, 340-7300 AU/mL). At week 24, 6 of 29 patients (21%) had a low titer of antibodies to adalimumab (range, 15-54 AU/mL), and 7 (24%) had a high titer of antibodies to adalimumab (range, 1640-55 700 AU/mL). One patient with a high titer at week 12 (474 AU/mL) had a low titer at week 24 (30 AU/mL); he received adalimumab from weeks 8 through 24 and was treated with oral prednisone after week 12 for asthma. All other patients had increasing titers of antibodies to adalimumab over time. The 3 patients who took concomitant methotrexate did not develop antibodies to adalimumab.

ADALIMUMAB TROUGH CONCENTRATIONS

Adalimumab trough concentrations ranged from undetectable to 22.6 mg/L. In patients receiving adalimumab (40 mg) every other week, the median adalimumab trough concentrations were 8.2 (range, 0.0-17.0) mg/L at week 12 and 4.8 (range, 0.0-22.6) mg/L at week 24. In **Figure 1**, the course of adalimumab trough concentrations is shown over 24 weeks in patients with and without antibodies to adalimumab. The median adalimumab trough concentrations varied significantly among patients with low, high, and no titers of antibodies to adalimumab (1.30 [range, 0.01-5.50], 0.0 [range, 0.0-0.0], and 9.6 [range, 0.0-22.6] mg/L, respectively; $P < .001$).

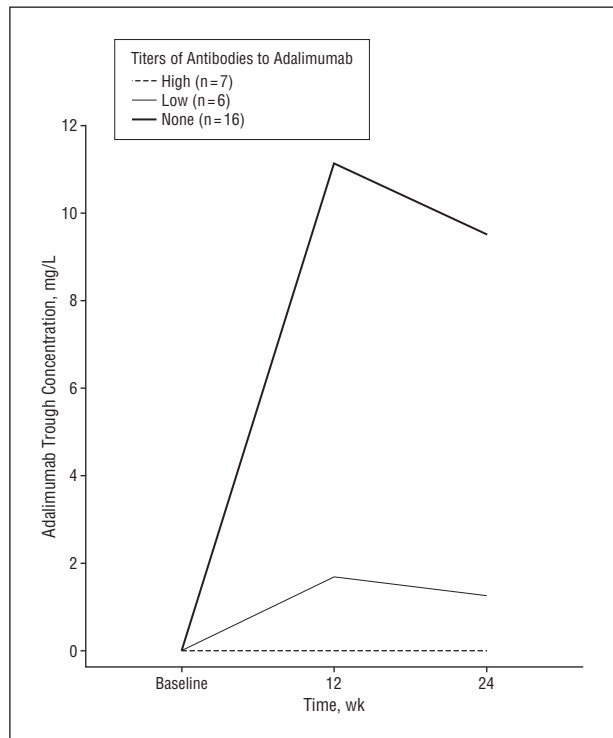


Figure 1. The median adalimumab trough concentrations were measured at weeks 12 and 24 for patients with low, high, and no titers of antibodies to adalimumab. At weeks 12 and 24, the differences among the 3 groups were statistically significant ($P = .001$ and $P < .001$, respectively). For patients with high titers of antibodies to adalimumab, a positive adalimumab trough concentration could probably have been obtained shortly after baseline. The adalimumab trough concentration at baseline is assumed to be 0 based on previous studies² and the fact that no patient had received adalimumab before baseline.

INCREASED DOSING FREQUENCY OF ADALIMUMAB

The adalimumab dosing interval was shortened in 2 patients at week 12 and in another 7 patients between weeks 12 and 24 because of ineffectiveness as decided by the treating dermatologist. In these 9 patients receiving adalimumab every week, the median adalimumab trough concentration was 1.7 (range, 0.0-13.3) mg/L at week 24. Adalimumab trough concentrations did not differ significantly between patients who used adalimumab every week vs every other week ($P = .54$).

One patient was treated with adalimumab approximately once every 25 days between weeks 12 and 24. This patient had no health insurance and paid out of pocket for treatment. His adalimumab trough concentration was undetectable (without antibodies to adalimumab).

CLINICAL RESPONSE AND CONCENTRATIONS OF ANTIBODIES TO ADALIMUMAB

Among patients with a good response on the PASI at week 12, only 1 patient had detectable antibodies to adalimumab (13 AU/mL); similarly among patients with a moderate response, only 1 patient had detectable antibodies to adalimumab (21 AU/mL). At week 24, both patients had increased titers of antibodies to adalimumab and no longer responded to adalimumab treatment. Among patients with

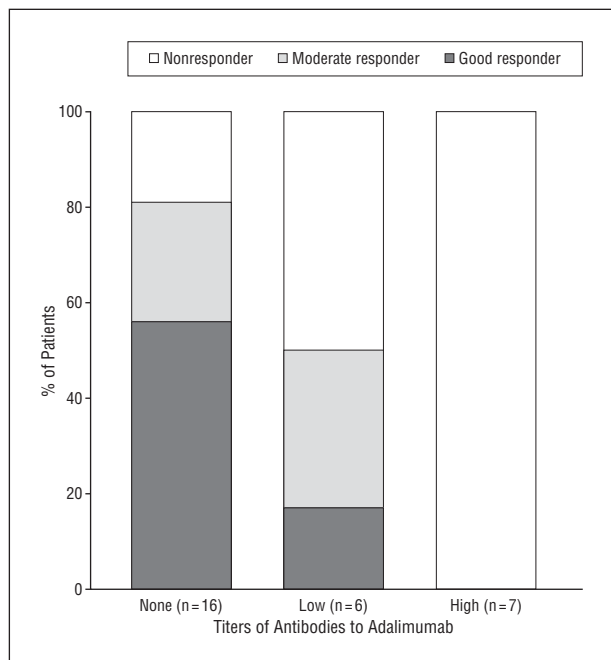


Figure 2. The percentages of nonresponders, moderate responders, and good responders on the Psoriasis Area and Severity Index are shown for patients with low, high, and no titers of antibodies to adalimumab at week 24. The difference among the 3 groups was statistically significant ($P < .001$).

a good response on the PASI at week 24, there was again only 1 patient with detectable antibodies to adalimumab (41 AU/mL). Two patients who were moderate responders had detectable antibodies to adalimumab at week 24 (15 and 19 AU/mL). All patients with high titers of antibodies to adalimumab at weeks 12 or 24 were nonresponders. However, not all nonresponders had high titers of antibodies to adalimumab (**Figure 2**). Differences in response rates among patients with low, high, and no titers of antibodies to adalimumab were significant at weeks 12 and 24 ($P = .04$ and $P < .001$, respectively).

Twelve of 17 patients (71%) without antibodies to adalimumab improved their response on the PASI between weeks 12 and 24, as opposed to 1 of 7 patients (14%) with antibodies to adalimumab. Differences between responses at weeks 12 and 24 were not significant for either group.

CLINICAL RESPONSE AND ADALIMUMAB TROUGH CONCENTRATIONS

At week 12, nonresponders had lower median adalimumab trough concentrations than good responders (4.2 [range 0.0-16.0] vs 11.0 [range 1.0-17.0] mg/L; $P = .046$). The median adalimumab trough concentration in moderate responders (4.4 [range, 1.0-10.0] mg/L) was not significantly different. At week 24, the median adalimumab trough concentrations differed significantly among good responders, moderate responders, and nonresponders (9.7 [range, 0.0-22.6], 8.9 [range, 3.2-12.6], and 0.0 [range, 0.0-13.3] mg/L, respectively; $P = .01$) (**Figure 3**). Data from a patient with a typical antibody response are shown in **Figure 4**; as the level of antibodies to adalimumab increased, the PASI increased and the adalimumab trough concentration decreased.

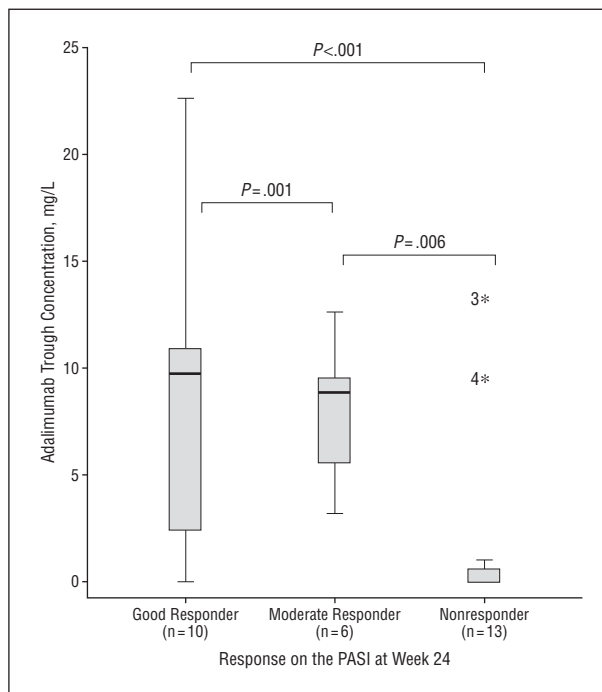


Figure 3. Adalimumab trough concentrations at week 24 for the different response levels on the Psoriasis Area and Severity Index (PASI). The 2 outliers (asterisks) in the nonresponder group were included in the analyses.

COMMENT

In this study, we have shown that antibodies to adalimumab are formed in a large portion of patients with plaque psoriasis; at the end of the study, 45% (13 of 29) of patients had developed antibodies to adalimumab. High titers of antibodies to adalimumab were particularly associated with undetectable adalimumab trough concentrations. We also showed that high titers of antibodies to adalimumab and low adalimumab trough concentrations were associated with impaired treatment outcome.

Response rates to adalimumab in this study are surprisingly lower than those in phase 3 trials,^{5,6} in which 53% and 71% of patients were good responders after 12 and 16 weeks, respectively, compared with 32% (9 of 28) in our cohort after 12 weeks; at week 24, the percentages of good responders for the phase 3 trials were 70% and 64% after 12 and 16 weeks, respectively, compared with 34% (10 of 29) in our cohort. This might be the result of selected populations in phase 3 trials vs the “normal” population with psoriasis having more comorbidities and concomitant medication regimens.⁸ However, another factor may be the selection of patients in our cohort since they were treated in tertiary psoriasis referral centers, and some had previously failed other systemic therapies.

Twelve of 13 patients (92%) who developed antibodies to adalimumab had previously been treated with etanercept vs 8 of 16 patients (50%) who did not develop antibodies to adalimumab, which was a significant difference. This is a notable finding that needs further investigation. However, the test for antibodies to adalimumab is specific, and cross-linking is unlikely. Furthermore, neutralizing antibodies to etanercept have not been demonstrated to date.

As shown in patients receiving infliximab who develop antibodies to infliximab,⁹ we assume that adalimumab and antibodies to adalimumab form complexes. These complexes may be removed by the liver and the spleen. This would explain the undetectable serum adalimumab trough concentrations in patients with high titers of antibodies to adalimumab compared with the clearly detectable serum adalimumab trough concentrations in patients without antibodies to adalimumab. Removal of the therapeutic agent by the formation of complexes would explain why all patients with high titers of antibodies to adalimumab were nonresponders. It has been speculated that dosage escalation may overload the capacity of the immune system to produce antibodies to adalimumab or may lead to immunologic tolerance.¹⁰

The proportion of our patients who developed antibodies to adalimumab is higher than that in other studies. In a phase 3 trial of patients treated with adalimumab for psoriasis that analyzed antibody formation, only 8.8% of patients tested positive for antibodies to adalimumab.⁶ However, patients may have been tested for antibodies even if they had received only 1 dose of adalimumab. Furthermore, no specific details about the methods of antibody testing were given.

In a study by Bartelds et al,² 17% of patients with adalimumab-treated rheumatoid arthritis developed antibodies to adalimumab after 28 weeks. That study used the same assay and practically the same setup as in the present study. An explanation for the difference in results might be concomitant methotrexate use. Among patients with rheumatoid arthritis who used concomitant methotrexate, the percentage with antibodies to adalimumab was significantly lower than the percentage without antibodies to adalimumab ($P = .003$). Of the patients using concomitant methotrexate (mean dosage, 19.4 mg/wk), 12% developed antibodies to adalimumab vs 38% of patients receiving adalimumab monotherapy. Furthermore, concomitant low-dose methotrexate has been shown to reduce the immunogenicity associated with infliximab treatment for rheumatoid arthritis.¹¹ In our cohort, only 3 patients used concomitant methotrexate; none of these patients developed antibodies to adalimumab. However, the sample number is too small to statistically analyze the effect of methotrexate on development of antibodies to adalimumab in our cohort.

Another factor in antibody formation may be related to patient genetics.¹⁰ Further investigation of this theory is needed. Also requiring more study is the finding of nonresponders to adalimumab therapy without evidence of antibody formation against adalimumab. The nonresponse of these patients cannot be explained based on current knowledge.

We analyzed few patients in our study. However, the small sample size should not be considered a limitation because the data analysis demonstrated statistically significant differences. Nevertheless, multiple regression analysis with a larger cohort could detect factors that might affect antibody formation such as concomitant methotrexate use and dosing interval changes.

In conclusion, antibodies to adalimumab are associated with lower serum adalimumab trough concentrations and with nonresponse or loss of response to adali-

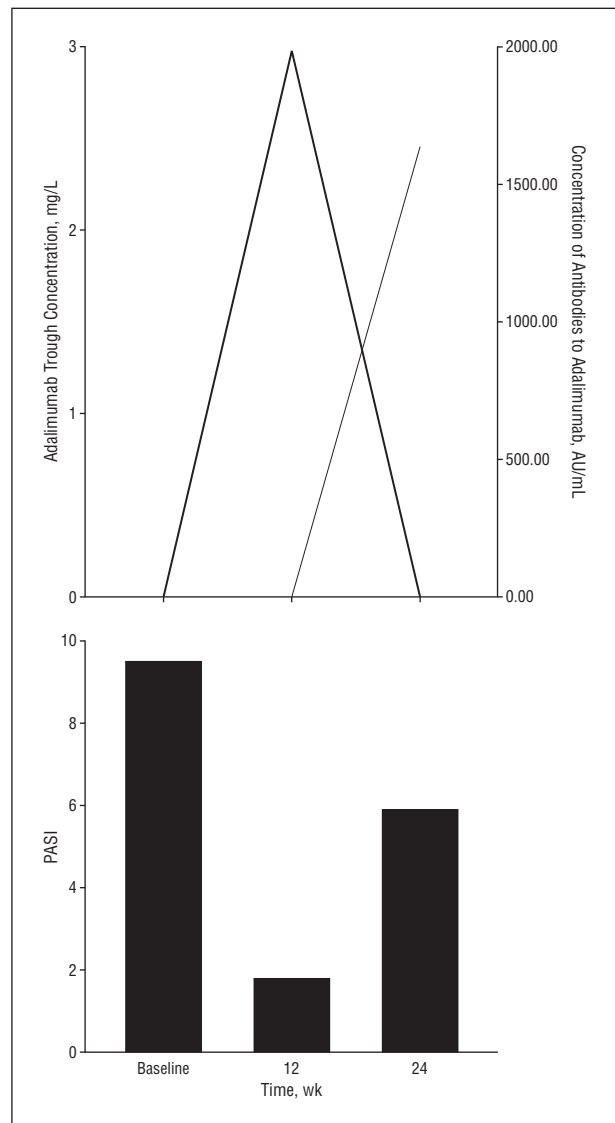


Figure 4. Data from a good responder at 12 weeks who developed a high titer of antibodies to adalimumab after week 12 and lost most response to treatment. PASI indicates Psoriasis Area and Severity Index; AU, arbitrary units.

mumab in patients with plaque psoriasis. We recommend testing for antibodies to adalimumab when patients lose response to adalimumab or do not respond at all, since spontaneous improvement is unlikely in the presence of high titers of antibodies to adalimumab. Further research is needed to identify risk factors for antibody development and factors affecting antibody development. Investigations are also needed to study how the effect of antibodies to adalimumab can be minimized.

Accepted for Publication: July 20, 2009.

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Author Contributions: Drs Lecluse and Wolbink had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Lecluse, Spuls, Bos, and

Wolbink. *Acquisition of data*: Lecluse, Driessen, de Jong, Stapel, and Wolbink. *Analysis and interpretation of data*: Lecluse, Spuls, Stapel, and Wolbink. *Drafting of the manuscript*: Lecluse, Spuls, and Wolbink. *Critical revision of the manuscript for important intellectual content*: Driessen, Spuls, de Jong, Stapel, van Doorn, Bos, and Wolbink. *Statistical analysis*: Lecluse, Spuls, and Wolbink. *Administrative, technical, or material support*: Lecluse, Driessen, van Doorn, and Wolbink. *Study supervision*: Lecluse, Spuls, Bos, and Wolbink.

Financial Disclosure: Dr de Jong has been involved in research funded by Biogen, Merck-Serono, Wyeth, Abbott, Schering-Plough, and Centocor; has received speaking and consulting fees from Biogen, Merck-Serono, Wyeth, Abbott, and Schering-Plough; and has received research grants from Merck-Serono and Wyeth.

Additional Contributions: Henk de Vrieze performed the assays. Menno de Rie, MD, PhD, helped in setting up the project. A consultant from the Clinical Epidemiology, Biostatistics, and Bioinformatics Department from the Academic Medical Center assisted with the statistical analysis.

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