Arthritis Care & Research
Vol. 62, No. 9, September 2010, pp 1335–1341
DOI 10.1002/acr.20211

ORIGINAL ARTICLE

Frequency and Effectiveness of Dose Increase of Adalimumab, Etanercept, and Infliximab in Daily Clinical Practice

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Objective. **To describe the frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in the treatment of rheumatoid arthritis (RA) in daily clinical practice.**

Methods. **All RA patients with a dose increase of tumor necrosis factor (TNF)–blocking therapy between January 1997 and January 2008 were selected from a register including data from RA patients starting a first TNF-blocking agent (the Dutch Rheumatoid Arthritis Monitoring registry). The primary outcome was change in Disease Activity Score in 28 joints (DAS28) at 3 months after dose increase. Secondary outcomes were the change in DAS28 at 6 months after dose increase, the European League Against Rheumatism response rates, and the percentages of patients reaching a DAS28 of ≤3.2 at 3 and at 6 months after dose increase. Furthermore, the effectiveness of dose increase was assessed for the different reasons for dose increase: nonresponse, loss of response, and partial response.**

Results. **During the study period, the dose was increased in 44 (12%) of the 368 adalimumab patients, 32 (8%) of the 420 etanercept patients, and 115 (36%) of the 323 infliximab patients. The change in DAS28 at 3 months and 6 months after dose increase was limited and only significant in etanercept patients at 3 months (−0.51; $P = 0.035$). Disease activity decreased significantly at 3 months from dose increase in the nonresponders and patients with loss of response (−0.66 and −0.99, respectively; both $P = 0.001$), but not in the partial responders.**

Conclusion. **Although dose increase was applied in all 3 TNF-blocking agents in daily clinical practice, these results suggest that the effectiveness of dose increase is limited.**

INTRODUCTION

Three tumor necrosis factor α (TNFα)–blocking agents are currently available for the treatment of rheumatoid arthritis (RA) in daily clinical practice in The Netherlands: infliximab, adalimumab, and etanercept. Each of these agents has proven to be efficacious in the treatment of RA, with response rates of up to 70% in the active treatment groups of randomized clinical trials (1–3). Despite these high response rates, the initial infliximab dose was increased in 31% of patients in daily clinical practice because of inadequate response to the initial dose during the first year of therapy (4), and in 7.1% and 4.8% of patients receiving adalimumab and etanercept, respectively.

Evidence about the effectiveness of dose increase of TNF-blocking therapy is, however, doubtful, and most studies have focused on infliximab. A dose increase of infliximab of 1.5 mg/kg was suggested to be effective in patients who had a lack of response or a flare response to infliximab at a dose of 3 mg/kg (5). Another study showed that a dose increase with 1 vial of 100 mg might be effective in patients with a partial loss of response to the initial infliximab dosing scheme (6). However, other studies

Data collection for the Dutch Rheumatoid Arthritis Monitoring cohort was supported by the Dutch National Health Insurance Board and the Dutch affiliations of Wyeth, Abbott, Schering-Plough, Roche, UCB, and Bristol-Myers Squibb.

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Dr. van Riel has received consultancy fees, speaking fees, and/or honoraria (less than $10,000 each) from Wyeth, Schering-Plough, Abbott, and Roche.

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Submitted for publication January 9, 2010; accepted in revised form March 31, 2010.

showed that the effect of a dose increase of infliximab was small (7,8) or not even better than continuing the initial dose after an incomplete response (9). In addition, increasing the dosage interval of adalimumab to 40 mg subcutaneously every week in patients with a lack of response to the initial dosage did not add benefit and was not more effective than shortening the dosage interval in the placebo group (10). So far, no studies have been published investigating the effectiveness of a dose increase in patients receiving etanercept. Furthermore, an important consequence of dose increase is the higher cost of therapy.

The current study was therefore conducted to further investigate and describe the frequencies and effectiveness of dose increase in 3 TNF-blocking agents, adalimumab, etanercept, and infliximab, in the treatment of patients with RA in daily clinical practice.

PATIENTS AND METHODS

Patients. For this descriptive study, data were used from the Dutch Rheumatoid Arthritis Monitoring registry. This registry includes patients with RA who started treatment with a TNF-blocking agent for the first time in daily clinical practice, and it was initially started in January 1997 in 1 hospital (the Radboud University Nijmegen Medical Centre). Since February 2003, the register contains data from 11 hospitals. At inclusion, patients were at least 18 years of age and fulfilled the 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria for RA (11). In addition, patients had to satisfy the Dutch criteria for reimbursement of TNF-blocking therapy: at least moderate to high disease activity (Disease Activity Score in 28 joints [DAS28] $\geq$3.2) and failure of $\geq$2 disease-modifying antirheumatic drugs (DMARDs), including optimal dosages of methotrexate (25 mg per week with a folic acid supplement). For this study, the ethics committee decided that no ethical approval was required.

Therapy. During the study period, the TNF-blocking agents available were adalimumab, etanercept, and infliximab. The choice of the TNF-blocking agent and the dosing scheme were at the discretion of the attending rheumatologist. In general, patients started with TNF-blocking agents following Dutch standard dosages: etanercept 25 mg given subcutaneously twice weekly (later changed to 50 mg subcutaneously weekly), adalimumab 40 mg given subcutaneously every 2 weeks, or infliximab 3 mg/kg given intravenously every 8 weeks after loading doses at weeks 0, 2, and 6. According to the Dutch product information, the infliximab dose can be increased if it is not effective from 12 weeks with steps of 1.5 mg/kg to a maximum dosage of 7.5 mg/kg every 8 weeks, or with a shortening of the dosage interval to a maximum of 3 mg/kg every 4 weeks. For adalimumab, the dosage interval may be shortened to 40 mg weekly if it is not effective. No recommendations have been formulated for the dose increase of etanercept. There was no fixed protocol for dose increase during the study period. Therefore, the decision to increase the dose of TNF-blocking therapy was at the discretion of the attending rheumatologist. Dose increase was possible without approval of the insurance companies. Treatment with a TNF-blocking agent could be combined with DMARDs and/or corticosteroids. Start and stop dates, doses, changes in doses, and the reasons for change were registered.

Outcomes and statistical analyses. All patients who started a first TNF-blocking agent prior to January 2008 were included in this analysis. Because we were interested in the effectiveness of dose increase in only those patients who continued the same TNF-blocking therapy, analyses were performed according to a per-protocol principle.

For the analyses, the total dosages of TNF-blocking therapy were calculated and expressed in mg per 2 weeks for adalimumab, in mg twice weekly for etanercept, and in mg/kg per 8 weeks for infliximab. In this calculation, changes in dosage interval were included.

At the start of the TNF-blocking therapy, patient characteristics were registered, including age, sex, disease duration, rheumatoid factor (RF) status, previous DMARDs received, and the presence of $\geq$1 erosions in the hands or feet. These characteristics were expressed as the mean $\pm$ SD or the median (interquartile range [IQR]) as appropriate. The 3 agents were compared using the Pearson's chi-square test for categorical data and using one-way analysis of variance or the Kruskal-Wallis nonparametric test for continuous data.

Disease activity was determined using the DAS28 (12), which was assessed by a trained study nurse at baseline, every 3 months for the first 2 years, and every 6 months thereafter. When the DAS28 was missing due to a missing value for the erythrocyte sedimentation rate, the erythrocyte sedimentation rate was imputed by means of single imputation by linear multivariate regression analysis using the values of the tender joint count, swollen joint count, and visual analog scale score for the general health of the patient.

We expected that increasing the dose of TNF-blocking therapy would be effective shortly after dose increase. Therefore, the primary outcome was the change in DAS28 at 3 months compared with the DAS28 before the dose increase using the paired Student's *t*-test. The secondary outcomes were the change in DAS28 at 6 months after dose increase compared with the DAS28 before the dose increase, the response rates defined by the European League Against Rheumatism (EULAR) response criteria (13) at 3 and at 6 months after dose increase, and the percentages of patients who reached a DAS28 of $\leq$3.2 at 3 and at 6 months after dose increase.

In order to identify a subgroup of patients in whom a dose increase might be more beneficial, the effectiveness of the dose increase was determined by the reason for the dose increase. Three reasons for dose increase were retrospectively defined: nonresponse, loss of response, and partial response. Nonresponse was defined as nonresponse according to the EULAR response criteria, loss of response was defined as an increase of $\geq$0.6 in the DAS28 at dose increase compared with the lowest DAS28 score before dose increase after an initial good or moderate EULAR response, and partial response was defined as an initial EULAR response without an increase of disease activity.

Primary and secondary analyses were repeated in the 3 subgroups.

All analyses were performed using the SPSS statistical package, version 16.0 (SPSS). *P* values less than 0.05 were considered significant.

RESULTS

Baseline characteristics. Between January 1997 and January 2008, a total of 1,111 patients started a TNF-blocking agent: 368 patients received adalimumab, 420 patients received etanercept, and 323 patients received infliximab as the initial agent. The maximum followup time was 55 months in the adalimumab patients, 96 months in the etanercept patients, and 94 months in the infliximab patients.

During this study period, the dose, interval, or both were increased in 44 (12.0%) of the 368 patients receiving adalimumab, in 32 (7.6%) of the 420 patients receiving etanercept, and in 115 (35.6%) of the 323 patients receiving infliximab. Dose increase was achieved for all patients receiving adalimumab by shortening the dosage interval; for the 32 etanercept patients, it was achieved by shortening the dosage interval in 20 (62.5%), by increasing the dose in 8 (25%), and by doing both in 4 (12.5%); and for the 115 infliximab patients, it was achieved by shortening the dosage interval in 49 (42.6%), by increasing the dose in 61 (53.0%), and by doing both in 5 (4.3%).

The median time to dose increase in this study was 10.5 months (IQR 14.3 months) in patients receiving adalimumab, 9.0 months (IQR 11.3 months) in patients receiving etanercept, and 6.0 months (IQR 3.0 months) in patients receiving infliximab. The dosage was increased from a mean of 40 mg every other week to a mean ± SD of 73.9 ± 18.5 mg every other week in the adalimumab patients, from a mean ± SD of 23.3 ± 4.7 mg to 36.5 ± 5.4 mg twice weekly in the etanercept patients, and from a mean ± SD of 3.3 ± 0.6 mg/kg to 5.2 ± 1.3 mg/kg every 8 weeks in the infliximab patients.

At 3 months, 6 (13.6%) of 44 adalimumab patients, 4 (12.5%) of 32 etanercept patients, and 8 (7.0%) of 115 infliximab patients had discontinued therapy within 3 months after dose increase, and at 6 months, 11 (25%) of the adalimumab patients, 5 (15.6%) of the etanercept patients, and 20 (17.4%) of the infliximab patients had discontinued therapy within 6 months after dose increase. According to the per-protocol analyses, the results of these data were not included in the analyses. A small number of patients did not reach 3 or 6 months of followup and were therefore censored: 5 (11.4%) of the adalimumab patients, 2 (6.3%) of the etanercept patients, and 1 (0.9%) of the infliximab patients at 3 months and 9 (20.5%) of the adalimumab patients, 4 (12.5%) of the etanercept patients, and 2 (1.7%) of the infliximab patients at 6 months. The DAS28 score at dose increase or 3 months thereafter was missing in 12 (36.4%) of the 33 patients remaining in the adalimumab group, 8 (30.8%) of the 26 patients in the etanercept group, and 32 (30.2%) of the 106 patients in the infliximab group. The DAS28 score at dose increase or 6 months thereafter was missing in 9 (37.5%) of the 24 remaining in the adalimumab group, 9 (39.1%) of the 23 remaining in the etanercept group, and 27 (29.0%) of the 93 remaining in the infliximab group. The missing scores were random because assessment visits had not taken place within the time window of the followup moments chosen for these analyses. In total, data from 21 (63.6%) of 33 adalimumab patients, 18 (69.2%) of 26 etanercept patients, and 74 (69.8%) of 106 infliximab patients were available for the primary outcome at 3 months and data from 15 (62.5%) of 24 adalimumab patients, 14 (60.9%) of 23 etanercept patients, and 66 (71%) of 93 infliximab patients were available for analyses of the secondary outcomes at 6 months.

For each agent, the characteristics at dose increase are shown in Table 1. Infliximab patients had a significantly longer disease duration ($P = 0.002$), were more often RF positive ($P = 0.050$), more often had an erosive disease ($P = 0.040$), and had failed more prior DMARDs ($P = 0.017$) than adalimumab patients and etanercept patients.

The effectiveness of dose increase of adalimumab, etanercept, and infliximab. The improvement in disease activity at 3 months after dose increase was small for all 3 TNF-blocking agents and was only significant in the patients receiving etanercept ($P = 0.035$) (Table 2). At 6 months after dose increase, no significant changes in disease activity were observed. Response rates at 3 and at 6 months were also limited, as were the percentages of patients reaching low disease activity (Table 2). The mean ± SD DAS28 scores reached at 3 and at 6 months after dose increase were 4.0 ± 1.3 and 3.7 ± 1.3 in the adalimumab patients, 4.0 ± 1.6 and 4.5 ± 1.3 in the etanercept patients, and 4.2 ± 1.0 and 3.8 ± 1.3 in the infliximab patients, respectively, which still reflected moderate disease activity.

The effectiveness of dose increase by reason for dose increase. The reason for dose increase could be defined in 150 (78.5%) of the 191 patients with a dose increase. In the other 41 patients (21.5%), data about the DAS28 at baseline, the lowest DAS28 before dose increase, and/or the DAS28 at the time of dose increase were missing.

Nonresponse was the reason for dose increase in 36 (24%) of the 150 patients, loss of response in 38 (25.3%) of the patients, and partial response in 76 (50.7%) of the patients. In the adalimumab group, most patients had a dose increase because of loss of response (41.2%). However, partial response was the most frequent reason for dose increase in the patients receiving etanercept (51.7%) and in those receiving infliximab (56.3%).

The characteristics of the patients by reason for dose increase at dose increase are shown in Table 3. As expected, the mean DAS28 at the time of dose increase was significantly higher in the nonresponders compared with the other 2 groups ($P < 0.0001$).

The mean DAS28 at the start of TNF-blocking therapy, the lowest DAS28 prior to dose increase, the DAS28 at dose increase, and the DAS28 at 3 and at 6 months thereafter for each reason for dose increase are shown in Figure 1. In the nonresponders, disease activity improved signif-

Table 1. Characteristics for each of the TNF-blocking agents at dose increase*

	Adalimumab (n = 44)	Etanercept (n = 32)	Infliximab (n = 115)	*P*
Women	30 (68.2)	22 (68.8)	84 (73.0)	ns
Age, mean ± SD years	52.3 ± 14.0	56.2 ± 12.6	57.5 ± 12.3	ns
Disease duration, median (25th, 75th percentile) years	7.1 (2.7–11.7)	4.0 (1.7–9.6)	9.6 (3.9–16.3)	0.002
Rheumatoid factor	27 (64.3)†	25 (78.1)	95 (82.6)	0.050
Erosions‡	27 (61.4)	14 (45.2)§	40 (72.7)¶	0.040
DAS28 at increase, mean ± SD#	4.1 ± 1.2	4.3 ± 1.1	4.3 ± 1.4	ns
HAQ at increase, mean ± SD**	1.0 ± 0.6	1.4 ± 0.7	1.2 ± 0.7	ns
Prior DMARDs, median (25th, 75th percentile)	3 (2–4)	3 (2–3)	3 (2–5)	0.017
Concomitant MTX	29 (65.9)	18 (56.3)	87 (75.7)	ns
Concomitant other DMARD	18 (40.9)	18 (56.3)	62 (53.9)	ns
Concomitant oral corticosteroids	13 (29.5)	11 (34.4)	32 (27.8)	ns

* Values are the number (percentage) unless otherwise indicated. TNF = tumor necrosis factor; ns = not significant; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate.
† Percentage taken from 42 patients.
‡ At least 1 erosion in hands or feet.
§ Percentage taken from 31 patients.
¶ Percentage taken from 55 patients.
# Data were missing in 4 (9.1%) of 44 patients receiving adalimumab, in 2 (6.3%) of 32 patients receiving etanercept, and in 10 (8.7%) of 115 patients receiving infliximab.
** Data were missing in 5 (11.4%) of 44 patients receiving adalimumab, in 3 (9.4%) of 32 patients receiving etanercept, and in 41 (35.7%) of 115 patients receiving infliximab.

icantly at 3 and at 6 months ($P = 0.001$ and $P = 0.014$) (Table 4). However, only 12% of the nonresponders reached low disease activity. In the patients with a dose increase due to loss of response, disease activity improved significantly only at 3 months, but not at 6 months ($P = 0.001$ and $P = 0.221$, respectively) (Table 4). Disease activity did not change in the partial responders at either 3 or at 6 months after dose increase (Table 4).

DISCUSSION

This study was conducted to describe the frequency and effectiveness of dose increase in 3 TNF-blocking agents, adalimumab, etanercept, and infliximab, in the treatment of patients with RA in daily clinical practice. This study showed that in one-third of the patients receiving infliximab, the initial dose was increased. In patients receiving adalimumab or etanercept, these proportions were considerably lower. If the dose was increased, the effectiveness was very small or lacking for all 3 of the TNF-blocking agents.

In the subgroups by reason for dose increase, the effectiveness of dose increase was determined in order to identify a group of patients in whom dose increase might be beneficial. Our results suggest that dose increase might be effective in primary nonresponders, although the disease activity remained moderate at 3 and 6 months after dose increase. The effect of dose increase was small in patients with loss of response and in partial responders to the initial dose.

The effectiveness of the dose increase found in our study in the patients receiving infliximab is comparable with the effectiveness found in previous studies by van Vollenhoven et al, van Vollenhoven and Klareskog, and Pavelka et al (7–9), which concluded that the gain of dose increase of infliximab was small, or not even better than that in the control group in which the dose was not increased. In contrast, another study in which the effect of dose increase after nonresponse or loss of response to infliximab was investigated showed an ACR 20% improvement criteria response rate in up to 80% of the subjects (5). In a study by Bartelds et al, dose increase led to a mean ± SD decrease

Table 2. The effectiveness of dose increase at 3 and at 6 months after dose increase for each of the TNF-blocking agents*

	Adalimumab (n = 44)	Etanercept (n = 32)	Infliximab (n = 115)
Primary outcome: change in DAS28 at 3 months, mean ± SD	−0.25 ± 1.04	−0.51 ± 0.94†	−0.22 ± 1.30
Secondary outcomes			
Response at 3 months‡	9/21 (42.9)	9/18 (50)	26/74 (35.1)
DAS28 at 3 months ≤3.2	8/21 (38.1)	6/19 (31.6)	18/77 (23.4)
Change in DAS28 at 6 months, mean ± SD	−0.27 ± 0.74	0.15 ± 1.34	−0.26 ± 1.31
Response at 6 months	3/15 (20)	2/14 (14.3)	22/66 (33.3)
DAS28 at 6 months ≤3.2‡	7/17 (41.2)	4/14 (28.6)	19/70 (27.1)

* Values are the number/total (percentage) unless otherwise indicated. All analyses were performed per protocol. See Table 1 for definitions.
† Significant within patient.
‡ Defined as a good or moderate European League Against Rheumatism response.

Table 3. Baseline characteristics by reason for dose increase*

	Nonresponse (n = 36)†	Loss of response (n = 38)†	Partial response (n = 76)†	*P*
Women	25 (69.4)	26 (68.4)	53 (69.7)	ns
Age, mean ± SD years	59.1 ± 13.9	53.6 ± 12.1	55.8 ± 12.0	ns
Disease duration, median (25th, 75th percentile) years	11.0 (4.3–16.4)	6.8 (3.7–11.9)	7.0 (3.1–13.9)	ns
Rheumatoid factor	27 (77.1)‡	28 (73.7)	61 (80.3)	ns
Erosions§	20 (64.5)	22 (73.3)	32 (60.4)	ns
DAS28 at increase, mean ± SD	5.5 ± 1.1	4.5 ± 1.0	3.7 ± 1.1	< 0.0001
HAQ at increase, mean ± SD¶	1.6 ± 0.7	1.1 ± 0.7	1.1 ± 0.7	0.004
Prior DMARDs, median (25th, 75th percentile)	3 (3–4)	3 (2–4)	3 (2–4)	ns
Concomitant MTX	27 (75.0)	31 (81.6)	46 (60.5)	ns
Concomitant other DMARD	15 (41.7)	17 (44.7)	41 (53.9)	ns
Concomitant oral corticosteroids	15 (41.7)	12 (31.6)	16 (21.1)	ns

* Values are the number (percentage) unless otherwise indicated. See Table 1 for definitions.
† Reason for discontinuation could not be determined due to missing values of the DAS28 score at baseline, at dose escalation, or the lowest DAS28 score before dose escalation in 10 (22.7%) of 44 in the adalimumab group, 3 (9.4%) of 32 in the etanercept group, and 28 (24.3%) of 115 in the infliximab group.
‡ N = 35 patients.
§ At least 1 erosion in the hands or feet. For nonresponse n = 31 patients, for loss of response n = 30 patients, and for partial response n = 53 patients.
¶ Data were missing in 6 (16.7%) of 36 in the nonresponse group, in 2 (5.3%) of 38 in the loss of response group, and in 15 (19.7%) of 76 in the partial response group.

in DAS28 of 1.7 ± 1.2 in 7 nonresponders to adalimumab (14). So far, no studies to our knowledge have been published investigating the effect of a dose increase in patients receiving etanercept in daily clinical practice. It should be noted that all of the abovementioned studies were observational studies except the one by Pavelka et al (9). As reported by van Vollenhoven, those improvements shown in observational studies might represent regression to the mean (15). This could very well explain the contradictory results mentioned above.

There are a few possible explanations for why a dose increase was more frequently observed in patients receiving infliximab than in those receiving adalimumab or etanercept in our study. First, recommendations for dose increase or shortening of the dosage interval are described in the product information of infliximab and adalimumab, but not in that of etanercept. Therefore, it was surprising

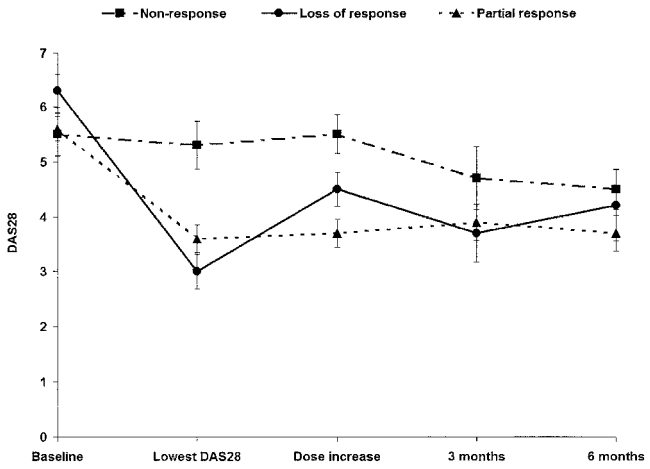

Figure 1. Mean (95% confidence interval) Disease Activity Score in 28 joints (DAS28) at baseline, lowest DAS28, DAS28 at dose increase, and DAS28 at 3 months and 6 months thereafter by reason for dose increase.

that the dose of etanercept was increased in 8% of the patients of our study population, which was able to happen because dose increase was independent of approval of the insurance companies in The Netherlands. Second, because infliximab was the first TNF-blocking agent available, physicians might have been inclined to try a dose increase in case of lack of effect because other options were not available yet. However, this did not affect the effectiveness of the dose increase in infliximab, which was comparable when only analyzing those patients who started infliximab after the availability of adalimumab and etanercept (data not shown). Third, the possibilities for the dose increase of infliximab may be more subtle. A fourth possible explanation may be the difference in immunogenicity between the 3 TNF-blocking agents, because previous studies have shown that patients receiving infliximab have more antibody formation than patients receiving adalimumab (14,16–18). Antibody formation may be associated with lower or undetectable serum levels of the agent and may lead to adverse events and loss of effect (14,16–19). Dose increase can be the solution to induce higher serum levels of the agent and to maintain low disease activity (5,14,16). Unfortunately, antibody formation and serum levels of the agents were not assessed in our study.

The observational design of this study had advantages and disadvantages. The results of this study reflect the effect of TNF-blocking agents in daily clinical practice closely. On the other hand, the percentage of missing data is considerable. Missing data could have resulted in an overestimation of the effect if nonresponders especially had missing data. However, data were mostly missing at random, and patients were assessed even when they stopped receiving TNF-blocking agents. Furthermore, because the results of this study are already negative, we do not think that complete data could have changed our conclusions. Another limitation inherent to observational designs is the lack of a control group. It would have been

Table 4. The effectiveness of dose increase at 3 and at 6 months after dose increase by reason for dose increase*

	Nonresponse (n = 36)	Loss of response (n = 38)	Partial response (n = 76)
Primary outcome: change in DAS28 at 3 months, mean ± SD†	−0.66 ± 0.92‡	−0.99 ± 1.15‡	0.05 ± 1.04
Secondary outcomes			
Response at 3 months§	11/25 (44)	13/22 (59.1)	16/52 (30.8)
DAS28 at 3 months ≤3.2	3/25 (12)	10/22 (45.5)	16/52 (30.8)
Change in DAS28 at 6 months, mean ± SD¶	−0.86 ± 1.30‡	−0.33 ± 1.15	−0.12 ± 1.14
Response at 6 months	9/17 (52.9)	5/19 (26.3)	11/46 (23.9)
DAS28 at 6 months ≤3.2§	2/17 (11.8)	4/19 (21.1)	18/46 (39.1)

* Values are the number/total (percentage) unless otherwise indicated. All analyses were performed per protocol. See Table 1 for definitions.
† At 3 months, 6 (16.7%) of the 36 nonresponders, 2 (5.3%) of the 38 patients with loss of response, and 7 (9.2%) of the 76 partial responders to the initial dose discontinued therapy within 3 months after dose increase, and none, 2 (5.3%), and 3 (3.9%) were censored, respectively, because they did not reach 3 months of followup at the end of the study period. The DAS28 score at dose increase or 3 months thereafter was missing in 5 (16.7%) of the 30 nonresponders, 12 (35.3%) of the 34 patients with loss of response, and 14 (21.2%) of the 66 partial responders to the initial dose.
‡ Significant within patient.
§ Response is defined as good or moderate European League Against Rheumatism response.
¶ At 6 months, 11 (30.6%) of the 36 nonresponders, 6 (16.7%) of the 38 patients with loss of response, and 11 (14.5%) of the 76 partial responders to the initial dose discontinued therapy within 6 months after dose increase, and 1 (2.8%), 5 (13.2%), and 6 (7.9%) were censored at 3 months, respectively, because they did not reach 6 months of followup at the end of the study period. The DAS28 score at dose increase or 6 months thereafter was missing in 7 (29.2%) of the 24 nonresponders, 8 (29.6%) of the 27 patients with loss of response, and 13 (22.0%) of the 59 partial responders to the initial dose.

interesting to compare the effectiveness of the dose increase of TNF-blocking therapy with the effectiveness of therapy on a stable dose. However, the observational design of this study was not appropriate for this kind of analysis. The most important reason for this is that the results might be confounded by indication because patients who need a dose increase will have a more active and therapy-resistant disease than those who do not need a dose increase. However, the fact that we showed no additional effect of dose increase (i.e., a negative result) makes the chance for a false-positive result zero. Therefore, there is no need for a control group seen from a methodologic point of view, and we only analyzed the effectiveness of dose increase within the patients who needed a dose increase. On the other hand, we observed that a dose increase might be beneficial in primary nonresponders. In order to investigate whether this is a real effect or regression to the mean, further research with a control group is needed.

An important consequence of dose increase is the higher cost of therapy. A dose increase in 8–36% of patients will result in an increase of 40–80% of the total costs of TNF-blocking agents (data not shown). Furthermore, van Vollenhoven estimated that worldwide, approximately €1 billion has been spent unnecessarily on infliximab (15). Additionally, Pavelka et al showed that the number of serious adverse events was higher in higher dose groups (9). The increase in costs and adverse events related to dose escalations stress the urgency of raising awareness among rheumatologists that antirheumatic drugs should be used optimally. Furthermore, the fact that the effectiveness of a dose increase of TNF-blocking therapy was very limited in our study raises the question of whether other therapeutic options might be more (cost-) effective in patients with inadequate response to TNF-blocking therapy.

In conclusion, the results of this descriptive study suggest that although dose increase is frequently applied in adalimumab, infliximab, and etanercept in daily clinical practice, the effectiveness of dose increase is limited. Only in nonresponders to the initial dose, dose increase might be beneficial, although disease activity was still moderate after dose increase. Therefore, the effectiveness of other therapeutic strategies, such as switching to a second TNF-blocking agent or a biologic agent with another mechanism of action, should be further investigated in patients with inadequate response to the first TNF-blocking agent.

ACKNOWLEDGMENTS

The authors would like to thank all of the research nurses and rheumatologists of the 11 departments of rheumatology for their participation and contribution in the data collection. Furthermore, the authors acknowledge T. van Gaalen, L. Schalkwijk, and C. Versteegden for the data processing, H. Groenewoud for the assistance in managing the database, and Drs. M. Creemers and A. van Ede for training the research nurses in assessing joint counts.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Blom had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Blom, Kievit, Kuper, Jansen, Visser, van de Laar, van Riel.

Acquisition of data. Blom, Kuper, Jansen, Visser, den Broeder, Brus, van de Laar.

Analysis and interpretation of data. Blom, Kievit, van de Laar, van Riel.

ROLE OF THE STUDY SPONSOR

Funding of the Dutch National Health Insurance Board and the Dutch affiliations of Wyeth, Abbott, Schering-Plough, Roche, UCB, and Bristol-Myers Squibb enabled the data collection for the Dutch Rheumatoid Arthritis Monitoring cohort. The study sponsors had no influence on the study design, data analysis, and

writing of the manuscript. The study sponsors approved the final version to be submitted for publication.

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