Concise Report

Titration of infliximab treatment in rheumatoid arthritis patients based on response patterns

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Objectives. To observe the course of the disease activity in rheumatoid arthritis (RA) patients treated with the standard infliximab dosing regimen and to adjust treatment guided by the pattern of disease activity.

Methods. All RA patients starting infliximab treatment were included and observed for at least 37 weeks. At infusion 4 (week 14), European League Against Rheumatism response was assessed. In moderate responders the dose was unchanged and the disease activity was carefully observed. In case of stable disease activity, the dose was increased at infusion 5 (week 22). In case of a temporary response the interval was reduced. Paired t-testing was applied to the disease activity score with 28-joint counts (DAS28) at week 22 and study endpoint.

Results. A total of 76 patients were included. Response after 14 weeks: good 22 (29%) patients, moderate 26 (34%) patients, and non-response in 21 patients. Seven patients (9%) dropped out before week 14 due to adverse events (5) or patients’ initiative (2). In patients with moderate response, the following disease course between infusion 4 and 5 was observed: improvement to good response 6, temporary response 6, stable disease activity 6, drop out 8. In moderate responders, interval reduction and dose increase resulted in a decrease in mean DAS28 from 5.1 to 3.6 \(P = 0.005\), mean interval 5.6 weeks, mean infliximab dose 4.8 mg/kg/8 week (endpoint) and from 4.1 to 3.6 \(P = 0.04\), mean infliximab dose 7.3 mg/kg/8 week (endpoint), respectively.

Conclusion. Three different patterns of disease activity were observed in moderate responders after 14 weeks of infliximab treatment, i.e. further improvement, no change in disease activity or a temporary response. Both interval reduction and dose increase significantly reduced disease activity, however, with different mean infliximab dosages. In good responders the response was often sustained over follow-up, whereas non-responders showed modest or no improvement despite dose adjustments.

Key words: Rheumatoid arthritis, Infliximab, Disease activity, Titration.

Introduction

Infliximab, a chimeric monoclonal antibody directed against tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), is efficacious in rheumatoid arthritis (RA) [1]. The recommended starting dose is 3 mg/kg, administered by intravenous infusion at weeks 0, 2 and 6 and every 8 weeks thereafter [2]. However, this dosage regimen seems to be insufficient in a subset of RA patients. In clinical practice, both dose increase (up to 10 mg/kg every 8 weeks) and interval reduction (to minimal 4 weeks) are being used [3–5].

At present no clear recommendations exist regarding the strategy that should be used in case of moderate or non-response. Previous studies have shown that dose titration as well as interval titration with TNF-\(\alpha\) blocking agents can be used to achieve disease activity improvement in individual RA patients [6, 7]. A large variation in dosage as well as in time interval was shown in these studies in order to maintain low disease activity.

In this open-label study, we evaluated the course of the disease activity with a disease activity score with 28-joint counts (DAS28) and the European League Against Rheumatism (EULAR) response criteria in RA patients starting infliximab treatment. In addition to this, the effect of dose increase and interval reduction on the disease activity was investigated in those patients who had a moderate response after 22 weeks. The decision to increase the dose or to reduce the interval was based on observations of the course of the DAS28 in the period between the 4th and 5th infusion.

Patients and methods

Study design

All consecutive patients with RA, according to the American College of Rheumatology (ACR) criteria [8], starting infliximab therapy between April 2002 and January 2004, were prospectively followed. According to the Dutch guidelines for biological therapies, infliximab was started in RA patients with active disease (DAS28 ≥ 3.2) after treatment failure of at least two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate up to 25 mg/week.
Infliximab treatment in RA patients based on response patterns

Evaluations
At the start of infliximab treatment, the following data were collected: age, sex, disease duration, rheumatoid factor (RF) positivity, the number of previously used DMARDs and the use of concomitant DMARDs and systemic corticosteroids. Follow-up visits took place on each infusion day just prior to infusion; in moderate responders, additional visits were made at weeks 18 and 20 (between the 4th and 5th infusion). Disease activity was assessed at each visit, using the DAS28, which is a validated composite score of the erythrocyte sedimentation rate tender and swollen joint count and the visual analogue scale general health of the patient [9]. Treatment response was evaluated at week 14 (4th infusion), using the EULAR response criteria [10], dividing patients into good, moderate and non-responders. All patients were followed for 38 weeks of infliximab treatment (37–41 weeks in patients who received an interval reduction). Reasons for discontinuation were recorded, if appropriate.

Treatment
Infliximab was started in the standard dosing regimen of 3 mg/kg body weight with infusions at week 0, 2, 6 and every 8 weeks thereafter. Doses were rounded off to 200 mg for patients with a body weight <70 kg and to 300 mg for patients of 70 kg or more.

Good responders. Infliximab was continued at 8-week intervals until week 38. If disease activity increased during follow-up, dose increases were possible after week 22.

Moderate responders. The dose was kept stable between week 14 (4th infusion) and week 22 (5th infusion). At week 22, infliximab treatment was tailored according to the course of the disease activity between weeks 14 and 22. Moderate responders with a stable disease activity in this period were assigned to the dose increase group in which the dose was increased to 6 mg/kg every 8 weeks. Prior to every upcoming infusion, disease activity was re-evaluated. If the DAS28 remained ≥3.2, the dose was further increased to 10 mg/kg/week.

According to the flare criteria [6], patients received an interval reduction if the DAS28 showed, after an initial improvement, an increase of more than 1.2 points between weeks 14 and 22, or an increase of more than 0.6 points up to a value above 5.1. (Fig. 1B). The new interval was calculated by subtracting 1 week from the week in which the patient flared. If the patient flared again despite the interval reduction, the interval was further reduced stepwise to a minimum of 4 weeks.

To be eligible for the tailored treatment protocol, patients were not allowed to have received changes in concomitant DMARDs within 6 weeks prior to baseline or changes in corticosteroids (oral or intramuscular) after week 8 of baseline until the end of the study.

Non-responders. The dose was increased to 6 mg/kg/week at week 14. Dose increases up to 10 mg/kg/week were possible in case of a persisting non-response. Patients who stopped before week 38 because of inefficacy were considered non-responders.

Statistical analysis
Normal distribution of the DAS28 was verified (Shapiro–Wilk’s statistic). Two-sided paired t-testing (P-value <0.05) was applied to the DAS28 at week 22 and at the end of the study for moderate responders in the dose increase group and in the interval reduction group. Analyses were done on an intention-to-treat basis. SPSS software was used for statistical analyses (version 11.0, SPSS inc., USA).

Results
A total of 76 RA patients started infliximab. Baseline characteristics were: mean age at start 55.7 yr [standard deviation (s.d.) 13.2], male sex 34%, median disease duration 7.4 yr (range 1.0–35.8), RF positivity 82%, mean DAS28 5.4 (s.d. 1.1) and median number of prior used DMARDs three (range 2–8). At the start of infliximab treatment, 67 patients (88%) used concomitant DMARDs, 55 (72%) used one DMARD and 12 (16%) used two DMARDs. Nineteen patients (25%) used prednisolone with a median dose of 8 mg/day (range 5–15). Seven (9%) patients were on infliximab monotherapy. Figure 2 shows the study flowchart with patient distribution.

Response to treatment at week 14
Twenty-two patients (29%) were good responders, 26 patients (34%) moderate responders and 21 patients (28%) were non-responders. Seven patients (9%) had stopped infliximab before week 14 [5 adverse events (AEs) and 2 patients’ initiative, see Fig. 2].

Good responders
Twenty-one out of 22 were still on infliximab at the end of the study. Thirteen patients (59%) had remained in their good-responder status, seven patients (32%) had a moderate response and one patient (5%) had changed into a non-responder, compared with baseline disease activity. One patient had discontinued infliximab because of an AE. Three patients had received a dose increase after week 14. No interval reductions were applied. The mean DAS28 was 4.9 (s.d. 0.9), 2.4 (s.d. 0.7) and 2.9 (s.d. 1.1) at baseline, week 14 and week 38 (39% change at week 14.

Fig. 1. (A) Mean DAS28 (s.d.) over time in patients with a good response and with a non-response at week 14. (B) Mean DAS28 (s.d.) over time in patients with a moderate response at week 14.
to baseline DAS28), respectively (Fig. 1A). The mean infliximab dose had increased from 3.6 mg/kg/8 week at the start to 3.9 mg/kg/8 week.

Concomitant therapy changes after week 14 in good responders. Concomitant DMARD therapy was reduced in four patients and stopped in three (one low disease activity and two AE). Oral prednisolone (median 6.5 mg/day at start, range 5–10) was reduced in three patients and stopped in one due to low disease activity. One patient received an intramuscular corticosteroid injection after an increase in disease activity.

Moderate responders

In the patients who were classified as moderate responders at week 14, three different patterns of disease activity were observed in the period between week 14 and 22: (A) improvement to good response \((n = 6)\), (B) stable pattern of disease activity \((n = 6)\) and (C) flare of disease activity after an initial improvement \((n = 6)\) (Fig. 2). Eight patients dropped out between weeks 14 and 22: four protocol violation, three AEs, one patient initiative. In the remaining moderate responders, concomitant DMARD treatment (used by 15 patients) and prednisolone treatment (used by two patients, median 8 mg/day, range 6–10) were kept stable throughout the study.

In patients who flared, the interval was reduced to 7 \((n = 1)\), 6 \((n = 3)\) and 5 weeks \((n = 3)\). One patient flared in the next interval and received a further interval reduction from 6 to 5 weeks. After reducing the interval, the DAS28 decreased by 1.5 (mean, s.d. 0.7). The mean DAS28 was 5.1 (s.d. 1.0) at week 22 and 3.6 (s.d. 0.8) at the endpoint \((P = 0.005, \text{compared with week 22})\). The mean interval was 5.6 weeks and the mean infliximab dose increased from 3.8 mg/kg/week at week 22 to 4.8 mg/kg/week at the endpoint.

In patients with a stable disease activity pattern, the dose was increased to 6 mg/kg/week at week 22. Two patients received a further dose increase to 10 mg/kg/week at week 30. The mean DAS28 was 4.1 (s.d. 0.7) at week 22 and 3.6 (s.d. 1.0) at the endpoint \((P = 0.04, \text{compared with week 22})\). The mean infliximab dose had increased from 4.0 mg/kg/week at week 22 to 7.3 mg/kg/week at the endpoint.

Patients who improved to good responders at week 22 remained good responders. The mean DAS28 was 2.7 (s.d. 0.4) at week 22 and 2.7 (s.d. 0.2) at week 38. No dose or interval adjustments were applied. The mean infliximab dose was 3.7 mg/kg/8 week.

Non-responders

At week 14, one patient was lost to follow-up and two patients stopped treatment due to inefficacy. All other patients received a dose increase. At the endpoint, 15 patients had continued treatment and three patients had stopped due to inefficacy. Four patients had received a further dose increase and three patients had received an interval reduction. Five patients improved to moderate responders and 10 patients remained non-responders.

The DAS28 decreased by 0.4 (median, range –1.6–3.3). The mean DAS28 was 5.5 (s.d. 1.2), 5.3 (s.d. 1.4) and 5.0 (s.d. 1.3) at baseline, week 14 and week 38 (9% change to baseline DAS28), respectively (Fig. 1A). The mean infliximab dose had increased from 3.4 mg/kg at the start to 5.7 mg/kg/8 week.

Concomitant therapy changes after week 14 in non-responders. Concomitant DMARD therapy was increased in two but, reduced in two patients because of side-effects and stopped in four (three inefficacy and one AE). Prednisolone dose (median 10 mg/day at start, range 5–15) was increased in two patients and started in one patient. Four patients received an intramuscular corticosteroid injection after week 14.

End of study evaluations

Overall, at the study endpoint, 25 patients (33%) were good responders, 19 (25%) moderate and 18 (24%) were non-responders (including five patients who had stopped due to inefficacy). Nine patients (12%) had stopped due to AEs and five (7%) due to other reasons. The AEs as reason for discontinuation were: two infusion reactions (patients on concomitant hydroxychloroquine and azathioprine, respectively), one drug-induced lupus erythematosus after 7 weeks of infliximab monotherapy [characterized by anti-nuclear antibodies (ANA) and anti double-stranded DNA (anti-ds-DNA) positivity, anaemia, thrombocytopenia, polyarthritis and proteinuria], one urosepsis with suspicion of bacterial discitis, one radicular...
syndrome, one wound abscess, one popular skin eruption, one diarrhoea and one hypertension. Two of these patients were hospitalized (urosepsis and radicular syndrome).

**Discussion**

In the present study, disease activity was closely observed in RA patients starting infliximab treatment. After 14 weeks of treatment, 29% had a good response, 34% had a moderate response, 28% were non-responders and 9% had stopped treatment. In most good responders the response was sustained over follow-up. In moderate responders, remarkably three different patterns of disease activity were observed between the 4th and 5th infusion: (A) further improvement to good response, (B) a constant moderate pattern of disease activity and (C) a flare of disease activity after an initial improvement. Non-responders showed modest or no improvement despite dose adjustments.

The different response patterns seen in moderate responders might be explained by individual variations in pharmacokinetics of infliximab [11]. Serum trough concentrations of infliximab show large differences between individual patients and correlate with response [11, 12]. It has been hypothesized that patients who flare during the 8-weekly interval receive adequate therapeutic dosages, but eliminate infliximab more rapidly from the bloodstream than do patients with a constant response pattern.

Treatment adjustments of infliximab occur frequently in daily clinical practice [3, 4]. The rationale for dose increases up to 10 mg/kg/8 week was provided by the ATTRACT trial, in which part of the outcome measurements showed a dose–response relationship [1]. The pharmacokinetic modelling study of the ATTRACT data showed that interval reduction might be more effective in raising serum infliximab concentrations than dose increase [11]. At present, no randomized controlled trial has been conducted to investigate the benefit of these two options.

In the present open-label study, infliximab treatment was tailored, guided by the observed disease activity patterns, in patients with a moderate response after 14 weeks of treatment in an open-label trial setting. Interval reduction and dose increase, both resulted in a statistically significant reduction in disease activity (despite the small number of patients receiving the adjustments). The infliximab dose was 1.5-fold higher in patients receiving a dose increase than in patients receiving an interval reduction (after recalculation to 8-weekly intervals). Costs are estimated after dose increase on 3506 euro plus 316 euro (cost receiving a dose increase than in patients receiving an interval adjustments). The infliximab dose was 1.5-fold higher in patients with high disease activity despite treatment adjustments.

**Key messages**

- Different patterns of disease activity can be observed in moderate responders to infliximab treatment
- Titration based on response patterns significantly reduced disease activity.

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**References**