Concise Report

Dose escalation of infliximab therapy in arthritis patients is related to diagnosis and concomitant methotrexate treatment: observational results from the South Swedish Arthritis Treatment Group register

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Objective. To study frequency of dose escalation in infliximab-treated patients and to identify possible predictors thereof.

Methods. Patients with chronic arthritis initiating their first course of anti-TNF treatment with infliximab at Lund University Hospital were included in a structured clinical follow-up protocol. Information on diagnosis, drug dosage, disease duration, previous and ongoing DMARDs, treatment start and cessation were prospectively collected during the period March 1999 through February 2007. All patients were started on a dose of 3 mg/kg at time 0, week 2, week 6 and then every eighth week independent of diagnosis and were followed for a period of 2 yrs.

Results. A total of 206 patients were included in the study. Thirty-two of the patients had PsA, 25 had AS and 149 patients had RA. A minor dose escalation, defined as less than doubling of the dosage, was observed for 53, 48 and 42% of the patients with PsA, AS and RA, respectively. The corresponding values for major dose escalation was observed for 19, 8 and 15% of the patients, respectively. Regression analysis showed that patients with a diagnosis of PsA (P = 0.03), longer follow-up period (P < 0.01), and lack of concomitant MTX treatment (P = 0.03) were significantly associated with risk of dose escalation.

Conclusion. Dose escalations were performed in 59% of all infliximab-treated patients during the first 2 yrs of treatment. Our data suggest that PsA patients might require higher dosages than RA and AS patients.

KEY WORDS: Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Spondarthritis, Anti-TNF-α therapy, Biologics register, Infliximab.

Introduction

Since the introduction of the TNF blocking agent infliximab, it has been acknowledged that some patients require dosage increments to achieve sufficient response [1–8]. There are differences in the recommended dosages depending on the diagnosis. However, as opposed to RA, to date no proper dose-finding studies have been performed for PsA or AS [9].

Also potential predictors of dose escalation have not been thoroughly studied [4]. These composite questions with potentially great impact on clinical decision making will probably not be addressed adequately using randomized controlled trials. Thus, evidence may rely on long-term prospective observational studies.

This study compares the frequencies of dose escalation of infliximab over a 2-yr period in patients with AS, PsA and RA receiving the same initial dose of 3 mg/kg every eighth week. The patients were followed using a structured clinical protocol developed by the South Swedish Arthritis Treatment Group (SSATG) [10, 11]. Furthermore, the objective was to identify potential predictors of dose escalation in this cohort.

Patients and methods

Data were collected in a database following a structured clinical protocol designed for drug monitoring as described previously [10, 11]. No formal approval from the ethical committee was necessary, as the protocol was designed to meet the legal documentation required in Sweden.

The patients were treated with anti-TNF therapy at the Department of Rheumatology, Lund University Hospital according to local guidelines, infliximab was infused at 3 mg/kg, rounded to the nearest 100 mg, at 0, 2, 6 and then every eighth week regardless of diagnosis. Thus, it should be noted that the initial infliximab dose for PsA and AS was 3 mg/kg. Subsequently, the treating physician could increase the dosage of infliximab in steps of 100 mg to a maximum of 500 mg administered at 4- to 8-week intervals. Dose adjustments were performed immediately prior to each scheduled infliximab administration based on clinical evaluation and relevant blood tests.

Method

Clinical data were prospectively collected immediately prior to infliximab infusions. At inclusion, the following data were recorded: year of disease onset, previous and concomitant DMARD treatment and systemic prednisolone dosage. At inclusion and at each follow-up visit the dose of administered infliximab was registered.

Arbitrarily, a dose escalation of <100% was defined as a minor dose escalation, whereas a dose escalation of ≥100% was defined as a major dose escalation.
Statistical analysis

Absolute differences between dose escalation in PsA, AS and RA patients according to definitions above were compared using chi-square test. Independent predictors of dose escalation were identified using a logistic regression model and association models. Subsequently, the predictors of dose escalation were modelled using a multivariate binary logistic regression model. The following variables were included in the analysis: age at inclusion, gender, disease duration at inclusion, baseline HAQ, baseline DAS28, baseline CRP-level, prednisolone usage, number of months after treatment initiation, diagnosis and concomitant DMARD. Assumptions for using the multivariate logistic regression model were checked and found valid. Level of significance was chosen to be $P < 0.05$.

Results

During the observational period, a total of 288 patients were enrolled in the study. In 59 patients dosing data were missing and 23 of the patients stopped therapy before finishing the initial loading phase. These patients were therefore excluded from the study (Fig. 1). Thus, 206 patients were eligible for the study. There were no statistical differences in age, sex, disease duration and concomitant DMARD usage between the drop-outs and the patients included in the study (data not shown).

Demographic data and clinical characteristics of patients ($n = 206$) studied are summarized in Table 1. In general, characteristics of patients included resemble patients with long-standing disease and previous failure of conventional DMARDs.

Dose escalation

Of all the infliximab-treated patients, 59% required dose escalation during the 2-yr follow-up period. A minor dose escalation, defined as less than doubling the dose, was made for 53, 42 and 48% of the patients with PsA, RA and AS, respectively (Table 2). The corresponding values for major dose escalation were 19, 15 and 8%, respectively. The absolute risk of any dose escalation when comparing the different diagnoses was not significant ($P = 0.12$). The dose escalations were performed by increasing the administered dosage in 28% of the patients, while 32% of the patients increased the frequency of infliximab administration. However, the remaining 40% of the patients had both increased dosage as well as dosing frequency.

There were no statistical differences in survival on drug between patients with PsA, RA or AS (data not shown).

Regression analysis

In order to search for predictors of dose escalation with infliximab a multivariate binary logistic regression model was created. When adjusting for differences in baseline data, concomitant MTX was associated with reduced risk for dose escalation (OR 0.28; 95% CI 0.09, 0.88; $P = 0.03$). A diagnosis of PsA showed a significant association with increment of infliximab dosage (OR 3.03; 95% CI 1.11, 8.23; $P = 0.03$). No significant interaction was found between concomitant MTX and diagnosis of the patients; however, there was a trend for better prevention of dose escalation in MTX-treated RA and PsA patients compared with AS. Finally, number of months after treatment initiation was significantly associated with dose escalation (OR 1.10; 95% CI 1.03, 1.19; $P < 0.01$). On the other hand, we did not find any correlation between predictive value of gender, age, CRP level, HAQ, DAS28 or disease duration at inclusion and dose escalation.

Discussion

In this study, the dosage of infliximab was increased in 59% of the patients during the first 2 yrs of treatment. A dose escalation was more likely to occur in patients who had PsA, no concomitant MTX and longer treatment duration.

The observed frequency of patients requiring an increased dose of infliximab is consistent with findings in other studies. Thus, in another observational cohort dose escalation was observed in 58% of the treated patients during a 3-yr follow-up period [4], and a systematic review reports overall increments in 54% of the infliximab-treated RA patients [1]. On the other hand, the START study reports a dose escalation fraction of 30%, but this is an extension of an RCT study setting with a follow-up time with possibility to dosage increment limited to 6 months only [8].

The reasons for the requirement of dose escalation could be various, and production of human anti-chimeric antibodies has been mentioned [12, 13]. On the other hand, results from the START trial suggest that low serum concentrations of infliximab may be a more important cause of lack of response or flare than antibodies [5].

It should be noted that in Sweden the treating physicians have no regulatory constraints on the dosages used. The observed data therefore reflects spontaneous decisions by physicians based merely on a clinical judgement of the patient. In this regard, patients in Lund were evaluated immediately prior to infliximab administration, i.e. at the time with the lowest possible drug concentration. Thus, we believe that our results reflect the maximum need for dose escalation, and it can be speculated that centres with other evaluation routines of patients would be less likely to increase the dose of infliximab.

![Fig. 1. Number of patients included in the study. Patients excluded due to missing data or premature treatment terminations are also presented.](image-url)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No dose escalation (%)</th>
<th>Minor dose escalation (%)</th>
<th>Major dose escalation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsA</td>
<td>28</td>
<td>53</td>
<td>19</td>
</tr>
<tr>
<td>RA</td>
<td>43</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>AS</td>
<td>44</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>n</td>
<td></td>
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</tbody>
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Table 1. Characteristics of patients receiving infliximab at baseline

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PsA ($n=32$)</th>
<th>RA ($n=149$)</th>
<th>AS ($n=25$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>46 (±13)</td>
<td>56 (±14)</td>
<td>45 (±13)</td>
</tr>
<tr>
<td>Female sex, % (n)</td>
<td>75 (24)</td>
<td>71 (105)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>10 (±8)</td>
<td>13 (±10)</td>
<td>17 (±13)</td>
</tr>
<tr>
<td>MTX users, % (n)</td>
<td>69 (22)</td>
<td>65 (97)</td>
<td>36 (9)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.2 (±0.6)</td>
<td>1.4 (±0.6)</td>
<td>0.9 (±0.6)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>17 (±22)</td>
<td>30 (±31)</td>
<td>27 (±30)</td>
</tr>
<tr>
<td>DAS28 score</td>
<td>4.7 (±1.1)</td>
<td>5.4 (±1.3)</td>
<td>4.0 (±1.1)</td>
</tr>
</tbody>
</table>

Values are the mean ± s.d. except where stated otherwise. HAQ: Health Assessment Questionnaire.

Table 2. Percentage of patients with no, minor (<100% dose increment) and major (>100% dose increment) dose escalation during 2 yrs of infliximab treatment grouped according to diagnosis
Previously, a number of prior DMARDs, glucocorticoid treatment at baseline and fewer swollen joints at baseline have been associated with dose escalation of infliximab in primarily RA patients [4]. We did not reproduce these findings, although lack of concomitant MTX has been closely associated with an increased number of previous DMARDs [11]. Thus it is unclear whether lack of concomitant MTX or an increased number of previous DMARDs per se, is leading to dose escalations. The lack of consistency might also reflect the limited study sizes, potential regional differences in administration of glucocorticoids and lack of control for mixed diagnosis in the study population by van Vollenhoven et al. [4].

On the other hand, we did find that PsA was associated with a greater risk of dose escalation. This might be explained by the fact that patients with PsA often have involvement of the skin in addition to the joints, and the psoriatic skin lesions have been shown to produce considerable amounts of TNF-α [14]. It is therefore plausible that this extra load of cytokines consumes more infliximab, and therefore requires higher dosages than RA and AS. It also gives some justification to the recommendations from the manufacturer regarding higher initial dosages in this group of patients despite lack of proper dose-finding studies. More interestingly, this study did not show any difference in dose escalation between patients with AS and RA. Thus, based on the current evidence we find no reason for different dosage recommendations for RA or AS.

The open nature poses limitations to the study [15–17]. Thus, confounding by indication and observation bias cannot be excluded. On the other hand, this study includes heterogenous patients and allows comparisons across different diagnosis, which is unlikely to happen in a controlled randomized study setting. Also, following the increasing introduction of new targeted therapies, it is unlikely that future cohort studies will be representative and powered for studying dose escalation of infliximab in more depth.

In conclusion, dose escalations were performed in 59% of all infliximab-treated patients during the first 2 yrs of treatment. The need for dose escalation is larger in patients with no concomitant MTX, PsA or with longer treatment duration.

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### Disclosure statement
L.E.K. and P.G. have received fees for speaking by Abbott, Wyeth and Schering-Plough. The other author has declared no conflicts of interest.

### References