Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity

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Abstract

Objective

Tocilizumab is effective in the treatment of rheumatoid arthritis (RA). A proportion of patients achieve low disease activity using a lower than registered starting dose. We investigated the feasibility of dose reduction to 4 mg/kg in patients who reached low disease activity at the registered dose of 8 mg/kg.

Methods

In this retrospective study, data were collected of 22 patients successfully treated with tocilizumab 8 mg/kg for about 6 months and tapered to 4 mg/kg because of low disease activity. In case of loss of disease control, the dose could be increased again to 8 mg/kg. The percentage of patients with successful dose reduction and difference in DAS28 was described.

Results

Mean DAS28 at time of dose reduction was 2.3 (SD 0.9). After 3 and 6 months follow-up, 77% (95% CI 54–91) and 55% (95% CI 32–76) of patients had successfully reduced the dose without losing disease control, respectively. DAS28 at 3 and 6 months was somewhat higher than baseline, 2.7 (SD 1.2) and 2.5 (SD 1.0) respectively. All patients who experienced worsening of disease activity after dose reduction regained low disease activity after dose escalation.

Conclusion

Dose reduction of tocilizumab seems feasible in a substantial proportion of patients. Dose escalation after flare was effective in all patients.

Key words

rheumatoid arthritis, tocilizumab, dose-response relationship

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Received on August 1, 2013; accepted in revised form on January 9, 2014.

Competing interests: none declared.

Introduction

Tocilizumab is an effective treatment in rheumatoid arthritis (RA) patients after failure of disease-modifying anti-rheumatic drugs (DMARD) and/or anti-TNF treatment (1-4). Tocilizumab can be given either as monotherapy (5, 6) or in combination with methotrexate or other DMARDs (1-4).

The optimal dosing of tocilizumab with regard to efficacy and safety is somewhat under debate. Registration in Europe indicates a starting dose of 8 mg/kg, compared to 4 mg/kg with escalation to 8 mg/kg based on clinical response in the United States (7, 8). Although previous research has demonstrated superior efficacy of the higher dose with regard to the clinical outcomes (9), the majority of patients responds as well to 4 mg/kg (1-4). Furthermore, radiographic change is similar between both starting doses (1). Risk of adverse events was analysed in a meta-analysis (10), revealing no statistical difference with regard to adverse events (AEs), serious adverse events (SAEs) and infections between patients treated with 8mg/kg and 4 mg/kg. However, a significantly greater risk of serious infections was found in the 8 mg/kg group, but after exclusion of one study this difference disappeared. On the other hand, a lower dose of tocilizumab is possibly associated with higher immunogenicity (1, 4). In conclusion, 8 mg/kg is safe and more effective, but a large proportion of patients would be adequately treated with 4 mg/kg as well. A personalised strategy – starting with 8 mg/kg, and tapering in case of low disease activity – could possibly lead to a more cost-effective dosing of tocilizumab.

The number of studies on dose reduction and discontinuation of other biologics – mostly TNF inhibitors – when disease activity is low is increasing. These studies show that a substantial proportion of patients are able to maintain low disease activity after dose reduction (11-14). Although such studies have not been done on tocilizumab to our knowledge, a stopping study showed that 35% and 13% of RA patients maintained a DAS28<3.2 24 and 52 weeks, respectively, after discontinuation of tocilizumab monotherapy (15). Recently, an international consensus statement on IL-6 blocking agents was published,(16) advising to start tocilizumab treatment with 8 mg/kg. Dose reduction to 4 mg/kg is advocated in case of adverse events. Also, a number of future research question is proposed in this consensus statement, with one of these being whether tocilizumab can be withdrawn or dose reduced in patients who have attained low disease activity. Therefore, in this proof of principle study, we examine the proportion of RA patients with successful dose reduction of tocilizumab to 4 mg/kg after achieving low disease activity at a 8 mg/kg dose. Secondary aims are to assess time to flare and the incidence of secondary ineffectiveness after dose escalation.

Materials and methods

Design

According to the treatment protocol of the Sint Maartenskliniek Nijmegen, RA patients start with tocilizumab 8 mg/kg every 4 weeks. After about 6 months, dose is reduced to 4 mg/kg if patients have low disease activity (DAS28<3.2 and/or judgement of rheumatologist). In case of loss of disease control after dose-reduction (DAS28>3.2 and/or judgement of the rheumatologist), the dose is increased again to 8 mg/kg. In this retrospective observational study, baseline patient-, disease- and treatment characteristics were collected as well as data on disease activity before and 3 and 6 months after dose reduction and when applicable 3 and 6 months after dose escalation.

Patients

Patients with RA (according to the 2010 ACR RA and/or 1987 ACR RA criteria and/or clinical diagnosis of the treating rheumatologist) treated according to the above mentioned protocol between September 2010 and April 2013 were included. Patients who reduced the dose to 4 mg/kg because of AEs only were excluded; patients with a combination of low disease activity and AEs were included. Written informed consent was obtained for retrospective data collection.

Statistical analyses

Descriptive statistics were provided with mean (± standard deviation (SD))

and median (interquartile ranges) depending on distribution. The proportion and 95% confidence interval (CI) of patients with successful dose reduction after 3 and 6 months was given. A Kaplan-Meier survival curve was used to plot proportion of patients after dose reduction still at a 4 mg/kg tocilizumab dose during 6 months follow-up. Baseline characteristics were compared between patients with successful dose reduction and patients who failed dose reduction at 6 months using Fisher's exact test, Student's *t*-test or Mann-Whitney U-test when appropriate.

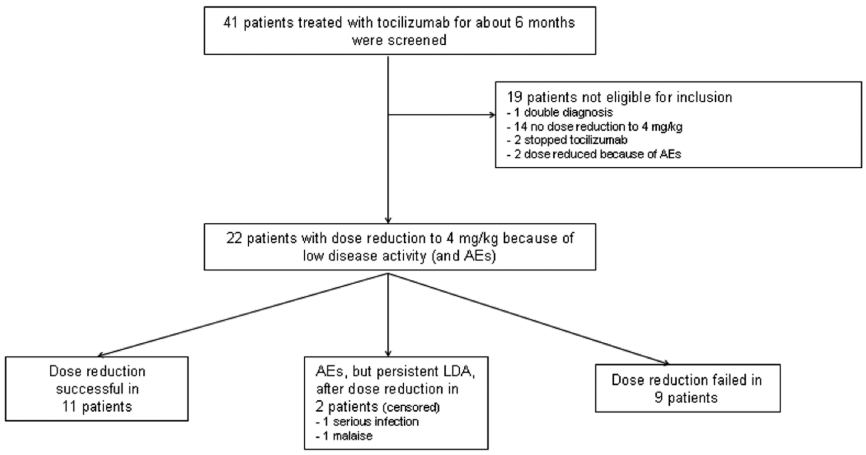

Fig. 1. Flow diagram of rheumatoid arthritis patients treated according to the dose reduction protocol. AEs: adverse events; LDA: low disease activity.

Results

Patients

Dose was reduced to 4 mg/kg in 22 patients because of low disease activity (Fig. 1). In 14 patients tocilizumab dose reduction was not attempted, mainly due to non-adherence to the local protocol. Table I shows the characteristics of the 22 patients at baseline (tocilizumab start 8 mg/kg). There was no statistically significant difference in the baseline characteristics between patients with successful dose reduction and patients who failed dose reduction at 6 months follow-up.

The mean duration of a 8 mg/kg dose before dose reduction to 4 mg/kg was 11 months (SD 6.2). In 5 patients tocilizumab dose was lowered to 4 mg/kg earlier than the local protocol prescribed (<6 months after tocilizumab start), because of AEs as well as low disease activity. No infusion reactions occurred during the study.

Table I. Baseline characteristics (start tocilizumab 8 mg/kg).

	All n=22	Successful dose reduction* n=13	Failed dose reduction n=9	*p*-value
Age, years (SD)	61 (12)	62 (12)	59 (13)	0.50
Woman, n (%)	20 (91)	11 (85)	9 (100)	0.49
Disease duration, years median [p25-p75]	10 [5-17]	10 [8-17]	10 [5-13]	0.48
Rheumatoid factor positive, n (%)	14 (64)	9 (69)	5 (56)	0.66
Anti-CCP positive, n (%)	14/19 (74)	9/11 (82)	5/8 (63)	0.60
Erosive disease, n (%)	13 (59)	9 (69)	4 (44)	0.38
DAS28 before starting Tocilizumab (SD)	4.9 (0.9)	5.0 (0.8)	4.9 (1.2)	0.85
Previous DMARDs, n median [p25-p75]	3 [2-5]	3 [2-4]	5 [3-6]	0.15
Previous biologicals, n median [p25-p75]	3 [2-5]	2 [1-4]	4 [2-5]	0.24
Concomitant DMARD, n (%)	11 (50)	6 (46)	5 (56)	1.00
Concomitant MTX, n (%)	6 (27)	2 (15)	4 (44)	0.18
Concomitant glucocorticoid, n (%)	14 (64)	6 (46)	8 (89)	0.07

*including censored patients.
Anti-CCP: anti-cyclic citrullinated peptide; DAS28: 28 joints disease activity score; DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate.

Proportion on 4 mg/kg tocilizumab

Three months after dose reduction to 4 mg/kg, 17 out of 22 patients, 77% (CI 54–91) used 4 mg/kg tocilizumab. After 6 months this was 11 out of 20 patients, 55% (CI 32–76%) (Fig. 2). Two patients were censored before the 6 months follow-up. They stopped tocilizumab after dose reduction because of AEs. Seven out of 9 flares after dose reduction (78%), occurred within the first 16 weeks.

Disease activity score

Figure 3 shows the DAS28 at different time-points. Mean DAS28 at time of dose reduction to 4 mg/kg tocilizumab was 2.3 (SD 0.9). Three months after dose reduction, DAS28 was 2.7 (SD 1.2) and after 6 months 2.5 (SD 1.0) in patients still using 4 mg/kg. Nine patients experienced a worsening of disease activity in the 6 six months after dose reduction to 4 mg/kg. In 7 patients tocilizumab was escalated to 8 mg/kg, in 2 patients dose was escalated to 6mg/kg (because of AEs on 8mg/kg). After tocilizumab dose escalation, 8 patients regained low disease activity based on clinical judgement, although in one patient time to regain low disease activity was more than 6 months. One patient stopped tocilizumab, because of persistent AEs, but with low disease activity. Mean DAS28 3 months after escalation to 6 or 8 mg/kg was 2.8 (SD 1.0), after 6 months 2.8 (SD1.1).

Co-medication

DMARD change after dose reduction occurred in 4 patients (1 stopped, 2 dose reduction, 1 dose escalation). All four of these patients still used 4 mg/kg tocilizumab after 6 months. Oral glucocorticoids were escalated in 2 patients after tocilizumab dose reduction; both patients also needed tocilizumab escalation. In 4 patients oral glucocorticoids were reduced or stopped after tocilizumab dose reduction, 3 of these patients needed tocilizumab escalation. Seven patients received either an intra-articular or intramuscular injection, in 4 of these patients tocilizumab was escalated.

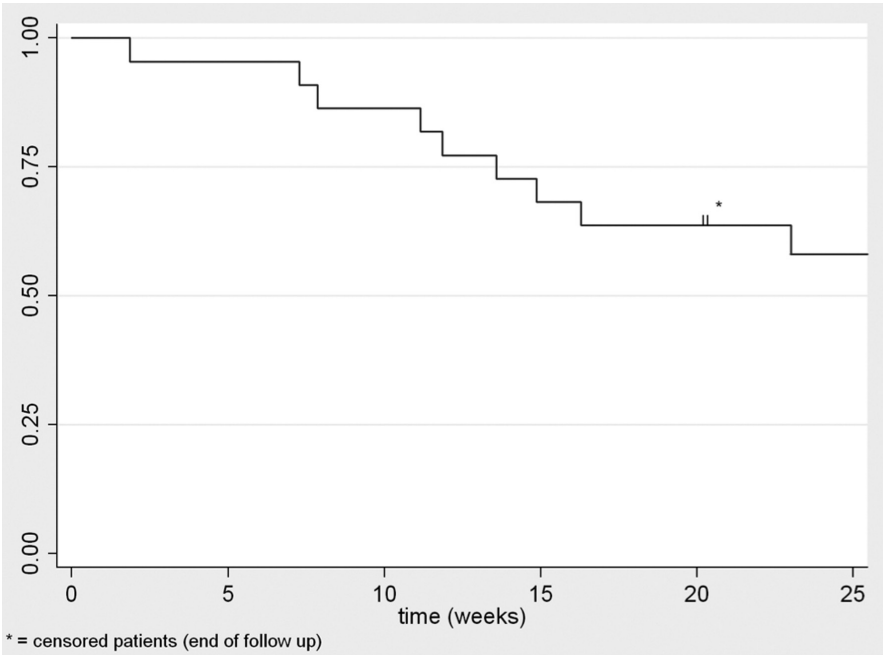

Fig. 2. Kaplan-Meier curve of tocilizumab 4 mg/kg.

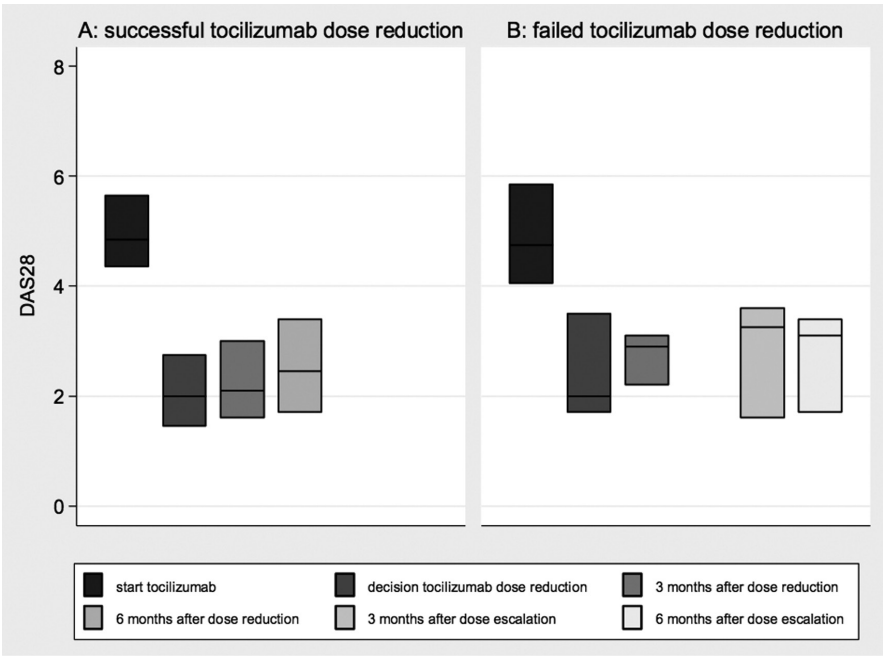

Fig. 3. Box-plots showing DAS28 at different time-points in patients with successful dose reduction at 6 months follow-up (**A**) and patients who fail in 6 months after dose reduction (**B**).

Discussion

In this study we demonstrated the feasibility and safety of dose reduction to 4 mg/kg tocilizumab in RA patients using 8 mg/kg for about six months with low disease activity. Three and six months after dose reduction a substantial proportion of patients still had low disease activity while using 4 mg/kg tocilizumab. Also, flares occurred predominantly in the first four months, and responded well to tocilizumab escalation in all patients.

Although this is a small retrospective study without a control group, we feel the results are promising as these are the first data presented on this topic. The proportion of patients doing well at a 4 mg/kg dose of over 50% that we found fits nicely within the expected range based on previous trials. The range of ACR50 response on 8 mg/kg tocilizumab in those trials is 29–53% and for 4 mg/kg tocilizumab 17–37%; although after different follow-up (1-4). Comparing these ranges shows a relative difference between 4 mg/kg and 8 mg/kg tocilizumab of about 40%, congruent with the more than 50% of patients maintaining response to 4 mg/kg in this study. We did not find predictors for successful those reduction after 6 months, this was not surprising because of the small number of patients in this study.

The mean DAS28 three and six months after dose reduction was somewhat higher than before dose reduction. This increase might be caused by an increase in disease activity caused by dose reduction in some patients. Another contributing factor could be a regression to the mean phenomenon, which has been described previously in RA patients (17). However, due to the lack of a control group these effects cannot be distinguished.

Change in co-medication after tocilizumab dose reduction could have influenced the results. However, change in DMARD was infrequent and mostly consisted of dose reduction. Change in glucocorticoids was more frequent, but occurred mostly temporarily in patients with worsening of disease activity after dose reduction who also needed tocilizumab escalation. Therefore, overestimation of the success rate of dose reduction due to increase of co-medication is unlikely.

An interesting finding in this study was the time to flare after dose reduction to 4 mg/kg. The large majority of flares occurred during the first 16 weeks after dose reduction; hereafter, flaring was infrequent. This finding has also been described in another dose reduction study in infliximab (11). For clinical practice, this means that it is quickly obvious whether successful dose reduction is feasible or not.

In conclusion, we found that dose reduction of tocilizumab from 8 to 4 mg/kg in responding RA patients is feasible in the majority of patients. Important questions that remain and should be targeted in larger studies with longer follow-up are for example safety, cost-

effectiveness and possible risk of progressive radiographic joint damage due to dose reduction. Furthermore, identification of predictors for successful dose reduction could lead to even more optimal personalised treatment of RA patients using tocilizumab by preventing unnecessary flares.

Acknowledgements

The authors would like to thank Michiel Minten for his help with data management.

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