

Original article

Abatacept and tocilizumab tapering in rheumatoid arthritis patients: results of SONATA—a retrospective, exploratory cohort study

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Abstract

Objectives As data on disease-activity-guided dose optimization of abatacept and tocilizumab are scarce, we explored the feasibility, effectiveness and safety of dose optimization of these biological DMARDs in RA patients in daily practice.

Methods RA patients who had been treated with abatacept or tocilizumab for ≥ 6 months, with DAS28 < 3.2 , were included. Four groups were identified: abatacept dose reduction (DR) and usual care (UC), and tocilizumab DR and UC. Successful DR and discontinuation entailed being on a lower dose than at baseline or having discontinued abatacept or tocilizumab, while maintaining disease activity score with ESR using 28 joint count (DAS28) < 3.2 . Proportions of patients with successful DR or discontinuation at 12 months were described. Maintenance of DR was investigated using Kaplan–Meier curves. Between-group differences in mean DAS28 and Health assessment questionnaire disability index (HAQ-DI) change (Δ) over 6 and 12 months were estimated.

Results One hundred and nineteen patients were included. DR was attempted in 13 of 28 (46%; 95% CI: 28, 66%) abatacept and 64 of 91 (70%; 95% CI: 60, 79%) tocilizumab patients. At 12 months, 3 of 11 (27%; 95% CI: 6, 61%) abatacept and 20 of 48 (42%; 95% CI: 28, 57%) tocilizumab patients were successfully tapered. One of 11 (9%; 95% CI: 0, 41%) abatacept and 5 of 48 (10%; 95% CI: 3, 23%) tocilizumab patients were successfully discontinued. Mean Δ DAS28 and Δ HAQ-DI at months 6 and 12 were not significantly different between DR and UC. For tocilizumab, DAS28 was significantly higher in the DR compared with the UC group at 6 months. Adverse events were comparable between groups.

Conclusion Abatacept and tocilizumab DR appears to be feasible and safe in clinical practice. No benefits in terms of fewer adverse events in the DR group were observed. Furthermore, DR was sub-optimal, because all patients were eligible for DR, but in a substantial number of patients no DR was attempted.

Key words: rheumatoid arthritis, biologic, abatacept, tocilizumab, dose reduction, tapering, discontinuation, withdrawal, dose optimization

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Introduction

The advantageous effects of biologic DMARD (bDMARD) treatment in RA on clinical, functional and radiographic outcomes have been well documented. However, bDMARDs are associated with adverse events (e.g. serious infections) and high costs [1, 2]. With this in

Key messages

- Abatacept and tocilizumab dose reduction is feasible and safe in daily clinical practice.
- No difference in adverse events was found between patients in whom dose reduction of abatacept or tocilizumab was attempted and patients who continued full dose abatacept or tocilizumab.
- Dose reduction is suboptimal, because not in all patients eligible for dose reduction an actual dose reduction attempt is undertaken.

mind, dose optimization becomes important, which entails: (i) starting treatment when it is needed; (ii) disease activity-guided dose reduction (DR) to the lowest effective level when a patient is doing well; (iii) discontinuing the drug when it is no longer required; and (iv) restarting or re-escalating in the event of a flare. Disease-activity-guided DR of TNF inhibitors (TNFi) in RA patients has proved to be feasible and safe [3–5] and has recently been included in RA management recommendations [6]; however, data on disease activity-guided dose optimization of non-TNFi bDMARDs are scarce.

Abatacept is a human fusion protein that selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T-cell activation. It is an effective treatment [either as monotherapy or in combination with a conventional synthetic DMARD (csDMARD)] in patients who are either csDMARD naïve or had an inadequate response to csDMARD or bDMARD [7–9]. Tocilizumab is a humanized mAb directed against the IL-6 receptor and is an effective treatment option after failure of a csDMARD or bDMARD, either as monotherapy or in combination with a csDMARD [10–13].

Few studies have been performed focusing on DR or discontinuation of abatacept or tocilizumab [14–19]. With regard to abatacept, Takeuchi *et al.* [15] observed abatacept-free remission in 22 of 34 (65%) patients after 1 year of discontinuation. Furthermore, in the Abatacept study to Gauge Remission and joint damage progression in methotrexate naïve patients with Early Erosive rheumatoid arthritis (AGREE) study, a double-blind randomized controlled trial, the efficacy of reduction of i.v. abatacept from 10 to 5 mg/kg in early RA patients was investigated [16], showing that the proportions of patients who lost DAS28-defined remission status were similar between groups at month 12. Also, the Assessing Very Early Rheumatoid arthritis Treatment study DREAM: Drug free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy study (AVERT) study showed that in early RA patients reaching low disease activity after abatacept treatment for 12 months, radiographic benefits were maintained at 6 months after withdrawal of abatacept [17].

With regard to tocilizumab, Nishimoto *et al.* [18] investigated discontinuation of tocilizumab in patients with early RA treated with tocilizumab monotherapy in the DREAM study. Low disease activity was maintained in 35% after 6 months and in 13% after 1 year. Furthermore, the effects of DR of tocilizumab were

described in a small retrospective study in 22 patients [19]. DR was successful in 55% of patients after 6 months, and all patients with worsening of disease activity after DR regained low disease activity after dose escalation.

Thus, data on disease activity-guided DR of abatacept or tocilizumab in RA are limited. Moreover, most studies have focused on early RA patients enrolled in clinical trials, leaving uncertainty regarding its feasibility in daily clinical practice. Therefore, we aimed to carry out a retrospective investigation of the feasibility (including frequency of DR attempts and persistence), effectiveness and safety of tapering of abatacept and tocilizumab in RA patients in daily practice.

Methods

Study design and participants

The Study ON Abatacept and Tocilizumab Attenuation is a retrospective explorative single-centre controlled cohort study, investigating disease activity and functioning in RA patients who reached low disease activity on abatacept or tocilizumab treatment and attempted DR, compared with control groups of patients who reached low disease activity on abatacept or tocilizumab treatment but never attempted DR. All patients at the rheumatology department of the Sint Maartenskliniek, a specialized hospital in Nijmegen, The Netherlands, who had been or were still being treated with either abatacept or tocilizumab were screened for eligibility. Patients were considered eligible if they were diagnosed with RA according to the 1987 and/or 2010 ACR criteria and/or clinical diagnosis by the treating rheumatologist and were treated at any time with abatacept and/or tocilizumab, reached low disease activity (DAS28-ESR <3.2) after 6 months of treatment and had ≥6 months of follow-up available.

Four cohorts were defined: abatacept DR group, abatacept usual care (UC) group, tocilizumab DR group and tocilizumab UC group. Patients who attempted DR because of low disease activity with or without adverse events were included in the DR group. Patients in whom DR was attempted solely because of adverse events were excluded. Patients who were eligible for DR but in whom no DR attempt was undertaken (because of either patient or physician preference or unspecified reasons) were included in the UC group. Patients who were treated

with both abatacept and tocilizumab were included in analyses only once, for the first bDMARD used.

All patients eligible for inclusion were asked for written informed consent for retrospective data collection. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in The Netherlands.

Procedures

Abatacept and tocilizumab were started, according to registration specifications: for abatacept either i.v. 500, 750 or 1000 mg/4 weeks depending on body weight, or s.c. 125 mg/week. Tocilizumab was administered either i.v. 8 mg/kg/4 weeks or s.c. 162 mg/week. Both were used as monotherapy or in combination with a csDMARD, preferably MTX.

Since 2010, a dose optimization protocol has been used in the Sint Maartenskliniek, which includes DAS28-steered DR when DAS28 <3.2 is reached in longstanding RA patients for ≥ 6 months (or DAS28 <2.6 if RA was diagnosed <3 years ago). This is done by tapering the dose for i.v. bDMARDs and by increasing the interval for s.c. bDMARDs. For abatacept and tocilizumab, the following DR regimens are used: (i) abatacept i.v.: DR of 250 mg every 3 months until discontinuation, or DR of 250 mg every 6 months until discontinuation in patients with a baseline dose of 500 mg; (2) abatacept s.c.: increasing the interval every 3 months, from 125 mg/7 days to once every 10, 14 and 21 days, then discontinuation; (iii) tocilizumab i.v.: DR every 3 months from 8 to 6 to 4 mg/kg/4 weeks, then discontinuation; and (iv) tocilizumab s.c.: increasing the interval every 3 months, from 162 mg/7 days to once every 10, 14 and 21 days, then discontinuation.

All treatment choices were left to the discretion of the treating rheumatologists. If symptoms of loss of disease control occurred, temporary treatment with NSAIDs or CSs was advised. If a flare persisted, either according to a flare criterion (DAS28 increase of >1.2 or >0.6 with current DAS28 >3.2) [20] or according to the judgement of the treating rheumatologist, the bDMARD was restarted or the dose was increased to the last efficacious dose. In case of persistently high disease activity, the dose was further reinstated up to the registered dose, after which, if disease activity remained high, the bDMARD was switched.

Outcomes

Patient, disease and treatment characteristics were collected, as were data on disease activity score with ESR using 28 joint count and functioning [Health assessment questionnaire disability index (HAQ-DI)]. Data were collected at the initiation of abatacept or tocilizumab, at baseline ($t=0$) and every 3 months thereafter. Baseline was defined as being eligible for DR. In the DR group, this moment was set at the initiation of DR. In the UC group, this moment was set at reaching low disease activity and using abatacept or tocilizumab for ≥ 6 months

(theoretical time of start of DR). Successful DR and discontinuation were defined as having a lower dose or longer interval than at baseline or complete withdrawal of the bDMARD, respectively, with concurrent low disease activity (DAS28 <3.2). Follow-up time was 12 months for all outcomes, except for survival analysis using the maximal follow-up until censoring or stopping of abatacept or tocilizumab.

Statistical analyses

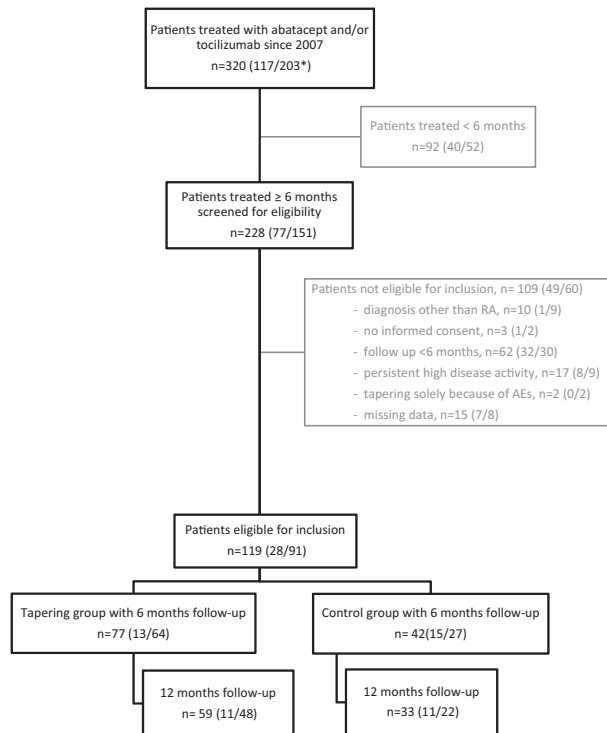
STATA/IC v13.1 (StataCorp., Texas, USA) was used for all analyses. Descriptive statistics were used for demographic data and provided with the mean (s.d.) or median (interquartile range, IQR) depending on distribution. Proportions and 95% CIs of patients in whom DR and discontinuation was considered successful at 12 months were described. The median time of persistence of successful DR and discontinuation was calculated. A survival analysis was done using a Kaplan–Meier curve for time to re-escalation attributable to high disease activity in the DR group. The prevalence of patients switching to other bDMARDs within 12 months and reasons for switching were compared between the DR group and the UC group for both abatacept and tocilizumab. Student's unpaired *t*-test was used to assess differences in the mean and mean change (Δ) in DAS28 and HAQ-DI at 6 and 12 months after becoming eligible in the DR vs UC group for abatacept and tocilizumab separately. Linear regression analyses for differences in DAS28 at 6 and 12 months between the DR and UC group were constructed to adjust for confounders specific for these outcomes. All baseline factors were checked for possible confounding. As a result of low patient numbers in subgroups, abatacept and tocilizumab were combined in these analyses. Only factors that resulted in a change in $\beta > 10\%$ or (in the event of too many factors relative to patient numbers) that were considered relevant were included in the final model. All factors were added to the model at once. The prevalences of pre-specified categories of serious adverse events were compared between the DR group and the UC group for both abatacept and tocilizumab. Frequencies of missing data were checked. In the event of single missing values, single imputation was applied by last observation carried forward or calculation of the mean of the previous and next value. For linear regression analyses, missing baseline values were imputed using multiple imputation (10 times).

Results

Patients

From January 2007 until June 2015, 320 patients were treated with abatacept and/or tocilizumab, of whom 119 patients were considered eligible. Twenty-eight patients were using abatacept: 13 (46%) in the abatacept DR group and 15 (54%) in the abatacept UC group. Ninety-one patients were using tocilizumab: 64 (70%) in the tocilizumab DR group and 27 (30%) in the tocilizumab

Fig. 1 Flow chart with patient disposition (*abatacept/tocilizumab)



*=abatacept/tocilizumab. AEs: adverse events.

UC group. Details and numbers of patients at follow-up are depicted in Fig. 1. Patient characteristics at initiation of abatacept or tocilizumab and at baseline are depicted in Table 1. No large between-group differences were observed. At baseline, the mean (s.d.) duration of abatacept use was 1.1 (0.4) years in the abatacept DR group and 0.7 (0.3) years in the abatacept UC group. For tocilizumab, the mean (s.d.) duration of tocilizumab use at baseline was 1.4 (0.4) years in the tocilizumab DR group and 0.7 (0.3) years in the tocilizumab UC group.

Medication use

At 12 months, 3 of 11 (27%; 95% CI: 6%, 61%) patients in the abatacept DR group were successfully tapered, with the i.v. dose being lowered by 50% in all 3 patients (from 750 to 375 mg i.v. every 4 weeks in 2 patients and from 500 to 250 mg i.v. every 4 weeks in 1 patient). For the tocilizumab DR group, 20 of 48 (42%; 95% CI: 28, 57%) were successfully tapered at 12 months, with the baseline i.v. dose of 8 mg/kg being lowered by to 6 mg/kg in 4 patients, to 5 mg/kg in 1 patient, to 4 mg/kg in 10 patients and to 2 mg/kg in 1 patient. For tocilizumab s.c., the dose was lowered from 162 mg/kg every 7 days to every 10 days in one patient, to every 14 days in two patients and to every 28 days in one patient. One of 11 (9%; 95% CI: 0, 41%) patients using abatacept and 5 of 48 (10%; 95% CI: 3, 23%) using tocilizumab were

successfully discontinued. Of these successfully tapered patients, in all 3 abatacept patients and in 12 tocilizumab patients, subsequent discontinuation could have been attempted, because these patients were experiencing persistent low disease activity, but this was not done for unknown reasons. In 1 of 13 (8%; 95% CI: 0, 36%) patients in the abatacept DR group and in 14 of 64 (22%; 95% CI: 13, 34%) patients in the tocilizumab DR group, more than one DR attempt was made in the first 6 months after baseline. The median time of DR with concurrent low disease activity was 6 months (25th to 75th percentile, 6–24) for abatacept and 9 months [6–18] for tocilizumab. The median time of discontinuation with concomitant low disease activity was 3 months for abatacept ($n = 1$) and 3 [3–6] months for tocilizumab.

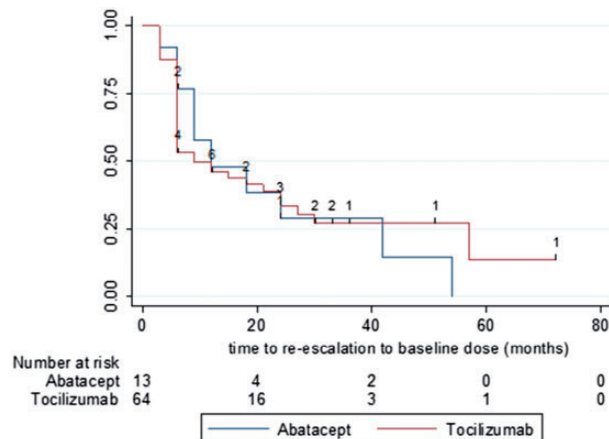
In Fig. 2, a Kaplan-Meier curve is depicted for time until re-escalation to baseline dose for both abatacept and tocilizumab, showing that tapering was persistent up to 72 months.

In patients who attempted DR, 22 of 77 (29%; 95% CI: 19, 40%) patients who re-escalated again were experiencing low disease activity at the time of re-escalation. Of these, 1 patient using abatacept and 17 patients using tocilizumab re-escalated the dose because of a subjective increase in disease activity (more complaints, but no increase in swollen joint counts and ESR). Four patients using tocilizumab initially reduced the dose because of adverse events (in combination

TABLE 1 Patient characteristics at initiation of abatacept or tocilizumab

Patient characteristics	Abatacept DR (n = 13)	Abatacept UC (n = 15)	Tocilizumab DR (n = 64)	Tocilizumab UC (n = 27)
Age, mean (s.d.), years	59 (14)	59 (12)	61 (11)	55 (17)
Female, n (%)	12 (92)	14 (93)	47 (73)	19 (70)
Weight, mean (s.d.), kg	73 (16)	74 (9)	75 (18)	75 (15)
Disease duration, median [p25–p75], years	15 [10–18]	17 [12–21]	12 [5–16]	9 [2–16]
RF positive, n (%)	12 (92)	12 (80)	51 (80)	19 (70)
Anti-CCP positive, n (%)	9 (69) ^a	12 (80) ^a	47 (73) ^a	17 (63) ^a
Erosive disease, n (%)	10 (77) ^a	9 (60) ^a	36 (56) ^a	10 (37) ^a
DAS28 (s.d.)	4.6 (0.9)	4.1 (1.4)	4.4 (1.2)	4.2 (1.1)
HAQ-DI (s.d.) ^b	1.8 (0.6)	1.5 (0.6)	1.5 (0.6)	1.7 (0.6)
i.v. administration, n (%)	11 (85)	9 (60)	56 (88)	19 (70)
s.c. administration, n (%)	2 (15)	6 (40)	8 (13)	8 (30)
Previous csDMARDs, median [p25–p75]	4 [3–5]	5 [3–6]	3 [2–4]	2 [2–3]
Previous bDMARDs, median [p25–p75]	4 [3–4]	4 [3–4]	3 [2–4]	3 [3–4]
Concomitant csDMARD, n (%)	7 (54)	6 (40)	30 (47)	17 (63)
Concomitant MTX, n (%)	4 (31)	5 (33)	11 (17)	10 (37)
Concomitant glucocorticoid, n (%)	5 (38)	9 (60)	45 (70)	17 (63)

bDMARD: biologic DMARD; csDMARD: synthetic DMARD; DR: dose reduction; DAS28: disease activity score with ESR using 28 joint count; HAQ-DI: Health assessment questionnaire disability index; UC: usual care. ^aAnti-CCP positivity: 14 of 119 (12%) missing data (2/13 abatacept DR; 2/15 abatacept UC; 8/64 tocilizumab DR; 2/27 tocilizumab UC). Erosive disease: 5 of 119 (4%) missing data (0/13 abatacept DR; 1/15 abatacept UC; 2/64 tocilizumab DR; 2/27 tocilizumab UC). ^bHAQ-DI: 33 of 119 (28%) missing data (4/13 abatacept DR; 3/15 abatacept UC; 21/64 tocilizumab DR; 5/27 tocilizumab UC).

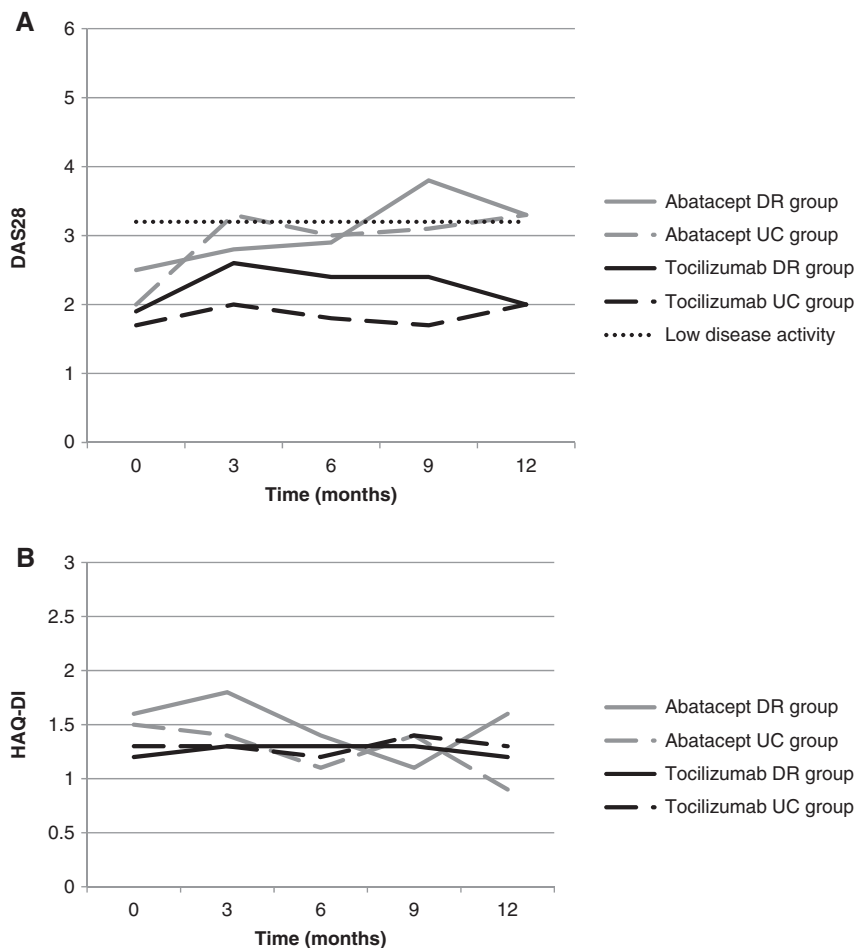
FIG. 2 Kaplan–Meier survival estimates until re-escalation to baseline dose for abatacept and tocilizumab

Hash marks indicate censored patients (end of follow-up).

with low disease activity) and re-escalated again once the adverse event was resolved. None of the patients re-escalating ended up on a higher dose than at baseline. The median time to reach low disease activity again after re-escalation was 4.5 [3–6] months in the abatacept DR group and 3 [3–6] months in the tocilizumab DR group. In the DR group, 5 of 13 (38%; 95% CI: 14, 68%) patients using abatacept were ultimately switched to another bDMARD: 2 were switched owing to secondary inefficacy after the DR attempt, 2 were switched

owing to secondary inefficacy later on (after being back at the baseline dose for a substantial amount of time) and 1 was switched owing to adverse events. Thirteen of 64 (20%; 95% CI: 11, 32%) patients using tocilizumab were ultimately switched to another bDMARD: 2 were switched owing to secondary inefficacy after DR, 8 were switched owing to secondary inefficacy later on, and 3 were switched owing to adverse events. In the UC group, 2 of 15 (13%; 95% CI: 2, 40%) patients using abatacept were switched to another bDMARD, both owing to

Fig. 3 (A) Mean DAS28 for abatacept and tocilizumab DR and UC groups from baseline to month 12. (B) Mean HAQ-DI for abatacept and tocilizumab DR and UC groups from baseline to month 12. Low disease activity was defined as DAS28 <3.2. DAS28: disease activity score with ESR using 28 joint count; DR: dose reduction; HAQ-DI: Health assessment questionnaire disability index; UC: usual care.



adverse events. For tocilizumab, 4 of 27 (15%; 95% CI: 4, 34%) were switched to another bDMARD: 3 owing to secondary inefficacy and 1 owing to adverse events.

Disease activity and functioning

Mean Δ DAS28 and Δ HAQ-DI at months 6 and 12 were univariately not significantly different between DR and UC groups in both abatacept and tocilizumab (Fig. 3 and supplementary Table S1, available at *Rheumatology Advances in Practice* online), although CIs were wide, especially for abatacept. Absolute DAS28 scores were univariately significantly higher for tocilizumab in the DR group than in the UC group at 6 months, but not at 12 months. No differences were seen for absolute DAS28 scores in the abatacept groups. However, when adjusted for confounders no significant or relevant

differences were seen for DAS28 course at 6 and 12 months: DAS28 difference adjusted for confounders [age, bDMARD (abatacept or tocilizumab), erosive disease, disease duration and DAS28 at baseline]: +0.28 higher in the DR group (−0.19 to 0.74) at 6 months and (adjusted for age, erosive disease, HAQ at start of the bDMARD and DAS28 at baseline) −0.34 lower in the DR group (−0.98 to 0.29) at 12 months.

Safety

In the DR groups, 4 of 13 (31%; 95% CI: 9, 61%) patients using abatacept and 38 of 64 (59%; 95% CI: 46, 71%) using tocilizumab experienced at least one adverse event. In the control groups, 2 of 15 (13%; 95% CI: 2, 40%) using abatacept and 14 of 27 (52%; 95% CI: 32, 71%) using tocilizumab experienced at least one

TABLE 2 Incidence densities of different adverse event categories per 100 patient-years

Incidence densities	Abatacept DR	Abatacept UC	Tocilizumab DR	Tocilizumab UC
Infections	11 (2.2–31)	0	19 (12–29)	28 (14–51)
Malignancies	0	3.8 (0.1–21)	1.5 (0.2–5.4)	5.1 (0.6–5.2)
Cardiovascular	0	3.8 (0.1–21)	1.5 (0.2–5.4)	0
Allergic reaction	0	3.8 (0.1–21)	0.7 (0.0–4.2)	2.6 (0.1–14)
Leucopenia	0	0	14 (8.5–22)	7.7 (1.6–23)
ALT increase	3.6 (0.1–20)	3.8 (0.1–21)	5.2 (2.1–11)	5.1 (0.6–19)
Surgery	7.1 (0.9–26)	7.7 (0.9–28)	0.7 (0.0–4.2)	2.6 (0.1–14.3)
Death	0	0	1.5 (0.2–5.4)	0
Other	11 (2.2–31)	7.7 (0.9–28)	9.7 (5.2–17)	10 (2.8–26)

ALT: alanine amino transferase; DAS28: disease activity score with ESR using 28 joint count; DR: dose reduction; HAQ-DI: Health assessment questionnaire disability index; UC: usual care. Incidence density per 100 patient-years. Abatacept DR: 28 observed person-years; abatacept UC: 26 observed person-years; tocilizumab DR: 134 observed person-years; tocilizumab UC: 39 observed person-years.

adverse event. Incidence densities of different categories are depicted in Table 2, and were not significantly different between groups.

Discussion

To our knowledge, this is the first study to investigate the feasibility, effectiveness and safety of the implementation of a dose optimization strategy of abatacept and tocilizumab in RA patients in daily clinical practice. We could confirm that disease activity, functioning and safety were comparable between patients in whom a DR attempt was undertaken and patients who never attempted DR, with the exception of a significantly higher DAS28 at 6 months in the tocilizumab DR group compared with the UC group. Furthermore, in the majority of patients who were successfully tapered at 12 months, the dosage was lowered $\geq 50\%$ or the interval between injections was doubled (or longer). Also, DR seems to be persistent in up to 30% of patients. However, the number of patients in whom DR was attempted was lower than expected, and tapering was not always done according to pre-specified protocolized tapering steps. Also, in both the abatacept DR and UC groups, mean DAS28 rose above the level of low disease activity during follow-up, in contrast to tocilizumab where DAS28 remained low. We would like to discuss these findings in more detail.

We found that change in disease activity, functioning and safety were comparable between patients who tapered and patients who did not taper. This finding is comparable to other studies showing that tapering is feasible and safe in abatacept and tocilizumab [15, 16, 18, 19, 21–24] and to disease-activity-guided tapering in TNFi [3–5]. However, direct comparison of results is hampered by the differences in tapering strategies (gradual tapering vs discontinuation without tapering first and dose lowering vs injection interval prolongation), criteria for successful tapering or discontinuation (low

disease activity vs remission and necessity to use CSs or csDMARDs), open label vs blinded tapering and follow-up time used in the studies.

The number of patients in whom a DR attempt was undertaken was lower than expected, considering that all included patients were eligible for DR. Furthermore, in the DR groups, the duration of abatacept and tocilizumab use before a DR attempt was made was much longer than in the UC groups. A reason for these low numbers and longer time before tapering could be timing. DR protocols have only been implemented fully in our clinic since 2014. Although DR was done multiple times in trial settings in our clinic, it could be postulated that the absence of an outpatient clinic protocol and lack of experience with DR outside of trial settings in the early years might have led to doctors being hesitant to DR. Furthermore, in contrast to s.c. TNFi, where tapering consists of injection interval prolongation, DR by lowering the dose has less obvious advantages to a patient, because the number of infusions needed remains the same. Thus, patients might have been more motivated to attempt DR after s.c. abatacept and tocilizumab became available. This argument is supported by a recent study showing that tapering of s.c. tocilizumab by injection spacing was more successful than tapering of i.v. tocilizumab by reduction of the dose [25]. Another possible explanation for the low percentage of DR attempts is the fact that abatacept and tocilizumab were initially reserved for RA patients being refractory to other bDMARDs. Selection of a worse patient population might induce hesitation from patients and physicians to attempt tapering, when improvement in disease activity has proved to be a difficult goal to reach in the first place. This might especially be true for discontinuation attempts, which were not made in the majority of DR patients. Finally, patients might have negative expectations about DR, which might cause hesitation to dose reduce or induce negative symptoms during DR, the so-called nocebo response [26, 27]. All these

factors are real-world issues, and future studies should investigate these facilitators and barriers for dose optimization.

Remarkably, we observed a rise in disease activity above the level of low disease activity in both abatacept groups during follow-up, whereas DAS28 remained below low disease activity in both tocilizumab groups. An explanation could be that in our centre, abatacept patients are more refractory to treatment than tocilizumab patients, and thus a (small) rise in disease activity might be accepted more often than in patients using tocilizumab. It could also be that DAS28 is underestimated in the tocilizumab groups owing to the inhibitory effects of tocilizumab on inflammation parameters. However, this would be most noticeable in DAS28-CRP, whereas we used DAS28-ESR. All in all, the apparent rise in disease activity in abatacept patients might constitute a spurious finding, explained by low patient numbers in the abatacept groups compared with the tocilizumab groups.

With regard to adverse events, we expected to find a lower incidence of adverse events in the DR groups, especially fewer infections, but cumulative incidences were comparable with the UC groups. This may be explained by the retrospective, exploratory design of the present study (with probable under-reporting of less severe adverse events) and the small numbers of patients in the subgroups. However, leucopenia was observed more often in both tocilizumab groups, which is a well-known adverse event of this bDMARD, and this might suggest that adverse events were reported properly. We did not, however, investigate radiographic progression, which would have provided further data on safety of tapering of abatacept and tocilizumab, especially in the long term.

Lastly, successful DR appears to be persistent in this study. A recent study reported persistent response up to 2 years in patients prolonging the tocilizumab interval from 4 to 5 or 6 weeks [28]. Other studies reported outcomes with a fixed follow-up time of 6–18 months [15, 16, 18, 19, 21–24], and our study adds that successful DR or discontinuation persists up to 72 months in a subset of patients. Although we did not investigate medication cost, one may infer that this is associated with a significant cost reduction.

Our study has some important limitations. Firstly, owing to the relatively low patient numbers, CIs are large and results should be interpreted with caution. Of course, although superiority tests could not demonstrate differences, this cannot be interpreted as proof of equivalence, as the latter needs comparison of the CI with an *a priori* chosen non-inferiority margin. Furthermore, at baseline, the prevalence of concomitant csDMARD use was low. However, abatacept and tocilizumab are equally effective as monotherapy compared with combination therapy, and indeed, are registered in the USA as such [29, 30]. Furthermore, at least for tocilizumab, it is shown that tapering is equally successful in patients with and without concomitant MTX [23]. Also,

concomitant csDMARD use has been shown not to be a predictor for successful DR [30].

In contrast to most other studies, we used low disease activity (DAS28 <3.2) instead of remission to define successful DR or discontinuation. This was done because remission is reached in only 30–80% of patients [31–35], because remission is not always attainable, and because protocol adherence of a physician to adjust medication in the event that disease activity rises above remission level is suboptimal (~65%) [35], reflecting discordance with this strict goal. Furthermore, lower disease activity before tapering has not been shown to be a predictor for a higher chance of successful tapering [36].

All in all, dose optimization of abatacept and tocilizumab in daily clinical practice appears to be feasible and safe in a clinical practice setting. However, no benefits in terms of fewer adverse events in the DR groups have yet been observed. Future research should provide further information on possible predictors of successful DR, long-term effects of dose optimization of these drugs, and the risk of radiographic joint damage. Furthermore, protocol adherence might be improved by research on possible facilitators and barriers of dose optimization.

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Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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