

Original article

Drug adherence, response and predictors thereof for tocilizumab in patients with rheumatoid arthritis: results from the Swedish biologics registerHelena Forsblad-d'Elia¹, Karin Bengtsson¹, Lars Erik Kristensen² and Lennart T. H. Jacobsson¹**Abstract**

Objective. To evaluate drug adherence, clinical response and predictors thereof for tocilizumab in patients with RA in routine care based on prospectively collected data from the Swedish biologics register, Anti-Rheumatic Therapies in Sweden.

Methods. RA patients who had started with tocilizumab from September 2008 until March 2012 were identified. Cox regression and logistic regression models were used.

Results. A total of 530 RA patients were included, of whom 80.6% were female, 64.7% were on concomitant DMARDs, of which 300 were on MTX and 12% were biologic naive. The overall 6 month, 1 and 2 year estimated drug continuations were 79%, 64% and 50%, respectively. In the multivariate analyses, a low initial level of CRP [hazard ratio (HR) 0.76/1s.d. (95% CI 0.63, 0.91)], high HAQ score [HR 1.23/1s.d. (95% CI 1.06, 1.44)] and prior exposure to different biologics [HR 1.43 (95% CI 1.12, 1.83)] were predictors for drug termination, whereas concomitant DMARD therapy was not. European League Against Rheumatism (EULAR) good, moderate, and no response were achieved by 184 (46.7%), 133 (33.8%) and 77 (19.5%) patients, respectively. Predictors for EULAR good response vs no response (at 2.5–8 months) were low HAQ [odds ratio (OR) 0.56/1s.d. (95% CI 0.40, 0.78)], high 28-joint DAS [OR 2.0/1s.d. (95% CI 1.44, 2.78)] and not being on prednisolone [OR 0.47 (95% CI 0.25, 0.88)] at baseline.

Conclusion. In this RA cohort treated with tocilizumab, the estimated 1 year drug continuation was 64% and 80% of the patients achieved a EULAR response. Drug discontinuation was not predicted by no concomitant DMARD, but by low CRP, high HAQ and prior exposure to biologics.

Key words: tocilizumab, register, outcome, drug survival, clinical response, predictor.

Rheumatology key messages

- Tocilizumab continuation and EULAR good response rates were not predicted by concomitant DMARD use in RA.
- Tocilizumab discontinuation was predicted by low CRP, high HAQ and exposure to biologics in RA.
- EULAR response, good or moderate, was achieved by tocilizumab in 80% of the RA patients.

Introduction

Treatment for RA has developed dramatically over recent decades, with the introduction of several new biologic drugs in addition to older DMARDs. One such agent is tocilizumab, which is a recombinant humanized mAb that acts as an IL-6 receptor antagonist. Randomized controlled trials (RCTs) have demonstrated efficacy in patients who are inadequate responders to MTX [1, 2], other DMARDs [3, 4] and TNF inhibitors [5], at the expense of a moderate increase in serious adverse effects. Data from

¹Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg and ²Department of Rheumatology, Lund University Hospital, Lund, Sweden

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Correspondence to: Helena Forsblad-d'Elia, Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Box 480, S-405 30 Gothenburg, Sweden. E-mail: helena.forsblad@vgregion.se

RCTs further suggest that tocilizumab may be as effective in monotherapy as when given in combination with MTX [6, 7].

Results from RCTs are limited by their strict inclusion criteria and their restricted time span, which hampers the generalizability of the results to clinical practice. It is therefore important to also follow and report drug adherence, effectiveness and side effects in a real-world setting. Observational data from Japan [8, 9] and Europe [10–12] have demonstrated drug continuation and response rates for tocilizumab in the range of those demonstrated in RCTs and similar to those for TNF inhibitors [13–18]. The observational studies have not reported extensively regarding predictors for drug discontinuation and response, partly due to limited sample sizes, ranging from 74 to 229 patients [8–12]. Since the knowledge about predictors to indicate which patients are likely to benefit the most from the available biologic drugs is limited, more data are needed on predictors and characteristics of response, on combination therapy and on drug adherence in clinical practice.

Our aims, based on the Anti-Rheumatic Therapies in Sweden (ARTIS) data, were thus to report on drug adherence to tocilizumab and on response, defined as European League Against Rheumatism (EULAR) response rates, as well as to identify predictors thereof among Swedish patients with RA who were receiving their first treatment course with tocilizumab in routine care.

Method

Patients

Patients with RA initiating treatment with tocilizumab in routine care during the period 20 September 2008 to 23 March 2012 were identified in the Swedish Rheumatology Quality (SRQ) register, which contains the ARTIS cohort of patients exposed to biologic treatment. Although it is not mandatory for treating clinicians to report to ARTIS, the coverage of the register is reported to be 87% [19].

Data on gender, age, year of RA onset, RA subtype (seropositive, seronegative, other), 28-joint DAS (DAS28) [20], 28-joint swollen joint count, 28-joint tender joint count, patient global assessment on a visual analogue scale (VAS), HAQ [21], ESR, CRP, concomitant DMARDs, concomitant prednisolone, previous biologics, dosage and interval of tocilizumab infusions and reason for withdrawal of tocilizumab were extracted from the register. The extracted information was carefully quality controlled for missing and odd data and a national quality coordinator contacted regional quality coordinators to fill in missing data and correct odd data. No imputations of remaining missing data were performed. Patients without a DAS28 score at the start of tocilizumab treatment and without a year of onset were excluded. If a patient had one or more treatment periods with tocilizumab, then the first period was chosen. Patients were mostly treated with tocilizumab 8 mg/kg every 4th week, which is the approved dose in Sweden. The dose could be reduced to 4 mg/kg every 4th week by the treating physician

according to the summary of product characteristics of tocilizumab. The study was approved by the Regional Ethics Board in Stockholm, Sweden, since the Stockholm County Council is responsible for the SRQ. The patients included in the SRQ have given their informed consent to be part of the quality register. Consent is documented in the SRQ. No consent from the patients was needed to use the collected data in the registry for this particular study.

Drug continuation

The overall, 6 month, 1 and 2 year drug continuation rates were estimated by survival analyses. Predictors of drug termination were searched for.

Clinical response

Clinical response was assessed by per protocol analysis by identifying registered DAS28 scores from 2.5 to 8 months follow-up ($n=394$). Within this interval, the first DAS28 score values were chosen. The percentages of patients with EULAR good, moderate or no response and of patients achieving low disease activity (LDA), DAS28 <3.2 or remission (DAS28 <2.6) were calculated [22]. Predictors of EULAR good response vs no response were searched for. In addition, treatment response at 6 months ($n=298$) is presented as both per protocol and intention to treat using the LUNDEX principle. The LUNDEX adjustment is an intention-to-treat method developed for the observational setting to account for both withdrawals from therapy and missing response recordings at certain points of follow-up. The equation for calculation of the LUNDEX is Fraction of starters still in the study at time $t \times$ Fraction responding at time t [23].

Discontinuation of tocilizumab

The rationale for terminating the drug treatment was investigated. Different options for discontinuing are available in the register: side effect, no effect, diminished effect, patient's decision, death, inactive disease/remission, pregnancy, other reason and unknown. The various reasons were grouped into safety: side effects; lack of efficacy: no effect and diminished effect; other: patient's decision, inactive disease/remission, pregnancy and other reason; and death.

Statistical analyses

Statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC, USA). Descriptive statistics are presented as mean (s.d.) or median (range). Continuation with tocilizumab was analysed by Kaplan–Meier curves with log-rank tests of equality across strata and with univariate and multivariate Cox proportional hazard regression analyses. Sensitivity analyses evaluating concomitant DMARD therapy time dependently was also performed. Patients' data were censored for any clinical follow-up beyond 15 months since the last visit. Predictors for EULAR good vs no response were assessed with univariate and multiple logistic regression analyses. Hazard ratios (HRs) and odds ratios (ORs) were for

TABLE 1 Characteristics of the 530 RA patients treated with tocilizumab included in the analyses

Characteristic	Value
Sex, <i>n</i> (%)	
Women	427 (80.6)
Men	103 (19.4)
Age, mean (s.d.), years	57.8 (12.7)
Disease duration, mean (s.d.), years	14.3 (10.7)
Seropositive RA, <i>n</i> (%)	396 (74.7)
Follow-up time, mean (s.d.), years	1.0 (0.8)
ESR, mean (s.d.), mm/1 h	36.2 (26.1)
CRP, mean (s.d.), mg/l (<i>n</i> = 529)	26.7 (31.8)
DAS28, mean (s.d.), score	5.4 (1.3)
HAQ, mean (s.d.), score (<i>n</i> = 493)	1.4 (0.6)
Concomitant DMARDs, <i>n</i> (%)	
MTX	273 (51.5)
MTX in combination with another DMARD	27 (5.1)
DMARD, expect MTX	43 (8.1)
No DMARD	187 (35.3)
MTX dose/week, mean (s.d.), mg (<i>n</i> = 299)	16.3 (5.5)
Glucocorticosteroid (prednisolone), <i>n</i> (%)	329 (62.1)
Prednisolone, mean (s.d.), dose/day, mg	8.0 (4.7)
Previous biologics, <i>n</i> (%)	
Biologic naive	63 (11.9)
≥1 TNF inhibitor and no other biologic	285 (53.8)
≥1 TNF inhibitor and abatacept or rituximab	182 (34.3)
Patients starting each year with tocilizumab, <i>n</i> (%)	
2008	1 (0.2)
2009	120 (22.6)
2010	196 (37.0)
2011	172 (32.5)
2012	41 (7.7)
Discontinuing tocilizumab during follow-up, <i>n</i> (%)	199 (37.5)
Reasons for discontinuing	
Safety: side effects	71 (35.7)
Lack of efficacy: no effect, diminished effect	87 (43.7)
Other: patients' decision, inactive disease/remission, pregnancy, other reason	37 (18.6)
Death	4 (2.0)

Data are presented for 530 patients, but where data are missing, the number of patients is given.

non-dichotomous variables expressed per 1 s.d. change of the analysed covariate. All tests were two-tailed and $P < 0.05$ was considered statistically significant.

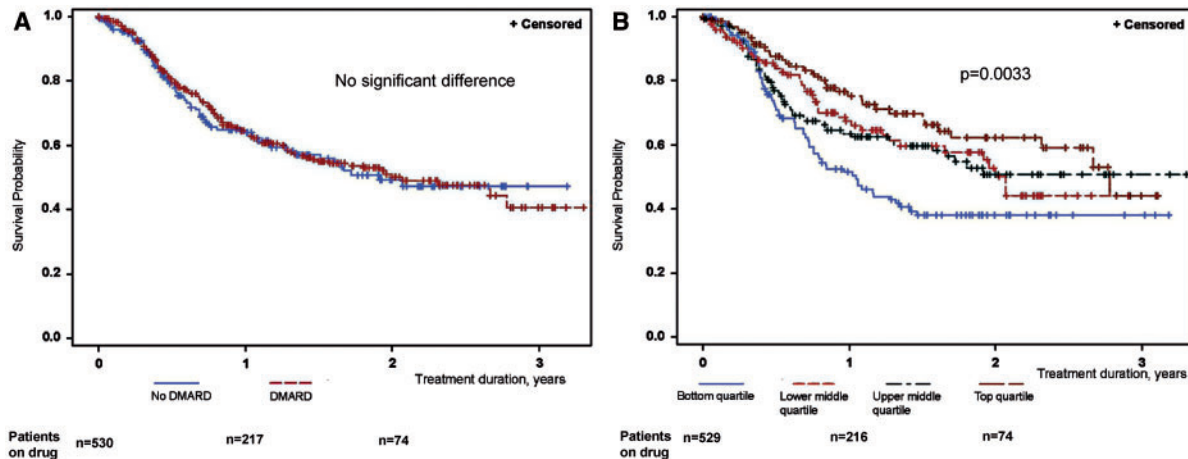
Results

A total of 648 RA patients started tocilizumab treatment, of which 530 (82%) were included in this report. For the remainder, information on the DAS28 score or disease duration at baseline was missing. Four hundred and twenty-seven (80.6%) were female. The mean age and disease duration at the start were 57.8 years (s.d. 12.7) and 14.3 years (s.d. 10.7), respectively. One hundred and eighty-seven patients (35.3%) started on monotherapy, whereas 343 (64.7%) were treated with concomitant DMARDs, of which 300 (56.6%) were treated with MTX. Baseline characteristics between patients with and without concomitant DMARD did not differ

significantly with regard to most variables (gender, age, proportion with seropositive RA, treated with glucocorticosteroids, follow-up time, ESR, CRP, DAS28, HAQ, reasons for discontinuing), although they had a shorter disease duration (13.4 vs 16.1 years, $P < 0.0045$) and less often were biologic naive (9.9 vs 15.5%, $P < 0.007$). Sixty-three (12%) patients were biologic naive, 285 (53.8%) were previously treated with one or more TNF inhibitor and 182 (34.3%) were treated with one or more TNF inhibitor and one or more other biologic drug (rituximab and/or abatacept). Of the 530 patients included, 199 patients stopped treatment with tocilizumab during the follow-up period. Reasons for discontinuation are shown in Table 1.

Drug continuation assessed by Kaplan–Meier curves

The overall 6 month, 1 and 2 year estimated drug continuation rates were 79%, 64% and 50%, respectively.

Fig. 1 Survival probability of tocilizumab with (A) concomitant DMARD or not and (B) CRP divided into quartiles

The continuation rates differed significantly depending on previous exposure to biologics ($P < 0.0003$). The estimated 1 year drug continuation rate was 81% for biologic-naïve patients, 66% for those previously treated with one or more TNF inhibitor and 54% for those previously treated with one or more TNF inhibitor and rituximab or abatacept. The mean follow-up time from the start of tocilizumab was 1.0 year (s.d. 0.8) and the median follow-up period was 0.78 years (range 0–3.3). Being on any DMARD or combination of DMARDs was not associated with longer drug continuation probability compared with those without concomitant DMARD therapy, whereas high levels of CRP compared with low levels (CRP divided into quartiles) predicted a longer drug maintenance probability ($P = 0.0033$) (Fig. 1).

Predictors for drug discontinuation assessed by Cox proportional hazard regression analyses

Univariate analyses revealed that female gender, initial low level of CRP and/or ESR, initial higher HAQ value and having been exposed to an increasing number of biologics were predictors for drug discontinuation. Age, disease duration, having seropositive RA, the level of DAS28, having concomitant treatment with any DMARD or being on steroids was not associated with drug discontinuation (Table 2). In a sensitivity analysis evaluating concomitant DMARD therapy in a time-dependent fashion, the result was similar [HR 1.08 (95% CI 0.80, 1.45)] to that only taking into account concomitant DMARD therapy at baseline [HR 0.96 (95% CI 0.72, 1.29)]. In the multivariate model, initial low CRP level, high HAQ level and having been exposed to previous biologics remained significant determinants for drug termination of tocilizumab (Table 2). The year of starting with tocilizumab was not associated with drug discontinuation. The year 2009 was used as the comparator year.

Clinical response assessed by the EULAR response criteria

Three hundred and ninety-four patients (74.3%) had one or more DAS28 value from between 2.5 and 8 months follow-up. Baseline characteristics between patients with and without data on response did not differ significantly with regard to most variables (gender, age, proportion with seropositive RA, treated with glucocorticosteroids, disease duration, ESR, CRP, DAS28, HAQ), although those with existing response data had a longer follow-up time [1.1 years (s.d. 0.8) vs 0.71 (s.d. 0.7), $P < 0.0001$] and more often stopped due to primary or secondary lack of efficacy (47% vs 31%, $P < 0.03$). The number and percentage of EULAR good, moderate, and no responders were 184 (46.7%), 133 (33.8%) and 77 (19.5%), respectively. Two hundred and five (52.0%) patients achieved LDA and 147 (37.3%) patients achieved remission according to the EULAR response criteria.

Six month clinical response assessed by the LUNDEX method

Two hundred and ninety-eight patients had DAS28 response data at the 6 month follow-up. In Table 3, both the per protocol response rates and the LUNDEX corrected response rates are shown. Overall, the LUNDEX correction decreased the response rates, with 7–10% due to treatment withdrawal compared with per protocol-reported responses. The LUNDEX responses ranged from 60.4% achieving EULAR moderate or good response to 28% achieving DAS remission at 6 months of follow-up.

Predictors for achieving EULAR good response

Logistic regression analyses were performed to search for predictors of EULAR good vs no response among the 394 patients with response data between 2.5 and 8 months of follow-up (Table 4). Significant predictors for EULAR good response vs no response in the multiple logistic regression

TABLE 2 Predictors for discontinuing tocilizumab in univariate and multivariate analyses

Variable	Univariate analyses, HR (95% CI)	Multivariate analyses, HR (95% CI)
Sex, men vs women	0.62 (0.41, 0.92)	0.80 (0.53, 1.21)
Age, per 1 s.d.	0.90 (0.78, 1.04)	0.94 (0.81, 1.09)
Disease duration, per 1 s.d.	0.99 (0.86, 1.13)	
Seropositive RA, yes vs no	0.91 (0.65, 1.28)	
ESR, per 1 s.d.	0.80 (0.69, 0.94)	
CRP, per 1 s.d.	0.79 (0.66, 0.93)	0.76 (0.63, 0.91)
DAS28, per 1 s.d.	1.07 (0.96, 1.19)	
HAQ, per 1 s.d.	1.23 (1.07, 1.41)	1.23 (1.06, 1.44)
DMARD, yes vs no	0.96 (0.72, 1.29)	
Glucocorticosteroid, yes vs no	1.11 (0.82, 1.49)	
Previous exposure to biologics, biologics naive vs ≥ 1 TNFi vs ≥ 1 TNFi and abatacept or rituximab	1.50 (1.19, 1.88)	1.43 (1.12, 1.83)

Significant predictors for discontinuing tocilizumab found in the univariate analyses (CRP, HAQ, previous exposure to biologics and age) were inserted in the multivariate model as independent covariates and discontinuing tocilizumab as the outcome. DAS28: 28-joint DAS; HR: hazard ratio; TNFi: TNF inhibitor.

TABLE 3 Clinical per protocol- and LUNDEX-corrected 6 month EULAR response rates to tocilizumab in 298 RA patients

6 month response	Per protocol response, %	LUNDEX-corrected response, %
EULAR response		
Good	44.3	34.9
Moderate	32.2	25.4
None	23.5	39.6
Disease activity		
Low disease activity, DAS28 <3.2	49.7	39.2
Remission, DAS28 <2.6	35.5	28.0

DAS28: 28-joint DAS; EULAR: European League Against Rheumatism.

analysis were low HAQ level, high DAS28 score and not being treated with glucocorticosteroids at baseline. Age, disease duration, having seropositive RA, initial level of CRP or ESR, concomitant treatment with any DMARD and previous exposure to biologics were not significant predictors of EULAR good response. Only 2 of the 394 patients stopped or started concomitant DMARD therapy between the baseline visit and this follow-up.

Discussion

This study presents drug continuation rates, clinical response and predictors thereof in a population of tocilizumab-treated RA patients in routine care. The maintenance rate of tocilizumab at 6 months is similar to those published previously in smaller observational studies [8, 10].

Due to the larger sample size and longer follow-up, we are able to extend these observations and search for predictors for drug survival and response. The drug survival rates observed for tocilizumab are in the lower range of what has been reported from previous studies of anti-TNF-treated RA patients [13–17]. On the other hand, the EULAR response rates are comparable to results from other cohorts [15].

In addition, this study identifies low CRP level, high exposure to previous biologics and higher HAQ level at baseline as predictors of tocilizumab termination. However, no differences were found between patients treated with or without concomitant DMARDs (mainly MTX). This is in accordance with RCTs such as the ADACTA (Adalimumab ACTemra) trial, suggesting tocilizumab provides good clinical response in monotherapy [24], and the ACT-RAY study, which demonstrated similar outcomes in patients with an inadequate MTX response, irrespective of whether tocilizumab was given as monotherapy or in combination with MTX [7], and also with a recently published observational retrospective study on tocilizumab [12]. In contrast, concomitant DMARDs seem to improve drug adherence and treatment response in anti-TNF-treated patients [11, 25].

The finding that the overall drug continuation rates for tocilizumab were somewhat lower than rates observed for cohorts of anti-TNF-treated patients [13–17] probably represents a channelling bias. Thus it was demonstrated in the current study of patients with a mean disease duration of 14.3 years that as many as 88% of patients had received courses of other biologic treatments prior to tocilizumab and 62.1% of the patients were on glucocorticosteroids, indicating a patient group with severe and long-standing disease. Moreover, higher exposure to different biologic treatments was associated with poor drug continuation. Patients not exposed to biologics showed an estimated 1 year continuation rate of 81%, compared

TABLE 4 Predictors for good vs no EULAR response in univariate and multivariate analyses

Variable	Univariate analyses, OR (95% CI)	Multivariate analyses, OR (95% CI)
Sex, women vs men	0.93 (0.50, 1.70)	
Age, per 1 s.d.	1.25 (0.96, 1.63)	
Disease duration, per 1 s.d.	0.97 (0.74, 1.26)	
Seropositive RA, yes vs no	1.00 (0.52, 1.94)	
ESR, per 1 s.d.	1.20 (0.91, 1.59)	
CRP, per 1 s.d.	1.22 (0.91, 1.64)	
DAS28, per 1 s.d.	1.43 (1.09, 1.88)	2.00 (1.44, 2.78)
HAQ, per 1 s.d.	0.74 (0.56, 0.98)	0.56 (0.40, 0.78)
DMARD, yes vs no	0.81 (0.45, 1.44)	
Glucocorticosteroid, yes vs no	0.52 (0.29, 0.93)	0.47 (0.25, 0.88)
Previous exposure of any biologics, yes vs no	0.64 (0.28, 1.47)	

Predictors of clinical response in patients with registered DAS28 scores at 2.5–8 months of follow-up ($n = 394$). Significant predictors found in the univariate analyses (DAS28, HAQ, glucocorticosteroids) were inserted in the multivariate model as independent covariates and EULAR good (1) vs no (0) response as the outcome. DAS28: 28-joint DAS; EULAR: European League Against Rheumatism; OR: odds ratio.

with the overall 1 year continuation rate of 64%. Taken together, these factors might explain the reason for the somewhat overall inferior drug adherence levels found in this study compared with studies of the first treatment course with TNF inhibitors.

The finding that a high HAQ score was significantly associated with earlier treatment termination is in line with studies of anti-TNF drug survival in RA patients [13, 15, 17]. In contrast, high CRP level at inclusion seemed to reduce treatment termination, which has also been demonstrated in anti-TNF-treated cohorts [17] and in a tocilizumab-treated cohort, where rapid normalization of CRP was associated with longer drug continuation rate [26]. Thus patients with a high level of systemic inflammation may have a larger potential for improvement in clinical status when an immunosuppressive drug such as tocilizumab is administered. On the other hand, the direct effect of tocilizumab on the IL-6–CRP axis gives an inherent laboratory response that might persuade the clinician to continue treatment despite a poor response in joint counts and patient-reported outcome.

In our study, the proportions reaching LDA or remission were 52% and 37%, respectively, which is slightly lower than or comparable to some previous observational studies [8–10, 12] and in phase IIIb trials [4, 27, 28]. In these studies, the proportions having had previous treatment with TNF inhibitors were in general lower [4, 8, 9, 27, 28]. The response rates were comparable to those reported from other observational cohorts for anti-TNF treatment [15, 29].

In order to study how the subgroup of patients adhering to tocilizumab experienced considerable clinical effect, we applied the LUNDEX index, a valuable tool for evaluating drug efficacy in observational studies [23]. For instance, we found that in the completer analyses, 44.3% of the patients displayed a good EULAR response, whereas the rate decreased to a modest level of 34.9% after applying the LUNDEX method. This illustrates the

importance of also reporting intention-to-treat data in the observational setting [23].

Several predictors of EULAR good response vs no response were discovered. High disease activity was identified as a predictor of EULAR good treatment response, whereas higher HAQ scores and prednisolone usage at treatment initiation predicted a reduced chance of responding to therapy. Leffers *et al.* [10] reported on tocilizumab from the Danish DANBIO registry that a higher baseline DAS28 score was associated with achieving a low DAS28 score and a lower HAQ score was associated with better response. Pers *et al.* [12] reported recently that low age, high CRP and no history of cardiovascular disease were predictors of EULAR response, but the impact of HAQ was not evaluated. Both these studies were based on much smaller cohorts compared with ours. In line with our results, a lower HAQ score at baseline as a predictor for EULAR response has also been found in anti-TNF-treated cohorts [15, 29, 30].

The observational character of this study, reflecting real-world experience in terms of drug continuation in a nationwide setting covering an estimated 87% of all patients with RA treated with biologics, represents a strength of this study [19]. On the other hand, the open, non-randomized nature of this study may induce bias in the process of selecting patients for particular treatments and the subsequent collection of data. Such confounding by indication is an inherent problem in all observational studies, which we tried to adjust for as far as possible in Cox regression modelling. Another limitation is that we have not been able to capture shorter interruptions in treatment with tocilizumab during follow-up.

Conclusion

In summary, tocilizumab treatment of RA patients in this clinical setting showed drug continuation rates and treatment responses similar to those in RCTs. Concomitant DMARDs did not have significant impact on drug

termination or response to treatment, supporting tocilizumab as an effective monotherapy biologic drug. Lower CRP levels, high exposure of previous biologics and higher HAQ levels at baseline predicted drug discontinuation.

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