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EXTENDED REPORT

Effectiveness of tocilizumab with and without synthetic disease-modifying antirheumatic drugs in rheumatoid arthritis: results from a European collaborative study

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ABSTRACT

Objectives To examine the effectiveness of tocilizumab (TCZ) with and without synthetic disease-modifying antirheumatic drugs (sDMARDs) in a large observational study.

Methods Patients with rheumatoid arthritis treated with TCZ who had a baseline visit and information on concomitant sDMARDs were included. According to baseline data, patients were considered as taking TCZ as monotherapy or combination with sDMARDs. Main study outcomes were the change of Clinical Disease Activity Index (CDAI) and TCZ retention. The prescription of TCZ as monotherapy was analysed using logistic regression. CDAI change was analysed with a mixed-effects model for longitudinal data. TCZ retention was analysed with a stratified extended Cox model.

Results Multiple-adjusted analysis suggests that prescription of TCZ as monotherapy varied according to age, corticosteroid use, country of the registry and year of treatment initiation. The change of disease activity assessed by CDAI as well as the likelihood to be in remission were not significantly different whether TCZ was used as monotherapy or in combination with sDMARDs in a covariate-adjusted analysis. Estimates for unadjusted median TCZ retention were 2.3 years (95% CI 1.8 to 2.7) for monotherapy and 3.7 years (lower 95% CI limit 3.1, upper limit not estimable) for combination therapies. In a covariate-adjusted analysis, TCZ retention was also reduced when used as monotherapy, with an increasing difference between mono and combination therapy over time after 1.5 years (p=0.002).

Conclusions TCZ with or without concomitant sDMARDs resulted in comparable clinical response as assessed by CDAI change, but TCZ retention was shorter under monotherapy of TCZ.

INTRODUCTION

Biological disease-modifying antirheumatic drugs (bDMARDs) have markedly changed the management and outcome of rheumatoid arthritis (RA). Tocilizumab (TCZ), a monoclonal anti-interleukin-6 receptor antibody, has proven to be efficacious in patients who did not respond to methotrexate (MTX) or other synthetic DMARDs (sDMARDs), as well as after failure to respond to tumour necrosis factor (TNF) antagonists, and to prevent the progression of structural damage.[1–3] These findings have led to the inclusion of TCZ in the algorithm of RA management as a first-line bDMARD after MTX failure similar to TNF antagonists or abatacept.[4]

Most international guidelines recommend the use of bDMARDs in combination with MTX or other sDMARDs in case MTX is not tolerated or contraindicated.[4] These recommendations are primarily based on the observation that MTX enhances the efficacy of TNF antagonists in both clinical trials and observational studies.[5–7] In two randomised clinical trials including adult patients with RA with inadequate response to MTX, patients were randomised to receive either intravenous TCZ as monotherapy or in combination with MTX. The results of these studies showed that, when considering some endpoints, the combination with MTX offered some advantage over TCZ as monotherapy. However, both strategies were associated with meaningful clinical and radiographic responses.[8–11] To date, however, data from large, observational, multinational studies on TCZ effectiveness are lacking.

The objective of this study, based on data from several European registries, was to analyse the characteristics of patients who were treated with TCZ as monotherapy and the effectiveness of TCZ, with particular attention to its use as monotherapy or in combination with MTX or different sDMARDs.

METHODS

Patient population

The TOcilizumab Collaboration of European Registries in RA is an investigator-led, industry-supported initiative with the aim to evaluate clinical aspects of TCZ use in patients with RA. Each registry obtained ethical approval for the use of anonymised data for research separately. The data-contributing registries were ATTRA (http://www.attra.registry.cz), Czech Republic (CS);

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DANBIO (http://www.danbio-online.dk), Denmark (DK); ROB-FIN (http://www.reumatologinenyhdistys.fi), Finland (FI); DREAM-RA (http://www.dreamregistry.nl), the Netherlands (NL); NOR-DMARD, Norway (NO); Reuma.pt (http://www.reuma.pt), Portugal (PT); ARBITER, Russia (RU); BioRx.si, Slovenia (SI); SRQ (Swedish Rheumatology Quality Register, http://www.srq.nu), Sweden (SE); SCQM (Swiss Clinical Quality Management in Rheumatic Diseases, http://www.scqm.ch), Switzerland (CH). All patients included in the different registries who had started treatment with TCZ by the end of 2013/beginning of 2014 were considered eligible for the present study if (1) the patient had a diagnosis of RA established by a rheumatologist, (2) the patient had initiated TCZ treatment after the end of 2008 at an age of 18 years or older, (3) a baseline visit within 90 days prior to start of TCZ was available and (4) baseline information on the use of sDMARD co-therapy were available. In the rare case of patients who have experienced several treatment courses (TCs) with TCZ (identified by a difference of at least 60 days between stop and restart of TCZ treatment) after 2008 for which the above-stated inclusion criteria were met, the earliest one was selected. Any follow-up visit for which the available information allowed to conclude, unambiguously, that it had occurred after the start of TCZ and before 60 days after stop of TCZ treatment was considered valid and included.

Exposure of interest

TCZ treatments were classified as either monotherapy ('TCZ') or as one of three types of combination therapy with sDMARDs such as (1) with MTX only ('TCZ+MTX'), (2) with MTX and at least one other sDMARD ('TCZ+MTX_{plus}') or (3) with at least one other sDMARD ('TCZ+other'), depending on the presence of concomitant sDMARDs at baseline.

Study outcomes

Our main focus was on investigating the change of disease activity following initiation of TCZ therapy in terms of Clinical Disease Activity Index (CDAI) and TCZ retention in relation to the type of TCZ therapy. TCZ retention was defined as the time from the start date of TCZ treatment until the TCZ discontinuation date. If TCZ had not been discontinued, TCZ retention was censored at the date of the last reported follow-up visit. For TCZ retention, only patients who had not been lost to follow-up immediately after start of TCZ and who were not from Russia where regular treatment with TCZ had been discontinued for administrative reasons in a number of patients were regarded eligible. We also used the disease activity score (DAS) 28 as a secondary outcome measure. The DAS28 calculation for a given patient was based on either the erythrocyte sedimentation rate (ESR) three*item formula (28 joint counts for tender and swollen joints and the ESR in mm/h) or the C reactive protein (CRP) three-item formula (with CRP in mg/L), depending on the amount of available and valid information for ESR and CRP, with a preference for the ESR-based formula. For 60% of patients, the ESR-based formula was used.

Covariates

The baseline covariates considered were sex, age, disease duration, number of previously used biologics, seropositivity (presence of rheumatoid factor (RF) or anticyclic citrullinated peptide antibodies (anti-CCP)), corticosteroid use, functional disability (Health Assessment Questionnaire (HAQ)), DAS28, year of TCZ treatment start and country of registry. Details on covariates are described in the online supplementary material.

Statistical methods

The prescription of TCZ as monotherapy versus in combination with sDMARDs in relation to patient characteristics at baseline was analysed using logistic regression analyses. CDAI and DAS28 change over time was visualised by means of smoothing using a local quadratic regression approach and analysed with mixed-effects models for longitudinal data. TCZ retention was analysed using Kaplan–Meier and Cox models, with the addition of time-varying covariate effects (extended Cox models). The frequency of disease remission (CDAI <2.8 or DAS28 <2.6) under treatment was assessed at various times post-TCZ start. For 16–34% of patients, depending on the analysis, information for at least one covariate was missing. We reanalysed our main analyses (prescription of monotherapy, TCZ retention and CDAI/DAS28 change) based on multiple imputation of missing covariate data. Detailed information on statistical methods, models and software is available from the online supplementary material.

RESULTS

A total of 2057 patients fulfilling all the inclusion criteria and providing a total of 13 131 follow-up visits were retrieved from the different registries. Of the 1498 patients with available information, all but 52 started TCZ treatment with a dose of ≥6 mg/kg. A flow chart of the patients considered eligible and included in the different analyses is shown in online supplementary figure S1.

Baseline patient characteristics associated with TCZ prescription

TCZ was most frequently initiated in combination with MTX (1011 TCs), followed by TCZ as monotherapy (577 TCs), TCZ with sDMARDs other than MTX (285 TCs) and, lastly, by TCZ in combination with MTX and other sDMARD(s) (184 TCs). For the majority of patients (89% for TCZ, 68% for TCZ +MTX, 61% for TCZ+MTX_{plus} and 73% for TCZ+other), sDMARD co-therapy did not change over time. A description of patient characteristics by type of TCZ treatment is provided in online supplementary table S1.

The results from a multiple-adjusted analysis of the probability of prescribing TCZ as monotherapy suggest that (1) countries differ in their prescription attitude with respect to TCZ as monotherapy, (2) TCZ as monotherapy has become more frequent over the years, (3) it is more frequently prescribed to older patients with RA and (4) it is more frequently prescribed to patients without concomitant corticosteroid therapy (table 1). Due to their effect on the prescription of monotherapy, these four covariates must be regarded as potential confounding variables with respect to TCZ treatment.

The results from an analysis based on multiple imputation of missing covariates were comparable to those from the reported complete-case analysis (data not shown).

Change of disease activity

The CDAI at baseline of TCZ initiation was influenced by country of registry, year of TCZ treatment initiation, the number of prior biologics and sex (online supplementary table S2). The CDAI decreased rapidly after the start of TCZ, regardless of whether TCZ was used as monotherapy or in combination with sDMARDs (figure 1). A virtually identical result was observed when disease activity was assessed using DAS28 (online supplementary figure S2). A covariate-adjusted longitudinal analysis of both CDAI and DAS28 provided similar results

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Table 1 Summary of baseline covariates and their relation to prescription of tocilizumab (TCZ) as monotherapy

Covariate		Summary (n=2057)	Prescription of TCZ as monotherapy	
			Proportion of mono (%)	OR (95% CI) for mono (n=1359)
Age (years)		55 (13.1) 56 (46–64)		1.38 (1.11 to 1.71) per 20 years more
Sex (%) (n=2056)	Male	21	24	Reference
	Female	79	29	1.30 (0.92 to 1.83)
Disease duration (years) (n=1900)		11.4 (9.5) 9.1 (4.1–16.1)		1.11 (0.96 to 1.27) per 10 years more
Seropositivity (%) (n=1891)	No	18	27	Reference
	Yes	82	28	1.08 (0.75 to 1.54)
Number of prior biologics (%) (n=2056)	0	19	29	Reference
	1	26	26	0.82 (0.54 to 1.25)
	≥2	55	28	0.76 (0.51to 1.13)
Corticosteroids (%) (n=2011)	No	51	33	Reference
	Yes	49	22	0.74 (0.56 to 0.99)
DAS28 (n=1914)		5.0 (1.4) 5.1 (4.1–6.0)		1.14 (0.89 to 1.45) per 2 units more
HAQ (n=1673)		1.4 (0.7) 1.5 (1.0–2.0)		0.95 (0.77 to 1.19) per 1 unit more
Year of TCZ initiation (%)	2009	15	19	Reference
	2010	23	22	1.23 (0.78 to 1.96)
	2011	20	24	1.40 (0.87 to 2.25)
	2012	22	35	2.07 (1.30 to 3.28)
	2013	20	38	2.58 (1.62 to 4.10)
Country (%)	Czech Republic	12.9	23	0.66 (0.39 to 1.12)
	Denmark	35.5	31	0.92 (0.60 to 1.39)
	Finland	2.3	11	0.36 (0.10 to 1.27)
	The Netherlands	2.4	28	–
	Norway	3.8	52	–
	Portugal	8.4	15	0.46 (0.24 to 0.87)
	Russia	4.1	11	0.30 (0.12 to 0.79)
	Slovenia	9.5	21	0.28 (0.14to 0.55)
	Sweden	6.4	38	1.41 (0.82 to 2.44)
	Switzerland	14.7	34	Reference

Sample sizes (n) equal the number of eligible patients presented in the header of column 'Summary' unless indicated otherwise. The column named 'Summary' provides a description of covariates in terms of mean (SD) and median (IQR) for discrete or continuous covariates and percentages for categorical covariates. The column named 'Proportion of mono' provides the frequency of monotherapy-initiated TCZ treatment for each category of a categorical covariate. The last column presents estimated ORs and 95% Wald CIs for prescribing TCZ as monotherapy (as compared to any type of combination therapy) based on multiple logistic regression. ORs for discrete or continuous covariates are presented for a difference corresponding approximately to the IQR. For categorical covariates, ORs with respect to the chosen reference category are shown. p Values from likelihood ratio tests for categorical covariates with more than two categories were 0.41 for number of prior biologics, <0.0001 for year of TCZ initiation and <0.0001 for country. The multiple logistic regression is based on all TCs with complete covariate information. The Netherlands (patchy data) and Norway (no HAQ recorded) lack TCs with complete covariate information.
DAS, disease activity score; HAQ, Health Assessment Questionnaire; TC, treatment courses.

with respect to the effect of TCZ treatment as monotherapy or in combination with sDMARDs. The estimated differences in CDAI between the four treatment groups at various times based on the longitudinal model are shown in table 2. Some covariates had significant effects on CDAI change, such as country of registry, year of TCZ treatment initiation and number of previously used biologics (online supplementary table S2). Similar results were obtained for DAS28 (see online supplementary material). An analysis based on multiple imputation of missing covariates provided results comparable to those from the complete-case analysis, especially with respect to the effect of type of TCZ treatment (data not shown). Combining the different combination therapy groups into one group resulted in the same conclusions for CDAI and DAS28 (data not shown).

The frequency of disease remission in terms of CDAI (CDAI<2.8), as assessed at various times after TCZ initiation, was about 20% overall (figure 2). At 6 months, the covariate-adjusted OR for CDAI remission in patients treated with TCZ in combination with MTX versus TCZ as monotherapy was 1.03 (95% CI 0.76 to 1.40). The respective OR at 12 months was 1.06 (95% CI 0.79 to 1.42). For 'TCZ +MTX_{plus}' and 'TCZ+other' versus 'TCZ', the ORs were 0.79 (95% CI 0.49 to 1.27) and 0.77 (95% CI 0.50 to 1.16) at 6 months and 0.81 (95% CI 0.52 to 1.28) and 0.81 (95% CI 0.54 to 1.21) at 12 months. Comparable data were observed for DAS28 remission (see online supplementary material), with the exception of an overall higher frequency of DAS28 remission in all treatment groups.

TCZ retention

Discontinuation of TCZ therapy was observed in 700 (39%) of the 1798 eligible patients. Main causes for discontinuation were lack of effectiveness (mentioned for 50% of discontinued patients for monotherapy and 52% for combination therapies)

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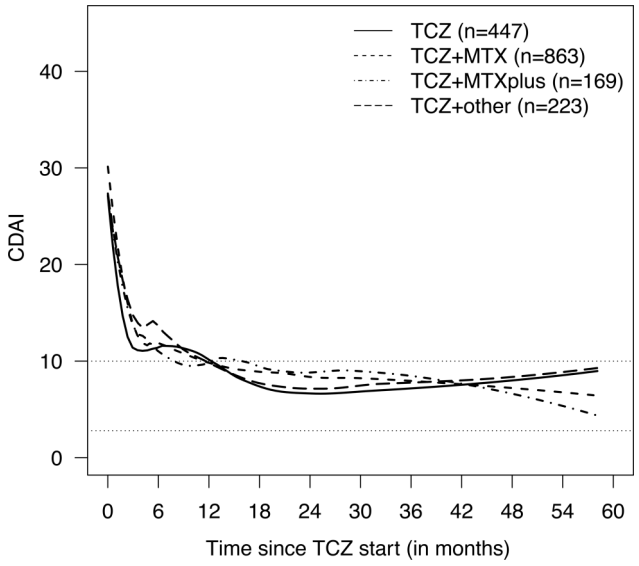

Figure 1 Smoothed time courses of Clinical Disease Activity Index (CDAI) by tocilizumab (TCZ) treatment. The data represent all 1702 eligible patients with at least one CDAI value totalling 9943 observations. Data were smoothed separately for each TCZ treatment using local quadratic regression. Treatment groups 'TCZ', 'TCZ+methotrexate (MTX)', 'TCZ+MTX$_{plus}$', and 'TCZ+other' represent TCZ as monotherapy and in combination with MTX, MTX+other synthetic disease-modifying antirheumatic drugs (sDMARD(s)), and at least one sDMARD other than MTX, respectively. Numbers of patients providing CDAI information beyond 12, 24, 36 and 48 months were 162, 76, 32 and 7 for 'TCZ', 427, 262, 133 and 41 for 'TCZ+MTX', 80, 41, 21 and 11 for 'TCZ+MTX$_{plus}$', and 90, 55, 27 and 11 for 'TCZ+other', respectively. Of note, all Swedish patients were excluded due to lack of a global physician's assessment of disease in this registry.

and safety issues (mentioned for 32% of discontinued patients for monotherapy and 28% for combination therapies). In 23 patients (5 from monotherapy and 18 from combination therapies), TCZ was discontinued due to disease remission.

Unadjusted estimates of TCZ retention curves suggest that, at later times, TCZ is more often discontinued when initiated as monotherapy, as compared to when initiated in combination therapy (all three types of combination therapy combined) (figure 3). Respective estimates for unadjusted median retention were 2.3 years (95% CI 1.8 to 2.7) for monotherapy and 3.7 years (lower 95% CI limit: 3.1, upper limit not estimable; see figure 3) for combination therapies. This conjecture was supported by the finding of a time-dependent effect of TCZ treatment on the hazard for TCZ discontinuation in both an unadjusted and covariate-adjusted analysis. In both cases, we observed an increasing difference with time after 1.5 years (table 3). Of all other covariates, only seropositivity and HAQ were found to significantly affect the hazard for TCZ discontinuation (online supplementary table S4). There were also major differences in TCZ retention curves between countries (online supplementary figure S4).

The results from the analysis based on multiple imputation of missing covariates were comparable to those from the reported complete-case analysis, particularly with respect to the effect of type of TCZ treatment (data not shown).

Table 2 Estimated differences in Clinical Disease Activity Index (CDAI) between type of tocilizumab (TCZ) treatments at various times

Time (months)	TCZ+MTX vs TCZ Estimate (95% CI)	TCZ+MTX$_{plus}$ vs TCZ Estimate (95% CI)	TCZ+other vs TCZ Estimate (95% CI)
2	0.44 (−0.94 to 1.81)	1.54 (−0.49 to 3.57)	1.90 (−0.01 to 3.80)
6	0.30 (−0.97 to 1.57)	1.38 (−0.51 to 3.27)	1.62 (−0.14 to 3.38)
12	0.10 (−1.10 to 1.30)	1.15 (−0.64 to 2.93)	1.22 (−0.44 to 2.87)
18	−0.10 (−1.35 to 1.14)	0.91 (−0.92 to 2.74)	0.81 (−0.87 to 2.51)
24	−0.31 (−1.70 to 1.08)	0.68 (−1.34 to 2.69)	0.41 (−1.47 to 2.29)

Estimated differences and 95% Wald-type CIs for each combination treatment versus monotherapy based on a covariate-adjusted longitudinal mixed effects analysis are shown. A positive difference means that CDAI under monotherapy is estimated lower than under the respective combination treatment at this time point. The p values (from F-tests) for an effect of type of TCZ treatment were 0.16 for the initial linear decrease over 2 months and 0.46 for the subsequent linear phase. All 1428 eligible patients with information on CDAI and complete covariate information were included. The distribution of patients between the four TCZ treatments was comparable to the whole population. Overall, 281 patients lacked a baseline CDAI and 242 provided only one CDAI value (for 176 of these this was the baseline value). Of note, all Swedish patients were excluded due to lack of a global physician's assessment of disease in this registry. All patients from the Netherlands were excluded due to incomplete data.
MTX, methotrexate.

DISCUSSION

This study included a large number of patients with RA from different European countries treated with TCZ in either monotherapy or in combination with MTX or different combinations of sDMARDs. Prescription of TCZ as monotherapy varied according to some intrinsic patient characteristics (age and use of corticosteroids), as well as the extrinsic factors, country of the registry and year of treatment initiation. The change of disease activity assessed by CDAI and DAS28, as well as the likelihood to be in remission, was not significantly different whether TCZ was used as monotherapy or in combination with sDMARDs. However, TCZ retention was more prolonged when TCZ was prescribed in combination with sDMARDs.

Despite current recommendations to use bDMARDs with MTX or other sDMARDs, several reports from different countries show that in routine practice approximately 30% of patients with RA receive bDMARDs as monotherapy. In this study, we observed that older patients were more likely to be treated with TCZ as monotherapy. This result is consistent with two other observational studies that have shown that monotherapy with bDMARDs is more often prescribed to older patients with also longer disease duration, a higher number of previous DMARDs and more comorbidities.[7 12] Thus, it is likely that patients treated in TCZ monotherapy represent a subgroup of patients who are more difficult to manage and exhibit intolerance to MTX and other sDMARDs. Unfortunately, comorbidities were not captured by most registries, thus limiting our analysis on the influence of other medical conditions on the use of TCZ as monotherapy. However, it is plausible that older multimorbid patients could have been preferentially treated with TCZ alone rather than in combination with MTX or other sDMARDs.

Taking advantage of the inclusion of registries representing different European countries, we have observed significant differences regarding the prescription of TCZ. Variations regarding local treatment recommendations, as well as TCZ licensing (in combination with MTX or sDMARDs), most likely explain these variations. The significant increase in the prescription of TCZ as monotherapy over the years, and particularly after 2012, is likely explained by the results of studies demonstrating that TCZ as monotherapy is a reasonable treatment option.[8 10] Furthermore, TCZ as monotherapy was significantly more efficacious than adalimumab as monotherapy in patients with RA with inadequate response to MTX.[13]

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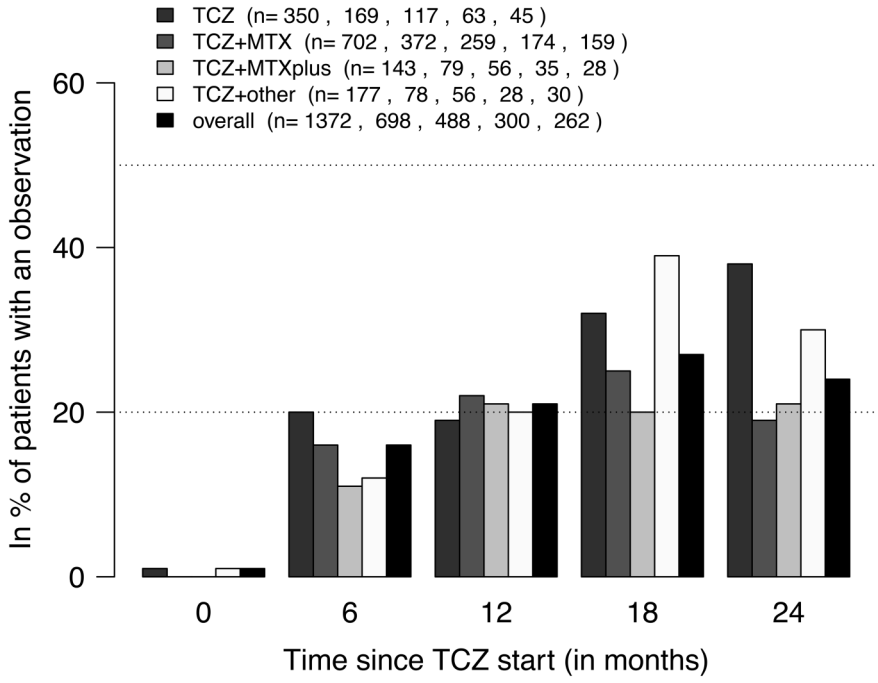

Figure 2 Frequency of Clinical Disease Activity Index (CDAI) remission (CDAI <2.8) by tocilizumab (TCZ) treatment. The numbers (n) shown in the legend indicate the number of ongoing treatment courses for which a CDAI value was available within ±30 days of a certain post-baseline time point. At none of the time points was there a significant difference between TCZ treatment types (Fisher's exact tests at 5% level). Treatment groups 'TCZ', 'TCZ+ methotrexate (MTX)', 'TCZ+MTX$_{plus}$' and 'TCZ+other' represent TCZ as monotherapy and in combination with MTX, MTX+other synthetic disease-modifying antirheumatic drugs (sDMARD(s)) and at least one sDMARD other than MTX, respectively.

The efficacy of TCZ as monotherapy in comparison to its use in combination with MTX or other sDMARDs in patients with RA with inadequate response to MTX has been examined in clinical trials. The ACT-RAY study examined the efficacy and safety of switching to TCZ monotherapy or adding TCZ to MTX in patients with active disease despite MTX therapy. The results after 24 weeks did not show any advantage of the combination over TCZ as monotherapy.[8] After 52 weeks, patients treated with TCZ in combination with MTX had a significantly higher percentage of DAS28 remission, a lower erosion score and a higher percentage of patients without radiographic progression. Of note, all other clinical endpoints did not differ between the two treatment groups.[9] After 104 weeks, the two treatment groups were also significantly different regarding changes in total radiographic and erosion scores but not for clinical endpoints.[10] Using a similar study design, other investigators showed that ACR response rates and the percentage of patients who achieved DAS28 remission after 52 weeks were not significantly different in the monotherapy group compared with the combination group (70.3% vs 72.2%).[14] Taken together, the results of these clinical trials suggest that concomitant use of MTX provides a slight advantage for some endpoints. A 24-week large open-labelled study comparing the efficacy and safety of TCZ used as monotherapy or in

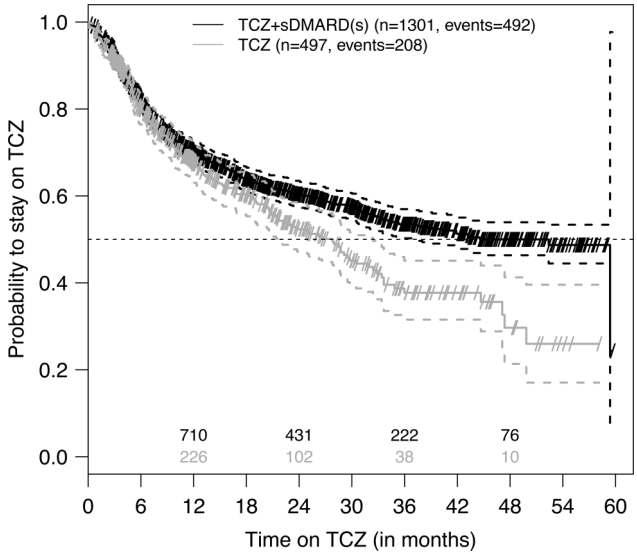

Figure 3 Kaplan–Meier plot of tocilizumab (TCZ) retention by TCZ treatment. These unadjusted data represent all 1798 eligible patients. Small diagonal lines indicate censored retention times (at date of last follow-up visit), dashed lines 95% CIs for the survival curves and numbers above the x-axis denote the numbers of patients known to be still at risk for TCZ discontinuation (ie, still on TCZ and not yet lost to follow-up). Treatment groups 'TCZ' and 'TCZ+ synthetic disease-modifying antirheumatic drugs (sDMARD(s))' represent TCZ as monotherapy and in combination with sDMARDs, respectively. For 'TCZ+sDMARD(s)' the upper 95% CI line does not cross the 50% line for the probability to stay on TCZ resulting in an unestimable upper 95% CI limit for the median retention time.

Table 3 Effect of tocilizumab (TCZ) monotherapy on hazard for TCZ discontinuation over time

	HR	95% CI	p Value
TCZ vs TCZ+sDMARD(s)			
In first 1.5 years	1.10	0.87 to 1.39	0.41*
At 2 years	1.54	1.19 to 1.99	0.003†
At 3 years	3.00	1.62 to 5.56	
At 4 years	5.86	2.07 to 16.57	

Shown are estimated HRs, 95% Wald CIs and associated p values at various times based on a country-stratified, covariate-adjusted extended Cox proportional hazards analysis of TCZ retention.
*p Value for the effect of TCZ treatment (monotherapy vs combination therapy) in the first 1.5 years,
†p Value for the change in the effect of TCZ treatment with time after 1.5 years. All 1198 eligible patients who had not been lost to follow-up immediately, were not from Russia and had complete covariate information were included (number of events=464). The distribution of patients and events between TCZ treatments was comparable to the case with all 1798 eligible patients. Of note, all patients from Norway and the Netherlands were excluded due to lack of complete covariate information.
sDMARD, synthetic disease-modifying antirheumatic drugs.

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combination with sDMARDs in 1681 patients with RA with inadequate response to sDMARDs or TNF inhibitors found that TCZ had comparable efficacy and safety when used as monotherapy or in combination with sDMARDs.[15] In an observational registry study from Japan, the odds to achieve DAS28 remission were not different in patients treated with TCZ alone or in combination with MTX. However, there was an increased probability for achieving remission for TCZ in combination compared with TCZ alone in a subset of patients with high baseline DAS28 >5.1.[16]

We observed that TCZ retention was shorter in patients treated with TCZ as monotherapy compared with the groups treated in combination with sDMARDs. Drug retention can be influenced by many factors, including effectiveness, tolerance, remission, costs and patients' or physicians' preferences. We could not easily explain this finding by differences in effectiveness or safety. The marked variations of treatment retention observed between registries could be reflective of differences in local licensing, treatment recommendations, economic situation or available treatment options. Of note, the difference in TCZ retention between mono and combination therapy of TCZ seemed irrelevant for the first 1.5 years and then increased over time. It is thus possible that after an initial improvement in disease activity patients under TCZ monotherapy start to flare sooner than patients under TCZ in combination with sDMARDs, leading to an increased hazard for TCZ discontinuation at later times. However, our data analysis did not show such a behaviour (data not shown). Of note, after a 104-week follow-up, the proportion of patients in the monotherapy group who withdrew because of lack of efficacy was numerically larger than in the combination treatment group in ACT-RAY.[10]

Our study included a relatively large group of patients followed longitudinally for several years, representative of different practices in Europe. It may, however, suffer from potential limitations inherent to the analysis of observational data. Confounding by indication may result in biased estimates for the effect of type of TCZ treatment. We counteracted this in our covariate-adjusted analyses, but we cannot exclude the presence of residual confounding by other unmeasured confounders. For example, apart from the number of biologics received prior to TCZ treatment, we have not considered any other information relating to previous treatments. Another possible confounder missing from our investigations is the presence of comorbidities. Missing data is another potential concern. We have rerun some of our analyses based on multiple imputation of missing covariates and obtained comparable results to our complete-case analysis, particularly for the type of TCZ treatment. We prefer the complete-case analysis over the multiple imputation approach for several reasons. A complete-case analysis is unbeatable in its simplicity and non-error-prone implementation. Furthermore, after careful consideration of the likely missingness mechanisms at work, we concluded that a complete-case analysis is more likely to give unbiased results than an analysis based on multiple imputation.[17–19] Our international collaboration was useful to increase the number of patients treated with TCZ for our analyses. However, we observed important heterogeneity between countries with a clear impact on treatment habits, the prescription of TCZ, as well as in drug retention that may lead to difficulty in interpreting the data.

In conclusion, we have found that age, corticosteroid use, country of residence and year of treatment initiation influenced prescription of TCZ as monotherapy. TCZ with or without concomitant sDMARDs resulted in comparable clinical response, but TCZ retention was reduced under TCZ monotherapy.

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Data sharing statement All the data are presented in the main manuscript and in the online supplementary material.

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Supplementary material (online only)

METHODS

Covariates

Disease duration at the baseline visit was calculated as the time from date of diagnosis to the baseline visit date except for patients from the Netherlands where only year of first symptoms was available. In this special case, it was calculated from June 15th of the year of first symptoms. Seropositivity was defined for each patient as follows: If RF or anti-CCP were positive, then seropositivity was set to "yes". Otherwise, if both were negative or one was negative and the other missing, then seropositivity was set to "no". Local laboratories determined levels of RF and anti-CCP and local cut-off values for positivity were applied. Corticosteroid use was set to "yes" if a patient was under corticosteroid therapy at the baseline visit and "no" otherwise. All patients who had started on or after January 1st 2013 were considered as having started in 2013, including those who had started beginning of 2014.

Statistical methods

The significance level was set at 5% for all analyses. Tests were two-sided. No correction for multiple testing was performed except when testing the effect of a categorical covariate with more than two levels. In those cases we used an F-test or a likelihood ratio test.

Summary statistics

Discrete or continuous variables are summarized in terms of mean, standard deviation, median, and first and third quartile. Categorical variables are summarized in terms of frequencies of categories. Treatment groups were compared using Kruskal–Wallis tests for discrete or continuous variables and Fisher's exact tests for categorical variables.

Prescription of TCZ as monotherapy

In order to examine whether the prescription of TCZ as monotherapy as compared to in combination with sDMARDs is affected by patient baseline characteristics, we modeled the probability for initiating TCZ as monotherapy in terms of patient characteristics using multiple (simultaneous consideration of all covariates) logistic regression with a logit link function. For each covariate, the results are presented in terms of odds ratios and two-sided 95%-Wald-type confidence intervals for prescribing TCZ as monotherapy.

Longitudinal analysis of DA

The CDAI and DAS28 values obtained at the baseline visit were carried forward to the start of TCZ therapy in cases where the baseline visit took not place on the day of TCZ therapy start. For Russian patients, where regular TCZ therapy was discontinued at six months post TCZ start, only visits until six months were considered for the analyses. The course of CDAI and DAS28 over time by TCZ treatment is visualized by means of smoothing using a local quadratic regression approach. The smoothing parameter was set by visual inspection. CDAI and DAS28 were modeled longitudinally using a linear mixed effects model with a biphasic linear time function, that is, an initial linear decrease after start of TCZ followed by a subsequent different linear behaviour over time (equivalent to a linear spline model with one knot and continuity restriction). The length of the initial linear phase resulting in the largest likelihood of the model among a few alternatives (30, 60, 91, and 182 days) was selected (60 days for both CDAI and DAS28). The biphasic model was implemented using two different time terms, time1 and time2, where time1 equaled time since TCZ start for the duration of the initial linear phase and duration of the initial linear phase thereafter (i.e. 60 days) and time2 equaled zero for the duration of the initial linear phase and time since TCZ start minus duration of the initial linear phase thereafter. Random intercept, time1, and time2 terms were allowed for each patient. All previously listed covariates except DAS28 at baseline and HAQ at baseline were included in the model. All covariates except TCZ treatment were allowed to

affect the baseline (intercept), the initial linear phase (that is an interaction with time1), and the subsequent linear phase (that is an interaction with time2). TCZ treatment was only allowed to affect the initial linear phase and the subsequent linear phase because the type of TCZ treatment can only be effective after start of TCZ. The effect of a categorical covariate with more than two levels on the baseline or any of the two subsequent linear phases was assessed based on F-tests. To assess whether a given covariate does at all affect the post-baseline course of DA we performed likelihood ratio tests with a model excluding both time interactions of that covariate. Effect estimates and two-sided 95%-Wald-type confidence intervals are presented. To illustrate the estimated effect of type of TCZ treatment we derived estimated differences between each combination treatment and monotherapy based on the fitted linear mixed effects model at various times post start of TCZ. For each estimated difference we derived two-sided 95%-Wald-type confidence intervals.

Frequency of disease remission under treatment

At baseline of TCZ therapy and at various times post-baseline (6, 12, 18, and 24 months) we calculated the frequency of remission (in terms of CDAI <2.8 as well as DAS28 < 2.6) based on the available data within a certain time window around a chosen time point. Any patient with an available baseline value contributed this data point to the baseline data set. For post-baseline time points we selected for each patient with ongoing TCZ treatment the value closest to the chosen time point (with a preference for the one obtained prior to the chosen time point in case of two closest) if within a time window of ± 30 days of the chosen time point. Any data obtained outside of all the selected time windows was disregarded. The frequency of remission was assessed with respect to the total number of available values at a given time point (overall or by TCZ treatment). Fisher's exact tests were used to test for independence of disease remission and TCZ treatment type at each time point.

Adjusted odds ratios for disease remission under treatment

Adjusted odds ratios for remission (in terms of CDAI and DAS28) of each TCZ combination treatment versus TCZ as monotherapy and corresponding 95%-confidence intervals at 6 and 12 months after start of TCZ therapy were derived based on the estimated covariate-adjusted biphasic linear mixed effects model for CDAI and DAS28. In order to do this we assumed that CDAI and DAS28 follow a logistic distribution with location parameter equal to the fitted linear predictor from the biphasic linear mixed effects model and scale parameter s equal to $\frac{\sqrt{3}}{\pi}$ times the estimated error standard deviation. Based on this logistic distribution we then derived log odds ratios and two-sided 95%-confidence intervals for remission (CDAI < 2.8 and DAS28 < 2.6) conditional on s at various times post TCZ start and exponentiated the results to get odds ratios and corresponding confidence intervals.

TCZ retention

Retention of TCZ was analyzed using methods for time to event data with right censoring. Patients with a censored retention time of zero were excluded. These were cases where a patient had been lost to follow-up immediately after start of TCZ, i.e. where there was neither a date recorded for TCZ discontinuation nor for a follow-up visit. In addition, all patients from Russia were excluded because regular treatment with TCZ was discontinued after 6 months due to administrative reasons in a number of patients. In cases where TCZ was discontinued immediately, i.e. on the same day as it was started, we added half a day to the time on TCZ.

To assess the effect of TCZ initiated as monotherapy ("TCZ") on the hazard for TCZ discontinuation compared to combination treatments we combined the three combination treatments ("TCZ+MTX", "TCZ+MTX_{plus}", and "TCZ+other") into one treatment group ("TCZ+sDMARD(s)").

For a description of unadjusted retention by TCZ treatment a Kaplan-Meier plot was used and unadjusted median retention times were derived for each TCZ treatment.

The hazard for TCZ discontinuation was modeled using an extended (i.e. allowing for time-dependent effects of covariates) Cox proportional hazards model stratified by country considering all other previously listed covariates. Stratification by country allows to model a different unspecified baseline hazard for each country (i.e., not assuming a proportional hazard for the different countries) at the cost of not providing a means to test for differences between countries. The effects of the other covariates were, however, assumed to be the same in all countries and to obey the proportional hazard assumption except for TCZ treatment. For TCZ treatment, the proportional hazard assumption was clearly violated and we therefore allowed for a non-proportional effect of TCZ treatment over time. The length of the initial phase (18 months), where we assumed a constant effect of TCZ treatment on the hazard for TCZ discontinuation, was selected among a few alternatives (0, 6, 12, 18, and 24 months) based on maximal likelihood. For each covariate, the results are presented in terms of hazard ratios and two-sided 95%-Wald-type confidence intervals. To illustrate its estimated effect over time, we derived hazard ratios for monotherapy versus combination therapies based on the fitted extended Cox model at various times post start of TCZ. For each estimated hazard ratio we derived two-sided 95%-Wald-type confidence intervals.

Multiple imputation of missing covariate data

Multiple imputation of missing baseline covariate information was performed under the "missing at random" (MAR) premise. We used the following variables as predictors in the imputation: country of registry, year of TCZ treatment start, TCZ treatment type, age at baseline, cumulative hazard at end of TCZ treatment duration (observed or censored), indicator for observed TCZ discontinuation, number of prior biologics, sex, corticosteroid use at baseline, DAS28 at baseline, estimated initial linear decrease in DAS28, estimated later

slope in DAS28, disease duration, seropositivity, HAQ, CDAI at baseline, estimated initial linear decrease in CDAI, and estimated later slope in CDAI. We imputed missing values using predictive mean matching for DAS28 at baseline, CDAI at baseline, disease duration, and HAQ, Bayesian linear regression for estimated slopes in DAS28 and CDAI, logistic regression for dichotomous variables (sex, corticosteroid use, and seropositivity), and a multinomial model for categorical variables with more than two levels (number of prior biologics). The imputed values for disease duration were forced to be consistent with the range of observed differences between age and disease duration. We generated 35 completed data sets, i.e. we ended up having 35 imputed values for each missing value in the original data set. Our final main analyses were then re-run based on each of the 35 completed data sets (restricting to the originally eligible patients for each analysis, e.g., 1798 for TCZ retention) and the results combined using "Rubin's rules" [1].

Software

Data were extracted from the different registries using locally established software and made available to the project statistician as EXCEL or .csv files. Data preparation and analysis was then performed with the R language and environment for statistical computing [2]. For logistic regression models we used the function glm of the base package stats. To fit smoothed courses of disease activity over time we used the function loess.smooth from package stats. To fit models for the longitudinal course of disease activity over time we used the function lme as well as the function anova (for F-tests or likelihood ratio tests) from package nlme. The function fisher.test from stats was used to test for independence of disease remission and TCZ treatment. For the analysis of TCZ retention we used the functions survfit, coxph, and cox.zph from the survival package. Multiple imputation of missing covariate data was done with the package mice [1].

RESULTS

Online supplementary Figure S1 details the number of patients who fulfilled an increasing number of inclusion criteria along with information on the number of eligible patients with complete covariate information. Of the 2057 patients, nine had previous experience with TCZ. The following covariates information was missing for some of the 2057 eligible patients (in increasing order of number of missing values): number of prior biologics (missing for 1 patient), sex (missing for 1 patient), corticosteroid use (missing for 46 patients), DAS28 at baseline (missing for 143 patients), disease duration (missing for 157 patients), seropositivity (missing for 166 patients), and HAQ (missing for 384 patients). The majority of patients missed information on only one of these variables. A total of 1360 eligible patients had complete covariate information and 1731 patients had complete covariate information when not considering HAQ and DAS28 at baseline. Regarding registries, the following orders were observed with respect to increasing proportions of missing covariate information: CS (16%), SI (21%), SE (21%), RU (26%), PT (29%), DK (34%), FI (34%), CH (41%), NL (98%), and NO (100%), and SE (1%), RU (5%), CH (5%), CS (9%), NO (10%), FI (13%), PT (13%), SI (21%), DK (22%), and NL (86%) (when not considering HAQ and DAS28 at baseline). Of note, the one Dutch patient with complete covariate information (including HAQ and DAS28 at baseline) was not considered for the respective analyses. In addition, Sweden's SRQ does not record the global physician's assessment of disease resulting in missing CDAI.

Change in disease activity

We have found no evidence for a difference between TCZ treatment types in the post-baseline time course of DAS28 based on the linear mixed effects model, but observed significant effects of similar directions as for CDAI: 1) for country, year of TCZ treatment initiation, sex, and, age on baseline DAS28 (higher with higher age) and 2) for country, year of TCZ treatment initiation, and number of previously used biologics on the post-baseline time course

(details not shown). Online supplementary Table S3 shows estimated differences in DAS28 between types of treatments at various times post start of TCZ based on our longitudinal model.

Based on the estimated covariate-adjusted mixed effects model we derived covariate-adjusted odds ratios for DAS28 remission. At 6 months the odds for DAS28 remission after starting TCZ in combination with MTX were 1.03 times the odds for DAS28 remission after starting TCZ as monotherapy (95%-confidence interval (CI): 0.76 to 1.40). The respective odds ratio (OR) at 12 months was 1.06 (95%-CI: 0.79 to 1.42). For "TCZ+MTX_{plus}" and "TCZ+other" versus "TCZ" the ORs were 0.79 (95%-CI: 0.49 to 1.27) and 0.77 (95%-CI: 0.50 to 1.16) at 6 months and 0.81 (95%-CI: 0.52 to 1.28) and 0.81 (95%-CI: 0.54 to 1.21) at 12 months, respectively.

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Online supplementary Table S1: Description of patient characteristics by type of TCZ treatment based on all eligible patients.

	TCZ (n=577)	**TCZ+MTX** (n=1011)	**TCZ+MTX$_{plus}$** (n=184)	**TCZ+Other** (n=285)
Age (yrs)* 	57 (13.6) 58 (48-67)	54 (12.8) 56 (46-63)	52 (13.2) 53 (45-62)	55 (12.3) 56 (47-63)
Female sex (%)	82 (n=576)	77	79	81
Disease duration (yrs)* 	12.5 (10.4) 10.0 (4.5-17.3) (n=517)	11.2 (9.5) 8.9 (3.8-15.7) (n=950)	9.1 (7.4) 7.3 (3.0-13.3) (n=167)	11.6 (8.7) 9.4 (4.7-15.8) (n=266)
Seropositivity (%)	83 (n=528)	82 (n=937)	84 (n=164)	81 (n=262)
Number of prior biologics (%)*		(n=1010)		
0	20	18	30	17
1	24	27	25	25
≥ 2	56	55	45	58
Corticosteroid use (%)*	39 (n=552)	52 (n=996)	60 (n=182)	51 (n=281)
DAS28	4.9 (1.4)	5.1 (1.4)	4.9 (1.4)	5.0 (1.4)

	5.0 (4.1-5.8) (n=520)	5.1 (4.2-6.0) (n=955)	4.9 (4.0-5.9) (n=175)	5.0 (4.1-6.0) (n=264)
HAQ	1.4 (0.7) 1.5 (1.0-2.0) (n=429)	1.4 (0.7) 1.5 (0.9-2.0) (n=841)	1.4 (0.7) 1.4 (1.0-1.9) (n=167)	1.5 (0.7) 1.5 (1.0-2.1) (n=236)
Year of TCZ treatment initiation (%)*				
2009	10	18	15	13
2010	18	25	25	23
2011	18	22	20	21
2012	27	19	18	21
2013	27	16	22	22
Country (%)*				
Czech Republic	10.6	14.7	10.3	12.6
Denmark	39.5	32.8	41.9	32.6
Finland	0.9	1.0	6.5	7.0

Netherlands	2.4	1.7	3.8	4.2
Norway	7.1	3.5	0.0	1.0
Portugal	4.5	8.6	25.0	5.3
Russia	1.5	5.1	2.7	6.3
Slovenia	7.1	14.1	1.6	3.2
Sweden	8.7	6.3	1.1	5.3
Switzerland	17.7	12.2	7.1	22.5

Sample sizes (n) equal the number of eligible patients presented in the column headers unless indicated otherwise. Mean (standard deviation) and median (interquartile range) are presented for discrete or continuous covariates and percentages for categorical covariates. Kruskal-Wallis tests were used for discrete or continuous covariates and Fisher's exact tests for categorical covariates. A p-value < 0.05 is indicated by * behind the covariate name.

Online supplementary Table S2: Results from covariate-adjusted longitudinal mixed effects analysis of CDAI (n = 1428).

	Estimate (in CDAI units)	**95%-CI**	**P**
Baseline	28.0	23.9, 32.0	< 0.0001
Sex (female vs male)	1.9	0.1, 3.7	0.041
Age (per 10 yrs more)	0.3	-0.3, 0.9	0.38
Disease duration (per 5 yrs more)	0.1	-0.3, 0.5	0.73
Seropositivity (yes vs no)	-1.4	-3.4, 0.6	0.18
Number of prior biologics			0.029
1 vs 0	-3.3	-5.8, -0.8	
2+ vs 0	-1.8	-4.2, 0.5	
Corticosteroid use (yes vs no)	0.7	-0.9, 2.3	0.40
Country			< 0.0001
CS vs CH	12.7	9.4, 16.1	
DK vs CH	3.3	0.7, 5.9	
FI vs CH	-1.8	-6.7, 3.2	
NO vs CH	1.0	-2.9, 4.9	
PT vs CH	7.2	3.8, 10.5	

RU vs CH	11.5	7.5, 15.5	
SI vs CH	17.5	14.3, 20.6	
Year of TCZ treatment initiation			< 0.0001
10 vs 09	-1.6	-4.0, 0.7	
11 vs 09	-3.6	-6.1, -1.1	
12 vs 09	-6.5	-8.9, -4.0	
13 vs 09	-5.1	-7.6, -2.5	
Initial linear decrease (over 2 months)	-16.6	-21.3, -12.0	< 0.0001
Sex (female vs male)	-1.6	-3.5, 0.4	0.11
Age (per 10 yrs more)	-0.2	-0.8, 0.5	0.56
Disease duration (per 5 yrs more)	-0.2	-0.6, 0.2	0.40
Seropositivity (yes vs no)	-0.4	-2.6, 1.7	0.69
Number of prior biologics			0.0001
1 vs 0	4.6	1.9, 7.3	
2+ vs 0	5.7	3.2, 8.2	
Corticosteroid use (yes vs no)	0.7	-1.0, 2.4	0.44
Country			< 0.0001

CS vs CH	-14.7	-18.6, -10.8	
DK vs CH	-4.7	-7.8, -1.5	
FI vs CH	-4.6	-10.5, 1.3	
NO vs CH	-2.2	-6.6, 2.2	
PT vs CH	-6.7	-10.5, -2.9	
RU vs CH	-11.2	-16.0, -6.5	
SI vs CH	-16.4	-20.1, -12.7	
Year of TCZ treatment initiation			< 0.0001
10 vs 09	2.4	-0.1, 4.9	
11 vs 09	4.4	1.8, 7.0	
12 vs 09	5.7	3.1, 8.2	
13 vs 09	6.3	3.4, 9.2	
TCZ treatment			0.16
TCZ+MTX vs TCZ	0.4	-0.9, 1.8	
TCZ+MTX_{plus} vs TCZ	1.5	-0.5, 3.6	
TCZ+other vs TCZ	1.9	-0.01, 3.8	
Subsequent linear phase (over 6 months)	-0.7	-1.6, 0.2	0.11
Sex (female vs male)	0.1	-0.2, 0.4	0.50
Age (per 10 yrs more)	-0.004	-0.1, 0.1	0.94
Disease duration	0.02	-0.05, 0.1	0.55

(per 5 yrs more)			
Seropositivity (yes vs no)	0.3	-0.1, 0.7	0.18
Number of prior biologics			0.59
1 vs 0	0.1	-0.4, 0.5	
2+ vs 0	-0.1	-0.6, 0.3	
Corticosteroid use (yes vs no)	0.1	-0.2, 0.4	0.40
Country			0.009
CS vs CH	-0.5	-1.2, 0.3	
DK vs CH	0.2	-0.3, 0.8	
FI vs CH	0.1	-1.4, 1.6	
NO vs CH	0.3	-0.6, 1.2	
PT vs CH	0.2	-0.4, 0.9	
RU vs CH	-2.2	-5.3, 0.9	
SI vs CH	-0.5	-1.2, 0.1	
Year of TCZ treatment initiation			0.69
10 vs 09	-0.0	-0.4, 0.3	
11 vs 09	-0.2	-0.6, 0.1	
12 vs 09	-0.3	-0.8, 0.2	
13 vs 09	-0.1	-2.0, 1.7	
TCZ treatment			0.46
TCZ+MTX vs TCZ	-0.2	-0.6, 0.2	

TCZ+MTX_{plus} vs TCZ	-0.2	-0.7, 0.3	
TCZ+other vs TCZ	-0.4	-0.9, 0.1	

Estimates shown for the baseline, initial linear decrease, and subsequent linear phase (over 6 months) are for a patient with the following reference covariate profile: seronegative male patient from Switzerland of mean age and with mean disease duration, starting TCZ as first biologic in 2009 without concomitant corticosteroid and conventional synthetic DMARD therapy. For discrete or continuous covariates the effect estimate and 95%-Wald-type confidence interval (CI) corresponding to a difference of approximately half the interquartile range is shown. For categorical covariates the difference of each category to the chosen reference category and associated 95%-CI is shown. Joint p-values (from F-tests) are reported for covariates modeled with more than one parameter (i.e. for all categorical covariates with more than two levels). All 1428 eligible patients with information on CDAI and complete covariate information were included. The distribution of patients between the four TCZ treatments was comparable to the whole population. Overall, 281 patients lacked a baseline CDAI and 242 provided only one CDAI value (for 176 of these this was the baseline value). Of note, all Swedish patients were excluded due to lack of a global physician's assessment of disease in this registry. All patients from Netherland were excluded due to patchy data. yrs=years, CH=Switzerland, CS=Czech Republic, DK=Denmark, FI=Finland, NO=Norway, PT=Portugal, RU=Russia, SI=Slovenia.

Online supplementary Table S3: Estimated differences in DAS28 between type of TCZ treatments at various times post start of TCZ (based on covariate-adjusted longitudinal mixed effects analysis of DAS28, n = 1700)

Time (months)	**TCZ+MTX vs TCZ** Estimate (95%-CI)	**TCZ+MTX$_{plus}$ vs TCZ** Estimate (95%-CI)	**TCZ+other vs TCZ** Estimate (95%-CI)
2	-0.004 (-0.15, 0.14)	0.11 (-0.11, 0.34)	0.13 (-0.07, 0.34)
6	-0.01 (-0.15, 0.12)	0.10 (-0.11, 0.31)	0.12 (-0.07, 0.31)
12	-0.03 (-0.16, 0.10)	0.09 (-0.11, 0.29)	0.09 (-0.08, 0.27)
18	-0.04 (-0.18, 0.10)	0.08 (-0.13, 0.29)	0.07 (-0.12, 0.26)
24	-0.05 (-0.21, 0.10)	0.07 (-0.17, 0.30)	0.05 (-0.17, 0.26)

Estimated differences and 95%-Wald-type confidence intervals (CI) for each combination treatment versus monotherapy are shown. A positive difference means that DAS28 under monotherapy is estimated lower than under the respective combination treatment at this time point. The p-values (from F-tests) for an effect of type of TCZ treatment were 0.36 for the initial linear decrease over 2 months and 0.87 for the subsequent linear phase. All 1700 eligible patients with information on DAS28 and complete covariate information were included. The distribution of TCs between the four TCZ treatments was comparable to the whole population. Overall, 80 patients lacked a baseline DAS28 and 279 provided only one DAS28 value (for 257 of these this was the baseline value).

Online supplementary Table S4: Results from country-stratified, covariate-adjusted extended Cox proportional hazards analysis of TCZ retention (n = 1198, number of events = 464).

	HR	**95%-CI**	**P**
TCZ treatment (TCZ vs TCZ+sDMARD(s))			
in first 1.5 yrs	1.10	0.87, 1.39	0.41[#]
at 2 yrs	1.54	1.19, 1.99	0.003[##]
at 3 yrs	3.00	1.62, 5.56	
at 4 yrs	5.86	2.07, 16.57	
Sex (female vs male)	1.08	0.85, 1.36	0.55
Age (per 20 yrs more)	1.03	0.89, 1.20	0.71
Disease duration (per 10 yrs more)	0.97	0.88, 1.07	0.54
Seropositivity (yes vs no)	0.65	0.52, 0.82	0.0003
Number of prior biologics			0.11
1 vs 0	0.76	0.56, 1.04	
2+ vs 0	0.95	0.71, 1.26	
Corticosteroid use (yes vs no)	0.97	0.80, 1.19	0.80
DAS28 (per 2 units more)	1.06	0.89, 1.26	0.50

HAQ (per 1 unit more)	1.18	1.02, 1.38	0.03
Year of TCZ treatment initiation			0.15
10 vs 09	1.09	0.84, 1.40	
11 vs 09	0.99	0.74, 1.33	
12 vs 09	1.09	0.79, 1.49	
13 vs 09	1.66	1.12, 2.47	

Shown are estimated hazard ratios (HRs), 95%-Wald confidence intervals (CIs), and associated p-values (P). For categorical covariates with more than two categories, the HR of each category with respect to the chosen reference category is presented. For discrete or continuous covariates HRs are shown for differences corresponding approximately to the interquartile ranges. For TCZ treatment (in terms of monotherapy ("TCZ") and combination therapies ("TCZ + sDMARD(s)")) several HRs are shown to illustrate its effect over time. [#] p-value for the effect of TCZ treatment in the first 1.5 years, [##] p-value for the change in the effect of TCZ treatment with time after 1.5 years. Joint p-values (from likelihood ratio tests) are reported for covariates modeled with more than one parameter (i.e. for all categorical covariates with more than two levels). All 1198 eligible patients who had not been lost to follow-up immediately, were not from Russia, and had complete covariate information were included. The distribution of patients and events between TCZ treatments was comparable to the case with all 1798 eligible patients. Of note, all patients from Norway and the Netherlands were excluded due to lack of complete covariate information. yrs = years.

Online supplementary Figure legends

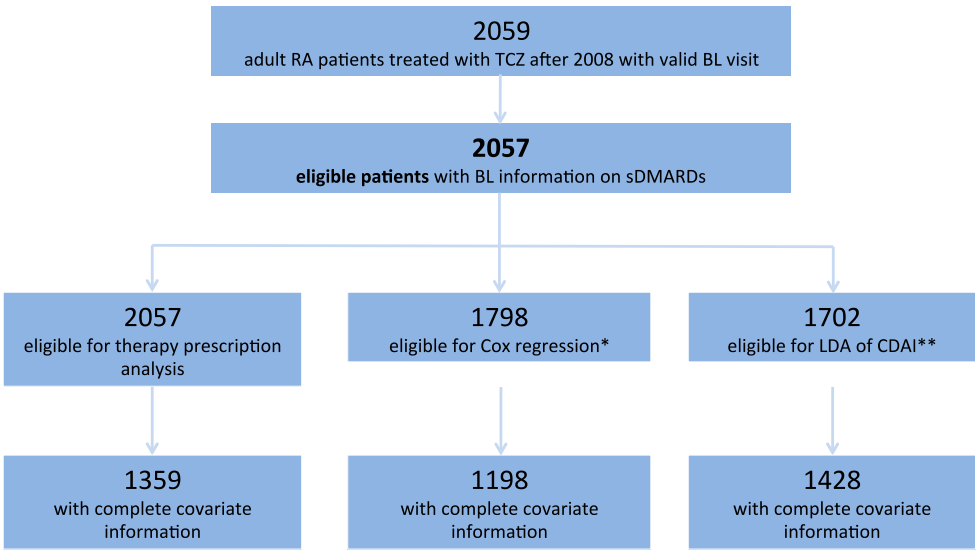
Online supplementary Figure S1. Flowchart of the study. The number of patients fulfilling increasing numbers of inclusion criteria as well as criteria for inclusion into the different types of analysis.

Online supplementary Figure S2. **Smoothed time courses of DAS28 by TCZ treatment.** The data represent all 2019 eligible patients with at least one DAS28 value totaling 12328 observations. Data were smoothed separately for each TCZ treatment using local quadratic regression. Treatment groups "TCZ", "TCZ+MTX", "TCZ+MTX_{plus}", and "TCZ+other" represent TCZ in monotherapy and in combination with MTX, MTX + other sDMARD(s), and at least one sDMARD other than MTX, respectively. Numbers of patients provinding DAS28 information beyond 12, 24, 36, and 48 months were, 205, 92, 37, and 9 for "TCZ", 480, 304, 152, and 45 for "TCZ+MTX", 82, 44, 25, and 12 for "TCZ+MTX_{plus}", and 107, 62, 31, and 12 for "TCZ+other", respectively.

Online supplementary Figure S3. Frequency of DAS28 remission (DAS28 < 2.6) by TCZ treatment. The numbers (n) shown in the legend indicate the number of ongoing treatment courses for which a DAS28 value was available within ± 30 days of a certain post-baseline time point. For baseline, all patients with a baseline DAS28 were used. At none of the time points was there a significant difference between TCZ treatment types (Fisher's exact tests at 5% level). Treatment groups "TCZ", "TCZ+MTX", "TCZ+MTX_{plus}", and "TCZ+other" represent TCZ in monotherapy and in combination with MTX, MTX + other sDMARD(s), and at least one sDMARD other than MTX, respectively.

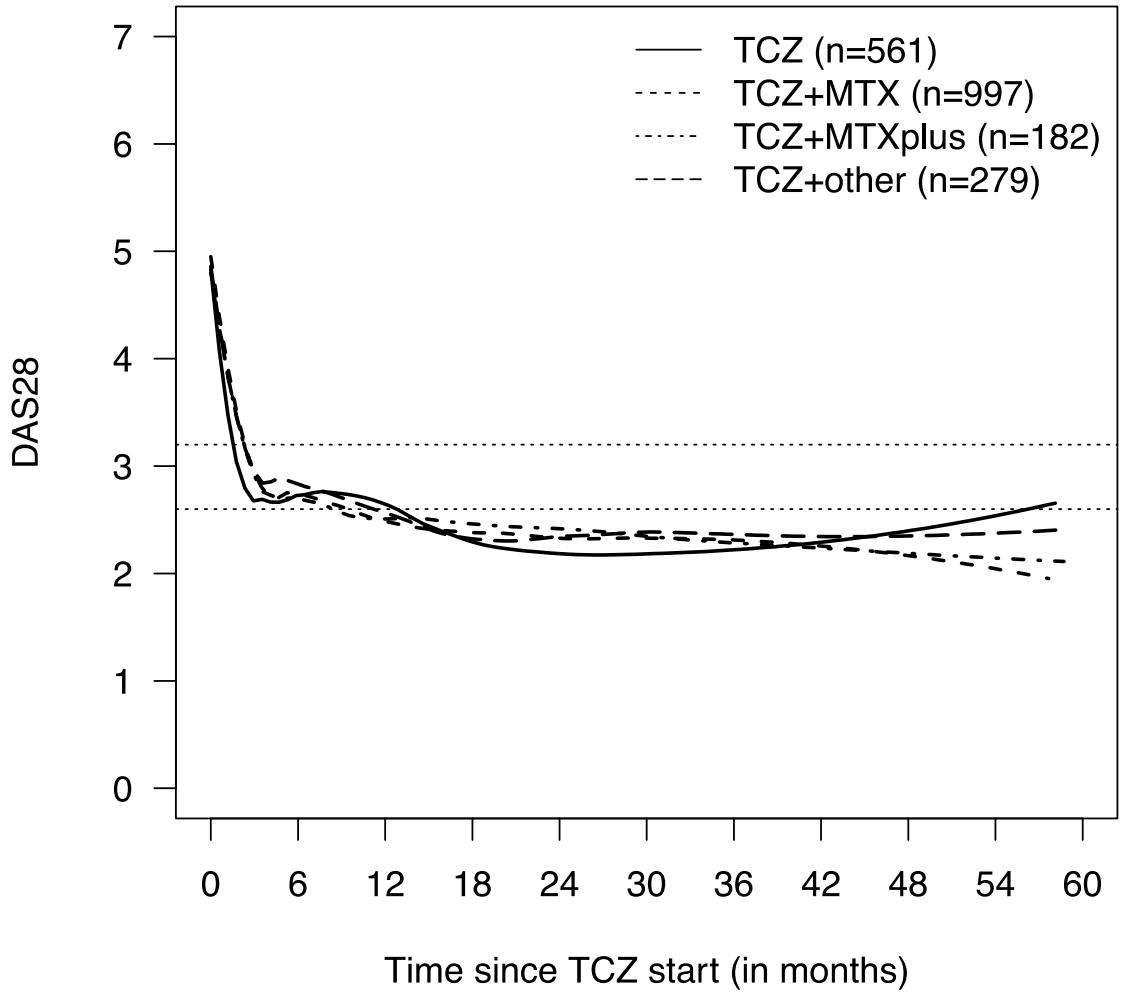
Online supplementary Figure S4. Kaplan-Meier plot of TCZ retention by country of registry. The data represent all 1798 eligible patients who had not been lost to follow-up immediately and were not from Russia. Small diagonal lines indicate censored retention times (at date of last follow-up visit).

Online supplementary Figure S1

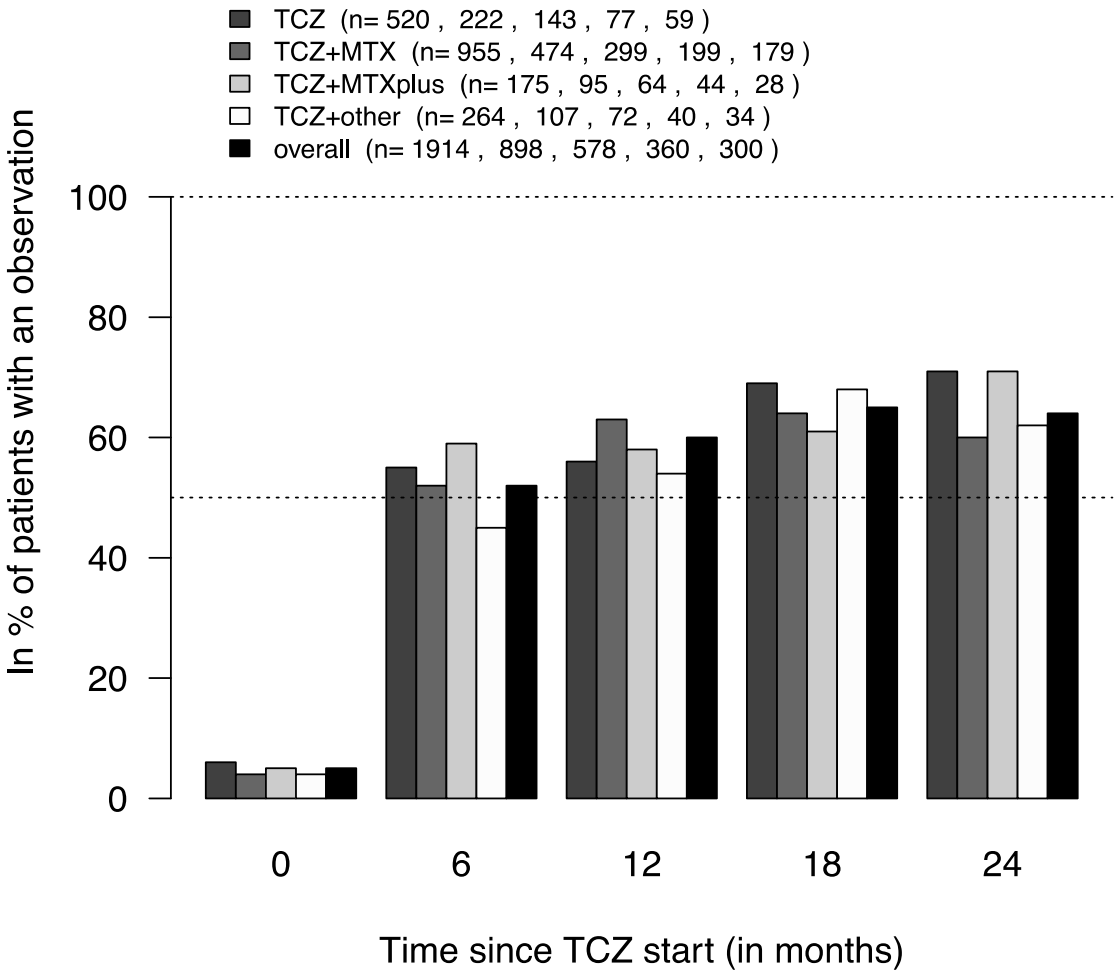


*patients with immediate loss to follow-up or patients from Russia were excluded; **patients for whom no CDAI assessments were available were excluded

Online supplementary Figure S2



Online supplementary Figure S3



Online supplementary Figure S4