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.

References

1. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equation in R. *Journal of Statistical Software* 2011; 45(3):1-67.
2. R RCT. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2013; URL http://www.R-project.org/.

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

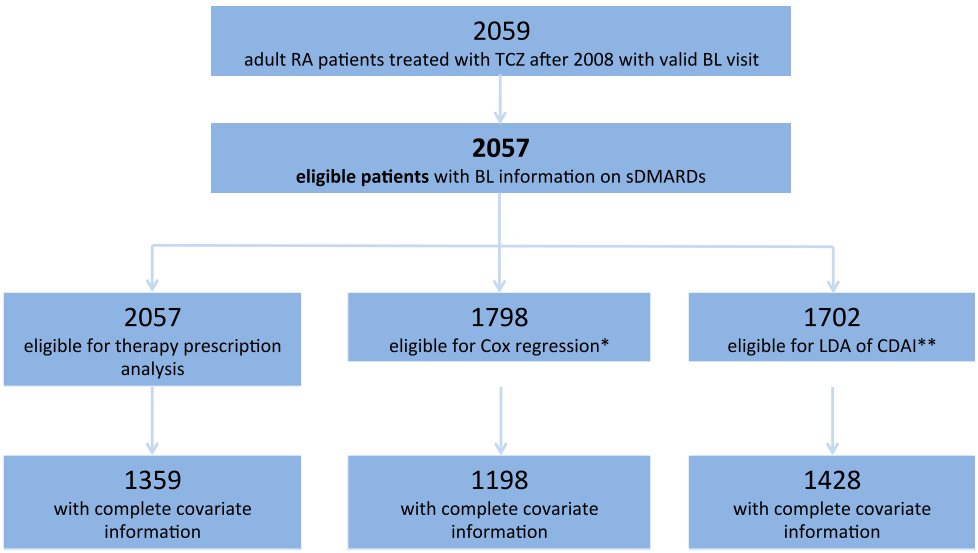
Online supplementary Figure S1. Flowchart of the study. The number of patients fulfilling increasing numbers of inclusion criteria as well as criteria for inclusion into the different types of analysis.

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.

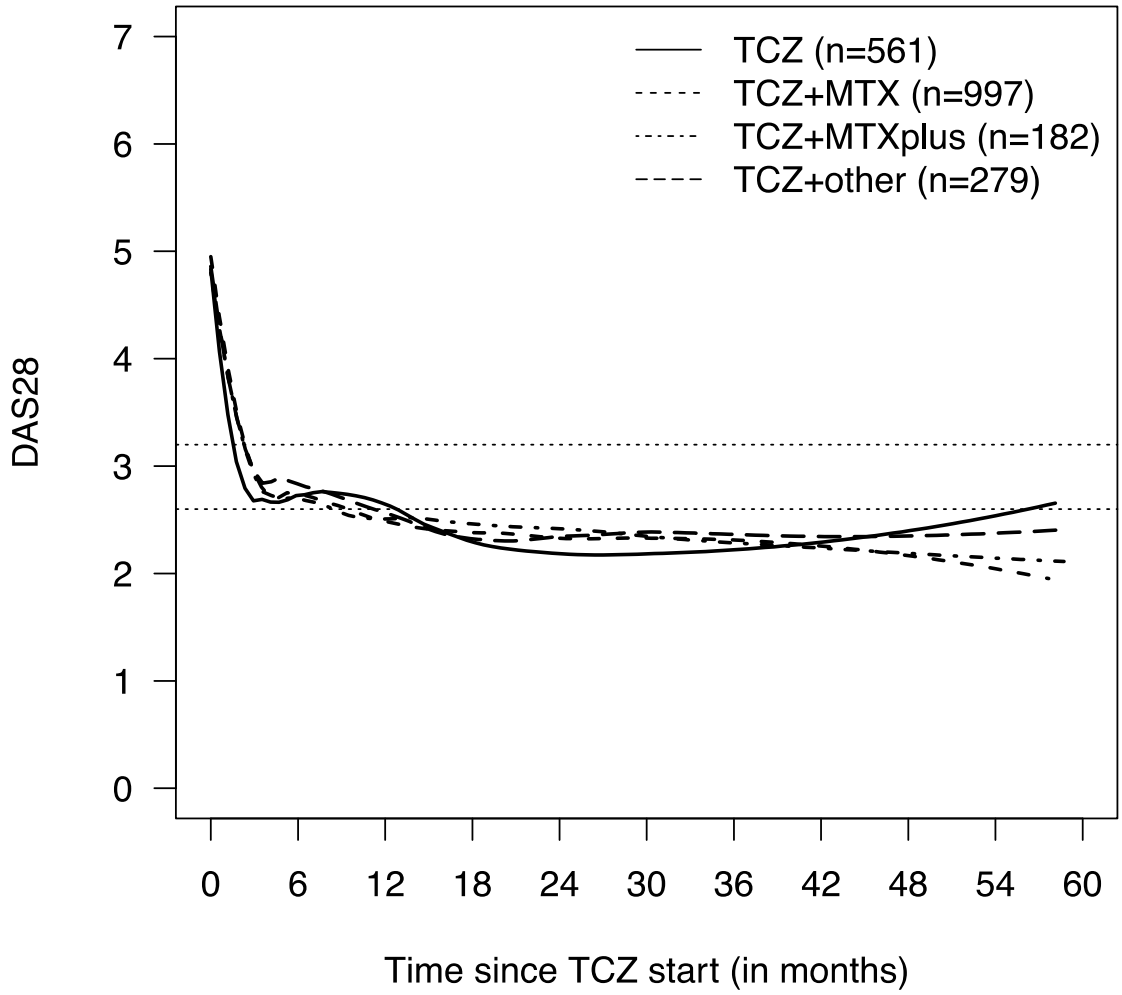
Online supplementary Figure S4. Kaplan-Meier plot of TCZ retention by country of registry. The data represent all 1798 eligible patients who had not been lost to follow-up immediately and were not from Russia. Small diagonal lines indicate censored retention times (at date of last follow-up visit).

Online supplementary Figure S1

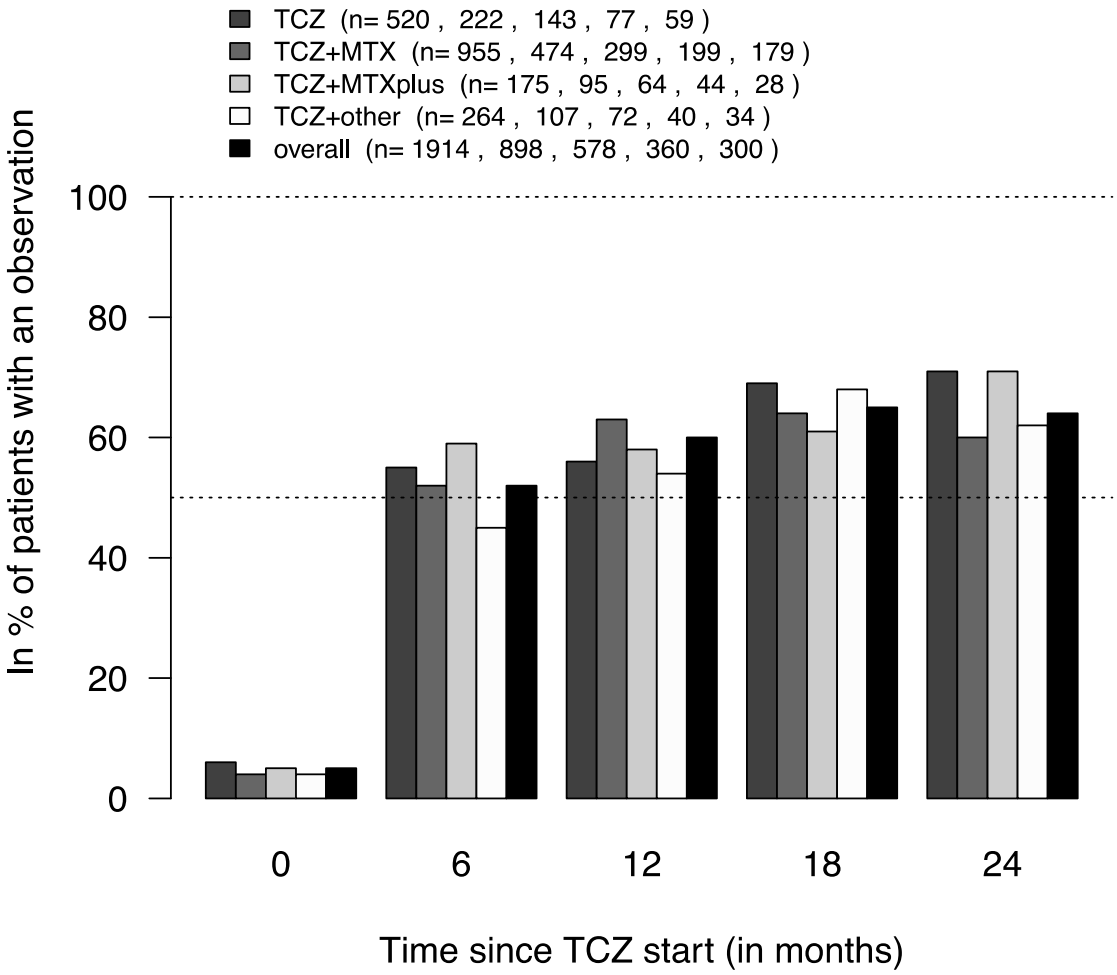


*patients with immediate loss to follow-up or patients from Russia were excluded; **patients for whom no CDAI assessments were available were excluded

Online supplementary Figure S2



Online supplementary Figure S3



Online supplementary Figure S4