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Comparative effectiveness of TNF inhibitors and tocilizumab with and without conventional synthetic disease-modifying antirheumatic drugs in a pan-European observational cohort of bio-naïve patients with rheumatoid arthritis

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ABSTRACT

Objectives: To compare treatment effectiveness in rheumatoid arthritis (RA) patients naïve to biological disease-modifying antirheumatic drugs (bDMARDs) treated with tocilizumab (TCZ) or TNF-inhibitor (TNFi) with (-combo) or without (-mono) conventional synthetic DMARDs (csDMARDs).

Methods: Patients with RA across 7 European registries, naïve to bDMARDs who initiated treatment with TCZ or TNFi from 2009 to 2016 were included. Drug retention rate was analyzed using Kaplan–Meier and Cox models, and CDAI over time by mixed models. The proportions of patients reaching CDAI low disease activity (LDA) and remission after one year were corrected for attrition.

Results: 6713 TNFi-combo, 3762 TNFi-mono, 646 TCZ-combo and 384 TCZ-mono were eligible. Crude median retention was 3.67 years (95%CI 3.41-3.83) for TNFi-combo, 4.14 (3.77-4.62) for TNFi-mono, 2.98 (2.76-3.34) for TCZ-combo and 3.63 years (3.34-5.03) for TCZ-mono. After adjustment for covariates, country and year of treatment initiation

stratification, hazards of discontinuation were lower for TCZ-mono (0.60, 95% CI 0.52-0.69) and TCZ-combo (0.66, 95% CI 0.54-0.81) compared to TNFi-combo. Adjusted CDAI evolution was not significantly different between groups. CDAI LDA and remission corrected for attrition were similar between TCZ with or without csDMARDs and TNFi-combo.

Conclusion: In routine care across 7 European countries, the adjusted drug retention, adjusted CDAI over time and attrition-corrected response proportion for RA patients were similar for bio-naïve patients if treated with TNFi-combo, TCZ-combo or TCZ-mono.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease which causes joint pain and inflammation, and can lead to joint destruction, loss of function and decreased quality of life [1]. Early treatment aiming to suppress or decrease disease activity can significantly improve the prognosis of patients. When treatment targets are not reached by conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), the current recommendations advocate the addition of biologic disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) [2]. Tocilizumab (TCZ) is a humanized antibody targeting the interleukin-6 receptor that has proven its effectiveness in decreasing disease activity and thus inhibiting structural damage and loss of function [3,4]. In the ADACTA randomized controlled trial, TCZ as monotherapy was more effective than adalimumab as monotherapy [5]. In a real-world study of non-bio-naïve European RA patients, the effectiveness of TCZ monotherapy and TCZ or TNF-inhibitors (TNFi) in combination with csDMARDs were comparable [6]. Similar findings were reported in a study from the US CORRONA cohort comparing TCZ as monotherapy to TNF-inhibitors in combination therapy in patients with prior TNFi use [7]. In general, bio-naïve patients have higher response rates to bDMARD therapy than patients with prior bDMARD use [8,9]. However, to our knowledge, no study evaluated effectiveness in a large number of bio-naïve patients receiving TCZ therapy. Therefore, this study is aimed at comparing the effectiveness of TCZ and TNFi as monotherapy or in combination with csDMARDs in patients with no prior use of bDMARDs or tsDMARDs using a collaboration of registries from several countries. Secondary objectives were to compare TCZ as monotherapy to TNFi in combination therapy with different types of csDMARDs and different dosage of methotrexate.

1. METHODS

The TOcilizumab Collaboration of European Registries in RA (TOCERRA) is an investigator-led, industry-supported, collaborative initiative involving several European registries with longitudinal data of RA patients initiating TCZ or TNFi which has been described elsewhere [6,9]. Local ethical approval was obtained and informed consent was given to the participants for each registry, and the Geneva Ethics Committee approved the collaboration study. For this study, only the registries that contributed with bDMARDs- and tsDMARDs-naïve patients treated by TCZ or TNFi were included, thus comprising 7 registries: Czech Republic (ATTRA), Italy (GISEA), Norway (NOR-DMARD), Portugal (Reuma.pt), Romania (RRBR), Slovenia (BioRx.si) and Spain (BIOBADASER). Patients were eligible if they had a diagnosis of RA established by a rheumatologist, started treatment with TCZ or a TNFi between January 1st, 2009 and March 15th, 2018, and have not been previously treated by a bDMARD or tsDMARD.

1.1. Exposure of interest

The main exposure of interest was the type of bDMARDs (TNFi and TCZ) with or without concomitant treatment with csDMARDs at baseline, thus comprising 4 groups: TNFi-combo, TNFi-mono, TCZ-combo, TCZ-mono.

As a secondary analysis, we compared the TCZ-mono group to the TNFi-combo group across different types of concomitant csDMARDs (MTX, MTX and at least one other csDMARD or at least one other csDMARD without MTX) and, for TNFi-combo with MTX only, across different dosage of MTX (categorized as having low-dose (<10 mg/week), medium-dose (10–15 mg/week) and high-dose (>15 mg/week)).

1.2. Study outcomes

Our main outcomes for assessing effectiveness consisted in three parts: (1) drug retention, (2) evolution of disease activity in terms of Clinical Disease Activity Index (CDAI) and (3) rates of CDAI remission (CDAI ≤2.8) and low disease activity (LDA, CDAI ≤ 10) [10,11]. Evolution of the Disease Activity Score-28 (DAS28), patient global assessment (PGA), physician global assessment (PhGA) and rates of DAS28 remission (DAS28 <2.6) [12,13] and LDA (DAS28 <3.2) were also analyzed as secondary endpoints.

bDMARD exposure was defined as the time from start date of treatment until the discontinuation date plus one month, as it was estimated that treatment should still be effective during the following month on disease activity (CDAI and DAS28). The exposure was censored at date of the last reported follow-up visit plus one month if treatment was not discontinued. We considered only the first course of bDMARD treatment. Indeed, if the patients switched to another bDMARD, he/she was no longer considered bio-naïve.

For the third part on CDAI and DAS28 remission and LDA rates, outcomes were analyzed at 1 year, as earlier evaluations were not feasible considering the frequency of assessments in most of the registries.

1.3. Covariates

The baseline covariates considered were age, gender, seropositivity, route of delivery (subcutaneous vs intravenous), ever smoking, use of glucocorticoids (GC), disease activity (CDAI and DAS28), functional disability (Health Assessment Questionnaire Disability Index, HAQ-DI), presence of comorbidities (cardiovascular disease, interstitial lung disease, infection, malignancy and/or neuropsychiatric disorder), year of treatment initiation and

country of registry. These covariates were assessed at baseline and not considered as time-varying. Information on the level of education was missing in 60% of patients and was not used for adjustment. We defined seropositivity as positive if RF or ACPA were positive, negative if both were negative and missing if one was missing and the other was negative. When no observed values for CDAI, DAS28 and HAQ-DI within a three-month window were available, they were imputed using a quadratic polynomial interpolation for each patient.

Previous csDMARD use was not assessed, as most patients were included in the registries only at the start of bDMARDs or tsDMARDs and previous use of csDMARDs before their inclusion in the registries was not well documented.

Statistical methods

1.4.1 Baseline characteristics

Baseline characteristics were compared using Chi-Squared test for categorical variables and Wilcoxon Rank sum test for continuous variables.

1.4.2 Analysis of drug retention

For the first analysis about drug retention, we used Kaplan–Meier and Cox models. Baseline hazards were allowed to vary by country of registries and year of treatment initiation in the Cox models. Missing covariates were imputed using multiple imputations with chained equations, using 50 samples. The Cox models were adjusted for each baseline covariates described in the Covariates section, except for calendar year of treatment initiation and country of registry which were used as stratification terms and level of education, which was not used considering its missingness.

1.4.3 Analysis of CDAI and DAS28 change over time

For the second analysis evaluating CDAI and DAS28 change over time, mixed-effects models for longitudinal data with a cubic effect of time were used. We did not include Spain into this analysis because this registry records CDAI and DAS28 only at baseline, excluding a total of 564 patients (312 TNFi-combo, 21 TNFi-mono, 195 TCZ-combo, 36 TCZ-mono). To assess whether the type of treatment had different trajectories of CDAI over time, we used a model with an interaction and another without and compared them using Bayesian Information Criteria (BIC). This BIC is less sensitive to obtaining significant effect only due do large sample size. The mixed-effect models were adjusted for each baseline covariates described in the Covariates section, except level of education.

1.4.4 Analysis of CDAI and DAS28 remission or LDA

For the third analysis evaluating one-year remission or LDA, crude proportions of patients reaching clinical response were calculated and compared with the Chi-Squared test. In addition, drug discontinuation was corrected using the LUNDEX index ([proportion of patients achieving response criteria] x [proportion of patients still adhering to therapy]) [14], combining clinical response and adherence to therapy. The purpose is to avoid a selection bias in favor of responders only when evaluating response, overestimating drug effectiveness. We computed confidence intervals around the differences in LUNDEX-corrected remission or LDA rates using bootstrap with 10,000 bootstrap samples. For the same reason as for the second analysis on CDAI and DAS28 change over time, we did not include the Spanish registry.

1.4.5 Sensitivity analysis

As a sensitivity analysis, we analyzed all outcomes excluding Italy, as Italy was the main contributor of bio-naïve patients, particularly as monotherapy, providing more than half of TNFi and TCZ-mono patients.

1.4.6 Evaluation of model adequacy and statistical package

We verified the absence of collinearity by a variance inflation factor and the absence of interaction between treatment and country before pooling the results.

We tested the validity of the Cox model regarding the assumptions of proportional hazards, linearity and absence of influential observations.

All analyses and tabulations were performed using R V.3.4.2 with the mice, car, survival, lme4 and lmertest packages.

2. RESULTS

2.1 Baseline characteristics

A total of 11,505 patients were retrieved before March 15th, 2018, including 6,713 TNFi-combo, 3,762 TNFi-mono, 646 TCZ-combo and 384 TCZ-mono patients at baseline (Table 1). Missing values are presented in Supplementary Table S1. All registries contributed to the four groups.

Patients with TCZ were older, with longer disease duration. Route of delivery was mostly subcutaneous for TNFi patients and intravenous for TCZ patients. Patients in monotherapy were younger, had longer disease duration, less frequently used glucocorticoids at baseline and were more often smokers. Patients with TNFi-combo had the most severe disease

characteristics at baseline (higher DAS28, CDAI, HAQ-DI, TJC, ESR and CRP). TNFi-mono had the least severe disease characteristics at baseline and were younger.

The baseline characteristics of the patients included in the sensitivity analysis excluding Italy are presented in the Supplementary Table S2, and details of patients with TNFi-combo and different types of csDMARDs or doses of MTX are presented in Supplementary Table S3 and S4.

2.2 Survival analyses

A total of 2864 TNFi-combo, 1200 TNFi-mono, 334 TCZ-combo and 121 TCZ-mono stopped treatment during follow-up. Crude median retention was 3.67 years (95% CI 3.41-3.83) for TNFi-combo, 4.14 years (3.77-4.62) for TNFi-mono, 2.98 years (2.76-3.34) for TCZ-combo, 3.63 years (3.34-5.03) for TCZ-mono.

After adjustment for covariates and stratification by country and year of treatment initiation, we found that, compared to TNFi-combo, hazards of discontinuation were higher for TNFi-mono (HR: 1.24, 95% CI 1.13-1.36, Table 2) and lower for TCZ-mono (0.60, 0.52-0.69) and TCZ-combo (0.66, 0.54-0.81). There was no statistically significant difference in hazards of discontinuation for TCZ-mono compared to TCZ-combo (1.10, 0.88-1.37). Female gender, younger age, shorter disease duration, presence of a comorbidity at baseline, smoking, use of glucocorticoids at baseline, intravenous delivery, higher HAQ-DI and DAS28 were associated with a higher risk of discontinuation.

Results were similar in the sensitivity analysis excluding the Italian registry.

For the subanalysis of TCZ vs TNFi patients with different types of csDMARDs, crude median retention among TNFi-combo patients with any type of csDMARDs was lower than for TCZ

patients (p<0.001, Supplementary Figure S1, panel A). Adjusted hazards of discontinuation were higher for TNFi-combo with any type of concomitants csDMARDs than TCZ-mono.

Among TNFi-combo patients with MTX only (n=3972), crude median drug retention was lower but not statistically significantly different compared to TCZ-mono (p=0.138, Supplementary Figure S1, panel B). Adjusted hazards of discontinuation were higher for TNFi-combo with any dosage of MTX than TCZ-mono.

The Cox models were valid regarding the assumptions of proportional hazards, linearity and absence of influential observations.

2.3 Evolution of CDAI and DAS28 over time

In all groups, CDAI score decreased rapidly during the first 2 years (Figure 2). After adjustment, the CDAI evolution was not significantly different between groups (lower BIC in the model without interaction between time and treatment group), although there was some difference in the average CDAI at any time during follow-up, which was higher in TNFi-mono, and lower with TCZ-combo (Table 3). Presence of comorbidity, glucocorticoids, higher HAQ-DI and CDAI at baseline were associated with higher CDAI at any time during follow-up. Results were similar in the sensitivity analysis excluding the Italian patients.

DAS28 evolution was similar between groups, however average DAS28 at any point during follow-up was lower in the TCZ-mono and TCZ-combo groups and higher for the TNFi-mono group compared to TNFi-combo. PGA and PhGA evolution were also not significantly different between groups.

CDAI evolution was not significantly different for TNFi-combo across any type of concomitant csDMARDs or doses of MTX compared to TCZ-mono.

2.4 CDAI and DAS28 LDA and remission at 1 year

2.4.1 Crude analysis

A total of 4,074 TNFi-combo, 2,086 TNFi-mono, 286 TCZ-combo and 203 TCZ-mono were still under the same treatment at one year, with respectively 17.7%, 17.6%, 18.2% and 16.6% in CDAI remission (p=0.97) and 72.9%, 79.0%, 73.4% and 68.5% in CDAI LDA (p<0.001). For DAS28, there were 36.1%, 33.5%, 64.4%, 54.3% (p<0.001) in remission and 61.0%, 71.1%, 82.2% and 75.8% (p<0.001) in LDA, respectively.

2.4.2 Attrition-corrected analysis

After LUNDEX correction for attrition, CDAI remission and LDA rates were similar, except for slightly higher rates of CDAI LDA in the TNFi-mono group (Figure 3). LUNDEX-corrected DAS28 remission rates and LDA were higher in the TCZ-mono and TCZ-combo groups than the TNFi-mono and TNFi-combo groups.

In the sensitivity analysis excluding Italian patients, the rates of LUNDEX-corrected CDAI remission were lower in the TNFi-mono (9.0%, Supplementary Figure S4) and TCZ-mono (10.2%) groups than the TNFi-combo (13.1%) and TCZ-combo (14.7%) groups. This difference was statistically significant for the TNFi-mono group but not the TCZ-mono group compared to TNFi-combo. LUNDEX-corrected CDAI LDA rates were similar between groups.

When comparing TNFi with different type of csDMARDs and dosage of MTX (Supplementary Figure S2 and S3) and TCZ-mono, there were no significant differences except for TCZ-mono vs TNFi with high dose of MTX favoring TCZ-mono.

3. DISCUSSION

Using data from the TOCERRA collaboration, we evaluated the effectiveness of tocilizumab and TNF-inhibitors with and without concomitant csDMARDs in patients naïve to bDMARDs and tsDMARDs. We found that, after adjustment for confounding factors, drug retention was higher in TCZ, whether as monotherapy or in combination therapy, than TNFi in combination therapy, and lower with TNFi as monotherapy.

CDAI evolution was not different between groups, after adjustment for confounders, although average CDAI at any time during follow-up was higher with TNFi-mono and lower for TCZ-combo.

Proportions of CDAI remission and LDA activity were similar in the main analysis, except for a slightly higher rate of LUNDEX-corrected CDAI remission in TNFi-mono patients. In the sensitivity analysis, patients with TNFi-mono and TCZ-mono seemed to have slightly lower proportion of remission, which was statistically significant for TNFi-mono but not TCZ-mono. These differences in results between the two analyses may be explained by important differences in patient and disease characteristics at baseline as the LUNDEX corrects for attrition but not for baseline characteristics, year of treatment initiation or country. In particular, TNFi-mono patients, mainly owing to patients from the Italian registry, had already the lowest disease activity values according to several parameters (DAS28, CDA, CRP, ESR and PGA) than the other group at baseline. Thus, a higher proportion of CDAI remission in TNFi-mono patients at one year is not unexpected. Overall, it also raises the question on how to account for bias and confounders in observational studies and how to interpret their results. To limit the effect of confounding and in particular confounding by indication, we

adjusted our analyses for several covariates except when using the LUNDEX, which allow an adjustment for attrition, but does not allow adjustment for covariates.

This study also shows that prescribing pattern may differ significantly from one country to another, as many patients were prescribed TCZ-mono in Italy. However, we found no significant interaction between country and treatment exposure, which allowed us to pool the results.

We also found that smoking, glucocorticoid use, higher HAQ-DI and higher CDAI at baseline were associated with higher CDAI at any time during follow-up, which may be due to a more severe pattern of disease.

Limitations of this study are partly inherent to its observational design. Unmeasured confounders cannot be accounted for. We were also unable to assess the previous use of csDMARDs as most patients are included in the registries only at the start of bDMARD or tsDMARD and previous use of csDMARDs before their inclusion in the registries was not well documented. Yet, as in clinical practice, bDMARDs and tsDMARDs are usually prescribed only after failing csDMARDs, we do not believe that this would have substantially changed the results. We also do not have details of the quality control processes for each registry and data quality for each variables. Outcomes may also be less precise than in a randomized controlled trial as for example for disease activity, which may not be measured exactly at one year and may have more missing data. As this initiative was supported by the industry, we also could compare only tocilizumab and TNF-inhibitors, as we did not have funding to analyze other treatment groups. However, the observational nature also allows a greater generalizability of the results, as patients were included without the strict inclusion and exclusion criteria of randomized controlled trials. The sample size was also large with a long

duration of follow-up and access to numerous covariates of interest. We also used several parameters of effectiveness with different analytic methods yielding a valuable picture of the effectiveness of the different treatment regimen tested.

We suggested in our previous study [6] that the longer retention with TCZ could be linked to the absence of other alternative after multiple bDMARDs failure. Comparable results were also found in a study from the CORRONA RA registry [7], which also considered bDMARD-experienced patients only. However, the presence of similar results in bio-naïve patients probably hints to other reasons for longer drug maintenance with TCZ, as, for instance, better tolerability or effectiveness. However, the exact reason for this could not be captured precisely in our study.

To our knowledge, no observational studies assessed the comparative effectiveness of TCZ and TNFi with and without csDMARDs as a first-line therapy. In the ADACTA randomized clinical trial, the efficacy of TCZ was superior to adalimumab as monotherapy in bio-naïve patients [5], and in the U-Act-Early trial of early arthritis, TCZ in combination with csDMARDs did not perform better than as monotherapy [16]. However, in the ACT-RAY study evaluating in csDMARD inadequate responders a switch strategy to TCZ only or an add-on strategy with TCZ and concomitant MTX, there were small differences between the groups regarding radiographic progression, which favored the add-on group [17].

Regarding the patient population, patients prescribed TCZ and TNFi as monotherapy or in combination therapy differed in several baseline characteristics. As in previous observational studies, focusing on bDMARD-experienced patients, TCZ is used in older patients with longer disease duration and patients treated as monotherapy less frequently used glucocorticoids [6,7,18]. However, in contrast to bDMARD-experienced patients where monotherapy was

more frequently prescribed to older patients [6,7,18], we did not find a clear pattern of prescription by age.

As in previous bDMARD studies, we found that female gender, presence of a comorbidity, smoking, use of glucocorticoids, higher HAQ-DI and DAS28 that may be linked to more difficult to treat patients were associated with a higher risk of drug discontinuation [6,19–21]. Patients treated as monotherapy (either TCZ or TNFi) had lower CRP levels at baseline, as patients with lower doses of MTX, suggesting that more aggressive treatment is prescribed to patients with higher levels of inflammatory markers. Younger age and shorter disease duration were also associated with higher discontinuation rates in our study but this association has been inconsistently described, with some studies pointing to higher discontinuation with longer disease duration[21] and older age [19,22,23], or no effect [23,24]. Subcutaneous delivery was associated with lower discontinuation rates, but it may be linked to a residual confounding of drugs or could be linked to other factors that are not fully captured. In a previous study of this collaboration looking at retention in TCZ patients by route of delivery, no difference was found between the intravenous or subcutaneous route [26].

Altogether, in regard to higher rates of retention, similar CDAI evolution and proportion of CDAI remission and LDA, our findings suggest that TCZ-combo and TCZ-mono are suitable alternatives to TNFi-combo. However, considering the lower rates of CDAI remission in the sensitivity analysis, although not significant for TCZ-mono, and the results of the ACT-RAY study, whenever possible TCZ and TNFi should be given in combination with csDMARDs. Yet, when csDMARDs are not tolerated or contraindicated, TCZ seems to be a more effective option than TNFi as monotherapy.

4. CONCLUSION

In conclusion, this real-world study shows that TCZ either as monotherapy or in combination with csDMARDs is an adequate alternative to TNFi in combination with csDMARDs in bDMARDs and tsDMARDs naïve patients and may be preferable over TNFi when csDMARDs are contraindicated or not tolerated.

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TABLES

Table 1 Baseline characteristics

N = 11505	TNFi-combo n=6713	TNFi-mono n=3762	TCZ-combo n=646	TCZ-mono n=384
Total number of visits (median [IQR])	4 [2-8]	3 [3-7]	2 [1-8]	2 [3-6]
Total patient-years	14924.8	6728.7	1511.7	676.0
Age, yr (median [IQR])	54.9 [45.4, 62.7]	52.0 [41.4, 61.3]	56.1 [46.2, 63.5]	54.8 [46.5, 64.5]
Female gender, n (%)	5265 (78.4)	2434 (64.7)	520 (80.5)	317 (82.6)
Education category				
0-10 years	1222 (32.3)	143 (31.3)	113 (44.8)	23 (31.1)
11-13 years	1955 (51.6)	225 (49.2)	104 (41.3)	40 (54.1)
>13 years	610 (16.1)	89 (19.5)	35 (13.9)	11 (14.9)
Ever smoker	1630 (36.6)	987 (38.2)	138 (30.3)	96 (36.8)
Comorbidity	2888 (64.2)	1375 (70.8)	294 (57.0)	136 (62.4)
Disease duration, yrs (median [IQR])	6.7 [2.4, 12.2]	9.7 [6.6, 15.1]	7.4 [3.5, 12.3]	10.0 [6.3, 16.4]
Seropositivity (RF and/or ACPA), n (%))	3597 (79.4)	659 (71.0)	371 (82.4)	134 (81.7)
Glucocorticoids	3634 (69.9)	532 (60.0)	391 (72.8)	84 (48.6)
Glucocorticoid dose, mg/day (median, IQR)	5.0 [5.0, 8.0]	5.0 [4.0, 8.0]	5.0 [5.0, 10.0]	5.0 [4.0, 7.5]
Route of delivery (subcutaneous)	4444 (88.4)	649 (91.3)	184 (36.4)	58 (37.4)
DAS28 (median [IQR])	5.2 [4.1, 6.2]	4.1 [3.7, 5.4]	4.7 [3.7, 6.2]	4.7 [4.1, 6.0]
CDAI (median, [IQR])	20.8 [15.0, 34.0]	17.6 [15.0, 23.0]	17.6 [17.6, 30.0]	17.6 [17.6, 30.0]
HAQ-DI (median, [IQR])	1.1 [1.0, 1.6]	1.0 [0.8, 1.3]	1.0 [1.0, 1.7]	1.0 [1.0, 1.6]
TJC (over 28 joints) (median, [IQR])	9.0 [4.0, 14.0]	5.0 [1.0, 11.0]	8.0 [3.0, 14.0]	7.0 [4.0, 12.0]
SJC (over 28 joints) (median, [IQR])	6.0 [2.0, 10.0]	3.0 [0.0, 8.0]	6.0 [2.0, 10.0]	5.0 [2.0, 9.0]
PGA (median, [IQR])	60.0 [40.0, 80.0]	60.0 [42.0, 80.0]	66.0 [41.2, 80.0]	62.0 [50.0, 80.0]
PhGA (median, [IQR])	50.0 [30.0, 70.0]	50.0 [30.0, 70.0]	50.0 [34.2, 70.0]	50.0 [40.0, 70.0]
ESR (mm/hour) (median, [IQR])	27.0 [15.0, 42.0]	22.0 [11.0, 38.0]	26.0 [10.0, 46.0]	26.5 [10.8, 48.2]
CRP (mg/L) (median, [IQR])	7.0 [2.0, 19.7]	1.6 [0.5, 5.1]	6.2 [1.1, 19.0]	2.1 [0.6, 9.0]

ACPA: anti–citrullinated peptide antibody; CDAI: Clinical Disease Activity Index; combo: in combination with conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score 28; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment

Questionnaire Disability Index; IQR: interquartile range; mono: as monotherapy; PGA: patient global assessment; PhGA: Physician global assessment; RF: rheumatoid factor; SJC: swollen joint counts; TCZ: tocilizumab; TJC: tender joint counts; TNFi: TNF inhibitor.

Table 2 Multivariable analysis of drug discontinuation

	HR	95%CI	p
TNFi-combo (comparator)	--	--	--
TNFi-mono	1.24	1.13-1.36	<0.001
TCZ-mono	0.60	0.52-0.69	<0.001
TCZ-combo	0.66	0.54-0.81	<0.001
Age, yr	1.00	0.99-1.00	0.03
Female gender	1.21	1.12-1.30	<0.001
Body Mass Index	1.00	0.99-1.01	0.85
Ever smoking	1.12	1.02-1.24	0.02
Comorbidity	1.13	1.04-1.23	0.003
Disease duration, yr	0.99	0.99-1.00	0.02
Seropositivity	1.00	0.91-1.11	0.92
Subcutaneous delivery	0.70	0.64-0.77	<0.001
Glucocorticoids	1.27	1.14-1.40	<0.001
HAQ-DI at baseline	1.09	1.05-1.13	<0.001
CDAI at baseline	1.00	1.00-1.00	0.69
DAS28 at baseline	1.16	1.12-1.20	<0.001

CDAI: Clinical Disease Activity Index; combo: in combination with conventional synthetic disease-modifying antirheumatic drug, DAS28: Disease Activity Score-28; HAQ-DI: Health Assessment Questionnaire Disability Index; mono: as monotherapy; TCZ: tocilizumab; TNFi: TNF-inhibitor.

Table 3 Multivariable analysis of CDAI over time

	Overall		
	coeff	**95%CI**	**p**
Treatment at baseline			
TNFi-combo (comparator)	--	--	--
TNFi-mono	1.13	0.32-1.94	0.006
TCZ-combo	-2.08	-3.25--0.91	<0.001
TCZ-mono	0.29	-1.61-2.18	0.77
Time, yr	-16.19	-16.71--15.68	<0.001
Age, yr	-0.02	-0.04-0.01	0.17
Female gender	0.40	-0.27-1.06	0.24
BMI	0.03	-0.02-0.08	0.27
Comorbidities	0.39	-0.17-0.95	0.17
Smoking	1.03	0.37-1.69	0.002
Disease duration, yr	-0.02	-0.06-0.02	0.28
Seropositivity	-0.39	-1.12-0.33	0.28
Route of bDMARDs delivery (subcutaneous)	-0.35	-1.12-0.42	0.37
Glucocorticoids	1.01	0.47-1.54	<0.001
HAQ-DI at baseline	1.70	1.27-2.13	<0.001
CDAI at baseline	0.36	0.32-0.40	<0.001
DAS28 at baseline	-0.12	-0.51-0.27	0.55

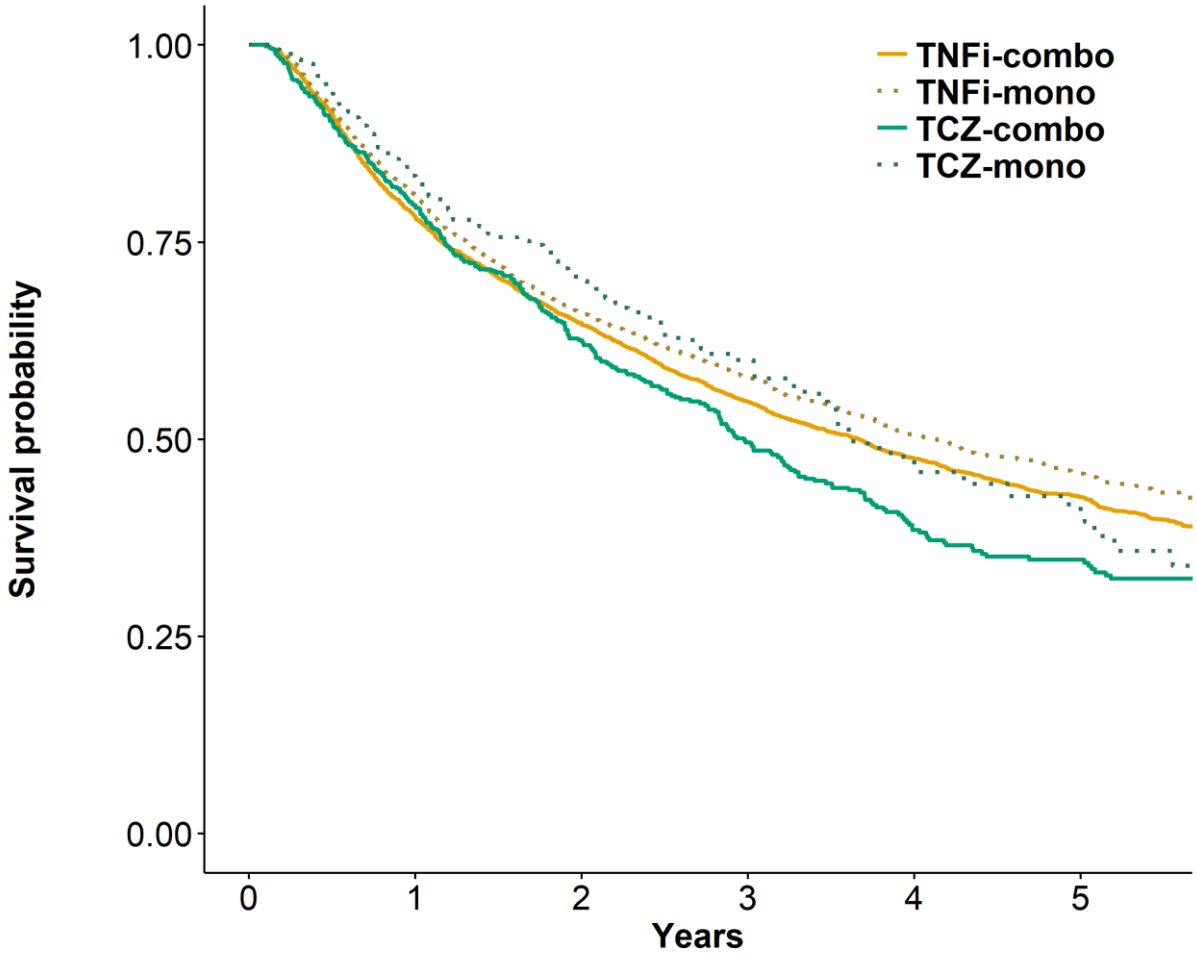
CDAI: Clinical Disease Activity Index; combo: in combination with conventional synthetic disease-modifying antirheumatic drug DAS28: Disease Activity Score 28, HAQ-DI: Health Assessment Questionnaire Disability Index; mono: as monotherapy; TCZ: tocilizumab, TNFi: TNF inhibitor.

FIGURE LEGENDS

Figure 1 Unadjusted Kaplan-Meier curves of drug discontinuation

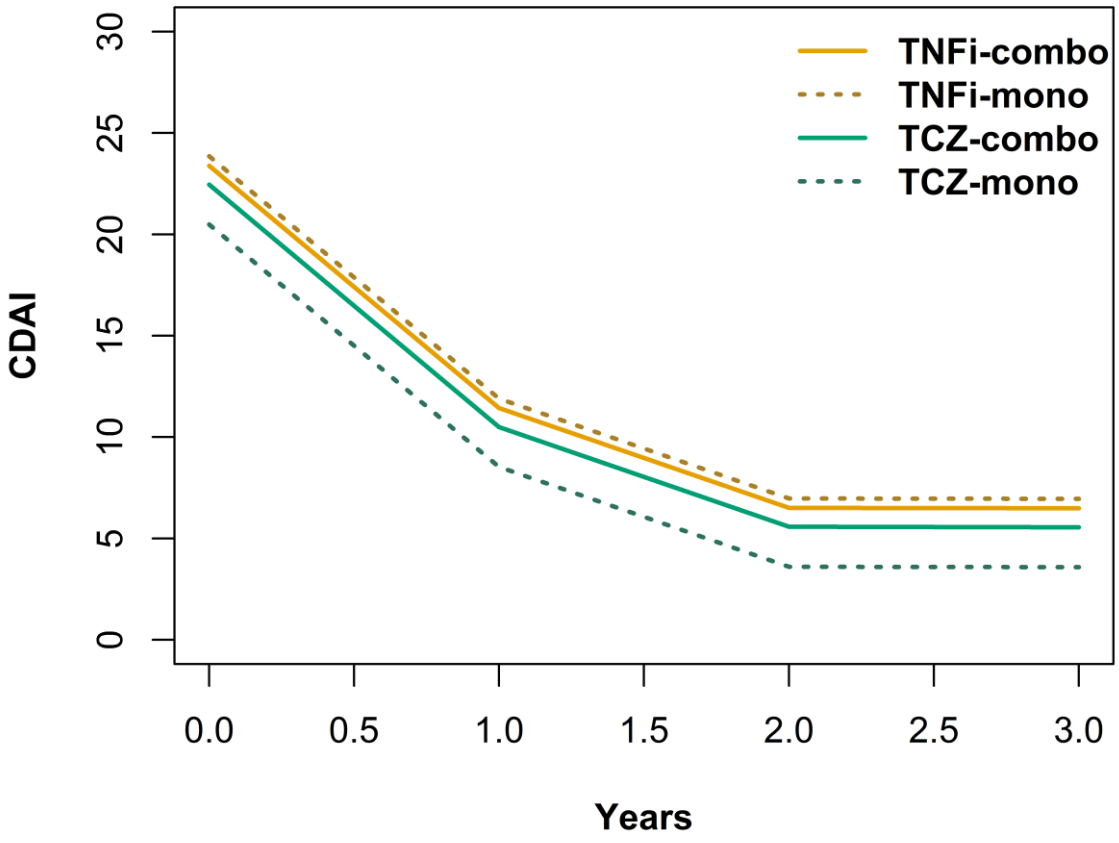
Figure 2 Multivariable analysis of CDAI over time modelled with a cubic effect of time and adjusted for age, gender, disease duration, seropositivity, presence of glucocorticoids, route of delivery (subcutaneous or intravenous), smoking, Health Assessment Questionnaire Disability Index score, Clinical Disease Activity Index, Disease Activity Score 28 and presence of a comorbidity at baseline. TNFi-combo, TNF inhibitor in combination with csDMARDs; TNFi-mono, TNF inhibitor as monotherapy; TCZ-combo, tocilizumab in combination with csDMARDs; TCZ-mono, tocilizumab as monotherapy.

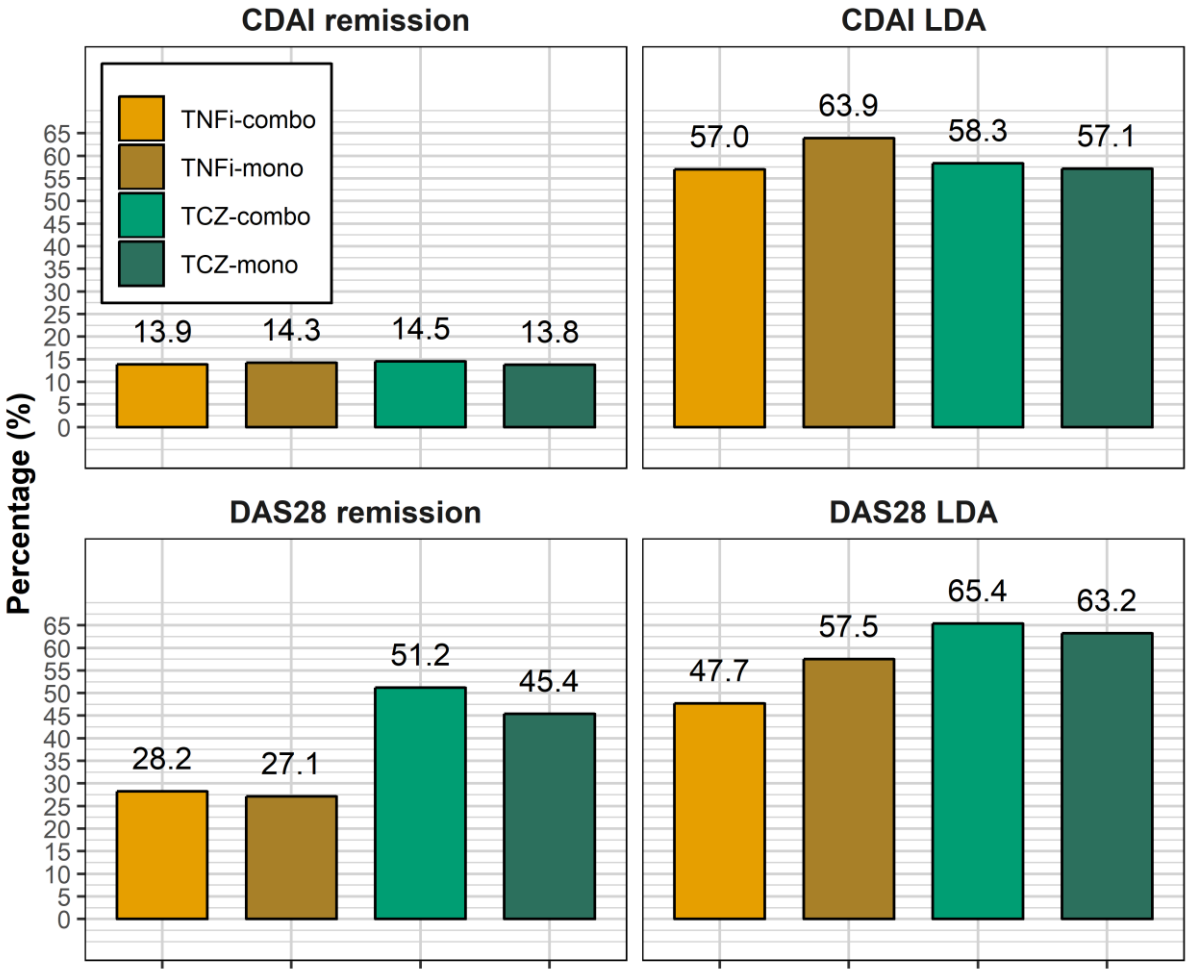
Figure 3 LUNDEX corrected clinical disease activity index (CDAI) and disease activity score-28 (DAS28) remission and low disease activity (LDA) at 1 year. TNFi-combo, TNF inhibitor in combination with csDMARDs; TNFi-mono, TNF inhibitor as monotherapy; TCZ-combo, tocilizumab in combination with csDMARDs; TCZ-mono, tocilizumab as monotherapy.



Patients at risk

TNFi-combo	6713	4258	2851	1822	1186	837
TNFi-mono	3762	2101	1330	853	528	232
TCZ-combo	646	418	283	188	118	87
TCZ-mono	384	230	134	76	38	25


CDAI
0
5
10
15
20
25
30
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Years
TNFi-combo
TNFi-mono
TCZ-combo
TCZ-mono


CDAI remission
CDAI LDA
DAS28 remission
DAS28 LDA
Percentage (%)
TNFi-combo
TNFi-mono
TCZ-combo
TCZ-mono
13.9
14.3
14.5
13.8
57.0
63.9
58.3
57.1
28.2
27.1
51.2
45.4
47.7
57.5
65.4
63.2