



Clinical science

Tocilizumab vs prednisone in established rheumatoid arthritis patients (TOPIRA): an investigator-initiated randomized clinical trial

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Abstract

Objectives: In rheumatoid arthritis (RA) patients with an insufficient response to conventional synthetic DMARDs (csDMARDs), both biologic DMARDs and low-to-moderate dose glucocorticoids are effective treatment options. However, direct comparative evidence on their relative effectiveness and safety is lacking.

Methods: This investigator-initiated, open-label, randomized trial compared 10 mg daily prednisone to weekly subcutaneous tocilizumab (TCZ, 162 mg), both added to stable csDMARD therapy, in a 12-month treat-to-target strategy. If treatment response was inadequate at 3 months, patients switched to the alternative arm. The primary end point was Clinical Disease Activity Index (CDAI) averaged over months 6–12. Secondary outcomes included the Glucocorticoid Toxicity Index (GTI), TCZ-related adverse events and radiographic progression.

Results: Sixty-five patients with established RA were included in the intention-to-treat population. TCZ was superior in reducing CDAI over months 6–12 (mean difference on square root scale: -0.64 ; 95% CI: -1.18 to -0.09). Treatment was switched in 28% (TCZ) and 52% (prednisone). No significant differences were observed in toxicity (GTI: $P=0.922$; TCZ-related adverse events: $P=1.00$) or in radiographic progression ($P=0.376$). On-treatment analyses yielded similar results.

Conclusion: TCZ led to greater improvement in disease activity than prednisone. There was no significant difference in joint damage progression over 12 months and there were no major differences in adverse events.

Clinical trial registration: EudraCT Number: 2017-003037-28

Keywords: rheumatoid arthritis, randomized clinical trial, prednisone, biologic DMARD.

Rheumatology key messages

- Tocilizumab is more effective than prednisone 10 mg at lowering disease activity in an established RA population.
- There was no major difference in adverse events between prednisone 10 mg/daily and TCZ 162mg/weekly over a 12-month period.
- Patients in the tocilizumab group had a higher rate of treatment retention over 12 months than in the prednisone group (72% vs 48%).

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease associated with joint damage, chronic pain, fatigue and functional disability, which can lead to

significantly reduced work participation and health-related quality of life.

Early induction and maintenance of remission through pharmacological intervention is the cornerstone of treatment

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of RA. To this end, several classes of DMARDs have become available in the past decades. After treatment failure of a conventional synthetic (cs)DMARD add-on therapy with another class of drugs is recommended, typically biologic (b) DMARDs such as an anti-TNF or anti-IL-6 agent. Low-medium dose glucocorticoids (GCs) may also be an option. The pros and cons of long-term GCs, as adjunct immunosuppressive medication in the treatment of RA, has been the subject of ongoing discussions for many years [1]. In low and medium doses GCs have been shown to have disease modifying properties when given for an extended period of time [2, 3]. A recent clinical trial in patients aged 65+ using low dose prednisolone showed a favourable balance of benefit and harm for this target population, while other reviews of trial data and long term safety have also shown limited toxicity of low-medium dose GC therapy [3–7]. The data on adverse events (AEs) for prolonged low-dose usage of corticosteroids is equivocal due to potential bias by indication (in observational studies) and selection of more healthy individuals in clinical trials [8, 9]. Current guidelines recommend cautious use and rapid tapering of GCs when initiated [10].

While both bDMARDs and GCs are effective treatments for the management of RA (added to a csDMARD), GCs incur far less costs. Even though costs for biologics have gone down somewhat in recent years, bDMARDs are not affordable for people in large parts of the world and healthcare spending in general is (too) high in many countries [11]. As such, GCs may be an attractive alternative when proven to not be relevantly worse than a bDMARD and safe [12, 13]. While indirect comparisons have shown that adding biologic agents or GCs to csDMARD therapy reduces disease activity and radiographic progression similarly, a direct comparison of their effectiveness and safety has never been performed in RA patients with insufficient response to a DMARD [14–16]. The current study aimed to assess the clinical effectiveness of treatment with the bDMARD tocilizumab (TCZ, a soluble IL-6 receptor blocker) compared with treatment with 10 mg prednisone daily, both as addition to current csDMARD therapy, in a treat-to-target strategy.

Methods

Study design and participants

The TOPIRA study (EudraCT number: 2017-003037-28) [17] was a multicentre, pragmatic, randomized, open-label trial. Patients were recruited at regular visits at the outpatient clinics at seven hospitals in the Netherlands. Recruitment was from February 2020 until September 2023. Written informed consent was obtained from all patients before the study. Patients were randomized in a 1:1 ratio to receive either TCZ (162 mg weekly, subcutaneous) or prednisone (10 mg daily) within a treat-to-target strategy. Randomization was done with variable block randomization, stratified per study-site. Participants and assessors were not blinded to the investigational product. In addition to the investigational product, patients on prednisone received osteoporosis prophylaxis (alendronic acid 70 mg/week and calcium/vitamin-D 500 mg/800 IE per day). Patients continued their csDMARDs throughout the study. Eligible patients were required to be at least 18 years old and meet the 2010 ACR/EULAR classification criteria for RA and have active disease. Active RA was defined as a Clinical Disease Activity Index (CDAI) >10, with at least one swollen joint according to the 28-joint

count, while maintaining a stable csDMARD regimen for at least 8 weeks prior to screening.

Exclusion criteria included any contraindication for systemic GC treatment or TCZ, as determined by the treating rheumatologist, and use of a targeted synthetic (ts)DMARD or bDMARD at initiation of study treatment. Wash-out periods were implemented according to regular care before initiating study medication, which in this case was cessation of study medication one half-life before the start of study medication. Patients had to discontinue systemic GC use at least 4 weeks prior to screening.

Randomized patients attended monthly visits until month 3, followed by visits every 3 months until month 12. Treatment modifications were implemented based on disease activity. After 3 months, patients were switched to the alternative treatment arm if they had moderate disease activity (CDAI >10) at two consecutive visits, high disease activity (CDAI >22) at any visit, or unacceptable side effects (in line with regular care). In cases of clinical remission (CDAI <2.8 with no swollen joints) at two consecutive visits, prednisone was tapered according to the schedule outlined in [Supplementary Table S1](#). TCZ was tapered to 162 mg every 2 weeks in the event of clinical remission and remained at that dose until the end of the study. If CDAI increased above 10 after tapering, the medication was resumed at 162 mg once per week. If disease activity remained high, further treatment adjustments were performed according to standard practice. The trial was initially designed to include 120 patients to detect an effect size of 0.6 in the change in CDAI from baseline to 12 months. However, recruitment was halted earlier due to recruitment challenges during the COVID pandemic. Study design and statistical analysis plan were revised at the time 45 patients had been enrolled, shifting the primary outcome from CDAI at 12 months to the repeated CDAI measurements at 6, 9 and 12 months to detect an effect size of 0.62. Recruitment was concluded after 65 patients had passed the recruitment deadline. These modifications were formally amended in the study protocol and approved by the medical ethics committee (protocol number: 19-419). The original protocol has been published previously [18].

Statistical analysis

The primary analysis was conducted in the intention-to-treat (ITT) population using a linear mixed model with a random intercept at patient level and CDAI at timepoints 6, 9 and 12 months as dependent variable. Covariates included baseline CDAI, study centre and the number of prior bDMARDs/tsDMARDs (0, 1–2 or >2). Sensitivity analyses included a per-protocol analysis, which included only patients who adhered to the treatment protocol (including switching according to protocol), and an on-treatment analysis, in which the current treatment at each visit was used as a variable instead of the initially assigned treatment.

Key secondary endpoints included AEs. GC-associated AEs were assessed using the Glucocorticoid Toxicity Index (GTI). We additionally evaluated TCZ-associated AEs of special interest (AESIs, [Supplementary Table S2](#)). Lastly, all possible or probable related AEs (including those measured in the GTI and AESIs) were separately analysed. Additional secondary endpoints included changes in other disease activity scores (DAS28, SDAI), radiographic progression over 12 months, and changes in HAQ index.

For most repeatedly measured secondary outcomes, statistical analyses followed the same approach as for the primary outcome, using either linear or logistic mixed-effects models, depending on the variable type (continuous or dichotomous). Appropriate transformations of data were applied if model assumptions were violated. Because there were only two timepoints, for radiographic progression, the Sharp–van der Heijde score at follow-up was analysed in a linear regression with treatment assignment as independent variable and the baseline Sharp–van der Heijde score as covariates.

For missing composite endpoints component data were imputed, to make use of the present data more effectively. Using predictive mean matching in the MICE package, using all other components and timepoint, 10 imputed datasets were generated. Reported coefficients and standard errors are pooled using Rubin's Rules [19].

All analyses were conducted in the ITT population, with a per-protocol and on-treatment analysis performed as sensitivity analysis.

Assessment of glucocorticoid toxicity

To quantify GC toxicity specifically, we utilized the Glucocorticoid Toxicity Index (GTI), which has been validated in multiple studies [20–22]. The GTI score was derived from scoring multiple domains, with a possible total ranging from –36 to 439. Detailed descriptions of the GTI domains and their respective weights are available in [Supplementary Table S3](#). The minimally clinically important difference has previously been established at about 10 points [23].

Assessments were performed every 3 months, except for bone mineral density and lipid assessments, which were conducted at baseline, 3 months (for lipids only) and at 12 months.

All statistical analyses were conducted using R version 4.4.1. Statistical significance was set at a two-sided α of 0.05.

Results

Patients

Patient characteristics are summarized in [Table 1](#). In total, 65 patients were randomized and included in the ITT analysis. Overall baseline demographics were balanced between the groups. The cohort consisted of established RA patients with a median disease duration of 13 years. Three patients withdrew before completion of the study in the prednisone group and two patients in TCZ group (7.7%, [Fig. 1](#)); available data up to drop-out were included in the analysis. Missing data before imputation is summarized in [Supplementary Table S4](#).

Primary outcome

In the ITT analysis, TCZ was more effective in reducing disease activity than prednisone. A square root transformation was applied since modelling the original CDAI values violated the normality assumption. For interpretability, we report the model results both in the transformed scale and in the original scale.

Six to 12 months after starting TCZ, patients had significantly lower disease activity than those on prednisone (difference in $\sqrt{\text{CDAI}}$: –0.64; 95% CI: –1.18 to –0.09). The difference on the original CDAI scale was 3.2 points in favour of TCZ (95% CI: –5.5 to –0.40) ([Fig. 2](#)). At the end of the follow-up period, 19 (out of 33) patients from the prednisone group had either switched to TCZ or stopped receiving any study medication ([Fig. 3](#)). For the TCZ group, eight (out of 32) patients had switched to prednisone or stopped receiving study medication at the end of the follow-up; six switched to prednisone and two to other medications. Of the seven patients that did not receive study medication at the end of follow-up, two were randomized to prednisone and three to TCZ. Of these patients, three were on csDMARDs only, two on a TNF inhibitor and two on a Janus kinase inhibitor at the

Table 1. Patient characteristics

	Overall	Prednisone	Tocilizumab	Missing
<i>n</i>	65	33	32	
Age, mean (s.d.), years	59.1 (11.6)	56.9 (11.7)	61.3 (11.3)	0 (0)
Female sex, <i>n</i> (%)	49 (75.4)	22 (66.7)	27 (84.4)	0 (0)
Time since diagnosis, mean (s.d.), years	13.3 (10.0)	12.6 (10.17)	14.0 (9.8)	0 (0)
Rheumatoid factor positive, <i>n</i> (%)	41 (63.1)	21 (63.6)	20 (62.5)	0 (0)
CCP positive, <i>n</i> (%)	41 (63.1)	22 (66.7)	19 (59.4)	0 (0)
Methotrexate use, <i>n</i> (%)	43 (66.2)	18 (54.5)	25 (78.1)	0 (0)
Methotrexate dose, median (IQR), mg/week	25.0 (15.0, 25.0)	25.0 (18.1, 25.0)	22.5 (15.0, 25.0)	0 (0)
Sulfasalazine use, <i>n</i> (%)	12 (18.5)	8 (24.2)	4 (12.5)	0 (0)
Leflunomide use, <i>n</i> (%)	8 (12.3)	6 (18.2)	2 (6.2)	0 (0)
Hydroxychloroquine use, <i>n</i> (%)	19 (29.2)	11 (33.3)	8 (25.0)	0 (0)
Other csDMARD use, <i>n</i> (%)	1 (1.5)	1 (3.0)	0 (0.0)	0 (0)
bDMARD or tsDMARD use at screening, <i>n</i> (%)	6 (9.2)	3 (9.1)	3 (9.4)	0 (0)
Number of previous csDMARDs, median (IQR)	1 (0, 1)	1 (0, 1)	1 (0, 1)	0 (0)
Previous use of bDMARD, <i>n</i> (%)	23 (35.4)	12 (36.4)	11 (34.4)	0 (0)
Previous use of JAK inhibitor, <i>n</i> (%)	1 (1.5)	1 (3.0)	0 (0.0)	0 (0)
Previous use of glucocorticoids, <i>n</i> (%)	53 (81.5)	24 (72.7)	29 (90.6)	0 (0)
Patient global assessment 0–100, median (IQR)	60.0 (50.0, 75.0)	60.0 (50.0, 75.0)	62.5 (50.0, 75.0)	0 (0)
Physician global assessment 0–10, median (IQR)	5.4 (4.4, 6.5)	5.4 (4.9, 6.0)	5.5 (4.4, 6.6)	0 (0)
Tender joint count, median (IQR)	4 (2, 9)	4 (2, 9)	5 (2, 10)	0 (0)
Swollen joint count, median (IQR)	5 (2, 8)	4 (2, 7)	6 (3, 9)	0 (0)
CDAI, median (IQR)	20.6 (16.1, 29.7)	20.0 (16.1, 29.7)	21.9 (16.3, 30.1)	0 (0)
BMI, mean (s.d.)	27.1 (3.8)	26.7 (3.8)	27.6 (3.8)	0 (0)
Mean arterial pressure, mean (s.d.), mmHg	100.8 (12.7)	100.7 (9.6)	100.8 (15.4)	0 (0)
Sharp/van der Heijde score, median (IQR)	20 (8, 40)	14 (7, 38)	27 (11, 43)	3 (4.6)

bDMARD: biologic DMARD; CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic DMARD; IQR: interquartile range; JAK: Janus kinase; tsDMARD, targeted synthetic DMARD.

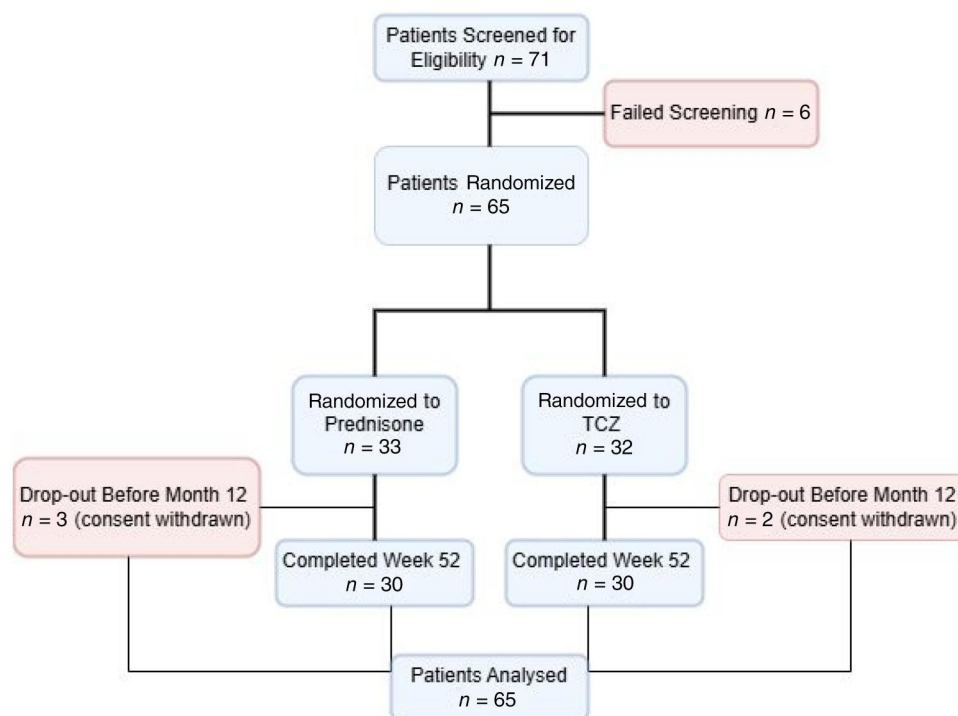


Figure 1. Trial flowchart. *n*: number; TCZ: Tocilizumab

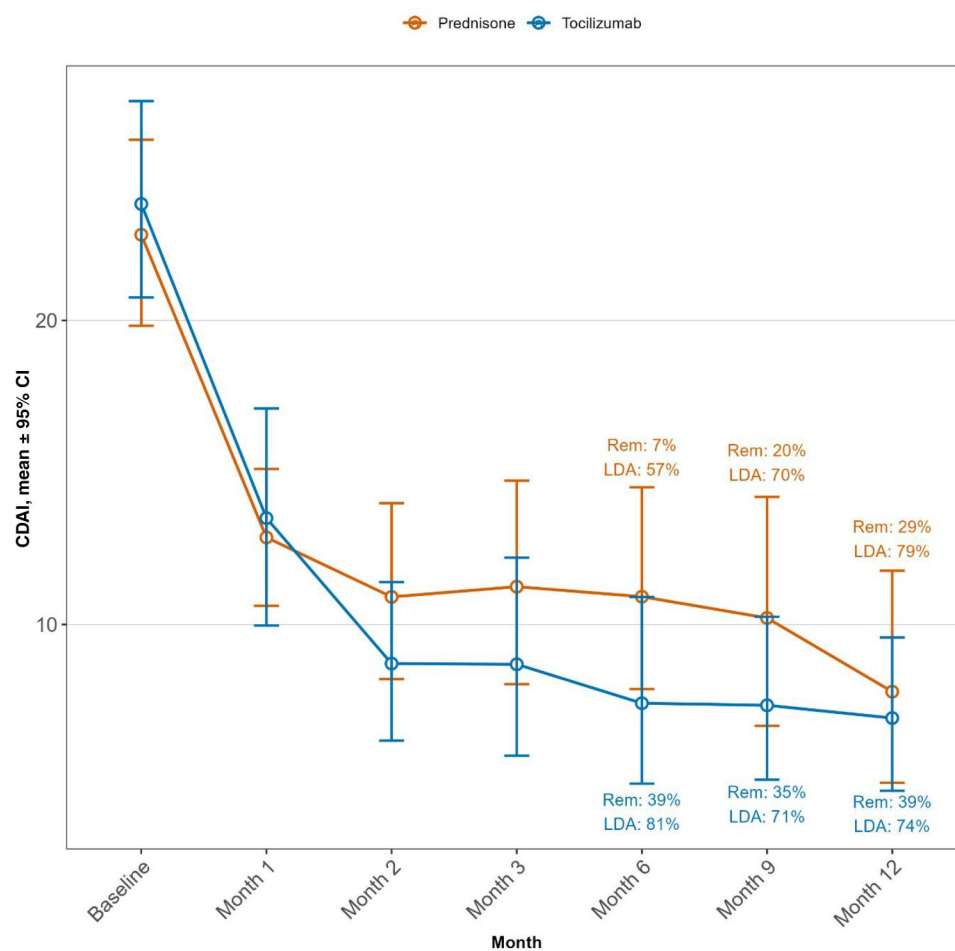


Figure 2. CDAL over time in intention-to-treat population. CDAL: Clinical Disease Activity Index; LD: CDAL low disease activity (≤ 10); Rem: CDAL remission (≤ 2.8)

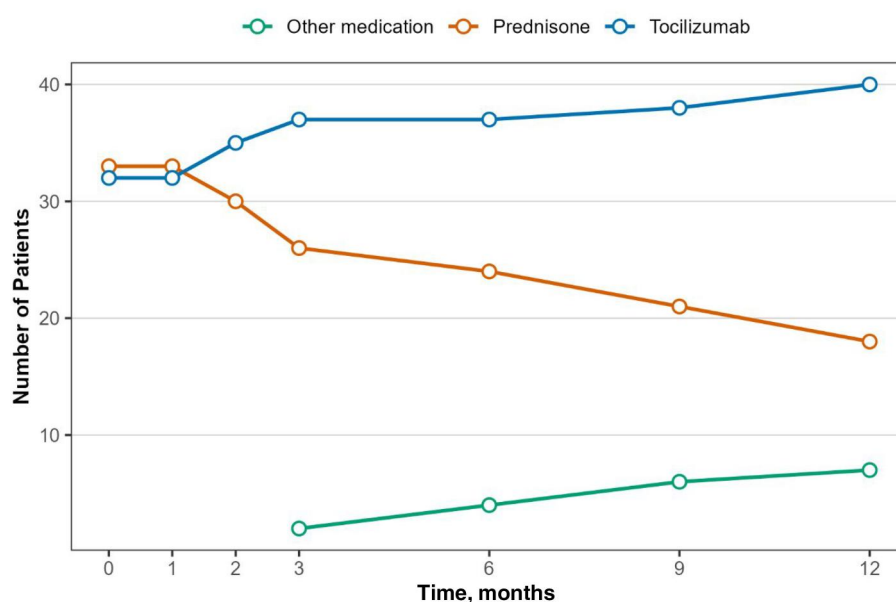


Figure 3. Medication switches over time

end of follow-up. Fourteen of the 19 switches in the prednisone group were due to inefficacy, and the remaining switches were reported due to AEs. In the TCZ group, four patients of eight switched because the treatment was ineffective, and four switched due to AEs.

Of the 33 patients originally randomized to prednisone 13 were able to start tapering during the study. From patients that switched from TCZ to prednisone one was able to taper their medication in the course of the study. Mean starting dose for patients originally on prednisone was 10 mg in accordance with protocol. Mean starting dose for patients that switched from TCZ to prednisone was 8.75 mg, since two of these patients started on lower doses of 5 and 7.5 mg, respectively. Mean dose of prednisone at the end of the study for these patients was 7.1 mg. In the TCZ group 11 out of 32 patients were able to start tapering. Mean dose at the start of the study was 162 mg/week and at the end of the study 137 mg/week. None of the patients that switched from prednisone to TCZ tapered their medication in the course of the study. The on-treatment analysis aligned with the primary results. $\sqrt{\text{CDAI}}$ was 0.9 points lower on average (95% CI: -1.5 to -0.4) for TCZ [5.3 (95% CI: -7.39 to -2.55) points on original scale]. Sensitivity analyses were consistent with the primary findings (see [Supplementary Table S5](#)). The per-protocol analyses contained 58 out of 65 patients who adhered strictly to the study protocol. [Figure 4](#) shows results for individual CDAI components. All components show a similar reduction and consistent difference between treatment groups over time.

Safety/GTI

The overall GC toxicity did not show a significant difference between the groups over twelve months in the ITT analysis. Since the normality assumption for residuals was violated, the Glucocorticoid Toxicity Index (GTI) was analysed using an inverse hyperbolic transformation [24]. The estimate was 0.08 in favour of TCZ, with a 95% CI of -1.02 to 0.86 on

the transformed scale. On the original scale, the estimated difference was -0.09 (95% CI: -1.09 to 1.57).

In the on-treatment analysis, the difference also did not reach statistical significance, but there was a trend suggesting lower GC toxicity in the TCZ group. The estimate was -0.426 in favour of TCZ, with a 95% CI of -1.25 to 0.44 on the transformed scale (-9.16 on the original scale).

When comparing the components of the GTI the largest difference between the groups was in the psychological domain (depression, mania, psychosis and sleep quality) ([Fig. 5](#)).

Other adverse events

The total number of AEs (GTI plus other AEs) did not differ significantly between treatment groups. In the ITT population, patients had a median of five AEs in the course of the study in the prednisone group and four AEs in the TCZ group ($P = 0.348$). Only one patient did not report any AE during the course of the study, and this patient was in the prednisone group. In the on treatment analysis, the rate of AEs was higher in the prednisone group [5.7 *vs* 3.1 AEs per person year, incidence rate-ratio 0.57 in favour of TCZ (95% CI: 0.44, 0.73)]. The most common AEs were insomnia, skin problems and minor infections ([Supplementary Table S6](#)). There were seven serious AEs during the whole study, five in the prednisone group and two in the TCZ group, mainly resulting from hospitalizations due to infections. These serious AEs all occurred in individual patients. The number of TCZ-associated AESIs did not differ between treatment groups in either the ITT (four events and patients in each group; $P = 1$) or on-treatment analyses (five events and patients in the TCZ group *vs* three in the prednisone group; $P = 1$).

Radiographic progression

The TCZ group had a 4-point higher Sharp-van der Heijde score on the original scale after 12 months, after baseline correction. This was not statistically significant (95% CI: -0.272 to 0.736 on the log1p scale, $P = 0.376$).

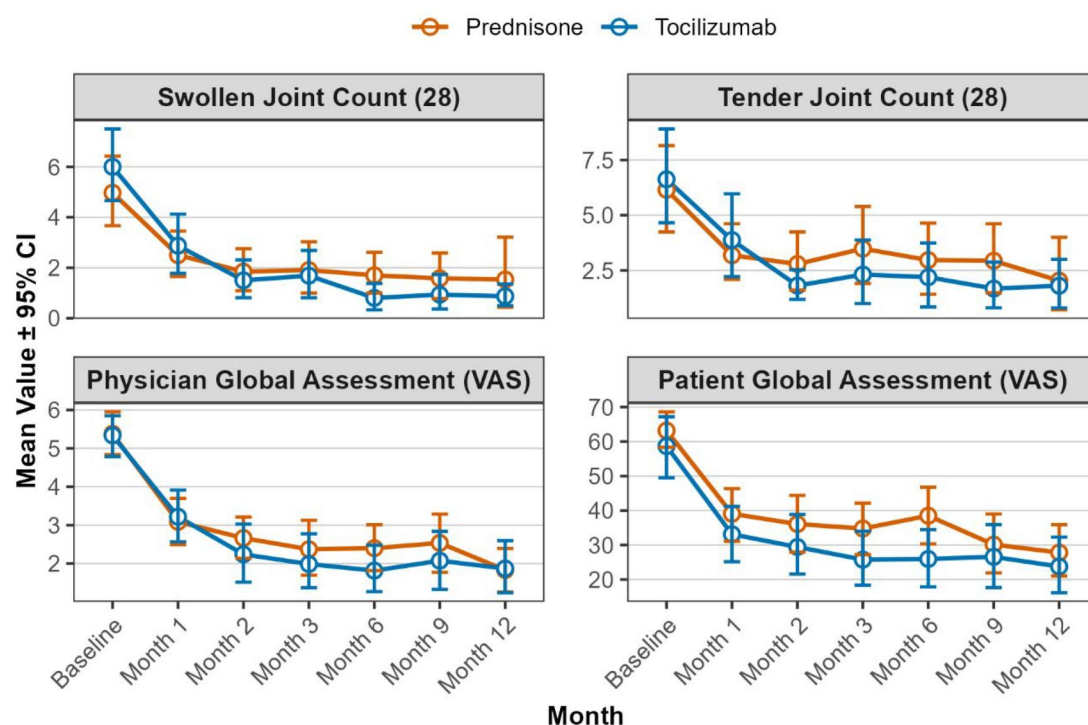


Figure 4. CDAI components over time in intention-to-treat population. CDAI: Clinical Disease Activity Index; VAS: visual analogue scale

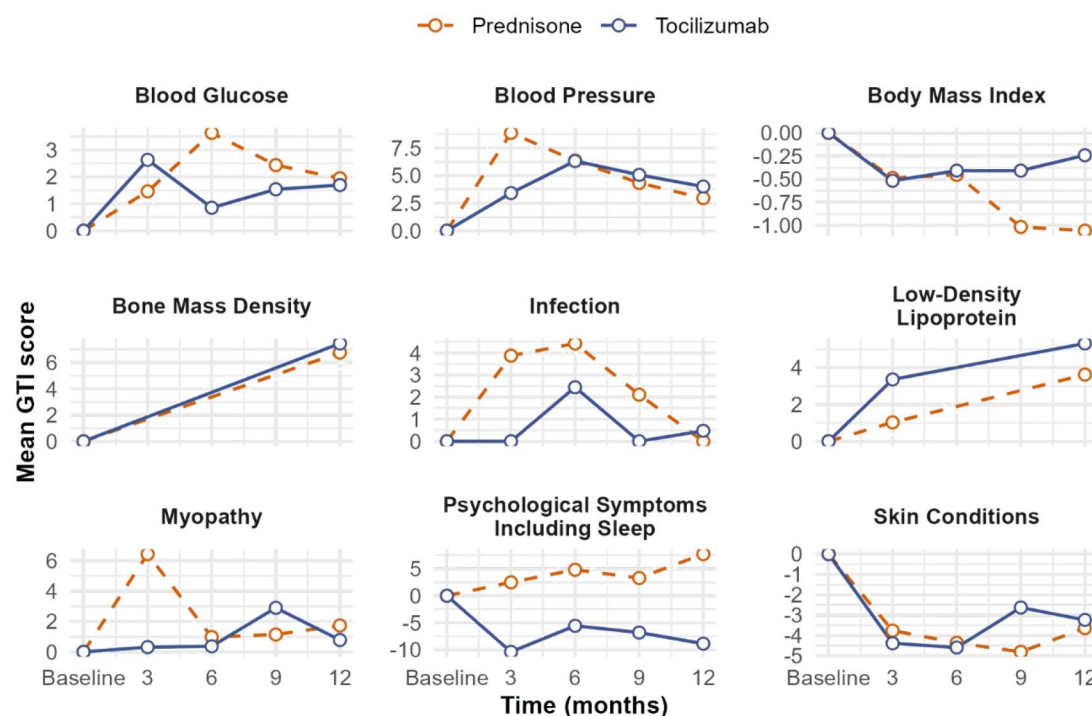


Figure 5. GTI over time by component in on-treatment population. Positive values indicate an increase in toxicity as compared with baseline; negative values indicate a decrease in toxicity compared with baseline. Values per component contribute to total GTI score. GTI: Glucocorticoid Toxicity Index

Other secondary endpoints

DAS28 and SDAI scores align with the CDAI outcomes. The mean difference of DAS28 scores was 0.28 on the natural logarithmic scale ($P=0.031$, mean difference of 1.83, with a 95% CI of -3.06 to -0.23 , on the original scale) and 1.38 ($P=0.019$) for SDAI scores on the square root scale, both favouring TCZ. There was no significant difference in HAQ

scores between the treatment arms (mean difference of 0.12 in favour of TCZ, $P=0.357$).

Discussion

TOPIRA is the first clinical trial to directly compare the therapeutic efficacy and safety of low-to-medium dose prednisone with a biologic agent in RA patients with insufficient

response to another DMARD. Our findings demonstrate that treatment with TCZ led to greater improvements in disease activity, as measured by the CDAI, over 6–12 months. Initially disease activity improved in both groups but stalled in the prednisone group after 3 months. Due to treat-to-target intervention both groups on average reached low-disease activity at the end of follow-up. At month 12, 18 patients were on prednisone, 50 on TCZ and 7 received no study medication. In the ITT analysis, TCZ treatment resulted in a modest but statistically significant additional reduction of ~3 CDAI points compared with prednisone. However, in the on-treatment analysis, this difference increased to 7 CDAI points. As such both results show a clinically important difference (MCID ~1 CDAI point) [25].

A previous indirect comparison has found that low to medium dose prednisone and TCZ in addition to methotrexate were equally effective [14]. Additionally, the NORD-STAR trial found (EudraCT 2011-004720-35; NCT01491815) [26, 27] that active conventional treatment, defined as a csDMARD combined with GC therapy (either orally tapered from 20 to 5 mg over 9 weeks or through intra-articular injections), showed similar effectiveness to TNF- α inhibitors or TCZ over a period of 6 months [28]. These studies were done in early DMARD-naïve and GC-naïve patients, which is markedly different from our population. As has been noted in the literature, a knowledge gap exists on the effectiveness of GCs in established RA [29]. Our research adds to the body of knowledge on this topic.

As can be discerned from Table 1, 35% of patients had already used bDMARDs before initiation of study medication. Interestingly this was not a significant effect modifier for the treatment effect (P of interaction = 0.392). Additionally, the MTX dose was not a significant effect modifier (P = 0.743).

The European Alliance of Associations for Rheumatology (EULAR) guidelines recommend GCs as a short-term adjuvant when starting or switching treatment DMARD therapy [10]. The findings in this study support this. Both TCZ and prednisone were effective at suppressing disease activity during the first month of treatment but on average, the CDAI did not improve much after month 2 in the prednisone group.

In terms of safety, with the caveat of relatively short treatment duration, no major differences were observed between treatment arms in overall AEs, though a trend favouring TCZ was noted. This aligns with prior research and meta-analysis, indicating that the long-term effects of low-dose GCs in terms of GC-related AEs are modest [3, 6]. A side note here is that these only included studies in which the prednisone dose was ≤ 7.5 mg/d, though similar results have been found in the CAMERA-II trial (ISRCTN70365169) [30] which used 10 mg/d of prednisone [7]. A recent study has additionally found that GC naïve patients develop higher levels of toxicity when initiating therapy than patients who have earlier received GCs, though this was generally with higher doses (median of 40 mg) and may also have been a selection effect [31]. Our population was mostly not naïve to GCs, which could explain the lack of significant differences in toxicity. Also, patients who have had previous negative experiences with prednisone may have been reluctant to enrol in our study.

We used a novel way of measuring GC toxicity with the Glucocorticoid Toxicity Index [22, 32]. We used the first published version of this index since it was publicly available at the inception of this study. In rheumatoid arthritis, only the second published version has been applied to date in prospective data [31]. We could not fully apply the 2.0 version retrospectively since some of the categories in the 2.0 version have

five weights as compared with three in the 1.0 version of the GTI. As a sensitivity analysis, we applied a modified version of GTI 2.0, using the new weights where possible and making inferences for the missing categories. This analysis yielded results that were consistent with our primary findings, suggesting that the choice of GTI version did not materially affect our conclusions. The mean difference between treatments in this modified GTI 2.0 was 1 point in favour of TCZ (P = 0.862).

Even though TCZ was more effective than prednisone, the cost-effectiveness of TCZ compared with GCs is still of interest. In resource-constrained settings prednisone may still be the preferred choice in terms of overall health gain with the available budget in such situations. A formal cost-effectiveness analysis will be the subject of a future study. In this trial, the mean medication cost per patient per year was €3890,- in the prednisone arm (of which €102,- was spent on prednisone and alendronic acid/vitamin D) and €9126,- in the TCZ arm (of which €10,- was spent on prednisone and alendronic acid/vitamin D), highlighting the substantial impact of drug prices on overall treatment costs [33, 34]. Strengths of our study include being the first head-to-head comparison in a randomized trial of prednisone *vs* a bDMARD (in this case TCZ) in RA patients with insufficient response to a DMARD. The study's pragmatic nature allowed an approach closer to actual clinical practice than in more controlled clinical trials.

The main limitation of our study was the sample size. Inclusion was stopped early due to recruitment issues related to the COVID-19 pandemic. Another reason for the sluggish recruitment rate might have been hesitancy with physicians and patients surrounding the use of GCs for extended periods of time as guidelines have moved against long-term usage [35]. To mitigate the smaller sample, the primary outcome measure and analysis were adjusted midway to align with the revised sample size for adequate statistical power. This study was open-label, and thus a measure of assessment bias could be introduced, most likely negatively towards prednisone. This could partly explain the high proportion of patients who switched from prednisone to TCZ during the study.

Although TCZ was found to be more effective in reducing disease activity, both treatments were effective and no differences in joint damage were observed. As such low-medium dose prednisone may be an appropriate low cost alternative to TCZ in patients with an insufficient response to DMARDs, while considering potential long-term side effects.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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