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. 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. TCZ retention was analysed with a stratified extended Cox model.

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);
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 sDMARDs (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.

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 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.
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+’ 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).
later times, TCZ is more often discontinued when initiated as monotherapy and 28% for combination therapies). In and safety issues (mentioned for 32% of discontinued patients using local quadratic regression. Treatment groups of 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+MTXplus’, 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.

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+MTXplus’, 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

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

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. 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. 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.

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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. 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. After 104 weeks, the two treatment groups were also significantly different regarding changes in total radiographic and erosion scores but not for clinical endpoints. 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%). Taken together, the results of these clinical trials suggest that concomitant use of MTX provides a slight advantage for some endpoints.

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+MTXplus’ 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.

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

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

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.
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. 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.

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.

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 therefore consider this analysis as more likely to give unbiased results than an analysis based on multiple imputation. 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.
Clinical and epidemiological research

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

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REFERENCES


