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BRIEF REPORT

Efficacy of Tocilizumab Monotherapy Versus Tocilizumab and Methotrexate Combination Therapy in the Prevention of Radiographic Progression in Rheumatoid Arthritis: An Analysis Using Individual Patient Data From Multiple Clinical Trials

Maxime M. A. Verhoeven,[1] Janneke Tekstra,[1] Johannes W. G. Jacobs,[1] Johannes W. J. Bijlsma,[1] Jacob M. van Laar,[1] Attila Pethö-Schramm,[2] Michelle E. A. Borm,[3] Floris P. J. Lafeber,[1] and Paco M. J. Welsing[1]

Objective. To compare the effects of preventing radiographic progression (in its 3 components) of tocilizumab (TCZ) monotherapy with those of TCZ and methotrexate (MTX) in combination therapy (TCZ + MTX), and to evaluate possible effect modifiers in this model.

Methods. Randomized trials that compared TCZ monotherapy to TCZ + MTX combination therapy for differences in radiographic progression were analyzed on an individual patient data level using mixed-effects models, and data were collected from 820 subjects with either early rheumatoid arthritis (RA) or established RA. Outcomes were classified as the absence of radiographic progression after 2 years (i.e., preventing radiographic progression) as measured by total Sharp/van der Heijde score (SHS), erosion score, and joint space narrowing (JSN) score. Effect modification by baseline joint damage, disease duration, and Disease Activity Score in 28 joints (DAS28) was studied.

Results. Overall, TCZ + MTX combination therapy was more effective in preventing radiographic progression compared to TCZ monotherapy, which was measured by total SHS score. However, in patients with early RA who had more joint damage compared to those with less joint damage at baseline (relative risk [RR] 1.02 versus RR 0.91, respectively) or in patients with a lower DAS28 score compared to those with a higher DAS28 score (RR 1.04 versus RR 0.92, respectively) at baseline, this advantage disappeared. In patients with established RA, the advantage of TCZ + MTX versus TCZ alone in the prevention of radiographic progression disappeared with a longer disease duration at baseline (RR 1.04 versus 0.83). Results of erosion scores as an outcome were in line with these findings, though findings for JSN scores were less clear.

Conclusion. Combination therapy with TCZ + MTX is more effective in preventing radiographic progression compared to TCZ monotherapy, but the effectiveness of TCZ monotherapy may approximate the effectiveness of TCZ + MTX in patients with early RA who have more joint damage and/or a lower DAS28 at baseline and in patients with established RA who have longer disease duration.

INTRODUCTION

Joint damage is a negative outcome in rheumatoid arthritis (RA) that leads to a decline in physical function and quality of life (1). However, methods in preventing radiographic progression of joint damage have improved over the last decades by early intensive treat-to-target treatment strategies with disease-modifying antirheumatic drugs (DMARDs), including biologic DMARDs

[1]Maxime M. A. Verhoeven, MSc, Janneke Tekstra, MD, PhD, Johannes W. G. Jacobs, MD, PhD, Johannes W. J. Bijlsma, MD, PhD, Jacob M. van Laar, MD, PhD, Floris P. J. Lafeber, PhD, Paco M. J. Welsing, PhD: University Medical Center Utrecht and Utrecht University, The Netherlands; [2]Attila Pethö-Schramm, MD, PhD: F. Hoffmann-La Roche, Basel, Switzerland; [3]Michelle E. A. Borm, PhD: Roche Nederland BV, Woerden, The Netherlands.

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Address correspondence to Maxime M. A. Verhoeven, MSc, Department of Rheumatology & Clinical Immunology G02.228, PO Box 85500, 3508GA Utrecht, The Netherlands. Email: m.m.a.verhoeven-15@umcutrecht.nl.

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SIGNIFICANCE & INNOVATIONS

- In the prevention of radiographic progression, combination therapy with tocilizumab (TCZ) and methotrexate (MTX) is generally more effective than TCZ monotherapy.
- In patients with early rheumatoid arthritis (RA), for those with more joint damage or lower counts on the Disease Activity Score in 28 joints (DAS28) at baseline, the efficacy of TCZ monotherapy may be equivalent to TCZ + MTX in the prevention of radiographic progression.
- In patients with established RA who have a longer disease duration, TCZ monotherapy may be equivalent to TCZ + MTX combination therapy in the prevention of radiographic progression.

(bDMARDs) (1). Consequently, detecting differences between effective treatment strategies in the prevention of radiographic progression is challenging, especially early in the disease course (2).

Joint damage remains an important outcome measure, as it objectively reflects irreversible damage (3) and the "disease-modifying" effects of treatment strategies (4). Methotrexate (MTX) is the most frequently used first-line DMARD in RA, but patients may need to switch to therapy with a DMARD/bDMARD or otherwise combine MTX with a DMARD/bDMARD because of adverse events and/or insufficient response to MTX. It is a clinical fact that a relevant subgroup of patients do not adhere to treatment with MTX because of side effects, aversion, or inadequate efficacy (4). Tocilizumab (TCZ) may then be a suitable option for these patients, as TCZ can be used with lower doses of MTX or even in the absence of MTX (i.e., as TCZ monotherapy) while still being effective in controlling disease activity as well as in the prevention of radiographic progression (5). However, it is not clear whether TCZ + MTX combination therapy has a better effect than TCZ monotherapy on preventing radiographic progression, the results of which would be relevant knowledge for clinical decision-making.

The aim of our study was to determine the effect of preventing radiographic progression, using individual patient data, with TCZ monotherapy compared to TCZ + MTX combination therapy on different components of radiographic progression and to identify possible effect modifiers. We hypothesized that, in general, a more intensive strategy (i.e., TCZ + MTX) would increase the effectiveness of preventing radiographic progression during treatment; however, this effect may vary among subgroups depending on disease phase and level of severity.

MATERIALS AND METHODS

Individual patient data were obtained from randomized controlled trials (RCTs) on RA that had at least 1 treatment arm with intravenously administered TCZ monotherapy, a treatment arm with TCZ in combination with MTX, and assessments of radiographs of the hands and feet of study participants at baseline and after 2 years of treatment (see Supplementary Materials, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). RCTs published until January 31, 2020 were selected for the present study. The Medical Research Involving Human Subjects Act was not applicable to this study as it concerned reanalysis of existing data. Trial data were made available free of charge by F. Hoffmann-La Roche.

A total of 4 RCTs that had at least 1 treatment arm wherein subjects received TCZ monotherapy intravenously and also a second treatment arm wherein subjects received combination therapy with TCZ + MTX were identified: ACT-RAY (n = 553) (6), FUNCTION (n = 1,164) (7), SURPRISE (n = 105) (8), and U-Act-Early (n = 317) (9). The Sharp/van der Heijde score (SHS) was used to measure radiographic progression in all trials. One RCT used a tight control treat-to-target approach, indicating that therapy could continuously be intensified (at 4-week intervals) when the treatment target was not achieved (9). Two RCTs were performed in subjects with early RA (7,9), and 2 trials tapered TCZ when remission status was achieved in subjects (8,9). In 2 RCTs, a stable dose of oral glucocorticoid (GC) use (≤10 mg/day of prednisone or equivalent) was permitted for use by patients alongside the study therapies investigated in those trials (6,7,10). In 3 RCTs (n = 2,034), individual patient data could be obtained (6,7,9). All 3 RCTs are registered (ClinicalTrials.gov identifiers: NCT00810199 [ACT-RAY], NCT01007435 [FUNCTION], and NCT01034137 [U-Act-Early]), and all patients provided written informed consent. In short, inclusion criteria included the following: a diagnosis of RA according to the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology criteria for RA (11), age 18 years or older, and the presence of moderate-to-active disease activity. Patients with early RA were DMARD-naive; patients with established RA had an insufficient treatment response to MTX.

Radiographs were assessed by a single reader in the FUNCTION and U-Act-Early trials, and by 2 independent readers in the ACT-RAY study; the average radiographic score in the ACT-RAY study was used in our analysis (for detailed information, see the Supplementary Materials, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). The percentage of missing data on radiographic outcomes in the individual trials is reported in their respective publications; the mean percentage of missing data was 29% for these trials. Patients with missing radiographic data were not different from patients who had radiographic data on joint damage, disease duration, and disease activity, all at baseline, nor did they differ between treatments arms within trials, and thus no imputation of missing data was performed.

Statistical analysis. The primary end point was defined as a subject not having radiographic progression versus having any

radiographic progression (i.e., an SHS score of >0) after 2 years, termed as "prevention of radiographic progression." Primary analyses were performed on total SHS scores, and secondary analyses were undertaken on erosion scores and joint space narrowing (JSN) scores. The different TCZ regimens that were compared were 8 mg/kg of intravenous TCZ every four weeks + a median 15 mg of MTX weekly (TCZ + MTX combination therapy) and 8 mg/kg of intravenous TCZ every four weeks (TCZ monotherapy).

Due to heterogeneity of patient populations and study results, we decided to analyze data from trials including MTX-naive patients with early RA separately from trials including patients with established RA. All analyses were performed according to the intention-to-treat principle and were adjusted for sex and age. Treatment effect modification by baseline joint damage, disease duration, and the Disease Activity Score in 28 joints (DAS28) was explored using these factors as covariates as well as in interaction terms with treatment in the models.

Logistic mixed-effects models with random intercept and random effect of treatment, both at study level, were used to analyze the data. If analysis results indicated that joint damage, disease duration, or DAS28 score at baseline were possible treatment effect modifiers (i.e., $P \leq 0.20$ for interaction term), stratified analyses were performed for these factors to better interpret the interaction, using log binomial regression (to obtain relative chances) and forest plots. Stratification was based on the median scores of effect modifiers. Patients with a score at or below this cutoff value were considered as being in the "low-level" subgroup, and patients with scores above this cutoff value were in the "high-level" subgroup. Relative chances of preventing radiographic progression were calculated using relative risk (RR) and 95% confidence intervals (95% CIs), with results graphically illustrated per group/subgroup. Furthermore, the absolute difference in the risk of preventing radiographic progression was calculated per subgroup. This was calculated using the RR and

Table 1. Patient characteristics per individualized RCT

	Early RA		Established RA
	U-Act-Early trial (9) (n = 232)	FUNCTION trial (7) (n = 857)	ACT-RAY trial (6) (n = 417)
Female sex, no. (%)	161 (69)	677 (79)	345 (83)
Age, mean ± SD years	53.9 ± 12.4	50.0 ± 13.0	52.8 ± 12.1
BMI, mean ± SD kg/m^2	26.0 ± 4.4	27.5 ± 6.2	26.2 ± 5.1
Duration of RA, years	0.1 (0.0–0.1)	0.6 (0.1–1.1)	5.5 (2.3–11.4)
Baseline DAS28, mean ± SD	5.1 ± 1.1	6.7 ± 1.1	6.3 ± 1.0
RF positivity, no. (%)	166 (72)	776 (91)	–
Total SHS score at baseline	0 (0–1)	1.5 (0.5–5.5)	29 (17.5–50.5)
Erosion SHS score at baseline	0 (0–0)	1 (0–3.5)	15.5 (10–24)
JSN SHS score at baseline	0 (0–0)	0 (0–1.5)	13.5 (7–27)
Δ in total SHS score	0 (0–1)	0 (0–0)	0 (0–0.5)
Δ in erosion SHS score	0 (0–1)	0 (0–0)	0 (0–0)
Δ in JSN SHS score	0 (0–0)	0 (0–0)	0 (0–0.5)
Initial treatment, no. (%)			
MTX monotherapy	74 (32)	211 (25)	–
TCZ + MTX, 8 mg/kg	78 (34)	220 (26)	215 (52)
TCZ + MTX, 4 mg/kg	–	211 (25)	–
TCZ monotherapy, 8 mg/kg	80 (34)	215 (25)	202 (48)
Glucocorticoid use, no. (%)	0 (0)	429 (37)	212 (51)
Total SHS score of 0 at baseline, no. (%)			
MTX monotherapy	53 (72)	55 (26)	–
TCZ + MTX, 8 mg/kg	58 (74)	55 (25)	0 (0)
TCZ + MTX, 4 mg/kg	–	44 (21)	–
TCZ monotherapy, 8 mg/kg	57 (71)	54 (25)	0 (0)
Δ in total SHS score per initial treatment			
MTX monotherapy	0 (0–0)	0 (0–0)	–
TCZ + MTX, 8 mg/kg	0 (0–0)	0 (0–0)	0 (0–0.5)
TCZ + MTX, 4 mg/kg	–	0 (0–0.5)	–
TCZ monotherapy, 8 mg/kg	0 (0–0)	0 (0–0)	0 (0–0)
Δ in total SHS score of 0, no. (%)			
MTX monotherapy	39 (53)	135 (64)	–
TCZ + MTX, 8 mg/kg	61 (78)	185 (84)	129 (60)
TCZ + MTX, 4 mg/kg	–	152 (72)	–
TCZ monotherapy, 8 mg/kg	55 (68)	172 (80)	111 (55)

* Except where indicated otherwise, values are the median (interquartile range). For the Disease Activity Score in 28 joints (DAS28), scores are measured on a 0 to 9.4 scale, with a higher score indicating more disease activity. For modified Sharp/van der Heijde score (SHS), a higher score indicates the presence of more radiographic joint damage. BMI = body mass index; JSN = joint space narrowing; MTX = methotrexate; RA = rheumatoid arthritis; RCT = randomized controlled trial; RF = rheumatoid factor; TCZ = tocilizumab.

the rate of no progression in the TCZ + MTX treatment group as reference; by multiplying these, the rate of no progression in the TCZ group was calculated. The difference between these rates of no progression is the absolute risk difference.

As an example to demonstrate the above calculations, the relative chance of preventing radiographic progression of 0.91 for TCZ monotherapy versus TCZ + MTX combination therapy can be translated into an absolute risk difference using the average percentage of patients treated with TCZ + MTX who have no progression in this group (reference rate of 91%). Using the RR and this reference rate, the percentage of patients treated with TCZ who had no progression would be 0.91 × 91% = 83%, and the absolute risk difference would be 91% – 83% = 8%.

All analyses were performed with SAS, version 9.4. *P* values less than or equal to 0.05 by 2-sided test were considered statistically significant.

RESULTS

Table 1 shows the characteristics of all 1,506 patients included in the analysis. In total, 1,089 patients were classified as having early RA and 417 patients were classified as having established RA. Baseline DAS28 scores were generally high (reflecting active disease), although they were slightly lower in the U-Act-Early trial—most likely due to inclusion criteria of this trial being less strict. The median change over 2 years in total SHS score as well as erosion and JSN scores was 0 in all trials and treatment arms (Table 1). The maximum change in total SHS score was 33, 31, and 23 in the U-Act-Early, FUNCTION, and ACT-RAY trials, respectively (data not shown).

Subgroup of patients with early RA. Overall, TCZ monotherapy resulted in less prevention of radiographic progression measured by total SHS score than TCZ + MTX combination therapy in patients with early RA (RR 0.96 [95% CI 0.90–1.03]). However, these effects were modified by baseline joint damage (TCZ alone versus TCZ + MTX; $P < 0.0$) and DAS28 score (TCZ alone versus TCZ + MTX; $P = 0.04$) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). In subgroups, the advantage of TCZ + MTX combination therapy versus TCZ monotherapy in total SHS scores disappeared in the subgroup with high-level joint damage at baseline compared to a subgroup with low-level joint damage at baseline (RR 1.02 [95% CI 0.87–1.18] versus RR 0.91 [95% CI 0.81–1.02] for the high-level and low-level joint damage subgroups, respectively); the advantage of TCZ + MTX compared to TCZ alone also disappeared when comparing a subgroup with low-level DAS28 scores at baseline compared to a subgroup with high-level DAS28 scores at baseline (RR 1.04 [95% CI 0.93–1.17] versus RR 0.92 [95% CI 0.83–1.03] for the low-level and high-level DAS28 score subgroups, respectively) (Figure 1 and Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). Translating these results to absolute differences in the chance of

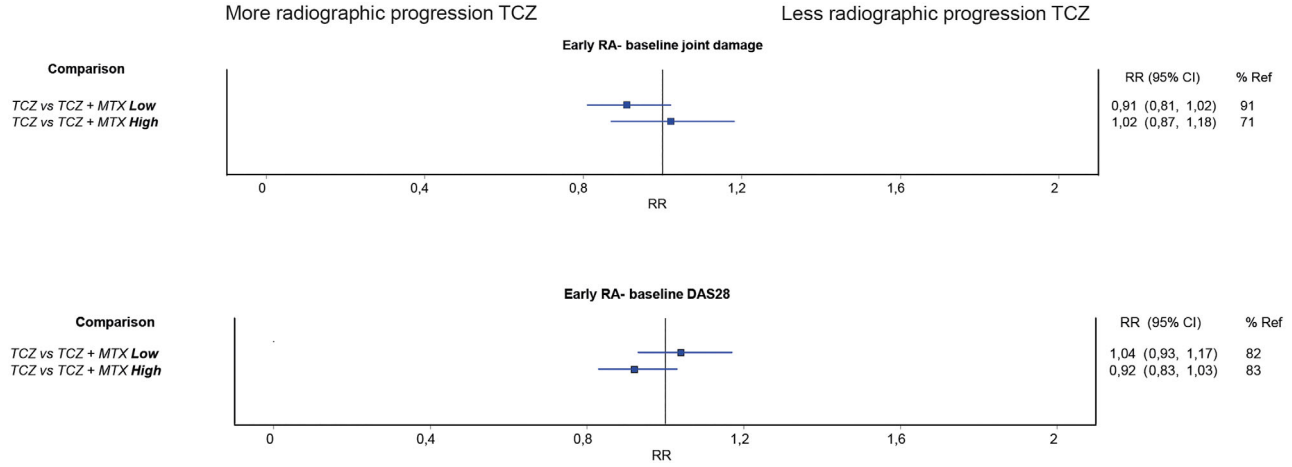

Figure 1. Relative chance (RR) of preventing radiographic progression in patients with early rheumatoid arthritis (RA) who received monotherapy with tocilizumab (TCZ) versus combination therapy with TCZ and methotrexate (MTX). Low-level and high-level baseline joint damage (indicated by a modified Sharp/van der Heijde score of ≤1 or >1) or disease activity (Disease Activity Score in 28 joints [DAS28] score of ≤6.37 or >6.37) were based on their respective median values in the data. In the subgroup with low-level baseline joint damage, 160 received TCZ monotherapy and 166 received TCZ + MTX combination therapy; in the subgroup with high-level baseline joint damage, 129 received TCZ monotherapy and 132 received TCZ + MTX combination therapy. In the subgroup with low-level baseline DAS28 scores, 149 received TCZ monotherapy and 145 received TCZ + MTX combination therapy; in the subgroup with high-level baseline DAS28 scores, 146 received TCZ monotherapy and 153 received TCZ + MTX combination therapy. Horizontal lines show the RR (95% confidence interval [95% CI]), which is based on stratified analyses that were controlled for age, sex, and DAS28 score at baseline. An RR higher than 1 is associated with less radiographic progression in the TCZ group. % Ref = proportion of patients with no progression in disease activity (i.e., based on raw data) in the reference group (i.e., the TCZ+ MTX group).

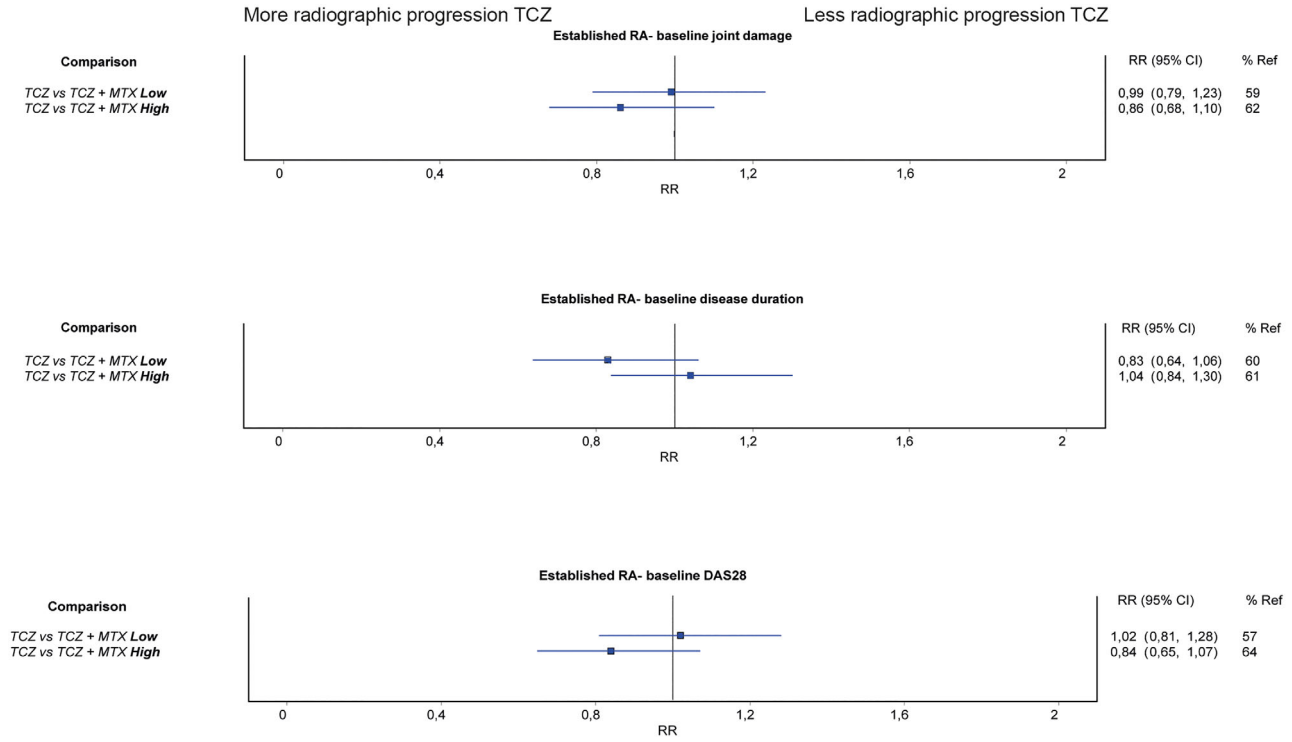

Figure 2. Relative chance (RR) of preventing radiographic progression in patients with established rheumatoid arthritis (RA) who received monotherapy with tocilizumab (TCZ) versus combination therapy with TCZ and methotrexate (MTX). In the subgroup with low-level baseline joint damage, 96 received TCZ monotherapy and 110 received TCZ + MTX combination therapy; in the subgroup with high-level baseline joint damage, 105 received TCZ monotherapy and 106 received TCZ + MTX combination therapy. In the subgroup with low-level baseline disease duration, 103 received TCZ monotherapy and 105 received TCZ + MTX combination therapy; in the subgroup with high-level baseline disease duration, 99 received TCZ monotherapy and 110 received TCZ + MTX combination therapy. In the subgroup with low-level Disease Activity Score in 28 joints (DAS28) scores at baseline, 103 received TCZ monotherapy and 104 received TCZ + MTX combination therapy; in the subgroup with high-level baseline DAS28 scores, 99 received TCZ monotherapy and 111 received TCZ + MTX combination therapy. Low-level and high-level joint damage (indicated by a modified Sharp/van der Heijde score of ≤28.5 or >28.5), disease duration (≤5.46 years or >5.46 years), and disease activity (DAS28 score of ≤6.37 or >6.37) all at baseline were based on their respective median values in the data. Horizontal lines show the RR (95% confidence interval [95% CI]), which is based on stratified analyses that were controlled for age, sex, and DAS28 score at baseline. An RR higher than 1 is associated with less radiographic progression in the TCZ group. % Ref = proportion of patients with no progression in disease activity (i.e., based on raw data) in the reference group (i.e., TCZ + MTX group). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524/abstract.

preventing radiographic progression in subgroups (for calculation details, see the Methods section) resulted in an absolute risk difference between TCZ monotherapy and TCZ + MTX combination therapy of 8% in patients with low-level baseline joint damage versus only 1% in those with high-level baseline joint damage. In the subgroup with low-level baseline disease activity, the risk difference was 3% compared to 7% in the subgroup with high-level baseline disease activity (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524).

Outcomes for erosion scores were partly in line with those for total SHS scores, with a RR of 1.03 (95% CI 0.91–1.17) for the subgroup with high-level baseline joint damage versus an RR of 1.02 (95% CI 0.93–1.10) for the subgroup with low-level baseline DAS28 score (see Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). This finding indicates that the advantage of TCZ + MTX versus TCZ alone also seemed to disappear in these subgroups. In the subgroup with low-level baseline joint damage, the absolute risk difference was 5% versus only 2% in the subgroup with high-level baseline joint damage (see Supplementary Table 3).

Regarding JSN scores, outcomes were less clear regarding the overall advantage of TCZ + MTX combination therapy; however, effect modification was observed for joint damage at baseline ($P = 0.20$) (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). In the subgroup with low-level baseline joint damage, the absolute risk difference was 3% versus 8% in the subgroup with high-level baseline joint damage (see Supplementary Table 3).

Subgroup of patients with established RA. Overall, TCZ monotherapy resulted in less prevention of radiographic progression (measured by total SHS scores) than TCZ + MTX combination therapy in patients with established RA (RR 0.96 [95% CI 0.87–1.07]). However, these effects were modified by baseline joint damage (TCZ versus TCZ + MTX; $P = 0.08$) and disease

duration (TCZ versus TCZ + MTX; $P = 0.04$) (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). In subgroups, the advantage of TCZ + MTX compared to TCZ alone in preventing radiographic progression (measured in total SHS scores) disappeared in those with high-level baseline disease duration compared to the subgroup with low-level baseline disease duration (RR 1.04 [95% CI 0.84–1.30] versus RR 0.83 [95% CI 0.64–1.06] for the subgroups with high-level and low-level disease duration, respectively) (Figure 2 and Supplementary Table 5, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). Translated to absolute differences in the chance of preventing radiographic progression between treatment regimens, the absolute risk difference was 10% in the subgroup with low-level baseline disease duration versus only 2% in the subgroup with high-level baseline disease duration (see Supplementary Table 6).

Outcomes for erosion scores were in line with those of total SHS scores, with an RR of 1.04 (95% CI 0.87–1.25) for the high-level baseline disease duration subgroup (see Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). In the subgroup with low-level baseline disease duration, the absolute risk difference was 10% versus only 3% in the subgroup with high-level baseline disease duration (see Supplementary Table 6).

For JSN scores as an outcome measure, results were less clear in regard to the overall advantage of TCZ + MTX; however, effect modification was observed ($P = 0.12$) (see Supplementary Table 4, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524). In the subgroup with low-level baseline disease duration, the absolute risk difference was 7% versus 0% in the subgroup with high-level baseline disease duration (see Supplementary Table 6).

DISCUSSION

In general, TCZ monotherapy was found to have a less preventative effect on radiographic progression than TCZ + MTX combination therapy; however, this effect was found to vary among patients depending on level of joint damage and disease activity as well as length of disease duration, all at baseline. When analyzing these modifying factors within the subgroups discussed in the present study, we found the effectiveness of TCZ monotherapy approximates that of TCZ + MTX combination therapy in patients with early RA who had lower DAS28 scores (i.e., low-level subgroup) or more joint damage (i.e., high-level subgroup) at baseline. The "window of opportunity" hypothesis (12) implies that RA is more susceptible to treatment in the first six months following disease onset. When symptoms are mild and slowly progressing (low disease activity), a considerable and unnoticed delay in diagnosis may result, and joint damage may have already occurred. These patients may have passed the "window of opportunity," and thus MTX treatment might have less of an additional effect on controlling disease activity (13). Actually, indeed, in the individual patient data used in this study, patients with early RA who had lower baseline DAS28 score more often had joint damage at baseline (see Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524), suggesting a late diagnosis of RA because of the presence of milder symptoms.

For patients with established RA, the effectiveness of TCZ monotherapy approximates that of TCZ + MTX combination therapy in the subgroup of patients with longer baseline disease duration (i.e., high-level subgroup). This might indicate that, with a longer disease duration, MTX is more often no longer effective in preventing radiographic progression when a conventional synthetic DMARD has shown to be insufficiently effective; consequently, the efficacy of this combination treatment predominantly relies on the added bDMARD (TCZ) (14). Baseline GC use may affect radiographic progression; however, radiographic progression was not different among subgroups in terms of disease duration (55% in the high-level group versus 58% in the low-level group), as well as in the disease activity subgroups, indicating that baseline GC use probably has not biased the differences we observed among the subgroups in the present study.

Overall results were in line for total SHS and erosion scores, but less clear for JSN scores. This may be due to the fact that JSN is a slow process, occurring far beyond the 2-year follow-up period, and can additionally be influenced by genetic and mechanical factors (e.g., osteoarthritis) (15), whereas erosion formation is mainly inflammation driven and more specific to RA.

The present study naturally has limitations. First, radiographs were assessed by different readers in the original trials, and radiographs were not reassessed specifically for the current analysis; a substantial portion of radiographic data was missing, although the influence of this missing data on our subgroup analysis was probably limited as patients with and without information on radiographic progression were not different in terms of baseline joint damage, disease duration, and disease activity (as well as in age, sex, and rheumatoid factor positivity). Second, although we used individual patient data from multiple studies, the total sample size is still relatively low for detecting effect modification. For the SURPRISE trial, unfortunately, data sharing was not possible due to legal considerations (8). However, despite the relatively low sample size, effect modifiers were detected. Even when we tested both interactions in the model (i.e., baseline SHS treatment and baseline DAS28 treatment) in early RA, both predictors were still modifiers. Outcomes of the analyses, based on 4 strata (see Supplementary Table 7, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24524), were in line with reported outcomes. Third, radiographic progression is usually lessened now due to the availability of better treatment, resulting in absolute chances of preventing radiographic progression varying between 0% and 12%, which indicates that differences in preventing radiographic progression may not be

clinically relevant in all subgroups. However, using combined data may thus be a suitable means to identify relevant treatment effect estimates in subgroups. We also considered the application of the minimal clinically important difference as a cutoff value for radiographic progression (16). However, as only a few patients met this criterion, meaningful analyses for the minimal clinically important difference were not feasible.

Despite these limitations, the present study used individual patient data from multiple RCTs that contained information from more than 1,500 patients with RA, which provided an exclusive opportunity to explore radiographic progression in patients treated with TCZ in the absence or presence of MTX in a more detailed manner. For the majority of patients, TCZ combination therapy with MTX is more effective in preventing radiographic progression compared to TCZ monotherapy. However, in patients with early RA who have more joint damage and/or lower DAS28 score at baseline and in patients with established RA who have longer disease duration, the efficacy of TCZ monotherapy might approximate that of TCZ + MTX combination therapy. In these specific subgroups, TCZ + MTX combination therapy may have no additional advantage in the prevention of radiographic progression.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms. Verhoeven had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Verhoeven, Tekstra, Welsing.
Acquisition of data. Verhoeven, Tekstra, Welsing.
Analysis and interpretation of data. Verhoeven, Tekstra, Jacobs, Bijlsma, van Laar, Pethö-Schramm, Borm, Lafeber, Welsing.

ADDITIONAL DISCLOSURES

Author Pethö-Schramm is an employee of F. Hoffmann-La Roche. Author Borm is an employee of Roche Nederland BV.

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