



**Universiteit
Leiden**
The Netherlands

Effect of Glucocorticoids on the Clinical and Radiographic Efficacy of Tofacitinib in Patients with Rheumatoid Arthritis: A Posthoc Analysis of Data from 6 Phase III Studies

Charles-Schoeman, C.; Heijde, D. van der; Burmester, G.R.; Nash, P.; Zerbini, C.A.F.; Connell, C.A.; ... ; Fleischmann, R.

Citation

Charles-Schoeman, C., Heijde, D. van der, Burmester, G. R., Nash, P., Zerbini, C. A. F., Connell, C. A., ... Fleischmann, R. (2018). Effect of Glucocorticoids on the Clinical and Radiographic Efficacy of Tofacitinib in Patients with Rheumatoid Arthritis: A Posthoc Analysis of Data from 6 Phase III Studies. *The Journal Of Rheumatology*, 45(2), 177-187. doi:10.3899/jrheum.170486

Version: Not Applicable (or Unknown)
License: [Leiden University Non-exclusive license](#)
Downloaded from: <https://hdl.handle.net/1887/76904>

Note: To cite this publication please use the final published version (if applicable).

Effect of Glucocorticoids on the Clinical and Radiographic Efficacy of Tofacitinib in Patients with Rheumatoid Arthritis: A Posthoc Analysis of Data from 6 Phase III Studies

Christina Charles-Schoeman, Désirée van der Heijde, Gerd R. Burmester, Peter Nash, Cristiano A.F. Zerbini, Carol A. Connell, Haiyun Fan, Kenneth Kwok, Eustratios Bananis and Roy Fleischmann

J Rheumatol 2018;45:177-187
<http://www.jrheum.org/content/45/2/177>

1. Sign up for TOCs and other alerts
<http://www.jrheum.org/alerts>
2. Information on Subscriptions
<http://jrheum.com/faq>
3. Information on permissions/orders of reprints
http://jrheum.com/reprints_permissions

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.

Effect of Glucocorticoids on the Clinical and Radiographic Efficacy of Tofacitinib in Patients with Rheumatoid Arthritis: A Posthoc Analysis of Data from 6 Phase III Studies

Christina Charles-Schoeman, Désirée van der Heijde, Gerd R. Burmester, Peter Nash, Cristiano A.F. Zerbini, Carol A. Connell, Haiyun Fan, Kenneth Kwok, Eustratios Bananis, and Roy Fleischmann

ABSTRACT. Objective. Tofacitinib has been investigated for the treatment of rheumatoid arthritis (RA) in phase III studies in which concomitant glucocorticoids (GC) were allowed. We analyzed the effect of GC use on efficacy outcomes in patients with RA receiving tofacitinib and/or methotrexate (MTX) or conventional synthetic disease-modifying antirheumatic drugs (csDMARD) in these studies.

Methods. Our posthoc analysis included data from 6 phase III studies (NCT01039688; NCT00814307; NCT00847613; NCT00853385; NCT00856544; NCT00960440). MTX-naïve patients or patients with inadequate response to csDMARD or biological DMARD received tofacitinib 5 or 10 mg twice daily alone or with csDMARD, with or without concomitant GC. Patients receiving GC (≤ 10 mg/day prednisone or equivalent) before enrollment maintained a stable dose throughout. Endpoints included the American College of Rheumatology (ACR) 20/50/70 response rates, rates of Clinical Disease Activity Index (CDAI)-defined low disease activity (LDA; CDAI ≤ 10) and remission (CDAI ≤ 2.8), and changes from baseline in CDAI, 28-joint count Disease Activity Score (DAS28-4)-erythrocyte sedimentation rate (ESR), Health Assessment Questionnaire-Disability Index (HAQ-DI), pain visual analog scale (VAS), and modified total Sharp score.

Results. Of 3200 tofacitinib-treated patients, 1258 (39.3%) received tofacitinib monotherapy and 1942 (60.7%) received tofacitinib plus csDMARD; 1767 (55.2%) received concomitant GC. ACR20/50/70 response rates, rates of CDAI LDA and remission, and improvements in CDAI, DAS28-4-ESR, HAQ-DI, and pain VAS with tofacitinib were generally similar with or without GC in monotherapy and combination therapy studies. GC use did not appear to affect radiographic progression in tofacitinib-treated MTX-naïve patients. MTX plus GC appeared to inhibit radiographic progression to a numerically greater degree than MTX alone.

Conclusion. Concomitant use of GC with tofacitinib did not appear to affect clinical or radiographic efficacy. MTX plus GC showed a trend to inhibit radiographic progression to a greater degree than MTX alone. (First Release November 15 2017; J Rheumatol 2018;45:177-87; doi:10.3899/jrheum.170486)

Key Indexing Terms:

TOFACITINIB
CLINICAL EFFICACY

GLUCOCORTICIDS

RHEUMATOID ARTHRITIS
RADIOGRAPHY

From the University of California at Los Angeles (UCLA), Los Angeles, California, USA; Leiden University Medical Center, Leiden, the Netherlands; Charité-University Medicine Berlin Free University and Humboldt University of Berlin, Berlin, Germany; Department of Medicine, University of Queensland, Queensland, Australia; Centro Paulista de Investigação Clínica, São Paulo, Brazil; Pfizer Inc., Groton, Connecticut; Pfizer Inc., Collegeville, Pennsylvania; Pfizer Inc., New York, New York; Metroplex Clinical Research Center and University of Texas Southwestern Medical Center, Dallas, Texas, USA.

Funded by Pfizer Inc. Medical writing support under direction from the authors was provided by Christina Viegmann, PhD, on behalf of Complete Medical Communications, and was funded by Pfizer Inc.

C. Charles-Schoeman has received research grants and consulting fees from Pfizer Inc. D. van der Heijde has received consulting fees from Pfizer Inc., and is the Director of Imaging Rheumatology BV. G.R. Burmester has received consulting fees from, and is on the speakers' bureau for, Pfizer

Inc. P. Nash has received research grants and honoraria for advice and lectures from AbbVie, Lilly, Novartis, Pfizer Inc., Sanofi, Roche, and UCB. C.A. Zerbini has received research grants from, and is on the speakers' bureau for, Pfizer Inc. R. Fleischmann has received research grants and consulting fees from Pfizer Inc.

C. Charles-Schoeman, MD, MS, Associate Professor of Medicine, UCLA; D. van der Heijde, MD, PhD, Professor of Rheumatology, Leiden University Medical Center; G.R. Burmester, MD, Professor of Medicine and Director, Department of Rheumatology and Clinical Immunology, Charité-University Medicine Berlin Free University and Humboldt University of Berlin; P. Nash, MBBS, FRACP, Director, Rheumatology Research Unit, Nambour Hospital, and Associate Professor, Department of Medicine, University of Queensland; C.A. Zerbini, MD, Director, Centro Paulista de Investigação Clínica; C.A. Connell, PhD, Senior Director of Clinical Research, Pfizer Inc., Groton; H. Fan, MS, Statistician/Director, Pfizer Inc., Collegeville; K. Kwok, MS, Director of

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is estimated to affect about 0.24% of the population worldwide¹. Characterized by systemic inflammation, persistent synovitis, and joint destruction², RA has the potential to have a significant effect on functional ability, with reduction in quality of life and work and social productivity³.

The goal of the treat-to-target approach for RA is to achieve remission; however, low disease activity (LDA) is acceptable if remission cannot be achieved⁴. To rapidly control pain and inflammation while awaiting the effects of other disease-modifying antirheumatic drug (DMARD) treatments, patients with RA often initially receive concomitant treatment with oral glucocorticoids (GC). Many rheumatology societies recommend the use of GC in combination with DMARD, with GC being tapered as soon as is clinically feasible^{4,5,6,7,8}.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID), administered as monotherapy or in combination with conventional synthetic DMARD (csDMARD), mainly methotrexate (MTX), in patients with moderate to severe active RA have been demonstrated in phase II^{9,10,11,12,13} and phase III^{14,15,16,17,18,19} studies of up to 24 months duration and in longterm extension studies with up to 105 months of observation^{20,21,22}. The safety of tofacitinib administered as monotherapy or in combination with csDMARD, with and without concomitant GC treatment, has been previously evaluated in the phase III program^{23,24,25}.

In the posthoc analysis reported here, we investigated the effect of concomitant GC use on clinical and radiographic outcomes in 6 phase III studies of tofacitinib versus MTX or placebo as monotherapy or in combination with csDMARD in patients with RA. Unlike studies that evaluated the effectiveness of initial GC therapy as part of the therapeutic strategy, our analysis included patients who were receiving GC prior to the start of their respective clinical trial, the dose of which was required to be maintained throughout their study^{26,27,28}.

MATERIALS AND METHODS

Study design. Our posthoc analysis included data from 6 randomized, double-blind phase III studies of tofacitinib in patients with RA stratified by GC use at baseline (Supplementary Figure 1, available with the online version of this article).

Two studies evaluated tofacitinib 5 and 10 mg BID as monotherapy: ORAL Start (NCT01039688), a 24-month study of tofacitinib versus MTX in patients who were MTX-naïve (n = 956)¹⁷, and ORAL Solo (NCT00814307), a 6-month study of tofacitinib versus placebo in patients (n = 610) with an inadequate response (IR) to ≥ 1 csDMARD or biologic DMARD (DMARD-IR)¹⁵.

Four studies evaluated tofacitinib 5 and 10 mg BID in combination with csDMARD versus placebo plus csDMARD: ORAL Scan (NCT00847613), a 24-month study of tofacitinib in MTX-IR (n = 797) receiving background MTX¹⁸; ORAL Standard (NCT00853385), a 12-month study in patients with MTX-IR (n = 717) receiving background MTX¹⁹; ORAL Sync (NCT00856544), a 12-month study of tofacitinib in patients with DMARD-IR (n = 792) who were receiving background csDMARD¹⁶; and ORAL Step (NCT00960440), a 6-month study in patients (n = 399) who had an IR to tumor necrosis factor inhibitors (TNFi) and were receiving background MTX¹⁴. All patients who were receiving oral GC (≤ 10 mg/day of prednisone or equivalent) prior to enrollment in the studies were required to remain on their baseline dose throughout the studies.

In ORAL Solo and ORAL Step, all patients receiving placebo advanced blindly to tofacitinib 5 or 10 mg BID at Month 3. In the other studies, patients receiving placebo who did not respond at Month 3 (< 20% reduction from baseline in swollen and tender joint counts) were advanced blindly to tofacitinib 5 or 10 mg BID; at Month 6, all remaining placebo patients were advanced to tofacitinib.

All studies were conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on Harmonisation, the Declaration of Helsinki, and the local country regulations. The study protocols were approved by the institutional review board or the independent ethics committee at each site^{14,15,16,17,18,19}. All patients provided written informed consent. No further ethical approval was required to conduct the analysis in our report, in accordance with the policy of our institutions.

Patients. Inclusion and exclusion criteria have been described previously^{14,15,16,17,18,19}. Briefly, eligible patients were aged ≥ 18 years with a diagnosis of RA and met the American College of Rheumatology (ACR) 1987 Revised RA Classification Criteria. Active disease was defined as the presence of ≥ 6 tender or painful joints (out of 68 specific joints examined) and ≥ 6 swollen joints (out of 66 specific joints examined; ≥ 4 for each in ORAL Sync) and erythrocyte sedimentation rate (ESR; Westergren method) > 28 mm/h, or high-sensitivity C-reactive protein level > 7 mg/l.

Assessments and outcomes. For the purposes of our posthoc analysis, efficacy was assessed at months 3, 6, 12, and 24 for ORAL Start, and at Month 3 for ORAL Solo and the pooled combination studies owing to placebo-treated patients advancing to tofacitinib at Month 3 in these studies. Therefore, outcomes for ORAL Start, ORAL Solo, and the pooled combination therapy studies are presented as separate groups for these reasons. Outcomes included the percentage of patients achieving ACR20, ACR50, or ACR70 responses (defined as an improvement from baseline of ≥ 20%, ≥ 50%, and ≥ 70%, respectively, in the number of tender and swollen joints, and at least 3 of the 5 ACR core component measures), and Clinical Disease Activity Index (CDAI)-defined LDA (CDAI ≤ 10) and remission (CDAI ≤ 2.8). Radiographic progression is reported for ORAL Start only, based on the change from baseline of ≤ 0.5 in the van der Heijde modified total Sharp score (mTSS, defined as no radiographic progression). The scoring of the radiographs was performed by 2 separate, central, blinded assessors. Changes from baseline in CDAI, 28-joint Disease Activity Score using the ESR (DAS28-4-ESR), Health Assessment Questionnaire-Disability Index (HAQ-DI), mTSS (ORAL Start only; mTSS data for ORAL Scan were not included in our posthoc analysis owing to the lack of a placebo arm post-months 3 and 6), and pain visual analog scale (VAS) were also evaluated.

Statistical analyses. Data from the 2 phase III monotherapy studies (ORAL Start and ORAL Solo) were analyzed individually, whereas data from the 4 combination therapy studies (ORAL Scan, ORAL Standard, ORAL Sync, and ORAL Step) were pooled for analysis. Unless otherwise stated, all efficacy analyses were based on the full analysis set, which included all patients who were randomized to the study and received ≥ 1 dose of the study drug. The analysis was based on concomitant baseline GC use; because of the design of the study, patients were required to maintain a stable GC dose throughout the study and initiation of a new GC agent was not allowed during the study.

Within each study cohort, disease activity in the tofacitinib treatment groups were compared with the respective comparator arm (MTX or placebo). These posthoc analyses were exploratory, with no multiplicity adjustments applied. A p value < 0.05 was considered statistically significant.

For the binary (response) endpoints, comparisons were performed between tofacitinib and the comparator arm using the normal approximation to the binomial proportions and missing data were imputed using non-responder imputation. Linear mixed-effect models were used to assess treatment effect over the comparator arm for continuous variables; missing data were handled within the model. Linear extrapolation was used to impute missing mTSS values in the tofacitinib and MTX treatment groups for ORAL Start.

RESULTS

Patients. A total of 4067 patients were included in our analysis, of whom 3200 patients received tofacitinib 5 or 10 mg BID, 186 received initial MTX monotherapy in ORAL Start, and 681 received placebo (Supplementary Table 1, Supplementary Figure 1; available with the online version of this article). Of the total patients, 1566 participated in the monotherapy studies (ORAL Start and ORAL Solo). Of the 956 patients from ORAL Start, 373, 397, and 186 received tofacitinib 5 and 10 mg BID and tofacitinib placebo, respectively. All patients ($n = 610$) from ORAL Solo were included in our analysis, with 243, 245, and 122 patients receiving tofacitinib 5 and 10 mg BID and placebo, respectively. Of the 2501 patients who received tofacitinib or placebo in the pooled phase III combination studies, 973, 969, and 559 patients received tofacitinib 5 and 10 mg BID and placebo, respectively.

Concomitant oral GC was received by 445 (46.5%) patients in ORAL Start, 350 (57.4%) in ORAL Solo, and 1454 (58.1%) in the pooled phase III combination studies (Supplementary Table 1; Supplementary Figure 1, available in the online version of this article). Patients received a mean GC dose range of 6.2–8.3, 6.4–7.0, and 6.1–6.3 mg/day in ORAL Start, ORAL Solo, and the pooled phase III combination studies, respectively.

Patient baseline demographics and disease characteristics were generally similar across all of the phase III studies (Supplementary Table 1, available with the online version of this article) other than patients from ORAL Start having a shorter mean RA disease duration (2.5–3.7 yrs) than patients in other phase III studies (ORAL Solo: 6.6–9.1 yrs; pooled combination therapy studies: 8.8–10.5 yrs), and the percentage of placebo patients in ORAL Solo who were rheumatoid factor–positive (RF+; 52.5%) was lower than in the pooled phase III studies (70.5%). Patient baseline demographics and disease characteristics were also generally similar regardless of whether patients were receiving GC at baseline, although mean C-reactive protein (CRP) at baseline and percentage of patients who were positive for anticyclic citrullinated peptide antibodies (anti-CCP) and RF, or who had CRP > 7 mg/l, were generally higher for patients with DMARD-IR (ORAL Solo) receiving GC than for those not receiving GC at baseline. Among the 4 pooled combination therapy studies, patient baseline demographics and disease characteristics were

generally similar, with a few exceptions, such as patients from ORAL Step previously failing treatment with TNFi and having longer mean disease duration compared with the other 3 studies (11.3–13.0 vs 6.9–10.2 yrs)^{14,16,18,19}.

Clinical and radiographic efficacy results in ORAL Start. Similar ACR20, ACR50, and ACR70 response rates were seen at months 6 and 24, irrespective of GC use, in patients receiving tofacitinib 5 or 10 mg BID or MTX (Figure 1). MTX-treated patients receiving GC achieved numerically higher ACR20 and ACR50 response rates at months 6 and 24 compared with those patients not receiving GC (with overlapping 95% CI; Figure 1A). A greater percentage of patients receiving either dose of tofacitinib achieved ACR20, ACR50, and ACR70 responses compared with patients receiving MTX, regardless of concomitant GC use (Figure 1).

At Month 24, the percentages of patients achieving CDAI LDA (CDAI ≤ 10) and remission (CDAI ≤ 2.8) with tofacitinib 5 mg or 10 mg BID were similar regardless of whether patients were receiving GC (Figure 2). Although the percentages of patients achieving CDAI LDA and remission were also similar between patients receiving MTX regardless of GC use, these were significantly lower ($p < 0.05$) than patients receiving either dose of tofacitinib.

At Month 3, the least squares mean (LSM) changes from baseline in CDAI, HAQ-DI, DAS28-4-ESR, and pain VAS were statistically greater for patients receiving either dose of tofacitinib compared with MTX, regardless of GC use (Table 1). Further, LSM changes from baseline in these outcomes were slightly greater, with overlapping 95% CI in patients receiving either dose of tofacitinib without GC, compared with those receiving GC (Table 1).

For both doses of tofacitinib, LSM changes from baseline in mTSS through Month 24 were generally similar when given with or without GC (Figure 3). However, the use of GC in patients treated with MTX appeared to inhibit radiographic progression to a greater extent than when GC were not used (Figure 3A). Patients treated with MTX without GC had the highest LSM change from baseline through Month 24 among all the treatment groups; however, the 95% CI overlapped between the 2 MTX subgroups.

Within each individual treatment group (tofacitinib 5 mg, tofacitinib 10 mg, and MTX), the percentage of patients with no radiographic progression at Month 24 were similar, irrespective of GC use (Figure 4). Further, a greater percentage of patients had no radiographic progression with tofacitinib compared with MTX, regardless of concomitant GC use.

Clinical efficacy results in ORAL Solo and pooled phase III studies of tofacitinib plus csDMARD. At Month 3, the ACR20, ACR50, and ACR70 response rates, and the percentage of patients achieving CDAI LDA and remission (for patients receiving tofacitinib 5 or 10 mg BID or placebo) were numerically similar (with overlapping 95% CI) between patients receiving GC and those not receiving GC (Table 2A, B). A greater percentage of patients achieved the above endpoints

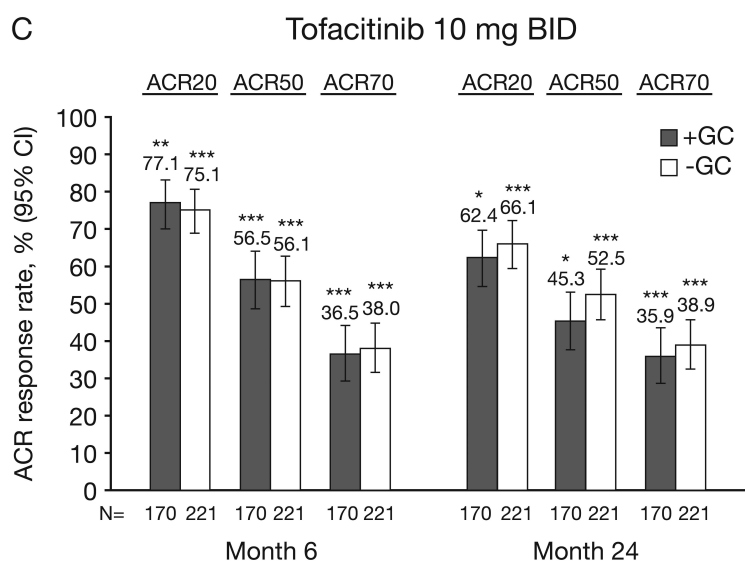
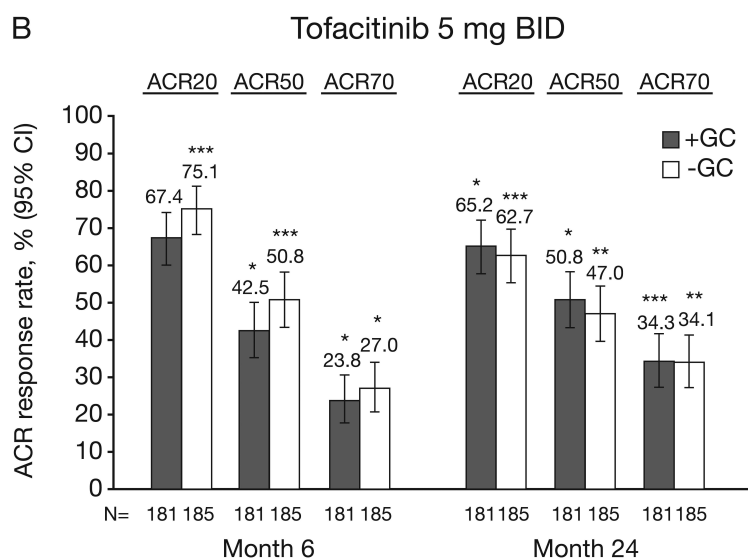
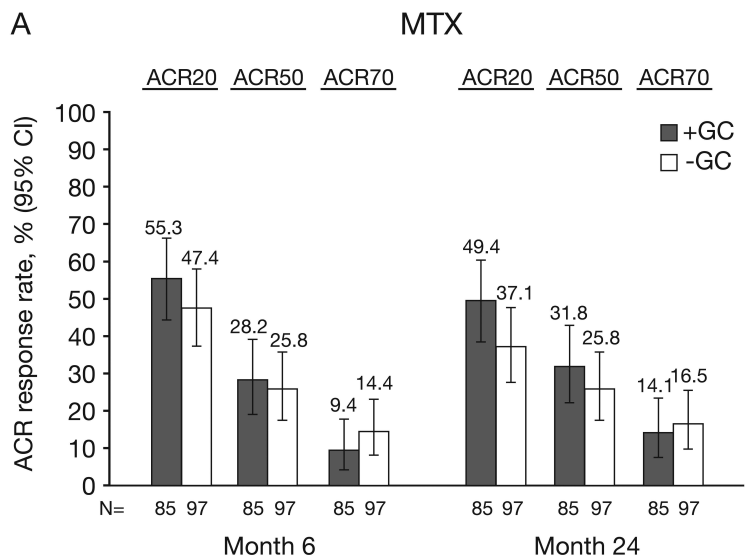


Figure 1. ACR20/50/70 response rates through Month 24 in patients receiving (A) MTX; (B) tofacitinib 5 mg BID; or (C) tofacitinib 10 mg BID \pm GC in ORAL Start (FAS, NRI). * $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$ (without multiplicity adjustment for exploratory analysis) vs MTX within the respective subgroup. ACR20/50/70: improvement of $\geq 20\%$, $\geq 50\%$, and $\geq 70\%$, respectively, in the American College of Rheumatology criteria; BID: twice daily; FAS: full analysis set; GC: glucocorticoids; MTX: methotrexate; NRI: non-responder imputation.

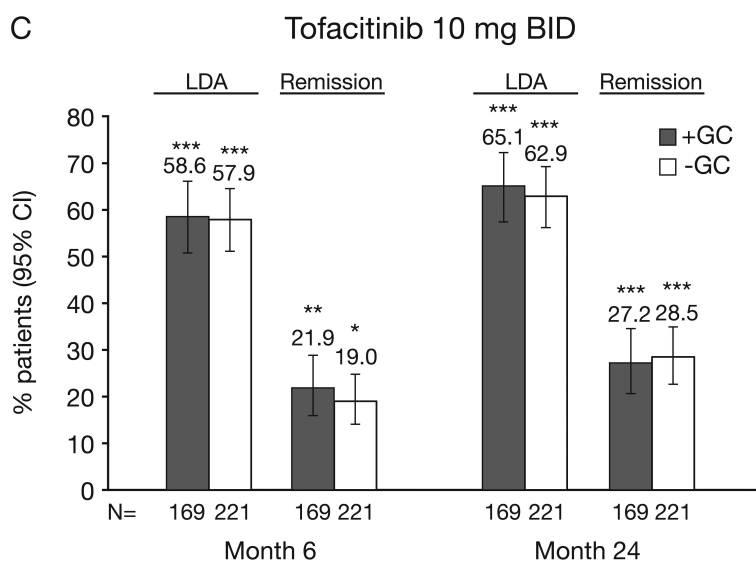
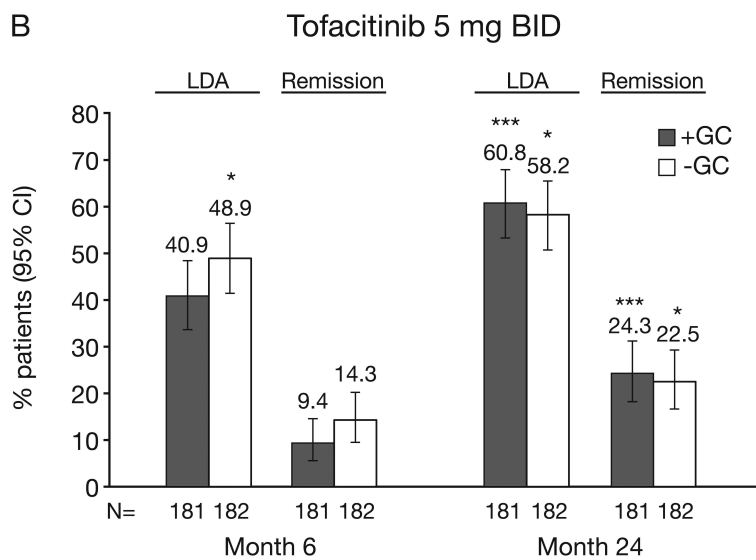
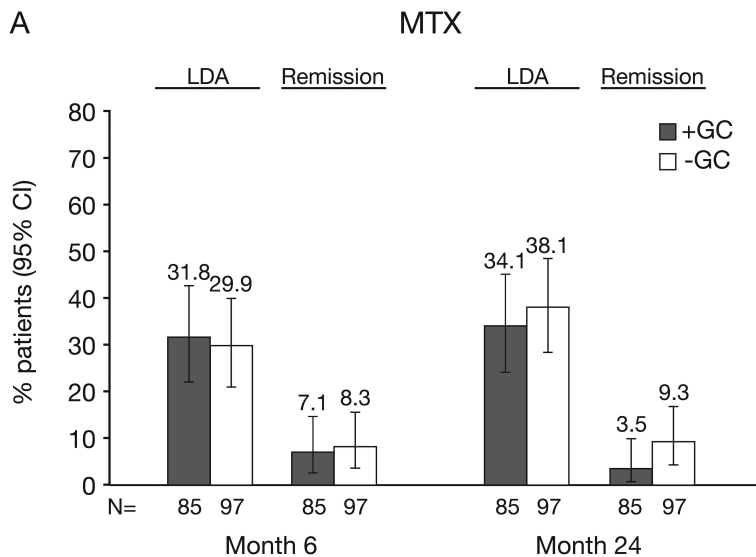


Figure 2. Rates of CDAI LDA (CDAI \leq 10) and CDAI remission (CDAI \leq 2.8) in patients receiving (A) MTX; (B) tofacitinib 5 mg BID; or (C) tofacitinib 10 mg BID \pm GC in ORAL Start (FAS, NRI). * $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$ (without multiplicity adjustment for exploratory analysis) vs MTX within the respective subgroup. BID: twice daily; CDAI: Clinical Disease Activity Index; FAS: full analysis set; GC: glucocorticoids; LDA: low disease activity; MTX: methotrexate; NRI: nonresponder imputation.

Table 1. LSM change from baseline in CDAI, HAQ-DI, DAS28-4-ESR, and pain VAS at Month 3 in patients receiving MTX, tofacitinib 5 or 10 mg BID ± GC in ORAL Start (FAS). Values are LSM change (95% CI).

| Variables | MTX | | Tofacitinib 5 mg BID | | Tofacitinib 10 mg BID | |
|-------------|---------------------------|---------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| | + GC, n = 78 ^a | - GC, n = 91 ^a | + GC, n = 172 ^a | - GC, n = 179 ^a | + GC, n = 165 ^a | - GC, n = 214 ^a |
| CDAI | -16.4 (-18.8 to -13.9) | -18.1 (-20.1 to -16.1) | -22.8*** (-24.5 to -21.1) | -24.7*** (-26.1 to -23.2) | -24.5*** (-26.2 to -22.7) | -26.1*** (-27.4 to -24.8) |
| HAQ-DI | -0.5 (-0.6 to -0.4) | -0.5 (-0.6 to -0.4) | -0.7* (-0.8 to -0.7) | -0.8** (-0.9 to -0.7) | -0.8*** (-0.9 to -0.7) | -0.9*** (-1.0 to -0.8) |
| DAS28-4-ESR | -1.5 (-1.8 to -1.2) | -1.6 (-1.9 to -1.4) | -2.3*** (-2.5 to -2.1) | -2.5*** (-2.6 to -2.3) | -2.5*** (-2.7 to -2.3) | -2.7*** (-2.9 to -2.5) |
| Pain VAS | -19.8 (-24.8 to -14.8) | -25.8 (-29.8 to -21.7) | -29.3* (-32.7 to -25.9) | -30.9* (-33.8 to -28.0) | -30.8** (-34.2 to -27.3) | -34.6** (-37.3 to -31.9) |

*p < 0.05; **p < 0.001; ***p < 0.0001 (without multiplicity adjustment for exploratory analysis) vs MTX within the respective subgroup. ^an based on HAQ-DI endpoint; however, patient numbers varied between outcome measures. BID: twice daily; CDAI: Clinical Disease Activity Index; DAS28-4-ESR: 28-joint Disease Activity Score using the erythrocyte sedimentation rate; FAS: full analysis set; GC: glucocorticoids; HAQ-DI: Health Assessment Questionnaire-Disability Index; LSM: least squares mean; MTX: methotrexate; VAS: visual analog scale.

with both doses of tofacitinib compared with placebo with or without csDMARD. Improvements from baseline in CDAI, HAQ-DI, DAS28-4-ESR, and pain VAS were also similar at Month 3 between tofacitinib-treated patients, with or without GC, although improvements tended to be numerically greater in patients not receiving GC (Table 2A, B).

DISCUSSION

The objective of our posthoc analysis was to examine the effect of GC on RA clinical and radiographic (ORAL Start only) outcomes in phase III studies of MTX-naïve patients receiving tofacitinib or MTX as monotherapy (ORAL Start), patients with DMARD-IR receiving tofacitinib or placebo as monotherapy (ORAL Solo), and in patients with MTX-IR and DMARD-IR receiving tofacitinib or placebo in combination with background csDMARD^{14,15,16,17,18,19}. Among these patients, those who used GC at baseline maintained the same GC dose throughout their study participation. To our knowledge, this is the first developmental drug program in RA to examine the effects of concomitant GC treatment in this patient population, and the first analysis to examine the efficacy of tofacitinib with and without concomitant baseline GC in a large phase III program. Our analysis differs from other studies that compare the efficacy of different RA treatments with and without GC as part of the initial therapeutic strategy, in that patients in our analysis did not initiate GC at baseline but instead had used GC through baseline while still having active disease at baseline.

Across all 6 phase III studies, the concomitant use of GC did not appear to affect the clinical efficacy of tofacitinib. Generally, similar rates of ACR20, ACR50, and ACR70 responses, and CDAI LDA and remission, were observed in tofacitinib-treated patients receiving GC compared with those who did not receive GC. Additionally, although GC such as prednisone have also been reported to inhibit radiographic progression in patients with RA^{29,30,31}, the concomitant use of GC did not affect the radiographic efficacy and rate of radiographic nonprogression in tofacitinib-treated patients in ORAL Start. A trend was observed, however, for greater inhibition of radiographic progression when MTX was given

with GC compared with MTX alone in ORAL Start. This trend is in line with previous studies, which have found that MTX plus low-dose GC results in better clinical and structural outcomes^{28,32} than MTX alone. The overlapping 95% CI between the 2 MTX subgroups may have been a result of the small sample size.

In general, response rates for ACR20, ACR50, ACR70, and CDAI LDA, as well as improvements in CDAI score, were numerically higher in placebo plus csDMARD-treated non-tofacitinib patients who received GC in the 4 phase III tofacitinib combination therapy studies, compared with those who did not; however, 95% CI overlapped. This may be a consequence of the small sample size in our analysis, and may also reflect that patients in our analysis were continuing rather than starting GC treatment. The results are consistent with several studies that have demonstrated that the treatment of early RA with csDMARD in combination with GC results in faster and more persistent disease control than csDMARD alone. Patients in the BARFOT GC study who received prednisolone together with DMARD showed higher remission rates and reduced radiographic progression after 4 years compared with csDMARD-treated patients who did not receive prednisolone³³. Similarly, in the Care in Early RA (CareRA) trial, more patients who received MTX with oral GC achieved remission and clinically meaningful HAQ responses by Week 16 compared with patients who received MTX without oral GC²⁷. In the Computer Assisted Management in early Rheumatoid Arthritis II (CAMERA-II) trial, MTX therapy together with GC resulted in more rapid improvement in DAS28, ESR, pain VAS, and HAQ versus MTX with placebo²⁸. However, it is important to note that unlike the phase III combination therapy studies reported here in which patients who enrolled in the trial were already receiving GC, patients in these studies were not receiving GC prior to the start of the studies.

The effect of GC use with other RA medications such as biological DMARD (bDMARD) has also been analyzed^{34,35,36}; however, the results of studies involving GC and bDMARD are less clear than those of csDMARD. There are conflicting reports regarding the concomitant use of GC

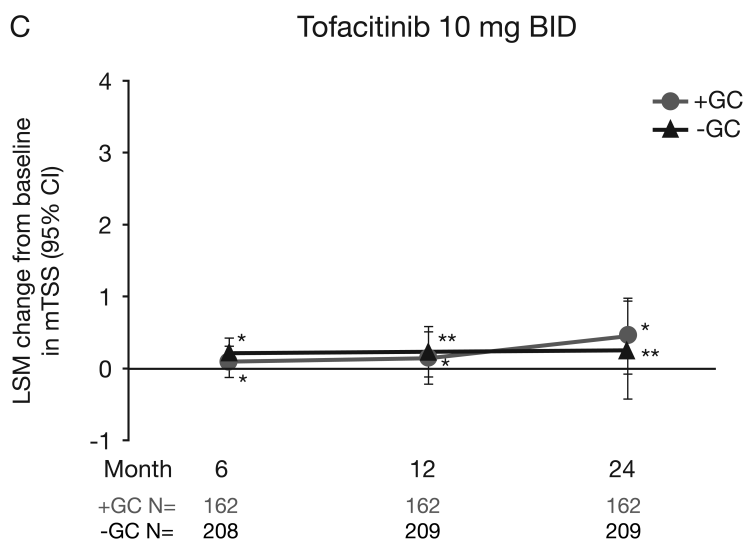
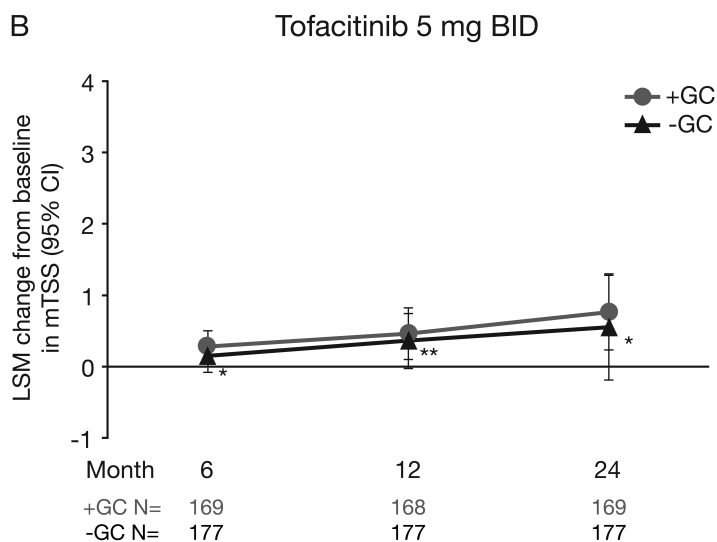
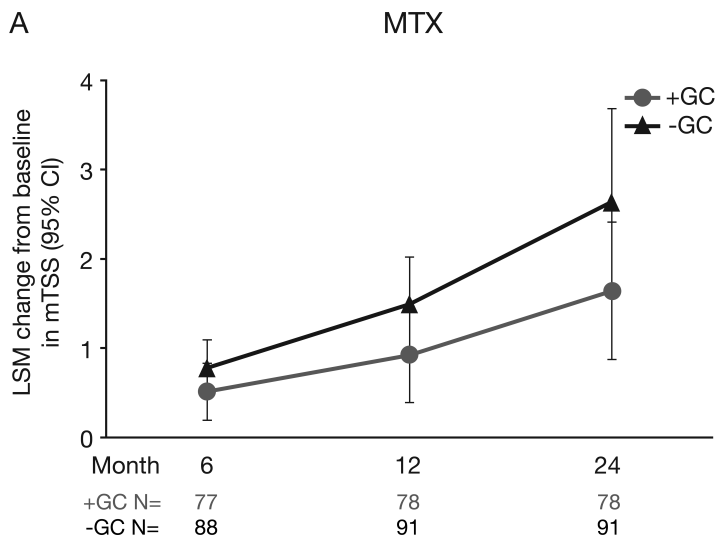


Figure 3. LSM changes from baseline in mTSS in ORAL Start for patients receiving (A) MTX; (B) tofacitinib 5 mg BID; or (C) tofacitinib 10 mg BID \pm GC (FAS). * $p < 0.05$; ** $p < 0.001$ (without multiplicity adjustment for exploratory analysis) vs MTX within the respective subgroup. BID: twice daily; FAS: full analysis set; GC: glucocorticoids; LSM: least squares mean; mTSS: modified total Sharp score; MTX: methotrexate.

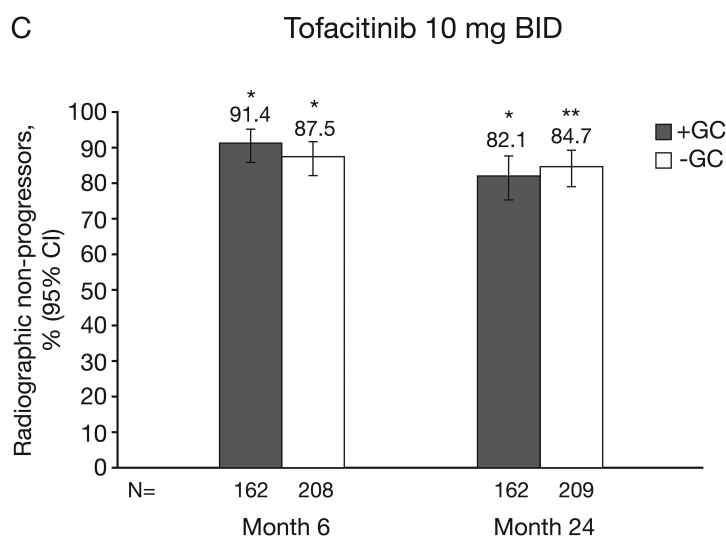
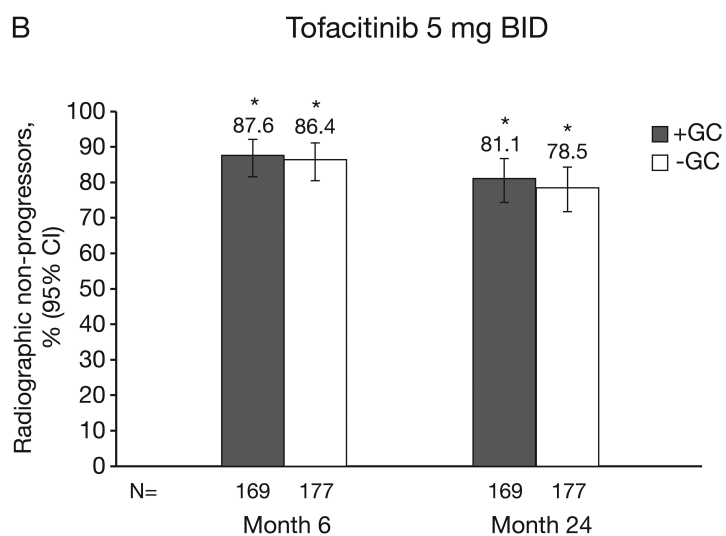
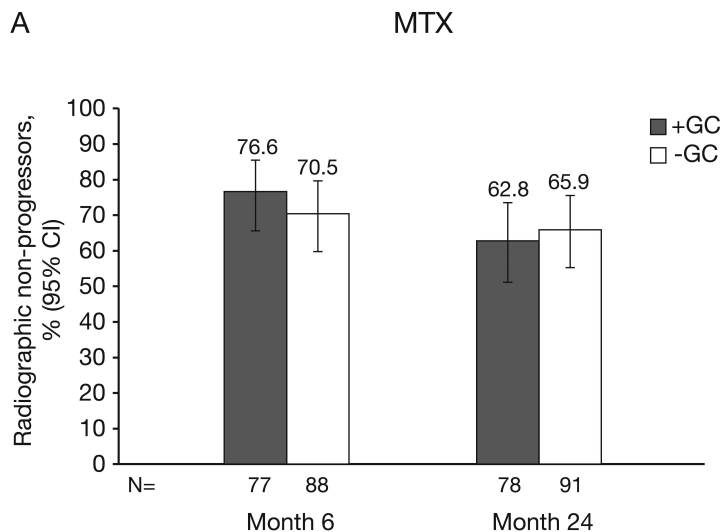


Figure 4. Percentage of radiographic nonprogressors in ORAL Start for patients receiving (A) MTX; (B) tofacitinib 5 mg BID; or (C) tofacitinib 10 mg BID \pm GC (FAS, NRI). * $p < 0.05$; ** $p < 0.001$ (without multiplicity adjustment for exploratory analysis) vs MTX within the respective subgroup. BID: twice daily; FAS: full analysis set; GC: glucocorticoids; MTX: methotrexate; NRI: nonresponder imputation.

Table 2A. Percentage of patients achieving ACR20/50/70 responses and CDAI LDA (≤ 10) and remission (≤ 2.8), and LSM changes from baseline in CDAI, HAQ-DI, DAS28-4-ESR, and pain VAS in patients receiving tofacitinib 5 or 10 mg BID \pm GC at Month 3 in ORAL Solo.

| Variables | Placebo | | Tofacitinib 5 mg BID | | Tofacitinib 10 mg BID | |
|-----------------------------------|---------------------------|---------------------------|----------------------------|----------------------------|---------------------------|----------------------------|
| | + GC, n = 71 ^a | - GC, n = 49 ^a | + GC, n = 139 ^a | - GC, n = 102 ^a | + GC n = 140 ^a | - GC, n = 102 ^a |
| Patients, FAS, NRI, % (95% CI) | | | | | | |
| ACR20 | 28.2 (18.1–40.1) | 24.5 (13.3–38.9) | 57.6*** (48.9–65.9) | 62.8*** (52.6–72.1) | 61.4*** (52.8–69.5) | 71.6*** (61.8–80.1) |
| ACR50 | 12.7 (6.0–22.7) | 12.2 (4.6–24.8) | 31.7** (24.0–40.1) | 30.4* (21.7–40.3) | 35.7*** (27.8–44.3) | 38.2** (28.8–48.4) |
| ACR70 | 5.6 (1.6–13.8) | 6.1 (1.3–16.9) | 16.6* (10.8–23.8) | 13.7 (7.7–22.0) | 19.3* (13.1–26.8) | 21.6* (14.0–30.8) |
| CDAI ≤ 10 | 9.9 (4.1–19.3) | 14.3 (5.9–27.2) | 28.1** (20.8–36.3) | 32.4* (23.4–42.3) | 30.0** (22.6–38.3) | 38.2** (28.8–48.4) |
| CDAI ≤ 2.8 | 2.8 (0.3–9.8) | 0.0 (0.0–7.3) | 6.5 (3.0–11.9) | 4.9* (1.6–11.1) | 8.6 (4.5–14.5) | 7.8* (3.5–14.9) |
| LSM change from baseline (95% CI) | | | | | | |
| CDAI | -11.5 (-14.8 to -8.2) | -12.7 (-16.3 to -9.1) | -20.5*** (-22.7 to -18.2) | -21.9*** (-24.3 to -19.6) | -22.1*** (-24.4 to -19.8) | -25.0*** (-27.4 to -22.5) |
| HAQ-DI | -0.2 (-0.4 to -0.1) | -0.1 (-0.3 to 0.1) | -0.5* (-0.6 to -0.4) | -0.5** (-0.6 to -0.4) | -0.6*** (-0.7 to -0.5) | -0.5** (-0.6 to -0.4) |
| DAS28-4-ESR | -1.1 (-1.5 to -0.8) | -1.1 (-1.4 to -0.7) | -1.9** (-2.1 to -1.6) | -2.0*** (-2.3 to -1.8) | -2.0*** (-2.3 to -1.8) | -2.3*** (-2.6 to -2.0) |
| Pain VAS | -12.0 (-18.0 to -6.0) | -11.0 (-17.6 to -4.3) | -26.0** (-30.1 to -21.9) | -27.2*** (-31.6 to -22.8) | -28.0*** (-32.2 to -23.9) | -33.4*** (-37.9 to -28.9) |

Table 2B. Percentage of patients achieving ACR20/50/70 responses and CDAI LDA (≤ 10) and remission (≤ 2.8), and LSM changes from baseline in CDAI, HAQ-DI, DAS28-4-ESR, and pain VAS in patients receiving tofacitinib 5 or 10 mg BID \pm GC at Month 3 in pooled studies of tofacitinib plus csDMARD.

| Variables | Placebo + csDMARD | | Tofacitinib 5 mg BID + csDMARD | | Tofacitinib 10 mg BID + csDMARD | |
|-----------------------------------|----------------------------|----------------------------|--------------------------------|----------------------------|---------------------------------|----------------------------|
| | + GC, n = 315 ^a | - GC, n = 231 ^a | + GC, n = 561 ^a | - GC, n = 384 ^a | + GC, n = 535 ^a | - GC, n = 410 ^a |
| Patients, FAS, NRI, % (95% CI) | | | | | | |
| ACR20 | 29.2 (24.2–34.6) | 22.5 (17.3–28.5) | 53.8*** (49.6–58.0) | 57.0*** (51.9–62.0) | 60.4*** (56.1–64.5) | 63.2*** (58.3–67.9) |
| ACR50 | 9.2 (6.3–13.0) | 6.9 (4.0–11.0) | 28.3*** (24.7–32.3) | 30.2*** (25.7–35.1) | 32.2*** (28.2–36.3) | 32.9*** (28.4–37.7) |
| ACR70 | 2.2 (0.9–4.5) | 1.7 (0.5–4.4) | 10.3*** (7.9–13.2) | 11.2*** (8.2–14.8) | 14.6*** (11.7–17.9) | 15.1*** (11.8–19.0) |
| CDAI ≤ 10 | 11.5 (7.7–16.3) | 7.8 (4.3–12.7) | 27.7*** (23.8–32.0) | 29.4*** (24.6–34.6) | 32.4*** (28.2–36.9) | 36.3*** (31.2–41.6) |
| CDAI ≤ 2.8 | 0.0 (0.0–1.6) | 0.6 (0.0–3.1) | 5.0*** (3.2–7.4) | 5.7** (3.5–8.8) | 5.2*** (3.4–7.6) | 7.8*** (5.2–11.1) |
| LSM change from baseline (95% CI) | | | | | | |
| CDAI | -9.8 (-11.2 to -8.4) | -8.6 (-10.3 to -7.0) | -17.9*** (-18.9 to -16.8) | -18.2*** (-19.4 to -16.9) | -19.8*** (-20.9 to -18.8) | -19.9*** (-21.1 to -18.7) |
| HAQ-DI | -0.2 (-0.2 to -0.1) | -0.2 (-0.2 to -0.1) | -0.4*** (-0.5 to -0.4) | -0.5*** (-0.5 to -0.4) | -0.5*** (-0.6 to -0.5) | -0.5*** (-0.6 to -0.5) |
| DAS28-4-ESR | -0.8 (-1.0 to -0.7) | -0.7 (-0.9 to -0.5) | -1.8*** (-1.9 to -1.7) | -1.8*** (-1.9 to -1.7) | -2.0*** (-2.1 to -1.9) | -2.0*** (-2.2 to -1.9) |
| Pain VAS | -8.7 (-11.3 to -6.1) | -9.6 (-12.6 to -6.6) | -23.8*** (-25.8 to -21.8) | -23.8*** (-26.1 to -21.4) | -25.7*** (-27.7 to -23.7) | -27.3*** (-29.5 to -25.1) |

* $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$ (without multiplicity adjustment for exploratory analysis) vs placebo within the respective subgroup. ^aNote: patient numbers given are from the FAS for ACR responses; however, patient numbers varied among outcome measures. Percentages are based on available data for each outcome measure. ACR20/50/70: an improvement of $\geq 20\%$, $\geq 50\%$, and $\geq 70\%$, respectively, in American College of Rheumatology criteria; BID: twice daily; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; DAS28-4-ESR: 28-joint Disease Activity Score using the erythrocyte sedimentation rate; FAS: full analysis set; GC: glucocorticoids; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDA: low disease activity; LSM: least squares mean; NRI: nonresponder imputation; VAS: visual analog scale.

with TNFi treatment. One study states that concomitant GC use is a predictor of decreased clinical response and remission in TNFi treatment³⁶, whereas another demonstrates that the use of GC was associated with higher odds of achieving remission in patients treated with TNFi³⁵. GC use prior to the enrollment of patients was not specified in the inclusion and exclusion criteria of these studies. Tocilizumab and abatacept have shown GC-sparing effects, in that the dose of GC may be reduced while the patient is receiving bDMARD without inhibiting clinical improvement in disease activity^{37,38}. Similarly, because the efficacy of tofacitinib may not be affected by concomitant GC therapy, it is possible that patients using both treatments may be able to reduce the dose of GC. A properly designed study would be needed to confirm these findings.

The effect of concomitant GC use on the safety profile of tofacitinib has previously been assessed^{23,24,25}. Rates of serious adverse events, discontinuation as a result of adverse

events, serious infection events, and herpes zoster were shown to be increased in patients treated with tofacitinib who received concomitant GC compared with those who did not^{23,24,25}. The results of our exploratory posthoc analysis suggest that the efficacy of tofacitinib is not affected by background GC use; however, further research is required to determine whether GC use can be tapered following the initiation of tofacitinib, to reduce the risk of adverse events while maintaining efficacy.

Limitations of our analysis include that it was performed posthoc, and the studies were not designed to compare efficacy and radiographic progression (ORAL Start only) in patients with and without concomitant GC use; therefore, any conclusions should be regarded as exploratory. Moreover, the patients in our analysis had active RA at the commencement of the studies despite receiving GC, indicating that they were only partially responsive to GC therapy. These results,

therefore, may not be generalizable to patients starting GC together with csDMARD, implying that caution must be taken when comparing the results from our analysis to other trials in which patients were GC-naïve prior to the commencement of the study. Further, it has previously been reported that rheumatologists may be more likely to initiate GC in patients with more severe RA³⁹. Although the baseline characteristics of patients in our analysis were generally similar, it is possible that the patients with RA receiving GC were less responsive to treatment than the patients who were not initially receiving GC. An additional limitation of our analysis is the estimation of GC dose using the protocol-required limits where the actual dose of GC was not available. Differences in the effects of GC dose on efficacy were also not explored. Further, the sample sizes of the study populations were limited, particularly in the monotherapy studies (ORAL Start and ORAL Solo), as was the length of the followup period. The longer-term effects of concomitant GC use on the efficacy and safety of tofacitinib are not yet known.

The concomitant use of GC may not affect the clinical efficacy of tofacitinib in MTX-naïve, DMARD-IR, and MTX-IR patients receiving tofacitinib as monotherapy or in combination with background csDMARD. Further, the radiographic efficacy of tofacitinib monotherapy in MTX-naïve patients did not appear to be affected by concomitant GC use. In contrast, MTX in combination with GC showed a trend of inhibiting radiographic progression to a greater degree than MTX alone. Further research, in the form of a randomized clinical trial evaluating efficacy in tofacitinib-treated GC-naïve patients with RA, with or without concomitant oral GC of varying dose, would be needed to definitively characterize the efficacy and safety profile of tofacitinib in combination with GC.

ACKNOWLEDGMENT

The authors thank the patients, investigators, and study teams involved in all the studies in the tofacitinib RA clinical program. The authors also thank Vara Bandi for statistical programming support, and E. Meggie Akyllbekova for support on statistical analyses.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

- Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1316-22.
- Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;376:1094-108.
- Strand V, Khanna D. The impact of rheumatoid arthritis and treatment on patients' lives. *Clin Exp Rheumatol* 2010;28:S32-40.
- Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3-15.
- Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492-509.
- Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016;68:1-26.
- Lau CS, Chia F, Harrison A, Hsieh TY, Jain R, Jung SM, et al. APLAR rheumatoid arthritis treatment recommendations. *Int J Rheum Dis* 2015;18:685-713.
- da Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. 2012 Brazilian Society of Rheumatology Consensus for the treatment of rheumatoid arthritis. [Article in English and Portuguese.] *Rev Bras Reumatol* 2012;52:152-74.
- Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum* 2012;64:617-29.
- Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum* 2012;64:970-81.
- Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum* 2009;60:1895-905.
- Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyozumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol* 2015;25:514-21.
- Tanaka Y, Suzuki M, Nakamura H, Toyozumi S, Zwillich SH, Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res* 2011;63:1150-8.
- Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013;381:451-60.
- Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495-507.
- Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2013;159:253-61.
- Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley J, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377-86.
- van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* 2013;65:559-70.
- van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Mejjide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508-19.
- Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, et al. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label,

- long-term extension studies. *J Rheumatol* 2014;41:837-52.
21. Yamanaka H, Tanaka Y, Takeuchi T, Sugiyama N, Yuasa H, Toyozumi S, et al. Tofacitinib, an oral Janus kinase inhibitor, as monotherapy or with background methotrexate, in Japanese patients with rheumatoid arthritis: an open-label, long-term extension study. *Arthritis Res Ther* 2016;18:34.
 22. Wollenhaupt J, Silverfield J, Lee EB, Terry K, Kwok K, Abramsky S, et al. Tofacitinib, an oral Janus kinase inhibitor, in the treatment of rheumatoid arthritis: safety and efficacy in open-label, long-term extension studies over 8 years [abstract]. *Arthritis Rheumatol* 2016;68:1647.
 23. Kivitz A, Haraoui B, Kaine J, Castellano V, Bananis E, Connell CA, et al. A safety analysis of tofacitinib 5 mg twice daily administered as monotherapy or in combination with background conventional synthetic DMARDs in a Phase 3 rheumatoid arthritis population [abstract]. *Arthritis Rheumatol* 2015;67:2143.
 24. Charles-Schoeman C, Burmester G, Nash P, Zerbini CA, Soma K, Kwok K, et al. Efficacy and safety of tofacitinib following inadequate response to conventional synthetic or biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2016;75:1293-301.
 25. Winthrop KL, Curtis JR, Lindsey S, Tanaka Y, Yamaoka K, Valdez H, et al. Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. *Arthritis Rheumatol* 2017;69:1960-8.
 26. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 2005;52:3360-70.
 27. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, et al. Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early rheumatoid arthritis: week 16 results from the randomized multicenter CareRA trial. *Arthritis Res Ther* 2015;17:97.
 28. Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012;156:329-39.
 29. Wassenberg S, Rau R, Zeidler H; Low-Dose Prednisolone Trial Group. A dose of only 5 mg prednisolone daily retards radiographic progression in early rheumatoid arthritis - the Low-Dose Prednisolone Trial. *Clin Exp Rheumatol* 2011;29:S68-S72.
 30. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev* 2007;CD006356.
 31. Graudal N, Jürgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. *Arthritis Rheum* 2010;62:2852-63.
 32. Gaujoux-Viala C, Nam J, Ramiro S, Landewé R, Buch MH, Smolen JS, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:510-5.
 33. Hafström I, Albertsson K, Boonen A, van der Heijde D, Landewé R, Svensson B; BARFOT Study Group. Remission achieved after 2 years treatment with low-dose prednisolone in addition to disease-modifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: an open 2-year continuation study. *Ann Rheum Dis* 2009;68:508-13.
 34. Markuse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YP, van Groenendael JH, Han KH, et al. Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: a randomized trial. *Ann Intern Med* 2016;164:523-31.
 35. Flouri I, Markatseli TE, Voulgari PV, Boki KA, Papadopoulos I, Settas L, et al. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival. *Semin Arthritis Rheum* 2014;43:447-57.
 36. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 2010;62:22-32.
 37. Saraux A, Rouanet S, Flipo RM, Poncet JC, Fardellone P, Hilliquin P, et al. Glucocorticoid-sparing in patients suffering from rheumatoid arthritis and treated with tocilizumab: the SPARE-1 study. *Clin Exp Rheumatol* 2016;34:303-10.
 38. Alten R, Nüßlein H, Galeazzi M, Lorenz HM, Nurmohamed MT, Bensen WG, et al. Decreased use of glucocorticoids in biological-experienced patients with rheumatoid arthritis who initiated intravenous abatacept: results from the 2-year ACTION study. *RMD Open* 2016;2:e000228.
 39. Mueller RB, Reshiti N, Kaegi T, Finckh A, Haile SR, Schulze-Koops H, et al. Does addition of glucocorticoids to the initial therapy influence the later course of the disease in patients with early RA? Results from the Swiss prospective observational registry (SCQM). *Clin Rheumatol* 2017;36:59-66.