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ORIGINAL RESEARCH

Tofacitinib Monotherapy in Rheumatoid Arthritis: Clinical Trials and Real-World Data Contextualization of Patients, Efficacy, and Treatment Retention

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Purpose: To evaluate the characteristics, efficacy, and retention of tofacitinib monotherapy in patients with rheumatoid arthritis using data from randomized controlled trials (RCTs) and real-world data (RWD).

Patients and Methods: Three patient groups receiving tofacitinib 5 mg twice daily (BID) monotherapy were defined for post hoc RCT/long-term extension (LTE) analyses: (1) disease-modifying antirheumatic drug (DMARD)-inadequate responder patients from phase 3/3b/4 RCTs; (2) methotrexate-naïve patients from a phase 3 RCT; and (3) index study patients continuing in an LTE study. Outcomes included low disease activity (LDA)/remission rates defined by Clinical Disease Activity Index (CDAI); Disease Activity Score in 28 joints (DAS28-4), erythrocyte sedimentation rate; DAS28-4, C-reactive protein (DAS28-4[CRP]); and rates of/time to discontinuation due to lack of efficacy/adverse events. RWD were identified by non-systematic literature searches of PubMed, Embase, and American College of Rheumatology/European Alliance of Associations for Rheumatology congress abstracts (2012–2022).

Results: RCT/LTE analyses included 1000/498 patients receiving tofacitinib 5 mg BID monotherapy. Baseline disease activity was high; patients tended to receive concomitant glucocorticoids; most were biologic DMARD-naïve. CDAI LDA rates were 32.2–62.2% for Groups 1/2 (months 3–12) and 64.0–70.7% for Group 3 (months 12–72). In Groups 1, 2, and 3, 4.0%, 15.6%, and 27.7% of patients, respectively, discontinued tofacitinib monotherapy due to lack of efficacy/adverse events. From 11 RWD publications, 16.6–66.1% received tofacitinib monotherapy. Consistent with clinical data, tofacitinib monotherapy effectiveness (month 6 CDAI LDA, 30.2%; month 3 DAS28-4[CRP] remission, 53.4%) and persistence were observed in RWD, with retention comparable to tofacitinib combination therapy.

Conclusion: Tofacitinib monotherapy demonstrated clinically significant responses/persistence in RCT/LTE analyses, with effectiveness observed and persistence comparable to combination therapy in RWD.

Trial Registration: NCT00814307, NCT02187055, NCT01039688, NCT00413699, NCT00661661 (ClinicalTrials.gov).

Keywords: autoimmune, JAK inhibitor, clinical practice, long-term, efficacy, retention

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that affects approximately 0.10–0.38% of people in regions across the world and is a significant contributor to global disability.[1,2] Current treatment guidelines from the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) recommend that patients with RA initiate treatment with a conventional synthetic disease-modifying antirheumatic drug (csDMARD) with the addition of a biologic (b)DMARD, such as a tumor necrosis factor inhibitor (TNFi), or targeted synthetic DMARD, such as a Janus kinase (JAK) inhibitor, in case of therapeutic failure.[3,4]

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Tofacitinib is an oral JAK inhibitor for the treatment of RA that can be used in combination with csDMARDs, such as methotrexate (MTX), or as monotherapy in patients who may be intolerant to csDMARDs.[3,4] Tofacitinib has been shown to be efficacious as monotherapy in phase 3 and 3b/4 randomized controlled trials (RCTs), reducing the signs and symptoms of RA in MTX-naïve patients receiving tofacitinib as a first-line therapy[5] and in patients with an inadequate response to csDMARDs or bDMARDs.[6,7]

While RCTs have long been considered the gold standard for evaluating the efficacy of interventions, with well-defined patient groups and specific inclusion/exclusion criteria, data from these trials can be complemented with real-world data (RWD) from settings more representative of clinical practice.[8,9] Therefore, in this analysis, we used RWD to contextualize the findings from RCTs and long-term extension (LTE) studies of patients with RA receiving tofacitinib 5 mg twice daily (BID) as monotherapy. Patient characteristics, tofacitinib efficacy, and treatment retention were evaluated to further inform clinical decision-making.

Materials and Methods

Post Hoc Analysis of Clinical Trial Data

Three groups of patients with RA receiving tofacitinib 5 mg BID monotherapy in RCTs and LTE studies were analyzed. Only patients treated with tofacitinib 5 mg BID were included in this analysis, as this is the recommended tofacitinib dosage for RA in line with product labeling and was the dosage for most patients treated in real-world settings. In line with the recommended use in the tofacitinib product label,[10,11] Group 1 consisted of patients with moderate to severe RA and an inadequate response to DMARDs from one phase 3 and one phase 3b/4 RCT: ORAL Solo (NCT00814307; phase 3),[6] which included patients with an inadequate response to ≥1 cs/bDMARD, and ORAL Strategy (NCT02187055; phase 3b/4),[7] which included MTX-inadequate responder patients. Group 2 comprised MTX-naïve patients with RA from the phase 3 RCT ORAL Start study (NCT01039688);[5] this group was analyzed separately and included for context. Group 3 included patients who received tofacitinib 5 mg BID monotherapy throughout the global LTE study ORAL Sequel (NCT00413699)[12] or the Japanese LTE study (NCT00661661).[13] Patients in Group 3 could have enrolled from any index study (ie not limited to ORAL Solo, ORAL Strategy, or ORAL Start) and therefore could have received index dosages other than 5 mg BID. In addition, patients in Group 3 may not have received tofacitinib as a monotherapy in their index studies. Full details of the study designs and inclusion/exclusion criteria are outlined in Supplementary Table 1.

All studies included in this post hoc analysis were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation and were approved by the institutional review board and/or independent ethics committee at each participating center (Supplementary Material- List of Investigators and Corresponding Ethics Committees or Institutional Review Boards). As all patients provided written informed consent, all of the data included in this analysis were covered by the original ethical/approval process. Consequently, no additional ethical review/approval was required for this post hoc analysis.

Assessments

Efficacy outcomes included the proportion of patients achieving Clinical Disease Activity Index (CDAI)-defined low disease activity (LDA) and remission (scores ≤10 and ≤2.8, respectively), Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR])-defined LDA and remission (scores ≤3.2 and <2.6, respectively), and DAS28-4, C-reactive protein (DAS28-4[CRP]) ≤3.2 and <2.6 (DAS28-4[CRP] scores have not been validated for LDA and remission but are commonly used in rheumatology). The rates of study discontinuation and time to study discontinuation due to lack of efficacy or adverse events (AEs) were analyzed.

Statistical Analyses

Rates for LDA, remission, and discontinuation due to lack of efficacy or AEs were summarized by treatment (tofacitinib 5 mg BID monotherapy) in each group of patients. Kaplan–Meier curves and survival estimates were generated for discontinuation due to lack of efficacy or AEs in each group.

Literature Search of Real-World Data

A non-systematic literature search was performed to identify publications that reported RWD for patients treated with tofacitinib monotherapy. PubMed, Embase, and ACR/EULAR congress abstracts were searched for publications between November 2012 (when tofacitinib was approved for the treatment of RA by the US Food and Drug Administration) and January 2022 using the following search terms: ("tofacitinib" OR "Xeljanz") AND ("rheumatoid arthritis" OR "arthritis, rheumatoid") AND ("monotherapy" OR "mono") AND ("RWD" OR "RWE" OR "real world" OR "real life" OR "cohort" OR "registry"). The authors also drew on their expert knowledge of the wider literature to provide articles of interest for additional context. Across outcomes, available RWD were presented to contextualize the clinical trial data.

Results

Patients

The RCT analysis included 1000 patients treated with tofacitinib 5 mg BID monotherapy (Group 1, n = 627; Group 2, n = 373); the LTE analysis (Group 3) included 498 patients. Generally, baseline disease activity (based on CDAI) was high, and most patients were bDMARD-naïve. Across groups, concomitant glucocorticoid use ranged from 46.9–57.1%. Patients in Group 2 had a shorter disease duration compared with Groups 1 and 3, and a higher proportion of patients in Group 3 was of an Asian background compared with Groups 1 and 2, owing to the fact this group included patients from the Japanese LTE study (Table 1).

In the literature search, 12 publications were found to contain relevant RWD for patients with RA receiving tofacitinib monotherapy, and these are summarized in Supplementary Table 2. The proportions of patients receiving tofacitinib monotherapy ranged from 16.6–66.1%.[14–24] Where data were available, patients in these RWD analyses tended to be older and have lower baseline disease activity compared with patients in the clinical trials (Table 1). Patients had lower tender and swollen joint counts and were less likely to be bDMARD-naïve in the RWD analyses compared with the RCT and LTE studies (Table 1).

Efficacy and Effectiveness

The proportion of patients achieving CDAI LDA (scores ≤10) in Group 1 and Group 2, respectively, increased over time from 32.2% and 40.0% at month 3 to 53.1% and 62.2% at month 12 (Figure 1A). In Group 3, the rates of achieving CDAI LDA remained stable over time through month 72 (64.0–70.7%; Figure 1A). Across groups, a lower proportion of patients achieved CDAI remission (scores ≤2.8) compared with CDAI LDA; however, in Groups 1 and 2, the proportions of patients achieving CDAI remission increased over time from 6.5% and 9.4% at month 3 to 16.9% and 19.9%, respectively, at month 12 (Figure 1B). In Group 3, the proportion of patients achieving CDAI remission increased over time from 27.2% at month 12 to 35.8% at month 72 (Figure 1B). There was only one article identified in the literature search that reported rates of achieving CDAI LDA (scores ≤10) at these time points.[15] In the US CorEvitas registry,[15] 30.2% of patients receiving tofacitinib monotherapy achieved CDAI LDA at month 6 (Figure 1A).

Rates of achieving DAS28-4(ESR) LDA (scores ≤3.2) in Groups 1 and Group 2, respectively, increased over time from 13.4% and 25.8% at month 3 to 27.5% and 39.1% at month 12 (Figure 1C). In Group 3, the proportion of patients achieving DAS28-4(ESR) LDA was generally similar through month 72 (45.9–51.1%; Figure 1C). A lower proportion of patients achieved DAS28-4(ESR) remission (scores <2.6) compared with LDA across groups. In Groups 1 and 2, respectively, the proportion of patients achieving DAS28-4(ESR) remission increased over time from 6.1% and 13.8% at month 3 to 13.6% and 21.5% at month 12 (Figure 1D). In Group 3, the proportions of patients achieving DAS28-4(ESR) remission were generally similar through month 72 (27.2–31.6%; Figure 1D). None of the articles identified in the literature search reported rates of achieving DAS28-4(ESR) LDA and remission for patients receiving tofacitinib monotherapy at these time points.

Across groups, the changes observed over time for the proportions of patients achieving DAS28-4(CRP) LDA (≤3.2) and remission (<2.6) were similar to those observed with DAS28-4(ESR) LDA and remission (Figure 2A and B). None of the articles identified in the literature search reported rates of achieving DAS28-4(CRP) LDA for patients receiving monotherapy. Only one article identified reported rates of achieving DAS28-4(CRP) remission for patients receiving

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Table 1 Demographics and Baseline Disease Characteristics for Patients Receiving Tofacitinib Monotherapy in Clinical Trials and Available RWD Sources

	Clinical Trial Data			RWD			
				Harnett et al[14]		Reed et al[15] (N=238)	Bird et al[16] (N=282)
	Group 1[a] (N=627)	Group 2[b] (N=373)	Group 3[c] (N=498)	Truven Market-Scan® (N=176)	Optum® Clinformatics® (N=60)		
Age, years							
Median (range)	52.0 (21.0–81.0)	52.0 (18.0–76.0)	56.0 (19.0–82.0)	-	-	-	-
Median (IQR)	-	-	-	-	-	59 (52–68)	-
Mean (SD)	50.7 (12.0)	50.3 (12.2)	54.7 (11.5)	55.7 (11.7)	55.8 (13.3)	-	62.0 (12.2)
Female, n (%)	526 (83.9)	286 (76.7)	424 (85.1)	141 (80.1)	46 (76.7)	193 (81.1)	226 (80.1)
Race, n (%)							
White	449 (71.6)	239 (64.1)	232 (46.6)	-	-	197 (82.8)	-
Asian	82 (13.1)	68 (18.2)	216 (43.4)	-	-	-	-
Black	23 (3.7)	13 (3.5)	5 (1.0)	-	-	-	-
Other	73 (11.6)	53 (14.2)	45 (9.0)	-	-	-	-
Disease duration							
Median (range), years	5.8 (0.2–42.3)	0.8 (0.0–44.0)	5.5 (0.0–38.0)	-	-	-	-
Median (IQR), years	-	-	-	-	-	10 (5–16)	-
Median, months	-	-	-	-	-	-	138.5
Mean (SD), years	8.3 (7.9)	2.9 (5.4)	7.7 (7.6)	2.9 (1.3)	3.0 (1.3)	-	
CDAI							
Median (range)	38.5 (10.7–75.3)	37.5 (11.5–74.3)	33.6 (11.8–71.9)	-	-	-	-
Median (IQR)	-	-	-	-	-	17.9 (9.8–27.0)	-
Joint count, mean (SD)							
TJC	16.0 (6.6)	15.3 (6.6)	12.9 (6.6)	-	-	-	7.3 (7.7)
SJC	11.3 (5.4)	11.7 (5.6)	10.5 (5.0)	-	-	-	6.9 (7.6)
Concomitant glucocorticoids, n (%)	358 (57.1)	175 (46.9)	277 (55.6)	156 (88.6)	54 (90.0)	65 (27.3)[d]	-
Glucocorticoid dose, mean (SD), mg/day	4.3 (9.1)	3.6 (5.7)	6.2 (3.4)	-	-	4.4 (1.0)[d]	-
csDMARD use, n (%)	-	-	-	116 (65.9)	36 (60.0)	-	-
Prior MTX use, n (%)	593 (94.6)	24 (6.4)	44 (8.8)	-	-	-	-
Prior non-MTX csDMARD use, n (%)	279 (44.5)	138 (37.0)	33 (6.6)	-	-	-	-
Prior bDMARD use, n (%)	-	-	-	149 (84.7)	43 (71.7)	215 (90.3)[e]	-
Prior TNFi use	25 (4.0)	0	1 (0.2)	-	-	-	-
Prior non-TNFi bDMARD use	31 (4.9)	0	2 (0.4)	-	-	-	-

Notes: All patients included in the clinical trial groups received tofacitinib 5 mg BID monotherapy; only patients who received tofacitinib 5 mg BID monotherapy throughout the LTE studies were included in Group 3. Patients in Group 3 enrolled in the LTE studies from any index study (ie not limited to ORAL Solo, ORAL Strategy, or ORAL Start) and could have received index dosages other than tofacitinib 5 mg BID. N may vary for specific endpoints. - represents where the variable of interest was not reported. [a]ORAL Solo (NCT00814307) and ORAL Strategy (NCT02187055). [b]ORAL Start (NCT01039688). [c]ORAL Sequel (NCT00413699) and Japanese study (NCT00661661). [d]Concomitant glucocorticoids were prednisone. [e]Value calculated based on bDMARD-naïve patients without taking into account any potentially missing patients.

Abbreviations: RWD, real-world data; N, total number of patients; IQR, interquartile range; SD, standard deviation; n, number of patients with characteristic; CDAI, Clinical Disease Activity Index; TJC, tender joint count; SJC, swollen joint count; csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; bDMARD, biologic disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor; BID, twice daily; LTE, long-term extension.

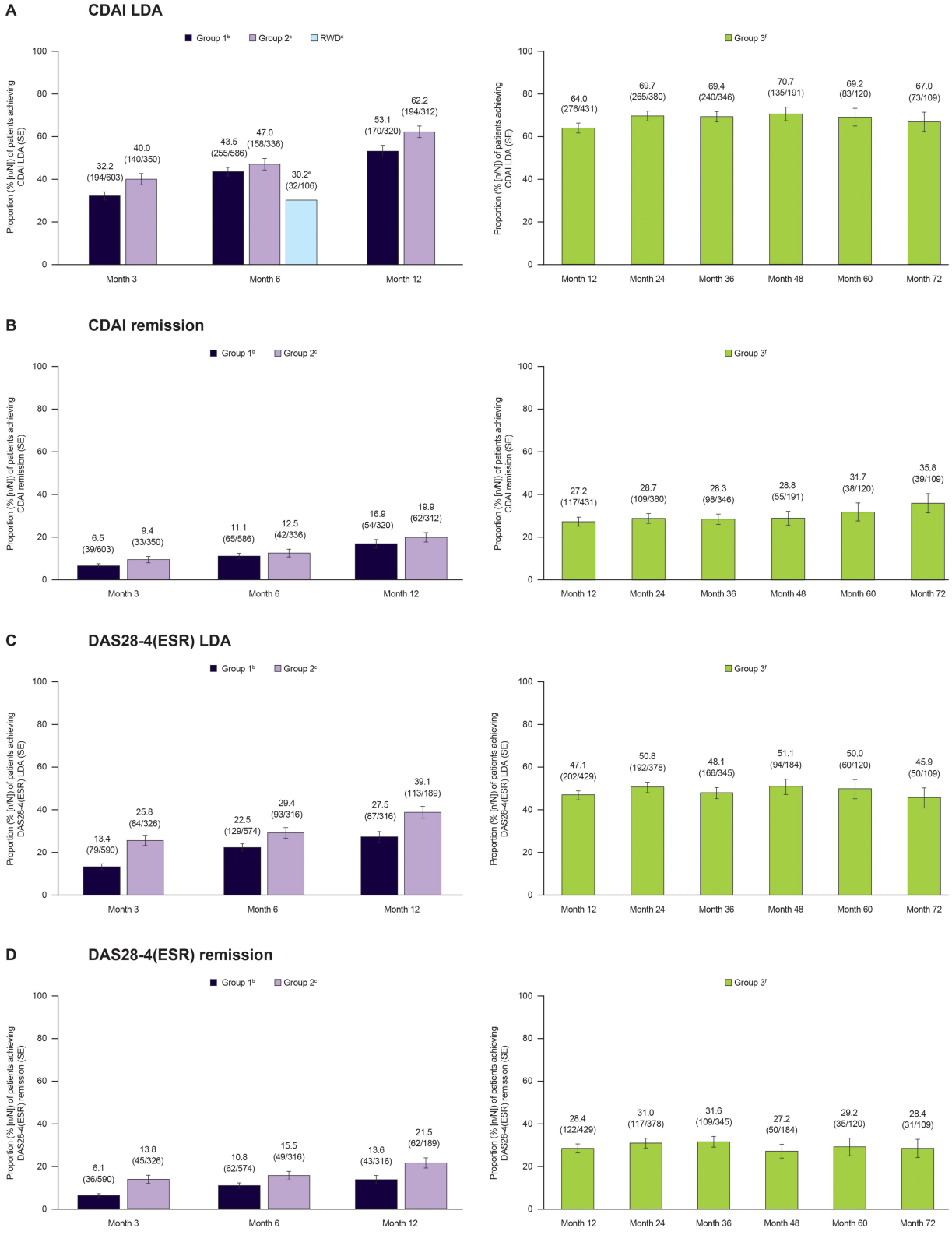

Figure 1 Rates of achieving (**A**) CDAI-defined LDA (≤10), (**B**) CDAI-defined remission (≤2.8), (**C**) DAS28-4(ESR)-defined LDA (≤3.2), and (**D**) DAS28-4(ESR)-defined remission (<2.6) in patients receiving tofacitinib monotherapy in clinical trials[a] and available RWD sources.

Notes: [a]All patients included in the clinical trial groups received tofacitinib 5 mg BID monotherapy; only patients who received tofacitinib 5 mg BID monotherapy throughout the long-term extension studies were included in Group 3. Patients in Group 3 enrolled from any index study (ie not limited to ORAL Solo, ORAL Strategy, or ORAL Start), and they could have received index dosages other than 5 mg BID. [b]ORAL Solo (NCT00814307) and ORAL Strategy (NCT02187055). [c]ORAL Start (NCT01039688). [d]US CorEvitas registry.[15] [e]RWD data are observed values (ie no imputation) with no available SE. [f]ORAL Sequel (NCT00413699) and Japanese study A3921041 (NCT00661661). BID, twice daily; CDAI, Clinical Disease Activity Index; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; LDA, low disease activity; n, number of patients achieving outcome; N, total number of patients; RWD, real-world data; SE, standard error.

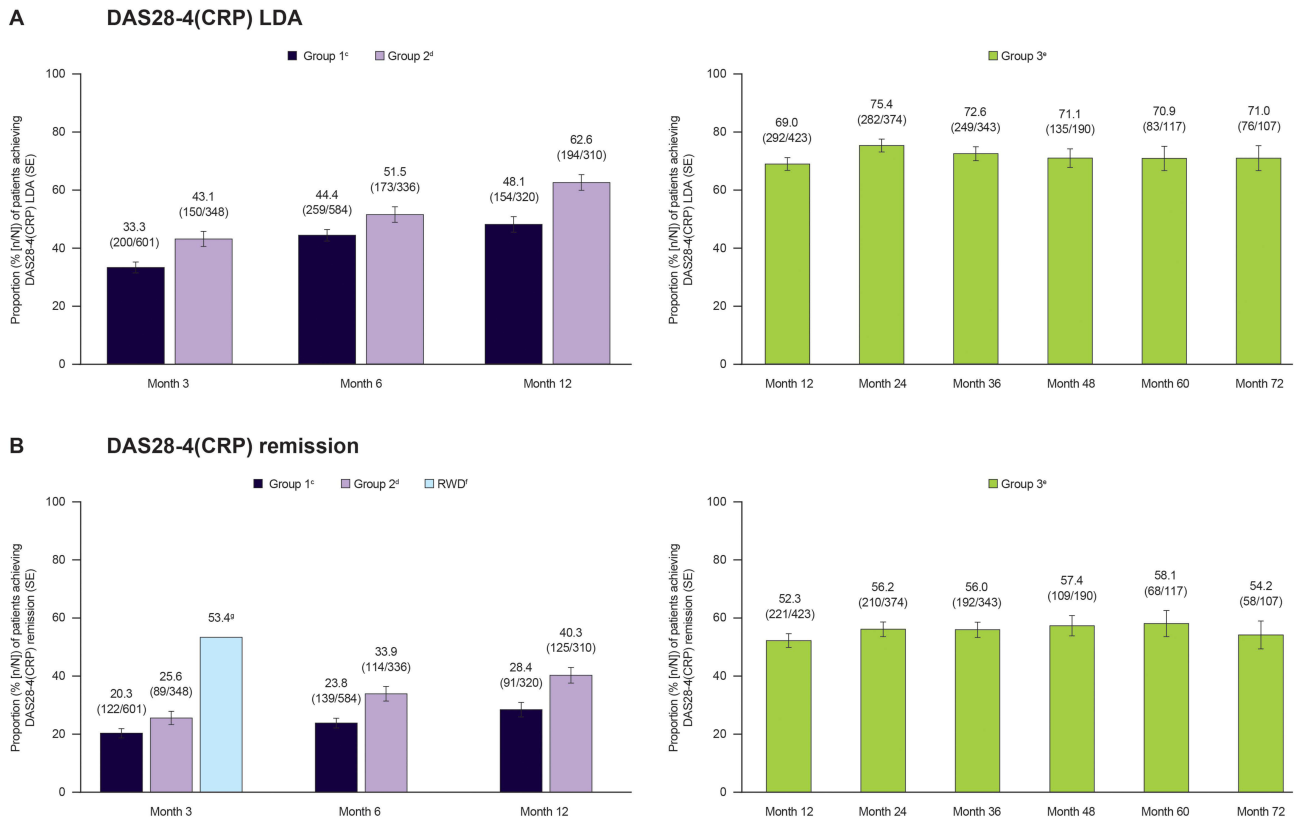

Figure 2 Rates of achieving (**A**) DAS28-4(CRP)-defined LDA (≤3.2)[a] and (**B**) DAS28-4(CRP)-defined remission (<2.6)[a] in patients receiving tofacitinib monotherapy in clinical trials[b] and available RWD sources.

Notes: [a]LDA and remission values for DAS28-4(CRP) (≤3.2 and <2.6, respectively) have not been validated but are commonly used in rheumatology. [b]All patients included in the clinical trial groups received tofacitinib 5 mg BID monotherapy; only patients who received tofacitinib 5 mg BID monotherapy throughout the long-term extension studies were included in Group 3. Patients in Group 3 enrolled from any index study (ie not limited to ORAL Solo, ORAL Strategy, or ORAL Start), and they could have received index dosages other than 5 mg BID. [c]ORAL Solo (NCT00814307) and ORAL Strategy (NCT02187055). [d]ORAL Start (NCT01039688). [e]ORAL Sequel (NCT00413699) and Japanese study A3921041 (NCT00661661). [f]OPAL dataset.[16] [g]RWD data are observed values (ie no imputation) with no n/N numbers and SE available. BID, twice daily; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; LDA, low disease activity; n, number of patients achieving outcome; N, total number of patients; OPAL, Optimizing Patient outcomes in Australian rheumatoLogy; RWD, real-world data; SE, standard error.

monotherapy at the corresponding time points.[16] In the Optimizing Patient outcomes in Australian rheumatoLogy (OPAL) dataset (Australia), 53.4% and 66.7% of patients receiving tofacitinib monotherapy achieved DAS28-4(CRP) remission at month 3 and month 18, respectively (Figure 2B; month 18 data not shown in relation to RCT data).[16]

Treatment Retention

Discontinuation due to lack of efficacy or AEs were reported in 4.0% (n/N: 25/627), 15.6% (n/N: 58/373), and 27.7% (n/N: 138/498) of patients in Group 1, Group 2, and Group 3, respectively. Kaplan–Meier plots of time to discontinuation are presented in Figure 3.

The literature search identified 7 publications, which included RWD on tofacitinib survival in patients with RA receiving monotherapy.[14,16–18,22,23,25] In the US Truven MarketScan® and Optum® Clinformatics® claims databases, 12-month mean (standard deviation) persistence with tofacitinib monotherapy was 135.9 (120.7) days and 125.4 (120.0) days, respectively.[14] These data were not significantly different compared with persistence with tofacitinib combination therapy. There were also no significant differences in retention in the Swiss Clinical Quality Management in RA registry with tofacitinib monotherapy versus tofacitinib administered with concomitant csDMARDs (hazard ratio 1.11, 95% confidence interval [CI] 0.91, 1.35]),[23] in pooled analyses of the Ontario Best Practices Research Initiative (OBRI) and Canadian Rhumadata® clinical database and registry (Kaplan–Meier log-rank p = 0.49),[17] or in separate OBRI and Canadian Rhumadata® analyses with tofacitinib monotherapy versus combination with MTX (Kaplan–Meier log-rank p = 0.31 and p = 0.932, respectively).[18,25] In the Turkish Hacettepe University biological database, the 1-year retention

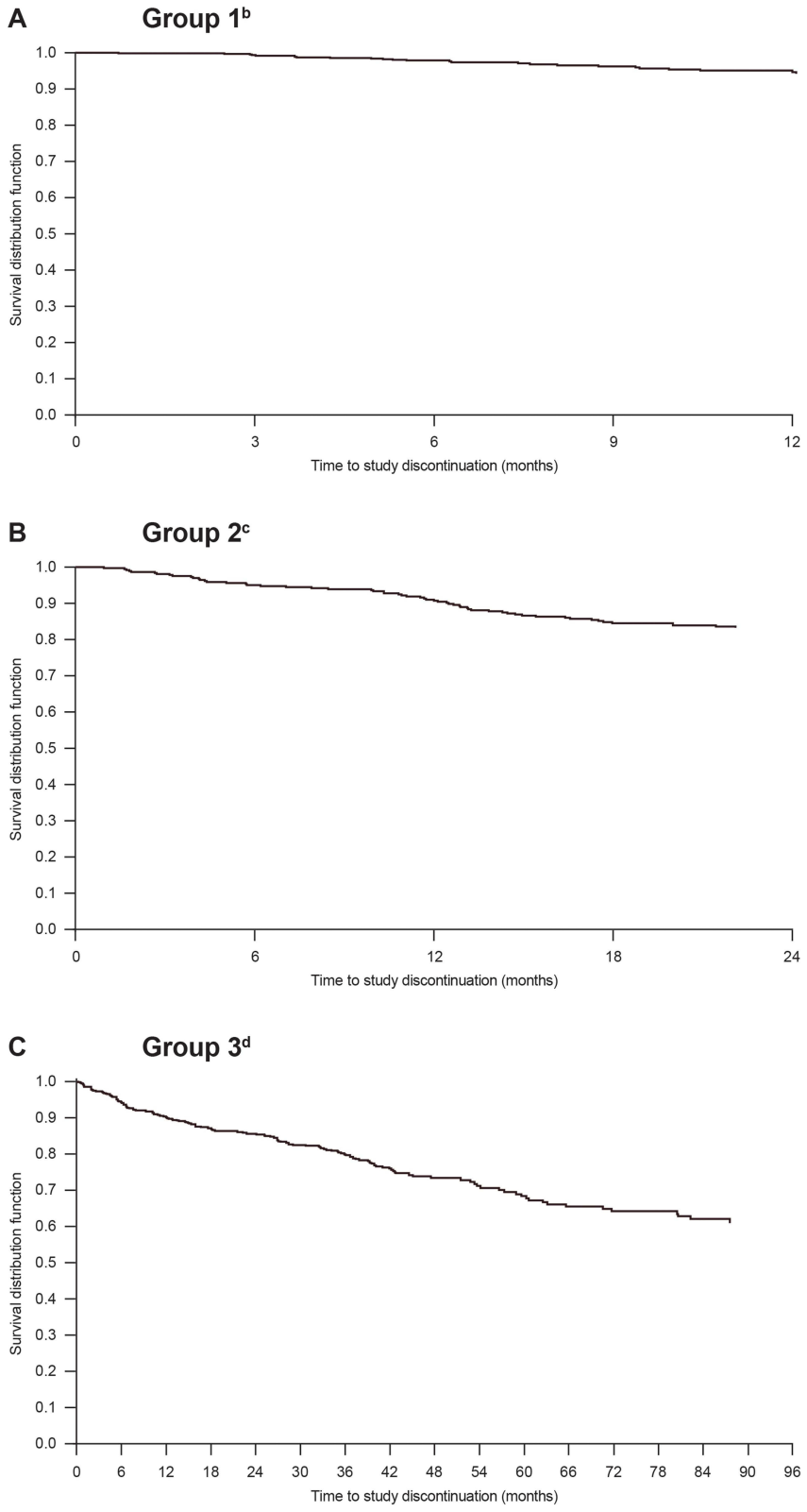

Figure 3 Kaplan–Meier plots of time to discontinuation of tofacitinib 5 mg Bid monotherapy due to lack of efficacy or adverse events in clinical trials[a]: (**A**) Group 1, (**B**) Group 2, and (**C**) Group 3.

Notes: [a]All patients included in the clinical trial groups received tofacitinib 5 mg BID monotherapy; only patients who received tofacitinib 5 mg BID monotherapy throughout the long-term extension studies were included in Group 3. Patients in Group 3 enrolled from any index study (ie not limited to ORAL Solo, ORAL Strategy, or ORAL Start), and they could have received index dosages other than tofacitinib 5 mg BID.[b]ORAL Solo (NCT00814307) and ORAL Strategy (NCT02187055). [c]ORAL Start (NCT01039688). [d]ORAL Sequel (NCT00413699) and Japanese study A3921041 (NCT00661661). BID, twice daily.

rate for tofacitinib monotherapy was 59.7% versus 64.8% for tofacitinib combination therapy (p = 0.76).[22] In the OPAL dataset (Australia), median persistence with tofacitinib monotherapy was 34.2 months (95% CI 30.3 to "not reached") compared with 32.7 months (95% CI 28.7 to "not reached") with tofacitinib combination therapy.[16]

The main reasons for discontinuing tofacitinib monotherapy in the OPAL dataset were "lack of efficacy" (24.7%), "better alternative" (14.8%), "adverse reaction" (14.0%), and "lack of efficacy/secondary failure" (9.6%).[16]

Discussion

While the efficacy and safety of tofacitinib have been demonstrated in RCTs and LTE studies,[5–7,12,13] the strict inclusion/exclusion criteria used in RCTs mean that trial populations are not fully representative of patients seen in clinical practice.[9] RWD can be used to complement these clinical trial data, providing evidence of effectiveness in real-world clinical practice.[8] This study sought to use RWD to contextualize the findings from RCTs and LTE studies of patients with RA receiving tofacitinib 5 mg BID (recommended dosage) monotherapy. We analyzed three separate patient groups from RCTs/LTE studies. Group 1 included patients with moderate to severe RA with an inadequate response to cs/bDMARDs, in line with the recommended use in the tofacitinib product label.[10,11] Group 2 (MTX-naïve patients who received tofacitinib 5 mg BID monotherapy) was included to provide additional context. Group 3, which included patients that enrolled in tofacitinib LTE studies, assessed the long-term efficacy and retention of tofacitinib 5 mg BID monotherapy.

In the analysis of clinical trial data, tofacitinib 5 mg BID monotherapy demonstrated clinically significant responses in patients with RA, as assessed by CDAI-, DAS28-4(ESR)-, and DAS28-4(CRP)-defined LDA and remission, as well as persistence. Discontinuation due to lack of efficacy or AEs occurred in <28% of patients treated with tofacitinib 5 mg BID in LTE studies; this is similar to the overall rate in ORAL Sequel, where 24% discontinued due to AEs, while 4% discontinued due to insufficient clinical responses.[12] Previous analyses of the tofacitinib phase 3/3b/4 RCTs showed that the most frequently reported AEs leading to discontinuation of tofacitinib 5 mg BID monotherapy included increased blood creatinine, RA, and cellulitis.[7,26] In the ORAL Sequel LTE, the most reported all-cause AEs by Preferred Term leading to discontinuation of all tofacitinib doses included pneumonia, increased blood creatinine, and herpes zoster.[12]

In line with clinical data, effectiveness (as assessed by CDAI-defined LDA at month 6 and DAS28-4[CRP] remission at month 3) and persistence of tofacitinib monotherapy were also observed in available RWD, with retention comparable with combination therapy.[14–18,22,23,25] It should be noted, however, that differences were observed between the clinical trials and those from analyses of RWD. For instance, 30.2% of patients who initiated tofacitinib monotherapy as a third- or fourth-line therapy in the US CorEvitas (formerly Corrona) registry achieved CDAI LDA at month 6,[15] while 43.5% and 47.0% of patients in Groups 1 and 2, respectively, achieved CDAI LDA at month 6. In addition, in the OPAL dataset in Australia, 53.4% of patients who received tofacitinib monotherapy achieved DAS28-4(CRP) remission at month 3;[16] this was higher than the proportion of patients who achieved DAS28-4(CRP) remission at month 3 in Groups 1 and 2 (20.3% and 25.6%, respectively). These differences could be due to differences in the baseline characteristics of patients enrolled in the RCTs and RWD studies. While the analyses of clinical data focused only on patients receiving tofacitinib monotherapy, variable rates (from 16–66%) of tofacitinib monotherapy use were seen in RWD. In addition, while patients in the clinical trials were mostly bDMARD-naïve, most patients in available RWD had prior bDMARD use. Indeed, in earlier studies of RWD, tofacitinib was often used as a third- or fourth-line therapy post-bDMARD.[15] However, tofacitinib is increasingly used as a first- or second-line treatment after csDMARD failure in patients with RA,[16,27,28] consistent with current EULAR guidelines (where a bDMARD or JAK inhibitor is recommended after csDMARDs),[4] and in line with previous reports on the cost-effectiveness of earlier tofacitinib treatment.[29,30] It should be noted that tofacitinib is indicated post-TNFi failure in certain locations such as the US.[10]

Tofacitinib has been shown to be efficacious as a monotherapy[5] and also in patients with an inadequate response to csDMARDs or bDMARDs.[6] In a head-to-head comparative study in patients with RA with a previous inadequate response to methotrexate, tofacitinib 5 mg BID monotherapy was not shown to be non-inferior to tofacitinib 5 mg BID in combination with MTX.[7] Nevertheless, at 6 months, ACR ≥50% response criteria was attained in 38% of patients with RA who received tofacitinib 5 mg BID monotherapy, while 43% achieved LDA (Simplified Disease Activity Index ≤11).[7] Given the potential for AEs during MTX treatment, the impact of discontinuing MTX on the clinical efficacy and

safety of tofacitinib in patients with RA has also been investigated. In a post hoc analysis of pooled data from two LTE studies, 70.4%/69.1% of patients who discontinued/continued MTX achieved CDAI remission or LDA at year 3, and month 3 remission/LDA rates were maintained at year 3 in most patients, irrespective of discontinuation.[31] Furthermore, in the phase 3b/4 RCT ORAL Shift, patients who achieved CDAI-defined LDA with tofacitinib modified-release 11 mg once daily plus MTX, and who subsequently withdrew MTX, did not have significant worsening of disease activity or unexpected safety issues.[32] In addition, in patients who achieved LDA with tofacitinib plus MTX and then withdrew MTX, non-inferiority of tofacitinib monotherapy versus tofacitinib in combination with MTX was shown.[32] These studies imply that patients who achieve CDAI-defined LDA may be able to discontinue concomitant MTX therapy and progress with tofacitinib monotherapy without a negative impact on disease activity or AEs.

The data reported in this analysis should be interpreted in the context of several limitations. The analyses of the clinical trial groups reported here were post hoc in nature. Patients enrolled in the RCT/LTE studies may have had tofacitinib exposure for up to 9.5 years, where the study population may change in terms of reaction to drugs and other medications taken during the studies. In addition, analyses of LTE studies may have included patients who received index dosages other than tofacitinib 5 mg BID. Although there are several RWD analyses of tofacitinib, only a few of them describe characteristics and outcomes specific to monotherapy. RWD also tended not to report results of the outcomes included in the analyses of clinical data (CDAI, DAS28-4[ESR], and DAS28-4[CRP]), and they were limited by observational study designs, which may lead to confounding or missing data and channeling biases. In addition, for analyses of RWD, we assumed that the tofacitinib dose was 5 mg BID, if not explicitly stated, given that this is the recommended dosage globally.[11]

Conclusions

The findings of this analysis demonstrated clinically significant responses and persistence of tofacitinib 5 mg BID monotherapy across three separate groups of patients with RA in RCT/LTE studies. Similarly, in RWD analyses of patients with RA treated with tofacitinib, effectiveness (CDAI-defined LDA and DAS28-4[CRP] remission) was shown, and persistence was comparable to tofacitinib combination therapy. Patients with RA who cannot tolerate MTX or for whom MTX treatment is inappropriate may benefit from treatment with tofacitinib 5 mg BID monotherapy. The limited availability of RWD for patients with RA receiving tofacitinib monotherapy, in addition to the different patient profiles found in real life, highlights the need for further research to better inform clinical decision-making.

Abbreviations

ACR, American College of Rheumatology; AE, adverse event; bDMARD, biologic disease-modifying antirheumatic drug; BID, twice daily; CDAI, Clinical Disease Activity Index; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; IQR, interquartile range; JAK, Janus kinase; LDA, low disease activity; LTE, long-term extension; MTX, methotrexate; OBRI, Ontario Best Practices Research Initiative; OPAL, Optimizing Patient outcomes in Australian rheumatoLogy; RA, rheumatoid arthritis; RCT, randomized controlled trial; RWD, real-world data; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor.

Data Sharing Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Ethics Approval and Informed Consent

All studies included in this pooled post hoc analysis were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation and were approved by the institutional review board and/or independent ethics committee at each participating center

(Supplementary Material- List of Investigators and Corresponding Ethics Committees or Institutional Review Boards. As all patients provided written informed consent, all of the data included in this analysis were covered by the original ethical/approval process. Consequently, no additional ethical review/approval was required for this post hoc analysis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

JP has acted as a consultant for AbbVie, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, Fresenius Kabi, Galapagos, Gilead, GSK, Janssen, Merck, Novartis, Pfizer Inc, Roche, Sandoz, Sanofi, and UCB, and has received grant/research support from Bristol Myers Squibb, Roche, Seattle Genetics, and UCB. AF has acted as a consultant for AbbVie, Bristol Myers Squibb, MSD, Pfizer Inc, Roche, and UCB, has received grant/research support from AbbVie, Bristol Myers Squibb, Eli Lilly, Galapagos, and Pfizer Inc, and has received speaker fees or honoraria from Eli Lilly and Pfizer Inc. LS-F has acted as a consultant for MSD, Novartis, Pfizer Inc, and Sanofi, has received grant/research support from Sandoz, has received speaker fees or honoraria from AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, GSK, and Janssen, and has reported educational activity for Gebro and Stada. PM has acted as an advisor or review panel member for AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, and UCB, and has received grant/research support from AbbVie and Novartis. HF, JLR, MV, and MM are employees and stockholders of Pfizer Inc. The authors report no other conflicts of interest in this work.

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