



# A Matching-Adjusted Indirect Comparison of Upadacitinib Versus Tofacitinib in Adults with Moderate-to-Severe Rheumatoid Arthritis

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## ABSTRACT

**Introduction:** Upadacitinib and tofacitinib are Janus kinase inhibitors approved for moderate-to-severe rheumatoid arthritis (RA). In the absence of head-to-head trials comparing their effectiveness, this study assessed the efficacy of upadacitinib 15 mg once-daily monotherapy/combination therapy against tofacitinib 5 mg twice-daily combination therapy among patients with RA using matching-adjusted indirect comparisons (MAICs).

**Methods:** The first of two MAICs used individual patient data (IPD) from the 14-week SELECT-MONOTHERAPY trial (upadacitinib [ $n = 217$ ] vs. methotrexate [ $n = 216$ ]) and published data from the ORAL Standard trial (tofacitinib + methotrexate [ $n = 204$ ] vs. methotrexate [ $n = 108$ ]). The second MAIC used

IPD from the 26-week SELECT-COMPARE trial (upadacitinib + methotrexate [ $n = 647$ ] vs. adalimumab + methotrexate [ $n = 324$ ]) and published data from ORAL Strategy (tofacitinib + methotrexate [ $n = 376$ ] vs. adalimumab + methotrexate [ $n = 386$ ]). Data from patients in the upadacitinib trials were re-weighted based on age, sex, race, swollen joint count 66/28, tender joint count 68/28, C-reactive protein (CRP), and patients' global assessments to match the patient characteristics in tofacitinib trials. After matching, ACR20/50/70 and clinical remission (SDAI[CRP]  $\leq 3.3$ , CDAI  $\leq 2.8$ , DAS28-ESR/CRP  $< 2.6$ ) were compared for upadacitinib vs. tofacitinib + methotrexate at month 3 and upadacitinib + methotrexate vs. tofacitinib + methotrexate at months 3 and 6 using Wald tests.

**Results:** At month 3, upadacitinib monotherapy patients experienced significantly larger improvement in ACR70 compared to tofacitinib + methotrexate (mean difference in difference [DID]: 9.9%;  $p = 0.019$ ), while upadacitinib + methotrexate was associated with higher ACR50 compared to tofacitinib + methotrexate (DID: 12.9%;  $p = 0.011$ ). At month 6, upadacitinib + methotrexate patients experienced significantly larger improvement in SDAI/CDAI/DAS28-ESR clinical remission compared to tofacitinib + methotrexate, with DIDs of 9.1%

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( $p = 0.011$ ), 7.5% ( $p = 0.038$ ), and 11.3% ( $p = 0.002$ ), respectively.

**Conclusions:** Compared to tofacitinib combination therapy, treatment with upadacitinib monotherapy and combination therapy were associated with improved outcomes at 3/6 months (monotherapy: ACR70; combination: ACR50, SDAI, CDAI, and DAS28-ESR remission).

**Keywords:** Combination therapy; Efficacy; Matching-adjusted indirect comparison; Monotherapy; Rheumatoid arthritis; Tofacitinib; Upadacitinib

### Key Summary Points

#### Why carry out this study?

Upadacitinib and tofacitinib are Janus kinase inhibitors approved as treatments for patients with moderate-to-severe rheumatoid arthritis who are intolerant or have insufficient response to methotrexate.

In the absence of head-to-head trials, this study compared the efficacy of upadacitinib 15 mg once daily (QD) monotherapy/combotherapy against tofacitinib 5 mg twice daily (BID) combination therapy with two matching-adjusted indirect comparisons (MAICs).

The first MAIC used individual patient data (IPD) from the SELECT-MONOTHERAPY (upadacitinib 15 mg QD vs. methotrexate) and published data from Oral Standard (tofacitinib 5 mg BID + methotrexate vs. methotrexate), while the second used IPD from SELECT-COMPARE (upadacitinib 15 mg QD + methotrexate vs. adalimumab 40 mg every other week (EOW) + methotrexate) and published data from ORAL Strategy (tofacitinib 5 mg BID + methotrexate vs. adalimumab 40 mg EOW + methotrexate).

#### What was learned from the study?

The results indicated that treatment with upadacitinib 15 mg QD monotherapy was associated with a significantly higher ACR70 response rate at 3 months compared to tofacitinib 5 mg BID + methotrexate.

In addition, upadacitinib 15 mg QD + methotrexate was associated with significantly improved outcomes at 3/6 months compared to tofacitinib 5 mg BID + methotrexate, including ACR50 at month 3, SDAI, CDAI, and DAS28-ESR remission at month 6.

These results provide physicians, payers, and other healthcare stakeholders with important evidence to support treatment decision-making in rheumatoid arthritis.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13207970>.

## INTRODUCTION

Janus kinase (JAK) inhibitors are targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) for adults with moderate-to-severe rheumatoid arthritis (RA) and inadequate response or intolerance to methotrexate (MTX-IR). Tofacitinib 5 mg twice daily (BID) was the first JAK inhibitor (JAK1 and JAK3) approved for this patient population by the United States Food and Drug Administration (FDA) in 2012 and by the European Medicines Agency (EMA) in 2017 [1, 2] for use as monotherapy and in combination with other conventional synthetic DMARDs (csDMARDs). The efficacy and safety of tofacitinib monotherapy or combination

therapy in adult csDMARD-experienced patients with RA were investigated in a series of phase III/IV clinical trials, including ORAL Scan [3], ORAL Sync [4], ORAL Standard [5], ORAL Solo [6], and ORAL Strategy [7]. In the ORAL Standard trial, tofacitinib 5 or 10 mg BID in combination with methotrexate demonstrated significantly superior efficacy compared with methotrexate alone, and similar efficacy compared with adalimumab 40 mg every other week (EOW) [5]. In the ORAL Strategy trial, tofacitinib 5 mg BID and methotrexate combination therapy was shown to be non-inferior to adalimumab 40 mg EOW and methotrexate combination therapy for the treatment of patients with MTX-IR RA; tofacitinib 5 mg BID monotherapy was not found to be non-inferior to either adalimumab 40 mg EOW + methotrexate or tofacitinib 5 mg BID + methotrexate [7].

Upadacitinib 15 mg once daily (QD), an oral, reversible, JAK1-selective inhibitor, was approved for the treatment of moderate-to-severe MTX-IR RA by the FDA in August 2019 and by the EMA in December 2019 [8, 9], as well as by other agencies in Canada, Japan, and Australia. The efficacy and safety of upadacitinib 15 mg QD in csDMARD-experienced patients with RA have been evaluated in multiple phase III trials, including SELECT MONOTHERAPY [10], SELECT COMPARE [11], and SELECT NEXT [12]. SELECT MONOTHERAPY reported that patients receiving upadacitinib 15 mg and upadacitinib 30 mg QD monotherapy achieved statistically significant improvements in clinical and functional outcomes versus those treated with methotrexate [10]. In the SELECT COMPARE trial, upadacitinib 15 mg QD in combination with methotrexate was associated with superior improvement in RA signs and symptoms (American College of Rheumatology 50% [ACR50], Disease Activity Score in 28 joints using C-reactive protein level [DAS23-CRP] score  $\leq 3.2$ , changes in pain severity score, and change in Health Assessment Questionnaire Disability Index) compared with both placebo + methotrexate and adalimumab 40 mg EOW + methotrexate [11]. Radiographic progression was also significantly lower with upadacitinib 15 mg QD combination therapy

versus methotrexate at 26 weeks in SELECT COMPARE [11].

Comparative effectiveness data comparing upadacitinib 15 mg QD and tofacitinib 5 mg BID can help inform treatment decisions made by healthcare providers, payers, and other stakeholders. However, no head-to-head clinical trials have compared the effectiveness of upadacitinib and tofacitinib. On the other hand, both JAK inhibitors have been studied in direct head-to-head studies with adalimumab or methotrexate, providing a common comparator for potential indirect comparison methods. The results of these trials have yielded different outcomes on various efficacy endpoints, which may be related to the differing efficacy profiles of upadacitinib 15 mg QD and tofacitinib 5 mg BID. Matching-adjusted indirect comparison (MAIC) is a technique that utilizes individual patient data (IPD) for one treatment and aggregate data for the other to provide comparative evidence after balancing differences in patient baseline characteristics [13, 14]. In this study, we conducted two MAICs to compare the efficacy of upadacitinib 15 mg QD monotherapy and upadacitinib 15 mg QD + methotrexate against tofacitinib 5 mg BID + methotrexate among MTX-IR patients with moderate-to-severe RA.

## METHODS

### Data Sources

A literature review was conducted to identify comparable phase III clinical trials of upadacitinib 15 mg QD monotherapy or combination therapy with methotrexate and tofacitinib 5 mg BID monotherapy or combination therapy with methotrexate among MTX-IR patients with moderate-to-severe RA. Three upadacitinib trials, including SELECT MONOTHERAPY [10], SELECT COMPARE [11], and SELECT NEXT [12], and five tofacitinib trials, including ORAL Scan [3], ORAL Sync [4], ORAL Standard [5], ORAL Solo [6], and ORAL Strategy [7], were considered for inclusion of the MAIC. Based on study population similarities and common comparators, SELECT MONOTHERAPY and ORAL

Standard were selected to compare upadacitinib 15 mg QD monotherapy vs. tofacitinib 5 mg BID + methotrexate; SELECT COMPARE and ORAL Strategy were selected to compare upadacitinib 15 mg QD + methotrexate vs. tofacitinib 5 mg BID + methotrexate. Upadacitinib 15 mg QD monotherapy and tofacitinib 5 mg BID monotherapy were not compared as the upadacitinib and tofacitinib monotherapy trials of MTX-IR patients did not share a common comparator arm.

The first MAIC used IPD from the 14-week SELECT MONOTHERAPY trial [10] and aggregated data extracted from the 12-month ORAL Standard [5] trial publications to compare upadacitinib 15 mg QD monotherapy vs. tofacitinib 5 mg BID + methotrexate. SELECT MONOTHERAPY was a randomized, double-blind, double-dummy phase III study that enrolled 648 patients with active RA [10]. Patients were randomized 2:2:1 to extended-release upadacitinib 15 mg monotherapy QD, extended-release upadacitinib 30 mg monotherapy QD, or to continue the previous dose of methotrexate as a blinded monotherapy study drug. ORAL Standard was a randomized, phase III clinical trial that enrolled 717 patients who received a diagnosis of active RA [5]. Patients were randomized 4:4:4:1:1 to tofacitinib 5 mg BID + methotrexate, tofacitinib 10 mg BID + methotrexate, adalimumab 40 mg EOW + methotrexate, methotrexate alone for 12 or 24 weeks followed by tofacitinib 5 mg BID, or methotrexate alone for 12 or 24 weeks followed by tofacitinib 10 mg BID. Table S1 lists the full details of the trial design and key inclusion/exclusion criteria of SELECT MONOTHERAPY and ORAL Standard. For this study, only the FDA-approved doses of upadacitinib (15 mg QD) and tofacitinib (5 or 10 mg BID) were compared.

The second MAIC utilized IPD from the 26-week SELECT COMPARE trial [11] and aggregated data extracted from the 12-month ORAL Strategy trial [7] publications to compare upadacitinib 15 mg QD + methotrexate vs. tofacitinib 5 mg BID + methotrexate. SELECT COMPARE was a randomized, double-blind phase III study that enrolled 1629 patients with active RA [11]. Patients were randomized 2:2:1

to either upadacitinib 15 mg QD + methotrexate, adalimumab 40 mg EOW + methotrexate, or to continue the previous dose of methotrexate as a blinded study drug. ORAL Strategy was a randomized, double-blind, triple-dummy, phase IIIb/IV clinical trial that enrolled 1146 patients with a diagnosis of active RA [7]. Patients were randomized 1:1:1 to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID + methotrexate, or adalimumab 40 mg EOW + methotrexate. Table S2 lists the full details of the trial design and key inclusion/exclusion criteria of SELECT COMPARE and ORAL Strategy.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. As this was a post hoc analysis of previously collected data, no institutional board review was required; details regarding patient consent and the institutional approvals of the included trials have been previously published [5, 7, 10, 11]. This analysis and the clinical trials from which data were included followed the principles of the Declaration of Helsinki.

### Efficacy Outcomes

Efficacy outcomes present with similar definitions and time-points in both the upadacitinib and tofacitinib trials were included in this study.

In the first MAIC comparing upadacitinib 15 mg QD monotherapy and tofacitinib 5 mg BID combination therapy, the proportions of patients achieving 20%, 50%, and 70% improvement in the ACR criteria (ACR20, ACR50, and ACR70) were compared at month 3, which was the primary endpoint for both trials. Outcomes at week 14 were used from the SELECT MONOTHERAPY trials and outcomes at week 12 were used from the ORAL Standard trial.

In the second MAIC comparing upadacitinib 15 mg QD + methotrexate combination therapy and tofacitinib 5 mg BID + methotrexate combination therapy, ACR20, ACR50, and ACR70 at month 3 and month 6 were assessed.

In addition, the proportions of patients achieving clinical remission based on the Disease Activity Score in 28 Joints- C-reactive Protein (DAS28-CRP < 2.6), Simple Disease Activity Index (SDAI  $\leq$  3.3), Clinical Disease Activity Index (CDAI  $\leq$  2.8), or the DAS28- Erythrocyte Sedimentation Rate (DAS28-ESR < 2.6) at month 6 were compared. Such outcomes at 3 months were not included due to the lack of data in ORAL Strategy. For both trials, outcomes at week 12 and at week 26 were used for the 3-month and 6-month analyses, respectively.

### Statistical Analyses

As the first step of the analysis, individual patients in the SELECT trials were re-weighted based on a list of baseline characteristics to match the average baseline characteristics reported in the ORAL trials. In this study, age, sex, race, swollen joint count 66/28 (SJC66), tender joint count 68/28 (TJC68), CRP, and patients' global assessment (PGA) were selected based on completeness, availability, and clinical relevance in both trials in each MAIC. Individual patients enrolled in the SELECT trials were excluded if they were missing baseline data for one of the variables included in the matching adjustment. The individual patient weights were estimated using a logistic regression model using the method of moments.

Next, the outcomes in the SELECT trials were weighted and compared with the observed outcomes in the ORAL trials using an anchor-based approach. Using this approach, the active treatment arms were compared relative to a common comparator (methotrexate in the first MAIC, and adalimumab 40 mg EOW + methotrexate in the second MAIC). In the first MAIC, the difference-in-difference (DID) risk between upadacitinib 15 mg QD monotherapy and tofacitinib 5 mg BID + methotrexate versus methotrexate and associated 95% confidence intervals (CI) were generated. In the second MAIC, the DID risk between upadacitinib 15 mg QD combination therapy and tofacitinib 5 mg BID + methotrexate versus

adalimumab + methotrexate and associated 95% CIs were generated.

Before matching, the baseline characteristics were compared between the two trials using Chi-squared tests for binary variables and Wald tests for continuous variables. After matching, all baseline characteristics and outcomes were compared using Wald tests. Non-responder imputation was used for missing binary outcomes and for patients who discontinued the study or received rescue therapy.

A Bonferroni correction was applied in the MAICs to control for multiplicity. After setting a family-wise error rate of 0.05, outcomes in the MAICs at 3 months were considered significant if their *p* values were below 0.017. In the MAICs at 6 months, a *p* value below 0.007 was considered statistically significant.

## RESULTS

### Upadacitinib 15 mg QD Monotherapy vs. Tofacitinib 5 mg BID Combination Therapy

In the SELECT MONOTHERAPY trial, 217 patients from the upadacitinib 15 mg QD arm and 216 patients from the methotrexate arm were included in the analysis. One patient in the upadacitinib 15 mg QD arm was excluded due to missing baseline data for PGA.

The baseline characteristics of each patient population are summarized in Table 1. Before matching, the SELECT MONOTHERAPY population (upadacitinib 15 mg QD arm) included fewer females (80.1 vs. 85.3%, respectively), more white patients (79.6 vs. 74.0%), and on average the patient population was older (mean age: 54.5 vs. 53.0 years) and had less severe disease (e.g., TJC68: 24.5 vs. 28.5; SJC66: 16.4 vs. 16.7) compared to the ORAL Standard population (tofacitinib 5 mg BID + methotrexate arm). After applying the weights, the baseline characteristics of patients enrolled in SELECT MONOTHERAPY matched those of the ORAL Standard population (Table 1).

The MAIC results comparing ACR20/50/70 at month 3 between the two treatments are presented in Fig. 1a (before matching) and Fig. 1b

**Table 1** Baseline characteristics of SELECT MONOTHERAPY (before and after matching) vs. ORAL standard

	Baseline characteristics of patients in SELECT MONOTHERAPY				Baseline characteristics of patients in ORAL Standard				<i>p</i> values (SELECT MONOTHERAPY vs. ORAL Standard) <sup>b</sup>			
	Before matching		After matching		Before matching		After matching		<i>p</i> before matching		<i>p</i> after matching <sup>b</sup>	
	UPA 15 mg QD <i>n</i> = 216 [A]	MTX <i>n</i> = 216 [B]	UPA 15 mg QD <i>n</i> = 216 [C]	MTX <i>n</i> = 216 [D]	TOFA 5 mg BID + MTX <i>n</i> = 204 [E]	MTX <i>n</i> = 108 [F]	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
Female, <i>n</i> (%)	80.1%	82.9%	85.3%	75.9%	85.3%	75.9%	0.202	0.180	1.000	0.202	0.180	1.000
Age (years), mean (SD)	54.5 ± 12.2	55.3 ± 11.1	53.0 ± 11.0	53.8 ± 11.0	53.0 ± 11.9	53.8 ± 13.8	0.207	0.322	1.000	0.207	0.322	1.000
Race—white, <i>n</i> (%)	79.6%	81.5%	74.0%	69.4%	74.0%	69.4%	0.212	0.021	1.000	0.212	0.021	1.000
Tender joint count 68, mean (SD) <sup>a</sup>	24.5 ± 15.1	25.2 ± 16.0	28.5 ± 17.3	27.3 ± 17.1	28.5 ± —	27.3 ± —	—	—	—	—	—	—
Swollen joint count 66, mean (SD) <sup>a</sup>	16.4 ± 11.0	16.9 ± 11.5	16.7 ± 10.6	16.7 ± 10.6	16.7 ± —	16.7 ± —	—	—	—	—	—	—
C-reactive protein (mg/l), mean (SD) <sup>a</sup>	14.0 ± 16.5	14.5 ± 17.3	14.9 ± 17.1	16.1 ± 19.6	14.9 ± —	16.1 ± —	—	—	—	—	—	—
Patient's global assessment, mean (SD)	62.2 ± 22.3	59.6 ± 21.8	59.9 ± 22.5	54.5 ± 23.0	59.9 ± 21.4	54.5 ± 21.3	0.267	0.047	1.000	0.267	0.047	1.000

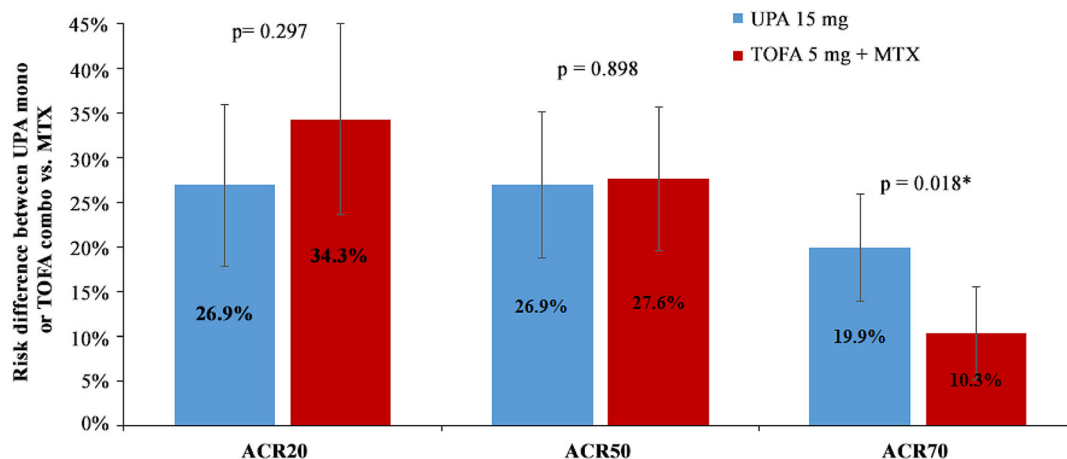
Patient baseline characteristics were derived from individual patient data for SELECT MONOTHERAPY and from van Vollenhoven et al. [5] for ORAL Standard

*BID* twice a day, *MTX* methotrexate, *QD* once daily, *SD* standard deviation, *TOFA* tofacitinib, *UPA* upadacitinib

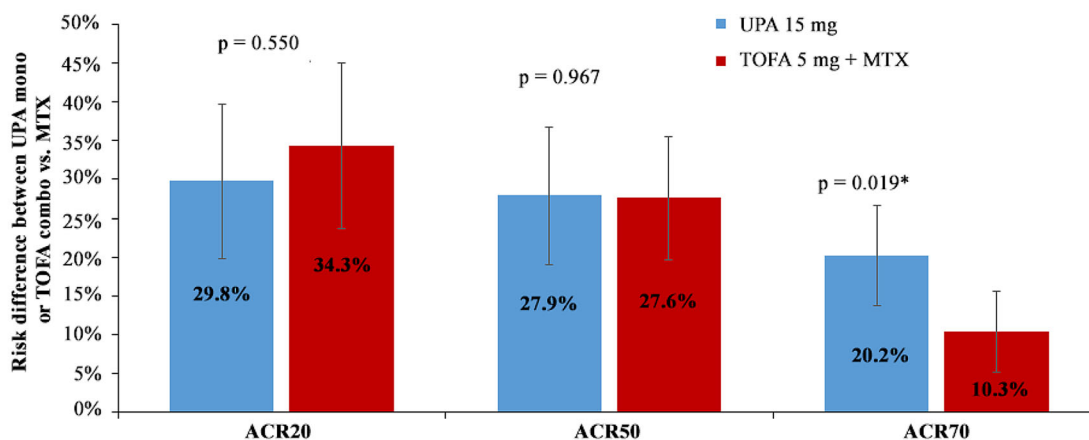
<sup>a</sup> ORAL Standard did not report SDs for tender joint count 68, swollen joint count 66, and C-reactive protein, and therefore no *p* values could be computed

<sup>b</sup> After matching, the effective sample sizes of upadacitinib 15 mg QD and MTX were 173 and 158, respectively

## i. Before matching



## ii. After matching



**Fig. 1** MAIC results for upadacitinib 15 mg QD vs. tofacitinib 5 mg BID + MTX relative to MTX at month 3, before (i) and after (ii) matching. <sup>a–b</sup>The error bars represent 95% confidence intervals. ACR20/50/70 American College of Rheumatology score- improvement from baseline by 20/50/70%, BID twice a day, MAIC matching-

adjusted indirect comparison, MTX methotrexate, QD once daily, TOFA tofacitinib, UPA upadacitinib. \* $p < 0.05$ . <sup>a</sup>Clinical remission outcomes were not reported for ORAL Standard at month 3. <sup>b</sup>Non-responder imputation was used for all missing binary outcomes where patients discontinued the study or received rescue therapy

(after matching). A significantly higher percentage of patients receiving upadacitinib 15 mg QD achieved ACR70 response compared to those receiving tofacitinib 5 mg BID, both before matching (DID [95% CI]: 9.6% [1.7%, 17.5%];  $p = 0.018$ ) and after matching (9.9% [1.6%, 18.2%];  $p = 0.019$ ). The ACR20 and ACR50 response rates relative to methotrexate

were numerically higher among patients receiving upadacitinib 15 mg QD but were not statistically significant.

After applying Bonferroni correction to control for multiplicity (significance threshold of  $p < 0.017$ ), the difference in the percentages of patients achieving ACR70 response were not significantly different between arms.

**Table 2** Baseline characteristics of SELECT COMPARE (before and after matching) vs. ORAL strategy

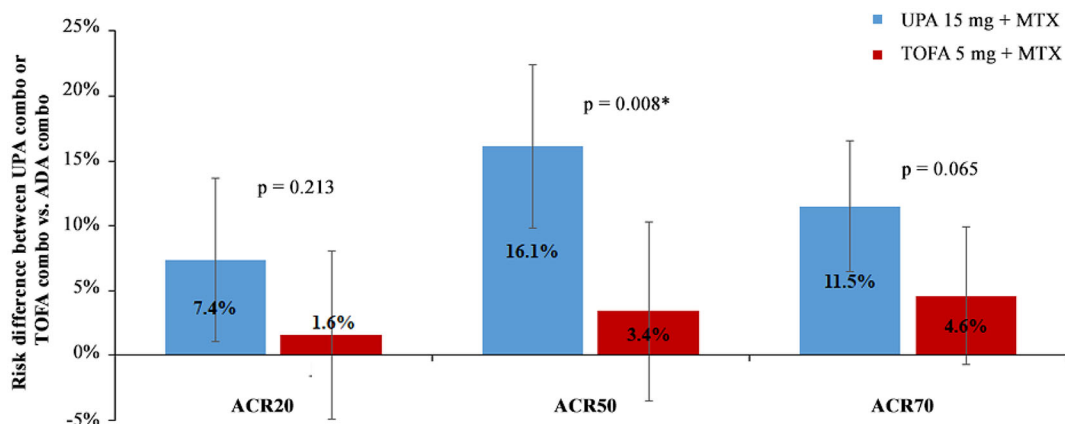
	Baseline characteristics of patients in SELECT COMPARE				Baseline characteristics of patients in ORAL Strategy				<i>p</i> values (SELECT COMPARE vs. ORAL Strategy) <sup>a</sup>			
	Before matching		After matching		Before matching		After matching		<i>p</i> before matching		<i>p</i> after matching <sup>a</sup>	
	UPA 15 mg QD + MTX [A] n = 647	ADA 40 mg EOW + MTX [B] n = 324	UPA 15 mg QD + MTX [C] n = 647	ADA 40 mg EOW + MTX [D] n = 324	TOFA 5 mg BID + MTX [E] n = 376	ADA 40 mg EOW + MTX [F] n = 386	Treatment [A] vs. [E]	Treatment [B] vs. [F]	Treatment [C] vs. [E]	Treatment [D] vs. [F]		
Female, <i>n</i> (%)	79.9%	79.3%	82.70%	82.90%	82.7%	82.9%	0.308	0.262	1.000	1.000		
Age (years), mean (SD)	54.3 ± 12.0	53.7 ± 11.7	50.0 ± 12.6	50.7 ± 11.8	50.0 ± 13.4	50.7 ± 13.4	0.002	0.002	1.000	1.000		
Race—white, <i>n</i> (%)	88.6%	89.2%	76.10%	75.90%	76.1%	75.9%	0.000	0.000	1.000	1.000		
Tender joint count 28, mean (SD)	15.0 ± 6.9	15.1 ± 7.0	15.6 ± 7.3	15.2 ± 7.0	15.6 ± 6.5	15.2 ± 6.7	0.181	0.920	1.000	1.000		
Swollen joint count 28, mean (SD)	11.4 ± 5.6	11.7 ± 5.5	11.8 ± 6.1	11.0 ± 5.3	11.8 ± 5.7	11.0 ± 5.4	0.326	0.083	1.000	1.000		
C-reactive protein (mg/l), mean (SD)	17.9 ± 22.5	19.9 ± 21.6	18.7 ± 23.6	16.7 ± 17.5	18.7 ± 21.9	16.7 ± 21.3	0.586	0.048	1.000	1.000		
Patient's global assessment, mean (SD)	64.3 ± 21.8	65.8 ± 21.1	61.7 ± 22.5	60.2 ± 22.6	61.7 ± 22.0	60.2 ± 23.5	0.068	0.001	1.000	1.000		

Patient baseline characteristics were derived from individual patient data for SELECT COMPARE and from Fleischmann et al. [7] for ORAL Strategy. ADA adalimumab, BID twice a day, EOW every other week, MTX methotrexate, QD once daily, SD standard deviation, TOFA tofacitinib, UPA upadacitinib

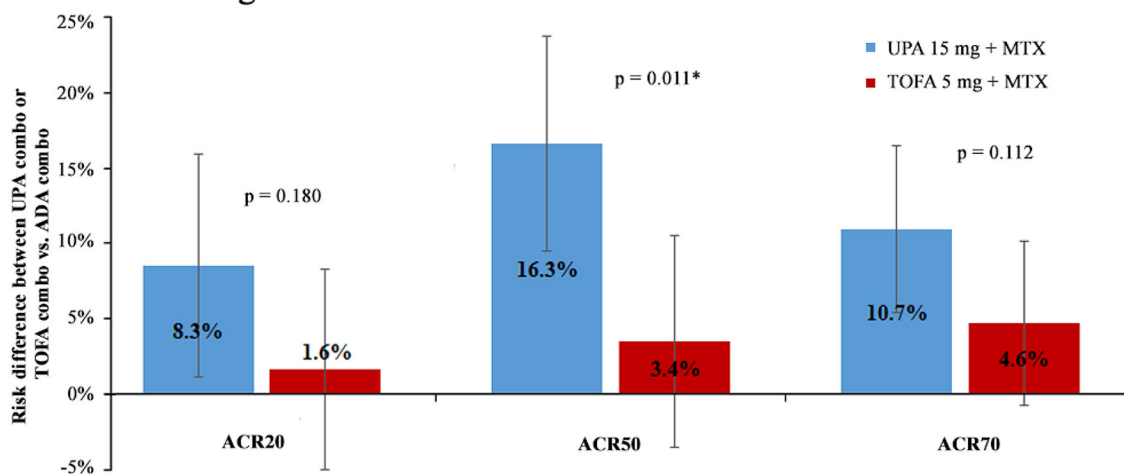
<sup>a</sup> After matching, the effective sample sizes of the UPA 15 mg QD and ADA 40 mg EOW + MTX arms were 480 and 228, respectively



i. Before matching



ii. After matching



**Fig. 2** MAIC results for upadacitinib 15 mg QD + MTX vs. tofacitinib 5 mg BID + MTX relative to adalimumab 40 mg EOW + MTX at month 3, before (i) and after (ii) matching. <sup>a</sup>The error bars represent 95% confidence intervals. *ACR20/50/70* American College of Rheumatology score-improvement from baseline by 20/50/70%, *ADA* adalimumab, *BID* twice a day, *EOW*

every other week, *MAIC* matching-adjusted indirect comparison, *MTX* methotrexate, *QD* once daily, *TOFA* tofacitinib, *UPA* upadacitinib. \**p* < 0.05. <sup>a</sup>All binary outcomes employed non-responder imputation. This method assumes that subjects with missing data did not achieve the outcome measure

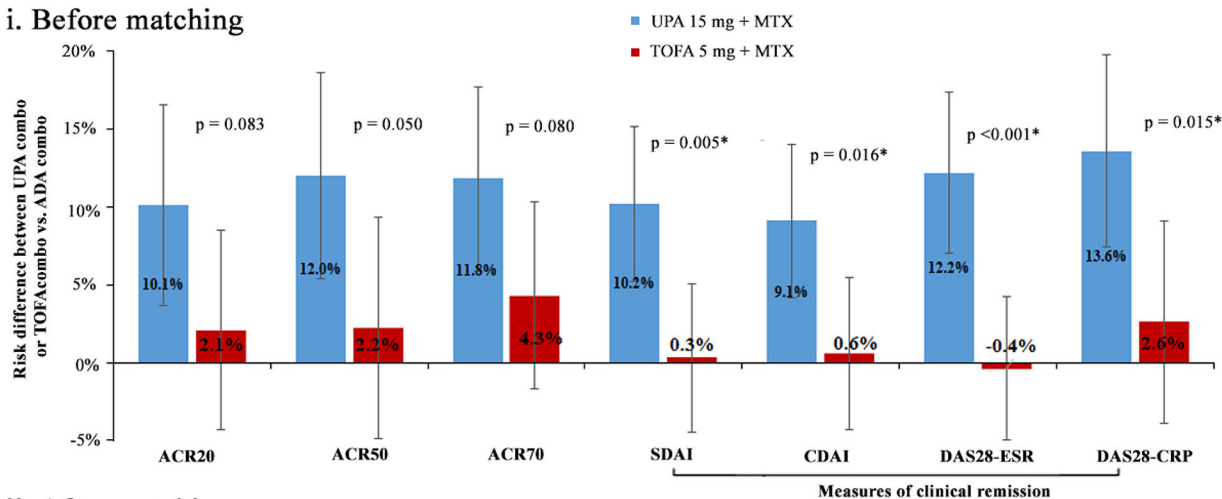
**Upadacitinib 15 mg Combination Therapy vs. Tofacitinib 5 mg BID Combination Therapy**

In the SELECT COMPARE trial, 651 patients from the upadacitinib 15 mg QD + methotrexate arm and 327 patients from the adalimumab 40 mg EOW + methotrexate arm were included in the analysis. Four patients in the upadacitinib 15 mg QD + methotrexate arm and three

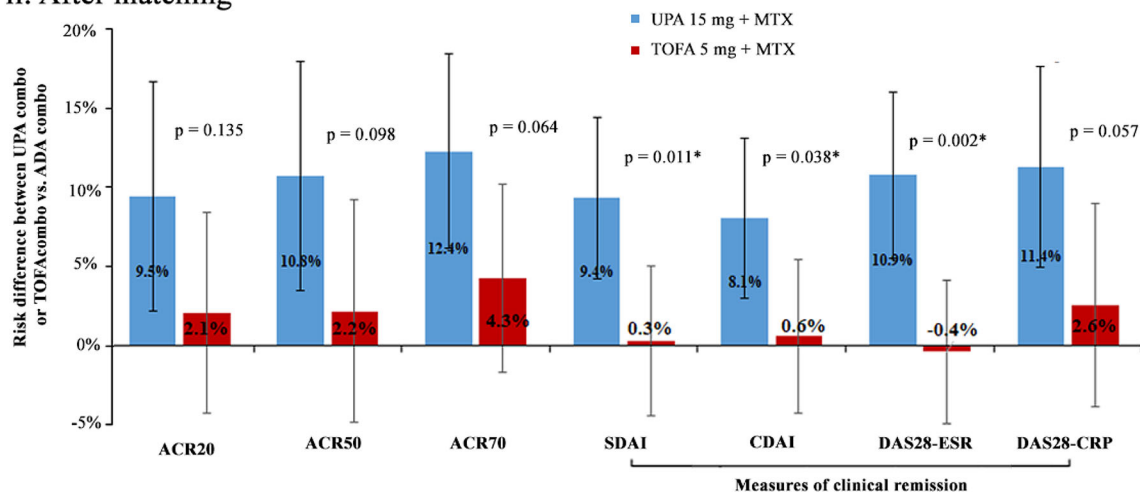
patients in the adalimumab 40 mg EOW + methotrexate arm were excluded due to missing baseline values for PGA.

The baseline characteristics of the patient populations included in the second MAIC are summarized in Table 2. Before matching, the population from the upadacitinib 15 mg QD + methotrexate arm included fewer females (79.9 vs. 82.7%), more white patients (88.6 vs. 76.1%), and on average, were older (mean age:

## i. Before matching



## ii. After matching



**Fig. 3** MAIC results for upadacitinib 15 mg QD + MTX vs. TOFA 5 mg BID + MTX relative to ADA 40 mg EOW + MTX at month 6, before (i) and after (ii) matching. <sup>a-d</sup>The error bars represent 95% confidence intervals. *ACR20/50/70* American College of Rheumatology score- improvement from baseline by 20/50/70%, *ADA* adalimumab, *BID* twice a day, *CDAI* Clinical Disease Activity Index, *DAS28-CRP* Disease Activity Score 28-joint C-reactive protein, *DAS28-ESR* Disease Activity Score 28-joint Erythrocyte Sedimentation Rate, *EOW* every other week, *MAIC* matching-adjusted indirect comparison, *MTX* methotrexate, *QD* daily, *SDAI* Simple Disease Activity Index, *SJC* swollen joint count, *TJC* tender joint count, *TOFA* tofacitinib, *UPA* upadacitinib. \* $p < 0.05$ . <sup>a</sup>Clinical remission based on DAS28-CRP and DAS28-ESR is defined as subjects with DAS28-CRP/ESR < 2.6; low disease activity based on DAS28-CRP and

DAS28-ESR is defined as patients with DAS28-CRP/ESR  $\leq 3.2$ ; clinical remission based on SDAI is defined as subjects with SDAI  $\leq 3.3$ ; clinical remission based on CDAI is defined as patients with CDAI  $\leq 2.8$ . Low disease activity based on CDAI is defined as patients with CDAI  $\leq 10$ . <sup>b</sup>At weeks 14, 18, and 22, SELECT-COMPARE patients who did not achieve  $\geq 20\%$  improvement in TJC and SJC compared to baseline received early escape treatment. Patients on placebo or adalimumab 40 mg EOW were switched to upadacitinib 15 mg QD and patients on upadacitinib 15 mg QD were switched to adalimumab 40 mg EOW. <sup>c</sup>ORAL Strategy did not have any early escape study design. <sup>d</sup>All binary outcomes employed non-responder imputation. This method assumed that subjects with missing data did not achieve the outcome measure

54.3 vs. 50.0 years) and had less severe disease (e.g., TJC68: 15.0 vs. 15.6; SJC66: 11.4 vs. 11.8) compared to the population from the tofacitinib 5 mg BID + methotrexate arm. After applying weights to the patients enrolled in SELECT COMPARE, the adjusted baseline characteristics matched those of the ORAL Strategy population (Table 2).

The MAIC results comparing ACR20/50/70 at month 3 between upadacitinib 15 mg QD combination therapy and tofacitinib 5 mg BID combination therapy are presented in Fig. 2a (before matching) and Fig. 2b (after matching). A significantly higher percentage of patients receiving upadacitinib 15 mg QD + methotrexate than those receiving tofacitinib 5 mg BID + methotrexate achieved ACR50 response, both before matching (DID [95% CI]: 12.7% [3.4%, 22.1%];  $p = 0.008$ ) and after matching (12.9% [3.0%, 22.7%];  $p = 0.011$ ). The ACR20 and ACR70 response rates were numerically higher among patients receiving upadacitinib 15 mg QD + methotrexate relative to adalimumab 40 mg EOW + methotrexate but were not statistically significant. After applying Bonferroni correction to control for multiplicity (significance threshold of  $p < 0.017$ ), the difference in the percentage of patients achieving ACR50 response remained statistically significant.

Comparisons of ACR20/50/70 and clinical remission based on different testing measures were conducted at month 6 (Fig. 3a and b). After matching, a significantly larger proportion of patients receiving upadacitinib 15 mg QD + methotrexate than those receiving tofacitinib 5 mg BID + methotrexate achieved clinical remission based on CDAI (7.5% [95% CI: 0.4%, 14.6%];  $p = 0.038$ ) and DAS28-ESR (11.3% [4.3%, 18.4%];  $p = 0.002$ ). Similarly, a significantly greater percentage of patients receiving upadacitinib 15 mg QD + methotrexate achieved clinical remission based on SDAI compared with those receiving tofacitinib 5 mg BID + methotrexate (9.1% [95% CI: 2.1%, 16.2%];  $p = 0.011$ ). No other significant differences were detected in this MAIC. After applying Bonferroni correction to control for multiplicity, results were considered significant if their  $p$  values were below 0.007. Using this

more stringent criterion, the difference in clinical remission based on the DAS28-ESR was statistically significant between the two arms.

## DISCUSSION

In the absence of head-to-head randomized trials comparing upadacitinib 15 mg QD and tofacitinib 5 mg BID among MTX-IR patients with moderate-to-severe RA, this study conducted two MAICs to indirectly compare the efficacy of upadacitinib 15 mg QD monotherapy and combination therapy with MTX versus tofacitinib 5 mg BID combination therapy. The MAICs incorporated IPD from the upadacitinib trials and aggregate data from the tofacitinib trials and adjusted for differences in patient characteristics across different trials to provide fair comparisons between the two treatments. The results from the MAICs indicate that treatment with upadacitinib 15 mg QD when used as monotherapy and in combination with methotrexate is associated with improved outcomes at 3/6 months compared to tofacitinib 5 mg BID + methotrexate.

This study provides additional evidence on the comparative efficacy between upadacitinib 15 mg QD and tofacitinib 5 mg BID for the treatment of MTX-IR patients with RA. A previous analysis by Song et al. used a Bayesian network meta-analysis (NMA) to compare the efficacy of upadacitinib 15 mg combination therapy and tofacitinib 5 mg BID combination therapy in patients with RA with inadequate response to csDMARDs or biologic DMARDs (bDMARDs) [15]. The study reported that upadacitinib 15 mg QD + methotrexate was more effective than tofacitinib 5 mg BID + methotrexate in terms of ACR20 response. This finding is generally consistent with the present study which observed that upadacitinib 15 mg QD + methotrexate was associated with significantly better improvement in ACR50 at month 3, SDAI clinical remission at month 6, CDAI clinical remission at month 6, and DAS28-ESR at month 6. This study also found that upadacitinib 15 mg QD monotherapy was associated with a significantly improved ACR70 response rate at month

3 compared with tofacitinib 5 mg BID + methotrexate. In addition, a recent NMA by Pope et al. compared the 12- and 24-week ACR 20/50/70 and DAS28-CRP reported among 11 trials of tofacitinib, baricitinib, and upadacitinib as monotherapy or combination therapy among MTX-IR patients with moderate-to-severe RA [16]. They reported that upadacitinib 15 mg had numerically higher efficacy and clinical remission rates, similar to the present analysis, but none of the differences in efficacy outcomes were statistically significant among the three JAK inhibitors in that NMA.

In addition to the comparative evidence provided by this study between upadacitinib 15 mg QD and tofacitinib 5 mg BID on ACR outcomes, the evidence provided by the inclusion of remission rates measured by CDAI, SDAI, and DAS28-ESR is important for several reasons. First, there is a lack of consensus regarding the ideal measure of disease activity in RA, so the use of several measures recommended by ACR [17] (e.g., CDAI, SDAI, and DAS28-ESR or CRP) provides a more comprehensive evaluation of the comparative efficacy. Second, the primary goals for the treatment of patients with RA are sustained remission or low disease activity [18, 19]. Patients who achieve remission have been reported to experience significantly better physical functioning, higher quality of life, and greater productivity as compared to more active disease states such as moderate or high disease activity [20]. Thus, the comparative efficacy of therapies demonstrated via clinical remission rates measured by CDAI, SDAI, and DAS28 (ESR or CRP) are important supplemental data to inform the decision-making of physicians, patients, and other stakeholders.

The improved outcomes associated with upadacitinib 15 mg QD monotherapy and combination therapy over tofacitinib 5 mg BID combination therapy observed in this MAIC may be attributed to the different mechanisms of action for the therapies [21, 22]. Tofacitinib is a first-generation JAK inhibitor targeting several JAK receptors (JAK1, JAK2, and JAK3), while upadacitinib, a second-generation JAK inhibitor, is highly selective for only JAK1 [23, 24]. Although direct evidence from population-level

studies is needed to assess the relationship between JAK receptor selectivity and treatment efficacy, several studies have suggested that the favorable efficacy outcomes of upadacitinib might be due to its high JAK1 selection [25, 26]. While the focus of the current study was to compare upadacitinib 15 mg versus tofacitinib 5 mg BID, future studies exploring upadacitinib's comparative efficacy versus other approved JAK inhibitors such as baricitinib may help in further understanding of JAK profiles. Additionally, newer JAK inhibitors such as peficitinib (a pan-JAK inhibitor approved in Japan and South Korea) [27, 28] and filgotinib (a JAK1 inhibitor approved in the EU and Japan) [29] may be approved in more global markets. Thus, the introduction of new therapies to the RA treatment landscape should warrant reevaluations of the comparative efficacy of all JAK inhibitors.

This study should be interpreted in light of several limitations. First, while the MAIC method accounts for cross-trial differences on observed baseline characteristics, reduces bias for indirect comparisons, and provides statistically reliable 95% CIs, differences in unobserved baseline characteristics may still exist and impact the results. Second, observed heterogeneity between the upadacitinib trials and tofacitinib trials which were nonadjustable may still confound the results. For example, in the comparison of upadacitinib 15 mg QD monotherapy vs. tofacitinib 5 mg BID combination therapy, the percentage of patients with prior exposure to bDMARDs could not be adjusted for because the SELECT MONOTHERAPY trial excluded such patients. However, the percentage of bDMARD-experienced patients was less than 10% in the ORAL Standard trial; thus, any effects on the results should be limited. Additionally, while ORAL Strategy excluded patients with prior exposure to glucocorticoid > 10 mg treatment in the previous 4 weeks, SELECT COMPARE did not exclude such patients. However, only two patients in SELECT COMPARE had such prior exposure. Third, ORAL Strategy did not allow for escape treatment while SELECT COMPARE gave all patients the opportunity to switch treatment starting at Week 14 if they did not achieve

≥ 20% improvement from baseline in TJC and SJC, which may impact the month 6 results. However, because similar percentages of patients in the upadacitinib 15 mg QD arm (19.2%) and the adalimumab 40 mg EOW arm (23.5%) switched treatment, the impact is expected to be limited.

## CONCLUSIONS

This study used MAIC methods to indirectly compare the efficacy of upadacitinib 15 mg QD monotherapy and combination therapy versus tofacitinib 5 mg BID combination therapy after adjusting for differences across trial populations. The results from the MAICs indicate that treatment with upadacitinib 15 mg QD when used as monotherapy and in combination with methotrexate is associated with improved outcomes at 3/6 months compared to tofacitinib 5 mg BID + methotrexate.

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**Data Availability.** The datasets generated during and/or analyzed during the current study are not publicly available due to the sensitive nature of the data.

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