MAYO CLINIC

Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Faping Wang, MD; Ling Sun, MD; Shaohua Wang, MD, MPH; John M. Davis, III, MD, MS; Eric L. Matteson, MD, MPH; M. Hassan Murad, MD; Fengming Luo, MD, PhD; and Robert Vassallo, MD

Abstract

Objective: To assess the efficacy and safety profiles of different dosing regimens of tofacitinib, baricitinib, and upadacitinib, novel selective oral Janus activated kinase inhibitors, in rheumatoid arthritis (RA).

Methods: Randomized controlled trials of tofacitinib (5 and 10 mg twice daily) baricitinib (2 and 4 mg daily), and upadacitinib (15 and 30 mg daily) in RA were identified from MEDLINE, EMBASE, and Cochrane databases through December 11, 2019. Random-effects models were used to estimate pooled mean differences and relative risks (RRs). American College of Rheumatology 20%, Health Assessment Questionnaire−Disability Index, adverse events, risk for infection, venous thromboembolic events, and malignancy were calculated.

Results: Twenty trials with an overall low risk of bias involving 8982 patients were identified. Tofacitinib, baricitinib, and upadacitinib improved RA control as determined by American College of Rheumatology 20% (RR, 2.03; 95% CI, 1.87 to 2.20) and Health Assessment Questionnaire−Disability Index scores (mean differences, −0.31; 95% CI, −0.34 to −0.28) compared with placebo. Adverse events were more frequent with upadacitinib, 30 mg, daily (RR, 1.15; 95% CI, 1.02 to 1.30); upadacitinib, 15 mg, daily (RR, 1.14; 95% CI, 1.02 to 1.27); and baricitinib, 4 mg, daily (RR, 1.13; 95% CI, 1.02 to 1.24). The risk for infection was highest with tofacitinib, 10 mg, twice daily (RR, 2.75; 95% CI, 1.72 to 4.41), followed by upadacitinib, 15 mg, daily (RR, 1.35; 95% CI, 1.14 to 1.60) and baricitinib, 4 mg, daily (RR, 1.28; 95% CI, 1.12 to 1.45). Data for venous thromboembolic events were not available for tofacitinib or baricitinib, but there was no increase in risk with upadacitinib (15 mg daily: RR, 2.34; 95% CI, 0.34 to 15.92).

Conclusion: Tofacitinib, baricitinib, and upadacitinib significantly improve RA control. Head-to-head Janus activated kinase inhibitor clinical trials are needed to further inform decision making.

 ■ Mayo Clin Proc. 2020;95(7):1404-1419

From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN (F.W., S.W., R.V.); Department of Respiratory and Critical Care Medicine (F.W., F.L.) and Research Center of Regeneration Medicine (L.S.), West

Affiliations continued at the end of this article.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent joint damage, as well as extra-articular manifestations affecting many other organ systems.[1,2] RA affects approximately 0.53% to 0.55% of adults in the United States and 0.5% to 1% in Europe[3,4] and negatively affects quality of life and life expectancy. Cytokines are critical drivers of inflammation in RA. Janus activated kinases (JAKs) are a family of intracellular tyrosine kinases that function as mediators of signaling downstream of multiple cytokines and growth factors involved in the pathogenesis of several inflammatory and autoimmune disorders.[5] The JAK family is composed of 4 members: JAK1, JAK2, JAK3, and receptor tyrosine kinase 2 (TYK2).[6,7] Given their ability to suppress the intracellular signaling events induced by multiple cytokines, JAK inhibitors have the potential to modulate several inflammatory pathways involved in the pathogenesis of RA.[8]

Mayo Clin Proc. ■ July 2020;95(7):1404-1419 ■ https://doi.org/10.1016/j.mayocp.2020.01.039
www.mayoclinicproceedings.org ■ © 2020 Mayo Foundation for Medical Education and Research

The development of biologic agents targeting specific molecules involved in autoimmunity and inflammation has revolutionized the treatment of RA. Three oral JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have been approved by the US Food and Drug Administration (FDA) for the treatment of RA.[9-11] Tofacitinib is a first-generation selective oral JAK1/3 inhibitor with less inhibition of JAK2 and TYK2, whereas baricitinib is a selective oral JAK1/2 inhibitor with moderate activity against TYK2 and significantly less inhibition of JAK3.[12] Upadacitinib is an oral JAK1-selective inhibitor.[13] These 3 JAK inhibitors have demonstrated efficacy in RA phase 2 and 3 clinical trials.[12] To compare the efficacy and adverse-effect profile of these 3 drugs in patients with RA, we performed a systematic review and meta-analysis of all published randomized controlled trials (RCTs).

METHODS

Data Sources and Searches

This systematic review was conducted based on recommendations found in the *Cochrane Handbook for Systematic Reviews of Interventions* and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[14] A systematic search of MEDLINE, EMBASE, and the Cochrane Library published up to December 11, 2019 using the search terms "tofacitinib" or "CP-690550" or "baricitinib" or "LY3009104" or "Olumiant" or "Xeljanz" or "incb28050" or "upadacitinib" or "ABT-494" or "RINVOQ" and "rheumatoid arthritis" was conducted. Additionally, a manual search of references from reports of clinical trials or review articles was performed to identify relevant trials. Only trials published in English were included, while trials published solely in abstract form were excluded. An example of the search strategy used to identify relevant trials published in Medline is presented in the Supplemental Table (available online at http://www.mayoclinicproceedings.org).

Study Selection

Two reviewers (F.W. and L.S.) independently selected trials for inclusion. For inclusion in the analysis, trials had to fulfill all the following criteria: (1) adult patients (aged ≥ 18 years) with active RA defined according to the American College of Rheumatology (ACR) 1987 revised criteria for RA[15]; (2) double-blind, randomized, placebo-controlled design; (3) intervention treatment with tofacitinib or baricitinib or upadacitinib; (4) determination of efficacy and safety outcomes, including ACR 20% (ACR20), Health Assessment Questionnaire—Disability Index (HAQ-DI, in which scores range from 0-3, with higher scores indicating greater disability), adverse events, serious adverse events, infections, serious infections, herpes zoster infection (independent of infection or serious infection occurrence), upper respiratory tract infection, venous thromboembolic events, and malignancy. ACR20 response was defined as at least 20% improvement in both tender joint count and swollen joint count and at least 20% improvement in 3 of 5 other core set measures: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function, or acute-phase reactant value.[16] For HAQ-DI scores, an improvement from baseline of 0.22 or more was defined as the minimal clinically important difference.[17,18] Serious adverse events were reported using conventional International Conference on Harmonization definitions[19] and not on the basis of the study protocol; the protocol required that adverse events or laboratory result abnormalities leading to permanent discontinuation of treatment with the study drug be designated as serious adverse events.[20]

Data Extraction

The following predefined variables were extracted: first author; year of publication; dosing of tofacitinib, baricitinib, or upadacitinib used; numbers of patients; duration of study periods; and outcome measures. Only data for the dosing schedules of tofacitinib, 5 or 10 mg, twice daily; baricitinib, 2 or 4 mg, once daily; and upadacitinib, 15 or 30 mg, daily were included in the analysis.

Risk-of-Bias Assessment

The risk of bias was assessed using the Cochrane risk-of-bias tool, which included 6 items: (1) adequacy of sequence generation, (2) allocation concealment, (3) blinding of participants and investigators, (4) blinding of outcome assessment, (5) incomplete outcome data, and (6) selective outcome reporting and other bias.[21] The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach.[22]

Statistical Analyses

Analysis was performed by intention to treat and included all randomly assigned participants to minimize bias. Mean differences (MDs) were estimated with 95% CIs for continuous outcomes. Relative risks (RRs) were estimated for dichotomous outcomes. The random-effects model was used to conduct a meta-analysis because of anticipated heterogeneity. Heterogeneity was measured using the I^2 statistic; $I^2>50\%$ indicated important heterogeneity.[23] The influence of different doses was explored as an a priori subgroup analysis. A two-tailed $P<.05$ was considered statistically significant. All analyses were performed using Stata (version 12.0; StataCorp) and Review Manager, version 5.3 (Nordic Cochrane Centre).

RESULTS

Search Results

The search retrieved 1011 potentially relevant publications (Figure 1), of which 116 were clinical trials. Clinical trials published only in abstract form (n=42) were excluded. A total of 46 trials were also excluded (descriptive quality-of-life trials or patient-reported outcomes on RCTs), and 8 trials were excluded due to the absence of placebo control. Ultimately, 20 clinical trials were included in the analysis.[20,24-42]

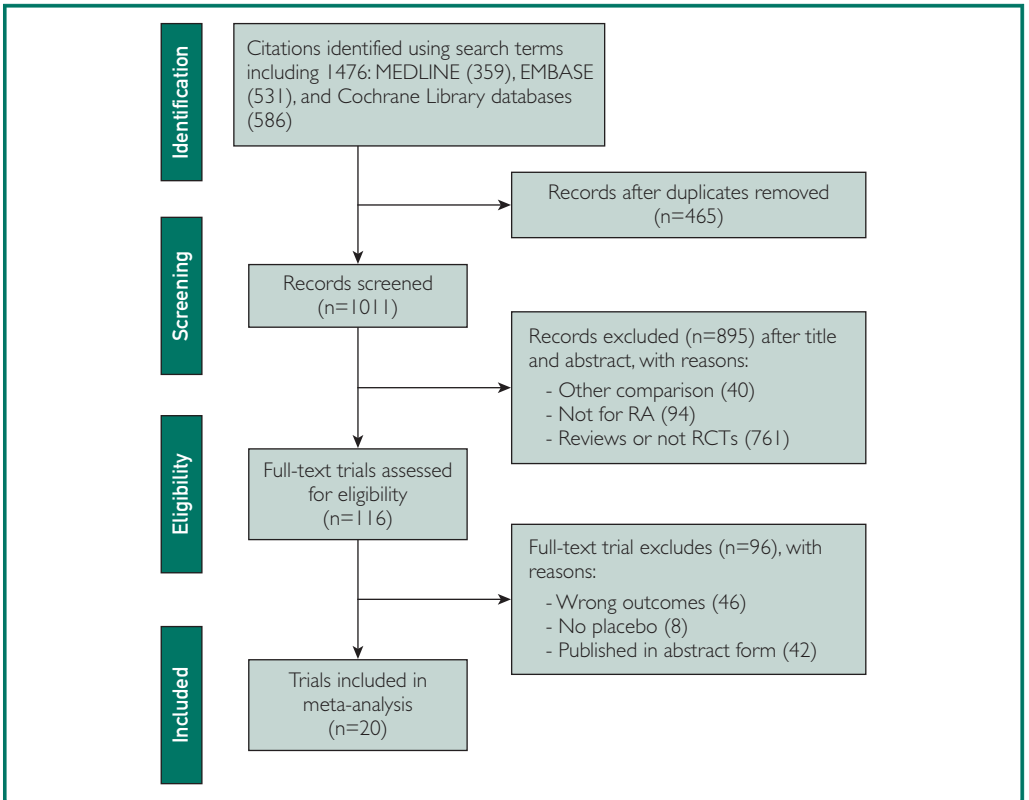

FIGURE 1. Flow chart of study selection. RA = rheumatoid arthritis; RCT = randomized controlled trial.

Mayo Clin Proc. ■ July 2020;95(7):1404-1419 ■ https://doi.org/10.1016/j.mayocp.2020.01.039
www.mayoclinicproceedings.org

Study Characteristics

The 20 trials included a total of 8982 unique patients. Characteristics of the included trials are summarized in Table 1. The range of treatment duration for trials included in this analysis was 4 to 24 weeks. Study drugs were administered orally in all trials. Of the 20 trials, 12 were designed to test tofacitinib; 5, baricitinib; and 3, upadacitinib. Three of 20 trials used monotherapy in treatment groups,[27,28,36] while combination therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX) or biologic DMARDs (bDMARDs; including tumor necrosis factor [TNF] inhibitors and interleukin 6–blocking antibodies) were used in the rest (Table 1). Six tofacitinib trials included patients with an inadequate DMARD response,[24,27,28,32,34,35] 5 with inadequate MTX response,[25,26,29,31,33] and 1 inadequate response to TNF inhibitors.[30] Three of the baricitinib trials included patients with an inadequate MTX response,[36-38] 1 with an inadequate TNF-inhibitor response,[20] and another included patients with inadequate disease control from csDMARD.[39] Two upadacitinib trials included patients with an inadequate bDMARD response,[40,41] and 1 with inadequate MTX response.[42] Key findings are summarized in Table 2.

Determination of Bias

The risk of bias was low for the 20 trials included in the meta-analysis (Figure 2A). Participants and investigators were blinded in all trials. Four of 20 trials did not describe the method of randomization and concealment of allocation.[24,25,27,29] Funnel plots and Egger's test were conducted for all outcomes, and no statistical evidence of publication bias was found (Supplemental Figure 1 for adverse events, available online at http://www.mayoclinicproceedings.org), except in the case of ACR20 (Figure 2B, Egger's $P<.001$).

Efficacy

Response rates based on ACR criteria (ACR20) and quality of life (HAQ-DI score) were used for efficacy assessment. Overall, all JAK inhibitors demonstrated efficacy in reducing disease activity. Pooled analysis showed that treatment was associated with a significantly higher rate of response by ACR20 (RR, 2.03; 95% CI, 1.87-2.20; $P<.001$), with moderate heterogeneity ($I^2=54.5\%$; $P<.001$; Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org) compared with placebo. Among all treatment groups, response rates defined by the ACR20 were highest for tofacitinib, 10 mg, twice daily (RR, 2.48; 95% CI, 1.97-3.14; $P<.001$), followed by tofacitinib, 5 mg, twice daily (RR, 2.16; 95% CI, 1.81-2.58; $P<.001$). However, the CIs for these estimates overlap, suggesting that this difference is likely due to chance. In addition, in the analysis of tofacitinib, 10 mg, twice daily, heterogeneity was significant ($I^2=63.2\%$; $P=.01$). The overall efficacy for tofacitinib as assessed by ACR20 was higher than for baricitinib and upadacitinib (RRs, 2.16 and 2.48 for tofacitinib, 5 mg and 10 mg, vs RRs, 1.73 and 1.85 for baricitinib, 2 mg and 4 mg, RRs, 1.96 and 1.90 for upadacitinib, 15 mg and 30 mg, respectively). Certainty in the evidence was judged to be moderate, mainly because of the possibility of publication bias (Table 3).

For HAQ-DI score, overall pooled analysis showed that all treatment groups were associated with significant decreases in HAQ-DI scores when compared with placebo (MD, −0.31; 95% CI, −0.34 to −0.28; $P<.001$) with no heterogeneity ($I^2=0\%$; $P=.63$; Supplemental Figure 3, available online at http://www.mayoclinicproceedings.org). Tofacitinib, 10 mg, twice daily was associated with the most statistically significant improvement in HAQ-DI score compared with placebo (MD, −0.38; 95% CI, −0.44 to −0.31; $P<.001$), followed by upadacitinib, 15 mg, daily (MD, −0.32; 95% CI, −0.37 to −0.26; $P<.001$) with no heterogeneity ($I^2=0\%$; $P=.50$). For baricitinib, 4 mg daily affected the HAQ-DI score more than 2 mg daily (MD, −0.26 vs −0.19), but a dose response was not apparent with upadacitinib, 30 mg, daily (MD, −0.29 vs −0.32: 30- vs 15-mg dose).

TABLE 1. Characteristics of Included 20 Trials[a,b]

Reference, year	Region	Trial Identifier	Analysis Duration (wk)	No. of Patients	Drug	Dose (mg)	Concomitant Medication	Participants
Kremer et al,[24] 2009	Worldwide	NCT00147498	6	126	Tofacitinib	5 twice daily	No DMARDs	DMARD-IR
Tanaka et al,[25] 2011	Japan	NCT00603512	12	81	Tofacitinib	5, 10 twice daily	MTX	MTX-IR
van Vollenhoven et al,[26] 2012	America and Europe	NCT00853385	24	513	Tofacitinib	5, 10 twice daily	MTX	MTX-IR
Fleischmann et al,[27] 2012	Worldwide	NCT00550446	24	169	Tofacitinib	5, 10 twice daily	Monotherapy	DMARD-IR
Fleischmann et al,[28] 2012	Worldwide	NCT00814307	12	610	Tofacitinib	5, 10 twice daily	Monotherapy	DMARD-IR
Kremer et al,[29] 2012	America and Europe	NCT00413660	12	214	Tofacitinib	5, 10 twice daily	MTX	MTX-IR
Burmester et al,[30] 2013	America and Europe	NCT00960440	12	399	Tofacitinib	5, 10 twice daily	MTX	TNFi-IR
Kremer et al,[32] 2013	Worldwide	NCT00856544	24	792	Tofacitinib	5, 10 twice daily	DMARDs	DMARD-IR
van der Heijde et al,[31] 2013	Worldwide	NCT00847613	24	797	Tofacitinib	5, 10 twice daily	DMARDs	MTX-IR
Boyle et al,[33] 2015	Worldwide	NCT00976599	4	29	Tofacitinib	10 twice daily	MTX	MTX-IR
Kremer et al,[35] 2015	Worldwide	NCT01484561	6	148	Tofacitinib	10 twice daily	Non-bDMARDs	DMARD-IR
Tanaka et al,[34] 2015	Japan	NCT00687193	12	157	Tofacitinib	5, 10 twice daily	Monotherapy	DMARD-IR
Keystone et al,[36] 2015	Worldwide	NCT01185353	12	202	Baricitinib	Once-daily 2, 4	Non-bDMARDs	MTX-IR
Tanaka et al,[37] 2016	Japan	NCT01469013	12	97	Baricitinib	Once-daily 2, 4	MTX	MTX-IR
Genovese et al,[20] 2016	Worldwide	NCT01721044	24	527	Baricitinib	Once-daily 2, 4	csDMARDs	TNFi-IR
Taylor et al,[38] 2017	Worldwide	NCT01710358	24	975	Baricitinib	4 once daily	csDMARDs	MTX-IR
Dougados et al,[39] 2017	Worldwide	NCT01721057	24	684	Baricitinib	Once-daily 2, 4	csDMARDs	csDMARD-IR
Burmester et al,[40] 2018	Worldwide	NCT02675426	12	661	Upadacitinib	Once-daily 15, 30	csDMARDs	bDMARD-IR
Genovese et al,[41] 2018	Worldwide	NCT02706847	12	498	Upadacitinib	Once-daily 15, 30	csDMARDs	bDMARD-IR
Fleischmann et al,[42] 2019	Worldwide	NCT02629159	12	1302	Upadacitinib	Once-daily 15	MTX	MTX-IR

[a]bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drug such as methotrexate; DMARD = disease-modifying antirheumatic drug; IR = inadequate response; MTX = methotrexate; TNFi = tumor necrosis factor inhibitor.

[b]The analysis duration reported here includes data during which trial participants received either placebo or drug and may be shorter than the study duration reported in the original research.

Safety

Reported adverse events in all trials showed that the overall incidence of adverse events was higher in groups receiving any JAK inhibitor compared with placebo (RR, 1.09; 95% CI, 1.05 to 1.13; $P<.001$; Supplemental Figure 4, available online at http://www.mayoclinicproceedings.org). Statistical heterogeneity was not observed ($I^2=11.4\%$; $P=.29$). For tofacitinib, the frequency of adverse events was similar to placebo in both the 5- and 10-mg dosing groups (RR, 1.05; $P=.22$ [5 mg]; and RR, 1.07 [$P=.1$ [10 mg]). Adverse events with baricitinib, 2 mg, daily were similar to placebo but reported adverse events with baricitinib, 4 mg, daily (RR, 1.13; 95% CI, 1.02 to 1.24, $P=.02$; $I^2=46.4\%$); upadacitinib, 15 mg (RR, 1.14; 95% CI, 1.02 to 1.27; $P=.02$; $I^2=41.4\%$) and 30 mg, daily (RR, 1.15; 95% CI, 1.02 to 1.30; $P=.03$; $I^2=0.0\%$) were higher than placebo. The Grading of Recommendations Assessment, Development and Evaluation quality of adverse events was judged to be moderate (Table 3), and the absolute effect was 50 fewer per 1000 (from 28 fewer to 73 more). However, there was no difference in the frequency of serious adverse events compared with placebo in any of the treatment groups (RR, 1.11; 95% CI, 0.86 to 1.42; $P=.42$; $I^2=16.2\%$; Supplemental Figure 5, available online at http://www.mayoclinicproceedings.org). Certainty in the evidence about the risks for serious adverse events was judged as moderate.

The risk for infection was not increased with tofacitinib, 5 mg, twice daily (RR, 1.5; 95% CI, 0.61 to 3.69; $P=.38$); baricitinib, 2 mg, daily (RR, 1.06; 95% CI, 0.72 to 1.57; $P=.78$); or upadacitinib, 30 mg daily (RR, 1.28; 95% CI, 0.96 to 1.70; $P=.1$), but was significantly increased with tofacitinib, 10 mg, twice daily (RR, 2.75; 95% CI, 1.72 to 4.41; $P<.001$); baricitinib, 4 mg, daily (RR, 1.28; 95% CI, 1.12 to 1.45; $P<.001$); and upadacitinib, 15 mg, daily (RR, 1.35; 95% CI, 1.14 to 1.60; $P=.001$; Supplemental Figure 6, available online at http://www.mayoclinicproceedings.org). Across all treatment groups, the overall incidence of serious infections (excluding herpes zoster infection) was similar to placebo (RR, 1.42; 95% CI, 0.93 to 2.17, $P=.10$) without heterogeneity ($I^2=0\%$; $P=.94$; Supplemental Figure 7, available online at http://www.mayoclinicproceedings.org). Certainty in the evidence about the risk for serious infections was low.

A statistically higher risk for herpes zoster infection was observed only with baricitinib, 4 mg, daily (RR, 3.81; $P=.01$) compared with placebo and not observed with baricitinib, 2 mg, daily (RR, 2.32; $P=.44$); tofacitinib (RR, 1.66; $P=.63$ [5 mg] and RR, 6.94; $P=.06$ [10 mg]); or upadacitinib (RR, 1.41; $P=.09$ [15 mg] and RR, 2.96; $P=.09$]30 mg]; Supplemental Figure 8, available online at http://www.mayoclinicproceedings.org). Certainty in the evidence about the risk for herpes zoster was low due to the wide CIs and small number of patients involved.

All the treatment regimens evaluated showed no significant increase in risk for upper respiratory tract infection, but overall the estimated RR was significantly higher than for placebo (RR, 1.32; 95% CI, 1.07 to 1.63; $P=.01$; Supplemental Figure 9, available online at http://www.mayoclinicproceedings.org), and the certainty in the evidence was moderate.

The upadacitinib trials included in the analysis reported data for venous thromboembolic events: thus, pooled analysis was only performed for upadacitinib. There were no reported venous thromboembolic events with upadacitinib, 30 mg, daily, whereas the incidence with upadacitinib, 15 mg, was similar to placebo (RR, 2.34; 95% CI, 0.34, 15.92; $P=.39$; Supplemental Figure 10, available online at http://www.mayoclinicproceedings.org). The analysis could not be extended to tofacitinib and baricitinib due to lack of data.

Only 7 trials reported the data for malignancy. The overall incidence of serious malignancy was similar to placebo (RR, 1.68; 95% CI, 0.57 to 4.95; $P=.34$; Supplemental Figure 11, available online at http://www.mayoclinicproceedings.org). Certainty in the evidence about the risk for venous thromboembolic events and malignancy was very low due

TABLE 2. Summary of Results Stratified by JAK Inhibitors Compared With Placebo Corresponding to Respective Outcomes[a]

Outcomes	Studies (n)	RR	Lower 95% CI	Upper 95% CI	I^2	Outcomes	Studies (n)	RR	Lower 95% CI	Upper 95% CI	I^2
ACR20						Infections					
All RCTs	19	2.03	1.87	2.20	54.5%	All RCTs	11	1.34	1.17	1.52	52.7%
Tofacitinib 5 mg bid	10	2.16	1.81	2.58	52.2%	Tofacitinib 5 mg bid	4	1.50	0.61	3.69	72.1%
Tofacitinib 10 mg bid	9	2.48	1.97	3.14	63.2%	Tofacitinib 10 mg bid	3	2.75	1.72	4.41	0%
Baricitinib 2 mg qd	4	1.73	1.38	2.16	55.4%	Baricitinib 2 mg qd	3	1.06	0.72	1.57	67.2%
Baricitinib 4 mg qd	5	1.85	1.63	2.11	36.3%	Baricitinib 4 mg qd	4	1.28	1.12	1.45	0%
Upadacitinib 15 mg qd	3	1.96	1.68	2.28	2.4%	Upadacitinib 15 mg qd	3	1.35	1.14	1.60	24.4%
Upadacitinib 30 mg qd	2	1.90	1.61	2.23	0%	Upadacitinib 30 mg qd	2	1.28	0.96	1.70	39.3%
HAQ-DI						Serious infections					
All RCTs	12	−0.31	−0.34	−0.28	0%	All RCTs	16	1.42	0.93	2.17	0%
Tofacitinib 5 mg bid	7	−0.30	−0.36	−0.24	0%	Tofacitinib 5 mg bid	6	2.08	0.43	10.02	0%
Tofacitinib 10 mg bid	6	−0.38	−0.44	−0.31	0%	Tofacitinib 10 mg bid	8	2.26	0.64	8.01	0%
Baricitinib 2 mg qd	2	−0.19	−0.30	−0.07	8.1%	Baricitinib 2 mg qd	4	0.97	0.28	3.37	30%
Baricitinib 4 mg qd	2	−0.26	−0.37	−0.15	0%	Baricitinib 4 mg qd	5	0.94	0.47	1.90	0%
Upadacitinib 15 mg qd	3	−0.32	−0.37	−0.26	0.0%	Upadacitinib 15 mg qd	3	2.23	0.88	5.64	0%
Upadacitinib 30 mg qd	2	−0.29	−0.37	−0.20	0.0%	Upadacitinib 30 mg qd	2	4.59	0.77	27.34	0%
Adverse events						Herpes zoster					
All RCTs	18	1.09	1.05	1.13	11.4%	All RCTs	10	2.57	1.43	4.62	0%
Tofacitinib 5 mg bid	8	1.05	0.97	1.13	0%	Tofacitinib 5 mg bid	3	1.66	0.21	13.28	0%
Tofacitinib 10 mg bid	9	1.07	0.99	1.15	1.3%	Tofacitinib 10 mg bid	2	6.94	0.89	54.06	0%
Baricitinib 2 mg qd	4	1.01	0.92	1.11	0%	Baricitinib 2 mg qd	3	2.32	0.27	19.93	37.4%
Baricitinib 4 mg qd	4	1.13	1.02	1.24	46.4%	Baricitinib 4 mg qd	4	3.81	1.35	10.71	0%
Upadacitinib 15 mg qd	3	1.14	1.02	1.27	41.4%	Upadacitinib 15 mg qd	3	1.41	0.44	4.45	0%
Upadacitinib 30 mg qd	2	1.15	1.02	1.30	0.0%	Upadacitinib 30 mg qd	2	2.96	0.59	14.83	0%
Serious adverse events						Upper respiratory tract infection					
All RCTs	18	1.11	0.86	1.42	16.2%	All RCTs	12	1.32	1.07	1.63	0%
Tofacitinib 5 mg bid	8	0.95	0.44	2.05	42.4%	Tofacitinib 5 mg bid	8	1.61	1.00	2.59	0%
Tofacitinib 10 mg bid	10	1.06	0.66	1.70	0%	Tofacitinib 10 mg bid	7	1.60	0.83	3.06	28.7%
Baricitinib 2 mg qd	4	0.69	0.38	1.25	0%	Baricitinib 2 mg qd	2	1.21	0.47	3.11	68.1%
Baricitinib 4 mg qd	5	1.12	0.77	1.63	0%	Baricitinib 4 mg qd	2	1.31	0.80	2.14	0%
Upadacitinib 15 mg qd	3	1.79	0.74	4.31	43.6%	Upadacitinib 15 mg qd	2	1.15	0.66	2.01	0%
Upadacitinib 30 mg qd	2	4.48	0.15	129.98	79.9%	Upadacitinib 30 mg qd	2	1.01	0.57	1.81	0%

Continued on next page

TABLE 2. Continued

Outcomes	Studies (n)	RR	Lower 95% CI	Upper 95% CI	I^2	Outcomes	Studies (n)	RR	Lower 95% CI	Upper 95% CI	I^2
Venous thromboembolic events						Malignancy					
All RCTs	3	2.34	0.34	15.92	0%	All RCTs	7	1.68	0.57	4.95	0%
Tofacitinib 5 mg bid	—	—	—	—	—	Tofacitinib 5 mg bid	1	1.50	0.06	36.62	—
Tofacitinib 10 mg bid	—	—	—	—	—	Tofacitinib 10 mg bid	—	—	—	—	—
Baricitinib 2 mg qd	—	—	—	—	—	Baricitinib 2 mg qd[b]	2	—	—	—	—
Baricitinib 4 mg qd	—	—	—	—	—	Baricitinib 4 mg qd	2	1.35	0.26	7.17	0%
Upadacitinib 15 mg qd	3	2.34	0.34	15.92	0%	Upadacitinib 15 mg qd	3	1.02	0.11	9.76	0%
Upadacitinib 30 mg qd[b]	2	—	—	—	—	Upadacitinib 30 mg qd	2	4.18	0.46	37.62	0%

[a]ACR20 = American College of Rheumatology 20%; bid = twice daily; HAQ-DI = Health Assessment Questionnaire–Disability Index; JAK = Janus activated kinase; qd = daily; RCT = randomized controlled trial; RR = relative risk.

[b]No events in placebo or JAK inhibitor group.

to the wide CIs and small number of patients involved.

DISCUSSION

This systematic review and meta-analysis compared the safety and efficacy of tofacitinib, baricitinib, and upadacitinib in patients with RA. Tofacitinib, 5 mg, twice daily; baricitinib, 2 mg, once daily; and upadacitinib, 15 mg, daily are currently FDA-approved for the treatment of adult patients with moderate to severely active RA with a prior inadequate response or intolerance to MTX,[43-45] whereas tofacitinib, 10 mg, twice daily; baricitinib, 4 mg, once daily; and upadacitinib, 30 mg once daily have not been approved for RA primarily because of concerns regarding toxicity. Tofacitinib, 10 mg, twice daily showed superiority in achieving ACR20 responses but was associated with increased toxicity relative to a lower dosing schedule or when compared with baricitinib and upadacitinib.

Several clinical trials have been conducted with the goal of defining the efficacy and safety of tofacitinib, baricitinib, and upadacitinib in active RA, but there are no head-to-head studies comparing these 3 drugs. Consistent with previous meta-analyses and network meta-analysis,[16,46-48] control of disease activity was highest with 10 mg of tofacitinib twice daily. In addition to higher risk for infection with 10-mg tofacitinib twice-daily and 15-mg daily upadacitinib dosing, recent reports have also raised concern for increased risk for venous thromboembolic disease, which was not reported in the tofacitinib and baricitinib trials included in the current meta-analysis.[49] An observational cohort study that evaluated the risk for venous thromboembolism in 34,074 patients with RA receiving tofacitinib and TNF inhibitors reported a numerically higher risk for venous thromboembolism in patients with RA treated with tofacitinib compared with the TNF-inhibitor group, but it was statistically insignificant.[48,50] A review of postmarketing safety data to the FDA's Adverse Event Reporting System did not reveal high reporting rates for venous thromboembolism specifically with the use of JAK inhibitor therapy but suggested that pulmonary thrombosis may be a classwide side effect associated

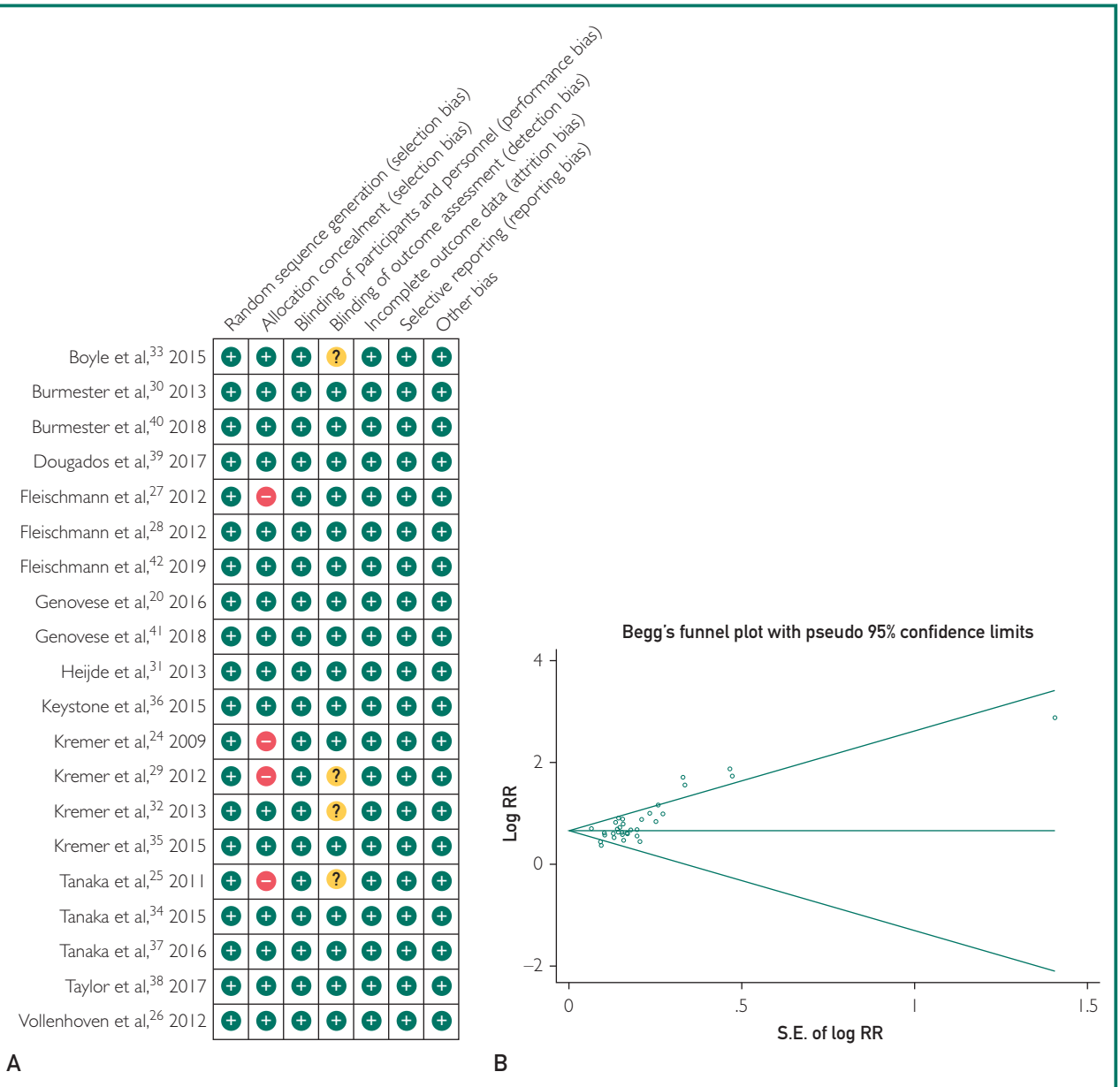

FIGURE 2. A, Risk-of-bias summary. B, Begg's funnel plot of tofacitinib, baricitinib, and upadacitinib on American College of Rheumatology 20% (ACR20). Open diamonds represent observed trials. RR = risk ratio, SE= standard error.

with JAK inhibitor therapy.[51] Unfortunately, the risk for venous thromboembolic disease with either tofacitinib or baricitinib could not be determined in the current meta-analysis because thrombotic events were not reported in the trials included. Similarly, definitive conclusions regarding the risk for thrombosis with upadacitinib could not be made in this analysis due to the relatively low numbers of trials included. In addition, another study reported extended 48-week follow-up of patients in the SELECT-COMPARE trial, which compared upadacitinib, placebo, and adalimumab and reported no increase in venous thromboembolic events at week 48.[52] The potential link between venous thromboembolism and JAK inhibitor therapy affirms the importance of prolonged longitudinal follow-up to adequately capture toxicities associated with the use of these novel agents over time.

Mayo Clin Proc. ■ July 2020;95(7):1404-1419 ■ https://doi.org/10.1016/j.mayocp.2020.01.039
www.mayoclinicproceedings.org

TABLE 3. Summary of Findings Including GRADE Quality Assessment of Evidence Trials[a]

Variables	No. of Studies	No. of Patients		Effect		Quality of the Evidence (GRADE)	Quality Domains and Assessments	Importance
		JAK Inhibitor[b]	Placebo	Relative (95% CI)	Absolute (95% CI)			
ACR20	15	3088/5640 (54.7%)	1310/4742 (27.6%)	RR 2.03 (1.87-2.20)	285 more per 1000 (from 240 more to 332 more)	⊕⊕⊕◯ Moderate	Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: not serious Other: publication bias strongly suspected[c,d]	Critical
Adverse events	17	3514/5777 (60.8%)	2599/4638 (56.0%)	RR 1.09 (1.05-1.13)	50 more per 1000 (from 28 more to 73 more)	⊕⊕⊕◯ Moderate	Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: not serious Other: none	Critical
Serious adverse events	18	238/5821 (4.1%)	163/4727 (3.4%)	RR 1.11 (0.86-1.42)	4 fewer per 1000 (from 5 fewer to 14 more)	⊕⊕⊕◯ Moderate	Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: not serious Other: none	Important

Continued on next page

TABLE 3. Continued

Variables	No. of Studies	No. of Patients		Effect		Quality of the Evidence (GRADE)	Quality Domains and Assessments	Importance
		JAK Inhibitor[b]	Placebo	Relative (95% CI)	Absolute (95% CI)			
Infection	11	1069/3130 (34.1%)	821/3203 (25.6%)	RR 1.34 (1.17-1.52)	87 more per 1000 (from 44 more to 133 more)	⊕⊕⊕◯ Moderate	Risk of bias: serious[d] Inconsistency: not serious Indirectness: not serious Imprecision: not serious Other: none	Important
Serious infection	14	60/4971 (1.2%)	145/4325 (3.3%)	RR 1.42 (0.93-2.17)	14 more per 1000 (from 2 fewer to 39 more)	⊕⊕◯◯ Low	Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: serious[e,f] Other: none	Important
Herpes zoster	10	47/3334 (1.4%)	64/3211 (2.0%)	RR 2.57 (1.43-4.62)	31 more per 1000 (from 9 more to 72 more)	⊕⊕◯◯ Low	Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: serious[e,f] Other: none	Important

Continued on next page

TABLE 3. Continued

Variables	No. of Studies	No. of Patients		Effect		Quality of the Evidence (GRADE)	Quality Domains and Assessments	Importance
		JAK Inhibitor[b]	Placebo	Relative (95% CI)	Absolute (95% CI)			
Upper respiratory tract infection	12	318/4541 (7.0%)	168/3258 (5.1%)	RR 1.32 (1.07-1.63)	17 more per 1000 (from 4 more to 32 more)	⊕⊕⊕◯ Moderate	Risk of bias: serious Inconsistency: not serious Indirectness: not serious Imprecision: not serious Other: none	Not important
Venous thromboembolic events	3	3/1420 (0.2%)	1/1432 (0.1%)	RR 2.34 (0.34-15.92)	1 more per 1000 (from 0 fewer to 10 more)	⊕◯◯◯ Very low	Risk of bias: serious Inconsistency: serious Indirectness: not serious Imprecision: serious[e,f] Other: none	Important
Malignancy	7	8/3034 (0.3%)	3/2888 (0.1%)	RR 1.68 (0.57-4.95)	1 more per 1000 (from 0 fewer to 4 more)	⊕◯◯◯ Very low	Risk of bias: serious Inconsistency: serious Indirectness: not serious Imprecision: serious[e,f] Other: none	Important

[a]ACR20 = American College of Rheumatology 20%; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RR = relative risk.
[b]The JAK inhibitor here specifically refers to tofacitinib, baricitinib, and upadacitinib.
[c]Some of the trials did not state the randomized method and concealment of allocation.
[d]Publication bias, including all 4 trials with no description of randomization, concealment of allocation, Egger *P*=.001.
[e]Wide CI.
[f]Small number of patients.

With regard to RA disease activity control, all treatment groups achieved greater disease control compared with placebo. Although all treatment groups achieved the minimal clinically important difference of HAQ-DI score, tofacitinib, 10 mg, twice daily was associated with the largest improvement among all treatment groups. These results should be interpreted with caution because the number of trials conducted with tofacitinib outnumbered those with baricitinib and upadacitinib and especially because of the lack of any head-to-head comparisons of these JAK inhibitors.

A prior Bayesian network meta-analysis[46] involving 12 RCTs of tofacitinib and baricitinib concluded that tofacitinib, 10 mg, twice daily combined with MTX, and baricitinib, 4 mg, once daily combined with MTX were the most clinically effective therapeutic options for patients with RA with an inadequate response to DMARDs or biologic therapy. In that meta-analysis, tofacitinib and baricitinib therapy were not associated with significant risk for serious adverse events.[46] However, that analysis did not include adverse-event analysis in their report and included fewer patients compared with the current study. Another Bayesian network meta-analysis[53] compared the efficacy and safety of 15 and 30 mg of upadacitinib combined with or without MTX, adalimumab monotherapy, or MTX monotherapy and concluded that 15 and 30 mg once daily in combination with MTX were associated with the highest disease control scores. In a separate network meta-analysis, the same authors compared with tofacitinib and upadacitinib and concluded that ACR20 response was highest with upadacitinib, 15 or 30 mg, daily in combination with MTX.[54]

These results must be interpreted with caution. In those network meta-analyses, the included trials were few, resulting in potential bias. In addition, for the tofacitinib and upadacitinib network meta-analysis,[54] not all the RCTs for tofacitinib were included, potentially also resulting in bias. Network meta-analysis was not performed in our study because the variation in distribution of inadequate response for DMARDs or biologic therapy would induce bias due to imbalance in the effect modifier among comparison groups.[55] Furthermore, due to the higher heterogeneity and publication bias found in ACR20 analysis, network meta-analysis would affect several pooled estimates as compared with just 1 pooled effect estimate obtained in conventional pairwise meta-analysis.[56] Another meta-analysis[57] identified increased risk for infections (including herpes zoster), similar to that observed in the current analysis, with the baricitinib dose of 4 mg daily. Finally, there are no published studies examining the relative efficacy of the various JAK inhibitors in direct comparative studies.

Baricitinib, 4 mg, daily and both doses of upadacitinib were associated with more adverse events compared with placebo; however, serious adverse events (other than herpes zoster infection) were similar to placebo. Infections were overall more frequent with tofacitinib, 10 mg, twice daily; baricitinib, 4 mg, daily; and upadacitinib, 15 mg, daily than with placebo. Among the treatment groups, a significantly increased risk for herpes zoster was identified with baricitinib, 4 mg, daily compared with placebo.

The RR for herpes zoster infection with tofacitinib therapy suggested by this meta-analysis should be interpreted with caution. The data included in the meta-analysis allow estimation on the RR for herpes zoster infection over a relatively short time frame (<1 year). A recent prospective observational 5-year study reported 2-fold increased risk for herpes zoster infection with tofacitinib therapy compared with bDMARDs.[58] A longer follow-up study (>9 years) of patients receiving tofacitinib (5 and 10 mg twice daily) reported 3.4 herpes zoster events per 100 patient-years.[59] Additionally, crude incidence rates of herpes zoster are 10-fold higher with tofacitinib, 10 mg, twice daily with concomitant csDMARDs and glucocorticoid therapy.[60] The herpes zoster risk is higher in all patients compared with placebo but varies across regions, with patients of Asian descent being at highest risk.[60]

There are several limitations to our study. The inclusion criteria of patients were not uniform among the trials. Fewer trials have been

Mayo Clin Proc. ■ July 2020;95(7):1404-1419 ■ https://doi.org/10.1016/j.mayocp.2020.01.039
www.mayoclinicproceedings.org

conducted with baricitinib and upadacitinib compared with tofacitinib, which may induce some level of uncertainty in the estimates of true effects, especially for upadacitinib. Although several trials shared many aspects of the overall design, there was also substantial heterogeneity, notably the study design, follow-up duration, different ethnic backgrounds, and duration of treatment. In addition, most trials were conducted in Europe and America. This is of particular relevance because some adverse effects, such as herpes zoster infection, may be significantly influenced by ethnicity (more prevalent in Asians), as well as the administration of concomitant glucocorticoid or other immunosuppressive therapy at baseline.[5,12,61,62] Another limitation results from the significant heterogeneity noted among trials evaluating ACR20. To account for this, a random-effects model was used but the correction is only partial, and possible sources of heterogeneity might include ethnicity and geographic factors, different enrollment criteria of participants, and the definable differences in study populations included. Finally, although assignment to placebo in most trials was for the duration of the trial, in some trials, a subgroup or all placebo-treated patients switched to treatment groups to address ethical concerns about continuing placebo treatment in patients with active disease. Therefore, we could only include the short-term data for comparing treatment with placebo so that long-term adverse effects could not be addressed.

CONCLUSION

Tofacitinib, baricitinib, and upadacitinib improve RA disease control and also improve quality of life. This efficacy appears to be counterbalanced by an increased risk for infection and, as suggested by recent data, the possibility of venous thromboembolic events. A notable increased risk for adverse events, particularly infections (especially herpes zoster), with baricitinib, 4 mg, daily and upadacitinib, 15 mg, daily was also observed. Longer-term follow-up and additional trials with head-to-head comparison of tofacitinib, baricitinib, and upadacitinib, as well as additional information from ongoing trials of these and other JAK inhibitors, including peficitinib and filgotinib, will be important to further determine both efficacy and the safety profile of these agents in the management of RA.

ACKNOWLEDGEMENTS

The assistance of Cynthia Beeler, MLIS, AHIP, and Patricia J. Erwin, MLS, from the Mayo Clinic Libraries with systematic review of the literature and identification of relevant studies for inclusion in the meta-analysis is greatly appreciated. Drs Wang and Sun contributed equally to this work.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACR20** = American College of Rheumatology 20%; **bDMARD** = biologic disease-modifying antirheumatic drug; **csDMARD** = conventional synthetic disease-modifying antirheumatic drug; **DMARD** = disease-modifying antirheumatic drug; **FDA** = US Food and Drug Administration; **GRADE** = Grades of Recommendation, Assessment, Development and Evaluation; **HAQ-DI** = Health Assessment Questionnaire—Disability Index **IR** = inadequate response; **JAK** = Janus activated kinase **MD** = mean difference; **MTX** = methotrexate; **RA** = rheumatoid arthritis; **RCT** = randomized controlled trial; **RR** = relative risk; **TNF** = tumor necrosis factor; **TNFi** = tumor necrosis factor inhibitor; **TYK2** = tyrosine kinase 2

Affiliations (Continued from the first page of this article.): China Hospital, Sichuan University, Chengdu, China; Division of Rheumatology and Department of Health Science Research, Mayo Clinic College of Medicine and Science (J.M.D., E.L.M.); and Evidence-Based Practice Center, Mayo Clinic, Rochester, MN (M.H.M.).

Grant Support: This study was supported by National Nature Science Foundation of China grant (NSFC no. 81470268, no. 81770072), Ministry of Science and Technology of the People's Republic of China (no. 2017YFC0107805), Science and Technology Support Program of Sichuan province (no. 2016SZ0002), Chengdu Science and Technology Bureau (no. 2018-CY02-00064-GX), and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYJC18021).

Potential Competing Interests: Dr Vassallo has received research grant support from Pfizer, Bristol Myers Squibb, and Sun Pharmaceuticals. Dr Matteson has received research grant support from Pfizer, Boehringer-Ingelheim, Bristol Myers Squibb, and Sun Pharmaceuticals and serves

on Advisory Boards for Boehringer-Ingelheim, Gilead Sciences, and Simply Speaking. Dr Davis has received research grant support from Pfizer and has served on advisory boards for Abbvie and Sanofi Genzyme. The remaining authors report no competing interests.

Correspondence: Address to Fengming Luo, MD, PhD, Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, 610041, China (fengmingluo@outlook.com); or Robert Vassallo, MD, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN 55902 (vassallo.robert@mayo.edu).

ORCID

M. Hassan Murad: https://orcid.org/0000-0001-5502-5975; Robert Vassallo: https://orcid.org/0000-0003-2328-0255

REFERENCES

1. Mahajan TD, Mikuls TR. Recent advances in the treatment of rheumatoid arthritis. *Curr Opin Rheumatol*. 2018;30(3):231-237.
2. Kawalec P, Sladowska K, Malinowska-Lipien I, Brzostek T, Kozka M. New alternative in the treatment of rheumatoid arthritis: clinical utility of baricitinib. *Ther Clin Risk Manag*. 2019;15:275-284.
3. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. *Rheumatol Int*. 2017;37(9):1551-1557.
4. Humphreys JH, Verstappen SM, Hyrich KL, Chipping JR, Marshall T, Symmons DP. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. *Ann Rheum Dis*. 2013;72(8):1315-1320.
5. Fragoulis GE, McInnes IB, Siebert S. JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58(suppl 1):i43-i54.
6. Sarzi-Puttini P, Ceribelli A, Marotto D, Batticciotto A, Atzeni F. Systemic rheumatic diseases: from biological agents to small molecules. *Autoimmun Rev*. 2019;18(6):583-592.
7. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med*. 2015;66:311-328.
8. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases [erratum for JAK inhibition as a therapeutic strategy for immune and inflammatory diseases: *Nat Rev Drug Discov*. 2017]. *Nat Rev Drug Discov*. 2017;17(1):78.
9. Traynor K. FDA approves tofacitinib for rheumatoid arthritis [news]. *Am J Health Syst Pharm*. 2012;69(24):2120.
10. Mogul A, Corsi K, McAuliffe L. Baricitinib: the second FDA-approved JAK inhibitor for the treatment of rheumatoid arthritis. *Ann Pharmacother*. 2019;53(9):947-953.
11. Duggan S, Keam SJ. Upadacitinib: first approval. *Drugs*. 2019;79(16):1819-1828.
12. Taylor PC. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58(suppl 1):i17-i26.
13. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet*. 2019;393(10188):2303-2311.
14. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: John Wiley and Sons; 2008.
15. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988;31(3):315-324.
16. Kawalec P, Mikrut A, Wisniewska N, Pilc A. The effectiveness of tofacitinib, a novel Janus kinase inhibitor, in the treatment of rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol*. 2013;32(10):1415-1424.
17. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum*. 2000;43(7):1478-1487.
18. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. *J Rheumatol*. 1993;20(3):557-560.
19. Center for Drug Evaluation and Research. E2A Clinical safety data management: definitions and standards for expedited reporting. https://docisolation.prod.fire.glass/?guid=7a7810a0-42af-4fd1-8972-9873175d3bdd. Accessed May 14, 2020.
20. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243-1252.
21. Higgins JP, Altman DG, Gotzsche PC, et al. Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
22. Murad MH, Montori VM, Ioannidis JP, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA*. 2014;312(2):171-179.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
24. Kremer JM, Bloom BJ, Breedveld FC, 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(7):1895-1905.
25. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi 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 (Hoboken)*. 2011;63(8):1150-1158.
26. van Vollenhoven RF, Fleischmann R, Cohen S, et al. ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367(6):508-519.
27. Fleischmann R, Cutolo M, Genovese MC, 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(3):617-629.
28. Fleischmann R, Kremer J, Cush J, et al. ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367(6):495-507.
29. Kremer JM, Cohen S, Wilkinson BE, 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(4):970-981.
30. Burmester GR, Blanco R, Charles-Schoeman C, et al. on behalf of the ORAL Step investigators. 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(9865):451-460.

31. van der Heijde D, Tanaka Y, Fleischmann R, et al. ORAL Scan Investigators. 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(3):559-570.
32. Kremer J, Li ZG, Hall S, 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(4):253-261.
33. Boyle DL, Soma K, Hodge J, et al. The JAK inhibitor tofacitinib suppresses synovial JAK1-STAT signalling in rheumatoid arthritis. *Ann Rheum Dis*. 2015;74(6):1311-1316.
34. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi 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(4):514-521.
35. Kremer JM, Kivitz AJ, Simon-Campos JA, et al. Evaluation of the effect of tofacitinib on measured glomerular filtration rate in patients with active rheumatoid arthritis: results from a randomised controlled trial. *Arthritis Res Ther*. 2015;17:95.
36. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Ann Rheum Dis*. 2015;74(2):333-340.
37. Tanaka Y, Emoto K, Cai Z, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: a 12-week, double-blind, randomized placebo-controlled study. *J Rheumatol*. 2016; 43(3):504-511.
38. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376(7):652-662.
39. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95.
40. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391(10139):2503-2512.
41. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018;391(10139):2513-2524.
42. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol*. 2019;71(11):1788-1800.
43. U.S. Food and Drug Administration. Full prescribing information for XELJANZ (tofacitinib) 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024,208246s010lbl.pdf. Accessed May 16, 2019.
44. U.S. Food and Drug Administration. Full prescribing information for OLUMIANT (baricitinib) 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf. Accessed May 16, 2019.
45. U.S. Food and Drug Administration. full prescribing information for RINVOQ™ (upadacitinib) 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf. Accessed December 2, 2019.
46. Bae SC, Lee YH. Comparison of the efficacy and safety of tofacitinib and baricitinib in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol*. 2019;78(6):559-567.
47. He Y, Wong AY, Chan EW, et al. Efficacy and safety of tofacitinib in the treatment of rheumatoid arthritis: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2013;14:298.
48. Kunwar S, Collins CE, Constantinescu F. Baricitinib, a Janus kinase inhibitor, in the treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials. *Clin Rheumatol*. 2018;37(10):2611-2620.
49. U.S. Food and Drug Administration. Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate 2019. https://www.fda.gov/drugs/drug-safety-and-availability/safety-trial-finds-risk-blood-clots-lungs-and-death-higher-dose-tofacitinib-xeljanz-xeljanz-xr. Accessed June 15, 2019.
50. Desai RJ, Pawar A, Weinblatt ME, Kim SC. Comparative risk of venous thromboembolism in rheumatoid arthritis patients receiving tofacitinib versus those receiving tumor necrosis factor inhibitors: an observational cohort study. *Arthritis Rheumatol*. 2019;71(6):892-900.
51. Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. *Drug Saf*. 2018;41(4):357-361.
52. Fleischmann RM, Genovese MC, Enejosa JV, et al. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis*. 2019;78(11):1454-1462.
53. Song GG, Lee YH. Comparative efficacy and safety of 15 and 30 mg upadacitinib administered to patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol*. 2019;79(1):103-111.
54. Song GG, Choi SJ, Lee YH. Comparison of the efficacy and safety of tofacitinib and upadacitinib in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Int J Rheum Dis*. 2019;22(8):1563-1571.
55. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med*. 2013;11:159.
56. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Ad Hoc Network Meta-analysis Methods Meeting Working Group. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Med*. 2011;9:79.
57. Bechman K, Subesinghe S, Norton S, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)*. 2019; 58(10):1755-1766.
58. Kremer J, Bingham C, Cappelli L, et al. OP0028 Post-approval comparative safety study of tofacitinib and biologic DMARDS: five—year results from a US-based rheumatoid arthritis registry. *Ann Rheum Dis*. 2019;78(Suppl 2):82-83.
59. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther*. 2019;21(1):89.
60. Winthrop KL, Curtis JR, Lindsey S, et al. Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. *Arthritis Rheumatol*. 2017;69(10):1960-1968.
61. Yamanaka H, Tanaka Y, Takeuchi T, 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.
62. Marra F, Lo E, Kalashnikov V, Richardson K. Risk of herpes zoster in individuals on biologics, disease-modifying antirheumatic drugs, and/or corticosteroids for autoimmune diseases: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2016;3(4):ofw205.