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ORIGINAL RESEARCH

Comparative Efficacy and Safety of Peficitinib Versus Tofacitinib and Baricitinib for Treatment of Rheumatoid Arthritis: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Introduction: Peficitinib, a Janus kinase (JAK) inhibitor, is approved for clinical use in Japan, Korea, and Taiwan, but head-to-head comparisons versus other JAK inhibitors are lacking. We indirectly compared peficitinib, tofacitinib, and baricitinib for rheumatoid arthritis treatment.

Methods: We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and congress archives up until February 12, 2019, for randomized controlled trials of peficitinib, tofacitinib, and baricitinib. Efficacy (American College of Rheumatology responses, disease activity scores, modified total Sharp score, Simplified Disease Activity Index [SDAI]) and safety outcomes were compared using a Bayesian network meta-analysis. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) consensus was followed for reporting results. A network meta-regression assessed the impact on outcomes of proportions of patients receiving concomitant methotrexate or of Asian ethnicity.

Results: The network meta-analysis included 21 randomized controlled trials. At 12 weeks, all evaluable efficacy outcomes were comparable or improved with peficitinib 150 mg and 100 mg once daily, versus baricitinib 2 and 4 mg once daily and tofacitinib 5 mg twice daily. At 24 weeks, efficacy outcomes were comparable or improved for each peficitinib dose versus baricitinib and tofacitinib. Risk of adverse events and serious adverse events at 12 weeks were similar with peficitinib 100 and 150 mg versus baricitinib and tofacitinib. The proportion of patients receiving concomitant methotrexate had no effect on any outcome analyzed, but Asian ethnicity had a positive effect on multiple efficacy outcomes.

Conclusions: Peficitinib had comparable efficacy versus tofacitinib and baricitinib for

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reduction in disease activity as measured by SDAI, and for reduction in progression of joint damage as measured radiographically. No notable differences in safety outcomes were observed. Further studies are required to better characterize the impact of ethnicity on the efficacy of JAK inhibitors.

Keywords: Baricitinib; Janus kinase inhibitor; Network meta-analysis; Peficitinib; Systematic literature review; Tofacitinib

Key Summary Points
Why carry out this study?
Peficitinib, a Janus kinase (JAK) inhibitor, has demonstrated efficacy and tolerability for the treatment of rheumatoid arthritis in Asian patients; however, head-to-head clinical trials comparing peficitinib with other JAK inhibitors are lacking.
We conducted a systematic literature review and network meta-analysis of randomized controlled trials to indirectly compare the efficacy and safety of peficitinib, tofacitinib, and baricitinib.
What was learned from this study?
Peficitinib (100 and 150 mg once daily) provided comparable or improved efficacy outcomes versus tofacitinib (5 mg twice daily) and baricitinib (2 or 4 mg once daily).
Safety of peficitinib, as measured by rates of adverse events and serious adverse events, was comparable to both tofacitinib and baricitinib.
For each of these JAK inhibitors versus placebo, Asian ethnicity was associated with a positive effect on multiple efficacy outcomes.

DIGITAL FEATURES

This article is published with digital features, including summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13626134.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized primarily by inflammation of the joint synovial membranes, but it can also manifest as vascular, bone, metabolic, and psychological disorders [1, 2]. As the goal of RA treatment is to achieve sustained remission or low disease activity (LDA), disease-modifying antirheumatic drugs (DMARDs) form the backbone of treatment regimens [3]. The recommended first-line therapies are conventional synthetic DMARDs (csDMARDs), primarily methotrexate (MTX); for patients who do not achieve sustained remission or LDA after 6 months, the csDMARD can be switched, or used in combination with a biologic DMARD or a targeted synthetic DMARD (tsDMARD) [3, 4].

Janus kinase (JAK) inhibitors are tsDMARDs that target the JAK family of tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2) [5]. JAKs transduce inflammatory cytokine signals from the cell membrane to the nucleus and are consequently implicated in the pathogenesis of RA [5]. At the time of this research, JAK inhibitors licensed for use (in any country) were tofacitinib [6], baricitinib [6], and peficitinib [7]; more recently, upadacitinib has also received approval [8].

Peficitinib (Smyraf®) is a pan-JAK inhibitor [7] that has demonstrated efficacy in phase 3 trials in Asia [9, 10], with a similar safety profile to other JAK inhibitors [7, 11]. It is approved for clinical use in Japan, Korea, and Taiwan, and is in late-stage clinical development in other Asian countries [7, 12, 13]. Tofacitinib (Xeljanz®) is an inhibitor of the JAK family that preferentially inhibits JAK1 and/or JAK3 over JAK2 [6, 14], while baricitinib (Olumiant®) is an inhibitor of JAK1 and JAK2 [15]. Both tofacitinib and baricitinib have shown efficacy and

tolerability in global phase 3 trials and are licensed for use in multiple countries worldwide [16, 17].

There is a lack of head-to-head clinical trials between currently available JAK inhibitors. Some indirect comparisons between JAK inhibitors [18–26], or between different peficitinib doses [27], have been reported, but these included only a restricted selection of efficacy and safety outcomes and/or did not investigate between-study heterogeneity. The aim of our research was to indirectly compare peficitinib versus tofacitinib and baricitinib for the treatment of patients with RA, over a broad range of clinical efficacy, structural, and safety outcomes.

METHODS

Search Strategy and Selection Criteria

A systematic literature review was conducted on February 12, 2019, to identify randomized controlled trials (RCTs) assessing the efficacy and/or safety of peficitinib, tofacitinib, or baricitinib in patient populations with RA and a history of DMARD use (Fig. 1). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) consensus was followed for reporting results [28]. Databases included were MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov trial registry. The archives of the American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (now the Association of Rheumatology Professionals) Annual Meetings were also searched (from inception via Ovid, with an additional manual search to capture the 2018 meeting records).

RCTs with a parallel design and comparable follow-up period were included; real-world studies, letters, comments, case reports, editorials, in vitro or animal studies, and systematic reviews were excluded. Also excluded from the database search were conference abstracts prior to 2016 and studies after completion of phase 3. No other restrictions on language, date or geographical scope were applied. In addition to information available in the public domain, clinical study reports from peficitinib trials were obtained to supplement any missing information. Searches were conducted according to the Participants, Interventions, Comparisons, Outcome, Study design (PICOS) statement [28], and a list of search terms used is provided in Supplementary file 1.

Following the identification of potential publications to be included, they were assessed to ascertain if multiple articles related to the same study; any systematic reviews identified from the searches were retrieved and their list of references screened for all potential sources of evidence. Duplicate results were removed; studies on DMARD-naïve patients were also excluded at this stage. Two independent reviewers conducted the study screening and identification. Any disagreements were resolved through discussion with a third reviewer. The methodological quality of the included studies was assessed using the Cochrane risk of bias tool [29]. Data extraction was conducted by one reviewer and validated by a second reviewer.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Interventions and Outcomes

The interventions studied were peficitinib (100 mg once daily, 150 mg once daily; as monotherapy or in combination with MTX); tofacitinib (5 mg twice daily, 11 mg once daily; as monotherapy or in combination with MTX); and baricitinib (2 mg once daily, 4 mg once daily; as monotherapy or in combination with MTX). Only interventions approved for clinical use were eligible and tofacitinib 10 mg twice daily was thus excluded from the network, given that this dose is not recommended for use in patients with RA [30, 31]. For studies where MTX was used concomitantly with JAK inhibitors, this requirement was applied across all treatment arms, including those with placebo comparators.

The following efficacy outcomes were analyzed for weeks 12 and 24 timepoints:

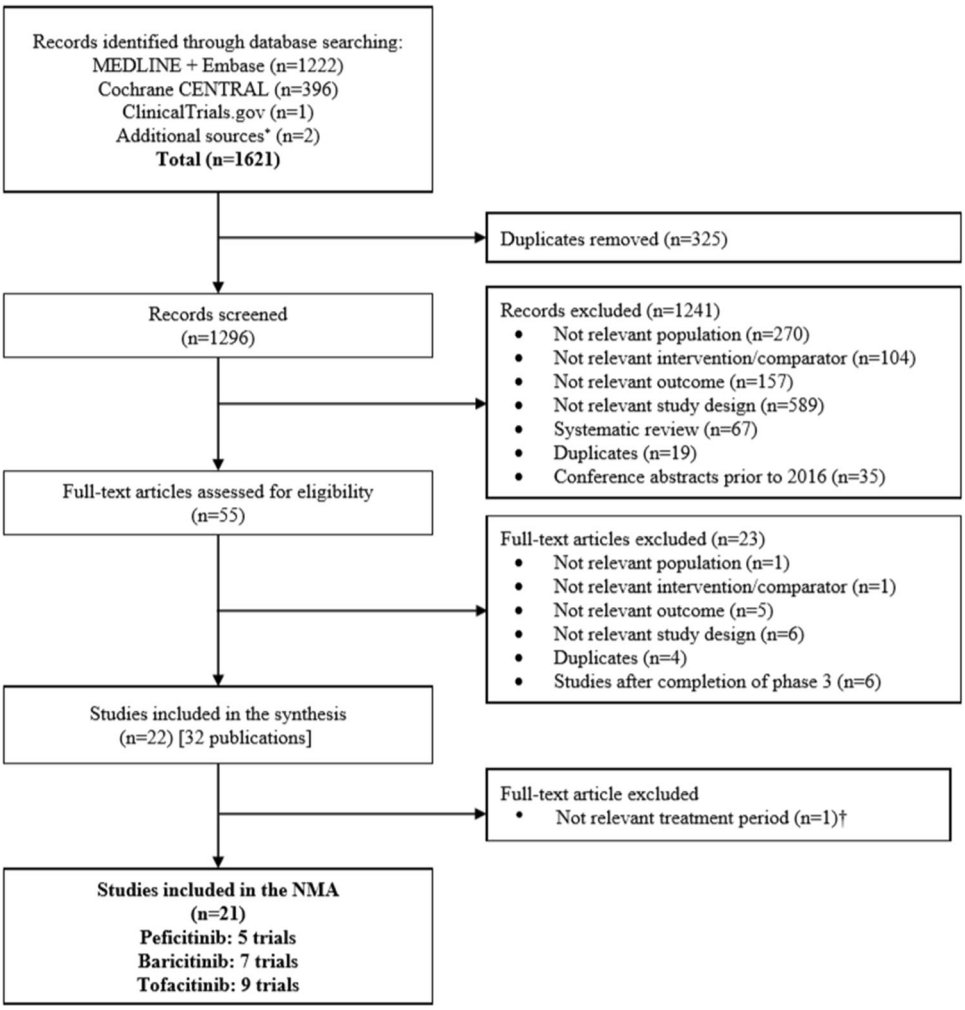

Fig. 1 Study selection flow chart. * Conference abstracts submitted to 2018 American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting in Chicago (https://acrabstracts.org/meetings/2018-acr-arhp-annual-meeting/). † The phase 2a study of tofacitinib by Kremer JM et al. *Arthritis Rheum* 2009 was omitted from the NMA and NMR due to its 6-week treatment period. *Cochrane CENTRAL* the Cochrane Central Register of Controlled Trials, *NMA* network meta-analysis, *NMR* network meta-regression

percentage of patients with ACR20/50/70 response; 28-joint disease activity score using C-reactive protein (DAS28-CRP) and using erythrocyte sedimentation rate (DAS28-ESR); the percentage of patients achieving DAS28-CRP/-ESR < 2.6 and ≤ 3.2; change from baseline in van der Heijde-modified total Sharp score (mTSS); percentage of patients with change from baseline in mTSS ≤ 0.5; Simplified Disease Activity Index (SDAI) score; and percentage of patients with SDAI ≤ 3.3. Safety outcomes analyzed were the overall incidence of adverse events (AEs) and incidence of serious adverse events (SAEs). Where available, data for the intention-to-treat (ITT) population were preferred over other analysis sets.

Data Analysis

An indirect treatment comparison between peficitinib and baricitinib or tofacitinib was conducted using a Bayesian network meta-analysis (NMA) plus a network meta-regression (NMR) to test the robustness of data after

adjusting for between-trial differences in baseline characteristics, in accordance with guidance from The UK National Institute for Health and Care Excellence (NICE) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [32–35].

Network Meta-Analysis

Clinical data were pooled using both fixed- and random-effects models (Supplementary file 2). Studies with a follow-up of 9–15 weeks were pooled together to define a 12-week network; similarly, studies with a follow-up of 20–-30 weeks were pooled together to define a 24-week network. For studies that included patients initially assigned to placebo and then switched to active treatment, only the period prior to switching was included.

For binary outcomes (expressed as the odds of an ACR20/50/70 response; remission as defined by DAS28-CRP/-ESR < 2.6 and SDAI ≤ 3.3; LDA as defined by DAS28-CRP/-ESR ≤ 3.2; and experiencing an AE or SAE), between-treatment differences were compared using posterior medians of odds ratios (OR) with 95% credibility intervals (CrI). For continuous variables (changes from baseline in DAS28-CRP/-ESR, SDAI and mTSS), posterior medians of between-treatment differences with 95% CrI were reported. The surface under the cumulative ranking curve (SUCRA) was calculated for each outcome and treatment.

Network Meta-Regression

An NMR was conducted to assess the impact of between-study heterogeneity on the magnitude of the relative effect versus the comparator arm, in accordance with the NICE Decision Support Unit guidelines (Supplementary file 3) [33]. The potential covariates investigated were the mean percentage of patients receiving concomitant MTX and the mean percentage of Asian patients, in each study (Table 1). For outcomes with a confirmed interaction between percentage of patients receiving MTX and magnitude of the effect, the mean dose of MTX in each study was also tested as a covariate. NMA models were preferred over NMR models unless the deviance information criterion (DIC) for the NMR model was lower by ≥ 5 points, indicating a meaningfully better fit.

RESULTS

Study Screening and Inclusion

A total of 1296 unduplicated records were identified (Fig. 1). Full-text analysis was conducted for 55 articles, and 22 RCTs (from 32 publications) were included in an initial synthesis. Of these, one study of tofacitinib (Kremer 2009) [36] was excluded as the treatment period was only 6 weeks. The remaining 21 trials (five peficitinib, seven baricitinib, and nine tofacitinib) had assessed JAK inhibitors for ≥ 12 weeks, reported relevant outcomes, and were included in the meta-analysis (Table 1). No RCTs assessing tofacitinib 11 mg once daily were identified.

The included studies were published between 2011 and 2019, with the number of patients per study ranging from 55 to 975; the total number of patients included in the NMA was 6542 (Table 1). The network of studies included in efficacy and safety comparisons is given in Fig. 2. For all included studies, the risk of bias in relation to method of treatment allocation and outcome reporting was judged to be low to unclear across all domains (Supplementary file 4).

NMA Results

All evaluable efficacy outcomes were significantly improved with both peficitinib 100 and 150 mg compared with placebo (Tables 2 and 3; Supplementary file 5). At 12 weeks, all evaluable efficacy outcomes were comparable or improved with peficitinib 150 mg versus baricitinib 2 or 4 mg and tofacitinib 5 mg (Table 2; Supplementary file 5). The efficacy of peficitinib 150 mg was significantly improved versus tofacitinib 5 mg for the proportion of patients achieving DAS28-ESR ≤ 3.2 (OR [95% CrI] 2.46 [1.10, 5.58]); versus baricitinib 2 mg regarding ACR50 response (OR [95% CrI] 1.63 [1.04,

Table 1 Summary of studies included in the NMA

Author, year	Intervention/comparator	Number of patients per treatment arm	Total number of patients*	Patients receiving concomitant MTX*		Number of Asian patients*	
				Number for each study, *n* (%)	Weighted mean across studies, %	Number for each study, *n* (%)	Weighted mean across studies, %
Trials assessing peficitinib					66.7%		70.9%
Takeuchi, 2016 [45]	PEF 100 mg (QD)	55	169	0		169 (100.0)	
	PEF 150 mg (QD)	58					
	PBO	56					
Kivitz, 2017 [43]	PEF 100 mg (QD)	84	234	234 (100.0)		0	
	PEF 150 mg (QD)	78					
	PBO	72					
Tanaka, 2019 [9]	PEF 100 mg (QD)	104	307	182 (59.3)		307 (100.0)	
	PEF 150 mg (QD)	102					
	PBO	101					
Takeuchi, 2019 [10]	PEF 100 mg (QD)	174	518	518 (100.0)		518 (100.0)	
	PEF 150 mg (QD)	174					
	PBO	170					
Genovese, 2017 [44]	PEF 100 mg (QD)	58	173	0		0	
	PEF 150 mg (QD)	64					
	PBO	51					

Table 1 continued

Author, year	Intervention/comparator	Number of patients per treatment arm	Total number of patients*	Patients receiving concomitant MTX*		Number of Asian patients*	
				Number for each study, *n* (%)	Weighted mean across studies, %	Number for each study, *n* (%)	Weighted mean across studies, %
Trials assessing tofacitinib					70.7%		25.5%
Kremer, 2009 [36] (omitted from NMA and NMR due to 6-week treatment period)	TOF 5 mg (BID)	61	126				
	PBO	65					
Tanaka, 2011 [52]	TOF 5 mg (BID)	27	55	55 (100.0)		55 (100.0)	
	PBO	28					
van Vollenhoven, 2012 (ORAL Standard) [53]	TOF 5 mg (BID)	204	312	312 (100.0)		(12.4)[†]	
	PBO to TOF 5 mg (BID)	56					
	PBO to TOF 10 mg (BID)	52					
Fleischmann, 2012 (phase 2b) [54]	TOF 5 mg (BID)	49	108	0		12 (11.1)	
	PBO	59					
Kremer, 2012 [55]	TOF 5 mg (BID)	71	140	140 (100.0)		0	
	PBO	69					
Fleischmann, 2012 (Oral Solo) [56]	TOF 5 mg (BID)	243	365	0		(15.2%)[‡‖]	
	PBO	122					
Burmester, 2013 (ORAL Step) [57]	TOF 5 mg (BID)	133	265	265 (100.0)		(5.6%)[§]	
	PBO	132					
Kremer, 2013 (ORAL Sync) [58]	TOF 5 mg (BID)	315	474	375 (79.1)		(34.6%)[†]	
	PBO to TOF 5 mg (BID)	79					
	PBO to TOF 10 mg (BID)	80					
van der Heijde, 2013 (ORAL Scan) [41]	TOF 5 mg (BID)	321	481	481 (100.0)		(29.9%)[#]	
	PBO to TOF 5 mg (BID)	81					
	PBO to TOF 10 mg (BID)	79					
Tanaka, 2015 [59]	TOF 5 mg (BID)	52	104	0		104 (100.0)	
	PBO	52					

Table 1 continued

Author, year	Intervention/comparator	Number of patients per treatment arm	Total number of patients*	Patients receiving concomitant MTX*		Number of Asian patients*	
				Number for each study, *n* (%)	Weighted mean across studies, %	Number for each study, *n* (%)	Weighted mean across studies, %
Trials assessing baricitinib					90.4%		27.8%
Keystone, 2015 [60]	BAR 2 mg (QD)	52	202	201 (99.5)		(14.3)‡ ¶	
	BAR 4 mg (QD)	52					
	PBO	98					
Tanaka, 2016 [61]	BAR 2 mg (QD)	24	97	97 (100.0)		97 (100.0)	
	BAR 4 mg (QD)	24					
	PBO	49					
Genovese, 2016 (RA-BEACON) [62]	BAR 2 mg (QD)	174	527	434 (82.3)		30 (5.7)	
	BAR 4 mg (QD)	177					
	PBO	176					
Taylor, 2017 (RA-BEAM) [63]	BAR 4 mg (QD)	487	975	975 (100.0)		282 (28.9)	
	PBO	488					
Dougados, 2017 (RA-BUILD) [64]	BAR 2 mg (QD)	229	684	512 (75.0)		120 (17.5)	
	BAR 4 mg (QD)	227					
	PBO	228					
Incyte Corporation, 2018 (NCT00902486) [37]**	BAR 4 mg (QD)	31	62	Not reported		0	
	PBO	31					
Eli Lilly and Company, 2019 (NCT02265705) [65] (RA-BALANCE)	BAR 4 mg (QD)	145	290	290 (100.0)		231 (79.7)	
	PBO	145					

BAR baricitinib, *BID* twice daily, *MTX* methotrexate, *NMA* network meta-analysis, *NMR* network meta-regression, *PBO* placebo, *PEF* peficitinib, *QD* once daily, *TOF* tofacitinib. Weighted means have been calculated unless otherwise stated

* For treatment arms included in NMA/NMR only

† Estimated by calculating the proportion of Asian sites as a percentage of sites designated 'rest of world', which was then used to estimate the number of Asian patients for the included treatment arms

‡ Exact numbers of Asian patients were not provided by treatment arm; percentage therefore calculated using total number of Asian patients across all treatment arms for study, including treatment arms not analyzed as part of the NMA and NMR

‖ Includes Russian Federation

§ Calculated as the proportion of Asian locations among all study centers *not* based in North America or Europe (46.7%), multiplied by the percentage of patients not in North America or Europe (12%)

Based on the proportion of study sites in Asia

¶ Based on patients recruited in India

** Study excluded from NMR adjusting for proportion of patients receiving MTX

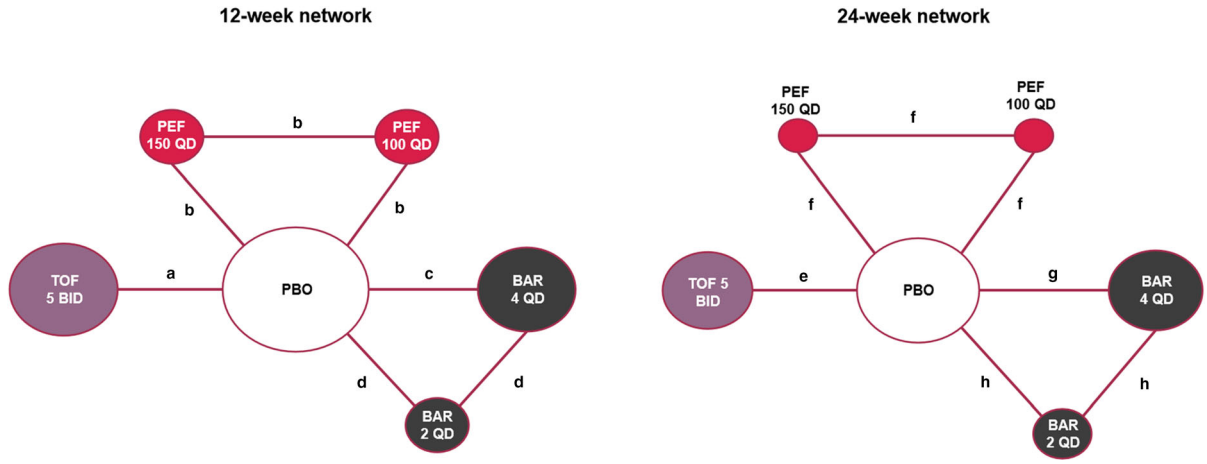

Fig. 2 Network of eligible comparisons for efficacy and safety of JAK inhibitors for RA. **a** Tanaka, 2011; van Vollenhoven, 2012; Fleischmann, 2012 (ph 2b); Kremer, 2012; Fleischmann, 2012 (Oral Solo); Burmester, 2013; van der Heijde, 2013; Tanaka, 2015. **b** Takeuchi, 2016; Kivitz, 2017; Tanaka, 2019; Takeuchi, 2019; Genovese, 2017. **c** Keystone, 2015; Tanaka, 2016; Genovese, 2016; Taylor, 2017; Dougados, 2017; Incyte Co., 2018; Eli Lilly and Co., 2019. **d** Keystone, 2015; Tanaka, 2016; Genovese, 2016; Dougados, 2017. **e** Fleischmann, 2012 (ph 2b); van Vollenhoven, 2012; Kremer, 2012; Kremer, 2013; van der Heijde, 2013. **f** Takeuchi, 2019. **g** Genovese, 2016; Taylor, 2017; Dougados, 2017; Eli Lilly and Co., 2019. **h** Genovese, 2016; Dougados, 2017. The size of each treatment node is proportional to the number of randomized patients, assumes all studies are included; the number of patients may differ for specific outcomes. *BAR* baricitinib, *BID* twice daily, *JAK* Janus kinase, *PBO* placebo, *PEF* peficitinib, *QD* once daily, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *TOF* tofacitinib

2.58]); and versus baricitinib 2 and 4 mg for reductions in SDAI score (OR [95% CrI] – 7.02 [– 9.76, – 4.32] and – 4.48 [– 6.97, – 1.98], respectively), achievement of SDAI ≤ 3.3 (OR [95% CrI] 7.79 [1.56, 115.30] and 6.42 [1.34, 92.81], respectively), achievement of DAS28-CRP ≤ 3.2 (OR [95% CrI] 2.94 [1.83, 4.79] and 2.02 [1.31, 3.18], respectively), and achievement of DAS28-ESR ≤ 3.2 (OR [95% CrI] 3.07 [1.59, 6.24] and 2.42 [1.31, 4.77], respectively) (Table 2; Supplementary file 5). At 12 weeks, peficitinib 100 mg was comparable to baricitinib 2 or 4 mg and tofacitinib 5 mg for almost all efficacy outcomes analyzed; peficitinib 100 mg provided significant improvement versus baricitinib 2 mg for reductions in SDAI score (OR [95% CrI] – 2.82 [– 5.58, – 0.08]) and the proportion of patients achieving DAS-CRP ≤ 3.2 (OR [95% CrI] 1.96 [1.22, 3.21]) (Table 3; Supplementary file 5). SUCRA rankings indicated that patients receiving peficitinib 150 mg were the most likely to achieve ACR20 or ACR50 response at 12 weeks, followed by tofacitinib 5 mg, baricitinib 4 mg, peficitinib 100 mg, baricitinib 2 mg, and placebo (Supplementary file 5). However, for ACR70 response at 12 weeks, baricitinib 2 and 4 mg were ranked above peficitinib 150 mg (Supplementary file 5).

At 24 weeks, all efficacy outcomes were comparable or improved with either peficitinib 150 or 100 mg versus baricitinib 2 or 4 mg and tofacitinib 5 mg (Tables 2 and 3; Supplementary file 6). ACR20 response, ACR50 response, and change from baseline in mTSS were improved with either peficitinib dose compared with baricitinib 2 or 4 mg and tofacitinib 5 mg (Tables 2 and 3; Supplementary file 6). Peficitinib 100 or 150 mg also provided significant improvement over tofacitinib 5 mg for change in DAS28-CRP scores and over baricitinib 2 mg for achievement of DAS28-CRP ≤ 2.6 (Tables 2 and 3; Supplementary file 6). Change from baseline in DAS28-CRP scores and achievement of mTSS ≤ 0.5 were also significantly improved with peficitinib 150 mg, but not peficitinib

Table 2 NMA results for relative efficacy and safety of peficitinib 150 mg QD versus comparator

Endpoint	Results for PEF 150 mg QD									
	At 12 weeks					At 24 weeks				
	vs. PBO	vs. PEF 100 mg QD	vs. BAR 2 mg QD	vs. BAR 4 mg QD	vs. TOF 5 mg BID	vs. PBO	vs. PEF 100 mg QD	vs. BAR 2 mg QD	vs. BAR 4 mg QD	vs. TOF 5 mg BID
ACR20	++	○	○	○	○	++	○	++	++	++
ACR50	++	++	++	○	○	++	○	++	++	++
ACR70	++	○	○	○	○	++	++	++	++	○
DAS28-CRP	++	○	○	○	○	++	○	++	○	++
DAS28-CRP $\leq$ 2.6	++	○	○	○	○	++	○	++	○	○
DAS28-CRP $\leq$ 3.2	++	++	++	++	○	n/a	n/a	n/a	n/a	n/a
DAS28-ESR	++	○	○	○	○	n/a	n/a	n/a	n/a	n/a
DAS28-ESR $\leq$ 2.6	++	○	○	○	○	n/a	n/a	n/a	n/a	n/a
DAS28-ESR $\leq$ 3.2	++	++	++	++	++	n/a	n/a	n/a	n/a	n/a
SDAI	++	++	++	++	n/a	n/a	n/a	n/a	n/a	n/a
SDAI $\leq$ 3.3	++	○	++	++	○	++	○	○	○	n/a
mTSS	n/a	n/a	n/a	n/a	n/a	++	○	++	++	++
mTSS $\leq$ 0.5	n/a	n/a	n/a	n/a	n/a	++	○	++	○	○
AEs	○	○	○	○	○	n/a	n/a	n/a	n/a	n/a

Table 2 continued

Endpoint	Results for PEF 150 mg QD											
	At 12 weeks					At 24 weeks						
	vs. PBO	vs. PEF 100 mg QD	vs. BAR 2 mg QD	vs. BAR 4 mg QD	vs. TOF 5 mg BID	vs. PBO	vs. PEF 100 mg QD	vs. BAR 2 mg QD	vs. BAR 4 mg QD	vs. TOF 5 mg BID
SAEs	○	○	○	○	○	n/a	n/a	n/a	n/a	n/a

ACR American College of Rheumatology, *AEs* adverse events, *BAR* baricitinib, *BID* twice daily, *CRP* C-reactive protein, *DAS28* disease activity score in 28 joints, *ESR* erythrocyte sedimentation rate, *n/a* analysis not feasible, *mTSS* modified total Sharp score, *NMA* network meta-analysis, *PEF* peficitinib, *PBO* placebo, *QD* once daily, *SAEs* serious adverse events, *SDAI* Simplified Disease Activity Index, *TOF* tofacitinib

++ Favors PEF 150 mg QD, significant

n/a No data/analysis not feasible

○ No significant difference

100 mg, over baricitinib 2 mg (Tables 2 and 3; Supplementary file 6). The highest SUCRA ranking for ACR20 and ACR50 responses at 24 weeks was achieved by peficitinib 150 mg, followed by peficitinib 100 mg, baricitinib 4 mg, tofacitinib 5 mg, baricitinib 2 mg, and placebo (Supplementary file 6). This ranking differed for ACR70 at 24 weeks, for which tofacitinib 5 mg ranked higher than did peficitinib 100 mg (Supplementary file 6). It was not possible to evaluate change from baseline in SDAI at 24 weeks due to a scarcity of data.

For safety outcomes, both peficitinib doses were comparable to placebo, baricitinib 2 or 4 mg, and tofacitinib 5 mg regarding the risk of AEs and SAEs at 12 weeks (Tables 2 and 3; Supplementary file 5). Due to a lack of data, it was not possible to evaluate risk of AEs and SAEs at 24 weeks.

NMA results by study are presented in Supplementary files 5 and 6.

NMR Results

Adjustment for Percentage of Patients Receiving MTX

Of the 21 studies included in the NMA, one study (Incyte Corporation 2018 [37]) was excluded from the estimation of the mean percentage of patients receiving concomitant MTX as it did not report this information (Table 1). Across the remaining studies, the weighted mean percentage of patients receiving MTX was 67, 67, and 90% for studies of peficitinib, tofacitinib, and baricitinib, respectively (Table 1). For all efficacy and safety analyses, there was no evidence for interaction between the percentage of patients receiving MTX and the magnitude of the treatment effect (Table 4). The analysis adjusting for mean MTX dose was therefore not performed.

The results of the NMA and NMR were consistent except for the comparisons of peficitinib 150 mg versus tofacitinib for achievement of DAS28-ESR $\leq$ 3.2 at week 12; peficitinib 150 mg versus baricitinib 2 mg for achievement of DAS28-CRP $\leq$ 2.6 at week 24; and peficitinib 100 mg versus baricitinib 2 mg for achievement of DAS28-CRP $\leq$ 2.6 at week 24 (Supplementary

Table 3 NMA results for relative efficacy and safety of peficitinib 100 mg QD versus comparator

Endpoint	Results for PEF 100 mg QD									
	At 12 weeks					At 24 weeks				
	vs. PBO	vs. PEF 150 mg QD	vs. BAR 2 mg QD	vs. BAR 4 mg QD	vs. TOF 5 mg BID	vs. PBO	vs. PEF 150 mg QD	vs. BAR 2 mg QD	vs. BAR 4 mg QD	vs. TOF 5 mg BID
ACR20	++	○	○	○	○	++	○	++	++	++
ACR50	++	−−	○	○	○	++	○	++	++	++
ACR70	++	○	○	○	○	++	−−	○	○	○
DAS28-CRP	++	○	○	○	○	++	○	○	○	++
DAS28-CRP $\leq$ 2.6	++	○	○	○	○	++	○	++	○	○
DAS28-CRP $\leq$ 3.2	++	−−	++	○	○	n/a	n/a	n/a	n/a	n/a
DAS28-ESR	++	○	○	○	○	n/a	n/a	n/a	n/a	n/a
DAS28-ESR $\leq$ 2.6	++	○	○	○	○	n/a	n/a	n/a	n/a	n/a
DAS28-ESR $\leq$ 3.2	++	−−	○	○	○	n/a	n/a	n/a	n/a	n/a
SDAI	++	−−	++	○	n/a	n/a	n/a	n/a	n/a	n/a
SDAI $\leq$ 3.3	++	○	○	○	○	++	○	○	○	n/a
mTSS	n/a	n/a	n/a	n/a	n/a	++	○	++	++	++
mTSS $\leq$ 0.5	n/a	n/a	n/a	n/a	n/a	++	○	○	○	○
AEs	○	○	○	○	○	n/a	n/a	n/a	n/a	n/a
SAEs	○	○	○	○	○	n/a	n/a	n/a	n/a	n/a

ACR American College of Rheumatology, *AEs* adverse events, *BAR* baricitinib, *BID* twice daily, *CRP* C-reactive protein, *DAS28* disease activity score in 28 joints, *ESR* erythrocyte sedimentation rate, *n/a* analysis not feasible, *mTSS* modified total Sharp score, *NMA* network meta-analysis, *PEF* peficitinib, *PBO* placebo, *QD* once daily, *SAEs* serious adverse events, *SDAI* Simplified Disease Activity Index, *TOF* tofacitinib

++ Favors PEF 100 mg QD, significant; −− favors comparator, significant

○ No significant difference; *n/a* no data/analysis not feasible

Table 4 Effect on outcomes of the percentage of patients receiving MTX

Endpoint	NMR adjusted for covariates							
	At 12 weeks				At 24 weeks			
	No. RCTs	% patients on MTX	Covariate effect*, median (95% CrI)	Inference (model)	No. RCTs	% patients on MTX	Covariate effect*, median (95% CrI)	Inference (model)
ACR20	20	69.8	− 0.043 (− 0.116; 0.029)	NS (RE)	10	83.6	0.050 (− 0.025; 0.125)	NS (FE)
ACR50	20	69.8	− 0.003 (− 0.051; 0.042)	NS (FE)	10	83.6	0.025 (− 0.067; 0.115)	NS (FE)
ACR70	20	69.8	0.009 (− 0.086; 0.101)	NS (RE)	10	83.6	0.073 (− 0.055; 0.196)	NS (FE)
DAS28-CRP	17	65.7	− 0.025 (− 0.092; 0.039)	NS (RE)	7	79.6	0.055 (− 0.054; 0.175)	NS (RE)
DAS28-CRP $\leq$ 2.6	13	70.5	0.023 (− 0.081; 0.123)	NS (RE)	6	92.9	0.086 (− 0.141; 0.316)	NS (FE)
DAS28-CRP $\leq$ 3.2	11	74.2	0.031 (− 0.037; 0.098)	NS (FE)	n/a	n/a	n/a	n/a
DAS28-ESR	15	66.4	− 0.031 (− 0.128; 0.064)	NS (RE)	n/a	n/a	n/a	n/a
DAS28-ESR $\leq$ 2.6	14	56.8	0.074 (− 0.037; 0.187)	NS (FE)	n/a	n/a	n/a	n/a
DAS28-ESR $\leq$ 3.2	11	74.2	0.039 (− 0.058; 0.136)	NS (FE)	n/a	n/a	n/a	n/a
SDAI	6	86.1	0.333 (− 0.654; 1.326)	NS (FE)	n/a	n/a	n/a	n/a
SDAI $\leq$ 3.3	9	90.7	− 0.166 (− 0.675; 0.254)	NS (FE)	4	89.3	0.117 (− 0.262; 0.485)	NS (FE)
mTSS	n/a	n/a	n/a	n/a	4	93.7	0.039 (− 0.141; 0.221)	NS (FE)
mTSS $\leq$ 0.5	n/a	n/a	n/a	n/a	4	93.7	− 0.009 (− 0.262; 0.240)	NS (FE)
AEs	15	67.7	0.022 (− 0.014; 0.057)	NS (FE)	n/a	n/a	n/a	n/a
SAEs	15	67.7	0.093 (− 0.015; 0.203)	NS (FE)	n/a	n/a	n/a	n/a

ACR American College of Rheumatology, *AEs* adverse events, *CrI* credibility interval, *CRP* C-reactive protein, *DAS28* disease activity score in 28 joints, *ESR* erythrocyte sedimentation rate, *FE* fixed-effects, *n/a* analysis not feasible, *mTSS* modified total Sharp score, *MTX* methotrexate, *NMR* network meta-regression, *NS* covariate effect not statistically significant, *RCT* randomized controlled trial, *RE* random-effects, *SAEs* serious adverse events, *SDAI* Simplified Disease Activity Index

* Change in effect size relative to placebo, per 10% change in the proportion of patients receiving concomitant MTX

files 7 and 8). The NMA was preferred over the NMR for all efficacy and safety comparisons, taking into account model simplicity, DIC values, and the reduced number of studies included in the NMR (Supplementary file 9).

Adjustment for Percentage of Asian Patients

All 21 studies were included in the estimation of the mean percentage of Asian patients. The weighted mean percentage of Asian patients was 71, 23, and 28% for studies of peficitinib, tofacitinib, and baricitinib, respectively (Table 1). A relationship between the percentage of Asian patients and the magnitude of treatment effect was observed for ACR20/50/70 responses, achievement of DAS28-ESR $\leq$ 3.2, and change in SDAI at week 12; and ACR50 response and mean change in DAS28-CRP at week 24 (Table 5). For all other efficacy and safety outcomes, the percentage of Asian patients had no significant effect (Table 5).

For the majority of outcomes, the NMA model was preferred based on lower DIC values, with the exception of ACR20/50/70 responses at week 12 (Supplementary files 10–12). The NMR models for ACR50 response and change in DAS28-CRP at week 24 had numerically lower DIC values; however, the magnitude of the difference was not considered meaningful and the simpler NMA model was preferred for these outcomes (Supplementary files 10 and 11).

Following adjustment for the percentage of Asian patients, the results of the NMR indicated that changes from baseline in mTSS at week 24 were not significant for peficitinib 100 and 150 mg versus baricitinib 2 and 4 mg or tofacitinib (Supplementary files 10 and 11). When compared with placebo, only peficitinib 150 mg showed significant improvement for change from baseline in mTSS at week 24, after adjustment for the percentage of Asian patients (Supplementary files 10 and 11).

DISCUSSION

This NMA demonstrated that peficitinib (100 and 150 mg once daily) was comparable to, and in some cases provided significant improvement over, tofacitinib (5 mg twice daily) and baricitinib (2 or 4 mg once daily) for control of disease symptoms (as measured by ACR20/50/70 responses), reduction of inflammatory states (DAS28-CRP and -ESR scores), and reduction in the rate of disease progression (mTSS and SDAI). Based on SUCRA rankings, peficitinib 150 mg had the highest probability of being the best treatment in terms of ACR20 response at both 12 and 24 weeks in the populations studied. Notably, both doses of peficitinib were associated with significantly improved rates of ACR20/50 responses and reduction of change from baseline in mTSS after 24 weeks of treatment, compared with tofacitinib and baricitinib. However, between-treatment differences in the proportion of patients achieving changes from baseline in mTSS of $\leq$ 0.5 were not significant except for peficitinib 150 mg versus baricitinib 2 mg. Of note, as extended-release tofacitinib 11 mg once daily is approved for use in the USA, this dose of tofacitinib was considered eligible for inclusion in the NMA and NMR; however, no RCTs assessing this regimen were identified and tofacitinib 11 mg therefore could not be included in our comparisons. It should also be highlighted that our NMA results did not take into account between-trial differences in baseline characteristics, which were instead analyzed in our subsequent NMR.

Our findings are broadly consistent with a previously published NMA comparing JAK inhibitors as monotherapy, which found that peficitinib 150 mg had significantly greater odds of achieving an ACR20 response at 12 to 24 weeks versus tofacitinib 5 mg and baricitinib 4 mg [26]. In contrast, an NMA of JAK inhibitors in combination with DMARDs ranked tofacitinib 10 mg + MTX above peficitinib 150 mg + MTX for ACR20 response at 12 to 24 weeks; however, the between-treatment differences in ACR20 response rates did not reach significance in this study [25]. Moreover, in our NMR, ACR20 responses were comparable between peficitinib 150 mg versus tofacitinib 5 mg and baricitinib 2 or 4 mg after adjustment for the proportion of Asian patients.

Encouragingly, our results showed that rates of AEs and SAEs for both peficitinib 100 and 150 mg were comparable to other JAK inhibitors and to placebo. A number of other previous

Table 5 Effect on outcomes of the percentage of Asian patients

Endpoint	NMR adjusted for covariates							
	At 12 weeks				At 24 weeks			
	No. RCTs	% Asian patients	Covariate effect*, median (95% CrI)	Inference (model)	No. RCTs	% Asian patients	Covariate effect*, median (95% CrI)	Inference (model)
ACR20	**21**	**40.7**	**0.118 (0.081; 0.156)**	**S (FE)**	10	32.0	0.052 (− 0.024; 0.129)	NS (FE)
ACR50	**21**	**40.7**	**0.119 (0.072; 0.168)**	**S (FE)**	**10**	**32.0**	**0.095 (0.001; 0.194)**	**S (FE)**
ACR70	**21**	**40.7**	**0.153 (0.076; 0.237)**	**S (FE)**	10	32.0	0.040 (− 0.101; 0.200)	NS (FE)
DAS28-CRP	18	43.1	0.011 (− 0.046; 0.069)	NS (RE)	**7**	**25.1**	**− 0.206 (− 0.322; − 0.089)**	**S (FE)**
DAS28-CRP ≤ 2.6	13	43.6	− 0.067 (− 0.151; 0.013)	NS (FE)	6	38.7	− 0.073 (− 0.211; 0.079)	NS (FE)
DAS28-CRP ≤ 3.2	11	51.6	0.006 (− 0.072; 0.088)	NS (FE)	n/a	n/a	n/a	n/a
DAS28-ESR	16	35.1	− 0.006 (− 0.081; 0.070)	NS (RE)	n/a	n/a	n/a	n/a
DAS28-ESR ≤ 2.6	14	45.2	0.047 (− 0.075; 0.166)	NS (FE)	n/a	n/a	n/a	n/a
DAS28-ESR ≤ 3.2	**12**	**41.7**	**0.107 (0.002; 0.218)**	**S (FE)**	n/a	n/a	n/a	n/a
SDAI	**6**	**58.7**	**− 0.580 (− 1.117; − 0.040)**	**S (FE)**	n/a	n/a	n/a	n/a
SDAI ≤ 3.3	9	50.2	− 0.052 (− 0.213; 0.124)	NS (FE)	4	38.1	0.160 (− 0.351; 0.694)	NS (FE)
mTSS	n/a	n/a	n/a	n/a	4	44.1	0.082 (− 0.316; 0.493)	NS (FE)
mTSS ≤ 0.5	n/a	n/a	n/a	n/a	4	44.1	− 0.030 (− 0.572; 0.485)	NS (FE)
AEs	16	43.8	0.012 (− 0.027; 0.052)	NS (FE)	n/a	n/a	n/a	n/a

Table 5 continued

Endpoint	NMR adjusted for covariates							
	At 12 weeks				At 24 weeks			
	No. RCTs	% Asian patients	Covariate effect*, median (95% CrI)	Inference (model)	No. RCTs	% Asian patients	Covariate effect*, median (95% CrI)	Inference (model)
SAEs	15	46.7	0.000 (− 0.122; 0.116)	NS (FE)	n/a	n/a	n/a	n/a

ACR American College of Rheumatology, *AEs* adverse events, *CrI* credibility interval, *CRP* C-reactive protein, *DAS28* disease activity score in 28 joints, *ESR* erythrocyte sedimentation rate, *FE* fixed-effects, *n/a* analysis not feasible, *mTSS* modified total Sharp score, *NMR* network meta-regression, *NS* covariate effect not statistically significant, *RCT* randomized controlled trial, *RE* random-effects, *S* covariate effect statistically significant, *SAEs* serious adverse events, *SDAI* Simplified Disease Activity Index. Bold text indicates analyses with significant covariate effects

* Change in effect size relative to placebo, per 10% change in the proportion of Asian patients

analyses have also found the rate of SAEs to be not significantly different between peficitinib and tofacitinib [25], peficitinib and baricitinib [26], and between tofacitinib, baricitinib, and peficitinib versus placebo [19, 25, 26, 38, 39]; an exception was for tofacitinib 5 mg as monotherapy, which was associated with a significantly lower rate of SAEs versus peficitinib 100 mg, baricitinib 4 mg, and placebo [26]. It should also be highlighted that an increased rates of herpes zoster-related disease (which was not assessed in our study) has been observed with JAK inhibitor treatment [39, 40]. We note, however, that these NMAs are not directly comparable due to differences in included interventions, methodology, and patient populations.

According to our NMR analyses, there was no evidence of an interaction between MTX and any of the efficacy and safety outcomes assessed. However, Asian ethnicity was associated with a positive effect on ACR20/50/70 responses, change from baseline in SDAI score, and the proportion of patients achieving DAS28-ESR $\leq$ 3.2 at week 12; and ACR50 response and change from baseline in DAS28-CRP score at week 24. This positive effect was observed with peficitinib, tofacitinib, and baricitinib. A greater beneficial effect of JAK inhibitors versus placebo was observed in studies with a higher proportion of Asian patients.

A notable finding from the current NMA was that some efficacy outcomes were improved with peficitinib (100 and 150 mg once daily) compared with tofacitinib (5 mg twice daily) and baricitinib (2 or 4 mg once daily): after 24 weeks of treatment, these included ACR20 response, ACR50 response, and change from baseline in mTSS. This may be the result of the relatively higher proportion of Asian patients in the peficitinib clinical trials than in tofacitinib and baricitinib trials; due to the interaction between Asian ethnicity and the responses listed in the previous paragraph, the relative efficacy of peficitinib versus the other two JAK inhibitors was reduced once analyses were adjusted for the percentage of Asian patients. These results are consistent with data from previous trials, which showed that tofacitinib had greater efficacy in Asian patients than in

patients of other ethnicities, for unknown reasons [41, 42]. We have also observed that peficitinib performed better in clinical trials in patients in Asian countries [9, 10] compared with those in a global trial reported by Kivitz et al. [43], despite the fact that patients in all three trials had had an inadequate response to MTX, and also predominantly moderate-to-severe RA according to baseline DAS28 or other validated composite measures of disease activity [9, 10, 43]. On the other hand, the findings of the Kivitz et al. study could be attributed to the high placebo effect in the study population (44% of placebo-treated patients had an ACR20 response at 12 weeks); this effect also showed large variability depending on region, and sensitivity analyses including only European centers did indicate superiority of peficitinib over placebo [43]. Similarly, patients in the Genovese et al. trial also had a high ACR20 response rate with placebo treatment (22% at 12 weeks); despite this, ACR20 response rates at 12 weeks with peficitinib were significantly higher at 48–56% for the total study population [44]. These relatively high placebo responses in non-Asian patients contrast with the average ACR20 response rates at 12 weeks of 11–31% among Asian patients who received placebo, across the phase 2 and phase 3 trials [9, 10, 45]. Further investigations are needed to elucidate the reasons underlying the interethnic differences observed in these trials.

Our research fills an important gap in this area by including peficitinib, one of the more recently approved JAK inhibitors and available only in some East Asian countries, in an indirect comparison with the globally available products tofacitinib and baricitinib. Strengths of our NMA include the assessment of multiple efficacy outcomes at both week 12 and week 24 timepoints; the inclusion of both AEs and SAEs in the analysis; and its conduct in line with ISPOR and NICE guidelines. Furthermore, we conducted an NMR analysis to enable us to assess the impact of between-study heterogeneity, regarding both concomitant MTX use and Asian ethnicity, on our findings. One limitation of this NMA and NMR is that the number of studies assessing outcomes at 24 weeks was lower than the number assessing outcomes at 12 weeks; in particular, safety outcomes were assessed only for the week 12 timepoint, as safety data for the peficitinib phase 3 studies were available only at weeks 12 and 52 [9, 10] and no SDAI data were available for comparisons at week 24. Furthermore, the literature review identified studies published up to February 2019, which is when our analyses were conducted, and we recognize that more recent studies have been omitted. Additionally, we did not compare the risk of AEs of special interest in RA patient populations: namely, serious infections, herpes zoster-related disease, and malignancy. Studies also allowed for cross-over from placebo to JAK inhibitor after 12–24 weeks owing to lack of efficacy and the ethical issue of long-term placebo treatment. Different methods were often adopted to account for missing data arising from either between-treatment cross-over and/or loss to follow-up. With regard to remission and LDA, our analyses defined these outcomes as scores of < 2.6 and ≤ 3.2, respectively, for both DAS28-CRP and DAS28-ESR; however, DAS28-CRP has been shown not to be interchangeable with DAS28-ESR based on the same cut-off thresholds [46].

The patients included in our analyses were predominantly those with a history of prior DMARD use, and our analyses may not extrapolate to patients who are DMARD-naïve. However, given current EULAR (European League Against Rheumatism) and APLAR guidelines [4, 47], patients who have had prior DMARD use are likely to be the target patient population for JAK inhibitors. For the NMR, covariate values (the percentage of patients receiving concomitant MTX and the percentage of Asian patients) were not adequately reported across all identified studies; this was particularly the case regarding the proportions of Asian patients and, for many RCTs, these values were estimated based on the location of study centers, which increases uncertainty of the outcomes. Furthermore, the high proportion of Asian patients in peficitinib studies may have adversely affected the NMR adjustment.

The analysis of mTSS at 24 weeks was based on only four trials, and the mean change from baseline observed in the placebo arms was inconsistent across the studies (peficitinib: 3.4; tofacitinib: 0.47; baricitinib: 0.7–0.8),

indicating noticeable between-trial heterogeneity. A further challenge to interpretation of the mTSS findings is posed by differences between studies in baseline MTX dose, particularly as the dose of MTX tends to be lower in Japan than in other countries [47, 48], and our analysis did not take into account the average dose that patients received in each study. mTSS scores also tend to be higher in Japanese patients than in other populations [49–51].

CONCLUSIONS

In conclusion, the results of this study suggest that peficitinib had comparable efficacy versus both tofacitinib and baricitinib for a majority of the outcomes assessed, and no notable differences in safety assessments were observed. Further analyses are required to better characterize efficacy of JAK inhibitors in different ethnicities, which may require going beyond RCTs.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with

human participants or animals performed by any of the authors.

Data Availability. Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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