Efficacy and safety of jakinibs in rheumatoid arthritis: a systematic review and meta-analysis

Yufeng Yin 1 · Mengru Liu 2 · Erye Zhou 1 · Xin Chang 1 · Michun He 1 · Mingjun Wang 1 · Jian Wu 1

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Abstract

Objectives To assess the efficacy and safety of jakinibs for the treatment of active rheumatoid arthritis (RA) in patients with an inadequate response or intolerance to conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs).

Methods A systematic search was conducted in PubMed, Embase, and the Cochrane Library. Randomized placebo-controlled trials (RCTs) of jakinibs in RA patients were eligible. The effective outcome was RA improvement to reach an American College of Rheumatology 20%/50%/70% (ACR20/50/70) response rate at weeks 12 and 24 after treatment. The safety outcomes included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to adverse events, infections, and serious infections.

Results Twenty-eight randomized, double-blind, controlled trials including 14,500 patients were included. At both weeks 12 and 24, the pooled analysis suggested effective treatment with jakinibs, represented as an increased clinical response of ACR20, ACR50, and ACR70. Subgroup analysis based on different types of jakinibs demonstrated that only peficitinib treatment had no impact on the clinical response of ACR50 or ACR70 at week 12. Jakinibs were associated with an increased incidence of infections at week 12 and TEAEs and infections at week 24. No increase in the risk of SAEs, discontinuations due to adverse events, or serious infections was observed in comparisons between treatment with jakinibs and treatment with placebo in these patients.

Conclusions Jakinibs are efficacious and well tolerated in RA patients up to 24 weeks, although they are associated with an increased risk of infectious complications.

Keywords Efficacy · Jakinib · Meta-analysis · Rheumatoid arthritis · Safety

Introduction

Rheumatoid arthritis (RA) is a systemic, chronic, and progressive inflammatory disease with a prevalence of approximately 5 per 1000 adults worldwide [1]. RA primarily affects peripheral joints, leading to synovitis as well as cartilage damage and bone erosion, leading to increased disability and mortality for affected patients [2]. Regarding the treat-to-target strategy, the primary goal of RA treatment is to achieve and maintain rapid remission or at least low disease activity if remission is not possible [3]. RA treatment is based on conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), particularly the anchor drug methotrexate [3]. During the past 2 decades, various options, particularly biologic DMARDs (bDMARDs), such as tumor necrosis factor (TNF) inhibitors available for RA treatment, have been developed [4]. Biologics, as foreign proteins, induce immunogenicity, likely leading to an inadequate response or intolerability [5]. Current...
studies have demonstrated that an American College of Rheumatology 20% improvement criterion (ACR20) cannot be achieved in up to 40% of RA patients treated with TNF inhibitors in a long-term follow-up [6]. Additionally, the restricted conditions for storage and handling and the high acquisition cost significantly increase the economic burden and reduce patient compliance [7]. Therefore, more options should be explored with mechanisms of action that are different from those of the currently used csDMARDs and biologics.

The activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signal transduction pathway plays a pivotal role in the pathogenesis and progression of RA [8]. JAK inhibitors (jakinibs) are small-molecule drugs that interfere with the activation of JAK and then attenuate immune activation of the signaling pathway and production of proinflammatory cytokines [9]. The incorporation of jakinibs has changed the treatment landscape of RA and various other rheumatological conditions, such as systemic lupus erythematosus, giant cell arteritis, and autoinflammatory diseases [10, 11]. Numerous phase II and III clinical studies have shown that treatment with jakinibs, either in combination with csDMARDs or as monotherapy, is beneficial in reducing disease activity in RA patients with an inadequate response or intolerance to csDMARDs or biologics [12, 13]. Many meta-analyses have revealed that jakinibs are associated with increased clinical efficacy and manageable safety compared with biologics or placebo in a short-term follow-up period [14–16]. However, most of the previous studies focused on a single drug, particularly tofacitinib and baricitinib, which were approved early to treat active RA [13]. To our best knowledge, jakinibs have rarely been analyzed as an exclusive entity for their efficacy and safety in RA patients. Therefore, in the present study, we assessed the efficacy and safety of jakinibs in the treatment of these patients via quantitative meta-analysis of data from recently released randomized controlled trials (RCTs).

**Data sources and search strategy**

We performed an exhaustive search for studies evaluating the efficacy and safety of jakinibs in patients with active RA in bibliographic databases, including PubMed, EMBASE, and the Cochrane Library, from their inceptions to February 1, 2020. The papers were not restricted concerning the publication status or language. A combination of the following keywords was used: “rheumatoid arthritis,” “ra,” and “protein kinases inhibitor” and “janus kinase inhibitor,” “jak inhibitor,” and “jakinib.” The search was independently performed by two investigators (YY and ML), and discrepancies in the study selection were resolved by consensus. The search strategy is listed in online supplementary table S1. The references in the enrolled trials or meta-analyses were also screened manually to find relevant original studies.

**Study selection**

The relevant data from the RCTs comparing the efficacy and safety of jakinibs with those of a placebo or biologics in the treatment of active RA were potentially eligible for inclusion. We included studies fulfilling the following inclusion criteria: (1) studies with samples of RA patients aged >18 years with an inadequate response or intolerance to csDMARDs or biologics; (2) studies in which jakinibs (including baricitinib, decernotinib, filgotinib, peficitinib, tofacitinib, and upadacitinib) alone or in combination with csDMARDs were compared with a placebo or csDMARDs in RA treatment for a minimum duration of 12 weeks; and (3) studies providing data for assessing the clinical effects and adverse events of jakinibs. Exclusion criteria included a nonrandomized design and an unqualified article type (abstracts without full-text publication, case reports, and duplications with the same samples).

**Data extraction and quality assessment**

The full-text paper of all the RCTs that were potentially available for inclusion was viewed by two independent investigators (YY and ML). Disagreements at any stage of the data extraction process were resolved by consensus. The modified Jadad tool for randomized clinical trials was used to assess the quality of studies included in the meta-analysis [18]. Jadad contains two questions for randomization and masking and one question assessing the description of withdrawals and/or dropouts. Studies with no less than 3 points are ranked as high quality [18]. The following data were extracted from the RCTs: researcher names, publication year, trial name and phase, numbers of centers and randomized subjects, jakinib type, drug regimen, follow-up period, and outcomes for efficacy and safety. The efficacy outcomes included ACR20, ACR50, and ACR70. Data on adverse events, including

**Methods**

This systematic review and meta-analysis adhered to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the meta-analysis of interventional studies [17]. The authors declare that all supporting data are available within the article and/or supplementary materials. This study did not require ethical approval or informed consent because all the analyses were based on previously published data. The study protocol was prospectively registered at International Prospective Register of Systematic Reviews (PROSPERO) (registration ID: CRD42020188015).
treatment-emergent adverse events, serious adverse events, discontinuations due to adverse events, infections, and serious infections, were also collected to explore the safety of jakinibs for the treatment of RA patients.

Statistical and sensitivity analysis

The meta-analyses were performed using the Mantel-Haenszel random effects model to determine the weight given to each study. Comparisons were made between jakinibs and placebo or between jakinibs with DMARDs and placebo with DMARDs. The incidences of adverse events after treatment were also assessed for each study. This produced a weighted estimate of the odds ratio (OR) with a 95% confidence interval (95% CI), considering the different samples. The heterogeneity across studies was examined using the chi-squared ($\chi^2$) test and qualified by $I^2$ statistics, ranging from 0 to 100%, in which a larger value indicated increasing heterogeneity. The likelihood of publication bias was assessed graphically by generating a funnel plot. All statistical analyses were performed using RevMan statistical software version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and Stata/MP version 13.0 (StataCorp, College Station, TX, USA). Two-sided $P$ values of 0.05 were considered statistically significant.

Results

Literature search and study characteristics

The details of the search program in this study are shown in Fig. 1. In total, 5800 articles were retrieved from PubMed, Embase, and the Cochrane Library after the initial implementation of the search strategy, and 3581 remained after duplicates were removed. After screening the titles and abstracts, 308 articles remained. Ultimately, 28 studies with 14,500 randomized RA patients met the eligibility criteria of the meta-analysis. Among these studies, efficacy was evaluated after treatment with jakinibs, including baricitinib (5 trials) [19–23], decernotinib (2 trials) [24, 25], filgotinib (3 trials) [26–28], peficitinib (3 trials) [29–31], tofacitinib (10 trials) [32–41], and upadacitinib (5 trials) [42–46]. In these trials, most of the RA patients were treated with jakinib monotherapy or jakinibs in combination with DMARDs, particularly methotrexate, in the treatment arms and placebo with or without DMARDs in the control arms; patients received methotrexate monotherapy in the control arms in only one study [37]. All the patients had discontinued treatment with bDMARDs more than 4 weeks before randomization; patients with prior bDMARDs use

![Fig. 1 Flowchart of the study selection](image-url)
were excluded in 6 studies [19, 20, 22, 23, 43, 46]. The characteristics of the selected trials and Jadad scores are summarized in Table 1 and online supplementary table S2.

**Overall efficacy**

The efficacy outcomes for all the included studies are summarized in Table 2. Twenty-four trials with 10,923 patients (7885 RA patients treated with jakinibs and 3038 controls) assessed the efficacy of jakinibs in RA patients at week 12. Trial sequential analysis was conducted to estimate the sample size required in all the included trials and is summarized in Table 3. A t test, which showed no significant evidence of asymmetry (online supplementary figure S1). A pooled analysis demonstrated that treatment with jakinibs was associated with improvement in the clinical response of ACR20 (OR=3.79, 95% CI: 3.14–4.59, P<0.001, χ²=5.84, I²=14.3%), ACR50 (OR=3.83, 95% CI: 3.29–4.46, P<0.001, χ²=25.06, I²=24%), and ACR70 (OR=4.63, 95% CI: 3.61–5.95, P<0.001, χ²=25.97, I²=27%) compared with control treatment (Fig. 2). At week 24, 10 trials focusing on the efficacy of jakinib treatment in RA patients revealed that jakinib treatment also significantly improved the clinical response of ACR20 (OR=3.08, 95% CI: 2.49–3.80, P<0.001, χ²=29.07, I²=66%), ACR50 (OR=3.46, 95% CI: 2.74–4.37, P<0.001, χ²=21.87, I²=59%), and ACR70 (OR=3.96, 95% CI: 3.11–5.05, P<0.001, χ²=12.75, I²=29%) compared with control treatment (online supplementary figure S2). Subgroup analysis based on different types of jakinibs illustrated that only peficitinib treatment had no impact on improvement in ACR50 (OR=3.32, 95% CI: 0.93–11.89, P=0.06, χ²=17.86, I²=89%) or ACR70 (OR=3.69, 95% CI: 0.93–14.59, P=0.06, χ²=8.17, I²=76%) at week 12. Heterogeneity testing showed a moderate degree of heterogeneity, with I²>85% (P_hetero<0.05). Publication bias was evaluated by a funnel plot, which showed no significant evidence of asymmetry (online supplementary figures S3, 4).

**Safety profile**

The safety profile of jakinibs compared with that of placebo during the placebo-controlled periods was reported in all the included trials and is summarized in Table 3. At week 12, infectious diseases were significantly increased after jakinib treatment compared with placebo (OR=1.21, 95% CI: 1.03–1.42, P=0.02, χ²=11.85, I²=7%). The commonly reported infections were upper respiratory tract infections, nasopharyngitis, and herpes zoster infections. Apart from these, no significant differences were found between jakinibs and the placebo regarding treatment-emergent adverse events (TEAEs) (OR=1.11, 95% CI: 1.00–1.23, P=0.05, χ²=22.81, I²=17%), SAEs (OR=0.97, 95% CI: 0.70–1.35, P=0.87, χ²=23.48, I²=15%), discontinuations due to adverse events (OR=1.02, 95% CI: 0.78–1.33, P=0.90, χ²=22.47, I²=11%), or serious infection (OR=1.18, 95% CI: 0.66–2.12, P=0.57, χ²=11.39, I²=0%) (online supplementary figure S5). At week 24, however, an enhanced risk of both TEAEs (OR=1.27, 95% CI: 1.07–1.51, P=0.007, χ²=16.23, I²=38%) and infectious diseases (OR=1.47, 95% CI: 1.26–1.71, P<0.001, χ²=6.16, I²=0%) in response to jakinibs compared with placebo was observed in RA patients. By contrast, no increase was observed in the risk of SAEs (OR=0.84, 95% CI: 0.62–1.13, P=0.25, χ²=11.36, I²=12%), discontinuations due to adverse events (OR=1.18, 95% CI: 0.90–1.54, P=0.23, χ²=8.80, I²=0%), or serious infection (OR=0.92, 95% CI: 0.58–1.46, P=0.74, χ²=2.58, I²=0%) in comparisons between treatment with jakinibs and treatment with placebo in these RA patients (online supplementary figure S6).

**Discussion**

A systematic review and meta-analysis is a statistical method that synthesizes quantitative data from separate but similar studies to provide a conclusion that has greater statistical power than any individual study due to the large number of subjects and greater statistical strength. Recent studies of RA treatment have shed light on the small molecules that inhibit intracellular kinases, particularly those from the JAK family [47]. In our meta-analysis of 28 RCTs with 14,500 participants worldwide, we compared the efficacy and safety of jakinibs with those of placebo or csDMARDs in treating patients with RA with an inadequate response or intolerance to csDMARDs or biologics. In most of the included studies, patients who had discontinued other bDMARDs at least 4 weeks could also participate. Most of the trials in this meta-analysis reported a significant improvement in the clinical response of ACR20/50/70 after jakinib treatment in the short-term follow-up. Notably, subgroup analysis showed that only peficitinib treatment had no impact on improvement in ACR50 and ACR70 at week 12, and no data concerning the long-term efficacy of peficitinib in RA were described. Regarding the safety profile, jakinibs were associated with an increase in the incidence of infectious diseases and TEAEs compared with placebo. These findings were consistent with a previous meta-analysis concerning a single type of jakinib [14]. The main strength of the meta-analysis is that most of the included studies were multiple RCTs with good designs and adequate sample sizes. A relatively comprehensive analysis of RA patients strictly recruited from hundreds of centers worldwide was developed. Only mild heterogeneity was observed among the included studies.

Methotrexate is considered the most preferred csDMARD and is generally offered as a first-line treatment for RA.
| Author (trial name) | Year | Phase | No. of centers | Randomised subjects | Jakinibs regimen | Jakinibs dosage | Control | Time (week) | Jadad score |
|--------------------|------|-------|----------------|---------------------|------------------|----------------|---------|-------------|-------------|
| **Baricitinib (JAK-1, 2)** |      |       |                |                     |                  |                |         |             |             |
| Dougados (RA-BUILD)   | 2017 | III   | 182            | 684                 | Baricitinib + MTX| 2 and 4 mg qd  | PLA + MTX| 12, 24      | 5           |
| Fleischmann (RA-BEGIN) | 2017 | III   | 198            | 588                 | Baricitinib + MTX| 4 mg qd        | PLA + MTX| 24          | 5           |
| Genovese (RA-BEACON)  | 2016 | III   | 178            | 527                 | Baricitinib + MTX| 2 and 4 mg qd  | PLA + MTX| 12, 24      | 5           |
| Keystone (RA-BEAM)    | 2015 | III   | 69             | 301                 | Baricitinib + MTX| 1, 2, 4 and 8 mg qd | PLA + MTX| 12          | 4           |
| Taylor (RA-BEAM)      | 2017 | III   | 281            | 1307                | Baricitinib + MTX| 4 mg qd        | PLA + MTX| 12, 24      | 5           |
| **Decernotinib (JAK-3)** |      |       |                |                     |                  |                |         |             |             |
| Fleischmann and Damjanov | 2015 | Ila  | 54             | 206                 | Decernotinib + 1 DMARDs| 25, 50, 100, or 150 mg bid | PLA + 1 DMARDs | 12          | 5           |
| Genovese and van Vollenhoven | 2016 | IIb  | 103            | 359                 | Decernotinib + MTX| 100, 150 or 200 mg qd; 100 mg bid | PLA + MTX | 12, 24      | 4           |
| **Filgotinib (JAK-1)** |      |       |                |                     |                  |                |         |             |             |
| Genovese (FINCH 2)    | 2019 | III   | 114            | 449                 | Filgotinib + 1-2 DMARDs| 100, or 200 mg qd | PLA + 1-2 DMARDs | 12          | 5           |
| Kavanaugh (DARWIN 2)  | 2016 | IIb   | 59             | 287                 | Filgotinib       | 50, 100, or 200 mg qd | PLA       | 12          | 5           |
| Westhovens (DARWIN 1) | 2017 | IIb   | 106            | 599                 | Filgotinib       | 50, 100, or 200 mg qd; 25, 50, or 100 mg bid | PLA       | 12, 24      | 4           |
| **Peficitinib (JAK-1, 3)** |      |       |                |                     |                  |                |         |             |             |
| Kivitz                | 2017 | IIb   | 43             | 379                 | Peficitinib + MTX| 25, 50, 100, or 150 mg qd | PLA + MTX | 12          | 3           |
| Takeuchi (RAJ4)       | 2019 | III   | 161            | 519                 | Peficitinib + MTX| 100, or 150 mg qd | PLA + MTX | 12          | 5           |
| Takeuchi and Tanaka   | 2016 | IIb   | 43             | 281                 | Peficitinib      | 25, 50, 100, or 150 mg qd | PLA       | 12          | 4           |
| **Tofacitinib (JAK-1, 3)** |      |       |                |                     |                  |                |         |             |             |
| Burmester (ORAL Step) | 2013 | III   | 82             | 399                 | Tofacitinib + MTX| 5, 10 mg bid | PLA + MTX | 12          | 5           |
| Fleischmann (ORAL Solo) | 2012 | III   | 94             | 611                 | Tofacitinib      | 5, 10 mg bid | PLA       | 12          | 5           |
| Fleischmann and Cutolo | 2012 | IIb   | 63             | 386                 | Tofacitinib      | 1, 3, 5, 10, 15 mg bid | PLA       | 12, 24      | 4           |
| Kremer (ORAL Sync)    | 2013 | III   | 114            | 795                 | Tofacitinib + ≥1 DMARDs | 5, 10 mg bid | PLA + ≥1 DMARDs | 12          | 5           |
| Kremer and Cohen      | 2012 | IIb   | 72             | 509                 | Tofacitinib + MTX| 1, 3, 5, 10, 15 mg bid; 20 mg qd | PLA + MTX | 12          | 5           |
| Lee                   | 2014 | III   | 151            | 958                 | Tofacitinib      | 5, 10 mg bid | MTX       | 24, 48, 96  | 4           |
| Tanaka and Suzuki     | 2011 | II    | 19             | 140                 | Tofacitinib + MTX| 1, 3, 5, 10 mg bid | PLA + MTX | 12          | 4           |
| Tanaka and Takeuchi   | 2015 | II    | 47             | 318                 | Tofacitinib      | 1, 3, 5, 10, 15 mg bid | PLA       | 12          | 4           |
| van der Heijde (ORAL Scan) | 2013 | III   | 111            | 797                 | Tofacitinib + MTX| 5, 10 mg bid | PLA + MTX | 24          | 5           |
| van Vollenhoven (ORAL Standard) | 2012 | III   | 115            | 717                 | Tofacitinib + MTX| 5, 10 mg bid | PLA + MTX | 24          | 5           |
| **Upadacitinib (JAK-1)** |      |       |                |                     |                  |                |         |             |             |
| Burmester (SELECT-NEXT) | 2018 | III   | 150            | 661                 | Upadacitinib     | 15, 30 mg qd | PLA       | 12          | 5           |
| Genovese (BALANCE 2)  | 2016 | IIb   | 63             | 300                 | Upadacitinib     | 3, 6, 12, or 18 mg bid; or 24 mg qd | PLA       | 12          | 5           |
| Genovese (SELECT-BEYOND) | 2018 | III   | 153            | 499                 | Upadacitinib     | 15, 30 mg qd | PLA       | 12          | 5           |
| Kremer (BALANCE 1)    | 2016 | IIb   | 123            | 276                 | Upadacitinib     | 3, 6, 12, or 18 mg bid | PLA       | 12          | 4           |
| Smolen (SELECT-MONOTHERAPY) | 2019 | III   | 138            | 648                 | Upadacitinib     | 15, 30 mg qd | PLA + MTX | 14          | 5           |

JAK, Janus kinase; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; PLA, placebo
| Author (trial name) | Time (wk) | Dosage | ACR20 | ACR50 | ACR70 |
|---------------------|----------|--------|-------|-------|-------|
| **Baricitinib**      |          |        |       |       |       |
| Dougados (RA-BUILD)  | 12       | Placebo| 90/228(39.5)| 29/228(12.7)| 7/228(3.1)|
|                     |          | 2 mg qd | 151/229(65.9) | 77/229(33.6)| 41/229(17.9)|
|                     |          | 4 mg qd  | 140/227(61.7) | 76/227(33.5)| 41/227(18.1)|
|                     | 24       | Placebo | 96/228(42.1) | 49/228(21.5)| 18/228(7.9)|
|                     |          | 2 mg qd  | 140/229(61.1) | 95/229(41.5)| 58/229(25.3)|
|                     |          | 4 mg qd  | 148/227(65.2) | 100/227(44.1)| 55/227(24.2)|
|                     | 52       | Placebo | 130/210(61.9) | 136/215(63.3)| 85/215(39.5)|
|                     |          | 4 mg qd  | 168/215(78.1) | 219/487(45.0)| 92/487(18.9)|
| **Fleischmann (RA-BEGIN)** | 24 | Placebo | 48/176(27.3) | 14/176(8.0)| 4/176(2.3)|
|                     |          | 2 mg qd  | 85/174(48.9) | 35/174(20.1)| 22/174(12.6)|
|                     |          | 4 mg qd  | 98/177(55.4) | 50/177(28.2)| 20/177(11.3)|
|                     | 24       | Placebo | 48/176(27.3) | 23/176(13.1)| 6/176(3.4)|
|                     |          | 2 mg qd  | 78/174(44.8) | 40/174(23.0)| 23/174(13.2)|
|                     |          | 4 mg qd  | 82/177(46.3) | 52/177(29.4)| 30/177(16.9)|
| **Genovese (RA-BEACON)** | 12 | Placebo | 40/98(40.8) | 10/98(10.2)| 2/98(2.0)|
|                     |          | 2 mg qd  | 28/228(53.8) | 9/228(17.3)| 4/228(7.7)|
|                     |          | 4 mg qd  | 39/227(50.0) | 18/227(34.6)| 12/227(23.1)|
|                     | 24       | Placebo | 196/488(40.2) | 219/487(45.0)| 92/487(18.9)|
|                     |          | 2 mg qd  | 179/488(36.7) | 200 mg | 94/488(19.3)|
|                     |          | 4 mg qd  | 360/487(73.9) | 246/487(50.5)| 145/487(29.8)|
| **Keystone**        | 12       | Placebo | 179/488(36.7) | 200 mg | 94/488(19.3)|
|                     |          | 2 mg qd  | 359/487(69.6) | 48/487| 133/487(27.9)|
|                     |          | 4 mg qd  | 360/487(73.9) | 246/487(50.5)| 145/487(29.8)|
| **Taylor (RA-BEAM)** | 12 | Placebo | 46/148(31.1) | 22/148(14.9)| 10/148(6.8)|
|                     |          | 100 mg qd| 88/151(57.5) | 49/153(32.0)| 22/153(14.4)|
|                     |          | 200 mg qd| 97/147(66.0) | 63/147(42.9)| 32/147(21.8)|
|                     | 24       | Placebo | 51/148(34.5) | 28/148(18.9)| 121/148(81)|
|                     |          | 100 mg qd| 84/153(54.9) | 54/153(35.3)| 31/153(20.3)|
|                     |          | 200 mg qd| 102/147(69.4) | 67/147(45.6)| 47/147(32.0)|
| **Decernotinib**    | 12       | Placebo | 13/71(18.3) | 5/71(7.0)| 2/71(2.8)|
|                     |          | 100 mg qd| 33/71(46.5) | 16/71(22.5)| 7/71(9.9)|
|                     |          | 150 mg qd| 48/72(66.7) | 28/72(38.9)| 8/72(11.1)|
|                     |          | 200 mg qd| 41/72(56.9) | 25/72(34.7)| 7/72(9.7)|
|                     | 24       | Placebo | 12/71(16.9) | 5/71(7.0)| 2/71(2.8)|
| **Genovese and van Vollenhoven** | 12 | Placebo | 46/148(31.1) | 22/148(14.9)| 10/148(6.8)|
|                     |          | 100 mg qd| 88/151(57.5) | 49/153(32.0)| 22/153(14.4)|
|                     |          | 200 mg qd| 97/147(66.0) | 63/147(42.9)| 32/147(21.8)|
| **Filgotinib**      | 12       | Placebo | 21/72(29.2) | 8/72(11.1)| 2/72(2.8)|
|                     |          | 50 mg qd  | 48/72(66.7) | 25/72(34.7)| 6/72(8.3)|
|                     |          | 100 mg qd| 46/70(65.7) | 26/70(37.1)| 13/70(18.6)|
|                     |          | 200 mg qd| 50/69(72.5) | 30/69(43.5)| 9/69(13.0)|
| **Kavanaugh (DARWIN 2)** | 12 | Placebo | 38/86(44.2) | 13/86(15.1)| 7/86(8.1)|
|                     |          | 50 mg qd  | 46/82(56.1) | 27/82(32.9)| 13/82(15.9)|
|                     |          | 100 mg qd| 54/85(63.5) | 32/85(37.6)| 18/85(21.2)|
|                     |          | 200 mg qd| 59/86(68.6) | 37/86(43.0)| 21/86(24.4)|
|                     |          | 25 mg qd  | 49/86(57.0) | 24/86(27.9)| 12/86(14.0)|
|                     |          | 50 mg qd  | 51/85(60.0) | 29/85(34.1)| 16/85(18.8)|
|                     | 24       | Placebo | 36/86(41.9) | 14/86(16.3)| 8/86(9.3)|
|                     |          | 50 mg qd  | 45/82(54.9) | 29/82(35.4)| 18/82(22.0)|
| **Westhovens (DARWIN 1)** | 12 | Placebo | 52/85(61.2) | 40/85(47.1)| 28/85(32.9)|

Table 2  Summary of the clinical efficacy outcomes of Jakinibs in rheumatoid arthritis
Table 2 (continued)

| Author (trial name) | Time (wk) | Dosage | ACR20 | ACR50 | ACR70 |
|---------------------|-----------|--------|-------|-------|-------|
| **Peficitinib**     |           |        |       |       |       |
| Kivitz              | 12        | Placebo| 32/72 (44.4) | 19/72 (26.4) | 8/72 (11.1) |
|                     |           | 25 mg qd | 29/66 (43.9) | 12/66 (18.2) | 6/66 (9.1) |
|                     |           | 50 mg qd | 48/78 (61.5) | 26/78 (33.3) | 12/78 (15.4) |
|                     |           | 100 mg qd | 39/84 (46.4) | 28/84 (33.3) | 14/84 (16.7) |
|                     |           | 150 mg qd | 45/78 (57.7) | 29/78 (37.2) | 15/78 (19.2) |
|                     |           | 200 mg qd | 63/86 (73.3) | 43/86 (50.0) | 25/86 (29.1) |
|                     |           | 25 mg bid | 48/86 (55.8) | 30/86 (34.9) | 18/86 (20.9) |
|                     |           | 50 mg bid | 51/85 (60.0) | 30/85 (35.3) | 20/85 (23.5) |
|                     |           | 100 mg bid | 67/84 (79.8) | 46/84 (54.8) | 33/84 (39.3) |
| **Tofacitinib**     |           |        |       |       |       |
| Burmester (ORAL Step) | 12        | Placebo| 32/131 (24.4) | 11/131 (8.4) | 2/131 (1.5) |
|                     |           | 5 mg bid | 55/132 (41.7) | 35/132 (26.5) | 18/132 (13.6) |
|                     |           | 10 mg bid | 64/133 (48.1) | 37/133 (27.8) | 14/133 (10.5) |
| Fleischmann (ORAL Solo) | 12        | Placebo| 33/122 (27) | 15/122 (12.3) | 7/122 (5.7) |
|                     |           | 5 mg bid | 145/243 (59.7) | 76/243 (31.3) | 37/243 (15.2) |
|                     |           | 10 mg bid | 161/245 (65.7) | 90/245 (36.7) | 50/245 (20.4) |
| Fleischmann and Cutolo | 12        | Placebo| 13/59 (22) | 6/59 (10.2) | 2/59 (3.4) |
|                     |           | 1 mg bid | 17/54 (31.5) | 6/54 (11.1) | 3/54 (5.6) |
|                     |           | 3 mg bid | 20/51 (39.2) | 12/51 (23.5) | 6/51 (11.8) |
|                     |           | 5 mg bid | 29/49 (59.2) | 18/49 (36.7) | 6/49 (12.2) |
|                     |           | 10 mg bid | 43/61 (70.5) | 27/61 (44.3) | 15/61 (24.6) |
|                     |           | 15 mg bid | 41/57 (71.9) | 29/57 (50.9) | 15/57 (26.3) |
|                     | 24        | Placebo| 15/25 (24.5) | 6/59 (10.2) | 4/59 (6.8) |
|                     |           | 1 mg bid | 13/54 (24.1) | 4/54 (7.4) | 3/54 (5.6) |
|                     |           | 3 mg bid | 19/51 (37.3) | 14/51 (27.5) | 7/51 (13.7) |
|                     |           | 5 mg bid | 25/49 (51.0) | 17/49 (34.7) | 10/49 (20.4) |
|                     |           | 10 mg bid | 40/61 (65.6) | 27/61 (44.3) | 23/61 (37.7) |
|                     |           | 15 mg bid | 38/57 (66.7) | 31/57 (54.4) | 19/57 (33.3) |
| Kremer (ORAL Sync)  | 12        | Placebo| 43/159 (27.0) | N/A | N/A |
|                     |           | 5 mg bid | 235/315 (74.6) | N/A | N/A |
|                     |           | 10 mg bid | 260/318 (81.8) | N/A | N/A |
| Kremer and Cohen    | 12        | Placebo| 23/69 (33.3) | N/A | N/A |
|                     |           | 1 mg bid | 32/70 (45.7) | N/A | N/A |
|                     |           | 3 mg bid | 36/68 (52.9) | N/A | N/A |
|                     |           | 5 mg bid | 36/71 (50.7) | N/A | N/A |
|                     |           | 10 mg bid | 43/74 (58.1) | N/A | N/A |
|                     |           | 15 mg bid | 42/75 (56.0) | N/A | N/A |
|                     |           | 20 mg bid | 43/80 (53.8) | N/A | N/A |
| Lee                 | 24        | Placebo| 94/186 (50.5) | 49/186 (26.3) | 22/186 (11.8) |
|                     |           | 5 mg bid | 266/373 (71.3) | 174/373 (46.6) | 141/373 (37.8) |
|                     |           | 10 mg bid | 302/397 (76.1) | 224/397 (56.4) | 101/397 (25.4) |
|                     | 48        | Placebo| 95/186 (51.1) | 63/186 (33.9) | 28/186 (15.1) |
|                     |           | 5 mg bid | 235/373 (67.8) | 186/373 (49.9) | 142/373 (38.1) |
|                     |           | 10 mg bid | 284/397 (71.5) | 221/397 (55.7) | 114/397 (28.7) |
|                     | 96        | Placebo| 79/186 (42.5) | 53/186 (28.5) | 28/186 (15.1) |
|                     |           | 5 mg bid | 239/373 (64.1) | 184/373 (49.3) | 128/373 (34.3) |
|                     |           | 10 mg bid | 255/397 (64.2) | 195/397 (49.1) | 149/397 (37.5) |
| Tanaka and Suzuki   | 12        | Placebo| 4/28 (14.3) | N/A | N/A |
|                     |           | 1 mg bid | 18/28 (64.3) | N/A | N/A |
|                     |           | 3 mg bid | 21/27 (77.8) | N/A | N/A |
|                     |           | 5 mg bid | 26/27 (96.3) | N/A | N/A |
|                     |           | 10 mg bid | 21/26 (80.8) | N/A | N/A |
However, biologics, particularly TNF inhibitors, administered as a first choice remain an established treatment option for patients who fail or have an inadequate response or intolerance to csDMARDs [48]. However, csDMARDs and biologics are not effective in many patients [49]. For these patients, jakinib treatment has greatly improved the management and reduced the disability from these debilitating diseases [11]. The use of small-molecule inhibitors, including jakinibs, has broadened the clinical armamentarium in the management of RA. Tofacitinib, the first jakinib approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), is a pan-JAK inhibitor with competitive inhibition of JAK1/2/3 and TYK2 in vitro and potent inhibition of JAK1/3 signaling components with five- to 100-fold increased selectivity over JAK2 in cellular assays [50]. Tofacitinib inhibits STAT-phosphorylation-dependent activation by binding these molecular targets, resulting in the restraint of gene transcription and subsequent cytokine production. Similarly, peficitinib is another pan-JAK inhibitor with more selective inhibition of JAK3 relative to tofacitinib. By contrast, baricitinib selectively inhibits JAK1/2 subtypes with greater potency than the JAK3 and TYK2 subtypes. Baricitinib has also been approved by the FDA and EMA for patients with moderate to severe RA with an inadequate response or intolerance to more than one DMARD as monotherapy or in combination with methotrexate [49]. The selective jakinibs include decernotinib (JAK3) and upadacitinib and filgotinib (JAK1) [1]. Unlike the biologics that are administered by injection, jakinibs are small molecules that can be administered orally. The current available evidence supports the efficacy of jakinibs in the short-term treatment of RA [11]. The main implications of our findings also suggest that jakinibs are beneficial and well tolerated even for RA patients who fail standard treatment with csDMARDs or bDMARDs.

The safety of the treatment options was determined based on the number of TEAEs, SAEs, discontinuations due to adverse events, infections, and serious infections. Our meta-analysis showed that the number of RA patients

Table 2 (continued)

| Author (trial name)         | Time (wk) | Dosage         | ACR20 | ACR50 | ACR70 |
|-----------------------------|-----------|----------------|-------|-------|-------|
| Tanaka and Takeuchi         | 12        | Placebo        | 8/52 (15.4) | N/A   | N/A   |
|                             |           | 1 mg bid       | 20/53 (37.7) | N/A   | N/A   |
|                             |           | 3 mg bid       | 36/53 (67.9) | N/A   | N/A   |
|                             |           | 5 mg bid       | 38/52 (73.1) | N/A   | N/A   |
|                             |           | 10 mg bid      | 45/53 (84.9) | N/A   | N/A   |
|                             |           | 15 mg bid      | 49/54 (90.7) | N/A   | N/A   |
| van der Heijde (ORAL Scan)  | 24        | Placebo        | 40/160 (25) | 13/160 (8.1) | 2/160 (1.3) |
|                             |           | 5 mg bid       | 165/321 (51.4) | 104/321 (32.4) | 47/321 (14.6) |
|                             |           | 10 mg bid      | 195/316 (61.7) | 138/316 (43.7) | 70/316 (22.2) |
| van Vollenhoven (ORAL Standard) | 24    | Placebo        | 30/106 (28.3) | N/A   | N/A   |
|                             |           | 5 mg bid       | 101/196 (51.5) | N/A   | N/A   |
|                             |           | 10 mg bid      | 103/196 (52.6) | N/A   | N/A   |
| Upadacitinib Burmester (SELECT-NEXT) | 12 | Placebo        | 79/221 (35.7) | 33/221 (14.9) | 13/221 (5.9) |
|                             |           | 15 mg qd       | 141/221 (63.8) | 84/221 (38.0) | 46/221 (20.8) |
|                             |           | 30 mg qd       | 145/219 (66.2) | 94/219 (42.9) | 59/219 (26.9) |
| Genovese (BALANCE 2)        | 12        | Placebo        | 23/50 (46) | 9/50 (18.0) | 3/50 (6.0) |
|                             |           | 3 mg bid       | 31/50 (62.0) | 19/50 (38.0) | 11/50 (22.0) |
|                             |           | 6 mg bid       | 34/50 (68.0) | 23/50 (46.0) | 14/50 (28.0) |
|                             |           | 12 mg bid      | 40/50 (80.0) | 25/50 (50.0) | 8/50 (16.0) |
|                             |           | 18 mg bid      | 32/50 (64.0) | 20/50 (40.0) | 13/50 (26.0) |
|                             |           | 24 mg qd       | 37/49 (75.5) | 19/49 (38.8) | 11/49 (22.4) |
| Genovese (SELECT-BEYOND)    | 12        | Placebo        | 48/169 (28.4) | 20/169 (11.8) | 11/169 (6.5) |
|                             |           | 15 mg qd       | 106/164 (64.6) | 56/164 (34.1) | 19/164 (11.6) |
|                             |           | 30 mg qd       | 93/165 (56.4) | 59/165 (35.8) | 30/165 (18.2) |
| Kremer (BALANCE 1)          | 12        | Placebo        | 19/56 (33.9) | 9/56 (16.1) | 2/56 (3.6) |
|                             |           | 3 mg bid       | 29/55 (52.7) | 13/55 (23.6) | 7/55 (12.7) |
|                             |           | 6 mg bid       | 32/55 (58.2) | 20/55 (36.4) | 14/55 (25.5) |
|                             |           | 12 mg bid      | 39/55 (70.9) | 23/55 (41.8) | 12/55 (21.8) |
|                             |           | 18 mg bid      | 37/55 (67.3) | 21/55 (38.2) | 12/55 (21.8) |
| Smolen (SELECT-MONOTHERAPY)  | 14        | Placebo        | 89/216 (41.2) | 32/216 (14.8) | 6/216 (2.8) |
|                             |           | 15 mg qd       | 148/217 (68.2) | 91/217 (41.9) | 50/217 (23.0) |
|                             |           | 30 mg qd       | 153/215 (71.2) | 112/215 (52.1) | 71/215 (33.0) |
treated with jakinibs who had TEAEs was higher than that in the placebo group. Further subgroup analysis, however, revealed that only one study [25] reported an increased incidence of TEAEs (59.9% vs. 42.3% for decernotinib vs. placebo, respectively) at week 24, such as headache (8.7%) and elevated levels of transaminases, lipoproteins, and creatinine. Additionally, because of their pharmacological action as JAK1/3 inhibitors, jakinibs can cause immunosuppression that induces serious infections. The most commonly reported infections were upper respiratory tract infections, nasopharyngitis, or herpes zoster infections. These conditions did not result in patient Fig. 2 Forest plot diagram for the efficacy of jakinibs according to ACR20 (a), ACR50 (b), and ACR70 (c) in patients with rheumatoid arthritis at 12 weeks.
withdrawal at week 12 or 24, as shown in our meta-analysis. However, there were similar rates of adverse events, including infections associated with jakinibs and TNF inhibitors such as adalimumab [23, 34]. Patients receiving jakinibs should be monitored, and larger trials conducted over longer study periods under pharmacovigilance are required to confirm the long-term safety of the drugs.

Some limitations in our analysis must be noted. First, only 28 studies meeting the inclusion criteria were finally included in our meta-analysis. However, it is reasonable to draw conclusions based on this meta-analysis because of the comprehensive literature search and efforts to obtain as much data as possible. Second, the follow-up periods were limited to 12 or 24 weeks in the final meta-analysis, and long-term studies with more than 52 weeks of follow-up were conducted in very few studies [20]. Longer comparative studies are required to evaluate the long-term effects of jakinib treatment. Third, the types of jakinibs used in each

Fig. 2 continued.
study and differences in the dosages administered also added to the heterogeneity. Because the different dosages of jakinibs were reported in the studies, the total number of all dosages for each jakinib was used in the final meta-analysis. A dose-response relationship was not observed in this meta-analysis. Subgroup analysis based on different dosages for individual jakinibs might be necessary to explore the proper dosage with a balance between therapeutic effects and side effects. Therefore, caution should be taken when interpreting the findings of this meta-analysis.

### Conclusions

To our best knowledge, this systematic review and meta-analysis estimating the efficacy and safety of 6 different jakinibs in the treatment of active RA patients is one of the most comprehensive. Jakinib therapy showed benefits in achieving ACR20/50/70 responses with acceptable safety profiles in these patients who were refractory to aggressive standard-of-care treatment in the short-term follow-up. Jakinibs can be considered a favorable option for patients with...
| Author (trial name) | Time (wk) | Dosage | TEAE | SAE | Discontinuation* | Infection disease | Serious infection |
|---------------------|-----------|--------|------|-----|-----------------|-------------------|-----------------|
| **Baricitinib**     |           |        |      |     |                 |                   |                 |
|                     | 12        | Placebo| 133/228 (58.3) | 8/228 (3.5) | 8/228 (3.5) | 53/228 (23.2) | 3/228 (1.3) |
|                     | 2 mg qd   |        | 122/229 (53.3) | 4/229 (1.7)  | 7/229 (3.1)  | 45/229 (19.7) | 1/229 (0.4)  |
|                     | 4 mg qd   |        | 135/227 (59.5) | 4/227 (1.8)  | 8/227 (3.5)  | 66/227 (29.1) | 2/227 (0.9)  |
|                     | 24        | Placebo| 161/228 (70.6) | 11/228 (4.8) | 10/228 (4.4) | 79/228 (34.6) | 4/228 (1.8)  |
|                     | 2 mg qd   |        | 154/229 (69.2) | 6/229 (2.6)  | 10/229 (4.4) | 70/229 (30.6) | 2/229 (0.9)  |
|                     | 4 mg qd   |        | 162/227 (71.4) | 12/227 (5.3) | 12/227 (5.3) | 96/227 (42.3) | 4/227 (1.8)  |
| Fleischmann         | 24        | Placebo| 136/210 (64.8) | 9/210 (4.3)  | 5/210 (2.4)  | 58/210 (27.6) | 2/210 (0.9)  |
| (RA-BEGIN)          |           | 4 mg qd| 146/215 (67.9) | 8/215 (3.7)  | 15/215 (7.0) | 70/215 (32.7) | 5/215 (2.3)  |
| Genovese            | 12        | Placebo| 96/176 (54.5)  | 7/176 (4.0)  | 4/176 (2.3)  | 35/176 (19.9) | 3/176 (1.7)  |
| (RA-BEACON)         |           | 2 mg qd| 107/174 (61.5) | 3/174 (1.7)  | 7/174 (4.0)  | 61/174 (35.1) | 3/174 (1.7)  |
|                     |           | 4 mg qd| 119/177 (67.2) | 11/177 (6.2) | 9/177 (5.1)  | 48/177 (27.1) | 3/177 (1.7)  |
| Keystone            | 12        | Placebo| 45/98 (45.9)   | 3/98 (3.1)   | 5/98 (5.1)   | 1/98 (0.0)    | 0/98 (0.0)    |
|                     |           | 2 mg qd| 24/52 (46.2)   | 1/52 (2.4)   | 1/52 (1.9)   | 2/52 (3.8)    | 0/52 (0.0)    |
| Taylor (RA-BEAM)    | 24        | Placebo| 295/488 (60.5)| 22/488 (4.5) | 17/488 (3.5) | 134/488 (27.5)| 7/488 (1.4)   |
| Decernotinib        |           |        |                  |              |                |                   |                 |
| Fleischmann and     | 12        | Placebo| 19/41 (46.3)   | 1/41 (2.4)   | 2/41 (4.9)   | 7/41 (17.1)    | 0/41 (0.0)    |
| Damjanov            |           | 25 mg bid| 12/41 (29.3)  | 0/41 (0.0)   | 0/41 (0.0)   | 5/41 (12.2)    | 0/41 (0.0)    |
|                     |           | 50 mg bid| 18/41 (43.9)  | 1/41 (2.4)   | 1/41 (2.4)   | 5/41 (12.2)    | 0/41 (0.0)    |
| Genovese and van     | 24        | Placebo| 30/71 (42.3)   | 4/71 (5.6)   | N/A           | N/A             | N/A            |
| Vollenhoven          |           | 100 mg qd| 37/71 (52.1)  | 3/71 (4.2)   | N/A           | N/A             | N/A            |
|                     |           | 150 mg qd| 44/72 (61.1)  | 6/72 (8.3)   | N/A           | N/A             | N/A            |
|                     |           | 200 mg qd| 49/72 (68.1)  | 5/72 (6.9)   | N/A           | N/A             | N/A            |
|                     |           | 100 mg bid| 42/72 (58.3)  | 7/72 (9.7)   | N/A           | N/A             | N/A            |
| Filgotinib          |           |        |                  |              |                |                   |                 |
| Genovese (FINCH 2)  | 12        | Placebo| 80/148 (54.1)  | 4/148 (2.7)  | 3/148 (2.0)  | 27/148 (18.2) | 2/148 (1.4)   |
|                     |           | 100 mg qd| 77/153 (50.3) | 6/153 (3.9)  | 6/153 (3.9)  | 29/153 (19.0) | 1/153 (0.7)   |
|                     |           | 200 mg qd| 82/147 (55.8) | 4/147 (2.7)  | 4/147 (2.7)  | 34/147 (23.1) | 1/147 (0.7)   |
| Kavanaugh (DARWIN 2)| 12        | Placebo| 28/72 (38.9)   | 1/72 (1.4)   | 4/72 (5.6)   | N/A             | 0/72 (0.0)    |
|                     |           | 50 mg qd| 29/72 (40.3)   | 1/72 (1.4)   | 1/72 (1.4)   | N/A             | 0/72 (0.0)    |
|                     |           | 100 mg qd| 23/70 (32.9)  | 0/70 (0.0)   | 0/70 (0.0)   | N/A             | 0/70 (0.0)    |
|                     |           | 200 mg qd| 30/69 (43.5)  | 3/69 (4.3)   | 1/69 (1.4)   | N/A             | 1/69 (1.4)    |
| Westhovens (DARWIN 1)| 24       | Placebo| 32/56 (57.1)   | 4/56 (7.1)   | 2/56 (3.6)   | 1/56 (1.8)     | 0/56 (0.0)    |
|                     |           | 50 mg qd| 33/63 (52.4)   | 0/63 (0.0)   | 2/63 (3.2)   | 4/63 (6.3)     | 0/63 (0.0)    |
|                     |           | 100 mg qd| 37/85 (43.5)  | 4/85 (4.7)   | 5/85 (5.9)   | 8/85 (9.7)     | 3/85 (3.5)    |
|                     |           | 200 mg qd| 50/86 (58.1)  | 2/86 (2.3)   | 3/86 (3.5)   | 7/86 (8.1)     | 1/86 (1.2)    |
|                     |           | 25 mg bid| 37/69 (53.6)  | 1/69 (1.4)   | 5/69 (7.2)   | 5/69 (7.2)     | 0/69 (0.0)    |
| Author (trial name) | Time (wk) | Dosage | TEAE | SAE | Discontinuation* | Infection disease | Serious infection |
|---------------------|-----------|--------|------|-----|-----------------|------------------|------------------|
| **Peficitinib**      |           |        |      |     |                 |                  |                  |
| Kivitz              | 12        | Placebo| 34/72| 0/72| 1/72 (1.4)      | N/A              | 0/72 (0.0)       |
|                    |           | 25 mg qd| 28/66| 0/66| 0/66 (0.0)      | N/A              | 0/66 (0.0)       |
|                    |           | 50 mg qd| 39/78| 0/78| 0/78 (0.0)      | N/A              | 0/78 (0.0)       |
|                    |           | 100 mg qd| 40/84| 2/84| 3/84 (3.6)      | N/A              | 1/84 (1.2)       |
|                    |           | 150 mg qd| 39/78| 1/78| 4/78 (5.1)      | N/A              | 1/78 (1.3)       |
| Takeuchi (RAJ4)     | 12        | Placebo| 84/170| 4/170| 7/170 (4.1)     | N/A              | 0/170 (0.0)      |
|                    |           | 100 mg qd| 89/174| 5/174| 5/174 (2.9)     | N/A              | 6/174 (3.4)      |
|                    |           | 150 mg qd| 104/174| 3/174| 5/174 (2.9)     | N/A              | 6/174 (3.4)      |
| Takeuchi and Tanaka | 12        | Placebo| 36/66| 1/56| 10/56 (17.9)   | N/A              | 12/56 (21.4)     |
|                    |           | 25 mg qd| 39/55| 1/55| 7/55 (12.7)    | N/A              | 18/55 (32.7)     |
|                    |           | 50 mg qd| 37/57| 2/57| 5/57 (8.8)    | N/A              | 14/57 (24.6)     |
|                    |           | 100 mg qd| 29/55| 3/55| 6/55 (10.9)   | N/A              | 7/55 (12.7)      |
|                    |           | 150 mg qd| 39/58| 0/58| 4/58 (6.9)    | N/A              | 17/58 (29.3)     |
| **Tofacitinib**     |           |        |      |     |                 |                  |                  |
| Burmester           | 12        | Placebo| 75/132| 6/132| 7/132 (5.3)    | N/A              | 0/132 (0.0)      |
|                   |           | 5 mg bid| 71/133| 2/133| 8/133 (6.0)    | N/A              | 0/133 (0.0)      |
|                   |           | 10 mg bid| 76/134| 6/134| 6/134 (4.5)   | N/A              | 0/134 (0.0)      |
| Fleischmann         | 12        | Placebo| 67/122| 6/122| 5/122 (4.1)    | N/A              | 0/122 (0.0)      |
| (ORAL Solo)         |           | 5 mg bid| 124/243| 2/243| 2/243 (0.8)   | N/A              | 0/243 (0.0)      |
|                   |           | 10 mg bid| 139/245| 5/245| 6/245 (2.4)   | N/A              | 1/245 (0.4)      |
| Fleischmann         | 24        | Placebo| 16/34| 2/34| 4/34 (5.9)    | N/A              | 1/34 (2.9)       |
| and Cutolo          |           | 1 mg bid| 19/37| 1/37| 4/37 (10.8)   | N/A              | 11/37 (29.7)     |
|                   |           | 3 mg bid| 18/34| 2/34| 3/34 (8.8)    | N/A              | 7/34 (20.6)      |
|                   |           | 5 mg bid| 27/49| 1/49| 1/49 (2.0)    | N/A              | 17/49 (34.7)     |
|                   |           | 10 mg bid| 36/61| 0/61| 1/61 (1.6)    | N/A              | 21/61 (34.4)     |
|                   |           | 15 mg bid| 27/49| 0/61| 1/61 (1.6)    | N/A              | 17/49 (33.3)     |
| Kremer             | 12        | Placebo| 97/159| 6/159| 2/159 (1.3)    | N/A              | 0/159 (0.0)      |
| (ORAL Sync)        |           | 5 mg bid| 166/315| 9/315| 13/315 (4.1)  | N/A              | 2/315 (0.6)      |
|                   |           | 10 mg bid| 169/318| 8/318| 13/318 (4.1)  | N/A              | 4/318 (1.3)      |
| Kremer and Cohen    | 24        | Placebo| 29/51| 0/51| 3/51 (5.9)    | N/A              | 3/51 (5.9)       |
|                   |           | 1 mg bid| 29/49| 1/49| 3/49 (6.1)    | N/A              | 7/49 (14.3)      |
|                   |           | 3 mg bid| 38/55| 2/55| 5/55 (10.0)   | N/A              | 2/55 (3.6)       |
|                   |           | 5 mg bid| 47/71| 4/71| 3/71 (4.2)    | N/A              | 16/71 (22.5)     |
|                   |           | 10 mg bid| 50/74| 7/74| 5/74 (6.8)    | N/A              | 13/74 (17.6)     |
|                   |           | 15 mg bid| 57/75| 6/75| 10/75 (13.3) | N/A              | 14/75 (18.7)     |
|                   |           | 20 mg bid| 41/67| 2/67| 6/67 (9.0)    | N/A              | 13/67 (19.4)     |
| Lee                | 24        | Placebo| 147/186| 22/186| 25/186 (13.4) | N/A              | 5/186 (2.7)      |
|                   |           | 5 mg bid| 297/373| 40/373| 40/373 (10.7) | N/A              | 11/373 (2.9)     |
|                   |           | 10 mg bid| 334/397| 43/397| 43/397 (10.8) | N/A              | 8/397 (2.0)      |
| Tanaka and Suzuki   | 12        | Placebo| N/A| 0/28| 2/28 (7.1)    | 6/28 (21.4)      | 0/28 (0.0)       |
|                   |           | 1 mg bid| N/A| 1/28| 0/28 (0.0)    | 3/28 (10.7)      | 0/28 (0.0)       |
|                   |           | 3 mg bid| N/A| 1/27| 2/27 (7.4)    | 8/27 (29.6)      | 0/27 (0.0)       |
|                   |           | 5 mg bid| N/A| 1/27| 4/27 (14.8)   | 3/27 (11.1)      | 0/27 (0.0)       |
|                   |           | 10 mg bid| N/A| 2/26| 4/26 (15.4)   | 11/26 (42.3)     | 0/26 (0.0)       |
| Tanaka and Takeuchi | 12        | Placebo| 23/52| 1/52| 2/52 (3.8)    | N/A              | 0/52 (0.0)       |
|                   |           | 1 mg bid| 21/53| 0/53| 0/53 (0.0)    | N/A              | 0/53 (0.0)       |
active RA with an inadequate response or intolerance to csDMARDs or bDMARDs. The results of our analysis should be confirmed in future studies with long-term exposure.

Abbreviations  ACR, American College of Rheumatology; bDMARD, Biologic disease-modifying antirheumatic drug; csDMARDs, Conventional synthetic disease-modifying antirheumatic drug; DMARD, Disease-modifying antirheumatic drug; EMA, European Medicines Agency; FDA, Food and Drug Administration; JAK, Janus kinase; OR, Odds ratio; RA, Rheumatoid arthritis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized controlled trial; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event; TNF, Tumor necrosis factor; 95% CI: 95% confidence interval

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Table 3 (continued)

| Author (trial name) | Time (wk) | Dosage | TEAE | SAE | Discontinuation* | Infection disease | Serious infection |
|---------------------|-----------|--------|------|-----|-----------------|------------------|------------------|
| upadacitinib        |           |        |      |     |                 |                  |                  |
| Burmester (SELECT-NEXT) | 12       | Placebo | 108/221 (48.9) | 5/221 (2.3) | 7/221 (3.2) | 47/221 (21.3) | 1/221 (0.5) |
|                     |           | 15 mg qd | 125/221 (56.6) | 9/221 (4.1) | 7/221 (3.2) | 64/221 (29.0) | 1/221 (0.5) |
|                     |           | 30 mg qd | 118/219 (53.9) | 6/219 (2.7) | 13/219 (5.9) | 69/219 (31.5) | 3/219 (1.4) |
| Genovese (BALANCE 2) | 12       | Placebo | 13/50 (26.0) | 0/50 (0.0) | 1/50 (2.0) | 7/50 (14.0) | 0/50 (0.0) |
|                     |           | 3 mg bid | 20/50 (40.0) | 0/50 (0.0) | 1/50 (2.0) | 10/50 (20.0) | 0/50 (0.0) |
|                     |           | 6 mg bid | 23/50 (46.0) | 2/50 (4.0) | 1/50 (2.0) | 7/50 (14.0) | 0/50 (0.0) |
|                     |           | 12 mg bid | 29/50 (58.0) | 1/50 (2.0) | 1/50 (2.0) | 12/50 (24.0) | 1/50 (2.0) |
|                     |           | 18 mg bid | 25/50 (50.0) | 3/50 (6.0) | 5/50 (10.0) | 11/50 (22.0) | 0/50 (0.0) |
|                     |           | 24 mg qd | 17/49 (34.7) | 2/49 (4.1) | 1/49 (2.0) | 9/49 (18.4) | 0/49 (0.0) |
| Genovese (SELECT-BEYOND) | 12       | Placebo | 95/169 (56.2) | 0/169 (0.0) | 9/169 (5.3) | 51/169 (30.2) | 0/169 (0.0) |
|                     |           | 15 mg qd | 91/164 (55.5) | 8/164 (4.9) | 4/164 (2.4) | 54/164 (32.9) | 1/164 (0.6) |
|                     |           | 30 mg qd | 111/165 (67.3) | 12/165 (7.3) | 15/165 (9.1) | 55/165 (33.3) | 4/165 (2.4) |
| Kremer (BALANCE 1) | 12       | Placebo | 25/56 (44.6) | 2/56 (3.6) | 2/56 (3.6) | 13/56 (23.2) | 1/56 (1.8) |
|                     |           | 3 mg bid | 26/55 (47.3) | 1/55 (1.8) | 0/55 (0.0) | 11/55 (20.0) | 0/55 (0.0) |
|                     |           | 6 mg bid | 31/55 (56.4) | 2/55 (3.6) | 6/55 (10.9) | 12/55 (21.8) | 0/55 (0.0) |
|                     |           | 12 mg bid | 37/55 (67.3) | 2/55 (3.6) | 2/55 (3.6) | 22/55 (40.0) | 0/55 (0.0) |
|                     |           | 18 mg bid | 39/55 (70.9) | 1/55 (1.8) | 2/55 (3.6) | 21/55 (38.2) | 0/55 (0.0) |
| Smolen (SELECT-MONOTHERAPY) | 14       | Placebo | 102/216 (47.2) | 6/216 (2.8) | 6/216 (2.8) | 57/216 (26.4) | 0/216 (0.0) |
|                     |           | 15 mg qd | 103/217 (47.5) | 11/217 (5.1) | 8/217 (3.7) | 42/217 (19.4) | 1/217 (0.5) |
|                     |           | 30 mg qd | 105/215 (48.8) | 6/215 (2.8) | 6/215 (2.8) | 54/215 (25.1) | 1/215 (0.5) |

TEAE, treatment-emergent adverse event; SAE, serious adverse event; PLAB, placebo.*Discontinuations due to adverse events; N/A, not applicable
Data availability All the data generated and analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate This study did not require ethical approval or informed consent because all the analyses were based on previously published data.

Consent for publication Not applicable.

Disclosures None.

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