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

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Research article

Keywords: rheumatoid arthritis, jakinib, efficacy, safety, meta-analysis

Posted Date: August 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-67254/v1

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 week 12 and 24 after treatment. The safety outcomes included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), discontinuations due to adverse events, infections and serious infections. Results Twenty-eight randomized, double-blind, controlled trials including 14500 patients were included. Both at week 12 and 24, the pooled analysis was suggestive of an effective treatment with jakinibs, represented as the increased clinical response of ACR20, ACR50 and ACR70. The 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 a period of 24 weeks, although they are associated with an increased risk of infectious complications.

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, and ultimately increases disability and mortality for affected patients [2]. As per 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]. The treatment of RA is based on conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), especially the anchor drug, methotrexate [3]. During the past two decades, various options, especially biologic DMARDs (bDMARDs), such as tumor necrosis factor (TNF) inhibitors available for the treatment of RA, have been developed [4]. Biologics, as foreign proteins, have the potential to induce immunogenicity, which may ultimately lead to 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 economic burden and reduce patient compliance [7]. Therefore, it seems particularly necessary to explore more options 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 the 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]. A large number of 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]. A great number of meta-analyses 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, especially tofacitinib or baricitinib, which were approved early for the treatment of active RA [13]. As far as we know, 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 a quantitative meta-analysis of data from recently released randomized controlled trials (RCTs).

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 since all analyses were based on previously published data.

Data sources and search strategy

We performed an exhaustive search for studies that evaluated 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 publication status or language. A combination of the following keywords was used: “rheumatoid arthritis”, “ra”, and “protein kinases inhibitor” “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, or upadacitinib) alone or in combination with csDMARDs were compared to 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, a nonplacebo comparative study, 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 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 upon consensus. The modified Jadad tool for randomized clinical trials was used to assess the quality of included studies 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 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 by 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 (χ^2) test and qualified by I^2 statistics, ranging from 0–100%, 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 14500 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 RA patients were treated with jakinib monotherapy or jakinibs in combination with DMARDs, especially 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]. The characteristics of the selected trials and Jadad scores are summarized in Table 1.

Table 1
Baseline study characteristics of randomized, placebo-controlled double-blinded trials of Jakinibs in rheumatoid arthritis.

Author (trial name)	Year	Phase	No. of centers	Randomised subjects	Jakinibs regimen	Jakinibs dosage	Control	Time (wk)	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	2015	IIb	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	IIa	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

JAK; Janus kinase; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; PLA, Placebo.

Author (trial name)	Year	Phase	No. of centers	Randomised subjects	Jakinibs regimen	Jakinibs dosage	Control	Time (wk)	Jadad score
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

JAK; Janus kinase; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; PLA, Placebo.

Author (trial name)	Year	Phase	No. of centers	Randomised subjects	Jakinibs regimen	Jakinibs dosage	Control	Time (wk)	Jadad score
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 + MTX	15, 30 mg qd	PLA + MTX	14	5

JAK; Janus kinase; MTX, methotrexate; DMARDs, disease-modifying antirheumatic drugs; PLA, Placebo.

Overall efficacy

Efficacy outcomes for all included studies are summarized in Table 2. Twenty-four trials with a total of 10,923 patients (7,885 RA patients treated with jakinibs and 3,038 controls) assessed the efficacy of jakinibs in RA patients at week 12. 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, χ^2 = 5.84, I^2 = 14.3%), ACR50 (OR = 3.83, 95% CI 3.29–4.46, P < 0.001, χ^2 = 25.06, I^2 = 24%), and ACR70 (OR = 4.63, 95% CI 3.61–5.95, P < 0.001, χ^2 = 25.97, I^2 = 27%) compared to control treatment (online supplementary figures S1). 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, χ^2 = 29.07, I^2 = 66%), ACR50 (OR = 3.46, 95% CI 2.74–4.37, P < 0.001, χ^2 = 21.87, I^2 = 59%), and ACR70 (OR = 3.96, 95% CI 3.11–5.05, P < 0.001, χ^2 = 12.75, I^2 = 29%) compared with control treatment (online supplementary figure S2). The 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, χ^2 = 17.86, I^2 = 89%) or ACR70 (OR = 3.69, 95% CI 0.93–14.59, P = 0.06, χ^2 = 8.17, I^2 = 76%) at week 12. Heterogeneity testing showed a moderate degree of heterogeneity, with I^2 > 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).

Table 2
Summary of the clinical efficacy outcomes of Jakinibs in rheumatoid arthritis.

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)
Fleischmann (RA-BEGIN)	24	Placebo	130/210 (61.9)	91/210 (43.3)	45/210 (21.4)
		4 mg qd	168/215 (78.1)	136/215 (63.3)	85/215 (39.5)
	52	Placebo	117/210 (55.7)	79/210 (37.6)	53/210 (25.2)
		4 mg qd	156/215 (72.6)	133/215 (61.9)	99/215 (46.0)
Genovese (RA-BEACON)	12	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)
Keystone	12	Placebo	40/98 (40.8)	10/98 (10.2)	2/98 (2.0)
		2 mg qd	28/52 (53.8)	9/52 (17.3)	4/52 (7.7)
		4 mg qd	39/52 (75.0)	18/52 (34.6)	12/52 (23.1)
Taylor (RA-BEAM)	12	Placebo	196/488 (40.2)	82/488 (16.8)	23/488 (4.7)
		4 mg qd	339/487 (69.6)	219/487 (45.0)	92/487 (18.9)
	24	Placebo	179/488 (36.7)	94/488 (19.3)	39/488 (8.0)
		4 mg qd	360/487 (73.9)	246/487 (50.5)	145/487 (29.8)
Decernotinib					
Fleischmann and Damjanov	12	Placebo	12/41 (29.3)	3/41 (7.3)	1/41 (2.4)
		25 mg bid	16/41 (39.0)	7/41 (17.1)	3/41 (7.3)
		50 mg bid	25/41 (61.0)	13/41 (31.7)	5/41 (12.2)
		100 mg bid	26/40 (65.0)	15/40 (37.5)	7/40 (17.5)
		150 mg bid	27/41 (65.9)	20/41 (48.8)	9/41 (22.0)
Genovese and van Vollenhoven	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)

Author (trial name)	Time (wk)	Dosage	ACR20	ACR50	ACR70
		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)
		100 mg bid	49/72 (68.1)	28/72 (38.9)	16/72 (22.2)
	24	Placebo	12/71 (16.9)	5/71 (7.0)	2/71 (2.8)
		100 mg qd	43/71 (60.6)	27/71 (38.0)	12/71 (16.9)
		150 mg qd	44/72 (61.1)	28/72 (38.9)	13/72 (18.1)
		200 mg qd	44/72 (61.1)	29/72 (40.3)	11/72 (15.3)
		100 mg bid	45/72 (62.5)	34/72 (47.2)	18/72 (25.0)
Filgotinib					
Genovese (FINCH 2)	12	Placebo	46/148 (31.1)	22/148 (14.9)	10/148 (6.8)
		100 mg qd	88/153 (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)	12148 (8.1)
		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)
Kavanaugh (DARWIN 2)	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)
Westhovens (DARWIN 1)	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 bid	49/86 (57.0)	24/86 (27.9)	12/86 (14.0)
		50 mg bid	51/85 (60.0)	29/85 (34.1)	16/85 (18.8)
		100 mg bid	66/84 (78.6)	46/84 (54.8)	26/84 (31.0)
	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)
		100 mg qd	52/85 (61.2)	40/85 (47.1)	28/85 (32.9)
		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)

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)
Takeuchi (RAJ4)	12	Placebo	37/170 (21.8)	13/170 (7.6)	4/170 (2.4)
		100 mg qd	102/174 (58.6)	52/174 (29.9)	21/174 (12.1)
		150 mg qd	112/174 (64.4)	80/174 (46.0)	41/174 (23.6)
Takeuchi and Tanaka	12	Placebo	6/56 (10.7)	3/56 (5.4)	1/56 (1.8)
		25 mg qd	13/55 (23.6)	4/55 (7.3)	0/55 (0.0)
		50 mg qd	18/57 (31.6)	5/57 (8.8)	1/57 (1.8)
		100 mg qd	30/55 (54.5)	17/55 (30.9)	9/55 (16.4)
		150 mg qd	38/58 (65.5)	17/58 (29.3)	7/58 (12.1)
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	15/59 (25.4)	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)

Author (trial name)	Time (wk)	Dosage	ACR20	ACR50	ACR70
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 qd	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	253/373 (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
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)

Author (trial name)	Time (wk)	Dosage	ACR20	ACR50	ACR70
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	
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)

Safety profile

The safety profile of jakinibs compared to 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, χ^2 = 11.85, I^2 = 7%). The commonly reported infections were upper respiratory tract infections, nasopharyngitis, or herpes zoster infections. Apart from these, there were no significant differences between jakinibs and the placebo with regard to treatment-emergent adverse events (TEAEs) (OR = 1.11, 95% CI 1.00-1.23, P = 0.05, χ^2 = 22.81, I^2 = 17%), SAEs (OR = 0.97, 95% CI 0.70–1.35, P = 0.87, χ^2 = 23.48, I^2 = 15%), discontinuations due to adverse events, (OR = 1.02, 95% CI 0.78–1.33, P = 0.90, χ^2 = 22.47, I^2 = 11%), or serious infection (OR = 1.18, 95% CI 0.66–2.12, P = 0.57, χ^2 = 11.39, I^2 = 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, χ^2 = 16.23, I^2 = 38%) and infectious diseases (OR = 1.47, 95% CI 1.26–1.71, P < 0.001, χ^2 = 6.16, I^2 = 0%) in response to jakinibs compared to placebo was observed in RA patients. In contrast, no increase in the risk of SAEs (OR = 0.84, 95% CI 0.62–1.13, P = 0.25, χ^2 = 11.36, I^2 = 12%), discontinuations due to adverse

events (OR = 1.18, 95% CI 0.90–1.54, P = 0.23, χ^2 = 8.80, I^2 = 0%), or serious infection (OR = 0.92, 95% CI 0.58–1.46, P = 0.74, χ^2 = 2.58, I^2 = 0%) was observed in comparisons between treatment with jakinibs and treatment with placebo in these RA patients (online supplementary figure S6).

Table 3
Summary of the safety profile of Jakinibs in rheumatoid arthritis.

Author (trial name)	Time (wk)	Dosage	TEAE	SAE	Discontinuation*	Infection disease	Serious infection
Baricitinib							
Dougados (RA-BUILD)	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 (67.2)	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 (RA-BEGIN)	24	Placebo	136/210 (64.8)	9/210 (4.3)	5/210 (2.4)	58/210 (27.6)	3/210 (1.4)
		4 mg qd	146/215 (67.9)	8/215 (3.7)	15/215 (7.0)	74/215 (34.4)	4/215 (1.9)
	52	Placebo	151/210 (71.9)	20/210 (9.5)	11/210 (5.2)	80/210 (38.1)	8/210 (3.8)
		4 mg qd	167/215 (77.7)	17/215 (7.9)	23/215 (10.7)	108/215 (50.2)	5/215 (2.3)
Genovese (RA-BEACON)	12	Placebo	96/176 (54.5)	7/176 (4.0)	4/176 (2.3)	35/176 (19.9)	3/176 (1.7)
		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)
	24	Placebo	112/176 (63.6)	13/176 (7.4)	7/176 (4.0)	55/176 (31.3)	5/176 (2.8)
		2 mg qd	123/174 (70.7)	7/174 (4.0)	7/174 (4.0)	76/174 (43.7)	4/174 (2.3)
		4 mg qd	137/177 (77.4)	18/177 (10.2)	11/177 (6.2)	70/177 (39.5)	6/177 (3.4)
Keystone	12	Placebo	45/98 (45.9)	3/98 (3.1)	5/98 (5.1)	N/A	0/98 (0.0)
		2 mg qd	24/52 (46.2)	3/52 (5.8)	1/52 (1.9)	N/A	2/52 (3.8)
		4 mg qd	22/52 (42.3)	0/52 (0.0)	1/52 (1.9)	N/A	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)

TEAE, treatment-emergent adverse event; SAE, serious adverse event; PLA, Placebo.*Discontinuations due to adverse events; N/A, not applicable.

Author (trial name)	Time (wk)	Dosage	TEAE	SAE	Discontinuation*	Infection disease	Serious infection
		4 mg qd	347/487 (71.3)	23/487 (4.7)	24/487 (4.9)	176/487 (36.1)	5/487 (1.0)
Decernotinib							
Fleischmann and Damjanov	12	Placebo	19/41 (46.3)	1/41 (2.4)	2/41 (4.9)	7/41 (17.1)	0/41 (0.0)
		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)
		100 mg bid	25/40 (62.5)	5/40 (12.5)	7/40 (17.5)	10/40 (25.0)	3/40 (7.5)
		150 mg bid	22/41 (53.7)	2/41 (4.9)	5/41 (12.2)	8/41 (19.5)	2/41 (4.9)
Genovese and van Vollenhoven	24	Placebo	30/71 (42.3)	4/71 (5.6)	N/A	N/A	N/A
		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)
	24	Placebo	100/148 (67.6)	5/148 (3.4)	3/148 (2.0)	38/148 (25.7)	2/148 (1.4)
		100 mg qd	97/153 (63.4)	8/153 (5.2)	6/153 (3.9)	52/153 (34.0)	1/153 (0.7)
		200 mg qd	102/147 (69.4)	6/147 (4.1)	5/147 (3.4)	53/147 (36.1)	3/147 (2.0)
Kavanaugh (DARWIN 2)	12	Placebo	28/72 (38.9)	1/72 (1.4)	4/72 (5.6)	N/A	0/72 (0.0)

TEAE, treatment-emergent adverse event; SAE, serious adverse event; PLA, Placebo.*Discontinuations due to adverse events; N/A, not applicable.

Author (trial name)	Time (wk)	Dosage	TEAE	SAE	Discontinuation*	Infection disease	Serious infection
		50 mg qd	29/72 (40.3)	1/72 (1.4)	1/72 (1.4)	N/A	1/72 (1.4)
		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)	1/56 (1.8)
		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)	4/85 (4.7)	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)
		50 mg bid	46/85 (54.1)	0/85 (0.0)	2/85 (2.4)	7/85 (8.2)	0/85 (0.0)
		100 mg bid	45/84 (53.6)	3/84 (3.6)	3/84 (3.6)	7/84 (8.3)	1/84 (1.2)
Peficitinib							
Kivitz	12	Placebo	34/72 (47.2)	0/72 (0.0)	1/72 (1.4)	N/A	0/72 (0.0)
		25 mg qd	28/66 (42.4)	0/66 (0.0)	0/66 (0.0)	N/A	0/66 (0.0)
		50 mg qd	39/78 (50.0)	0/78 (0.0)	0/78 (0.0)	N/A	0/78 (0.0)
		100 mg qd	40/84 (47.6)	2/84 (2.4)	3/84 (3.6)	N/A	1/84 (1.2)
		150 mg qd	39/78 (50.0)	1/78 (1.3)	4/78 (5.1)	N/A	1/78 (1.3)
Takeuchi (RAJ4)	12	Placebo	84/170 (49.4)	4/170 (2.4)	7/170 (4.1)	N/A	0/170 (0.0)
		100 mg qd	89/174 (51.1)	5/174 (2.9)	5/174 (2.9)	N/A	6/174 (3.4)
		150 mg qd	104/174 (59.8)	3/174 (1.7)	5/174 (2.9)	N/A	6/174 (3.4)
Takeuchi and Tanaka	12	Placebo	36/56 (64.3)	1/56 (1.8)	10/56 (17.9)	12/56 (21.4)	0/56 (0.0)
		25 mg qd	39/55 (70.9)	1/55 (1.8)	7/55 (12.7)	18/55 (32.7)	0/55 (0.0)

TEAE, treatment-emergent adverse event; SAE, serious adverse event; PLA, Placebo.*Discontinuations due to adverse events; N/A, not applicable.

Author (trial name)	Time (wk)	Dosage	TEAE	SAE	Discontinuation*	Infection disease	Serious infection
		50 mg qd	37/57 (64.9)	2/57 (3.5)	5/57 (8.8)	14/57 (24.6)	0/57 (0.0)
		100 mg qd	29/55 (52.7)	3/55 (5.5)	6/55 (10.9)	7/55 (12.7)	0/55 (0.0)
		150 mg qd	39/58 (67.2)	0/58 (0.0)	4/58 (6.9)	17/58 (29.3)	0/58 (0.0)
Tofacitinib							
Burmester (ORAL Step)	12	Placebo	75/132 (56.8)	6/132 (4.5)	7/132 (5.3)	N/A	0/132 (0.0)
		5 mg bid	71/133 (53.4)	2/133 (1.5)	8/133 (6.0)	N/A	0/133 (0.0)
		10 mg bid	76/134 (56.7)	2/134 (1.5)	6/134 (4.5)	N/A	0/134 (0.0)
Fleischmann (ORAL Solo)	12	Placebo	67/122 (54.9)	6/122 (4.9)	5/122 (4.1)	N/A	0/122 (0.0)
		5 mg bid	124/243 (51.0)	1/243 (0.4)	2/243 (0.8)	N/A	0/243 (0.0)
		10 mg bid	139/245 (56.7)	5/245 (2.0)	6/245 (2.4)	N/A	1/245 (0.4)
Fleischmann and Cutolo	24	Placebo	16/34 (47.1)	2/34 (5.9)	1/34 (2.9)	6/34 (17.6)	1/34 (2.9)
		1 mg bid	19/37 (51.4)	1/37 (2.7)	4/37 (10.8)	11/37 (29.7)	2/37 (5.4)
		3 mg bid	18/34 (52.9)	2/34 (5.9)	3/34 (8.8)	7/34 (20.6)	0/34 (0.0)
		5 mg bid	27/49 (55.1)	1/49 (2.0)	1/49 (2.0)	17/49 (34.7)	0/49 (0.0)
		10 mg bid	36/61 (59.0)	0/61 (0.0)	1/61 (1.6)	21/61 (34.4)	0/61 (0.0)
		15 mg bid	35/57 (61.4)	5/57 (8.8)	3/57 (5.3)	19/57 (33.3)	1/57 (1.8)
Kremer (ORAL Sync)	12	Placebo	97/159 (61.0)	6/159 (3.8)	2/159 (1.3)	N/A	0/159 (0.0)
		5 mg bid	166/315 (52.7)	9/315 (2.9)	13/315 (4.1)	N/A	2/315 (0.6)
		10 mg bid	169/318 (53.3)	8/318 (2.5)	13/318 (4.1)	N/A	4/318 (1.3)
Kremer and Cohen	24	Placebo	29/51 (56.9)	0/51 (0.0)	3/51 (5.9)	3/51 (5.9)	0/51 (0.0)
		1 mg bid	29/49 (59.2)	1/49 (2.0)	3/49 (6.1)	7/49 (14.3)	0/49 (0.0)

TEAE, treatment-emergent adverse event; SAE, serious adverse event; PLA, Placebo.*Discontinuations due to adverse events; N/A, not applicable.

Author (trial name)	Time (wk)	Dosage	TEAE	SAE	Discontinuation*	Infection disease	Serious infection
		3 mg bid	38/55 (69.1)	2/55 (3.6)	2/55 (3.6)	11/55 (20.0)	2/55 (3.6)
		5 mg bid	47/71 (66.2)	4/71 (5.6)	3/71 (4.2)	16/71 (22.5)	1/71 (1.4)
		10 mg bid	50/74 (67.6)	7/74 (9.5)	5/74 (6.8)	13/74 (17.6)	1/74 (1.4)
		15 mg bid	57/75 (76.0)	6/75 (8.0)	10/75 (13.3)	14/75 (18.7)	0/75 (0.0)
		20 mg qd	41/67 (61.2)	2/67 (3.0)	6/67 (9.0)	13/67 (19.4)	1/67 (1.5)
Lee	24	Placebo	147/186 (79.0)	22/186 (11.8)	25/186 (13.4)	N/A	5/186 (2.7)
		5 mg bid	297/373 (79.6)	40/373 (10.7)	40/373 (10.7)	N/A	11/373 (2.9)
		10 mg bid	334/397 (84.1)	43/397 (10.8)	41/397 (10.3)	N/A	8/397 (2.0)
Tanaka and Suzuki	12	Placebo	N/A	0/28 (0.0)	2/28 (7.1)	6/28 (21.4)	0/28 (0.0)
		1 mg bid	N/A	1/28 (3.6)	0/28 (0.0)	3/28 (10.7)	0/28 (0.0)
		3 mg bid	N/A	1/27 (3.7)	2/27 (7.4)	8/27 (29.6)	0/27 (0.0)
		5 mg bid	N/A	1/27 (3.7)	4/27 (14.8)	3/27 (11.1)	0/27 (0.0)
		10 mg bid	N/A	2/26 (7.7)	4/26 (15.4)	11/26 (42.3)	0/26 (0.0)
Tanaka and Takeuchi	12	Placebo	23/52 (44.2)	1/52 (1.9)	2/52 (3.8)	N/A	0/52 (0.0)
		1 mg bid	21/53 (39.6)	0/53 (0.0)	0/53 (0.0)	N/A	0/53 (0.0)
		3 mg bid	23/53 (43.4)	3/53 (5.7)	1/53 (1.9)	N/A	0/53 (0.0)
		5 mg bid	29/52 (55.8)	2/52 (3.8)	2/52 (3.8)	N/A	0/52 (0.0)
		10 mg bid	32/53 (60.4)	2/53 (3.8)	3/53 (5.7)	N/A	0/53 (0.0)
		15 mg bid	28/54 (51.9)	1/54 (1.9)	0/54 (0.0)	N/A	0/54 (0.0)
van der Heijde (ORAL Scan)	12	Placebo	73/160 (45.6)	5/160 (3.1)	5/160 (3.1)	N/A	0/160 (0.0)
		5 mg bid	157/321 (48.9)	12/321 (3.7)	15/321 (4.7)	N/A	2/321 (0.6)

TEAE, treatment-emergent adverse event; SAE, serious adverse event; PLA, Placebo.*Discontinuations due to adverse events; N/A, not applicable.

Author (trial name)	Time (wk)	Dosage	TEAE	SAE	Discontinuation*	Infection disease	Serious infection
		10 mg bid	171/316 (54.1)	10/316 (3.2)	14/316 (4.4)	N/A	2/316 (0.6)
van Vollenhoven (ORAL Standard)	12	Placebo	51/108 (47.2)	2/108 (1.9)	3/108 (2.8)	N/A	1/108 (0.9)
		5 mg bid	106/204 (52.0)	12/204 (5.9)	14/204 (6.9)	N/A	3/204 (1.5)
		10 mg bid	94/201 (46.8)	10/201 (5.0)	10/201 (5.0)	N/A	4/201 (2.0)
	24	Placebo	16/59 (27.1)	2/59 (3.4)	0/59 (0.0)	N/A	0/59 (0.0)
		5 mg bid	7/28 (25.0)	0/28 (0.0)	1/28 (3.6)	N/A	0/28 (0.0)
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)

TEAE, treatment-emergent adverse event; SAE, serious adverse event; PLA, Placebo.*Discontinuations due to adverse events; N/A, not applicable.

Author (trial name)	Time (wk)	Dosage	TEAE	SAE	Discontinuation*	Infection disease	Serious infection
		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; PLA, Placebo.*Discontinuations due to adverse events; N/A, not applicable.

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 can inhibit intracellular kinases, especially those from the JAK family [47]. In our meta-analysis of 28 RCTs with 14500 participants worldwide, we compared the efficacy and safety of jakinibs with those of placebo or csDMARDs in the treatment of patients with RA with an inadequate response or intolerance to csDMARDs or biologics. The majority of trials in this meta-analysis reported a significant improvement in the clinical response of ACR20/50/70 after jakinib treatment in a short-term follow-up. Of note, the 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. With regard to 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. It developed a relatively comprehensive analysis of RA patients strictly recruited from hundreds of centers worldwide. Only mild heterogeneity was observed among the included studies.

Methotrexate is considered to be the most preferred csDMARD and is generally offered as a first-line treatment for RA. On the other hand, biologics, especially 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 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 to be 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 5- 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. In contrast, baricitinib selectively inhibits the 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 depicted that the number of RA patients treated with jakinibs who experienced 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 (decernotinib 59.9% vs. placebo 42.3%) at week 24, which included headache (8.7%) and elevated levels of transaminases, lipoproteins, and creatinine. Moreover, because of their pharmacological action, which is acting as JAK1/3 inhibitors, jakinibs have the potential to cause immunosuppression that induces serious infections. The most commonly reported infections were upper respiratory tract infections, nasopharyngitis, or herpes zoster infections. This did not result in patient withdrawal at week 12 or 24, as shown in our meta-analysis. On the other hand, 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 needed to confirm the long-term safety of the drugs.

Some limitations in our analysis need to 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 due to the comprehensive literature search and efforts to obtain as much as 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 needed to evaluate the long-term effects of jakinib treatment. Third, the types of jakinibs used in each study and differences in the dosages administered also added to the heterogeneity. Since 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

In summary, jakinib therapy showed benefits in achieving ACR20/50/70 responses with acceptable safety profiles in active RA patients who were refractory to aggressive standard-of-care treatment in a short-term follow-up. Jakinibs can be considered a favorable option for patients with 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

Declarations

Acknowledgments

Not applicable.

Author contributions

YY, ML and JW contributed to the conception and design. YY, ML, MH and MW contributed to the collection and assembly of the data. YY and JW contributed to the analysis and interpretation of the data. YY and JW contributed to drafting and revision of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (81771782, 81801595, 81601415), the Special Foundation of Diagnosis and Treatment for Key Clinical Diseases of Suzhou City (LCZX201802), the Science and Technology Development Plan for Medical Device of Suzhou City (SLT201902), Young Medical Talent Project of Jiangsu Province (QNRC2016754), and the Science and Technology Plan Project of Suzhou City (SYS2019043).

Availability of data and materials

All data generated and analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study did not require ethical approval or informed consent since all analyses were based on previously published data.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to disclose. Data on which the study is based are publicly available.

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Figures

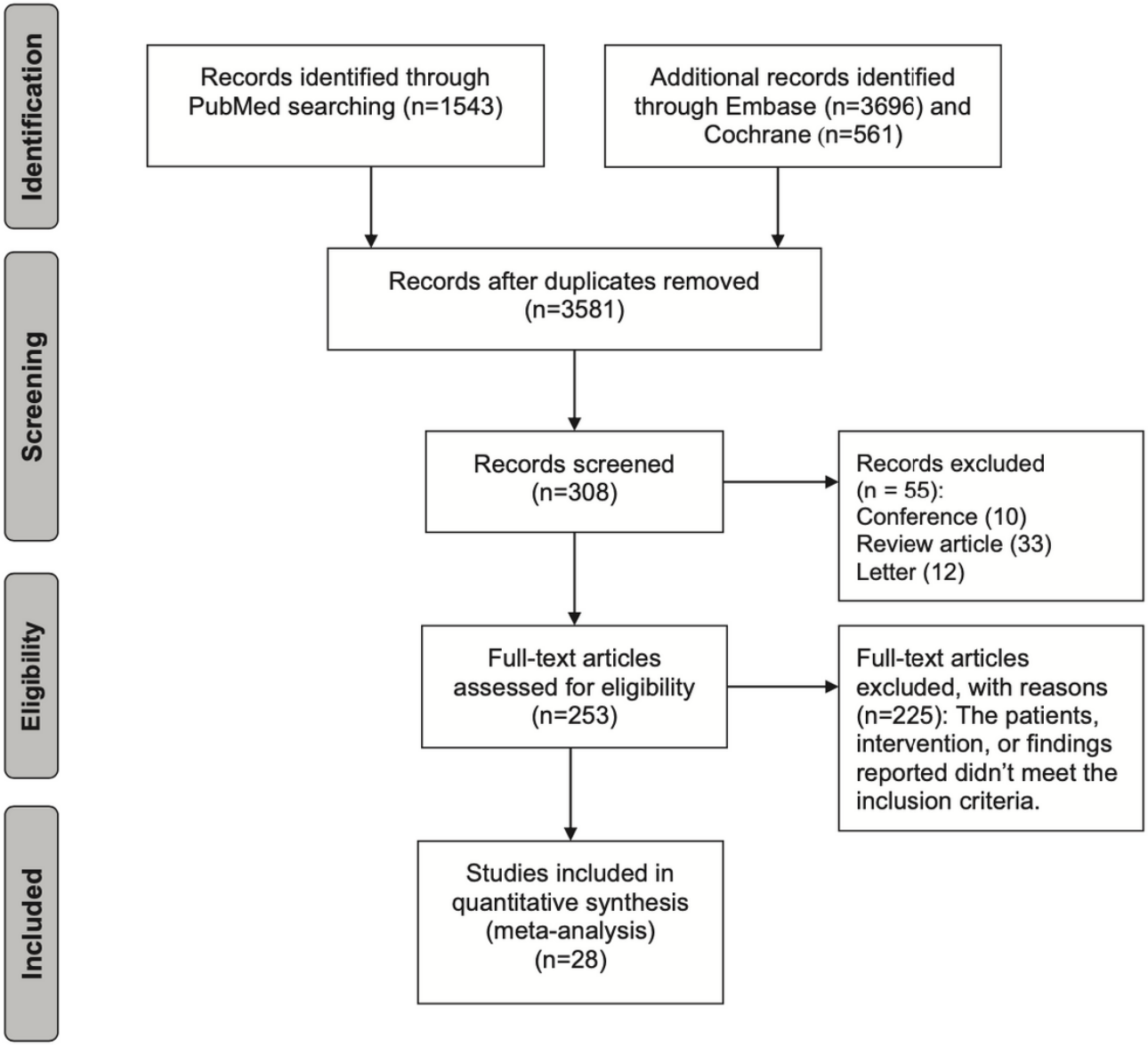

Figure 1

Flowchart of the study selection.

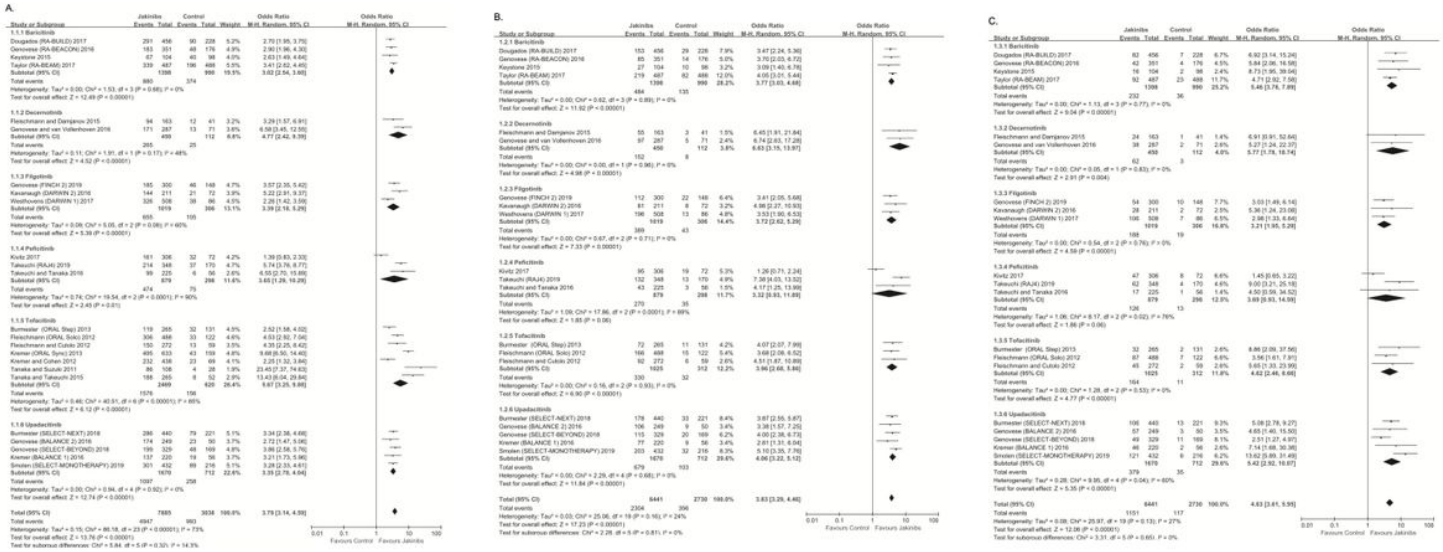

Figure 2

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.

Supplementary Files

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