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Fourteen small molecule and biological agents for psoriatic arthritis

A network meta-analysis of randomized controlled trials

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Abstract

Background: The comparative efficacy and safety of small molecule and biological agents in the treatment of psoriatic arthritis (PsA) remain unknown.

Objectives: To compare the efficacy and safety of 14 small molecule and biological agents by network meta-analysis (NMA).

Methods: Relevant randomized controlled trials involving biological treatments for PsA were identified by searching PubMed, Cochrane Library, EMBASE, Web of Science, and Clinicaltrials.gov and by manual retrieval, up to June 2018. NMA was conducted with Stata 14.0 based on the frequentist method. Effect measures were odds ratios (ORs) with 95% confidence intervals (CIs). Intervention efficacy and safety were ranked according to the surface under the cumulative ranking curve (SUCRA).

Results: A total of 30 studies involving 10,191 adult subjects were included. According to NMA, ≥ 20% improvement in modifed American College of Rheumatology response criteria (ACR20) response, Psoriasis Area and Severity Index 75 (PASI75) response, and serious adverse events rate (SAEs) were observed. In direct comparisons, most of the biologics performed better than placebo in terms of ACR20 response rate and PASI75 response rate. Additionally, all medicines were comparable to placebo in terms of SAEs except secukinumab. In terms of mixed comparisons, with regard to the ACR20 response, etanercept (ETN) and infliximab (IFX) were more effective than golimumab (GOL), with ORs of 3.33 (95% CI: 1.17–9.48) and 1.24 (95% CI: 0.61–2.52), respectively. For PASI75 response, IFX was superior to certolizumab pegol (OR = 10.08, 95% CI: 1.54–75.48). In addition, these medicines were comparable to each other in terms of SAEs. ETN and IFX were shown to have the most favorable SUCRA for achieving improved ACR20 and PASI75 responses, respectively, while ABT-122 exhibited the best safety according to the SUCRA for SAEs. Considering both the efficacy (ACR20, PASI75) and safety (SAEs), GOL, ETN, and IFX are the top 3 treatments.

Conclusions and Implications: Direct and indirect comparisons and integrated results suggested that the 3 anti- tumor necrosis factor -α biologics (GOL, ETN, and IFX) can be considered the best treatments for PsA after comprehensive consideration of efficacy and safety.

Abbreviations: ABA = abatacept, ABT = ABT-122, ACR20 = ≥ 20% improvement in modifed American College of Rheumatology response criteria, ADA = adalimumab, APR = apremilast, BRD = brodalumab, CI = confidence interval, CLA = Clazakizumab, CTLA4 = cytotoxic T-lymphocyte associated protein 4, CZP = certolizumab pegol, EMA = European Medicines

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QM and XZ contributed equally and should be considered co-first authors.

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Agency, ETN = etanercept, FDA = Food and Drug Administration, GOL = golimumab, IFX = infliximab, IL = interleukin, IXE = ixekizumab, JAK = janus kinase, NMA = network meta-analysis, OR = odds ratio, PASI75 = ≥75% reduction in Psoriasis Area and Severity Index, PBO = Placebo, PDE-4 = Type-4 cyclic nucleotide phosphodiesterase, PsA = psoriatic arthritis, RCT = randomized controlled trial, SAEs = serious adverse events, SEC = secukinumab, TNF = tumor necrosis factor, TOF = Tofacitinib, UST = ustekinumab.

Keywords: biological agents, network meta-analysis, psoriatic arthritis, small molecule

1. Introduction

Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease characterized by swelling and pain in the peripheral joints, resulting in structural damage, disability, and a profound alteration of patients' lives.[1,2] There is a close relationship between PsA and psoriasis. Up to 30% of patients with psoriasis are affected by PsA.[2] The global PsA prevalence and incidence are 133 out of every 100,000 subjects and 83 per 100,000 patient year, respectively.[3] Disease-modifying antirheumatic drugs and nonsteroidal anti-inflammatory drugs are the primary initial treatment options for PsA.[4] For patients who are nonresponsive or are intolerant to the initial treatment, biological therapy and small molecules are recommended as secondary treatment according to several international guidelines.[5,6]

Among all of the biologics, agents targeting tumor necrosis factor (TNF)-α remain the first choice for PsA.[4] To date, 5 such agents, namely adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETN), golimumab (GOL), and infliximab (IFX), have been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Unfortunately, there are still some patients that exhibit intolerance or primary or secondary nonresponsiveness to anti-TNF-α therapy. Our in-depth knowledge of the pathogenesis of PsA has enabled the development of more targeted therapies for the management of these conditions. So far, emerging clinical evidence suggests that another class of biologics, including anti-interleukin (IL)-17 (secukinumab [SEC], ixekizumab [IXE], and brodalumab [BRD]), anti-IL-12/23 (ustekinumab [UST]), and cytotoxic T-lymphocyte associated protein 4 immune globulin (CTLA-4-Ig) (abatacept [ABA]), or small molecule therapies, such as type-4 cyclic nucleotide phosphodiesterase (PDE-4) inhibitor (apremilast [APR]) and Janus kinase (JAK) inhibitor (tofacitinib [TOF]), should be used for these patients. These agents are either recently approved or being tested in clinical trials and have demonstrated encouraging results. Fully human monoclonal antibodies (mAbs) targeting IL-17A, SEC, and IXE, were registered for PsA in 2016 by the FDA[7] and in 2015 by the EMA[8] for SEC and in 2017 by the FDA[9] for IXE. UST, a fully human mAb targeting the shared p40 subunit of IL-12 and IL-23, was approved in 2013 by the FDA[10] and in 2014 by the EMA.[11] ABA, a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4, was approved for PsA therapy in 2017 in the USA[12] and in 2017 by the EMA.[13] APR, an oral small molecule inhibitor of PDE-4, was approved for the treatment of PsA in 2014 by the FDA[14] and the EMA.[15] Although not yet approved, clinical evidence has shown that clazakizumab (CLA), a mAb with high affinity and specificity for the IL-6 cytokine[16]; BRD, an IL-17 receptor competitive blocker that prevents IL-17 from activating the receptor[17]; TOF, an inhibitor of JAKs[18]; and ABT-122 (ABT), a TNF-α- and IL-17A-targeted dual variable domain immunoglobulin,[19] are promising for the treatment of PsA.

Since patients with PsA require lifelong treatment, convincing evidence of the comparative efficacy and safety of these biologics is needed. However, there has been no comprehensive comparison of all biologics and small molecules in terms of efficacy and safety to date. To compare the efficacy and safety of small molecule therapy (APR and TOF) and biological therapy, including anti-TNF-α (ETN, IFX, ADA, CZP, and GOL), anti-IL-12/23 (UST), anti-IL-17 (SEC, IXE, and BRD), anti-IL-6 (CLA), CTLA-4-Ig (ABA), and TNF-α/IL-17 dual (ABT) therapies, a network meta-analysis (NMA) was conducted for patients with PsA.

2. Methods

2.1. Inclusion and exclusion criteria

This study was registered on the Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42018099258. The inclusion criteria were as follows: the study design was a randomized controlled trial (RCT) of patients who were diagnosed with PsA (aged ≥18 years old). RCTs with any pairwise comparison of small molecule or biologic therapy or placebo (PBO) were eligible. The main outcome measures were the proportion of patients achieving

≥20% improvement in modified American College of Rheumatology response criteria (ACR 20) or ≥ 75% reduction in Psoriasis Area and Severity Index (PASI75) response and the proportion of patients with serious adverse events (SAEs). Exclusion criteria included non-RCT literature, incomplete data, case reports, reviews, animal experiments, conference papers, and duplicate published literature.

2.2. Search strategy

Relevant RCT studies were identified by searching PubMed, Cochrane Library, EMBASE Web of Science, and Clinicaltrials.gov and by manual retrieval up to June 2018. The keywords used for searching were as follows: "psoriatic arthritis", "tumor necrosis factor alpha inhibitor", "interleukin inhibitor", "cytotoxic T-lymphocyte associated protein 4", "type-4 cyclic nucleotide phosphodiesterase inhibitor", "tofacitinib", "etanercept", "infliximab", "adalimumab", "golimumab", "certolizumab pegol", "ustekinumab", "secukinumab", "ixekizumab", "brodalumab", "clazakizumab", "abatacept", "apremilast", and "randomized controlled trial" (see details in Supplemental Digital Content [Appendix 1, http://links.lww.com/MD/E609])

2.3. Data extraction and quality assessment

Two researchers independently selected the studies and screened them, and a third researcher was involved to resolve disagree-

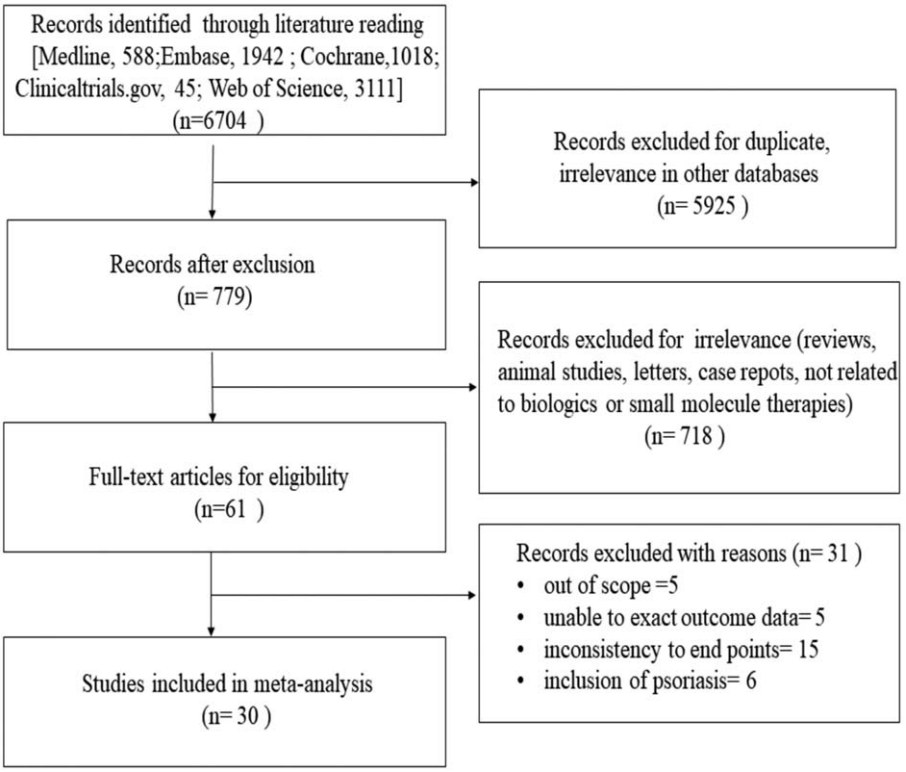

Figure 1. Flow diagram of the study selection process.

ments. The data extracted included authors, publication years, sample size, intervention measures, and course of treatment. Quality evaluation was carried out by the random method, allocation concealment, blind method, loss of visitation, and baseline situation, according to the Cochrane risk of bias tool.[20]

2.4. Statistical analysis

We provide a narrative synthesis of the findings from the included studies structured around the type of intervention, target population characteristics, type of outcome, and intervention content. We combined direct evidence using pairwise meta-analysis and direct and indirect evidence using a frequentist NMA. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the intergroup effects for binary variables. The heterogeneity between the studies was evaluated using Cochran Q test and the I^2 statistic, and we considered a P-value for Cochran Q test $<.1$ and an I^2 value greater than 50% as significant heterogeneity. All meta-analyses were conducted using the random effects model. In the NMA, we assessed inconsistencies in direct and indirect comparisons using the node-splitting method. The probability of efficacy rankings was measured by the surface under the cumulative ranking curve (SUCRA), and a comparison-adjusted funnel plot was used to identify evidence of small sample effects in the intervention network.

The statistical analysis for the NMA was performed using Stata 14.0 (StataCorp, College Station, TX), and a net relation diagram, contribution graph, inconsistency check chart, comparison-adjusted funnel plot, and forest plot were drawn using the network graphs package. The report was conducted and is presented in accordance with the PRISMA statement for NMA.[21]

3. Results

3.1. Characteristics and quality of eligible studies

Of the 6704 titles screened, 111 records had their abstracts assessed. Of those, 61 full-text studies were assessed for eligibility. Finally, a total of 30 publications involving 10,191 adults met the inclusion criteria for this review (Fig. 1). The characteristics (including the patient eligibility and concomitant medication) of the included studies are summarized in Table 1 and Supplemental Digital Content (table S1, http://links.lww.com/MD/E610). To be noted, the patients enrolled in the clinical trials on the non-TNF-a inhibitors for PsA were not uniformly required to be those who previously failed or could not tolerate TNF-a inhibitors. Across all interventions, the mean age of patients ranged from 43.5 to 53.0 years, the percentage of male patients ranged from 28.6% to 62.3%, and the RCT period ranged from 12 weeks to 24 weeks. The methodological quality of the literature is summarized in Figure 2. It can be seen that most studies were randomized and double-blinded. Accordingly, the funnel plots for ACR20 (Fig. 3A), PASI75 (Fig. 3B), and SAEs (Fig. 3C) are almost symmetric, indicating little publication bias.

3.2. Network evaluations of statistical associations

The evidence network diagram (Fig. 4) confirmed the transitivity of NMA by checking direct and indirect evidence. There were 16 pairwise comparisons that included 14 interventions in the

Table 1

Characteristics of the patients from the included randomized controlled trials.

ID	Study	Data sources	Groups	Number of patients	Male (%)	Age (yr)	Disease duration (yr)	Follow up time (wk)*	Swelling joints	Tender joints	CRP (mg/L)
1	Antoni 2005 (1)[22]	IMPACT 2	Placebo	100	51 (51.0)	46.5±11.3	NA	14 wk	14.4±8.9	25.1±13.3	23.0±34.0
			Infliximab (5 mg/kg) at weeks 0, 2, 6, 14 and 22	100	71 (71.0)	47.1±12.8	NA		13.9±7.9	24.6±14.1	19.0±21.0
2	Antoni 2005 (2)[23]	IMPACT	Placebo	52	30 (57.7)	45.2±9.7	11.0±6.6	16 wk	14.7±8.2	20.4±12.1	31.1±38.1
			Infliximab (5 mg/kg) at week 0, 2, 6 and 14	52	30 (57.7)	45.7±11.1	11.7±9.8		14.6±7.5	23.7±13.7	21.7±27.0
3	Cutolo 2016[24]	PALACE 2	Placebo	159	74 (46.5)	51.2±11.0	7.8±8.3	16 wk	9.2±6.6	18.0±13.5	NA
			Apremilast 20 mg bid	163	68 (41.7)	50.9±11.8	7.8±8.6		10.4±7.8	20.3±16.6	NA
			Apremilast 30 mg bid	162	67 (41.4)	50.5±11.2	6.8±7.6		10.3±8.1	21.8±16.8	NA
4	Edwards 2016[25]	PALACE 3	Placebo	169	68 (40.2)	49.5±11.6	6.8±6.5	16 wk	11.1±7.9	18.3±14.9	1.00±1.35
			Apremilast 20 mg bid	169	79 (46.8)	49.6±12.1	7.5±7.6		11.4±9.1	20.8±16.8	0.97±1.51
			Apremilast 30 mg bid	167	79 (46.7)	49.9±11.4	7.7±7.7		11.6±8.7	20.9±14.4	1.15±1.88
5	Genovese 2007[26]	Stanford University	Placebo	49	25 (51.0)	47.7±11.3	7.2±7.0	12 wk	18.4±12.1	29.3±18.1	NA
			Adalimumab 40 mg q2w	51	29 (56.9)	50.4±11.0	7.5±7.0		18.2±10.9	25.3±18.3	NA
6	Gladman 2017[18]	OPAL Beyond	Placebo	131	51 (38.9)	49.0±12.6	NA	12 wk	10.5±9.0	19.8±14.9	80.0±61.0
			Tofacitinib 5 mg bid	131	67 (51.1)	49.5±12.3	NA		12.1±10.6	20.5±13.0	85.0±65.0
			Tofacitinib 10 mg bid	132	58 (43.9)	51.3±10.9	NA		12.8±11.2	25.5±17.5	82.0±62.0
7	Gottlieb 2009[27]	NCT00267956	Placebo	70	37 (52.9)	47.5 (40.0–55.0)	6.2 (2.8–13.7)	12 wk	7.0 (5.0–14.0)	16.0 (9.0–32.0)	7.0 (3.0–11.0)
			Ustekinumab 90 mg or 63 mg at week 0,1,2,3	76	45 (59.2)	50.0 (42.0–60.5)	4.9 (2.4–10.7)		10.0 (6.0–16.0)	19.5 (10.0–33.5)	4.0 (3.0–8.0)
8	Kavanaugh 2017[28]	GO-VIBRANT	placebo	239	121 (50.6)	46.7±12.5	5.3±5.9	14 wk	14.1±8.2	26.1±14.4	2.0±2.0
			Golimumab 2mg/kg at weeks 0, 4 and then q8w	241	128 (53.1)	45.7±11.3	6.2±6.0		14.0±8.4	25.1±13.8	1.9±2.5
9	Kavanaugh 2009[29]	GO-REVEAL	Placebo	113	69 (61.1)	47.0±10.6	7.6±7.9	14 wk	13.4±9.8	21.9±14.7	1.3±1.6
			Golimumab 50 mg q4w	146	89 (61.0)	45.7±10.7	7.2±6.8		14.1±11.4	24.0±17.1	1.3±1.6
			Golimumab 100 mg q4w	146	86 (58.9)	48.±10.9	7.7±7.8		12.0±8.4	22.5±15.7	1.4±1.8
10	Kavanaugh 2014[30]	NCT01172938	Placebo	168	88 (52.4)	51.1±12.1	7.3±7.1	16 wk	12.8±8.8	23.3±15.2	1.1±1.4
			Apremilast 20 mg bid	168	85 (50.6)	48.7±11.0	7.2±6.8		12.5±9.5	22.2±15.9	0.9±1.4
			Apremilast 30 mg bid	168	76 (45.2)	51.4±11.7	8.1±8.1		12.8±7.8	23.1±14.5	0.8±1.0
11	McInnes 2013[31]	PSUMMIT 1	Placebo	206	108 (52.4)	48.0 (39.0–57.0)	NA	24 wk	12 (8.0–19.0)	22.0 (13.0–33.0)	9.6 (6.0–18.6)
			Ustekinumab 45 mg at week 0, 4 and then q12w	205	106 (51.7)	48.0 (39.0–55.0)	NA		10 (7.0–15.0)	18.0 (12.0–28.0)	10.0 (5.9–21.1)
			Ustekinumab 90 mg at week 0, 4 and then q12w	204	116 (56.9)	47.0 (38.5–54.0)	NA		10 (7.0–16.0)	20.0 (12.0–32.0)	12.3 (6.5–21.7)
12	Mease 2011[32]	NCT00534313	Placebo	42	23 (54.8)	52.6±12.0	NA	24 wk	10.5±7.9	21.3±15.3	1.3±2.7
			Abatacept 10 mg/kg on days 1, 15, 29 and then q28d	40	26 (0.65)	50.8±10.5	NA		12.5±8.7	25.2±15.6	1.5±1.8
			Abatacept 3mg/kg on days 1, 15, 29 and then q28d	45	22 (48.9)	50.3±9.9	NA		10.3±6.9	22.7±14.6	1.8±2.4
			Abatacept 30/10 mg/kg on days 1, 15, 29 and then q28d	43	18 (41.9)	51.5±9.8	NA		10.3±7.1	19.6±11.4	2.2±5.2
13	Mease 2018 (1)[33]	FUTURE 5	Placebo	332	161 (48.5)	49.0±12.1	NA	16 wk	11.7±10.8	21.2±16.2	NA
				220	111 (50.5)	48.4±12.9	NA		12.1±10.5	21.2±15.9	NA

(*continued*)

Table 1
(continued).

ID	Study	Data sources	Groups	Number of patients	Male (%)	Age (yr)	Disease duration (yr)	Follow up time (wk)*	Swelling joints	Tender joints	CRP (mg/L)
			Secukinumab 150 mg with loading dose at week 0, 1, 2,3 and then q4w								
			Secukinumab 150 mg with loading dose at week 0, 1, 2,3 and then q4w	222	120 (54.1)	48.8 ± 11.8	NA		11.9 ± 10.3	21.8 ± 16.0	NA
			Secukinumab300 mg with loading dose at week 0, 1, 2,3 and then q4w	222	108 (48.6)	48.9 ± 12.8	NA		10.0 ± 8.0	19.8 ± 15.1	NA
14	Mease 2014 (1)[34]	RAPID-PsA	Placebo	136	57 (41.9)	47.3 ± 11.1	7.9 ± 7.7	12 wk	10.4 ± 7.6	19.9 ± 14.7	9.0 (0.2–131.0)
			Certolizumab pegol 200 mg q2w	138	64 (46.4)	48.2 ± 12.3	9.6 ± 8.5		11.0 ± 8.8	21.5 ± 15.3	7.0 (0.2–238.0)
			Certolizumab pegol 400 mg q4w	135	62 (45.9)	47.1 ± 10.8	8.1 ± 8.3		10.5 ± 7.5	19.6 ± 14.8	8.7 (0.1–87.0)
15	Mease 2014 (2)[17]	NCT 01516957	Placebo	55	25 (45.5)	53 ± 13	8.4 ± 7.5	12 wk	12.8 ± 8.5	25.0 ± 16.2	NA
			Brodalumab 140 mg on day 1 and at week1, 2, 4, 6, 8, and 10	57	20 (35.1)	53 ± 10	9.4 ± 7.5		13.6 ± 10.5	27.0 ± 16.4	NA
			Brodalumab 280 mg on day 1 and at week 1, 2, 4, 6, 8, and 10	56	16 (28.6)	51 ± 12	8.1 ± 7.9		11.4 ± 9.3	20.8 ± 15.3	NA
16	Mease 2018 (2)[19]	NCT02349451	Placebo	24	12 (50.0)	47.7 ± 13.7	7.6 ± 7.2	12 wk	13.4 ± 11.4	19.0 ± 14.7	NA
			Adalimumab 40 mg q2w	72	39 (54.2)	50.5 ± 12.0	8.4 ± 9.2		14.0 ± 10.6	23.4 ± 17.0	NA
			ABT-122 120 mg qw	71	34 (47.9)	51.0 ± 12.4	5.9 ± 7.1		12.7 ± 10.4	21.7 ± 14.6	NA
			ABT-122 240 mg qw	73	36 (49.3)	47.4 ± 13.8	7.5 ± 8.2		14.8 ± 11.8	23.6 ± 14.3	NA
17	Mease 2005[35]	Swedish Medical Center	Placebo	162	89 (54.9)	49.2 ± 11.1	9.2 ± 8.7	12 wk	14.3 ± 11.1	25.8 ± 18.0	1.4 ± 1.7
			Adalimumab 40 mg q2w	151	85 (56.3)	48.6 ± 12.5	9.8 ± 8.3		14.3 ± 12.2	23.9 ± 17.3	1.4 ± 2.1
18	Mease 2000[36]	Minor and James Medical	Placebo	30	18 (60.0)	43.5 (24.0–63.0)	9.5 (1.0–30.0)	12 wk	14.0 (8.0, 23.0)	22.5 (11, 32)	14.0 (7.0, 28.0)
			Etanercept 25 mg q2w	30	16 (53.3)	46.0 (30.0–70.0)	9.0 (1.0–31.0)		14.7 (7.0, 24.0)	19.0 (10, 39)	12.0 (8.0, 22.0)
19	Mease 2016[16]	NCT01490450	Placebo	41	18 (43.9)	48.0 ± 10.5	8.5 ± 9.1	16 wk	11.2 ± 9.3	21.2 ± 13.8	11.0 ± 13.7
			Clazakizumab 25 mg q4w	41	18 (43.9)	49.8 ± 14.1	9.6 ± 9.0		12.4 ± 9.3	23.0 ± 16.4	13.2 ± 16.3
			Clazakizumab 100 mg q4w	42	22 (52.4)	49.3 ± 10.8	5.6 ± 7.1		13.8 ± 12.0	19.0 ± 13.5	17.4 ± 16.9
			Clazakizumab 200 mg q4w	41	21 (51.2)	44.7 ± 13.8	4.7 ± 6.1		10.8 ± 7.4	16.6 ± 10.4	16.2 ± 20.1
20	Mease 2017 (1)[37]	NCT01860976	Placebo	211	99 (46.9)	49.8 ± 11.3	8.3 ± 8.1	16 wk	11.1 ± 7.2	19.3 ± 13.1	14.3 ± 30.3
			Abatacept 125 mg qw	213	92 (43.2)	51.0 ± 10.7	8.8 ± 8.3		12.1 ± 7.8	21.0 ± 13.4	14.0 ± 20.9
21	Mease 2015[38]	FUTURE 1	Placebo	202	96 (47.5)	48.5 ± 11.2	NA	16 wk	14.9 ± 13.1	25.1 ± 18.4	NA
			Secukinumab 10mg/kg at week 0,2,4, and 75 mg q4w	202	84 (41.6)	48.8 ± 12.2	NA		12.7 ± 11.1	23.4 ± 17.2	NA
			Secukinumab 10mg/kg at week 0,2,4, and 150 mg q4w	202	96 (47.5)	49.6 ± 11.8	NA		12.5 ± 9.4	23.8 ± 16.4	NA
22	Mease 2017 (2)[39]	SPIRIT-P1	Placebo	106	48 (45.3)	50.6 ± 12.3	6.3 ± 6.9	24 wk	10.6 ± 7.3	19.2 ± 13.0	15.1 ± 23.6
			Ixekizumab 80 mg q4w	107	45 (42.1)	49.1 ± 10.1	6.2 ± 6.4		11.4 ± 8.2	20.5 ± 13.7	12.8 ± 16.4
			Ixekizumab 80 mg q2w	103	48 (46.6)	49.8 ± 12.6	7.2 ± 8.0		12.1 ± 7.2	21.5 ± 14.1	15.1 ± 25.9
			Adalimumab 40 mg q2w	101	51 (50.5)	48.6 ± 12.4	6.9 ± 7.5		9.9 ± 6.5	19.3 ± 13.0	13.2 ± 19.1
23	Nash 2017[40]	SPIRIT-P2	Placebo	118	56 (47.5)	51.5 ± 10.4	9.2 ± 7.3	24 wk	10.3 ± 7.4	23.0 ± 16.2	12.1 ± 19.6

(*continued*)

Table 1

(continued).

ID	Study	Data sources	Groups	Number of patients	Male (%)	Age (yr)	Disease duration (yr)	Follow up time (wk)*	Swelling joints	Tender joints	CRP (mg/L)
			Ixekizumab q4w	122	63 (51.6)	52.6±13.6	11.0±9.6		13.1±11.2	22.0±14.1	17.0±27.5
			Ixekizumab q2w	123	50 (40.7)	51.7±11.9	9.9±7.4		13.5±11.5	25.0±17.3	13.5±26.1
24	Mease 2004[41]	Seattle Rheumatology Associates	Placebo	104	47 (45.2)	47.3	9.2	24 wk	NA	NA	NA
			Etanercept 25 mg twice weekly	101	58 (57.4)	47.6	9.0		NA	NA	NA
25	Nash 2018 (1)[42]	FUTURE3	Placebo	137	59 (43.1)	50.1±12.6	6.6±6.9	16 wk	10.3±16.2	21.9±16.2	NA
			Secukinumab 150mgat week 0, 1, 2, 3, 4, and then q4w	138	61 (44.2)	50.1±11.7	7.7±8.5		11.2±9.2	23.3±18.1	NA
			secukinumab 300 mg at week 0, 1, 2, 3, 4, and then q4w	139	67 (48.2)	49.3±12.9	8.3±9.2		8.9±6.4	19.7±14.8	NA
26	Nash 2018 (2)[43]	ACTIVE	Placebo	109	44 (40.4)	48.0±13.8	3.6±5.5	16 wk	10.0±5.9	18.4±14.2	1.25±1.6
			Apremilast 30 mg bid	110	52 (47.3)	50.7±12.2	4.0±4.5		9.0±4.9	17.2±12.7	1.44±1.6
27	Ritchlin 2014[44]	PSUMMIT2	Placebo	104	51 (49.0)	48.0 (38.5–56.0)	5.5 (2.3–12.2)	24 wk	11.0 (7.0–18.0)	21.0 (11.0–30.0)	8.5 (4.6- 22.0)
			Ustekinumab 45 mg at week 0, 4, and then q12w	103	48 (46.6)	49.0 (40.0–56.0)	5.3 (2.3–12.2)		12.0 (8.0–19.0)	22.0 (15.0- 33.0)	13.0 (4.5- 36.3)
			Ustekinumab 90 mg at week 0, 4, and then q12w	105	49 (46.7)	48.0 (41.0- 57.0)	4.5 (1.7- 10.3)		11.0 (7.0–17.0)	22.0 (14.0–36.0)	10.1 (4.8- 19.8)
28	Schett 2012[45]	NCT00456092	Placebo	68	32 (47.1)	51.1	7.3	12 wk	9.5	21.3	14.9 (3.0–23.7)
			Apremilast 20 mg bid	69	43 (62.3)	50.9	8.4		10.6	20.6	10.4 (3.0–65.4)
			Apremilast 40 mg qd	67	32 (46.4)	49.9	7.6		8.4	23.2	10.9 (3.0–95.0)
29	Wells 2018[46]	PALACE 4	Placebo	176	90 (45.9)	50.5±11.6	3.4±5.1	16 wk	11.3±7.6	19.6±13.7	1.1±2.7
			Apremilast 20 mg bid	175	80 (45.5)	49.2±12.0	3.2±4.7		11.3±7.8	21.1±15.1	0.9±1.1
			Apremilast 30 mg bid	176	80 (35.1)	48.4±12.5	3.6±5.0		10.9±8.6	19.5±14.4	0.8±1.1
30	McInnes 2014[47]	NCT00809614	Placebo	14	6 (28.6)	47.6±8.1	5.4 (3.8)		9.5±5.4	22.6±11.0	6.2 (1.3–39.7)
			Secukinumab 10 mg/kg q3w	28	7 (50.0)	46.7±11.3	6.3 (6.8)		8.3±5.6	23.5±19.4	4.9 (0.3–43)

* RCT length; qd: once per day; bid: twice a day; q28d: every 28 days; qw: once per week; q2w: every 2 weeks; q3w: every 3 weeks; q4w: every 4 weeks; q8w: every 8weeks; q12w: every 12 weeks; NA = not available.

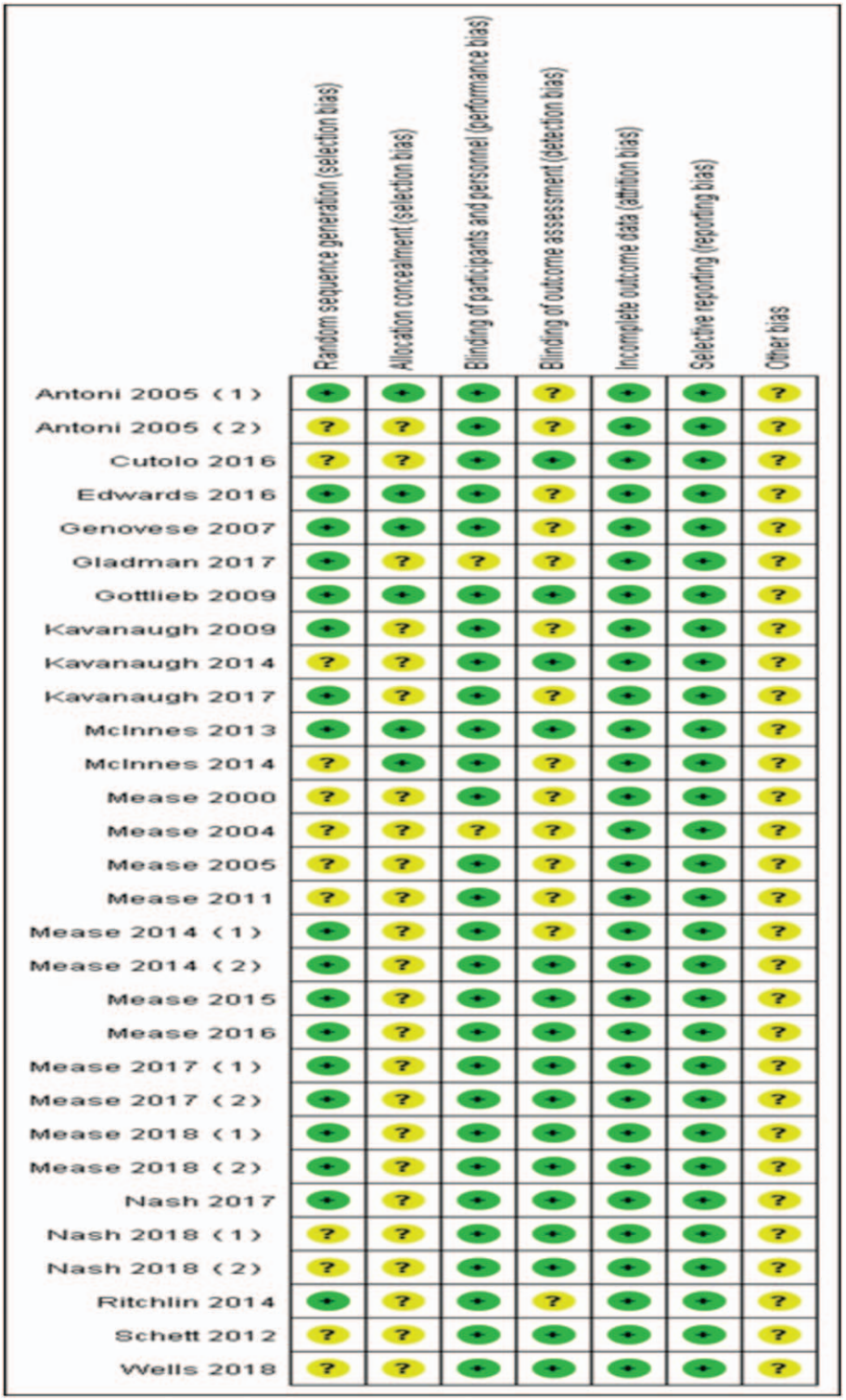

Figure 2. Review authors' judgments about each risk of bias item presented as percentages across all included studies.

NMA: IFX, APR, ADA, TOF, UST, GOL, ABA, SEC, CZP, BRD, ETN, CLA, IXE, ABT, and PBO.

3.3. Meta-analysis of direct treatment effects

Via traditional meta-analysis, we obtained direct evidence by comparing 14 medicines with PBO (Table 2). First, IFX, APR, ADA, UST, GOL, ABA, SEC, CZP, BRD, ETN, CLA, and IXE were highly effective in comparison to PBO for ACR20 responses. Second, IFX, APR, UST, ABA, SEC, BRD, ETN, and CLA were more effective than PBO for PASI75 responses. Lastly, in terms of SAEs, no medicine was significantly different from PBO.

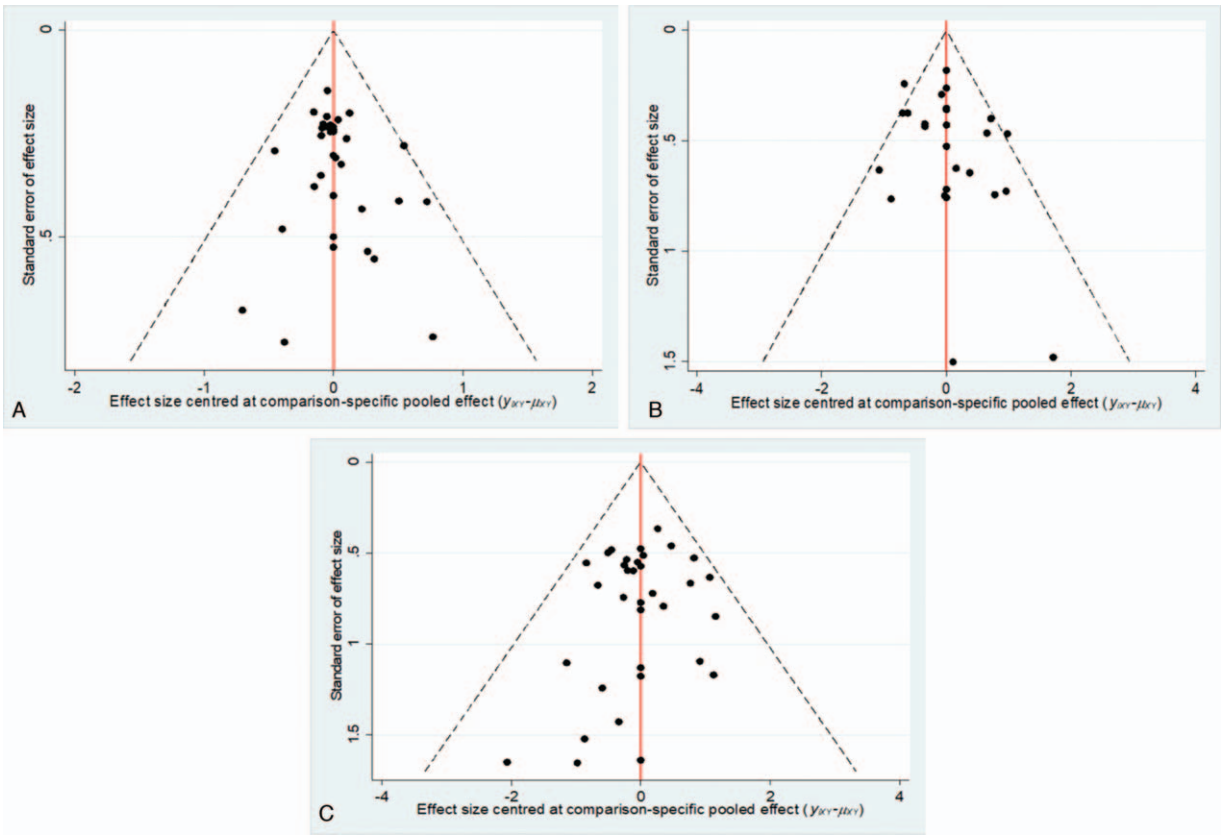

Figure 3. (A) Funnel plot ACR20 at the end of RCT length (B) Funnel plot PASI75 at the end of RCT length. (C) Funnel plot SAEs until week 24.

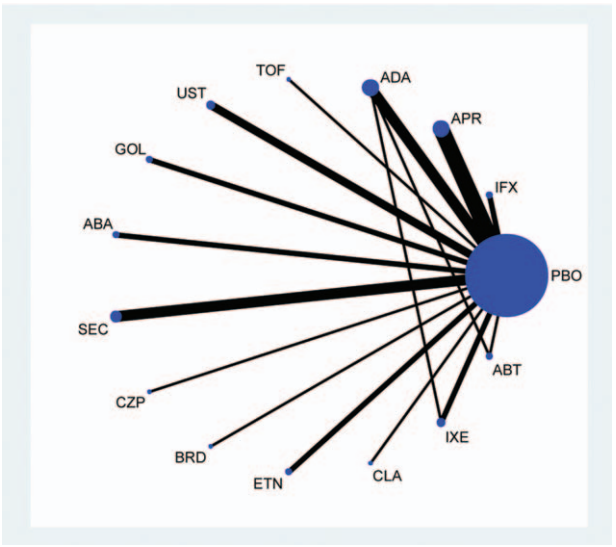

Figure 4. Evidence network diagram of the network meta-analysis comparisons. Note: The width of each connecting line is proportional to the number of RCTs comparing each pair of treatments, and the size of each treatment node (circle) is proportional to the number of randomized participants (sample size). Solid lines indicate direct comparison evidence, such as SEC versus PBO. No solid line is shown for indirect comparison evidence, such as the comparison between SEC and BRD. PBO, placebo; IFX, infliximab; APR, apremilast; ADA, adalimumab; TOF, tofacitinib; UST, ustekinumab; GOL, golimumab; ABA, abatacept; SEC, secukinumab; CZP, certolizumab pegol; BRD, brodalumab; ETN, etanercept; CLA, clazakizumab; IXE, ixekizumab; ABT, ABT-122.

Table 2

Results of pooled odds ratios of the direct comparisons of each biologic or small molecular agent vs placebo.

Intervention	ACR20 OR [95%CI]	PASI75 OR [95%CI]	SAEs OR [95%CI]
vs PBO			
IFX	**12.94 (7.02, 23.88)**	**65.26 (14.12,301.59)**	1.36 (0.46,4.06)
APR	**2.39 (1.95, 2.94)**	**4.34 (2.31,8.18)**	0.76 (0.45,1.29)
ADA	0.47 (0.23–1.00)	0.27 (0.04,1.69)	3.96 (0.47,33.29)
TOF	0.96 (0.30,3.03)	0.16 (0.02,1.44)	0.16 (0.00,5.22)
UST	6.67 (4.15,10.70)	**23.32 (6.13,88.81)**	0.68 (0.21,2.21)
GOL	3.01 (1.88,4.82)	2.94 (0.89,9.71)	0.66 (0.13,3.38)
ABA	2.61 (1.92,3.55)	**14.09 (5.59,35.51)**	0.40 (0.13,1.24)
SEC	10.46 (7.29,15.00)	**11.55 (4.29,31.09)**	**0.39 (0.16,0.93)**
CZP	2.05 (1.42,2.96)	5.35 (0.91,31.47)	0.84 (0.29,2.48)
BRD	4.02 (3.27,4.94)	NA	0.69 (0.37,1.28)
ETN	3.81 (2.41,6.02)	**10.98 (3.90,30.89)**	1.81 (0.59,5.54)
CLA	2.76 (1.26,6.05)	**6.04 (1.82,20.05)**	1.98 (0.20,19.79)
IXE	34.86 (13.07,92.97)	**17.79 (4.25,74.46)**	0.84 (0.21,3.40)
ABT	0.74 (0.27,2.08)	0.74 (0.18,3.06)	1.34 (0.24,7.43)

Values listed as OR [95%CI]. Significant results are in bold. ABA = abatacept, ABT = ABT-122, ACR = American College of Rheumatology, ADA = adalimumab, APR = apremilast, BRD = brodalumab, CI = confidence interval, CLA = clazakizumab, CZP = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, IXE = ixekizumab, NA = not available, PASI = Psoriasis Area and Severity Index, OR = odds ratio, PBO = placebo, SAEs = serious adverse events, SEC = secukinumab, TOF = tofacitinib, UST = Ustekinumab.

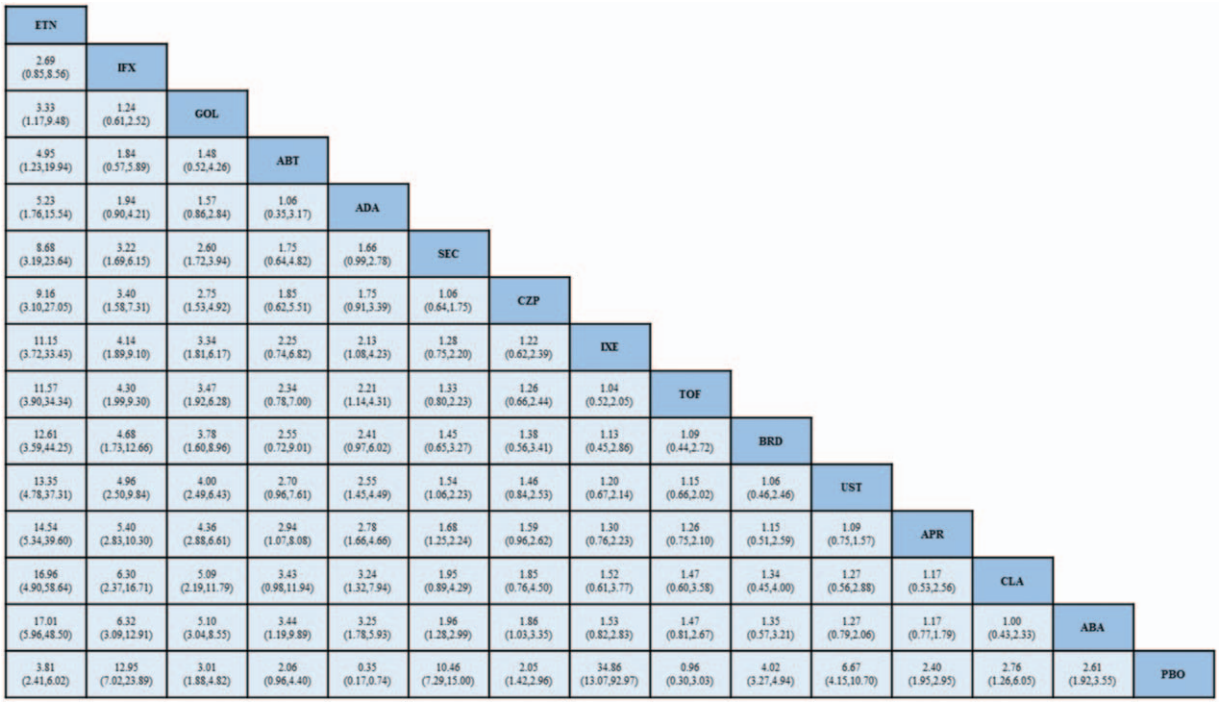

Figure 5. League tables showing the ACR20 rate results of the network meta-analyses comparing the effects of all drugs including odds ratios and 95% confidence intervals. Odds ratio>1means the top left treatment is better. Note: PBO, placebo; IFX, infliximab; APR, apremilast; ADA, adalimumab; TOF, tofacitinib; UST, ustekinumab; GOL, golimumab; ABA, abatacept; SEC, secukinumab; CZP, certolizumab pegol; BRD, brodalumab; ETN, etanercept; CLA, clazakizumab ; IXE, ixekizumab; ABT, ABT-122.

Pooled effect sizes suggested that, compared with PBO, most biologics, irrespective of dose, improved ACR20 at week 24, excluding ADA (ACR20: OR = 0.35, 95% CI: 0.17–0.74), TOF (ACR20: OR = 0.96, 95% CI: 0.30–3.03), and ABT (ACR20: OR = 0.74, 95% CI: 0.27–2.08). Moreover, for PASI75, IFX, APR, UST, ABA, SEC, BRD, ETN, and CLA were more effective than PBO. However, in terms of SAEs, no medicine was significantly different from PBO.

The heterogeneity assessment indicated the heterogeneity within ADA vs PBO, ETN vs PBO in ACR20, ADA vs PBO, ETN vs PBO,GOL vs PBO, and IXE vs PBO in PASI75, and GOL vs PBO in SAEs was statistically significant ($I^2 > 50\%$), while there was low heterogeneity in the other direct comparisons (Supplemental Digital Content [Table S2, http://links.lww.com/MD/E611]).

3.4. NMA of the efficacy and safety in RCTs

We carried out both direct and indirect comparisons among these medicines using frequentist NMA (Figs. 5–7). The results were in agreement with those of traditional meta-analysis. Significant improvements in ACR20 response, PASI75 response, and SAEs were observed by NMA. IFX, APR, UST, ABA, SEC, BRD, ETN, and CLA showed significant increases in ACR20 and PASI75 responses compared to those of PBO.

For direct comparisons, it can be seen from Figure 5 that most of the biologics performed better than PBO in terms of ACR20 response rate, excluding ABT (OR = 2.06, 95% CI: 0.96–4.40), TOF (OR = 0.96, 95% CI: 0.30–3.03), and ADA (OR = 0.47, 95% CI: 0.23–1.00). Moreover, there was a large proportion of biologics with improved PASI75 responses compared to that of PBO, excluding ADA (OR = 0.27, 95% CI: 0.04–1.69), GOL (OR = 2.94, 95% CI: 0.98–9.71), ABT (OR = 0.74, 95% CI: 0.18–3.06), CZP (OR = 5.35, 95% CI: 0.91–31.47), and TOF (OR = 0.16, 95% CI: 0.02–1.44). However, these medicines were comparable to PBO in terms of SAEs, except for SEC (OR = 0.39, 95% CI: 0.16–0.93).

In terms of mixed comparisons, with regard to the ACR20 response, ETN and IFX were more effective than GOL, with ORs of 3.33 (95% CI: 1.17–9.48) and 1.24 (95% CI: 0.61–2.52), respectively. For PASI75, IFX was superior to CZP (OR = 10.08, 95% CI: 1.54–75.48). In addition, these medicines were comparable to each other in terms of SAEs.

The inconsistency between direct and indirect comparisons for the outcomes was calculated. As shown in Figure 8, all loops were consistent, as their 95% CIs included 0 according to the forest plots, indicating that the results of our NMA are relatively reliable.

3.5. Ranking of treatments by efficacy and safety

As shown in Figures 5 and 6, ENT and IFX are listed in the top left of the diagonal of the league tables for the most favorable SUCRA for achieving ACR20 and PASI75 responses, respectively. Whereas PBO was listed in the bottom right of the diagonal of the league tables, there were no significant differences in SAE responses (Fig. 7). In fact, ABT had the lowest probability of SAEs (Fig. 7). A relative ranking of the 10 interventions based on their SUCRA is shown in Table 3, with the results giving the probability that each treatment is the most effective and safe regimen. The results indicate that ENT and IFX are the best treatments for achieving ACR20 and PASI75 responses, respectively and that ABT is the best in terms of safety according to the SUCRA of SAEs. Furthermore, as shown in Figure 9, all

IFX													
1.98 (0.28,14.30)	IXE												
2.80 (0.37,21.36)	1.41 (0.23,8.78)	ADA											
3.67 (0.45,29.78)	1.85 (0.28,12.35)	1.31 (0.18,9.30)	ETN										
4.63 (0.78,27.67)	2.33 (0.49,11.02)	1.66 (0.33,8.41)	1.26 (0.23,6.83)	UST									
5.65 (0.91,34.90)	2.85 (0.58,14.00)	2.02 (0.38,10.66)	1.54 (0.29,8.23)	1.22 (0.32,4.62)	GOL								
5.94 (0.94,37.71)	2.99 (0.59,15.14)	2.12 (0.39,11.52)	1.62 (0.28,9.48)	1.28 (0.32,5.14)	1.05 (0.25,4.40)	SEC							
7.69 (0.77,76.51)	3.88 (0.47,32.26)	2.75 (0.31,24.15)	2.10 (0.22,19.55)	1.66 (0.24,11.63)	1.36 (0.19,9.85)	1.29 (0.17,9.57)	ABT						
10.80 (1.54,75.48)	5.44 (0.96,30.71)	3.86 (0.64,23.26)	2.94 (0.45,19.05)	2.33 (0.51,10.60)	1.91 (0.40,9.05)	1.82 (0.37,8.85)	1.40 (0.17,11.36)	CZP					
12.21 (1.17,126.97)	6.15 (0.70,53.73)	4.36 (0.47,40.18)	3.33 (0.34,32.48)	2.64 (0.36,19.45)	2.16 (0.28,16.45)	2.05 (0.26,15.99)	1.59 (0.13,18.67)	1.13 (0.13,9.61)	ABA				
15.02 (2.87,78.64)	7.57 (1.87,30.65)	5.37 (1.22,23.56)	4.09 (0.87,19.20)	3.24 (1.07,9.86)	2.66 (0.85,8.32)	2.53 (0.75,8.49)	1.95 (0.31,12.13)	1.39 (0.36,5.40)	1.23 (0.19,8.08)	APR			
22.18 (3.18,154.58)	11.18 (1.99,62.86)	7.93 (1.32,47.61)	6.05 (0.94,39.01)	4.79 (1.06,21.68)	3.93 (0.83,18.52)	3.73 (0.77,18.12)	2.88 (0.36,23.28)	2.05 (0.38,11.16)	1.82 (0.21,15.40)	1.48 (0.38,5.70)	TOF		
65.26 (14.12,301.59)	17.79 (4.25,74.46)	0.27 (0.04,1.69)	10.98 (3.90,30.89)	23.32 (6.13,88.81)	2.94 (0.89,9.71)	11.55 (4.29,31.09)	0.74 (0.18,3.06)	5.35 (0.91,31.47)	14.09 (5.59,35.51)	4.34 (2.31,8.18)	0.16 (0.02,1.44)	PBO	
87.90 (10.93,707.11)	44.29 (6.71,292.28)	31.42 (4.48,220.20)	23.96 (3.20,179.44)	18.98 (3.50,102.92)	15.56 (2.76,87.54)	14.79 (2.56,85.39)	11.43 (1.24,105.48)	8.14 (1.27,52.04)	7.20 (0.75,69.60)	5.85 (1.24,27.58)	3.96 (0.62,25.25)	0.17 (0.05,0.55)	CLA

Figure 6. League tables showing the PASI75 rate results of the network meta-analyses comparing the effects of all drugs including odds ratios and 95% confidence intervals. Odds ratio>1means the top left treatment is better. C) For SAEs: odds ratio>1means the top left treatment is better. Note: PBO, placebo; IFX, infliximab; APR, apremilast; ADA, adalimumab; TOF, tofacitinib; UST, ustekinumab; GOL, golimumab; ABA, abatacept; SEC, secukinumab; CZP, certolizumab pegol; ETN, etanercept; CLA, clazakizumab; IXE, ixekizumab; ABT, ABT-122.

ABT													
0.42 (0.03,5.35)	GOL												
0.41 (0.03,5.72)	0.97 (0.23,3.99)	UST											
0.24 (0.02,2.79)	0.56 (0.19,1.63)	0.58 (0.16,2.09)	SEC										
0.24 (0.02,3.43)	0.57 (0.13,2.44)	0.59 (0.12,2.96)	1.01 (0.27,3.80)	ADA									
0.25 (0.01,4.49)	0.59 (0.09,3.75)	0.61 (0.08,4.43)	1.05 (0.18,6.01)	1.04 (0.14,7.76)	TOF								
0.22 (0.02,2.49)	0.51 (0.19,1.41)	0.53 (0.15,1.83)	0.91 (0.41,2.04)	0.90 (0.25,3.25)	0.87 (0.16,4.84)	APR							
0.20 (0.01,3.12)	0.46 (0.09,2.41)	0.48 (0.08,2.86)	0.83 (0.18,3.81)	0.82 (0.13,5.07)	0.79 (0.09,6.78)	0.91 (0.20,4.05)	ETN						
0.19 (0.01,2.67)	0.46 (0.11,1.84)	0.48 (0.10,2.30)	0.82 (0.24,2.84)	0.81 (0.16,4.00)	0.78 (0.11,5.54)	0.90 (0.27,3.00)	0.99 (0.17,5.84)	ABA					
1.34 (0.24,7.43)	0.66 (0.13,3.38)	0.68 (0.21,2.21)	0.39 (0.16,0.93)	3.96 (0.47,33.29)	0.16 (0.00,5.22)	0.76 (0.45,1.29)	1.81 (0.59,5.54)	0.40 (0.13,1.24)	PBO				
0.12 (0.01,2.29)	0.29 (0.04,1.96)	0.30 (0.04,2.31)	0.51 (0.08,3.16)	0.51 (0.06,4.04)	0.49 (0.05,5.22)	0.56 (0.09,3.37)	0.62 (0.07,5.67)	0.63 (0.08,4.74)	0.50 (0.05,5.04)	CLA			
0.12 (0.01,1.66)	0.29 (0.07,1.15)	0.29 (0.06,1.41)	0.51 (0.14,1.78)	0.50 (0.10,2.49)	0.48 (0.07,3.46)	0.56 (0.17,1.87)	0.61 (0.10,3.63)	0.62 (0.13,2.89)	0.73 (0.25,2.19)	0.99 (0.13,7.51)	IFX		
0.08 (0.00,2.28)	0.20 (0.02,2.29)	0.20 (0.02,2.62)	0.35 (0.03,3.77)	0.34 (0.03,4.56)	0.33 (0.02,5.60)	0.38 (0.04,4.06)	0.42 (0.03,6.25)	0.43 (0.03,5.41)	1.45 (0.78,2.68)	0.68 (0.04,11.93)	0.69 (0.05,8.77)	BRD	
0.09 (0.01,1.27)	0.22 (0.05,0.89)	0.22 (0.05,1.09)	0.38 (0.11,1.37)	0.38 (0.07,1.92)	0.36 (0.05,2.65)	0.42 (0.12,1.45)	0.46 (0.08,2.79)	0.47 (0.10,2.22)	1.18 (0.40,3.49)	0.74 (0.10,5.75)	0.75 (0.16,3.61)	1.10 (0.08,14.19)	CZP
0.07 (0.00,1.30)	0.17 (0.03,1.10)	0.17 (0.02,1.29)	0.30 (0.05,1.76)	0.29 (0.04,2.26)	0.28 (0.03,2.93)	0.33 (0.06,1.88)	0.36 (0.04,3.18)	0.36 (0.05,2.65)	1.20 (0.29,4.85)	0.58 (0.05,6.30)	0.58 (0.08,4.30)	0.85 (0.05,14.62)	0.78 (0.10,5.80)

Figure 7. League tables showing the SAEs rate results of the network meta-analyses comparing the effects of all drugs including odds ratios and 95% confidence intervals. Odds ratio<1 means the topsleft treatment is better. Note: PBO, placebo; IFX, infliximab; APR, apremilast; ADA, adalimumab; TOF, tofacitinib; UST, ustekinumab; GOL, golimumab; ABA, abatacept; SEC, secukinumab; CZP, certolizumab pegol; BRD, brodalumab; ETN, etanercept; CLA, clazakizumab; IXE, ixekizumab; ABT, ABT-122.

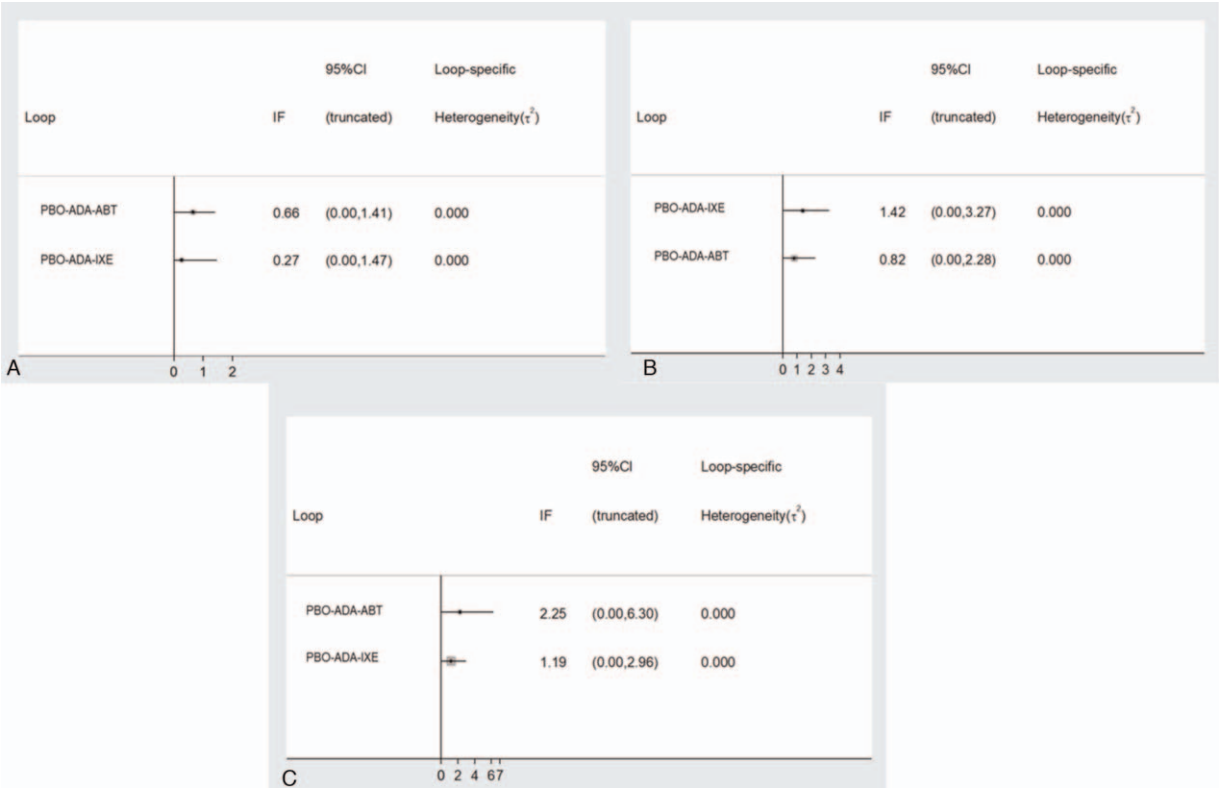

Figure 8. Forest plots of inconsistency check for all closed loops in the network. (A) Forest plots of inconsistency check for all closed loops in the network o ACR20 response; (B) Forest plots of inconsistency check for all closed loops in the network o PASI75 response; (C) Forest plots of inconsistency check for all closed loops in the network o SAEs rate. Note: PBO, placebo; ADA, adalimumab; IXE, ixekizumab; ABT, ABT-122.

biologics were ranked by their overall probability of being the best treatment after considering the efficacy (ACR20 and PASI75) and safety (SAEs). It can be seen that GOL, ENT, and IFX are the top three treatments after considering both efficacy (ACR20 and PASI75) and safety (SAEs).

Table 3

Ranking of treatments according to SUCRAs.

	Efficacy		Safety
Treatment	ACR20, %	PASI75, %	SAEs, %
GOL	85.7	58.9	80.8
ETN	99.4	69.8	50.6
IFX	89.9	94.3	30.1
ABT	74.5	50.4	88.1
ADA	74.2	77.3	58.9
UST	31.5	65.3	78.9
SEC	58.4	56.6	60.2
IXE	42.9	86	17.9
TOF	41.1	22.4	58.9
CZP	54.6	40.5	20.4
APR	25.5	30.1	55
ABA	16.8	38.9	50
BRD	34.8	NA	27.5
CLA	20.6	3.7	33.8
PBO	0.3	5.8	38.8

ABA = abatacept, ABT = ABT-122, ACR = American College of Rheumatology, ADA = adalimumab, APR = apremilast, BRD = brodalumab, CLA = clazakizumab, CZP = certolizumab pegol, ETN = etanercept, GOL = golimumab, IFX = infliximab, IXE = ixekizumab, NA = not available, PASI = Psoriasis Area and Severity Index, PBO = placebo, SAEs = serious adverse events, SEC = secukinumab, SUCRA = surface under the cumulative ranking curve, TOF = tofacitinib, UST = ustekinumab.

4. Discussion

Many patients with PsA also have refractory arthritis or even mutilans arthritis.[48] Most of the therapeutic drugs for PsA are based on the experience of rheumatoid arthritis, but there is not enough evidence to suggest that these drugs are capable of preventing the progression of PsA. Due to recent knowledge of the pathogenesis of PsA, a variety of biological agents and small molecules have began to be used for treatment. TNF-α plays a key role in the pathogenesis of psoriasis and PsA, indicating that these diseases may be treated by blocking TNF-α. Other key target cytokines include IL-6, IL-12/23, and IL-17, among others.[49,16] The PDE-4 and JAK-STAT pathways also play important roles in the pathogenesis of psoriasis and PsA.[50] However, there is a lack of comprehensive comparisons of the efficacy and safety of individual small molecule and biological agents. This study used NMA to directly and indirectly compare the efficacy (ACR20 and PASI75 responses) of 14 small molecule and biological agents and their safety (SAEs) and to perform a comprehensive ranking. Available and potentially valuable biological agents, including inhibitors of the TNF-α, IL-6, IL-12/23, IL-17, CTLA-4-Ig, TNF-α/IL-17a, PDE-4, and JAK pathways, were targeted for combined analysis and ranked from the perspective of efficacy and safety, so as to provide a reference for the clinical treatment of PsA.

Our meta-analysis showed that the three anti-TNF-α agents (GOL, ETN, and IFX) are in turn the three best therapeutic agents for PsA after considering the efficacy (ACR20 and PASI75 responses) and safety (SAEs). Thus, TNF-α inhibitors remain the first choice for the treatment of PsA. GOL is a fully humanized anti-TNF-α IgG mAb, whose recommended dose is a 50 mg subcutaneous injection every month for the treatment of PsA.[51]

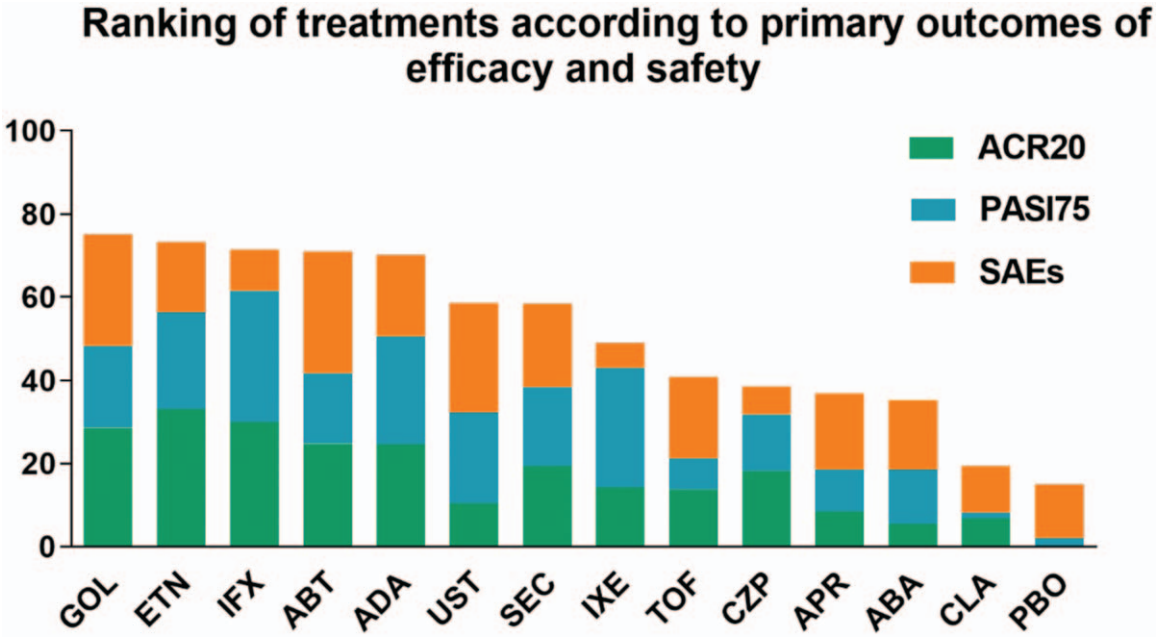

Figure 9. Ranking of treatments according to primary outcomes: SUCRAs of efficacy and safety. Note: The cumulative percentages after normalization (0–100) are shown in the key. Every drug was scored with points up to a maximum of 33.3 for ACR20, PASI75 and SAEs (overall maximum score 100), with data from SUCRAs. There is no treatment of BRD in this ranking, for lack of data of PASI75. Note: PBO, placebo; IFX, infliximab; APR, apremilast; ADA, adalimumab; TOF, tofacitinib; UST, ustekinumab; GOL, golimumab; ABA, abatacept; SEC, secukinumab; CZP, certolizumab pegol; ETN, etanercept; CLA, clazakizumab ; IXE, ixekizumab; ABT, ABT-122.

In a multicenter RCT, treatment of PsA patients with GOL via 50 mg subcutaneous injection and treatment with PBO resulted in ACR20 responses of 48% and 9%, respectively.[52] ETN is a genetically engineered protein composed of a fusion of human TNFR2 dimer and a partial Fc of IgG1.[53] It binds alone to the TNF trimer, allowing ETN to bind to TNF at a 1:1 ratio. Treatment with ETN can reduce the expression of vascular endothelial growth factor, IL-23, IL-17, and IL-22, among others.[54] IFX is a single human-mouse anti-TNF-α mAb. It binds to TNF-α to prevent TNF-α from combining with its receptors.[55] IFX can also bind to complement factors to induce apoptosis when binding to TNF-α on the cell surface. The application of IFX in the treatment of PsA patients can reduce bone loss in the hand. According to our NMA results, in terms of the ACR20 response, ETN and IFX are more effective than GOL and ADA, with ORs of 3.33 (95% CI: 1.17–9.48) and 3.22 (95% CI: 1.69–6.15), respectively. The above results suggest that anti-TNF-α agents remain the best choice for biotherapy of PsA, in consideration of their efficacy and safety. However, more multicenter experiments for the comparison of efficacy and safety between anti-TNF-α agents should be conducted to obtain more direct experimental evidence.

Notably, in this meta-analysis, with regard to the ACR20 response, ETN, a total human recombinant protein with a bivalent p75TNFR2 extracellular segment fused with Fc, was superior to IFX, an anti-TNF-α mAb.[56] The most obvious difference between the 2 drugs is how their structures recognize the receptor binding domain of TNF-α. The binding site of ETN consists of 2 adjacent subunits of the active form of TNF-α. This means that ETN binds to TNF-α in a 1:2 ratio, whereas IFX recognizes TNF-α epitopes by binding to TNF-α in a 1:1 ratio. Moreover, as mentioned above, IFX produces a complement effect, which can cleave surface cells, such as macrophages.[57] ETN, in contrast, does not possess a complete antibody structure and thus does not exhibit complement-dependent cytotoxicity. The present study also found that small molecules (APR and TOF) and other immunological agents are not more effective than anti-TNF-α therapy in the treatment of PsA.

Moreover, other biological agents and small molecule therapies were compared and analyzed in this NMA. This is the first meta-analysis to include the targeted therapy drug ABT, which targets 2 anti-inflammatory factors. Interestingly, although ABT is a double-targeted inhibitor of TNF-α and IL-17A,[58] it did not show better therapeutic effect than the single-targeted anti-TNF-α inhibitors. As shown by Mease et al,[19] the similar efficacies of ABT and ADA suggest that the effects of ABT are primarily the result of inhibition of TNF-α. Thus, the anti-IL-17a property of ABT may contribute little additive observed treatment effects. The reason for this may be related to the correlation in changes in gene expression and DNA methylation at week 4 with the 28-joint count disease activity score (DAS28-hsCRP) response. At the same time, ABT ranked first in terms of SAEs, showing that ABT is safe and does not increase SAEs even though it is a dual-inflammatory factor inhibitor.

Although small molecule therapy (APR and TOF) and other immunological agents did not show a more effective therapeutic response than anti-TNF-α therapy, in terms of ACR20, PASI75, and SAEs, UST (IL-12/23 inhibitor) and SEC/IXE (IL-17 inhibitors) were the top 3 agents after the anti-TNF-α agents. UST is a fully human mAb that blocks the activity of p40, a protein subunit common to IL-12 and IL-23.[59] UST therefore has the ability to reduce the biological activity of IL-12 and IL-23. Both SEC and IXE are humanized mAbs that selectively bind to and neutralize IL-17A and block the binding of IL-17A and IL-17R, thereby functioning as anti-inflammatory factors.[38,60] IXE also attenuates keratinocyte proliferation and epidermal hyper-

plasia by inhibiting the expression of adhesion molecules and pro-inflammatory cytokines. In this study, it was found that IXE plays a more prominent role in PASI75 response, indicating that its effect on PsA lesions is more obvious. However, there is still a lack of multicenter experimental studies to confirm this finding.

There are some limitations to this study. First, our inclusion criteria stipulated that the included studies must be RCTs. In addition, in consideration of ethical and other factors, most clinical studies were conducted for 12 to 16 weeks. Our results therefore do not represent the long-term efficacy and safety of these drugs. More data on long-term efficacy and safety from multicenter experimental studies are urgently needed. Second, since there was a lack of head-to-head studies in our NMA, most comparisons between drugs were indirect, resulting in a reduction in the reliability of the evidence. Third, there were several comparisons with high heterogeneity, such as GOL vs PBO in PASI75 and SAEs, but we cannot perform the inconsistency test due to lack of a closed loop so that the impacts of heterogeneity on the effect estimates can only be determined in future studies. Therefore, the results of this NMA should be interpreted with caution.

5. Conclusion

Our study suggests that 3 anti-TNF-α biologics, GOL, ETN, and IFX, can be considered the best treatments for PsA after comprehensive consideration of efficacy (ACR20 and PASI75 responses) and safety (SAEs). More large-scale and long-term clinical trials are still needed to obtain direct evidence for other small molecule therapies and biological agents.

Author contributions

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