International Immunopharmacology 75 (2019) 105841

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Treatment of plaque psoriasis with IL-23p19 blockers: A systematic review and meta-analysis

Shanshan Xu[a,b,1], Xiaoyi Zhang[c,1], Meijuan Pan[d], Zongwen Shuai[d], Shengqian Xu[d], Faming Pan[a,b,*]

[a] Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China
[b] The Key Laboratory of Major Autoimmune Diseases, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China
[c] Department of Health Toxicology, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China
[d] Department of Rheumatism and Immunity, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, China

ARTICLE INFO

Keywords:
Psoriasis
IL-23p19
Guselkumab
Risankizumab
Tildrakizumab
Meta-analysis

ABSTRACT

Objectives: Interleukin(IL)-23 is a key cytokine in the pathogenesis of psoriasis, this meta-analysis was to analyze the efficacy and safety of IL-23p19 blockers in patients with plaque psoriasis.
Methods: A systematic review of the literature was performed to collect double-blind randomized controlled trials(RCTs). The pooled relative risk(RR) with 95% confidence interval(CI) was calculated. All analyses were conducted with intention-to-treat basis.
Results: A total of 13 studies contained 5155 plaque psoriasis patients were included in our meta-analysis. The results indicated that IL-23p19 blockers had better efficacy than placebo for Psoriasis Area Severity Index score reductions from baseline of 75% or more (PASI75) (RR = 11.47, $P < 0.001$) and static Physician's Global Assessment score of 0 or 1(sPGA0/1) (RR = 11.32, $P < 0.001$). IL-23p19 blockers have similar safety with placebo about the incidence of adverse events(AEs) (RR = 1.22, $P = 0.096$) and serious adverse events(SAEs) (RR = 2.93, $P = 0.965$), but IL-23p19 blockers carried an increased incidence rate of infections (RR = 1.39, $P < 0.001$). While compared with adalimumab and ustekinumab, IL-23p19 blockers were more effective and had the similar tolerance. Among three IL-23p19 blockers, guselkumab was the most efficacious treatments, and risankizumab was better tolerated than the others.
Conclusion: The IL-23p19 blockers have excellent efficacy and great safety in plaque psoriasis patients, but long-term safety remains to be determined.

1. Introduction

Psoriasis is a chronic immune-mediated inflammatory disease manifesting in the skin or joints [1,2]. Among the various subtypes of psoriasis, plaque psoriasis is the most familiar, accounting for about 90% of the total number of patients [1,3]. It occurs mostly in young adults and the prevalence of psoriasis was 0.51% to 11.43% in adults and 0% to 1.37% in children, with an average of 1%~4% [4–6]. Patients with psoriasis are usually associated with a variety of complications, such as cardiovascular diseases, metabolic syndrome, malignant tumors, infections and mood disorders, which seriously affect the quality of life and aggravate the burden [7,8]. On account of severe psychological burden, it is often untoward to achieve ideal efficacy compared with other autoimmune diseases. In the treatment of psoriasis, in addition to nonsteroidal anti-inflammatory drugs (NSAIDs) and some conventional drugs, biological agents targeting tumor necrosis factor (TNF)-α and interleukin-23/-17 axis have been widely studied and applied recently [9].

Interleukin-23, a pro-inflammatory cytokine, has key regulatory role in the pathogenesis of psoriasis [9–11]. IL-23 is composed of p19 subunit and p40 subunit, of which p40 subunit is also one of the components of IL-12, while p19 subunit is the unique subunit of IL-23 [9]. IL-23 is involved in the development and progression of psoriasis by inducing and maintaining T helper (Th) 17 cells, Th22 cells, innate lymphoid cells, and the effector cytokines IL-17, IL-22, and TNF-α [11]. Inhibitors targeting IL-23p19 include risankizumab (BI 655066/

* Corresponding author at: Department of Epidemiology & Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui 230032, China.
E-mail address: famingpan@ahmu.edu.cn (F. Pan).
[1] Shanshan Xu and Xiaoyi Zhang contributed equally to this work and should be considered co-first author.

https://doi.org/10.1016/j.intimp.2019.105841
Received 2 July 2019; Received in revised form 18 August 2019; Accepted 19 August 2019
Available online 26 August 2019
1567-5769/ © 2019 Elsevier B.V. All rights reserved.

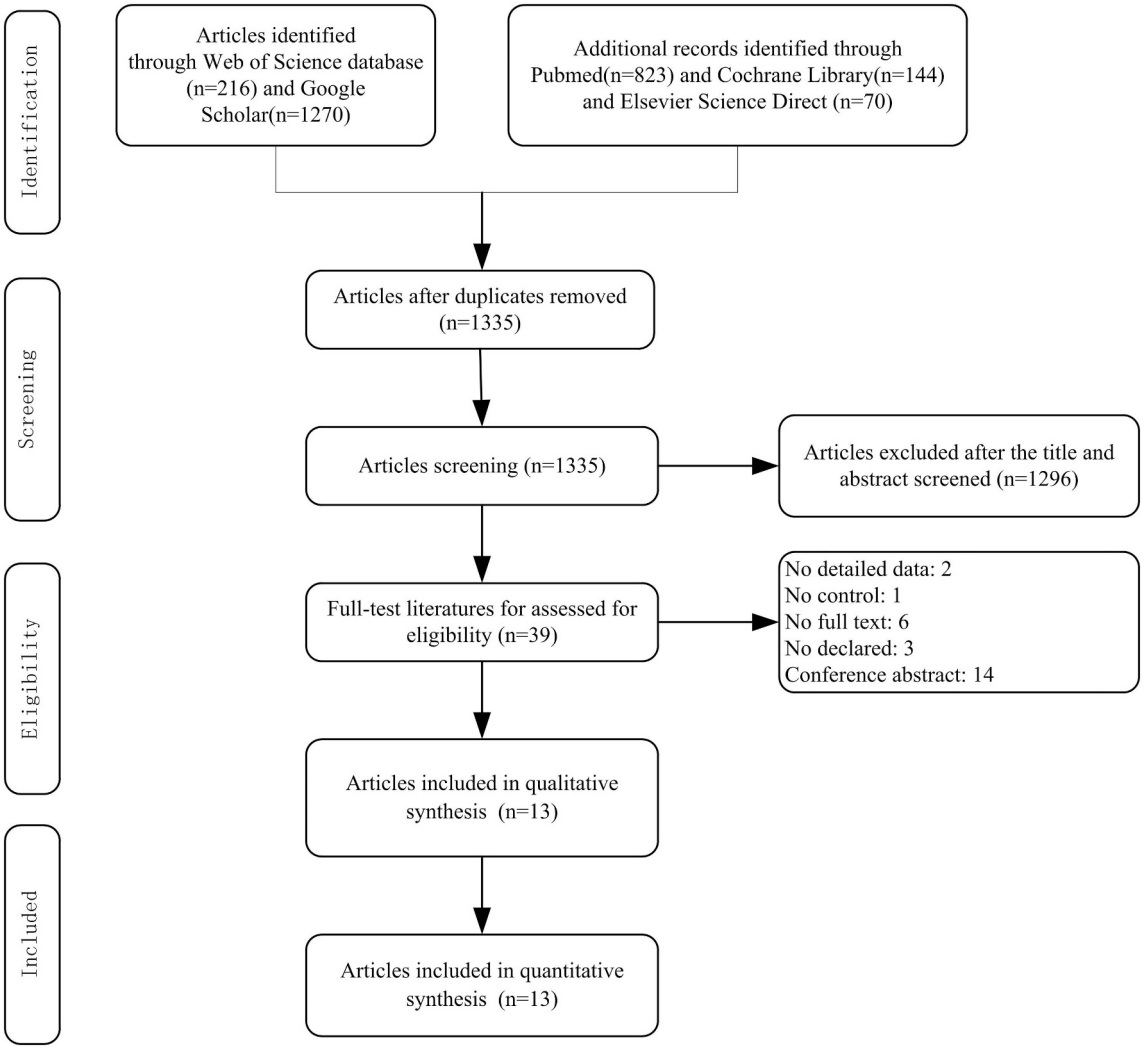


Fig. A. Flowchart of study selection.

ABBV066; Humanized, IgG1), guselkumab (CNTO1959; Fully human, IgG1), tildrakizumab (MK 3222; Humanized, IgG1), brazikumab (Fully human, IgG2) and mirikizumab (Humanized, IgG4) [9,12,13]. Howard and his colleagues demonstrated for the first time that guselkumab had good efficacy and tolerance, suggesting that anti-IL-23p19 was a promising treatment strategy [14]. Hereafter, increasing studies have been conducted on IL-23p19 inhibitors.

Although many studies have proved that IL-23p19 inhibitors were effective and safe, but some results showed inconsistent conclusions. James indicated that there was no statistically significant difference in the efficacy of tildrakizumab and placebo [15], and the infection rate of risankizumab was higher than that of placebo [16], which was different from other studies [14,17–24]. Additionally, there was no study or analysis compared the efficacy or safety of three different IL-23 inhibitors. This meta-analysis is the first comprehensive analysis of the efficacy and safety of IL-23p19 inhibitors, and compared with inhibitors of different targets, so as to provide further reliable basis for clinical application and selection of different inhibitors.

2. Materials and methods

2.1. Publication search

We systematically retrieved the double-blind randomized controlled trials investigating the efficacy and safety of risankizumab, tildrakizumab or guselkumab in approved dosages in the electronic database of PubMed, Web of Science, Cochrane Library, Elsevier Science Direct and Google Scholar databases (up to NOV. 20, 2018). Keywords and search strategy were as follows: “IL-23 inhibitor” or “IL-23” or “IL-23p19” or “anti-il-23” or “risankizumab” or “BI 655066” or “ABBV066” or “guselkumab” or “CNTO1959” or “tildrakizumab” or “MK 3222” or “brazikumab” or “MEDI2070” or “AMG139” or “mirikizumab” or “LY3074828” combined with “psoriasis”. In addition, the references of these articles were also screened to find other relevant articles.

2.2. Selection criteria

The inclusion criteria were as follows: (1) The type of article was double-blind randomized controlled trial; (2) The patients were adults, and they had stable (≥6 months) moderate-to-severe chronic plaque psoriasis (with or without psoriatic arthritis/PsA) at both screening and baseline (randomization) with body surface area(BSA) involvement 10% or greater, Psoriasis Area Severity Index (PASI) 12 or greater, and static Physician's Global Assessment (sPGA) score 3 or greater; (3) The paper provided detailed data of efficacy and safety parameters; (4) The follow-up time was 16 weeks, if missing, the closest follow-up time was selected as the measurement time of each indicator; (5) The study was published in English. We excluded case-control studies, cohort studies, review articles, meta-analysis, conference abstracts, case reports and unpublished articles.

Table 1
Characteristics of randomized controlled trials included in this meta-analysis.

Authors (years)	NCT	Medications	N	Age (year)	Male N(%)	White N(%)	Time of follow-up	Biologic agents N(%)	PsA N(%)	BSA	PASI	DLQI score	Modified Jadad scale
Howard 2014	NA	GUS 100 mg, sc	5	NA	4 (80)	5 (100)	16 weeks	NA	NA	NA	NA	NA	4
		Placebo, sc	4	NA	3 (75)	3 (75)		NA	NA	NA	NA	NA	
Kenneth 2015	NCT01483599	GUS, sc	208	44.00	149 (72)	189 (91)	16 weeks	85 (41)	52 (25)	24.60 ± 14.48	20.90 ± 8.05	NA	7
		Ada 40 mg, sc	43	50.00	30 (70)	39 (91)		26 (60)	11 (26)	26.80 ± 16.80	20.20 ± 7.58	NA	
		Placebo, sc	42	46.50	28 (67)	39 (93)		15 (36)	12 (29)	27.50 ± 19.26	21.80 ± 9.98	NA	
James 2015	NCT01577550	RIS, sc/iv	31	42.40	25 (81)	28 (90)	24 weeks	NA	NA	NA	18.50	NA	7
		Placebo, sc/iv	8	50.60	6 (75)	8 (100)		NA	NA	NA	17.40	NA	
Papp 2015	NCT01225731	TIL 100 mg, sc	89	45.50 ± 12.80	76 (85)	73 (82)	16 weeks	23 (26)	15 (17)	NA	NA	NA	7
		TIL 200 mg, sc	86	43.20 ± 12.60	65 (76)	73 (85)		22 (26)	15 (17)	NA	NA	NA	
		Placebo, sc	46	45.90 ± 11.70	38 (83)	35 (76)		13 (28)	11 (24)	NA	NA	NA	
Andrew 2016	NCT02207231	GUS 100 mg, sc	329	43.90 ± 12.74	240 (73)	262 (80)	16 weeks	71 (22)	64 (20)	28.30 ± 17.10	22.10 ± 9.49	14.00 ± 7.48	7
		Ada 40 mg, sc	334	42.90 ± 12.58	249 (75)	277 (83)		70 (21)	62 (19)	28.60 ± 16.66	22.40 ± 8.97	14.40 ± 7.29	
		Placebo, sc	174	44.90 ± 12.90	119 (69)	145 (83.3)		34 (20)	30 (18)	25.80 ± 15.93	20.40 ± 8.74	13.30 ± 7.12	
Kristian 2016	NCT02207244	GUS 100 mg, sc	496	43.70 ± 12.20	349 (70)	408 (82)	16 weeks	101 (20)	89 (18)	28.50 ± 16.40	21.90 ± 8.80	14.70 ± 6.90	7
		Ada 40 mg, sc	248	43.20 ± 11.90	170 (69)	200 (81)		49 (20)	44 (18)	29.10 ± 16.70	21.70 ± 9.00	15.00 ± 6.90	
		Placebo, sc	248	43.30 ± 12.40	173 (70)	206 (83)		54 (22)	46 (19)	28.00 ± 16.50	21.50 ± 8.00	15.10 ± 7.20	
Kim 2017	NCT02054481	RIS 180 mg, sc	42	45.00 ± 14.00	29 (69)	40 (95)	12 weeks	NA	12 (29)	26.30 ± 16.70	20.00 ± 8.00	NA	7
		Ust 45/90 mg, sc	40	45.00 ± 12.00	27 (68)	34 (85)		NA	14 (35)	24.60 ± 13.20	20.00 ± 6.00	NA	
Kristian 2017	NCT01722331	TIL 100 mg, sc	309	46.40 ± 13.10	207 (67)	217 (70)	12 weeks	71 (23)	NA	29.70 ± 17.44	20.00 ± 7.85	13.90 ± 6.68	7
		TIL 200 mg, sc	308	46.90 ± 13.20	226 (73)	209 (68)		71 (23)	NA	30.90 ± 17.79	20.70 ± 8.51	13.20 ± 6.87	
		Placebo, sc	155	47.90 ± 13.50	100 (65)	101 (65)		35 (23)	NA	29.60 ± 17.28	19.30 ± 7.07	13.20 ± 7.25	
Kristian 2017	NCT01729754	TIL 100 mg, sc	307	44.60 ± 13.60	220 (72)	279 (91)	12 weeks	39 (13)	NA	34.20 ± 18.44	20.50 ± 7.63	14.80 ± 7.24	7
		TIL 200 mg, sc	314	44.60 ± 13.60	225 (72)	284 (90)		38 (12)	NA	31.80 ± 17.16	19.80 ± 7.52	13.20 ± 7.03	
		Placebo, sc	156	46.40 ± 12.20	112 (72)	144 (92)		20 (13)	NA	31.30 ± 14.75	20.00 ± 7.57	13.70 ± 6.98	
Kenneth 2018	NCT02684370	RIS 150 mg, sc	304	48.30 ± 13.40	212 (70)	200 (66)	16 weeks	104 (34)	85 (28)	26.20 ± 15.40	20.60 ± 7.70	13.00 ± 7.00	7
		Ust 45/90 mg, sc	100	46.50 ± 13.40	70 (70)	74 (74)		30 (30)	23 (23)	25.20 ± 14.70	20.10 ± 6.80	13.60 ± 7.30	
		Placebo, sc	102	49.30 ± 13.60	79 (77)	71 (70)		40 (39)	36 (35)	27.90 ± 17.20	20.50 ± 6.70	12.30 ± 6.20	
Kenneth 2018	NCT02684357	RIS 150 mg, sc	294	46.20 ± 13.70	203 (69)	255 (87)	16 weeks	118 (40)	74 (25)	26.20 ± 15.90	20.50 ± 7.80	13.50 ± 7.40	7
		Ust 45/90 mg, sc	99	48.60 ± 14.80	66 (67)	91 (92)		43 (43)	27 (27)	20.90 ± 12.10	18.20 ± 5.90	11.70 ± 6.60	
		Placebo, sc	98	46.30 ± 13.30	67 (68)	87 (89)		42 (43)	32 (33)	23.90 ± 15.70	18.90 ± 7.30	12.90 ± 6.70	
Mamitaro 2018	NCT02325219	GUS 100 mg, sc	63	47.80 ± 11.07	47 (75)	NA	16 weeks	11 (18)	10 (16)	37.90 ± 21.48	26.73 ± 12.20	10.30 ± 7.27	7
		Placebo, sc	64	48.30 ± 10.56	54 (84)	NA		10 (16)	10 (16)	33.60 ± 18.39	25.92 ± 12.34	10.60 ± 7.74	
Nemoto 2018	NCT01484587	GUS 100 mg, sc	5	NA	4 (80)	NA	24 weeks	NA	0 (9)	37.80 ± 25.29	19.60 ± 8.51	NA	7
		Placebo, sc	4	NA	3 (75)	NA		NA	1 (25)	22.00 ± 12.96	18.70 ± 4.73	NA	

NCT: National Clinical Trials; N: number of patients; PsA: Psoriatic arthritis; BSA: body surface area; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; RIS: Risankizumab; TIL: Tildrakizumab; GUS: Guselkumab; Ust: Ustekinumab; Ada: Adalimumab; sc: subcutaneous injection; iv: intravenous injection; NA: not available.

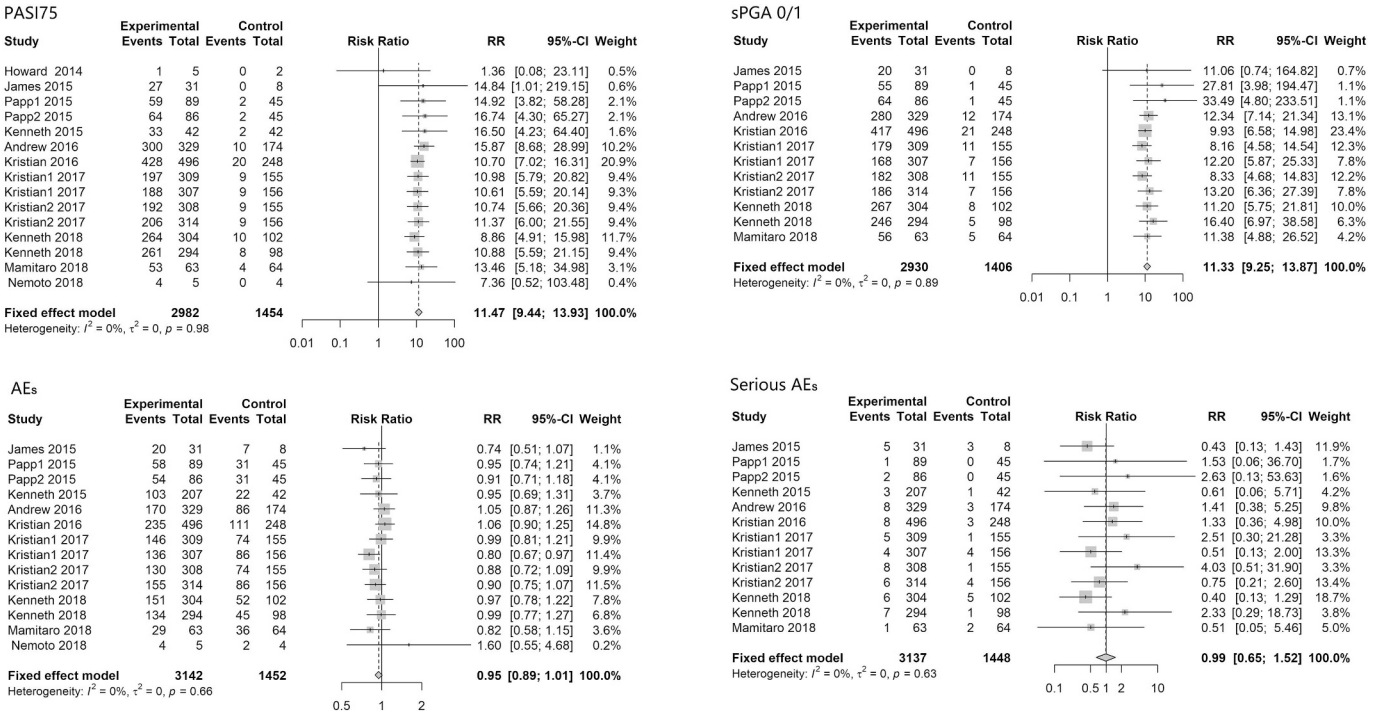


Fig. B. Primary efficacy and safety outcomes of IL-23p19 inhibitors in the treatment of plaque psoriasis versus placebo. PASI: Psoriasis Area and Severity Index; sPGA: static Physician's Global Assessment; AEs: adverse events; SAEs: serious adverse events.

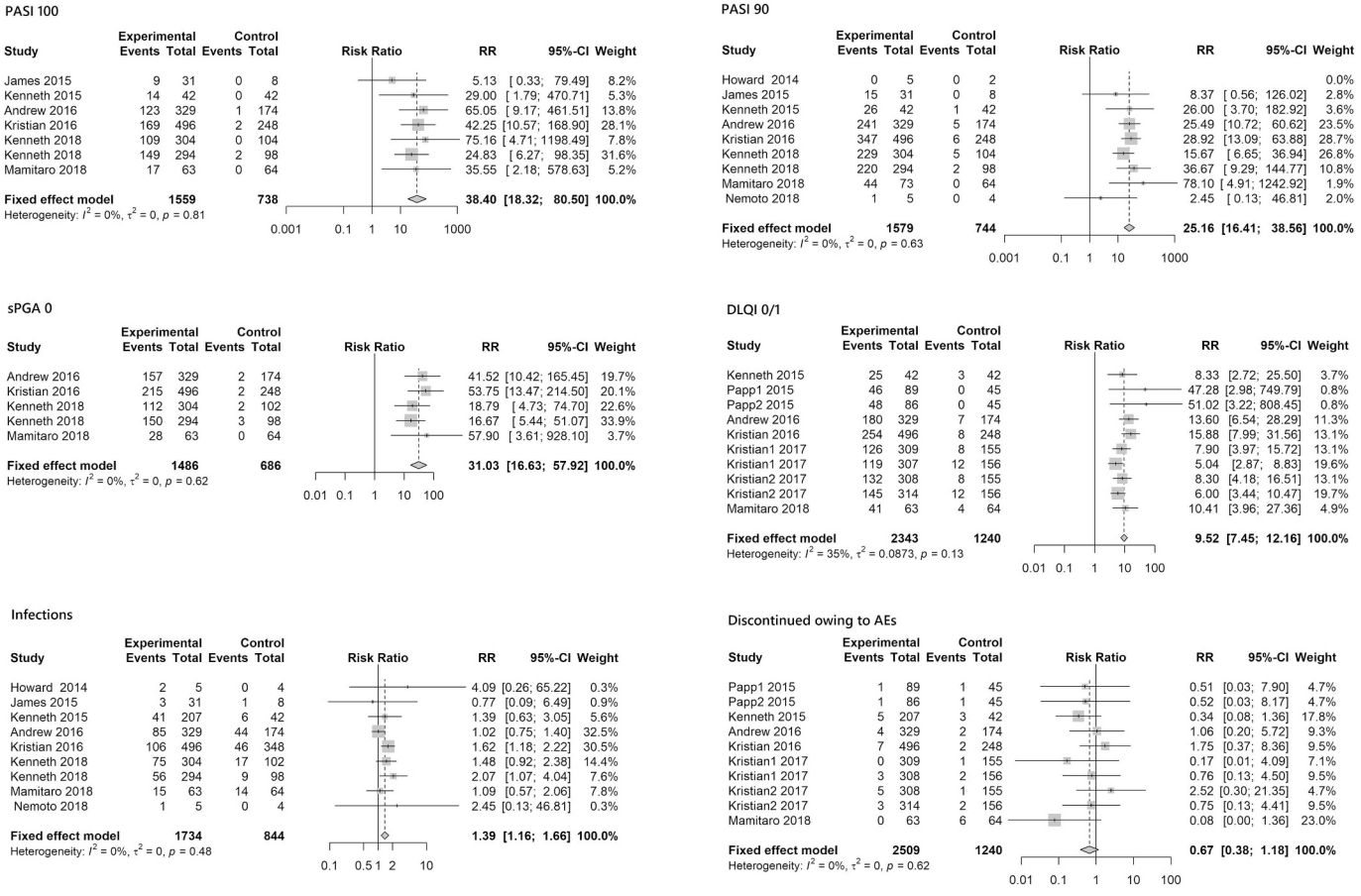


Fig. C. Secondary indicators of IL-23p19 inhibitors in the treatment of plaque psoriasis versus placebo. PASI: Psoriasis Area and Severity Index; sPGA: static Physician's Global Assessment; DLQI: Dermatology Life Quality Index; AEs: adverse events.

Comparison | Efficacy (PASI75) (95%CI) | Safety (AEs) (95%CI)

ADA	1.00 (0.77, 1.15)	1.08 (0.95, 1.52)	0.52 (0.39, 1.85)	**1.22 (1.16, 1.24)**	1.48 (0.98, 2.26)
0.31 (0.21, 0.49)	GUS	1.27 (0.90, 1.32)	0.55 (0.34, 2.12)	**1.21 (1.01, 1.62)**	1.47 (0.85, 2.95)
37.36 (24.21, 63.43)	**119.13 (76.74, 195.24)**	PBO	0.43 (0.37, 1.64)	1.13 (0.76, 1.30)	1.36 (0.64, 2.37)
0.55 (0.27, 1.18)	1.81 (0.84, 3.67)	**0.02 (0.01, 0.03)**	RIS	2.31 (0.66, 3.16)	2.25 (0.93, 5.33)
1.13 (0.55, 2.35)	**3.60 (1.74, 7.44)**	**0.03 (0.02, 0.05)**	1.93 (0.88, 4.99)	TIL	1.21 (0.84, 1.83)
1.79 (0.79, 3.64)	**5.90 (2.50, 11.10)**	**0.05 (0.02, 0.08)**	**3.08 (1.86, 4.84)**	1.57 (0.64, 3.33)	UST

Fig. D. Efficacy and safety of the 6 treatments. RIS: Risankizumab; TIL: Tildrakizumab; GUS: Guselkumab; UST: Ustekinumab; ADA: Adalimumab; PBO: placebo.

2.3. Data extraction

For each article we enrolled, article quality was evaluated by modified Jadad scale and data extraction was performed by two researchers simultaneously and independently. The extracted information was listed as follows: first author's name, publication year, national clinical trial number, medications, the cases, age, male ratio and white ratio of different groups, PsA, BSA, PASI and Dermatology Life Quality Index score (DLQI) at baseline. The efficacy parameters were PASI score reductions from baseline of 75% or more (PASI75), 90% or more (PASI90), 100% (PASI100), sPGA score of 0 or 1 (clear or almost clear), sPGA 0 (clear) and DLQI of 0 or 1. The safety parameters were adverse events (AEs), serious adverse events (SAEs), infections and discontinued owing to AEs. And the PASI75, sPGA0/1, AEs and SAEs were primary indices, the other parameters were secondary indices. Any disagreement was discussed with the third researcher (Faming Pan). For missing data in the article, we try to send an email to the author to get relevant data.

2.4. Statistical analysis

All statistical analyses were proceeded by packages of “meta” and “metafor” in R 3.5.1 software and WinBUGS (MRC Biostatistics Unit, Cambridge, UK). The relative risk (RR) and 95% confidence interval (CI) of efficacy and safety parameters were calculated for each enrolled studies. Heterogeneity was assessed by Q test and I^2 statistic. When the heterogeneity was statistically significant ($P < 0.1$ or $I^2 > 50\%$), we used the random effects model to evaluate the overall effect, otherwise, the fixed effect model was used. We did a random-effects model within a Bayesian framework using Markov chain Monte Carlo methods in WinBUGS for determining the priority of these drugs. Subgroup analysis and meta-regression analysis were implemented to analyze the efficacy and safety in diverse inhibitors and identify possible control measures. Subgroup analysis was stratified by drugs and time of follow-up. Meta-regression analysis was performed by publication year, drugs, number of patients, male ratio, white ratio, time of follow-up, biologic agents and PsA. Sensitivity analysis was conducted to find whether one or more studies deviated from the overall results. Funnel plot, Begg's rank correlation test and Egger's linear regression were performed to evaluate the publication bias. A two-tailed $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Literature search and study characteristics

We searched 2523 articles in total, 1188 articles were excluded owing to duplication. After the title and abstract browsing, we excluded 1296 articles and only read the full text of 39 articles. Finally, 13 articles [14–24] contained 3190 plaque psoriasis patients with IL-23p19 blockers, and 1965 patients with controls (1101 patients with placebo, 625 patients with adalimumab and 239 patients with ustekinumab) were included. The process of study selection was shown in Fig. A. There were four eligible studies with risankizumab, three with tildrakizumab and six with guselkumab, whereas none with brazikumab or mirikizumab. The follow-up time was almost 16 weeks and a few were 12 or 24 weeks. The Modified Jadad scale scores of enrolled studies ranged from 4 to 7, with only one study having the medium-quality score of 4. All studies were published from 2014 to 2018. The characteristics of enrolled studies were represented detailedly in Table 1.

3.2. Results of meta-analysis

3.2.1. IL-23p19 blockers versus placebo

There was no significant heterogeneity between the enrolled studies (all $I^2 < 50.0\%$, $P > 0.1$), hence the fixed effect model was performed. There were significant differences in PASI75 (RR = 11.469, 95% CI = 9.441 to 13.934) and sPGA 0/1 (RR = 11.327, 95% CI = 9.251 to 13.868) between groups (Fig. B). Meanwhile, IL-23p19 inhibitors were well tolerated and the incidence of AEs (RR = 0.949, 95% CI = 0.892 to 1.009) and SAEs (RR = 0.990, 95% CI = 0.645 to 1.520) (Fig. B) was similar to that of the placebo group. However, there was an increased incidence rate of infections (RR = 1.387, 95% CI = 1.160 to 1.659) with IL-23p19 inhibitors (Fig. C). Comparing in secondary indicators between the two groups was outlined in the Fig. C.

3.2.2. IL-23p19 blockers versus adalimumab

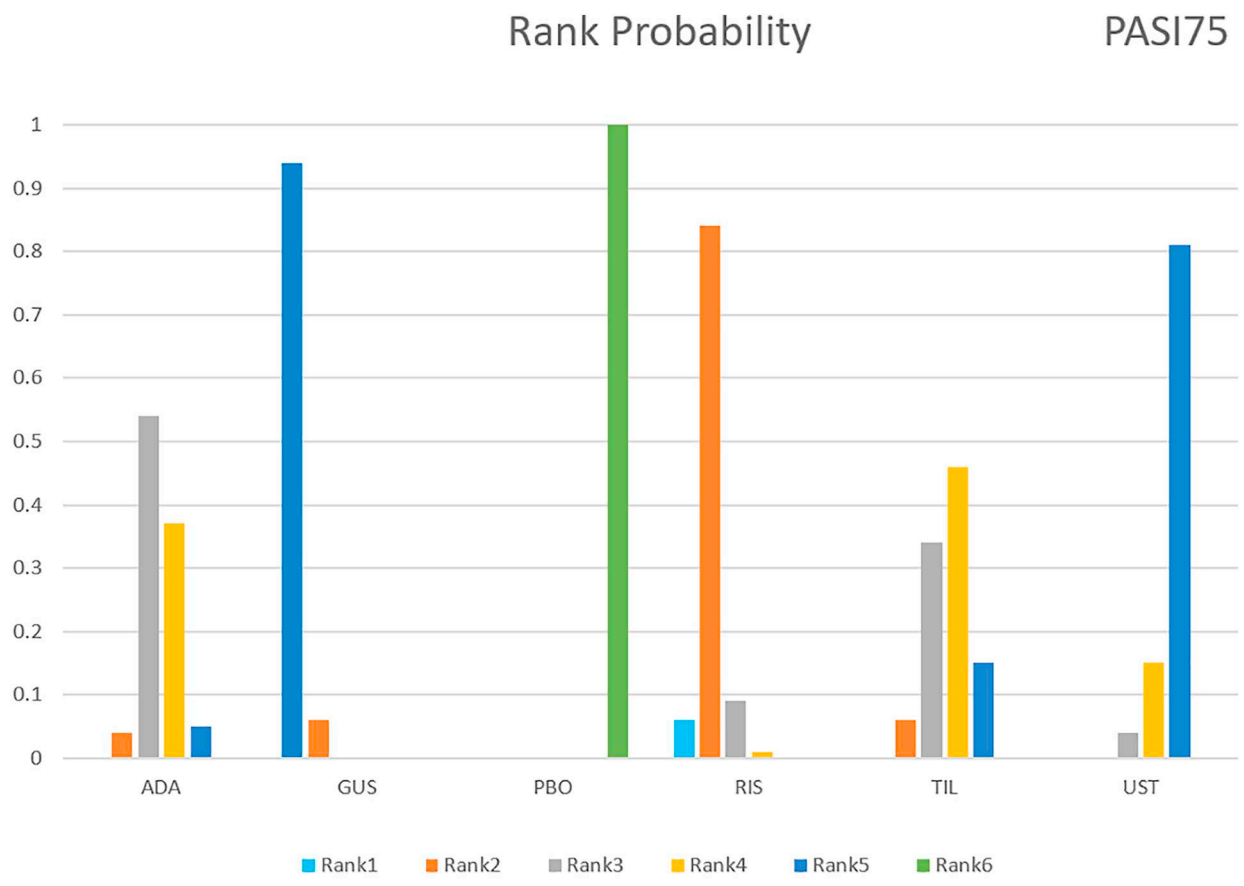
There were significant differences in PASI100 (RR = 1.851, 95% CI = 1.538 to 2.229), PASI90 (RR = 1.480, 95% CI = 1.348 to 1.624), PASI75 (RR = 1.246, 95% CI = 1.177 to 1.318) and DLQI 0/1 (RR = 1.398, 95% CI = 1.242 to 1.575) (Fig. S1). Moreover, the incidence of AEs (RR = 0.986, 95% CI = 0.891 to 1.092), SAEs (RR = 0.924, 95% CI = 0.462 to 1.847), infections (RR = 1.003, 95% CI = 0.832 to 1.208) and discontinued owing to AEs (RR = 0.784, 95% CI = 0.366 to 1.680) (Fig. S1) in IL-23p19 inhibitors was not significantly different from that of adalimumab.

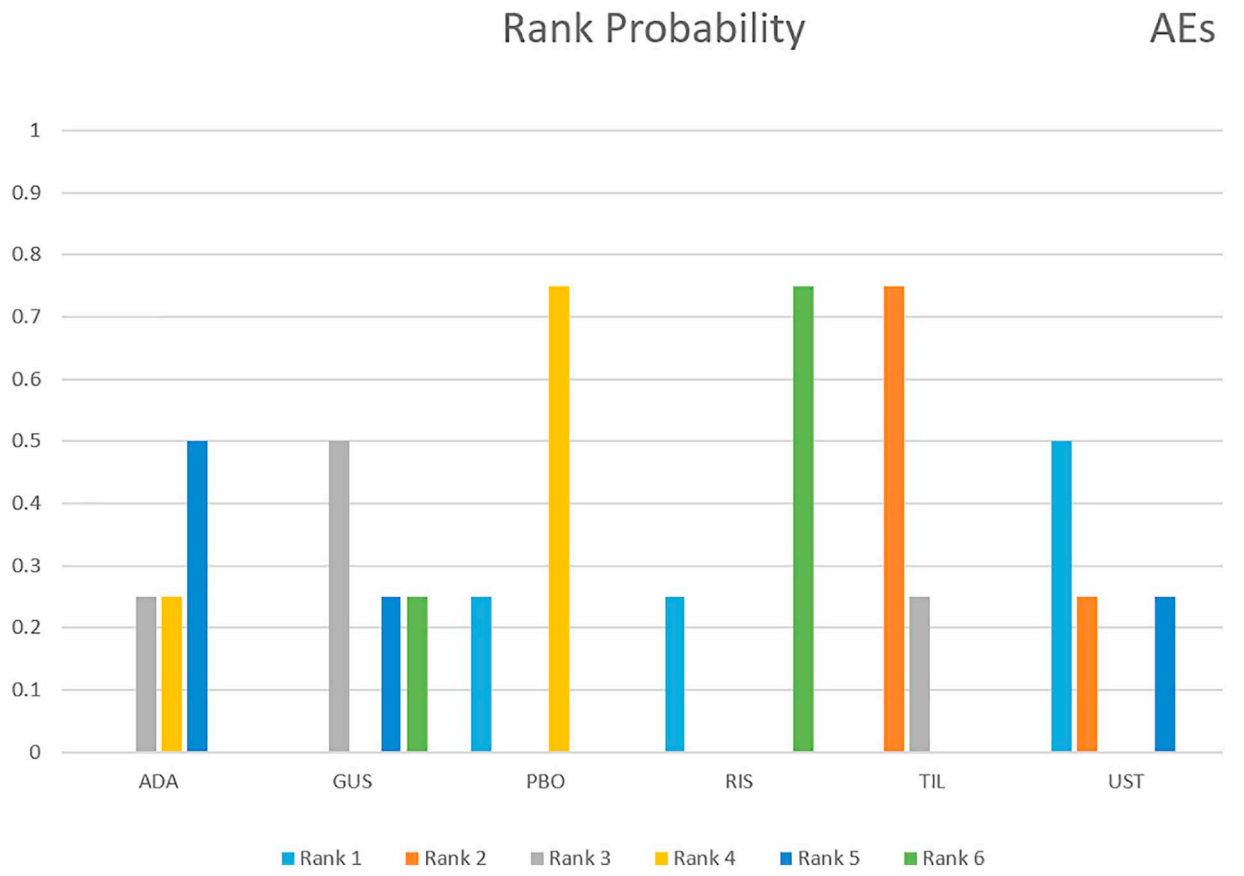
3.2.3. IL-23p19 blockers versus ustekinumab

Research results showed that IL-23p19 inhibitors may be more effective than ustekinumab, which were analyzed from PASI100 (RR = 2.430, 95% CI = 1.828 to 3.229), PASI90 (RR = 1.539, 95% CI = 1.327 to 1.786), PASI75 (RR = 1.252, 95% CI = 1.146 to 1.368) and sPGA 0/1 (RR = 1.286, 95% CI = 1.162 to 1.422). There was no significant difference in the incidence of AEs (RR = 0.926, 95% CI = 0.805 to 1.065), SAEs (RR = 0.903, 95% CI = 0.770 to 1.058), infections (RR = 1.035, 95% CI = 0.758 to 1.413) and discontinued owing to AEs (RR = 0.425, 95% CI = 0.101 to 1.799) (Fig. S2) between IL-23p19 inhibitor and ustekinumab.

3.2.4. The comprehensive comparison of the drugs

Fig. D summarized the comprehensive comparison of the drugs, which showed: 1) all drugs were significantly more efficacious than placebo; 2) the efficacy of guselkumab was better than that of adalimumab; 3) the efficacy of risankizumab was superior to ustekinumab; 4) there were no significant differences between all prevention therapeutic measures in the safety except that guselkumab and adalimumab were more tolerable than tildrakizumab. Fig. E showed the distribution of probabilities of each treatment being ranked at each of the possible 6





(caption on next page)

Fig. E. Ranking for efficacy (PASI75) and safety (AEs). Rank1 demonstrate that the biologics is more effective in PASI75, and Rank 6 proved the best safety in AEs. PASI: Psoriasis Area and Severity Index; AEs: adverse event.

Table 2
Subgroup analysis of efficacy and safety in plaque psoriasis.

Indices	Subgroups	N	RR (95%CI)	*Z*	*P*	Test of heterogeneity	
						I^2	*P*
PASI75	Drugs						
	RIS	3	9.916(6.410 to 15.339)	10.32	< 0.001	0.0%	0.853
	TIL	6	11.413(8.424 to 15.461)	15.72	< 0.001	0.0%	0.990
	GUS	6	12.453(9.112 to 17.019)	15.82	< 0.001	0.0%	0.621
	Time of follow-up						
	12 weeks	4	10.926(7.935 to 15.045)	14.65	< 0.001	0.0%	0.999
	16 weeks	9	11.788(9.207 to 15.094)	19.56	< 0.001	0.0%	0.786
	24 weeks	2	12.191(1.674 to 88.752)	2.47	0.014	0.0%	0.692
sPGA 0/1	Drugs						
	RIS	3	13.137(7.835 to 22.026)	9.77	< 0.001	0.0%	0.784
	TIL	6	11.056(8.090 to 15.110)	15.08	< 0.001	0.0%	0.494
	GUS	3	10.854(7.982 to 14.760)	15.21	< 0.001	0.0%	0.817
	Time of follow-up						
	12 weeks	4	9.977(7.241to 13.748)	14.06	< 0.001	0.0%	0.638
	16 weeks	7	12.238(9.414 to 15.910)	18.71	< 0.001	0.0%	0.776
	24 weeks	1	11.531(0.770 to 172.646)	1.77	0.077	NA	NA
AE	Drugs						
	RIS	3	0.965(0.825 to 1.129)	0.44	0.659	4.5%	0.351
	TIL	6	0.896(0.822 to 0.977)	2.48	0.013	0.0%	0.789
	GUS	5	0.949(0.892 to 1.009)	0.36	0.717	0.0%	0.608
	Time of follow-up						
	12 weeks	4	0.890(0.807 to 0.981)	2.34	0.019	0.0%	0.535
	16 weeks	8	0.995(0.916 to 1.080)	0.12	0.903	0.0%	0.904
	24 weeks	2	0.881(0.608 to 1.276)	0.67	0.503	51.8%	0.150
SAE	Drugs						
	RIS	3	0.623(0.292 to 1.328)	1.23	0.220	18.3%	0.294
	TIL	6	1.239 (0.618 to 2.483)	0.60	0.546	0.0%	0.524
	GUS	4	1.114(0.503 to 2.467)	0.27	0.791	0.0%	0.827
	Time of follow-up						
	12 weeks	4	1.155(0.553 to 2.413)	0.38	0.701	20.0%	0.290
	16 weeks	8	1.012(0.565 to 1.814)	0.04	0.967	0.0%	0.731
	24 weeks	1	0.430(0.129 to 1.431)	1.38	0.169	NA	NA

N: number of studies; RR: relative risk; *Z:* statistic; PASI: Psoriasis Area and Severity Index; RIS: Risankizumab; TIL: Tildrakizumab; GUS: Guselkumab; sPGA: static Physician's Global Assessment; AE: adverse event; SAE: serious adverse event; NA: not available.

positions. Guselkumab was likely the most efficacious treatments, and risankizumab may be better tolerated than the others. The evaluation of inconsistency showed there was a cycle (RIS-UST-PBO) and the 95% CI of its inconsistent factor included 0, indicated there was no significant inconsistency between the direct and indirect results of this study. The DIC in fixed-effect and randomized-effect method were very close, suggested the results were stable.

3.3. Subgroup analysis

In the subgroups of different drugs and time of follow-up, the PASI75 of the IL-23p19 inhibitors group was significantly higher than the placebo group (all $P < 0.05$) (Table 2). Meanwhile, the probability of sPGA 0/1 in patients treated with IL-23p19 inhibitor was significantly higher in all subgroups than in placebo-treated patients, with the exception of the group of 24 weeks. The incidence of AEs was lower than placebo in subgroups of tildrakizumab (RR = 0.896, 95% CI = 0.822 to 0.977) and the time of follow-up of 12 weeks (RR = 0.890, 95% CI = 0.807 to 0.981). Furthermore, the incidence of SAEs was not significantly different in disparate subgroups (all $P > 0.05$).

3.4. Meta-regression analysis

To further identify possible sources of heterogeneity, meta-regression analysis was performed by publication year, drugs, number of patients, male ratio, white ratio, time of follow-up, biologic agents and PsA. The results indicated that none of these factors were significantly associated with the parameters of efficacy and safety (all $P > 0.05$) (Table 3).

3.5. Sensitivity analysis and publication bias

The results in Fig. S3 showed that no matter which study was omitted, the overall statistical significance does not change, indicating that our results were statistically robust. The results of funnel plot were visually showed in Fig. S4. Egger's and Begg's test did not detect significant publication bias across the included studies in PASI75, AEs and SAEs ($P > 0.05$, the Data not shown). Meanwhile, Begg's test did not find significant publication bias in sPGA 0/1 ($P > 0.05$), but Egger's test detected significant publication bias ($P = 0.023$). The possible reasons may be the insufficient study numbers and inconsistent drug dose.

4. Discussion

Recently, immune factors involved in the occurrence, development and maintenance of psoriasis have been widely accepted. Meanwhile, studies have reported that psoriasis lesions were the result of interaction between various maladjusted cytokines in the innate and adaptive immune systems and resident skin cells [1]. An animal study showed that the intervention of IL-23 in susceptible mice could lead to psoriasis-like lesions, and IL-23 expression was elevated in the human psoriasis tissue [25–27], which further testifies that IL-23 may be a pathogenic factor of human psoriasis. In the diagnosis and evaluation of psoriasis, PASI

Table 3
Meta-regression analysis coefficients for efficacy and safety in plaque psoriasis.

Indices	Variables	Tau-squared	Coefficient (SE)	95% CI	*P*
PASI75	Publication year	< 0.0001	−0.0821(0.1099)	[−0.3196, 0.1555]	0.469
	RIS	< 0.0001	−0.2114(0.2734)	[−0.8071, 0.3844]	0.454
	TIL	< 0.0001	−0.0677(0.2221)	[−0.5516, 0.4162]	0.766
	N	< 0.0001	−0.0001(0.0006)	[−0.0014, 0.0011]	0.810
	Male N(%)	< 0.0001	0.0113(0.0288)	[−0.0511, 0.0736]	0.703
	White N(%)	< 0.0001	0.048(0.0101)	[−0.0174, 0.0270]	0.643
	Time of follow-up	< 0.0001	0.0100(0.0461)	[−0.0895, 0.1096]	0.831
	Biologic agents	< 0.0001	−0.0032(0.0116)	[−0.0292, 0.0227]	0.787
	PsA	< 0.0001	−0.0188(0.0247)	[−0.0773, 0.0397]	0.472
sPGA 0/1	Publication year	< 0.0001	−0.0185(0.1289)	[−0.3057, 0.2686]	0.888
	RIS	< 0.0001	0.1744(0.3062)	[−0.5184, 0.8672]	0.583
	TIL	< 0.0001	−0.0471(0.2231)	[−0.5518, 0.4575]	0.837
	N	< 0.0001	−0.0006(0.0006)	[−0.0019, 0.0008]	0.389
	Male N(%)	< 0.0001	0.0404(0.0308)	[−0.0281, 0.1091]	0.218
	White N(%)	< 0.0001	0.0071(0.0112)	[−0.0183, 0.0326]	0.541
	Time of follow-up	< 0.0001	0.0419(0.0494)	[−0.0682, 0.1521]	0.416
	Biologic agents	< 0.0001	0.0054(0.0143)	[−0.0270, 0.0377]	0.717
	PsA	< 0.0001	0.0117(0.0279)	[−0.0601, 0.0836]	0.692
AE	Publication year	< 0.0001	−0.0091(0.0320)	[−0.0788, 0.0605]	0.780
	RIS	< 0.0001	−0.0842(0.0948)	[−0.2929, 0.1244]	0.393
	TIL	< 0.0001	−0.1270(0.0704)	[−0.2819, 0.0280]	0.099
	N	< 0.0001	0.0003(0.0002)	[−0.0001, 0.0008]	0.165
	Male N(%)	< 0.0001	−0.0078(0.0071)	[−0.0234, 0.0077]	0.294
	White N(%)	< 0.0001	−0.0036(0.0032)	[−0.0108, 0.0036]	0.290
	Time of follow-up	< 0.0001	0.0080(0.0123)	[−0.0187, 0.0347]	0.525
	Biologic agents	< 0.0001	−0.0041(0.0037)	[−0.0042, 0.0125]	0.294
	PsA	< 0.0001	−0.0026(0.0089)	[−0.0237, 0.0184]	0.776
SAE	Publication year	< 0.0001	−0.0414(0.2132)	[−0.5107, 0.4278]	0.850
	RIS	< 0.0001	−0.7331(0.5718)	[−2.0070, 0.5409]	0.229
	TIL	< 0.0001	−0.0252(0.5587)	[−1.2700, 1.2196]	0.965
	N	< 0.0001	0.0114(0.0011)	[−0.0011, 0.0039]	0.241
	Male N(%)	< 0.0001	−0.0829(0.0590)	[−0.2129, 0.0470]	0.188
	White N(%)	0.0460	−0.0271(0.0232)	[−0.0788, 0.0246]	0.270
	Time of follow-up	< 0.0001	−0.0676(0.0609)	[−0.2017, 0.0666]	0.291
	Biologic agents	< 0.0001	−0.0003(0.0261)	[−0.0578, 0.0584]	0.991
	PsA	< 0.0001	−0.0721(0.0584)	[−0.2150, 0.0707]	0.263

PASI: Psoriasis Area and Severity Index; RIS: Risankizumab; TIL: Tildrakizumab; GUS: Guselkumab; sPGA: static Physician's Global Assessment; AE: adverse event; SAE: serious adverse event; N: number of patients; PsA: Psoriatic arthritis; NA: not available.

response and sPGA are the most commonly used. The Psoriasis Area and Severity Index (PASI) score has been used to quantify disease severity of erythema, infiltration or thickness, scaling and the extent of lesions in patients [1]. Meanwhile, static psoriasis global assessment (sPGA) was also used to assess the severity of the condition. In this meta-analysis, the above two indicators were used as the main efficacy indicators, and AEs and SAEs as the main safety indicators to comprehensively analyze and compare the efficacy and safety of IL-23p19 inhibitors.

The results indicated significant positive benefits for the IL-23p19 inhibitor (risankizumab, tildrakizumab and guselkumab) on the PASI response and sPGA 0/1 compared with placebo and active control. It was consistent with the conclusions of several reviews [28–31], but was inconsistent with the results of some studies in part indexes [14,15,24]. The reason for the inconsistency may be that the sample size of the three studies is small (< 30) and the representativeness is insufficient, which is also the main footing for this meta-analysis. The incidence of adverse events and serious adverse events was not significantly different between the groups, but there was an increased incidence rate of infections. According to the existing research reports, the infection caused by treatment has not evolved into a serious infection or other serious adverse events. The possible reasons for the increase of infection rate are the potential infection before treatment and the short follow-up time, so the specific reasons need to be further studied. The results of comprehensive comparison showed that guselkumab was likely the most efficacious treatments, and risankizumab may be better tolerated than the others. In previous studies, IL-23p19 inhibitors have not been directly compared, and the results of this study may provide some indirect evidence for clinical application. But the conclusion still needs to be verified by randomized controlled trials with a lager sample size.

Adalimumab is a biological agent targeted at TNF-α, which has been proved to have good efficacy in other autoimmune diseases. Although its efficacy in psoriasis is better than placebo, it is unknown compared with IL-23p19 inhibitor. The results of this meta-analysis showed IL-23p19 inhibitor, guselkumab, had superior efficacy to adalimumab in the achievement of PASI response and DLQI 0/1, with a similar incidence rate of safety indicators (AEs, SAEs, infections and discontinued owing to AEs). Studies have shown that IL-23 was associated with TNF-α production and biological effects [9–11]. Combined with the above conclusion, IL-23 may play a more pivotal role in the pathogenesis of psoriasis than TNF-α, but this conjecture requires larger RCTs and more basic mechanism researches to verify.

Ustekinumab targeting at p40 subunit of IL-23/IL-12 is the most studied therapeutic drug targeting IL-23/-17 axis, and has shown excellent efficacy and safety in treatment of psoriasis [9,32,33]. In this study, risankizumab showed superior efficacy to ustekinumab, as evidenced by the achievement of PASI response and sPGA 0/1, and was as well tolerated as ustekinumab. It is well known that the target of both drugs is IL-23, the only difference is that risankizumab targets at p19 and ustekinumab targets at p40, and ustekinumab both inhibit IL-23 and IL-12. An animal study has shown that IL-12 may inhibit the development of skin inflammation and have an anti-psoriasis effect [34]. Based on this result, we speculated that the possibility for this difference may be the indirect inhibition of IL-12 by p40-targeted inhibitors, which may inhibit the improvement of psoriasis. The other possible causes needed to explore by further institutional studies.

There was publication bias in the Egger's test of sPGA 0/1, but there was no publication bias in the Begg's test, the results were inconsistent. The possible reasons include the small size of studies included and the differences between different statistical methods. Additionally, a

comprehensive comparison of multiple indicators was conducted in this meta-analysis, it would not affect the overall effect of this meta. Any comparison and analysis about brazikumab and mirikizumab could not be done because the RCTs about them have not been done or published by retrieving in ClinicalTrials.gov. At the same time, there are many studies on risankizumab or guselkumab under way or not published. In the future, we will further include these studies and increase the number of studies, so as to obtain more stable and accurate conclusions. In addition, because of the lack of relevant researches, this study did not compare IL-23 inhibitors with secukinumab, an IL-17 inhibitor. But there are two RCTS evaluating the comparative efficacy of guselkumab and secukinumab are currently ongoing, the findings will provide direct evidence.

There are several limitations in this study. First, we have excluded the articles of no full text, no declared and conference abstract, which may bias the authentic result. Second, the small number of studies and the doses were not exactly the same in different studies, the above reasons may affect the overall results. Finally, some of the studies enrolled had small samples, which could give rise to a lower statistical power.

5. Conclusion

This meta-analysis showed that IL-23p19 blockers had good efficacy and safety in patients with plaque psoriasis, and had a better efficacy than other types of inhibitors (adalimumab, ustekinumab) without other adverse events. Among three IL-23p19 blockers, guselkumab was the most efficacious treatments, and risankizumab was better tolerated than the others. But long-term safety and the maintenance of efficacy remains to be determined, future studies should focus more on long-term follow-up.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105841.

Funding

The study was sponsored by the National Natural Science Foundation of China (81273169, 81573218 and 81773514).

Declaration of competing interest

All authors state that there is no conflict of interest.

Acknowledgements

We would like to acknowledgement the National Natural Science Foundation of China for its financial support.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

References

[1] W.H. Boehncke, M.P. Schon, Psoriasis, Lancet 386 (9997) (2015) 983–994.
[2] M. Lebwohl, Psoriasis, Lancet 361 (9364) (2003) 1197–1204.
[3] J.E. Greb, A.M. Goldminz, J.T. Elder, et al., Psoriasis, Nat. Rev. Dis. Primers 2 (2016) 16082.
[4] I.M. Michalek, B. Loring, S.M. John, A systematic review of worldwide epidemiology of psoriasis, J. Eur. Acad. Dermatol. Venereol. 31 (2) (2017) 205–212.
[5] R. Parisi, D.P. Symmons, C.E. Griffiths, et al., Global epidemiology of psoriasis: a systematic review of incidence and prevalence, J. Invest. Dermatol. 133 (2) (2013) 377–385.
[6] C.E.M. Griffiths, J.M. van der Walt, D.M. Ashcroft, et al., The global state of psoriasis disease epidemiology: a workshop report, Br. J. Dermatol. 177 (1) (2017) e4–e7.
[7] J. Takeshita, S. Grewal, S.M. Langan, et al., Psoriasis and comorbid diseases: epidemiology, J. Am. Acad. Dermatol. 76 (3) (2017) 377–390.
[8] K.L. Goff, C. Karimkhani, L.N. Boyers, et al., The global burden of psoriatic skin disease, Br. J. Dermatol. 172 (6) (2015) 1665–1668.
[9] G.E. Fragoulis, S. Siebert, I.B. McInnes, Therapeutic targeting of IL-17 and IL-23 cytokines in immune-mediated diseases, Annu. Rev. Med. 67 (2016) 337–353.
[10] L. Puig, The role of IL 23 in the treatment of psoriasis, Expert. Rev. Clin. Immunol. 13 (6) (2017) 525–534.
[11] M.J. Gooderham, K.A. Papp, C.W. Lynde, Shifting the focus - the primary role of IL-23 in psoriasis and other inflammatory disorders, J. Eur. Acad. Dermatol. Venereol. 32 (7) (2018) 1111–1119.
[12] A. Markham, Guselkumab: first global approval, Drugs 77 (13) (2017) 1487–1492.
[13] A. Markham, Tildrakizumab: first global approval, Drugs 78 (8) (2018) 845–849.
[14] H. Sofen, S. Smith, R.T. Matheson, et al., Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis, J. Allergy Clin. Immunol. 133 (4) (2014) 1032–1040.
[15] J.G. Krueger, L.K. Ferris, A. Menter, et al., Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial, J. Allergy Clin. Immunol. 136 (1) (2015) 116–124 (e7).
[16] K.B. Gordon, B. Strober, M. Lebwohl, et al., Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials, Lancet 392 (10148) (2018) 650–661.
[17] K.B. Gordon, K.C. Duffin, R. Bissonnette, et al., A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis, N. Engl. J. Med. 373 (2) (2015) 136–144.
[18] K. Papp, D. Thaci, K. Reich, et al., Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial, Br. J. Dermatol. 173 (4) (2015) 930–939.
[19] A. Blauvelt, K.A. Papp, C.E. Griffiths, et al., Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial, J. Am. Acad. Dermatol. 76 (3) (2017) 405–417.
[20] K. Reich, A.W. Armstrong, P. Foley, et al., Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial, J. Am. Acad. Dermatol. 76 (3) (2017) 418–431.
[21] K.A. Papp, A. Blauvelt, M. Bukhalo, et al., Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis, N. Engl. J. Med. 376 (16) (2017) 1551–1560.
[22] K. Reich, K.A. Papp, A. Blauvelt, et al., Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials, Lancet 390 (10091) (2017) 276–288.
[23] M. Ohtsuki, H. Kubo, H. Morishima, et al., Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study, J. Dermatol. 45 (9) (2018) 1053–1062.
[24] O. Nemoto, K. Hirose, S. Shibata, et al., Safety and efficacy of guselkumab in Japanese patients with moderate-to-severe plaque psoriasis: a randomized, placebo-controlled, ascending-dose study, Br. J. Dermatol. 178 (3) (2018) 689–696.
[25] J.R. Chan, W. Blumenschein, E. Murphy, et al., IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis, J. Exp. Med. 203 (12) (2006) 2577–2587.
[26] M. Elliott, J. Benson, M. Blank, et al., Ustekinumab: lessons learned from targeting interleukin-12/23p40 in immune-mediated diseases, Ann. N. Y. Acad. Sci. 1182 (2009) 97–110.
[27] A.A. Levin, A.B. Gottlieb, Specific targeting of interleukin-23p19 as effective treatment for psoriasis, J. Am. Acad. Dermatol. 70 (3) (2014) 555–561.
[28] M. Nakamura, K. Lee, C. Jeon, et al., Guselkumab for the treatment of psoriasis: a review of phase III trials, Dermatol. Ther. (Heidelb) 7 (3) (2017) 281–292.
[29] M. Amin, K. Darji, D.J. No, et al., Review of phase III trial data on IL-23 inhibitors tildrakizumab and guselkumab for psoriasis, J. Eur. Acad. Dermatol. Venereol. 31 (10) (2017) 1627–1632.
[30] W. Tausend, C. Downing, S. Tyring, Systematic review of interleukin-12, interleukin-17, and interleukin-23 pathway inhibitors for the treatment of moderate-to-severe chronic plaque psoriasis: ustekinumab, briakinumab, tildrakizumab, guselkumab, secukinumab, ixekizumab, and brodalumab, J. Cutan. Med. Surg. 18 (3) (2014) 156–169.
[31] S.S. Kolli, S.D. Gabros, A. Pona, et al., Tildrakizumab: a review of phase II and III clinical trials, Ann. Pharmacother. 53 (2018) 413–418.
[32] C.L. Leonardi, A.B. Kimball, K.A. Papp, et al., Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1), Lancet 371 (9625) (2008) 1665–1674.
[33] K.A. Papp, R.G. Langley, M. Lebwohl, et al., Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2), Lancet 371 (9625) (2008) 1675–1684.
[34] P. Kulig, S. Musiol, S.N. Freiberger, et al., IL-12 protects from psoriasiform skin inflammation, Nat. Commun. 7 (2016) 13466.