Quantitative evaluation to efficacy and safety of therapies for psoriasis: A network meta-analysis

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Abstract

Therapies treating psoriasis can be categorized into five classes according to their mechanism: anti-metabolites (AM), anti-interleukin-12/23 agents (anti-IL12/23), anti-interleukin-17 agents (anti-IL17), anti-T-cell agent (ANT), and anti-tumor necrosis factor-α agent (anti-TNF-α). This network meta-analysis (NMA) aimed to give a quantitative and systemic evaluation of safety and efficacy for the five kinds of therapies mentioned above. Odds ratios and mean differences were calculated to evaluate binary and continuous outcomes, respectively. Forest plots were conducted to show the performance of pair-wise comparison of above therapies in each outcome, and surface under the cumulative ranking curves was given to evaluate the relative ranking of above therapies in each outcome. Node splitting was conducted to evaluate the consistency between direct and indirect evidence. Direct comparisons from 65 studies (32,352 patients) were included in this NMA. Our results showed an excellent efficacy of anti-IL12/23 and anti-IL17. However, these two therapies and anti-TNF-α were revealed to have a high possibility to cause adverse effects (AEs) such as infections. Additionally, node splitting showed that no inconsistency appeared between the direct and indirect comparisons. Anti-IL12/23 was the most recommended therapy according to this NMA. Anti-IL17 had similar efficacy to anti-IL12/23 but should be applied with caution since it has poor performance in safety outcomes.

Introduction

Psoriasis, characterized by quick and excessive growth of the skin's epidermal layer,[1] is a common, chronic, and systemic disease, affecting 1–3% of the world population. It is widely considered as a genetic disease and could be affected by some environmental factors.[2] Up to now, various therapies are available for psoriasis, including phototherapy, topical treatment, systemic therapies, and biologic drugs.[3]

The biologic drugs can be classified into five classes based on their mechanism: anti-metabolites (AM), anti-tumor necrosis factor-α agent (anti-TNF-α), anti-T-cell agent (ANT), anti-interleukin-12/23 agents (anti-IL12/23), and anti-interleukin-17 agents (anti-IL17). It is reported that methotrexate, an AM, has been applied

as a valid systemic treatment for psoriasis patients over 48 years.[4] However, it is relevant to hepatotoxicity and

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myelosuppression.[5] Besides, the TNF is widely regarded as an important cytokine involved in the pathophysiology of psoriasis. Therefore, monoclonal antibodies, such as adalimumab and infliximab, which antagonized TNF, were applied in the treatment of psoriasis.[6,7]

Relevant studies showed that psoriasis was possibly an autoimmune disease where the activation of skin-directed T-cells performed an important role.[8] Alefacept, a recombinant protein, has the ability to block T-cell's proliferation and activation by combining with CD2 on the surface of T-cells. Alefacept can also induce selective CD45RO+ T-cell apoptosis by interacting with the immunoglobulin receptors FcγRIII on the accessory cells.[9] Other drugs, such as efalizumab and itolizumab, are humanized monoclonal antibodies which could directly deal with the pathogenic T-cells by binding to CD11a or CD6 and inhibit T-cell functions, such as activation, trafficking, and migration.[10–12]

Meanwhile, it has been discovered that TNF is produced by the immune pathways stimulated by two interleukins, interleukin-12 (IL-12) and interleukin-23 (IL-23).[13] This discovery indicates that both IL12 and IL23 play a pivotal role in the psoriasis development. In addition, IL-17A and IL-17RA were also found related to the disease severity because of the elevated levels of IL-17A in the diseased skin and blood of patients with psoriasis.[14] Etanercept, a human fusion TNF soluble receptor, is used to prevent the TNF-mediated inflammatory response and applied for the therapy of psoriatic arthritis and chronic plaque.[15]

To make an effective and safe decision in treatment of psoriasis, it is necessary to conduct reliable evidences of comparison among these drugs. A number of traditional meta-analysis studies had been done to make comparison between two therapies, which indicated that all the therapies are more effective than placebo (PBO). But they cannot compare several therapies simultaneously. Therefore, the network meta-analysis (NMA) is required to synthesize all valuable evidences from randomized control trials (RCTs), combining both direct and indirect evidences, to convincingly draw the conclusions about competitive efficacy and safety information.

Woolacott et al. made the comparisons among three biological therapies, efalizumab, infliximab, and etanercept, and two nonbiological therapies.[16] Adalimumab was taken into consideration in the work of Bansback et al.[17] After then, with the development of biological treatment, more NMA were conducted, such as the works of Reich et al.[18] and Lin et al.,[19] who added the ustekinumab, which antagonizes IL-12/23p40. Besides, Nast et al.[20] assessed the efficacy and safety of treatments of systemic long-term treatments. Recently, Gomez-Garcia et al.[21] used the new 2015 PRISMA statement for the NMA and evaluated the comparative short-term efficacy and tolerance of the agents. Jabbar-

Lopez et al. established the relative efficacy and tolerability of six monoclonal antibodies. None of them compared the biotics from the level of large classes.

The primary objective of our study was to give an extension to the existing NMAs to evaluate the efficacy and safety of different treatment agents. More agents were taken in account to provide more reliable conclusion. Moreover, the ranking possibility in specific efficacy and safety were also presented to help making optimal decision in clinical drug using. Besides, no NMA similar to this study, with sufficient samples and consideration of all therapies, had been done yet.

Materials and methods

Search strategy

To get the relevant studies, the following three electronic databases were taken into our retrieval: Chinese National Knowledge Infrastructure, PubMed, and Embase. Regardless of the limitation of language, key terms "psoriasis," "antimetabolites," "macrolides," "antibodies, monoclonal," "etanercept" as well as their acronyms were searched in this work. Besides, the reference lists were examined to identify the potentially available studies.

Inclusion and exclusion criteria

All included trials must satisfy the following criteria: (i) the studies must be RCTs; (ii) the patients involved in the studies must be diagnosed as psoriasis; and (iii) relevant outcomes should be contained. Besides, duplicate RCTs or the studies with isolated comparison were excluded.

Outcome measure and data extraction

Data extraction was conducted by two reviewers independently, and following characteristics of each study were extracted from the original documents: (i) the basic information, including the first author, country, published year, and blinding; (ii) the patients characteristics, including ages, gender ratio, and disease duration; (iii) efficacy outcomes, including the Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), and Physician's Global Assessment (PGA); (iv) safety outcomes, including the incidence of all AEs, infection, nasopharyngitis, headache, and upper respiratory tract infection (URTI).

Statistical analysis

Odds ratio (OR) with corresponding 95% credible interval (CrI) were used to evaluate the binary outcomes. Mean difference with corresponding 95% CrI were applied to assess the continuous outcomes. Meanwhile,

forest plots were drawn to visually present the relative efficacy and safety of different comparisons for each outcome. Consistency between direct and indirect comparison was analyzed by the node-splitting method. $p<0.05$ indicated a significant inconsistency for a specific comparison. Moreover, surface under the cumulative ranking curves (SUCRAs) were calculated to present the ranking probability of each treatment to find the relatively optimal treatment to improve the efficacy and decrease the incidence of adverse events. Software R (version 3.2.3) and STATA (version 13.0) were used to implement the NMA.

Results

Included studies

In the retrieval, 1562 records were identified at the beginning, and 17 records were added manually. Among them, 573 duplicates were removed, and 989 records were left. After 242 records excluded during screening, 432 records were full-text assessed. Finally, 75 studies and 25,108 patients were included in our NMA.[4–6,9–14,22–87] The flow chart was shown in Figure 1. The details of specific treatment, the characteristics of patients, and outcomes of each trail were provided in Table 1. The study sample sizes ranged from 33 to 1831. The follow-up period ranged from six weeks to 120 weeks. Among 58 trails, five trails failed to provide age range of the patients,[27,29,49,59,62,70] while six trails failed to provide gender ratios of the patients.[14,27,49,59,70,86] The mean disease duration was 17.5 years (range 5.6–22.8). Besides, disease severity was assessed containing all the trails with a baseline PASI score of 19.9 (range 5.5–33.1) and a body surface area (BSA) of 28.8% (range 5.1–49.8). Jadad score of included RCTs was shown in Table S1. Meanwhile, the network diagram was shown in Figure 2. The area of dots represents the number of patients in the therapy, and the width of lines stands for the number of references including the comparison.

NMA results for PASI reduction

Table 2 showed the network comparison of different treatments for PASI reduction. In terms of PASI 75, it shows that anti-IL12/23 and anti-IL17 are significantly superior compared with PBO (OR = 43.0, 95% CrI: 27.9–66.7; OR = 62.2, 95% CrI: 36.6–104.6, respectively). (OR = 5.9, 95% CrI: 2.5–13.7) and ANT (OR = 2.44, 95% CrI: 1.3–4.8).

According to PASI 75, all the therapies had significantly higher ORs compared with PBO. Furthermore, anti-IL12/23, anti-IL17, and anti-TNF-α were estimated to be more effective than AM (OR = 13.6, 95% CrI: 5.2–35.2; OR = 19.5, 95% CrI: 7.0–53.0; OR = 5.9, 95% CrI: 2.5–13.7, respectively) and ANT considering PASI 75 (OR = 5.6, 95% CrI: 2.7–11.6; OR = 8.0, 95% CrI: 3.6–17.5; OR = 2.44, 95% CrI: 1.3–4.8, respectively).

For the comparison of treatments under PASI 90 reduction, all treatments were statistically more effective than PBO. Moreover, anti-IL17 was significantly better than other treatments. Meanwhile, it was revealed that anti-IL12/23 had significantly higher ORs than AM (OR = 11.0, 95% CrI: 3.3–35.5) and anti-TNF-α (OR = 2.39, 95% CrI: 1.19–4.62). Besides, anti-TNF-α had a better performance than AM (OR = 2.2, 95% CrI: 1.2–3.9). The visualized result was also provided in Figure 3.
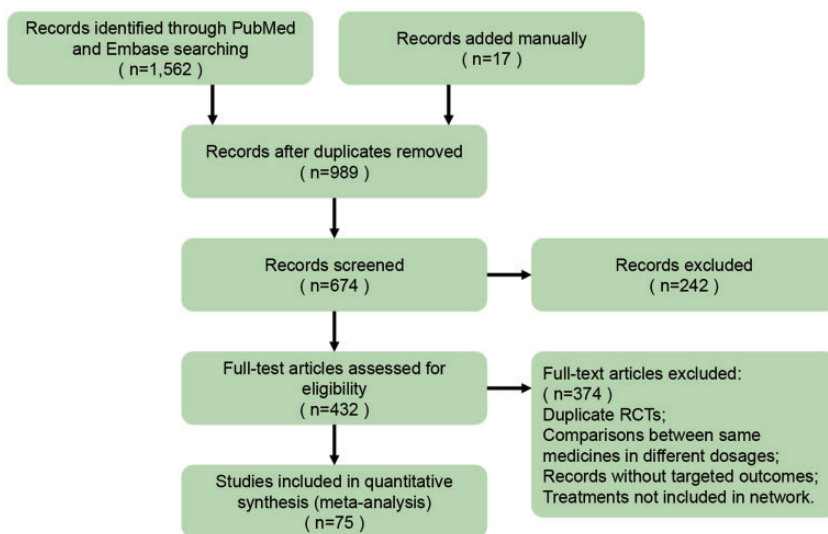

Figure 1. PRISMA flow chart.
RCTs: randomized control trials.

Table 1. Baseline population characteristics of included studies.

Author	Year	Country	Follow-up	Type	Intervention	N	Age	Male (%)	Disease Duration (years)	HPA	Affected BSA (%)	PASI
Papp	2008	Canada	12 weeks	anti-IL12/23	Ustekinumab	820	45.1 ± 12.1	69.2	19.3 ± 11.7	26.2	25.9 ± 15.5	19.4 ± 6.8
				PBO	Placebo	410	47.0 ± 12.5	69	20.8 ± 12.2	25.6	26.1 ± 17.4	19.4 ± 7.5
Revicki	2008	USA	16 weeks	anti-TNF-α	Adalimumab	103	42.8 ± 12.3	64.1	17.6 ± 10.0	22.3	33.7 ± 20.0	20.1 ± 7.4
				AM	Methotrexate	108	41.9 ± 11.9	66.7	19.0 ± 10.3	17.6	32.6 ± 20.7	19.5 ± 7.4
				PBO	Placebo	53	40.7 ± 11.4	67	18.9 ± 8.71	20.8	28.4 ± 16.1	19.2 ± 6.9
Blauvelt	2015	USA	12 weeks	anti-IL17	Secukinumab	118	45.1 ± 12.6	64.4	18.0 ± 11.9	–	33.3 ± 17.9	20.7 ± 7.9
				PBO	Placebo	59	46.5 ± 14.1	66.1	20.2 ± 14.2	–	32.2 ± 17.4	21.1 ± 8.5
Dubertret	2006	Germany	12 weeks	ANT	Efalizumab	529	44.0 ± 12.0	67.3	19.3 ± 11.5	–	37.1 ± 20.2	23.6 ± 6.7
				PBO	Placebo	264	45.3 ± 12.1	67.4	21.0 ± 10.2	–	36.2 ± 20.7	23.0 ± 9.6
Barker	2011	UK	16 weeks	anti-TNF-α	Infliximab	653	44.1 ± 33.9	67	18.8 ± 11.6	–	31.9 ± 16.5	21.4 ± 8.0
				AM	Methotrexate	215	41.9 ± 27.1	69	17.0 ± 10.3	–	31.0 ± 15.0	21.1 ± 7.6
Asahina	2010	Japan	16 weeks	anti-TNF-α	Adalimumab	123	47.7 ± 12.8	84.2	14.2 ± 9.29	–	43.3 ± 19.4	25.4 ± 8.9
				PBO	Placebo	46	43.9 ± 10.7	89.1	15.5 ± 8.83	–	46.7 ± 19.9	29.1 ± 11.8
Chaudhari	2001	USA	10 weeks	anti-TNF-α	Infliximab	22	35.1 ± 11.2	72.7	–	–	–	26.6 ± 10.3
				PBO	Placebo	11	45.0 ± 12.0	72.7	–	–	–	20.3 ± 5.5
Gordon	2003	USA	12 weeks	ANT	Efalizumab	369	45.2 ± 14.3	68	19.1 ± 15.2	–	28.0 ± 21.2	19 ± 6.9
				PBO	Placebo	187	45.7 ± 13.7	71	19.0 ± 13.0	–	27.0 ± 20.0	19 ± 6.7
Gottlieb	2004	USA	10 weeks	anti-TNF-α	Infliximab	198	44.1 ± 14.1	73.7	16.0 ± 11.1	29.3	–	–
				PBO	Placebo	51	45.0 ± 16.3	60.8	16.0 ± 11.8	33.3	–	–
Gottlieb	2011	USA	12 weeks	anti-IL12/23	Briakinumab	138	43.6 ± 14.3	64.5	16.1 ± 12.5	19.6	23.6 ± 16.6	18.4 ± 7.2
				anti-TNF-α	Etanercept	141	43.1 ± 12.5	69.5	17.0 ± 12.7	22.7	24.1 ± 15.0	19.4 ± 8.0
				PBO	Placebo	68	44.0 ± 13.6	69.1	19.1 ± 13.2	20.6	23.8 ± 15.5	18.5 ± 6.9
Gottlieb	2003	USA	24 weeks	anti-TNF-α	Etanercept	57	48.2 ± 11.7	58	–	28	–	–
				PBO	Placebo	55	46.5 ± 14.7	67	–	35	–	–
Menter	2008	USA	12 weeks	anti-TNF-α	Adalimumab	814	44.1 ± 13.2	67.1	18.1 ± 11.9	27.5	25.8 ± 15.5	19.0 ± 7.1
				PBO	Placebo	398	45.4 ± 13.4	64.6	18.4 ± 11.9	28.4	25.6 ± 14.8	18.8 ± 7.1
Ohtsuki	2014	Japan	12 weeks	anti-IL17	Secukinumab	58	51.9 ± 11.8	89.7	15.6 ± 10.3	13.8	42.0 ± 23.4	26.7 ± 10.5
				PBO	Placebo	29	50.2 ± 13.6	79.3	14.1 ± 10.9	13.8	32.7 ± 16.9	21.4 ± 10.3
Ortonne	2003	France	24 weeks	ANT	Alefacept	339	–	–	19.0 ± 17.0	–	20.0 ± 19.7	13.0 ± 12.2
				PBO	Placebo	168	–	–	20.0 ± 18.5	–	23.5 ± 20.7	14.0 ± 9.7
Leonardi	2003	USA	12 weeks	anti-TNF-α	Etanercept	486	44.8 ± 0.8	65	18.6 ± 10.9	–	29.9 ± 10.6	18.4 ± 6.7
				PBO	Placebo	166	45.6 ± 1.0	63	18.4 ± 10.9	–	28.8 ± 10.4	18.3 ± 6.6
Paul	2015	France	12 weeks	anti-IL17	Secukinumab	121	46.6 ± 14.2	76.7	21.0 ± 13.5	23.3	26.4 ± 12.8	18.9 ± 6.4
				PBO	Placebo	61	43.7 ± 12.7	62.3	19.9 ± 12.2	19.7	25.7 ± 14.7	19.4 ± 6.7
Krueger	2002	USA	12 weeks	ANT	Alefacept	367	45.4 ± 15.8	71	–	–	–	–
				PBO	Placebo	186	45 ± 14.5	68	–	–	–	–
Mease	2000	USA	12 weeks	anti-TNF-α	Etanercept	30	46.0 ± 10.0	53	19.0 ± 7.5	100	–	–
				PBO	Placebo	30	43.5 ± 9.7	60	17.5 ± 7.2	100	–	–
Feldman	2005	USA	10 weeks	anti-TNF-α	Infliximab	198	–	–	–	–	–	–
				PBO	Placebo	51	–	–	–	–	–	–

(continued)

Table 1. Continued.

Author	Year	Country	Follow-up	Type	Intervention	N	Age	Male (%)	Disease Duration (years)	HPA	Affected BSA (%)	PASI
Menter	2005	USA	12 weeks	ANT	Efalizumab	369	45.3±14.2	68	19.3±15.2	–	–	–
				PBO	Placebo	187	44.9±11.4	70.6	19.3±13.0	–	–	–
Leonardi	2005	USA	12 weeks	ANT	Efalizumab	328	45.5±13.5	71.1	16.7±14.7	–	29.9±18.2	18.9±11.4
				PBO	Placebo	170	41.7±12.5	72.9	18.5±13.7	–	29.4±18.7	19.0±12.0
Papp	2006	Canada	12 weeks	ANT	Efalizumab	450	45.6±12.5	67.3	18.4±12.1	–	27.7±15.8	19.14±7.5
				PBO	Placebo	236	46.3±12.1	59.3	17.5±11.1	–	26.8±15.2	18.69±7.0
Kimball	2008	USA	10 weeks	anti-IL12/23	Briakinumab	150	46.0±15.0	77	18.0±10.9	30	23.0±12.6	19.0±6.3
				PBO	Placebo	30	49.0±14.4	73	21.0±12.4	30	21.0±9.21	16.0±2.9
Reich	2005	Germany	10 weeks	anti-TNF-α	Infliximab	301	42.6±11.7	69	19.1±11.0	31	34.1±19.0	22.9±9.3
				PBO	Placebo	77	43.8±12.6	79	17.3±11.1	29	33.5±18.0	22.8±8.7
Tyring	2006	USA	12 weeks	anti-TNF-α	Etanercept	311	45.8±12.8	65	20.1±12.3	35	27.2±18.2	18.3±7.6
				PBO	Placebo	307	45.6±12.1	70	19.7±11.4	33	27.2±17.2	18.1±7.4
Lebwohl	2003	USA		ANT	Alefacept	339	45.3±14.7	62	19.0±17.0	–	20.0±19.7	13.2±12.3
				PBO	Placebo	168	46.5±15.0	65	20.0±18.5	–	23.5±20.7	14.3±9.9
Papp	2005	Canada	12 weeks	anti-TNF-α	Etanercept	390	44.5±14.7	67	18.1±14.9	26	25.0±17.5	16.1±12.6
				PBO	Placebo	193	44.0±15.5	64	17.5±12.4	26	20.0±21.2	16.0±13.8
Torii	2010	Japan	10 weeks	anti-TNF-α	Infliximab	35	46.9±13.0	62.9	14.2±8.91	28.6	–	31.9±12.8
				PBO	Placebo	19	43.3±12.3	73.7	11.1±6.51	36.8	–	33.1±15.6
Menter	2007	USA	12 weeks	anti-TNF-α	Infliximab	627	44.5±13.0	65	19.1±11.7	28.3	28.7±16.4	20.4±7.5
				PBO	Placebo	208	44.4±12.5	69.2	17.8±10.8	26	28.4±17.6	19.8±7.7
Igarashi	2012	Japan	12 weeks	anti-IL12/23	Ustekinumab	126	–	75.8	17.3±10.7	11.3	46.6±19.7	28.7±11.2
				PBO	Placebo	32	–	83.9	16.0±11.2	3.1	49.8±22.5	30.3±11.8
Gordon	2006	USA	12 weeks	anti-TNF-α	Adalimumab	95	44.0±15.5	66	18.0±11.5	24	25.0±19.5	14.5±10.0
				PBO	Placebo	52	43.0±12.5	65	19.0±9.72	31	28.0±17.0	16.0±8.725
Krueger	2007	USA	12 weeks	anti-IL12/23	–	256	44.0±13.0	81	17.3±13.5	20	27.4±18.1	19.0±7.9
				PBO	Placebo	64	44.0±14.0	72	16.9±11.0	19	26.6±18.4	19.9±8.3
Saurat	2008	Switzerland	16 weeks	anti-TNF-α	Adalimumab	108	42.9±12.6	64.8	17.9±10.1	21.3	–	20.2±7.5
				AM	Methotrexate	110	41.6±12.0	66.4	18.9±10.2	17.3	–	19.4±7.4
				PBO	Placebo	53	40.7±11.4	66	18.8±8.70	20.8	–	19.2±6.9
van de Kerkhof	2008	Netherlands	12 weeks	anti-TNF-α	Etanercept	96	45.9±12.8	61.5	19.3±11.3	15.6	26.5±15.0	21.4±9.3
				PBO	Placebo	46	43.6±12.6	54.4	17.3±8.20	10.9	30.3±17.8	21.0±8.7
Landells	2015	Multi	12 weeks	anti-IL12/23	Ustekinumab	73	14.8±1.7	44.4	5.60±3.80	–	31.9±23.2	21.7±10.4
				PBO	Placebo	37	15.6±1.5	54.1	6.20±5.00	–	27.4±16.4	20.8±8.0
Poulin	2014	Canada	16 weeks	anti-TNF-α	Adalimumab	49	49.0±11.4	42.9	14.9±16.3	14.3	8.90±11.9	8.8±8.2
				PBO	Placebo	23	54.8±11.4	34.8	11.5±9.94	4.3	5.10±6.96	5.7±4.5
Langley	2014	Canada	12 weeks	anti-IL17	Secukinumab	490	44.9±13.5	69	17.4±11.1	23.3	32.8±19.3	22.5±9.2
				PBO	Placebo	248	45.4±12.6	69.4	17.3±12.4	27.4	29.7±15.9	21.4±9.1
Ellis	2001	USA	12 weeks	ANT	Alefacept	170	44.0±11.5	72.4	18.0±15.0	–	25.0±18.75	20.0±11.5
				PBO	Placebo	59	42.0±12.2	59.3	18.0±9.75	–	20.0±17.5	15.0±17.2

(continued)

Table 1. Continued.

Author	Year	Country	Follow-up	Type	Intervention	N	Age	Male (%)	Disease Duration (years)	HPA	Affected BSA (%)	PASI
Papp	2001	Canada	8 weeks	ANT	hu1124	97	44.5 ± 12.9	63	22.8 ± 12.6	–	29.4 ± 13.9	19.1 ± 7.3
				PBO	Placebo	48	42.3 ± 12.3	67	17.8 ± 10.0	–	21.5 ± 10.4	16.2 ± 4.4
Nakagawa	2016	Multi	12 weeks	anti-IL17	Brodalumab	113	46.4 ± 11.8	78.4	14.9 ± 10.9	13.5	43.7 ± 25.9	27.9 ± 14.3
				PBO	Placebo	38	46.6 ± 10.8	71.1	16.8 ± 11.4	18.4	37.8 ± 21.4	23.9 ± 8.9
Gordon	2014	USA	16 weeks	anti-TNF-α	Adalimumab	43	–	70	19.3 ± 12.8	26	26.8 ± 16.8	20.2 ± 7.6
				anti-IL12/23	Guselkumab	208	–	72	18.5 ± 12.2	25	24.6 ± 14.5	20.9 ± 8.0
				PBO	Placebo	42	–	67	18.0 ± 13.3	29	27.5 ± 19.3	21.8 ± 9.9
Griffiths	2015	UK	12 weeks	anti-IL17	Ixekizumab	771	46.0 ± 13.0	66	18.0 ± 12.0	–	28.0 ± 17.0	21.0 ± 8.0
				anti-TNF-α	Etanercept	382	46.0 ± 14.0	70	18.0 ± 12.0	–	28.0 ± 17.0	21.0 ± 8.0
				PBO	Placebo	193	46.0 ± 12.0	71	18.0 ± 13.0	–	29.0 ± 17.0	21.0 ± 8.0
Lebwohl	2015	USA	12 weeks	anti-IL17	Brodalumab	1222	45.0 ± 13.0	69	19.0 ± 12.0	19	27.0 ± 17.0	20.3 ± 8.2
				anti-IL12/23	Ustekinumab	300	–	–	–	–	–	–
				PBO	Placebo	309	–	–	–	–	–	–
Thaçi	2015	Germany	16 weeks	anti-IL17	Secukinumab	337	45.2 ± 13.9	68	19.6 ± 12.9	20.5	32.6 ± 17.8	21.7 ± 8.5
				anti-IL12/23	Ustekinumab	339	44.6 ± 13.6	74.3	16.1 ± 11.2	15.9	32.0 ± 16.8	21.5 ± 8.1
Youn	2010	South Korea	12 weeks	anti-IL12/23	Ustekinumab	61	40.9 ± 12.7	82	11.9 ± 7.50	16.4	41.8 ± 24.4	25.2 ± 11.9
				PBO	Placebo	60	40.4 ± 10.1	88.3	13.9 ± 7.30	11.7	35.8 ± 21.4	22.9 ± 8.6
Zhu	2013	China	12 weeks	anti-IL12/23	Ustekinumab	160	40.1 ± 12.4	78.1	14.6 ± 8.90	8.8	35.1 ± 18.5	23.2 ± 9.5
				PBO	Placebo	162	39.2 ± 12.2	75.9	14.2 ± 8.60	8.6	35.1 ± 19.6	22.7 ± 9.5
Gordon	2010	USA	12 weeks	anti-IL12/23	Briakinumab	139	44.9 ± 12.9	66.9	16.3 ± 12.0	23.7	24.9 ± 17.8	19.4 ± 7.9
				anti-TNF-α	Etanercept	139	45.2 ± 14.8	61.2	15.2 ± 2.10	33.1	24.7 ± 13.9	18.5 ± 6.0
				PBO	Placebo	72	45.0 ± 13.9	63.9	15.5 ± 11.7	20.8	22.1 ± 13.4	18.3 ± 6.4
Papp	2014	Canada	12 weeks	anti-IL12/23	Briakinumab	981	45.7 ± 13.2	67.9	18.9 ± 12.3	29.6	24.8 ± 16.3	19.1 ± 7.5
				PBO	Placebo	484	45.1 ± 13.5	70.9	19.2 ± 11.9	31	25.7 ± 16.9	19.3 ± 7.3
Papp	2015	Canada	16 weeks	anti-IL12/23	Tildrakizumab	309	43.2 ± 12.9	74	–	–	–	–
				PBO	Placebo	46	45.9 ± 11.7	83	–	–	–	–
Papp	2014	Multi	120 weeks	anti-IL17	Brodalumab	148	–	–	–	–	–	–
				PBO	Placebo	33	–	–	–	–	–	–
Krupashankar	2014	Multi	12 weeks	ANT	Itolizumab	180	40.7 ± 11.0	76.7	–	–	–	21.3 ± 8.5
				PBO	Placebo	43	43.3 ± 13.0	74.4	–	–	–	21.9 ± 8.9
Bachelez	2015	France	12 weeks	anti-TNF-α	Etanercept	335	42.0 ± 14.0	70	18.0 ± 15.2	21	25.0 ± 20.9	19.4 ± 12.9
				PBO	Placebo	107	46.0 ± 15.0	66	17.0 ± 14.0	24	26.0 ± 17.0	19.5 ± 10.5
Micali	2015	Italy	6 weeks	anti-TNF-α	Etanercept	58	41.8 ± 13.0	65.5	–	–	–	20.2 ± 13.7
				PBO	Placebo	62	41.5 ± 16.7	72.6	–	–	–	19.4 ± 12.6
Papp	2013	Canada	12 weeks	anti-IL17	Secukinumab	103	46.1 ± 12.6	69	19.8 ± 12.6	31	26.0 ± 19.3	21.6 ± 11.5
				PBO	Placebo	22	45.9 ± 10.8	63.6	21.4 ± 14.8	27.3	26.0 ± 18.8	21.7 ± 8.5
Reich	2013	Germany	10 weeks	anti-TNF-α	Infliximab	222	45.7 ± 13.5	68	20.5 ± 12.0	–	–	21.5 ± 8.7
				PBO	Placebo	219	43.3 ± 13.0	71	17.5 ± 11.0	–	–	21.2 ± 7.7

(continued)

Table I. Continued.

Author	Year	Country	Follow-up	Type	Intervention	N	Age	Male (%)	Disease Duration (years)	HPA	Affected BSA (%)	PASI
Mease	2016	USA	24 weeks	PBO	Placebo	106	50.6±12.3	45.3	16.0±13.8	–	–	6.2±7.5
				anti-TNF-α	Adalimumab	101	48.6±12.4	50.5	15.7±12.7	–	–	5.5±6.5
Kavanaugh	2016	USA	24 weeks	PBO	Placebo	92	47.4±12.8	48.9	16.0±12.6	–	28.4±26.1	13.9±12.5
				anti-IL12/23	Ustekinumab	164	45.7±11.7	57.9	15.9±11.5	–	30.1±25.6	14.8±12.4
Blauvelt	2016	Portland	52 weeks	anti-IL17	Secukinumab	337	45.2±13.9	68	19.7±12.8	20.5	–	21.7±8.5
				anti-IL12/23	Ustekinumab	339	44.6±13.7	74.3	16.1±11.2	15.9	–	21.5±8.1
Blauvelt	2017	Multi	16 weeks	anti-IL12/23	Guselkumab	329	43.9±12.74	72.9	17.9±6.22	–	28.3±17.1	22.1±9.49
				anti-TNF-α	Adalimumab	334	42.9±12.58	82.9	29.8±6.48	–	28.6±16.66	22.4±8.97
				PBO	Placebo	174	44.9±12.9	83.3	28.9±6.89	–	25.8±15.93	20.4±8.74
Kavanaugh	2017	USA	24 weeks	anti-TNF-α	Golimumab	241	45.7±11.3	53.1	6.2±6	–	196±81.3	11±9.9
				PBO	Placebo	239	46.7±12.5	50.6	5.3±5.9	–	198±82.8	8.9±9
Lacour	2017	Multi	12 weeks	anti-IL17	Secukinumab	121	43.9±14.41	71	20.6±14.54	–	30.1±16.66	22±8.85
				PBO	Placebo	60	43.7±12.74	62.3	19.9±12.2	–	25.7±19.7	19.4±6.7
Nash	2017	Multi	24 weeks	anti-IL17	Ixekizumab	245	52.6±13.6	52	15.7±12.3	–	12.5	6.4±7.9
				PBO	Placebo	118	51.5±10.4	47	15.3±12.6	–	9	5.2±6.3
Papp	2017	Multi	16 weeks	anti-TNF-α	Adalimumab	77	13±3.3	45	5±3.8	–	17.7±20.4	18.9±10
				AM	MTX	37	13.4±3.5	30	5.1±3.8	–	30.3±21.2	19.2±10
Papp	2016	Multi	12 weeks	anti-IL17	Brodalumab	351	46±12	73	20±13	–	25.1±15.3	19.4±6.6
				PBO	Placebo	220	47±13	73	21±12	–	26.9±17.1	19.7±7.7
Reich	2017	USA	16 weeks	anti-IL12/23	Guselkumab	496	43.7±12.2	70.4	17.9±12	–	28.5±16.4	21.9±8.8
				anti-TNF-α	Adalimumab	284	43.2±11.9	68.5	17.6±11.7	–	19.1±16.5	21.7±9
				PBO	Placebo	284	43.3±12.4	69.8	17.9±11.9	—	28±16.5	21.5±8
Reich	2017	Germany	16 weeks	anti-TNF-α	Etanercept	83	40±14.1	59	18.1±1.7	–	29.9±6.8	18.1±11.7
				PBO	Placebo	84	43.4±14.9	70.2	16.6±12.1	–	29.5±6.6	16.6±12.1
Reich	2017	Germany	16 weeks	anti-IL12/23	Tildrakizumab	617	46.4±13.1	67		–	29.7±17.44	20±7.85
				PBO	Placebo	155	47.9±13.5	65		–	29.6±17.28	19.3±7.07
				anti-IL12/23	Tildrakizumab	621	44.6±13.6	72		–	34.2±18.44	20.5±7.63
				anti-TNF-α	Etanercept	313	46.4±12.2	72		–	31.3±14.75	20±7.57
				PBO	Placebo	156	45.8±14	71		–	31.6±16.58	20.2±7.36
Reich	2017	Germany	12 weeks	anti-IL12/23	Ustekinumab	166	44±13.33	67.5	18.2±12	–	27.5±16.7	39.4±30.8
				anti-IL17	Ixekizumab	136	42.7±12.7	66.2	18±11.1	–	26.7±16.5	42.9±33.3
Paller	2008	Multi	12 weeks	anti-TNF-α	Etanercept	106	14±3.25	52		–	–	16.7±9.9
				PBO	Placebo	105	13±3.25	50		–	–	16.4±11.175
Bachelez	2015	Multi	12 weeks	anti-TNF-α	Etanercept	335	42±14	70	18±15.25	2.1	25±20.875	19.4±12.9
				PBO	Placebo	107	46±15	66	17±14	24	26±17	19.5±10.55
Cai	2016	China	12 weeks	anti-TNF-α	Adalimumab	338	43.1±11.91	75.1	14.8±10.15	12.7	24.4±3.48	28.2±12
				PBO	Placebo	87	43.8±12.45	66.7	15.8±10.31	12.5	23.6±2.86	25.6±10.98
Gordon	2016	Multi	12 weeks	anti-IL17	Ixekizumab	875	46±13	66.9	19±12	–	–	20±7
				PBO	Placebo	431	46±13	70.3	20±12	–	–	20±9

(continued)

Table 1. Continued.

Author	Year	Country	Follow-up	Type	Intervention	N	Age	Male (%)	Disease Duration (years)	HPA	Affected BSA (%)	PASI
Gordon	2015	Multi	16 weeks	anti-TNF-α	Adalimumab	43	50	70	91.6 ± 19.88	–	–	20.2 ± 7.58
				PBO	Placebo	42	46.5	67	93.6 ± 22.62	–	–	21.8 ± 9.98
				anti-ILI12/23	Guselkumab	208	–	70	–	–	–	–
Gottlieb	2016	Multi	16 weeks	anti-ILI17	Secukinumab	137	52.4 ± 12.6	58.8	7.5 ± 8.8	–	28.8 ± 5.7	8.7 ± 10.4
				PBO	Placebo	68	50.9 ± 13	50	11.8 ± 10.4	–	28.8 ± 5.7	7.7 ± 7.3
Leonardi	2012	Multi	12 weeks	anti-ILI17	Ixekizumab	58	48 ± 11	57	21 ± 12	–	22 ± 18	19.2 ± 8
				PBO	Placebo	27	45 ± 13	52	15 ± 11	–	19 ± 12	16.5 ± 5.3

HPA: history of psoriatic arthritis (%); BSA: biologic systemic agents; PASI: psoriasis area and severity index; AM: anti-metabolites; anti-TNF-α: anti-tumor necrosis factor-α agents; ANT: anti-T-cell agents; anti-ILI12/23: anti-interleukin-12/23 agents; anti-ILI17: anti-interleukin-17agents; PBO: placebo; MTX: methotrexate.
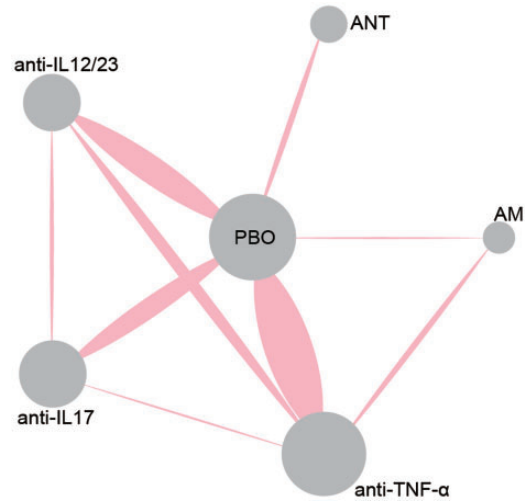
Figure 2. Network diagram of all included studies. Each node represents a medicine type; the diameters of circles represent the number of people involved, and the widths of lines between two nodes represent the number of study involved in the head-to-head comparison.
AM: anti-metabolites; anti-IL12/23: anti-interleukin-12/23 agents; anti-IL17: anti-interleukin-17 agents; ANT: anti-T-cell agent; anti-TNF-α: anti-tumor necrosis factor-α agent.

NMA result for DLQI and PGA

Table 3 showed the network comparison of different treatments for DLQI and PGA. In view of DQLI, only two drugs, anti-IL12/23 and anti-TNF-α were superior compared with PBO (OR = 13.8, CrI: 4.6–23.3; OR = 9.6, CrI: 1.2–18.1, respectively). Considering PGA, all drugs were superior compared with PBO, and anti-IL12/23, anti-IL17, and anti-TNF-α had better PGA compared with AM (OR = 6.62, 95% CrI: 1.68–25.79; OR = 21.54, 95% CrI: 4.57–101.49; OR = 4.06, 95% CrI: 1.20–13.60, respectively) and ANT (OR = 11.94, 95% CrI: 4.48–31.82; OR = 38.36, 95% CrI: 11.47–134.29; OR = 7.32, 95% CrI: 2.8–18.73, respectively). In addition, anti-IL17 was estimated to be superior to anti-TNF-α (OR = 5.31, 95% CrI: 1.93–14.88). The forest plots were presented in Figure 4.

NMA result for AEs

Table 4 showed the network comparison of different treatments for adverse events. According to all adverse events (AAE), only anti-IL17 showed a significant result that it had more AAE than PBO (OR = 0.68, 95% CrI: 0.48–0.97). In view of incidence of infection, anti-IL12/23, anti-IL17, and anti-TNF-α showed more infection cases than PBO (OR = 1.28, 95% CrI: 1.11–1.48; OR = 1.32, 95% CrI: 1.05–1.68; OR = 1.28, 95% CrI: 1.12–1.48, respectively). Besides, anti-TNF-α was associated with statistically significant increased odds of

Table 2. Network comparison of different treatments for PASI reduction in psoriasis patients.

	PBO	AM	ANT	Anti-IL12/23	Anti-ILI7	Anti-TNF-α
PASI 50						
PBO	—	**3.16 (1.31, 7.69)**	**4.31 (2.86, 6.49)**	**49.4 (27.11, 90.02)**	**5.64 (1.11, 32.79)**	**18.36 (12.68, 26.84)**
AM	0.32 (0.13, 0.76)	—	1.36 (0.51, 3.63)	**15.64 (5.37, 45.60)**	1.79 (0.28, 12.81)	**5.81 (2.51, 13.74)**
ANT	0.23 (0.15, 0.35)	0.73 (0.28, 1.97)	—	**11.47 (5.58, 23.81)**	1.31 (0.24, 7.92)	**4.26 (2.46, 7.46)**
Anti-IL12/23	0.02 (0.01, 0.04)	0.06 (0.02, 0.19)	0.09 (0.04, 0.18)	—	**0.12 (0.02, 0.73)**	**0.37 (0.18, 0.75)**
Anti-ILI7	0.18 (0.03, 0.90)	0.56 (0.08, 3.60)	0.76 (0.13, 4.14)	8.67 (1.36, 49.40)	—	3.25 (0.53, 17.64)
Anti-TNF-α	0.05 (0.04, 0.08)	0.17 (0.07, 0.40)	0.23 (0.13, 0.41)	2.69 (1.34, 5.42)	0.31 (0.06, 1.88)	—
PASI 75						
PBO	—	**3.19 (1.32, 7.69)**	**7.69 (4.31, 14.01)**	**42.95 (27.94, 66.69)**	**62.18 (36.6, 104.58)**	**18.73 (13.46, 26.58)**
AM	0.31 (0.13, 0.76)	—	2.41 (0.85, 7.03)	**13.60 (5.21, 35.16)**	**19.49 (7.03, 52.98)**	**5.93 (2.53, 13.74)**
ANT	0.13 (0.07, 0.23)	0.41 (0.14, 1.17)	—	**5.58 (2.69, 11.59)**	**8.00 (3.63, 17.46)**	**2.44 (1.25, 4.81)**
Anti-IL12/23	0.02 (0.01, 0.04)	0.07 (0.03, 0.19)	0.18 (0.09, 0.37)	—	1.43 (0.77, 2.64)	**0.44 (0.27, 0.71)**
Anti-ILI7	0.02 (0.01, 0.03)	0.05 (0.02, 0.14)	0.12 (0.06, 0.28)	0.70 (0.38, 1.30)	—	**0.30 (0.17, 0.56)**
Anti-TNF-α	0.05 (0.04, 0.07)	0.17 (0.07, 0.39)	0.41 (0.21, 0.80)	2.29 (1.40, 3.71)	3.29 (1.79, 5.99)	—
PASI 90						
PBO	—	**3.78 (1.26, 11.47)**	**10.07 (2.44, 49.40)**	**41.68 (24.78, 70.11)**	**90.02 (46.53, 179.47)**	**18.92 (12.43, 29.08)**
AM	0.26 (0.09, 0.79)	—	2.66 (0.43, 18.17)	**11.02 (3.35, 35.52)**	**24.05 (6.69, 84.77)**	**5.00 (1.75, 14.30)**
ANT	0.10 (0.02, 0.41)	0.38 (0.06, 2.32)	—	4.14 (0.77, 18.73)	**9.03 (1.62, 42.52)**	1.88 (0.36, 8.25)
Anti-IL12/23	0.02 (0.01, 0.04)	0.09 (0.03, 0.30)	0.24 (0.05, 1.30)	—	**2.18 (1.03, 4.62)**	**0.45 (0.26, 0.80)**
Anti-ILI7	0.01 (0.01, 0.02)	0.04 (0.01, 0.15)	0.11 (0.02, 0.62)	0.46 (0.22, 0.97)	—	**0.21 (0.10, 0.44)**
Anti-TNF-α	0.05 (0.03, 0.08)	0.20 (0.07, 0.57)	0.53 (0.12, 2.75)	2.20 (1.25, 3.90)	4.81 (2.27, 10.07)	—

Bold: data with statistically significant difference, which is highlighted in the upper region of each outcome. PASI 50: ≥50% reduction in psoriasis area and severity index; PASI 75: ≥75% reduction in psoriasis area and severity index; PASI 90: ≥90% reduction in psoriasis area and severity index; AM: anti-metabolites; anti-TNF-α: anti-tumor necrosis factor-α agents; ANT: anti-T-cell agents; anti-ILI2/23: anti-interleukin-12/23 agents; anti-ILI7: anti-interleukin-17 agents; PBO: placebo.
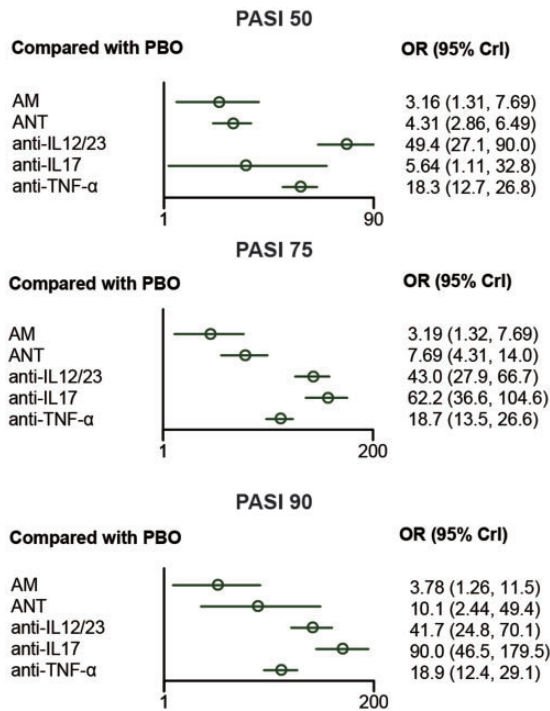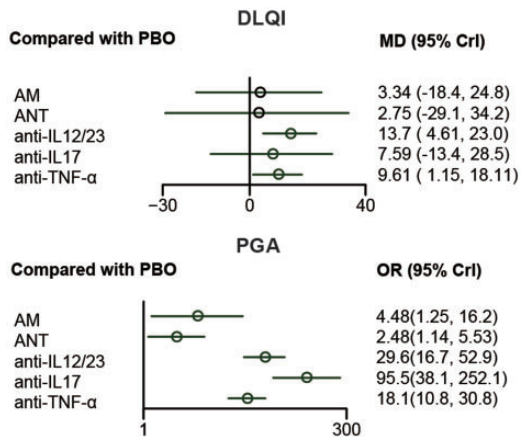
Figure 3. Forest plots for different treatment effects in psoriasis area and severity index reduction in psoriasis patients.
AM: anti-metabolites; anti-IL12/23: anti-interleukin-12/23agents; anti-IL17: anti-interleukin-17 agents; ANT: anti-T-cell agent; anti-TNF-α: anti-tumor necrosis factor-α agent; PBO: placebo; PASI 50: ≥50% reduction in psoriasis area and severity index; PASI 75: ≥75% reduction in psoriasis area and severity index; PASI 90: ≥90% reduction in psoriasis area and severity index.

nasopharyngitis compared with PBO (OR = 0.64, 95% CrI: 0.42–0.94). In view of headache, few of them demonstrated a significant difference. ANT, anti-IL17, and anti-TNF-α was assessed to be worse compared with PBO (OR = 1.54, 95% CrI: 1.14–2.10; OR = 1.77, 95% CrI: 1.12–2.83; OR = 1.40, 95% CrI: 1.06–1.88, respectively). As for URTI, only AM was associated with statistically stronger URTI compared with PBO and all the other inventions. Meanwhile, the network comparisons for incidence of withdrawal due to the AE showed that compared with patients using PBO, patients using IL12/23 or TNF-α had statistically higher possibility to keep on (OR = 0.64, 95% CrI: 0.42–0.98; OR = 0.64, 95% CrI: 0.46–0.92, respectively). In addition, AM was associated with higher withdrawal probability than other inventions. The forest plots of the random-effects model were shown in Figure 5.

Ranking of treatments

The SUCRA values for different treatments for all outcomes was calculated in order to determine the best method for curing psoriasis, and the calculated numbers

Table 3. Network comparison of different treatments for Dermatology Life Quality Index and Physician's Global Assessment in psoriasis patients.

	PBO	AM	ANT	Anti-IL12/23	Anti-IL17	Anti-TNF-α
Dermatology Life Quality Index						
PBO	—	3.34 (−18.48, 24.82)	2.75 (−29.15, 34.17)	**13.75 (4.61, 23.03)**	7.59 (−13.44, 28.50)	**9.61 (1.15, 18.11)**
AM	−3.34 (−24.82, 18.48)	—	−0.55 (−39.1, 37.58)	10.44 (−12.65, 33.71)	4.29 (−25.36, 33.83)	6.25 (−14.6, 27.26)
ANT	−2.75 (−34.17, 29.15)	0.55 (−37.58, 39.10)	—	10.98 (−21.69, 44.20)	4.80 (−33.03, 42.39)	6.83 (−25.58, 39.77)
Anti-IL12/23	−13.75 (−23.03, −4.61)	−10.44 (−33.71, 12.65)	−10.98 (−44.2, 21.69)	—	−6.15 (−29.1, 16.45)	−4.13 (−15.66, 7.49)
Anti-IL17	−7.59 (−28.5, 13.44)	−4.29 (−33.83, 25.36)	−4.80 (−42.39, 33.03)	6.15 (−16.45, 29.10)	—	2.02 (−19.49, 23.74)
Anti-TNF-α	−9.61 (−18.11, −1.15)	−6.25 (−27.26, 14.60)	−6.83 (−39.77, 25.58)	4.13 (−7.49, 15.66)	−2.02 (−23.74, 19.49)	—
Physician's Global Assessment						
PBO	—	**4.48 (1.25, 16.28)**	**2.48 (1.14, 5.53)**	**29.67 (16.78, 52.98)**	**95.58 (38.09, 252.14)**	**18.17 (10.80, 30.88)**
AM	0.22 (0.06, 0.80)	—	0.55 (0.12, 2.51)	**6.62 (1.68, 25.79)**	**21.54 (4.57, 101.49)**	**4.06 (1.20, 13.60)**
ANT	0.40 (0.18, 0.88)	1.80 (0.40, 8.17)	—	**11.94 (4.48, 31.82)**	**38.86 (11.47, 134.29)**	**7.32 (2.80, 18.73)**
Anti-IL12/23	0.03 (0.02, 0.06)	0.15 (0.04, 0.59)	0.08 (0.03, 0.22)	—	**3.25 (1.21, 8.94)**	0.61 (0.32, 1.20)
Anti-IL17	0.01 (0.00, 0.03)	0.05 (0.01, 0.22)	0.03 (0.01, 0.09)	0.31 (0.11, 0.83)	—	**0.19 (0.07, 0.52)**
Anti-TNF-α	0.06 (0.03, 0.09)	0.25 (0.07, 0.84)	0.14 (0.05, 0.36)	1.63 (0.84, 3.16)	5.31 (1.93, 14.88)	—

Bold: data with statically significant difference, which is highlighted in the upper region of each outcome. AM: anti-metabolites; anti-TNF-α: anti-tumor necrosis factor-α agents; ANT: anti-T-cell agents; anti-IL12/23: anti-interleukin-12/23 agents; anti-IL17: anti-interleukin-17 agents; PBO: placebo.

Figure 4. Forest plots for different treatment effects of Dermatology Life Quality Index and Physician's Global Assessment in psoriasis patients.
AM: anti-metabolites; anti-IL12/23: anti-interleukin-12/23 agents; anti-IL17: anti-interleukin-17 agents; ANT: anti-T-cell agent; anti-TNF-α: anti-tumor necrosis factor-α agent; PBO: placebo; DLQI: Dermatology Life Quality Index; PGA: Physician's Global Assessment – minimal or cleared.

were listed in Table 5. The result showed that anti-IL12/23 had better efficacy in $\geq 50\%$ reduction in PASI (0.997) and led to better Dermatology Life Quality (0.842), but for better efficacy in PASI, it is indicated that anti-IL17 had the most possibility to rank the first among all six drugs (PASI 75: 0.980, PASI 90: 0.995, PGA: 0.998). Meanwhile, anti-TNF-α had good performance in PASI 50, 75, and 90. However, AM and ANT showed less efficacy. As for ranking of incidence of AE, it showed that none of the interventions were better than PBO except for ANT in AAE outcome. And anti-IL17 showed worse effect in both AAE and infection (AAE: 0.281, infection: 0.352).

Inconsistency analysis

The direct and indirect evidences for each comparison under all outcomes, as well as network results, were presented in Table 6. $p < 0.05$ suggested a significant inconsistency between direct and indirect evidence. Overall, no inconsistency was found for each comparison under all outcomes (all $p > 0.05$), which indicated reliable results of the current NMA.

Discussion

Undoubtedly, as the NMA results revealed, all included therapies showed significant efficacy when compared with PBO in terms of all the efficacy outcomes except for DLQI, which in general corresponded to the results of previous RCTs. Meanwhile, the efficacy and safety of these therapies were certainly different from each other.

First of all, as was shown in the NMA results, anti-IL12/23 was proved to be the most ideal therapy among the included therapies. Its excellent efficacy as well as mild AEs was revealed. Additionally, its extraordinary efficacy and safety were also proved by previous RCTs, which corresponded with the results of previous RCT studies.[25,29] Ustekinumab, an antibody agent binding to the shared p40 subunit of IL 12/23, was the most widely researched agent among the therapies mentioned above. It bound to the interleukins specifically and prevented their binding with respective receptors, thus blocked the downstream signaling cascades.[25] Meanwhile, briakinumab, another research focus with analogous structure and function with ustekinumab, also showed an excellent performance clinically. Tildrakizumab and guselkumab are also experimental monoclonal antibodies (Statement on a Nonproprietary Name Adopted by the USAN Council—Tildrakizumab; Statement on A Nonproprietary Name Adopted by the USAN Council—Guselkumab) designed to block IL-23. However, such agents still required more research to promote its clinical appliance.

Second, anti-IL17 showed a satisfactory efficacy performance in this NMA. It was revealed that this therapy had a similar efficacy with anti-IL12/23. These anti-IL17 monoclonal antibody agents including ixekizumab, brodalumab, and secukinumab selectively bind to the IL 17 and neutralize the bioactivity of this cytokine.[22] Though its efficacy was excellent, the safety of this therapy was not very good.

Third, ANT showed a weaker efficacy; however, its total AE ranked the first among the relevant therapy, and as a result, it can be regarded as a milder treatment in the clinical appliance.

Fourth, anti-TNF-α showed weaker efficacy than anti-IL-17 or anti-IL12/23 accompanied with a stronger AE; as a result, it was not recommended in this NMA research. As revealed in the introduction part, interleukins stimulate T-cells to produce TNF causing psoriasis. These biological agents work on the stimulation interleukins, the producer T-cells, and the final production TNF, respectively. The selectivity of these therapies gave them totally different mechanism and excellent efficacy. However, infection, the major AE of the above-mentioned biological agents according to the NMA results and previous studies,[88,89] was still a severe problem to be solved. Additionally, a number of relevant biological agents were still at the stage of laboratory research, requiring more clinical studies and appliances.

Finally, AM did not work well in both efficacy and AE outcomes, which made is the least satisfactory therapy.

Table 4. Network comparison of different treatments for adverse events in psoriasis patients.

All adverse events (upper region: Infection)

	PBO	AM	ANT	Anti-IL12/23	Anti-IL17	Anti-TNF-α
PBO	—	1.02(0.63, 1.67)	1.15 (0.96, 1.36)	**1.28 (1.11, 1.48)**	**1.32 (1.05, 1.68)**	**1.28 (1.12, 1.48)**
AM	0.79 (0.39, 1.55)	—	1.12 (0.66, 1.90)	1.25 (0.76, 2.05)	1.30 (0.75, 2.20)	1.25 (0.78, 2.03)
ANT	1.21 (0.76, 1.90)	1.54 (0.67, 3.53)	—	1.11 (0.89, 1.40)	1.15 (0.86, 1.57)	1.12 (0.89, 1.40)
Anti-IL12/23	0.88 (0.67, 1.15)	1.12 (0.55, 2.29)	0.73 (0.43, 1.23)	—	1.04 (0.84, 1.27)	1.01 (0.84, 1.19)
Anti-IL17	**0.68 (0.48, 0.97)**	0.87 (0.40, 1.86)	0.57 (0.32, 1.00)	0.77 (0.53, 1.13)	—	0.97 (0.75, 1.26)
Anti-TNF-α	0.82 (0.63, 1.08)	1.05 (0.55, 2.01)	0.68 (0.40, 1.16)	0.93 (0.68, 1.30)	1.21 (0.79, 1.86)	—

Nasopharyngitis (upper region: Headache)

	PBO	AM	ANT	Anti-IL12/23	Anti-IL17	Anti-TNF-α
PBO	—	1.58 (0.73, 3.32)	**1.54 (1.14, 2.10)**	1.48 (0.97, 2.27)	**1.77 (1.12, 2.83)**	**1.40 (1.06, 1.88)**
AM	0.81 (0.31, 2.12)	—	0.98 (0.44, 2.23)	0.94 (0.41, 2.23)	1.12 (0.47, 2.75)	0.90 (0.44, 1.84)
ANT	0.76 (0.18, 3.13)	0.93 (0.17, 5.26)	—	0.96 (0.57, 1.63)	1.14 (0.66, 2.01)	0.91 (0.61, 1.38)
Anti-IL12/23	0.66 (0.43, 0.98)	0.81 (0.29, 2.25)	0.86 (0.2, 3.82)	—	1.19 (0.72, 2.01)	0.95 (0.58, 1.54)
Anti-IL17	0.70 (0.44, 1.07)	0.85 (0.30, 2.44)	0.91 (0.21, 4.10)	1.06 (0.64, 1.77)	—	0.8 (0.46, 1.35)
Anti-TNF-α	**0.64 (0.42, 0.94)**	0.79 (0.31, 1.95)	0.84 (0.19, 3.71)	0.97 (0.59, 1.60)	0.91 (0.52, 1.62)	—

Upper respiratory tract infection (upper region: Withdrawal)

	PBO	AM	ANT	Anti-IL12/23	Anti-IL17	Anti-TNF-α
PBO	—	2.25 (0.91, 5.81)	0.70 (0.44, 1.13)	**0.64 (0.42, 0.98)**	0.73 (0.45, 1.19)	**0.64 (0.46, 0.92)**
AM	**0.11 (0.02, 0.48)**	—	**0.31 (0.11, 0.86)**	**0.28 (0.10, 0.75)**	**0.32 (0.11, 0.89)**	**0.29 (0.12, 0.67)**
ANT	1.01 (0.39, 2.51)	**9.12 (1.63, 62.18)**	—	0.90 (0.49, 1.70)	1.03 (0.53, 1.99)	0.91 (0.52, 1.65)
Anti-IL12/23	0.83 (0.61, 1.12)	**7.46 (1.70, 41.26)**	0.82 (0.31, 2.18)	—	1.14 (0.66, 1.97)	1.01 (0.62, 1.67)
Anti-IL17	0.66 (0.41, 1.00)	**5.93 (1.31, 39.25)**	0.66 (0.23, 1.82)	0.80 (0.49, 1.26)	—	0.89 (0.51, 1.58)
Anti-TNF-α	0.90 (0.71, 1.15)	**8.17 (1.95, 45.60)**	0.90 (0.34, 2.39)	1.09 (0.77, 1.57)	1.38 (0.86, 2.29)	—

Bold: data with statically significant difference; in the upper regions, columns are compared with rows, while lower regions are opposite. AM: anti-metabolites; anti-TNF-α: anti-tumor necrosis factor-α agents; ANT: anti-T-cell agents; anti-IL12/23: anti-interleukin-12/23 agents; anti-IL17: anti-interleukin-17 agents; PBO: placebo.
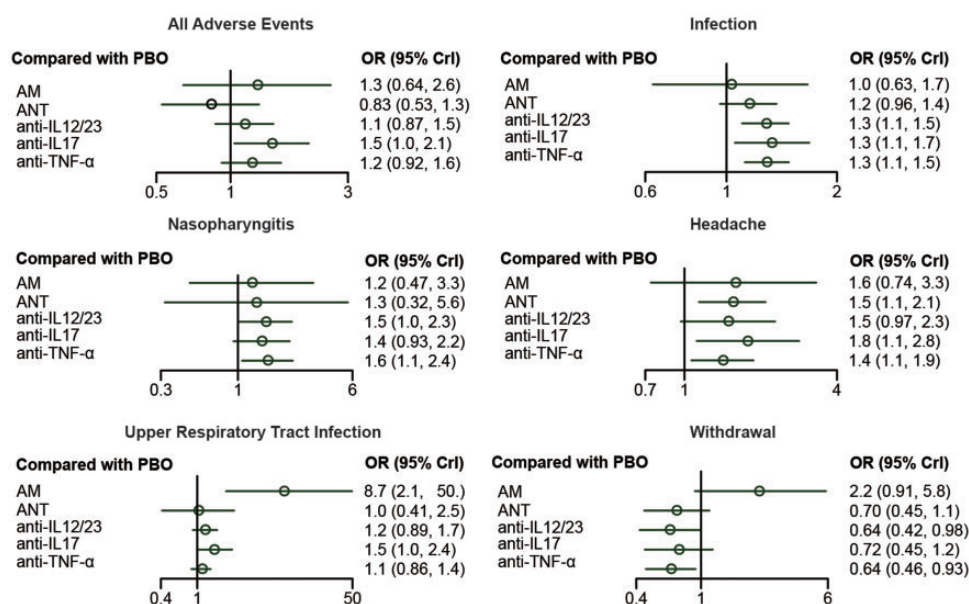
Figure 5. Forest plots for different treatment effects of adverse events in psoriasis patients.
AM: anti-metabolites; anti-IL12/23: anti-interleukin-12/23 agents; anti-IL17: anti-interleukin-17 agents; ANT: anti-T-cell agent; anti-TNF-α: anti-tumor necrosis factor-α agent; PBO: placebo.

Table 5. Surface under the cumulative ranking curve (SUCRA) values for different treatments for all outcomes in psoriasis patients.

Outcomes	PBO	AM	ANT	Anti-IL12/23	Anti-IL17	Anti-TNF-α
PASI 50	0.171	0.421	0.520	0.997	0.571	0.819
PASI 75	0.167	0.341	0.493	0.854	0.980	0.666
PASI 90	0.168	0.356	0.518	0.829	0.995	0.632
DLQI	0.342	0.495	0.506	0.842	0.617	0.699
PGA	0.171	0.465	0.368	0.823	0.998	0.676
AAE	0.782	0.474	0.904	0.580	0.281	0.480
Infection	0.910	0.761	0.643	0.427	0.352	0.407
Nasopharyngitis	0.874	0.643	0.588	0.454	0.517	0.423
Headache	0.972	0.501	0.495	0.554	0.363	0.615
URTI	0.861	0.171	0.745	0.602	0.415	0.706
Withdrawal	0.359	0.179	0.702	0.800	0.669	0.791

PASI 50: ≥50% reduction in psoriasis area and severity index; PASI 75: ≥75% reduction in psoriasis area and severity index; PASI 90: ≥90% reduction in psoriasis area and severity index; DLQI: Dermatology Life Quality Index; PGA: Physician's Global Assessment – minimal or cleared; AAE: all adverse events; URTI: upper respiratory tract infection; AM: anti-metabolites; anti-TNF-α: anti-tumor necrosis factor-α agents; ANT: anti-T-cell agents; anti-IL12/23: anti-interleukin-12/23 agents; anti-IL17: anti-interleukin-17 agents; PBO: placebo.

In this NMA research, there also existed some limitations. First of all, most of included studies reported the latest biological agents comparing with PBO or traditional therapy AM. However, direct RCT studies between these different treatments were still required for the unchallengeable authority of clinical experimental data. Besides, this NMA did not evaluate the treatment of mild psoriasis and topical therapies indicated for patients whose affected area is less than 10% of the BSA.[90,91] The majority of this research and relevant works focused on severe psoriasis, and little attention was paid to the topical therapies like vitamin D and emollient. Finally, in this NMA, we divided the drugs treating psoriasis into five classes and regarded each whole class as a therapy; the efficacy and safety performance of interclass drug was not revealed in this NMA.

In conclusion, the efficacy and safety of some therapies of psoriasis were evaluated comprehensively and quantitatively in this NMA; monoclonal antibody agents of IL 12/23 and IL 17 were two recommended agents according to the results, while anti-IL17 should be used in caution since it has severe side effects.

Table 6. Comparison of direct and indirect evidences of treatments for psoriasis.

Study	PASI 75		PGA		AAE		Nasopharyngitis		Headache		URTI		Withdrawal	
	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR
AM vs. PBO														
Direct		2.50 (0.70, 9.80)		3.70 (0.35, 36.0)		1.10 (0.33, 4.00)		1.20 (0.28, 5.90)		1.20 (0.32, 5.00)		—		4.30 (0.45200)
Indirect	0.544	4.50 (1.20, 17.0)	0.756	5.50 (1.00, 30.0)	0.988	1.10 (0.48, 2.70)	0.989	1.20 (0.27, 5.20)	0.555	2.10 (0.72, 5.60)	—	—	0.538	2.00 (0.73, 5.90)
Network		3.10 (1.30, 7.40)		4.40 (1.02, 17.0)		1.30 (0.65, 2.60)		1.20 (0.47, 3.20)		1.60 (0.69, 3.30)		—		2.30 (0.89, 5.90)
Anti-ILI2/23 vs. PBO														
Direct		51.0 (30.0, 86.0)		—		1.10 (0.76, 1.50)		1.30 (0.82, 2.50)		1.10 (0.69, 2.00)		1.10 (0.81, 1.60)		0.65 (0.40, 1.10)
Indirect	0.146	16.0 (3.70, 71.0)	—	—	0.403	1.60 (0.68, 3.80)	0.604	1.40 (0.66, 5.20)	0.246	2.10 (0.86, 5.10)	0.433	1.60 (0.69, 4.00)	0.642	0.89 (0.26, 2.90)
Network		43.0 (27.0, 67.0)		—		1.10 (0.87, 1.50)		1.50 (1.00, 2.30)		1.50 (0.99, 2.20)		1.20 (0.89, 1.70)		0.65 (0.42, 0.99)
Anti-ILI7 vs. PBO														
Direct		50.0 (28.0, 86.0)		—		1.60 (1.10, 2.50)		1.60 (0.96, 2.50)		2.00 (1.20, 3.50)		1.70 (1.00, 3.00)		0.83 (0.47, 1.50)
Indirect	0.101	140 (42.0, 960)	—	—	0.356	1.10 (0.55, 2.30)	0.558	1.20 (0.49, 2.70)	0.396	1.30 (0.52, 3.10)	0.494	1.20 (0.54, 2.70)	0.394	0.49 (0.17, 1.50)
Network		62.0 (37.0, 130)		—		1.50 (1.00, 2.10)		1.40 (0.94, 2.20)		1.80 (1.10, 2.80)		1.50 (1.00, 2.50)		0.73 (0.45, 1.20)
Anti-ILI7 vs. Anti-ILI2/23														
Direct		2.30 (0.85, 6.50)		2.10 (0.43, 11.0)		1.10 (0.62, 1.80)		0.82 (0.39, 1.80)		0.96 (0.46, 2.00)		1.00 (0.49, 2.30)		0.82 (0.36, 1.90)
Indirect	0.224	1.10 (0.51, 2.30)	0.463	4.60 (1.20, 20.0)	0.266	1.60 (0.94, 2.80)	0.568	0.87 (0.54, 2.20)	0.399	1.50 (0.72, 3.30)	0.500	1.50 (0.80, 2.80)	0.387	1.30 (0.65, 2.60)
Network		1.40 (0.76, 2.60)		3.30 (1.20, 9.10)		1.30 (0.88, 1.90)		0.93 (0.57, 1.60)		1.20 (0.60, 1.50)		1.30 (0.79, 2.10)		1.10 (0.64, 2.00)
Anti-TNF-α vs. Anti-ILI2/23														
Direct		0.40 (0.21, 0.79)		0.51 (0.22, 1.10)		1.10 (0.69, 1.80)		1.00 (0.47, 2.20)		—		0.77 (0.45, 1.30)		1.10 (0.50, 2.30)
Indirect	0.588	0.53 (0.25, 1.10)	0.511	0.73 (0.29, 1.80)	0.840	1.00 (0.54, 1.90)	0.916	1.00 (0.48, 2.10)	—	—	0.470	1.00 (0.63, 1.60)	0.871	1.00 (0.54, 2.10)
Network		0.44 (0.27, 0.73)		0.62 (0.31, 1.20)		1.10 (0.77, 1.50)		1.00 (0.62, 1.70)		—		0.91 (0.62, 1.30)		1.00 (0.63, 1.60)
Anti-TNF-α vs. Anti-ILI17														
Direct		0.19 (0.03, 1.00)		0.19 (0.02, 1.60)		—		—		—		—		0.51 (0.13, 1.90)
Indirect	0.568	0.33 (0.18, 0.65)	0.931	0.17 (0.05, 0.54)	—	—	—	—	—	—	—	—	0.368	1.00 (0.56, 1.90)
Network		0.30 (0.17, 0.55)		0.18 (0.06, 0.54)		—		—		—		—		0.89 (0.52, 1.60)

URTI: upper respiratory tract infection; PASI 75: ≥75% reduction in psoriasis area and severity index; PGA: Physician's Global Assessment – minimal or cleared; AAE: all adverse events; AM: anti-metabolites; anti-TNF-α: anti-tumor necrosis factor-α agents; ANT: anti-T-cell agents; anti-ILI2/23: anti-interleukin-12/23 agents; anti-ILI7: anti-interleukin-17 agents; PBO: placebo.

Author Contributions

Declaration of Conflicting Interests

Funding

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