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REVIEW ARTICLE

Efficacy of Immunobiologic and Small Molecule Inhibitor Drugs for Psoriasis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Background Psoriasis is an immune-mediated inflammatory disease for which treatment has evolved over the past few years due to the introduction of immunobiologic and small molecule inhibitor medications. A better understanding of the comparative efficacies of drugs may help doctors to choose the most appropriate treatment for patients.

Objective The aim of this study was to conduct a systematic review and meta-analysis to assess the efficacy of immunobiologic and small molecule inhibitor drugs for patients with moderate to severe psoriasis.

Data Sources The EMBASE, PUBMED, LILACS, Web of Science and ClinicalTrials.org databases were searched for trials published to 21 July 2016.

Study Selection Only randomized, double-blind, placebo-controlled clinical trials that evaluated the efficacy of immunobiologics or small molecule inhibitors for moderate to severe plaque-type psoriasis were selected by two independent authors. No restrictions were used.

Data Extraction and Synthesis Two authors independently extracted the data and a random-effects model meta-analysis was performed.

Main Outcomes and Measures The Psoriasis Area and Severity Index (PASI) 75 was considered the primary outcome, measured at the primary endpoint of each study.

Results Thirty-eight studies were included in our analysis. The overall pooled effect favored biologics and small molecule inhibitors over placebo (risk difference [RD] 0.59, 95% confidence interval [CI] 0.58–0.60). Ixekizumab at a dose of 160 mg on week 0 and then every 2 weeks (RD 0.84, 95% CI 0.81–0.88), brodalumab 210 mg (RD 0.79, 95% CI 0.76–0.82), infliximab 5 mg/kg (RD 0.76, 95% CI 0.73–0.79), and secukinumab 300 mg (RD 0.76, 95% CI 0.71–0.81) showed a greater chance of response (PASI 75) when compared with placebo.

Limitations The methodology of a traditional meta-analysis does not allow for drugs to be ranked. Included studies used short-term endpoints (10–16 weeks) to evaluate the primary outcome, therefore long-term efficacy could not be determined.

Conclusions and Relevance The anti-IL-17 drugs brodalumab, ixekizumab and secukinumab showed an equal or greater chance of helping patients achieve a 75% improvement on PASI compared with other reviewed drugs.

Electronic supplementary material The online version of this article (doi:10.1007/s40268-016-0152-x) contains supplementary material, which is available to authorized users.

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Key Points

Anti-tumor necrosis factor and anti-interleukin (IL)-12/23 have been shown to be effective in treating patients with moderate to severe psoriasis.

Anti-IL-17 drugs showed an equal or greater chance of leading patients to a 75% improvement when compared with other biologics/small molecule inhibitors.

Ixekizumab showed higher efficacy among FDA-approved drugs when a 90 or 100% improvement over the baseline Psoriasis Area and Severity Index was analyzed.

1 Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease, where an intricate immune process, mainly driven by the T-helper (Th) 1/Th17 branch of the immune system, leads to persistent inflammation [1–3].

The treatment of psoriasis has been revolutionized by the introduction of biologic and small molecule inhibitor targeted therapy. Several of these therapies have been released and are available for general use, such as infliximab [4], adalimumab [5], ustekinumab [6], apremilast [7], etanercept [8], ixekizumab [9], and secukinumab [10], while others are in phase II or later trials, e.g. brodalumab [11], guselkumab [12], certolizumab pegol [13], and tofacitinib [14]. On the other hand, studies on the efficacy of briakinumab were halted because of safety concerns during phase III trials [15].

Schmitt et al. [16] recently carried out a meta-analysis that included studies that evaluated systemic treatments for psoriasis (biologics or not) published before October 2012. This review did not include anti-IL-17 drugs, and infliximab 5 mg/kg was superior to ustekinumab, adalimumab and etanercept. Xiong et al. published a systematic review that only included secukinumab, one of the anti-IL-17 biologic drugs, and concluded that anti-IL-17 drugs would be more efficacious than currently available biologics [17]. Also in 2015, Chen et al. performed a meta-analysis comparing only anti-IL-17 drugs, and reported a greater chance of response of brodalumab 140 mg, followed by ixekizumab 25 mg and secukinumab 150 mg [18].

As new drugs have emerged in the last few years [9, 11, 13, 14], it is important to update previous reviews to provide the best evidence on the efficacy of recent treatments for psoriasis. This study aimed to systematically review the evidence on the efficacy of biologic and small molecule inhibitor drugs for the treatment of moderate to severe psoriasis

2 Methods

This systematic review and meta-analysis was conducted using the recommendations of the Cochrane Initiative, and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19].

2.1 Search Strategy/Databases Searched/Eligibility Criteria

The research question ("What is the efficacy, measured by the improvement of 75% over baseline Psoriasis Area and Severity Index (PASI), of biologic and small molecule inhibitor drugs for moderate to severe psoriasis patients when compared to placebo?") was formulated using the PICO method (Population, Intervention, Comparator, Outcome). The EMBASE, PUBMED, LILACS, Web of Science and ClinicalTrials.org databases were searched for double-blind, randomized, placebo-controlled clinical trials (RCTs) published to 21 July 2016. Search strategies involved use of the terms 'psoriasis AND (abatacept OR apremilast OR CC-10004 OR adalimumab OR D2E7 OR briakinumab OR ABT-480 OR brodalumab OR certolizumab OR etanercept OR TNF Fc OR fezakizumab OR golimumab OR guselkumab OR CNTO1959 OR infliximab OR ixekizumab OR secukinumab OR Ly-2439821 OR sifalimumab OR siplizumab OR tasocitinib OR tofacitinib OR ustekinumab OR CNTO-1275 OR AbGn-168 OR RG-4934 OR APG-2305 OR MK-3222)'. Studies published online or in print, or studies in press were reviewed. Although we considered all languages eligible for the review, only studies published in English were found to be relevant.

Initially, duplicate studies were excluded and two researchers (AVEC and RPD) independently reviewed the titles and abstracts to exclude those studies that were clearly irrelevant. The reviewers then evaluated the full text of the remaining manuscripts and relevant articles were identified. Disagreements were solved by consensus. Randomized clinical trials were eligible for inclusion in the present review if they fulfilled the following criteria: human-based, double-blind, randomized, placebo-controlled clinical trials that evaluated adult patients and used the Psoriasis Area and Severity Index (PASI) as a measurement for psoriasis severity. Phase II studies were only included if the studied drugs or doses were identified in further phase III studies, or if drugs or doses were already

approved by the US FDA. In the case of studies with multiple study arms, including approved and non-approved drugs or doses, only the arms containing approved drugs/doses were included in the meta-analysis. Head-to-head studies without a placebo arm were excluded from the analysis, and studies that evaluated the improvement of psoriatic arthritis as a primary outcome were also excluded. The reference lists of the articles included in the review were searched for additional studies.

The primary efficacy outcome was the number of patients who experienced a 75% improvement in disease status, measured by the PASI (PASI 75), at the time of the primary efficacy assessment. Secondary outcomes were 90% improvement (PASI 90) and 100% improvement (PASI 100) in disease status.

2.2 Data Extraction

Using a standardized protocol [20] entirely based on the Cochrane handbook for systematic reviews and interventions, reviewers extracted the following items from each study: authors; year of publication; intervention and comparator; total number of patients randomized; trial duration; mean disease duration; mean age of patients; mean baseline PASI; number of patients achieving PASI 75, 90 and 100; and prior use of biologic or concomitant medications. Effect estimates were extracted with 95% confidence intervals (CI). Any disagreement was also solved by consensus. It was decided not to use any quality assessment of the studies (i.e. JADAD), and to evaluate its impact on the estimated pooled effect using meta-regression/sensitivity analysis. Data regarding randomization, blinding, and complete reporting of the study results were also extracted to evaluate the risk of bias [20].

2.3 Statistical Analysis

Effect measures were reported as the pooled risk difference (RD), and an RD >0 denoted that those subjects who received the 'new drug' showed a higher risk of presenting the outcome. The overall pooled effect of any treatment versus placebo was estimated by running a separate analysis, with all treatment patients gathered in one group and all placebo patients in another group, to avoid the unit-of-analysis error. The number needed to treat (NNT) was also calculated.

Heterogeneity among studies was assessed using the Q-test and I^2, and a random-effects model was used. Sensitivity analysis was performed excluding phase II studies when heterogeneity was found to be >50%. A funnel plot and Egger's test were used to investigate publication bias. We performed meta-regression to assess the influence of mean baseline PASI, previous use of biologics, and duration of the disease on the heterogeneity among studies.

Meta-analysis using data extracted from the studies was performed using STATA v.14 software for Mac (StataCorp LP, College Station, TX, USA). Forest plots, funnel plots, and risk of bias assessment graphs were developed using Review Manager Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3 Results

Overall, 9544 records were identified through a database search, with 5 additional records identified through a search of the bibliographical references of published meta-analyses. After removing duplicates, 6513 records were screened and 6181 were excluded (3822 were not RCTs, 2039 did not pertain to psoriasis, 122 pertained to drugs not encompassed in this review, and 198 were additional duplicates).

Among the 332 articles selected for full-text review, 292 were excluded for the following reasons: 201 were not RCTs, 16 were RCTs that did not use placebo as the comparator, 45 due to the lack of PASI as the primary outcome, 5 were studies in the pediatric population, 4 were phase II studies without further confirmatory phase III studies, 8 were studies with doses not approved by the FDA, 9 pertained to psoriatic arthritis, and 4 were additional duplicates (Fig. 1).

A total of 40 studies [4, 5, 7–9, 11, 14, 21–53] were included in the meta-analysis, providing 56 comparisons of 11 different interventions. In total, 22,884 patients were evaluated. The medications studied were adalimumab, apremilast, brodalumab, etanercept, infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab. Of the 40 studies included in the meta-analysis, 6 used a 10-week endpoint, 6 used a 16-week endpoint, and 28 used a 12-week endpoint. Primary endpoints for outcomes assessment were correlated with the induction period of the drugs and can be considered short-term therapy. All studies shared similar inclusion criteria and baseline characteristics (Table 1). Risk of bias assessment showed that high risk of bias was low among the studies (Online Resource 1 and 2).

At FDA-approved dose regimens, 1054 patients were randomized to adalimumab, 650 to apremilast, 2957 to etanercept (535–50 mg/wk, and 2422–100 mg/wk), 844 to infliximab, 1169 to ixekizumab, 691 to secukinumab, and 1678 to ustekinumab (949–45 mg, and 729–90 mg). With regard to drugs still not approved by the FDA, 2554 patients were randomized to brodalumab (1278–140 mg, and 1276–210 mg) and 2197 to tofacitinib (1124–5 mg, and 1073–10 mg).

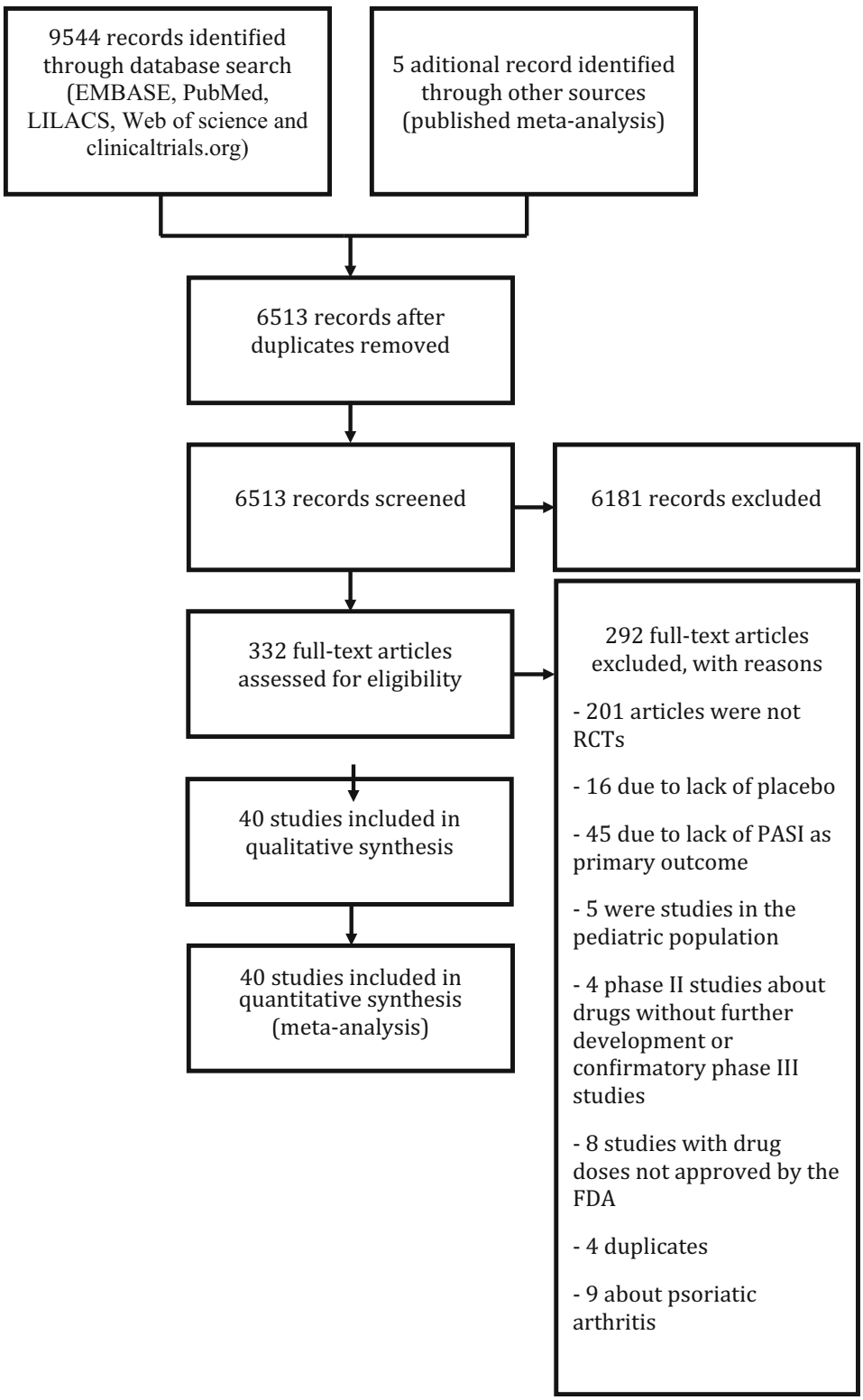


Fig. 1 PRISMA statement diagram for database searches for meta-analysis of the efficacy of biologics and small molecule inhibitors for psoriasis. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *RCTs* randomized controlled trials, *PASI* Psoriasis Area and Severity Index

Considering PASI 75 as the primary endpoint, ixekizumab (160 mg week 0 and 80 mg every 2 weeks) was the drug that achieved the higher RD (0.84, 95% CI 0.81–0.88), followed by brodalumab at a dose of 210 mg (weeks 0, 1, 2, 4, 6, 8, and 10) [RD 0.79, 95% CI 0.76–0.82). Figure 2 shows the remaining comparisons. Infliximab 5 mg/kg (RD 0.76, 95% CI 0.73–0.79) and secukinumab 300 mg (RD 0.76, 95% CI 0.71–0.81) performed comparably. The overall pooled effect favored treatment when compared with placebo (RD 0.59, 95% CI

Table 1 Clinical trial identification and summary categorized by drug[a]

Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Adalimumab	Asahina, 2010 [22]	Adalimumab sc (40 mg EOW)[c]	38 (169)	24	14.2	47.8	25.4	PASI 75/wk 16
		Adalimumab sc (80 mg wk 0 + 40 mg EOW starting wk 1)	43 (169)	24	14	44.2	30.2	PASI 75/wk 16
		Adalimumab sc (80 mg EOW)[c]	42 (169)	24	11.6	43.5	28.2	PASI 75/wk 16
		Placebo	46 (169)	24	15.5	43.9	29.1	PASI 75/wk 16
	Gordon, 2006 [5]	Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EOW starting week 1)	46 (148)	60	21	46	16.7	PASI 75/wk 12
		Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)[c]	50 (148)	60	18	44	14.5	PASI 75/wk 12
		Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)[c]	50 (148)	60	18	44	14.5	PASI 75/wk 12
		Placebo	52 (148)	60	19	43	16	PASI 75/wk 12
	Gordon 2015 [48]	Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks)[c]	42 (293)	52	19.4	46	19.4	PASI 75/wk 16
		Guselkumab 100 mg sc (every 8 weeks)[d]	42 (293)	52	18.3	41.5	20.4	PASI 75/wk 16
		Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks)[c]	42 (293)	52	18	44.5	22.3	PASI 75/wk 16
		Guselkumab 15 mg sc (every 8 weeks)[c]	41 (293)	52	17.3	45	21.5	PASI 75/wk 16
		Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks)[c]	41 (293)	52	19.5	43	20.9	PASI 75/wk 16
		Adalimumab sc (80 mg wk 0 and 1, then EOW)	43 (293)	52	19.3	50	20,2	PASI 75/wk 16
		Placebo	42 (293)	52	18	46.5	21.8	PASI 75/wk 16
	Menter, 2008 [32]	Adalimumab 40 mg sc (80 mg wk 0 and 40 mg EOW starting week 1)	814 (1212)	52	18.1	44.1	19	PASI 75/wk 16
		Placebo	398 (1212)	52	18.4	45.4	18.8	PASI 75/wk 16
	Saurat, 2007 [39]	Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EOW starting wk 1)	108 (271)	16	17.9	42.9	20.2	PASI 75/wk 16
		Methotrexate oral (7.5 mg until 25 mg/wk)[c]	110 (271)	16	18.9	41.6	19.4	PASI 75/wk 16
		Placebo	53 (271)	16	18.8	40.7	19.2	PASI 75/wk 16
Apremilast	Papp, 2012 [7]	Apremilast 10 mg orally bid[c]	89 (352)	24	18	44.4	18.1	PASI 75/wk 16
		Apremilast 20 mg orally bid[c]	87 (352)	24	19.2	44.6	18.5	PASI 75/wk 16
		Apremilast 3 0 mg orally bid	88 (352)	24	19.2	44.1	19.1	PASI 75/wk 16
		Placebo	88 (352)	24	19.6	44.1	18.1	PASI 75/wk 16
	Papp, 2015 [35]	Apremilast 30 mg bid	562 (844)	52	19.8	45.8	18.7	PASI 75/wk 16
		Placebo	282 (844)	52	18.7	46.5	19.4	PASI 75/wk 16

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Brodalumab	Lebwohl, 2015 Amagine2 [21]	Brodalumab 210 mg sc EOW	612 (1831)	52	19	45	18.6	PASI 75/wk 12
		Brodalumab 140 mg sc EOW	610 (1831)	52	19	45	18.9	PASI 75/wk 12
		Ustekinumab	300 (1831)	52	19	45	18.9	PASI 75/wk 12
		Placebo	309 (1831)	52	18	44	18.6	PASI 75/wk 12
	Lebwohl, 2015 Amagine3 [21]	Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	624 (1881)	52	18	45	18,7	PASI 75/wk 12
		Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	629 (1881)	52	17	45	18.1	PASI 75/wk 12
		Ustekinumab	313 (1881)	52	18	45	18.7	PASI 75/wk 12
		Placebo	315 (1881)	52	18	44	19	PASI 75/wk 12
	Papp, 2012 [11]	Brodalumab 70 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)[c]	39 (198)	12	20.7	42.1	18.8	PASI 75/wk 12
		Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	39 (198)	12	19.2	44	19.4	PASI 75/wk 12
		Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	40 (198)	12	17.1	42.1	20.6	PASI 75/wk 12
		Brodalumab 280 mg sc monthly[c]	42 (198)	12	19.3	42.3	17.9	PASI 75/wk 12
		Placebo	38 (198)	12	18.3	41.8	18.9	PASI 75/wk 12
Etanercept	Bachelez, 2015 [45]	Tofacitinib 5 mg bid	330 (1106)	12	16	44	21	PASI 75/wk 12
		Tofacitinib 10 mg bid	332 (1106)	12	17	44	21	PASI 75/wk 12
		Etanercept 100 mg/wk	336 (1106)	12	18	42	19.4	PASI 75/wk 12
		Placebo	108 (1106)	12	17	46	19.5	PASI 75/wk 12
	Bagel, 2012 [23]	Etanercept sc (100 mg/wk)	62 (124)	24	17.5	39	15.5	PASI 75/wk 12
		Placebo	62 (124)	24	11.9	42	15.2	PASI 75/wk 12
	Gottlieb, 2003 [26]	Etanercept sc (50 mg/wk)	57 (112)	24	23	48.2	17.8	PASI 75/wk 12
		Placebo	55 (112)	24	20	46.5	19.5	PASI 75/wk 12
	Gottlieb, 2011 [49]	Etanercept sc (100 mg/wk)	141 (347)	12	17	43.1	19.4	PASI 75/wk 12
		Briakinumab 200 mg sc (wks 0 and 4 then 100 mg wk 8)	138 (347)	12	16.1	43.6	18.4	PASI 75/wk 12
		Placebo	68 (347)	12	19.1	44	18.5	PASI 75/wk 12
	Griffiths, 2015 Uncover-2 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	347 (1224)	12	18	45	19	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	351 (1224)	12	19	45	20	PASI 75/wk 12
		Etanercept (100 mg/wk)	358 (1224)	12	19	45	19	PASI 75/wk 12
		Placebo	168 (1224)	12	19	45	21	PASI 75/wk 12

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
	Griffiths, 2015 Uncover-3 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	385 (1346)	12	18	46	21	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	386 (1346)	12	18	46	21	PASI 75/wk 12
		Etanercept (100 mg/wk)	382 (1346)	12	18	46	21	PASI 75/wk 12
		Placebo	193 (1346)	12	18	46	21	PASI 75/wk 12
	Langley, 2014 Fixture [29]	Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)	327 (1306)	52	15.8	44.5	23.9	PASI 75/wk 12
		Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	327 (1306)	52	17.3	45.4	23.7	PASI 75/wk 12
		Etanercept sc (100 mg/wk)	326 (1306)	52	16.4	43.8	23.2	PASI 75/wk 12
		Placebo	326 (1306)	52	16.6	44.1	24.1	PASI 75/wk 12
	Leonardi, 2003 [31]	Etanercept sc (25 mg/wk)[c]	160 (652)	24	19.3	44.4	18.2	PASI 75/wk 12
		Etanercept sc (50 mg/wk)	162 (652)	24	18.5	45.4	18.5	PASI 75/wk 12
		Etanercept sc (100 mg/wk)	164 (652)	24	18.6	44.8	18.4	PASI 75/wk 12
		Placebo	166 (652)	24	18.4	45.6	18.3	PASI 75/wk 12
	Mease, 2000 [8]	Etanercept sc (50 mg/wk)	19 (38)	12	19	46	10.1	PASI 75/wk 12
		Placebo	19 (38)	12	17.5	43.5	6.0	PASI 75/wk 12
	Papp, 2005 [50]	Etanercept sc (50 mg/wk)	204 (611)	24	21.5	46	16.9	PASI 75/wk 12
		Etanercept sc (100 mg/wk)	203 (611)	24	18.1	44.5	16.1	PASI 75/wk 12
		Placebo	204 (611)	24	17.5	44	16	PASI 75/wk 12
	Strober, 2011 [51]	Etanercept sc (100 mg/wk)	139 (350)	12	15.2	45.2	18.5	PASI 75/wk 12
		Briakinumab 200 mg sc (wks 0 and 4, then 100 mg wk 8)	139 (350)	12	16.3	44.9	19.4	PASI 75/wk 12
		Placebo	72 (350)	12	15.5	45	18.3	PASI 75/wk 12
	Tyring, 2007 [42]	Etanercept sc (100 mg/wk	311 (618)	96	20.2	45.8	18.3	PASI 75/wk 12
		Placebo	307 (618)	96	19.7	45.5	18.1	PASI 75/wk 12
	Van der Kerkhof, 2008 [28]	Etanercept sc (50 mg/week)	96 (142)	24	19.3	45.9	21.4	PASI 75/wk 12
		Placebo	46 (142)	24	17.3	43.6	21	PASI 75/wk 12

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Infliximab	Chaudari, 2001 [4]	Infliximab 5 mg/kg iv (wks 0, 2 and 6)	11 (33)	10	ND	51	22.1	PASI 75/wk 10
		Infliximab 10 mg/kg iv (wks 0, 2 and 6)[c]	11 (33)	10	ND	35	26.6	PASI 75/wk 10
		Placebo	11 (33)	10	ND	45	20.3	PASI 75/wk 10
	Gottlieb, 2004 [47]	Infliximab 3 mg/kg iv (wks 0, 2 and 6)	99 (249)	30	18	45	20	PASI 75/wk 10
		Infliximab 5 mg/kg iv (wks 0, 2 and 6)	99 (249)	30	16	44	20	PASI 75/wk 10
		Placebo	51 (249)	30	16	45	18	PASI 75/wk 10
	Menter, 2007 [33]	Infliximab 3 mg iv (wks 0, 2 and 6)	313 (835)	50	18.1	43.4	20.1	PASI 75/wk 10
		Infliximab 5 mg iv (wks 0, 2 and 6)	314 (835)	50	19.1	44.5	20.4	PASI 75/wk 10
		Placebo	208 (835)	50	17.8	44.4	19.8	PASI 75/wk 10
	Reich, 2005 [38]	Infliximab 5 mg iv (wks 0, 2, 6, and then every 8 wks)	301 (317)	50	19.1	42.6	22.9	PASI 75/wk 10
		Placebo	77 (317)	50	17.3	43.8	22.8	PASI 75/wk 10
	Torri, 2010 [40]	Infliximab 5 mk/kg iv (wks 0, 2, 6 and 8)	35 (54)	78	14.2	46.9	31.9	PASI 75/wk 10
		Placebo	19 (54)	78	11.1	43.3	33.1	PASI 75/wk 10
	Yang, 2012 [43]	Infliximab 5 mk/kg iv (wks 0, 2, 6, 14 and 22)	84 (129)	26	16	40.1	23.9	PASI 75/wk 10
		Placebo	45 (129)	26	16	39.4	25.3	PASI 75/wk 10
Ixekizumab	Griffiths, 2015 Uncover-2 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	347 (1224)	12	18	45	19	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	351 (1224)	12	19	45	20	PASI 75/wk 12
		Etanercept (100 mg/wk)	358 (1224)	12	19	45	19	PASI 75/wk 12
		Placebo	168 (1224)	12	19	45	21	PASI 75/wk 12
	Griffiths, 2015 Uncover-3 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	385 (1346)	12	18	46	21	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	386 (1346)	12	18	46	21	PASI 75/wk 12
		Etanercept (100 mg/wk)	382 (1346)	12	18	46	21	PASI 75/wk 12
		Placebo	193 (1346)	12	18	46	21	PASI 75/wk 12
	Gordon, 2016 Uncover-1 [53]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	433 (1296)	12	19	46	20	PASI 75/wk 12
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	433 (1296)	12	20	45	20	PASI 75/wk 12
		Placebo	431 (1296)	12	20	46	20	PASI 75/wk 12

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Secukinumab	Blauvelt, 2014 [24]	Secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8)	59 (177)	12	18	45.1	20.7	PASI 75/wk 12
		Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, 8)[c]	59 (177)	12	20.4	46	20.5	PASI 75/wk 12
		Placebo	59 (177)	12	20.2	46.5	21.1	PASI 75/wk 12
	Langley, 2014 Erasure [29]	Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	245 (738)	52	17.5	44.9	22.3	PASI 75/wk 12
		Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	327 (1306)	52	17.3	45.4	23.7	PASI 75/wk 12
		Placebo	248 (738)	52	17.3	45.4	21.4	PASI 75/wk 12
	Langley, 2014 Fixture [29]	Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)	327 (1306)	52	15.8	44.5	23.9	PASI 75/wk 12
		Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	327 (1306)	52	17.3	45.4	23.7	PASI 75/wk 12
		Etanercept sc (100 mg/wk)	326 (1306)	52	16.4	43.8	23.2	PASI 75/wk 12
		Placebo	326 (1306)	52	16.6	44.1	24.1	PASI 75/wk 12
	Paul, 2014 [37]	Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, 8)	61 (182)	52	20.6	43.9	22	PASI 75/wk 12
		Secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8)	60 (182)	52	21	46.6	18.9	PASI 75/wk 12
		Placebo	61 (182)	52	19.8	43.7	19.4	PASI 75/wk 12
Tofacitinib	Bachelez [45]	Tofacitinib 5 mg bid	330 (1106)	12	16	44	21	PASI 75/wk 12
		Tofacitinib 10 mg bid	332 (1106)	12	17	44	21	PASI 75/wk 12
		Etanercept 100 mg/wk	336 (1106)	12	18	42	19.4	PASI 75/wk 12
		Placebo	108 (1106)	12	17	46	19.5	PASI 75/wk 12
	Papp, 2012 [14]	Tofacitinib 2 mg orally bid	49 (197)	16	16.5	29	21.5	PASI 75/wk 12
		Tofacitinib 5 mg orally bid	49 (197)	16	16.4	29	21.2	PASI 75/wk 12
		Tofacitinib 15 mg orally bid	49 (197)	16	16.9	31	22.6	PASI 75/wk 12
		Placebo	50 (197)	16	17.2	36	21.5	PASI 75/wk 12
	Papp, 2015 OPT1 [52]	Tofacitinib 5 mg orally bid	363 (900)	16	16	46	19.5	PASI 75/wk 12
		Tofacitinib 10 mg bid	360 (900)	16	16.9	46	20.4	PASI 75/wk12
		Placebo	177 (900)	16	15.7	45	19.8	PASI 75/wk 12
	Papp, 2015 OPT2 [52]	Tofacitinib 5 mg orally bid	382 (959)	16	15.2	47	20.7	PASI 75/wk 12
		Tofacitinib 10 mg bid	381 (959)	16	15.2	44	19.3	PASI 75/wk 12
		Placebo	196 (959)	16	16.4	45	20.1	PASI 75/wk 12

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients randomized (total patients)	Total trial duration (weeks)	Mean disease duration (years)	Mean age of patients	Mean Baseline PASI	Primary outcome measure/primary endpoint
Ustekinumab	Igarashi, 2011 [27]	Ustekinumab 45 mg (wks 0, 4 and every 12 wks)	64 (157)	72	15.8	45	30.1	PASI 75/wk 12
		Ustekinumab 90 mg (wks 0, 4 and every 12 wks)	62 (157)	72	17.3	44	28.7	PASI 75/wk 12
		Placebo	31 (157)	72	16	49	30.3	PASI 75/wk 12
	Leonardi, 2008 [30]	Ustekinumab 45 mg sc (wks 0, 4 and every 12 wks)	255 (766)	76	19.7	44.8	20.5	PASI 75/wk 12
		Ustekinumab 90 mg sc (wks 0, 4 and every 12 wks)	256 (766)	76	19.6	46.2	19.7	PASI 75/wk 12
		Placebo	255 (766)	76	20.4	44.8	20.4	PASI 75/wk 12
	Tsai, 2011 [41]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)	61 (121)	28	11.9	40.9	25.2	PASI 75/wk 12
		Placebo	60 (121)	28	13.9	40.4	22.9	PASI 75/wk 12
	Zhu, 2013 [44]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)	160 (332)	32	14.6	40.1	23.2	PASI 75/wk 12
		Placebo	162 (332)	32	14.2	39.2	22.7	PASI 75/wk 12

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication[b]
Adalimumab	Asahina, 2010 [22]	Adalimumab sc (40 mg EOW)[c]	28	22	14	ND	No/no
		Adalimumab sc (80 mg wk 0 + 40 mg EOW starting wk 1)	35	27	17	ND	No/no
		Adalimumab sc (80 mg EOW)[c]	38	34	26	ND	No/no
		Placebo	9	2	0	ND	No/no
	Gordon, 2006 [5]	Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EOW starting week 1)	ND	24	ND	5	ND/no
		Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)[c]	ND	40	ND	13	ND/no
		Adalimumab 40 mg sc (80 mg wk 0 and 1 + 40 mg/wk starting wk 2)[c]	ND	40	ND	13	ND/no
		Placebo	ND	2	ND	0	ND/no
	Gordon 2015 [48]	Guselkumab 200 mg sc (wk 0, 4 and every 12 weeks)[c]	ND	34	24	12	20 (42)/ND
		Guselkumab 100 mg sc (every 8 weeks)[c]	ND	33	26	14	17 (42)/ND
		Guselkumab 50 mg sc (wk 0, 4 and every 12 weeks)[c]	ND	34	19	8	15 (42)/ND
		Guselkumab 15 mg sc (every 8 weeks)[c]	ND	31	14	5	14 (41)/ND
		Guselkumab 5 mg sc (wk 0, 4 and every 12 weeks)[c]	ND	18	14	4	19 (41)/ND
		Adalimumab sc (80 mg wk 0 and 1, then EOW)	ND	30	19	11	26 (43)/ND
		Placebo	ND	2	1	0	15 (42)/no

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication[b]
	Menter, 2008 [32]	Adalimumab 40 mg sc (80 mg wk 0 and 40 mg EOW starting week 1)	ND	578	366	163	97 (814)/no
		Placebo	ND	26	8	4	53 (398)/no
	Saurat, 2007 [39]	Adalimumab 40 mg sc (80 mg wk 0 + 40 mg EOW starting wk 1)	95	86	55	18	No/no
		Methotrexate oral (7.5 mg until 25 mg/wk)[c]	68	39	15	8	No/no
		Placebo	16	10	6	1	No/no
Apremilast	Papp, 2012 [7]	Apremilast 10 mg orally bid[c]	ND	10	ND	ND	ND/no
		Apremilast 20 mg orally bid[c]	ND	25	ND	ND	ND/no
		Apremilast 3 0 mg orally bid	ND	36	ND	ND	ND/no
		Placebo	ND	5	ND	ND	ND/no
	Papp, 2015 [35]	Apremilast 30 mg bid	ND	183	55	ND	162 (562)/no
		Placebo	ND	14	1	ND	80 (282)/no
Brodalumab	Lebwohl, 2015 Amagine2 [21]	Brodalumab 210 mg sc EOW	ND	528	ND	272	177 (612)/no
		Brodalumab 140 mg sc EOW	ND	406	ND	157	179 (610)/no
		Ustekinumab	ND	210	ND	65	84 (300)/no
		Placebo	ND	25	ND	2	90 (309)/no
	Lebwohl, 2015 Amagine3 [21]	Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	ND	531	ND	229	157 (624)/yes
		Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	ND	435	ND	170	160 (629)/yes
		Ustekinumab	ND	217	ND	58	75 (313)/yes
		Placebo	ND	19	ND	1	76 (315)/yes
	Papp, 2012 [11]	Brodalumab 70 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)[c]	20	13	7	4	16 (39)/no
		Brodalumab 140 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	35	30	28	15	10 (39)/no
		Brodalumab 210 mg sc (wks 0, 1, 2, 4, 6, 8, and 10)	36	33	30	25	17 (40)/no
		Brodalumab 280 mg sc monthly[c]	34	28	24	12	19 (42)/no
		Placebo	6	0	0	0	16 (38)/no

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication[b]
Etanercept	Bachelez, 2015 [45]	Tofacitinib 5 mg bid	216	130	69	ND	35 (330)/no
		Tofacitinib 10 mg bid	266	210	119	ND	29 (332)/no
		Etanercept 100 mg/wk	269	197	108	ND	37 (336)/no
		Placebo	22	6	1	ND	12 (108)/no
	Bagel, 2012 [23]	Etanercept sc (100 mg/wk)	52	37	16	ND	6 (62)/no
		Placebo	4	3	1	ND	7 (62)/no
	Gottlieb, 2003 [26]	Etanercept sc (50 mg/wk)	ND	17	ND	ND	No/no
		Placebo	ND	1	ND	ND	No/no
	Gottlieb, 2011 [49]	Etanercept sc (100 mg/wk)	ND	79	ND	ND	20 (141)/no
		Briakinumab 200 mg sc (wks 0 and 4 then 100 mg wk 8)	ND	113	ND	ND	39 (138)/no
		Placebo	ND	5	ND	ND	10 (68)/no
	Griffiths, 2015 Uncover-2 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	ND	315	248	142	84 (347)/yes
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	ND	269	207	107	85 (351)/yes
		Etanercept (100 mg/wk)	ND	149	67	19	76 (358)/yes
		Placebo	ND	4	1	1	43 (168)/yes
	Griffiths, 2015 Uncover-3 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	ND	336	262	145	58 (385)/yes
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	ND	325	252	135	58 (386)/yes
		Etanercept (100 mg/wk)	ND	204	98	28	60 (382)/yes
		Placebo	ND	14	6	0	33 (193)/yes

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication[b]
	Langley, 2014 Fixture [29]	Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)	ND	249	175	78	38 (327)/no
		Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	ND	219	137	47	45 (327)/no
		Etanercept sc (100 mg/wk)	ND	142	67	14	45 (326)/no
		Placebo	ND	16	5	0	35 (326)/no
	Leonardi, 2003 [31]	Etanercept sc (25 mg/wk)[c]	65	23	5	ND	No/no
		Etanercept sc (50 mg/wk)	94	55	19	ND	No/no
		Etanercept sc (100 mg/wk)	121	81	36	ND	No/no
		Placebo	24	6	1	ND	No/no
	Mease, 2000 [8]	Etanercept sc (50 mg/wk)	ND	5	ND	ND	ND/yes
		Placebo	ND	0	ND	ND	ND/yes
	Papp, 2005 [50]	Etanercept sc (50 mg/wk)	124	66	20	ND	No/no
		Etanercept sc (100 mg/wk)	147	94	39	ND	No/no
		Placebo	18	6	1	ND	No/no
	Strober, 2011 [51]	Etanercept sc (100 mg/wk)	ND	55	19	8	1 (139)/no
		Briakinumab 200 mg sc (wks 0 and 4, then 100 mg wk 8)	ND	112	77	40	15 (139)/no
		Placebo	ND	5	3	0	3 (72)/no
	Tyring, 2007 [42]	Etanercept sc (100 mg/wk	230	146	65	ND	ND/no
		Placebo	43	15	3	ND	ND/no
	Van der Kerkhof, 2008 [28]	Etanercept sc (50 mg/week)	66	36	13	ND	ND/no
		Placebo	4	1	1	ND	ND/no
Infliximab	Chaudari, 2001 [4]	Infliximab 5 mg/kg iv (wks 0, 2 and 6)	ND	9	ND	ND	No/no
		Infliximab 10 mg/kg iv (wks 0, 2 and 6)[c]	ND	8	ND	ND	No/no
		Placebo	ND	2	ND	ND	No/no
	Gottlieb, 2004 [47]	Infliximab 3 mg/kg iv (wks 0, 2 and 6)	83	71	45	ND	32 (99)/no
		Infliximab 5 mg/kg iv (wks 0, 2 and 6)	96	87	57	ND	33 (99)/no
		Placebo	11	3	1	ND	16 (51)/no
	Menter, 2007 [33]	Infliximab 3 mg iv (wks 0, 2 and 6)	ND	220	116	ND	49 (313) No
		Infliximab 5 mg iv (wks 0, 2 and 6)	ND	237	142	ND	45 (314)/no
		Placebo	ND	4	1	ND	27 (208)/no
	Reich, 2005 [38]	Infliximab 5 mg iv (wks 0, 2, 6, and then every 8 wks)	274	242	172	ND	No/no
		Placebo	6	2	1	ND	No/no
	Torri, 2010 [40]	Infliximab 5 mk/kg iv (wks 0, 2, 6 and 8)	ND	24	ND	ND	ND/no
		Placebo	ND	0	ND	ND	ND/no
	Yang, 2012 [43]	Infliximab 5 mk/kg iv (wks 0, 2, 6, 14 and 22)	79	68	48	ND	ND/no
		Placebo	6	1	0	ND	ND/no

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication[b]
Ixekizumab	Griffiths, 2015 Uncover-2 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	ND	315	248	142	84 (347)/yes
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	ND	269	207	107	85 (351)/yes
		Etanercept (100 mg/wk)	ND	149	67	19	76 (358)/yes
		Placebo	ND	4	1	1	43 (168)/yes
	Griffiths, 2015 Uncover-3 [46]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	ND	336	262	145	58/ (385)Yes
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	ND	325	252	135	58 (386)/yes
		Etanercept (100 mg/wk)	ND	204	98	28	60 (382)/yes
		Placebo	ND	14	6	0	33 (193)/yes
	Gordon, 2016 Uncover-1 [53]	Ixekizumab sc (160 mg wk 0 and 80 mg every 4 wks)[c]	ND	357	279	145	168 (432)/no
		Ixekizumab (160 mg wk 0 and 80 mg every 2 wks)	ND	386	307	153	173 (433)/no
		Placebo	ND	17	2	0	181 (431)/no
Secukinumab	Blauvelt, 2014 [24]	Secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8)	ND	45	36	25	23 (59)/no
		Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, 8)[c]	ND	41	27	5	28 (59)/no
		Placebo	ND	0	0	0	26 (59)/no
	Langley, 2014 Erasure [29]	Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	ND	174	95	31	73 (245)/no
		Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	ND	219	137	47	45 (327)/no
		Placebo	ND	11	3	2	73 (248)/no
	Langley, 2014 Fixture [29]	Secukinumab 300 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)	ND	249	175	78	38 (327)/no
		Secukinumab 150 mg sc (wks 0, 1, 2, 3 and 4, then wks 8 and 12)[c]	ND	219	137	47	45 (327)/no
		Etanercept sc (100 mg/wk)	ND	142	67	14	45 (326)/no
		Placebo	ND	16	5	0	35 (326)/no
	Paul, 2014 [37]	Secukinumab 150 mg sc (wks 0, 1, 2, 3, 4, 8)	ND	44	33	10	15 (61)/no
		Secukinumab 300 mg sc (wks 0, 1, 2, 3, 4, 8)	ND	53	24	16	15 (60)/no
		Placebo	ND	2	0	0	13 (61)/no
Tofacitinib	Bachelez [45]	Tofacitinib 5 mg bid	216	130	69	ND	35 (330)/no
		Tofacitinib 10 mg bid	266	210	119	ND	29 (332)/no
		Etanercept 100 mg/wk	269	197	108	ND	37 (336)/no
		Placebo	22	6	1	ND	12 (108)/no
	Papp, 2012 [14]	Tofacitinib 2 mg orally bid	ND	12	ND	ND	10 (49)/no
		Tofacitinib 5 mg orally bid	ND	20	ND	ND	15 (49)/no
		Tofacitinib 15 mg orally bid	ND	33	ND	ND	10 (49)/no
		Placebo	ND	1	ND	ND	16 (50)/no

Table 1 continued

Drug	Author, year	Intervention/comparator	No. of patients achieving PASI 50	No. of patients achieving PASI 75	No. of patients achieving PASI 90	No. of patients achieving PASI 100	Prior immunobiologic treatment/concomitant systemic medication[b]
	Papp, 2015 OPT1 [52]	Tofacitinib 5 mg orally bid	ND	145	72	ND	113 (363)/no
		Tofacitinib 10 mg bid	ND	213	140	ND	113 (360)/no
		Placebo	ND	11	1	ND	53 (177)/no
	Papp, 2015 OPT2 [52]	Tofacitinib 5 mg orally bid	ND	173	93	ND	92 (382)/no
		Tofacitinib 10 mg bid	ND	223	148	ND	97 (381)/no
		Placebo	ND	22	10	ND	47 (196)/no
Ustekinumab	Igarashi, 2011 [27]	Ustekinumab 45 mg (wks 0, 4 and every 12 wks)	53	38	21	ND	1 (64)/no
		Ustekinumab 90 mg (wks 0, 4 and every 12 wks)	52	42	27	ND	No/no
		Placebo	4	2	1	ND	No/no
	Leonardi, 2008 [30]	Ustekinumab 45 mg sc (wks 0, 4 and every 12 wks)	213	171	106	32	134 (255)/no
		Ustekinumab 90 mg sc (wks 0, 4 and every 12 wks)	220	170	94	28	130 (256)/no
		Placebo	26	8	5	0	128 (255)/no
	Tsai, 2011 [41]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)	51	41	30	5	13 (61)/no
		Placebo	8	3	1	0	9 (61)/no
	Zhu, 2013 [44]	Ustekinumab 45 mg sc (wks 0, 4 and then every 12 wks)	146	132	107	38	19 (160)/no
		Placebo	32	18	5	1	11 (162)/no

EOW every other week, *bid* twice daily, *sc* subcutaneous, *iv* intravenous, *ND* not disclosed, *PASI* Psoriasis Area and Severity Index

[a] Studies with multiple treatment arms were included more than once in the table

[b] Number of patients who received prior biologic or small molecule therapy (total number of patients on study drug)

[c] Drugs or doses not included in the final analysis

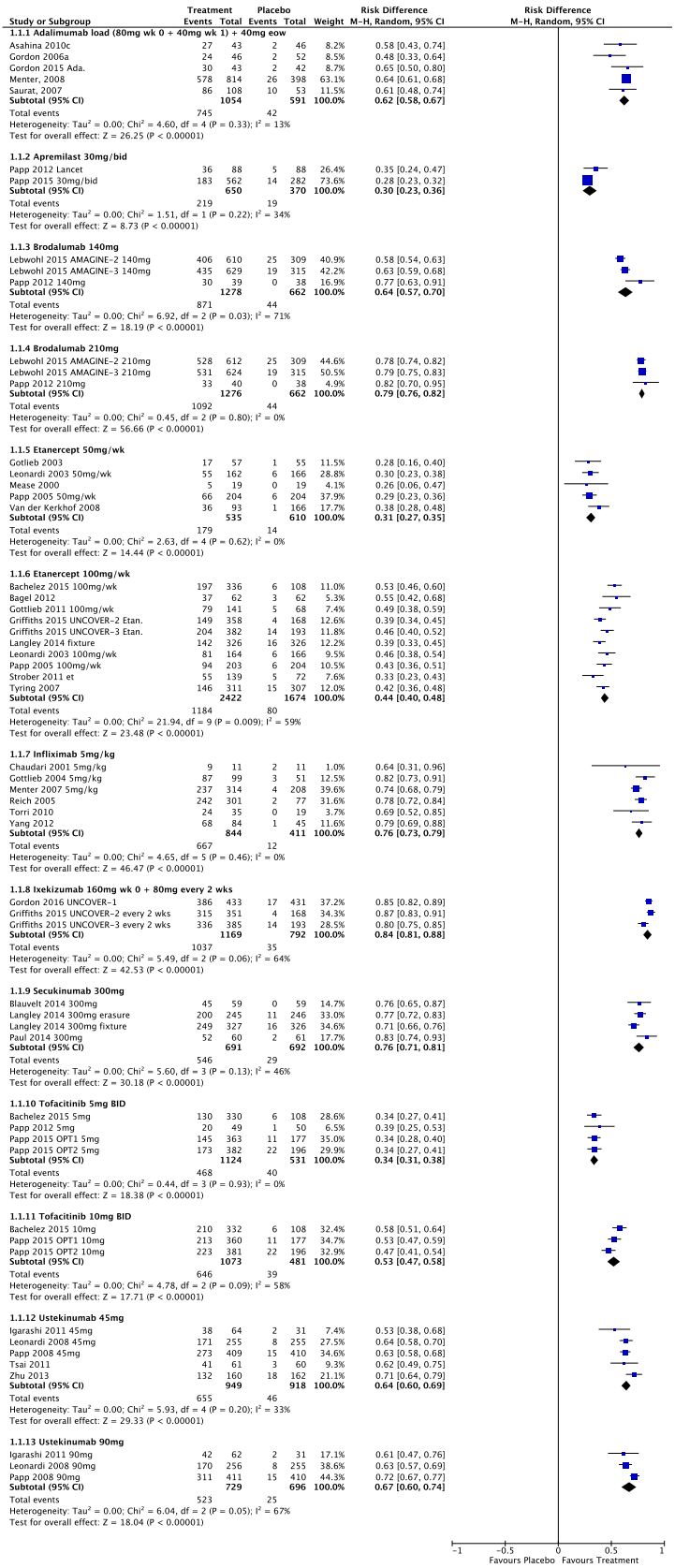


Fig. 2 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 75% response rate of biologic and small molecule inhibitor therapies for moderate to severe psoriasis in randomized, placebo-controlled trials. *CI* confidence interval, *M-H* Mantel–Haenszel, *EOW* every other week, *df* degrees of freedom, *bid* twice daily

0.58–0.60) [Fig. 3]. When analyzing PASI 75 as an outcome, the estimated NNT for ixekizumab, brodalumab 210 mg, infliximab and secukinumab was 1.19, 1.26, 1.31 and 1.31, respectively. A summary of comparisons is reported in Table 2.

When PASI 90 was used as an outcome, both doses of brodalumab—210 mg (RD 0.75, 95% CI 0.61–0.89) and 140 mg (RD 0.72, 95% CI 0.57–0.86—achieved a higher chance of improvement, followed by ixekizumab (RD 0.69, 95% CI 0.65–0.72). Secukinumab and infliximab showed the same RD, with exactly the same CI (RD 0.53, 95% CI 0.46–0.60). The remaining comparisons are reported in Fig. 4. The overall pooled effect favored treatment in relation to placebo (RD 0.39, 95% CI 0.38–0.40) [Fig. 5].

Brodalumab 210 mg was also the drug that achieved higher RD if PASI 100 was used as the outcome (RD 0.44, 95% CI 0.35–0.53). The approved drugs performed as follows: ixekizumab (RD 0.37, 95% CI 0.35–0.40), secukinumab (RD 0.28, 95% CI 0.22–0.34), adalimumab (RD 0.18, 95% CI 0.12–0.24), and ustekinumab 45 mg

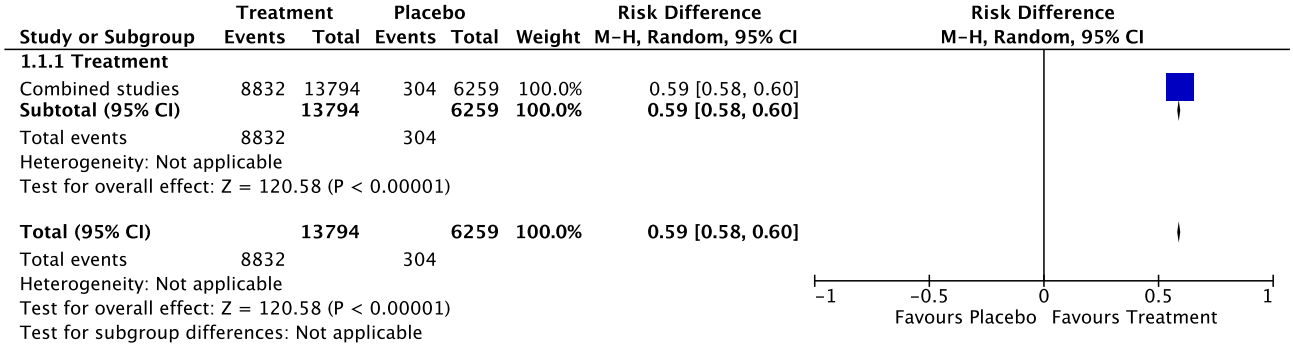


Fig. 3 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 75% response rate of all treatments combined for moderate to severe psoriasis in randomized, placebo-controlled trials (overall pooled effect). *CI* confidence interval, *M-H* Mantel–Haenszel

Table 2 Summary of results for drugs and doses sorted by drug class

Drug class	Drug/dose	PASI 75		PASI 90		PASI 100		Primary endpoint (weeks)
		RD (95% CI)	NNT	RD (95% CI)	NNT	RD (95% CI)	NNT	
Anti-TNF	Adalimumab load (80 mg week 0 + 40 mg week 1) + 40 mg EOW	0.62 (0.58–0.67)	1.61	0.43 (0.39–0.46)	2.32	0.18 (0.12–0.24)	5.55	12–16
	Etanercept 100 mg/wk	0.44 (0.40–0.48)	2.27	0.22 (0.18–0.25)	4.54	0.05 (0.04–0.07)	20	12
	Etanercept 50 mg/wk	0.31 (0.27–0.35)	3.22	0.10 (0.07–0.13)	10	0.06 (0.01–0.10)	16.6	12
	Infliximab 5 mg/kg	0.76 (0.73–0.79)	1.31	0.53 (0.46–0.60)	1.88	ND	ND	10
	Overall pooled effect	0.54 (0.47–0.60)	1.85	0.28 (0.21–0.35)	3.57	0.10 (0.04–0.16)	10	–
Anti-IL-12/23	Ustekinumab 90 mg	0.67 (0.60–0.74)	1.49	0.42 (0.30–0.54)	2.38	0.15 (0.07–0.22)	6.66	12
	Ustekinumab 45 mg	0.64 (0.60–0.69)	1.56	0.45 (0.35–0.55)	2.22	0.16 (0.10–0.21)	6.25	12
	Overall pooled effect	0.65 (0.62–0.69)	1.53	0.44 (0.37–0.51)	2.27	0.15 (0.11–0.19)	6.66	–
Anti-IL-17	Brodalumab 210 mg	0.79 (0.76–0.82)	1.26	0.75 (0.61–0.89)	1.33	0.44 (0.35–0.53)	2.27	12
	Brodalumab 140 mg	0.64 (0.57–0.70)	1.56	0.72 (0.57–0.86)	1.38	0.26 (0.23–0.30)	3.84	12
	Ixekizumab 160 mg week 0 and 80 mg every 2 weeks	0.84 (0.81–0.88)	1.19	0.69 (0.65–0.72)	1.44	0.37 (0.35–0.40)	2.70	12
	Secukinumab 300 mg	0.76 (0.71–0.81)	1.31	0.53 (0.46–0.60)	1.88	0.28 (0.22–0.34)	3.57	12
	Overall pooled effect	0.76 (0.70–0.82)	1.31	0.61 (0.54–0.68)	1.63	0.35 (0.30–0.40)	2.85	–
Small molecule inhibitors (anti-JAK/anti-PD4)	Tofacitinib 10 mg	0.53 (0.47–0.58)	1.88	0.36 (0.33–0.39)	2.77	ND	ND	12
	Tofacitinib 5 mg	0.34 (0.31–0.38)	2.94	0.19 (0.17–0.22)	5.26	ND	ND	12
	Apremilast 30 mg bid	0.30 (0.23–0.36)	3.33	ND	ND	ND	ND	16
	Overall pooled effect	0.43 (0.30–0.55)	2.32	0.27 (0.13–0.42)	3.7	ND	ND	–

PASI Psoriasis Area and Severity Index, *RD* risk difference, *CI* confidence interval, *NNT* number needed to treat, *EOW* every other week, *bid* twice daily, *JAK* Janus kinase, *PD4* phosphodiesterase 4, *ND* not determined, *TNF* tumor necrosis factor, *IL* interleukin

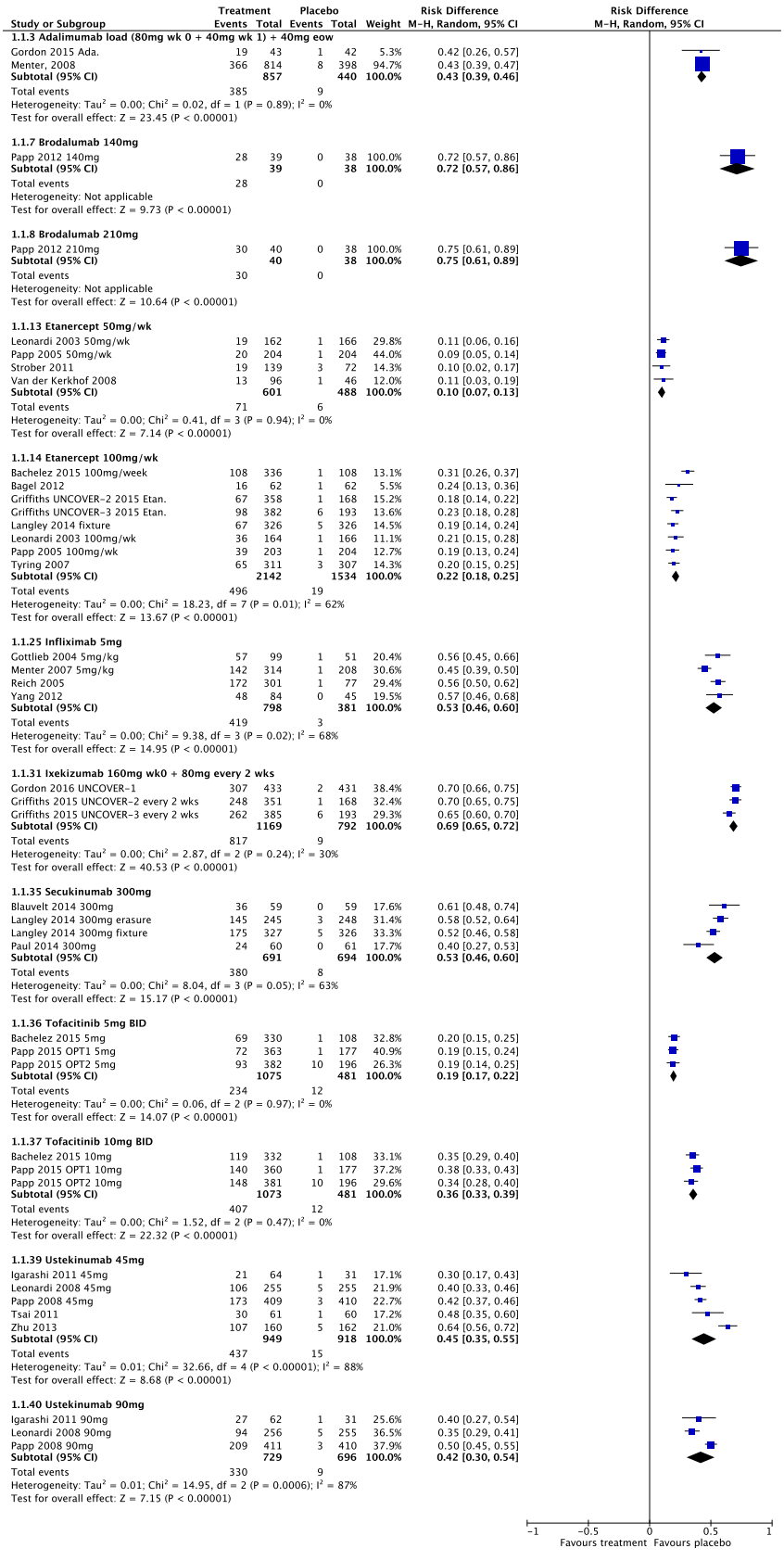


Fig. 4 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 90% response rate of biologic and small molecule inhibitor therapies for moderate to severe psoriasis in randomized, placebo-controlled trials. *CI* confidence interval, *M-H* Mantel–Haenszel, *EOW* every other week, *df* degrees of freedom, *bid* twice daily

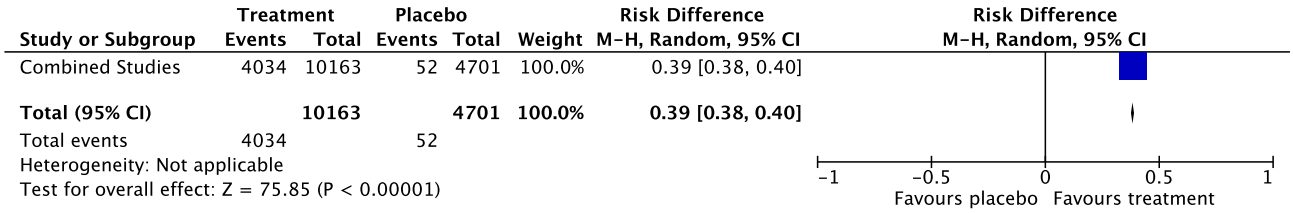


Fig. 5 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 90% response rate of all treatments combined for moderate to severe psoriasis in randomized, placebo-controlled trials (overall pooled effect). *CI* confidence interval, *M-H* Mantel–Haenszel

(RD 0.16, 95% CI 0.10–0.21). Other comparisons are reported in Fig. 6. The overall pooled effect of treatment versus placebo was also favorable towards treatment (RD 0.24, 95% CI 0.23–0.25) [Fig. 7].

Heterogeneity (I^2) on the PASI 75 outcome analysis was below 40% in the following drugs: adalimumab ($I^2 = 13\%$), apremilast ($I^2 = 34\%$), brodalumab 210 mg ($I^2 = 0\%$), etanercept 50 mg ($I^2 = 0\%$), infliximab ($I^2 = 0\%$), tofacitinib 5 mg ($I^2 = 0\%$), and ustekinumab 45 mg ($I^2 = 33\%$). Moderate heterogeneity was found in the etanercept 100 mg ($I^2 = 59\%$), secukinumab ($I^2 = 46\%$), and tofacitinib 10 mg ($I^2 = 58\%$) groups. In addition, substantial heterogeneity was seen in the following groups: brodalumab 140 mg ($I^2 = 71\%$), ixekizumab ($I^2 = 64\%$), and ustekinumab 90 mg ($I^2 = 67\%$) [Fig. 2]. Heterogeneity for remaining outcomes (PASI 90 and 100) have been reported in Figs. 4 and 6.

The funnel plot of the PASI 75 outcome did not disclose discrepancies with regard to the magnitude of the effect measured and study size. PASI 90 and PASI 100 funnel plots are not typical, and the lack of symmetry observed may be an indication of publication bias (Online Resource 3, 4, and 5).

Meta-regression was performed to evaluate the contribution of mean baseline PASI, previous use of biologics, and duration of the disease to the heterogeneity among studies (Online Resource 6). None of these variables explained the heterogeneity.

4 Discussion

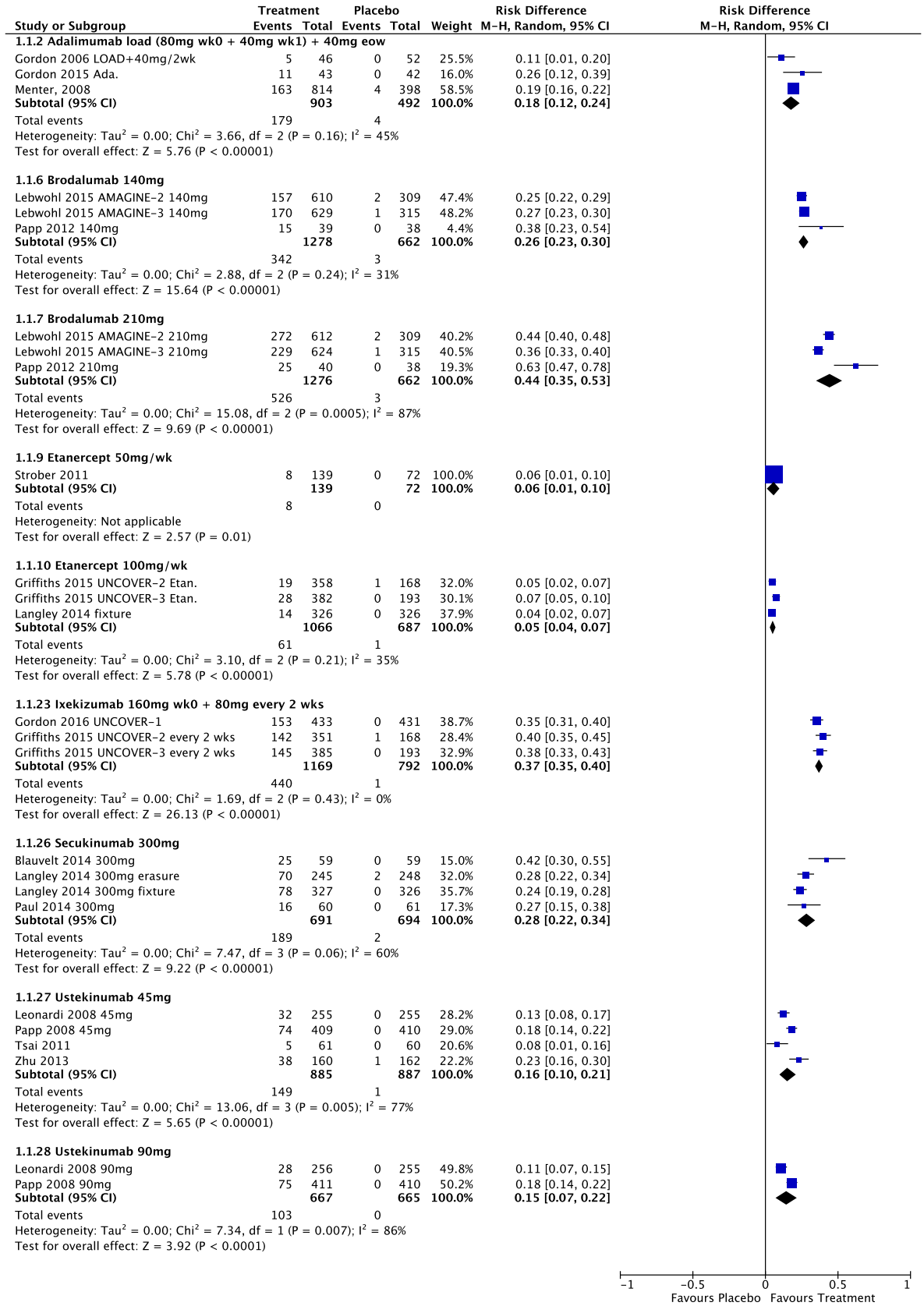
In the present review, anti-IL-17 drugs performed very well. Ixekizumab presented the higher RD in the primary outcome (PASI 75), while brodalumab (210 mg) performed well, following ixekizumab on the primary outcome and achieving a higher RD on both secondary outcomes (PASI 90 and PASI 100). Nevertheless, as the CI overlapped, ixekizumab, brodalumab 210 mg, and secukinumab should be considered as having similar performances, even with different RDs. On the other hand, ixekizumab and brodalumab 210 mg were superior to all remaining drugs, with the exception of infliximab and secukinumab, when PASI 75 was the outcome (no overlapping of the CI).

When analyzing PASI 90 as an outcome, brodalumab (both doses) had the higher RD, but the performance of ixekizumab was similar to the overlapped CI. Nevertheless, it is important to emphasize that only one brodalumab study [11] (both dosages) could be identified that used PASI 90 as an outcome; however, a low number of patients were enrolled in this study. Therefore, the results regarding brodalumab at this particular outcome should be considered with caution. Ixekizumab was also the best performing drug, and was superior than all the remaining approved medications (no overlapping of the CI). Ixekizumab also showed the highest RD among approved drugs at PASI 100, and was superior to all remaining medications (no overlapping of the CI) when drugs were compared with placebo. At the same outcome, brodalumab 210 mg achieved a higher RD than ixekizumab, but effectiveness was comparable as the CI overlapped. The number of studies included in the analysis of PASI 100 outcome for brodalumab was higher, enrolling more than 1200 patients, which makes these findings more robust than the findings for brodalumab when PASI 90 was analyzed.

Among the newer small molecule inhibitor drugs, tofacitinib, an anti-Janus kinase 1, also performed well at a dose of 10 mg, being superior to lower-dose etanercept when compared with placebo, and comparable to higher-dose etanercept and adalimumab and low-dose brodalumab (overlapping CI), considering PASI 75 as the primary outcome.

On the other hand, apremilast, an anti-phosphodiesterase 4 drug, performed poorly. Nevertheless, it is comparable to low-dose etanercept (50 mg/week) and low-dose tofacitinib (5 mg) at the primary outcome. PASI 90 and 100 analyses could not be performed for apremilast as no studies that could supply the appropriate data were identified.

In accordance with previous meta-analyses [16, 52], infliximab also performed well among approved biologics. At both dosages (45 and 90 mg), ustekinumab had basically the same performance, which may be explained by the fact that the included studies did not stratify the analysis by patient weight and dosage. The order of


Treatment
Placebo
Risk Difference
Risk Difference
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.2 Adalimumab load (80mg wk0 + 40mg wk1) + 40mg eow
Gordon 2006 LOAD+40mg/2wk 5 46 0 52 25.5% 0.11 [0.01, 0.20]
Gordon 2015 Ada. 11 43 0 42 16.0% 0.26 [0.12, 0.39]
Menter, 2008 163 814 4 398 58.5% 0.19 [0.16, 0.22]
Subtotal (95% CI) 903 492 100.0% 0.18 [0.12, 0.24]
Total events 179 4
Heterogeneity: Tau² = 0.00; Chi² = 3.66, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 5.76 (P < 0.00001)
1.1.6 Brodalumab 140mg
Lebwohl 2015 AMAGINE-2 140mg 157 610 2 309 47.4% 0.25 [0.22, 0.29]
Lebwohl 2015 AMAGINE-3 140mg 170 629 1 315 48.2% 0.27 [0.23, 0.30]
Papp 2012 140mg 15 39 0 38 4.4% 0.38 [0.23, 0.54]
Subtotal (95% CI) 1278 662 100.0% 0.26 [0.23, 0.30]
Total events 342 3
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 15.64 (P < 0.00001)
1.1.7 Brodalumab 210mg
Lebwohl 2015 AMAGINE-2 210mg 272 612 2 309 40.2% 0.44 [0.40, 0.48]
Lebwohl 2015 AMAGINE-3 210mg 229 624 1 315 40.5% 0.36 [0.33, 0.40]
Papp 2012 210mg 25 40 0 38 19.3% 0.63 [0.47, 0.78]
Subtotal (95% CI) 1276 662 100.0% 0.44 [0.35, 0.53]
Total events 526 3
Heterogeneity: Tau² = 0.00; Chi² = 15.08, df = 2 (P = 0.0005); I² = 87%
Test for overall effect: Z = 9.69 (P < 0.00001)
1.1.9 Etanercept 50mg/wk
Strober 2011 8 139 0 72 100.0% 0.06 [0.01, 0.10]
Subtotal (95% CI) 139 72 100.0% 0.06 [0.01, 0.10]
Total events 8 0
Heterogeneity: Not applicable
Test for overall effect: Z = 2.57 (P = 0.01)
1.1.10 Etanercept 100mg/wk
Griffiths 2015 UNCOVER-2 Etan. 19 358 1 168 32.0% 0.05 [0.02, 0.07]
Griffiths 2015 UNCOVER-3 Etan. 28 382 0 193 30.1% 0.07 [0.05, 0.10]
Langley 2014 fixture 14 326 0 326 37.9% 0.04 [0.02, 0.07]
Subtotal (95% CI) 1066 687 100.0% 0.05 [0.04, 0.07]
Total events 61 1
Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 5.78 (P < 0.00001)
1.1.23 Ixekizumab 160mg wk0 + 80mg every 2 wks
Gordon 2016 UNCOVER-1 153 433 0 431 38.7% 0.35 [0.31, 0.40]
Griffiths 2015 UNCOVER-2 every 2 wks 142 351 1 168 28.4% 0.40 [0.35, 0.45]
Griffiths 2015 UNCOVER-3 every 2 wks 145 385 0 193 32.9% 0.38 [0.33, 0.43]
Subtotal (95% CI) 1169 792 100.0% 0.37 [0.35, 0.40]
Total events 440 1
Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 26.13 (P < 0.00001)
1.1.26 Secukinumab 300mg
Blauvelt 2014 300mg 25 59 0 59 15.0% 0.42 [0.30, 0.55]
Langley 2014 300mg erasure 70 245 2 248 32.0% 0.28 [0.22, 0.34]
Langley 2014 300mg fixture 78 327 0 326 35.7% 0.24 [0.19, 0.28]
Paul 2014 300mg 16 60 0 61 17.3% 0.27 [0.15, 0.38]
Subtotal (95% CI) 691 694 100.0% 0.28 [0.22, 0.34]
Total events 189 2
Heterogeneity: Tau² = 0.00; Chi² = 7.47, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 9.22 (P < 0.00001)
1.1.27 Ustekinumab 45mg
Leonardi 2008 45mg 32 255 0 255 28.2% 0.13 [0.08, 0.17]
Papp 2008 45mg 74 409 0 410 29.0% 0.18 [0.14, 0.22]
Tsai 2011 5 61 0 60 20.6% 0.08 [0.01, 0.16]
Zhu 2013 38 160 1 162 22.2% 0.23 [0.16, 0.30]
Subtotal (95% CI) 885 887 100.0% 0.16 [0.10, 0.21]
Total events 149 1
Heterogeneity: Tau² = 0.00; Chi² = 13.06, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 5.65 (P < 0.00001)
1.1.28 Ustekinumab 90mg
Leonardi 2008 90mg 28 256 0 255 49.8% 0.11 [0.07, 0.15]
Papp 2008 90mg 75 411 0 410 50.2% 0.18 [0.14, 0.22]
Subtotal (95% CI) 667 665 100.0% 0.15 [0.07, 0.22]
Total events 103 0
Heterogeneity: Tau² = 0.00; Chi² = 7.34, df = 1 (P = 0.007); I² = 86%
Test for overall effect: Z = 3.92 (P < 0.0001)
-1
-0.5
0
0.5
1
Favours Placebo
Favours Treatment

◀**Fig. 6** Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 100% response rate of biologic and small molecule inhibitor therapies for moderate to severe psoriasis in randomized, placebo-controlled trials. *CI* confidence interval, *M-H* Mantel–Haenszel, *EOW* every other week, *df* degrees of freedom

effectiveness, measured by RD, in which infliximab 5 mg/kg, ustekinumab 90 mg, ustekinumab 45 mg, adalimumab, etanercept 100 mg, and etanercept 50 mg were positioned in this meta-analysis, was the same as that reported by Schmitt et al. in a recent meta-analysis [16]. Using a different meta-analysis methodology (Bayesian, network meta-analysis), Reich et al. [54] identified a similar ranking with regard to the chance of a PASI 75 response, with the exception of the etanercept 100 mg response rate, which was not contemplated in the study. It is important to note that a rank of RD is somewhat deceiving as the CI may overlap. Nevertheless, the concordance of the rank seen in the work of Reich et al., which used a Bayesian analysis, and the RD rank found in this work, indicates a consistent trend [54].

It is important to emphasize that the objective of this meta-analysis was to compare active treatments against placebo. A limitation to this work is that it is not inherently designed to make indirect comparisons of active treatments and, as previously stated, overlapping CIs determine that drugs are equally effective. A further Bayesian network meta-analysis should be performed to address this issue and, eventually, allow indirect comparisons to rank active treatments.

Considering approved doses and PASI 75 as an outcome, heterogeneity inside each group has been found to be low ($I^2 \leq 40\%$) or moderate ($I^2 > 40$, $\leq 60\%$) [20] for all comparisons, except for ustekinumab 90 mg ($I^2 = 67\%$), brodalumab ($I^2 = 71\%$), and ixekizumab ($I^2 = 64\%$). The heterogeneity of ustekinumab at a higher dose may be explained by the grouped analysis of populations of different weights (>100 or <100 kg). After performing sensitivity analysis, the heterogeneity found in the brodalumab subgroup was found to be due to a phase II study [11] with a low number of participants; heterogeneity for the brodalumab subgroup decreased to 48% after exclusion of this particular study. No reason was found to account for heterogeneity in the ixekizumab group, neither in meta-regression (Online Resource 6) nor in the sensitivity analysis. Heterogeneity of the pooled overall efficacy of active treatments compared with placebo was high, but this intergroup heterogeneity was expected due to the number of different treatments analyzed and the unit of analysis error. Meta-regression was performed to analyze the impact of PASI score prior to treatment, duration of psoriasis, or previous use of biologic or small molecule inhibitor drugs on heterogeneity. None of the pre-defined variables influenced the results. Random-effects meta-analysis was performed as an attempt to incorporate heterogeneity.

Risk of bias assessment showed a small percentage of high risk of bias categorization among the included studies. On the other hand, 50% of the studies did not explicitly disclose the random sequence generation or allocation concealment (selection bias) well enough, although being categorized as having an unclear risk of bias.

The funnel plot of the primary outcome (PASI 75) was interpreted as being symmetrical and therefore it is less likely that publication bias may have been present. Larger studies are based on the mean RD at the top of the plot. The lack of smaller studies is responsible for the empty space found at the bottom of the plot, but one can assume this is due to the inclusion and exclusion criteria of the systematic review (only placebo-controlled RCTs). Two smaller studies are found on the plot but they are symmetrically positioned on each side of the mean RD. PASI 90 and 100 funnel plot were asymmetric, and both showed smaller studies to be highly efficacious, resulting in a plot that had an empty lower left quadrant. One explanation for this asymmetry is that studies that evaluated less effective drugs may have chosen not to report PASI 90 and 100, while studies evaluating more effective drugs tend to report these outcomes. Therefore, publication bias cannot be ruled out.

The time of outcomes assessment may also be a limitation in the interpretation of the results. As the majority of RCTs used a 12-week timeframe, extrapolation of the results for longer periods may not be appropriate.

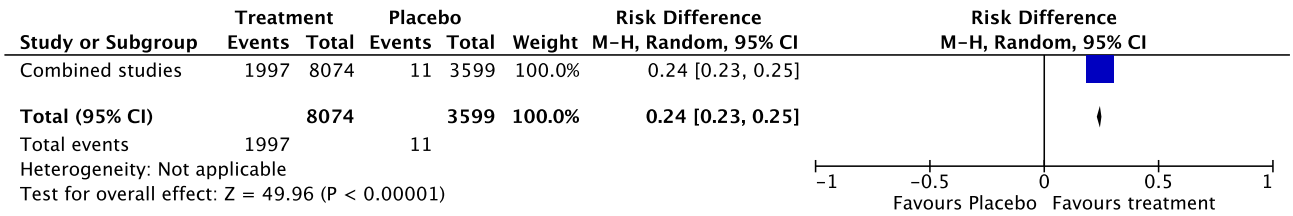


Fig. 7 Meta-analysis (random-effects model) of the Psoriasis Area and Severity Index 100% response rate of all treatments combined for moderate to severe psoriasis in randomized, placebo-controlled trials (overall pooled effect). *CI* confidence interval, *M-H* Mantel–Haenszel

5 Conclusions

This meta-analysis showed that biologics and small molecule inhibitors are highly effective for the treatment of moderate to severe psoriasis, and that anti-IL-17 drugs have the same, or even greater, efficacy than anti-tumor necrosis factor (TNF) and anti-IL-12/23 drugs when PASI 75 or PASI 90 are used as the outcome. If PASI 100 is used as the outcome, newer drugs such as anti-IL-17 tend to perform better than anti-TNF and anti-IL-12/23 drugs. As the number of newer biologic and small molecule inhibitor drugs increases, the efficacy of these drugs compared with placebo, found in this meta-analysis, can help doctors to choose what the most appropriate treatment is for each particular patient.

Compliances with Ethical Standards

Funding None.

Conflict of interest André Vicente Esteves de Carvalho has received research support and is a speaker/advisory board program participant receiving honoraria for Abvie, Jansen, Novartis and Leo Pharma. Rodrigo Pereira Duquia, Bernardo Lessa Horta and Renan Rangel Bonamigo have no conflicts of interest.

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