Biologic Therapy for Psoriatic Arthritis or Moderate to Severe Plaque Psoriasis: Systematic Review with Pairwise and Network Meta-Analysis

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Abstract: *Background*: A comprehensive assessment of the risk-benefit profile of biologic agents in psoriasis is lacking. We conducted a network meta-analysis of randomized trials on biologic agents in psoriasis.

Methods: Trials on biologic agents in psoriasis (including psoriatic arthritis) were sought in several databases. Endpoints were ≥75% Reduction in the Psoriasis Area and Severity Index (PASI75), ≥20% improvement in the American College of Rheumatology core set of outcomes (ACR20), serious adverse events (SAE), and adverse events (AE) at the longest available non-cross-over follow-up. Random-effect methods were used to obtain pairwise and network pooled estimates.

Results: A total of 52 trials with 17,617 patients and 9 different biologic agents included, with 52% affected by psoriatic arthritis. After an average follow-up of 18 weeks, treatment with placebo was associated with a 5.9% (5.2%-6.6%) rate of PASI75, 17.4% (15.1%-19.6%) of ACR20, 2.4% (1.9%-2.8%) of SAE, and 51.8% (50.2%-53.4%) of AE. Several biologic agents provided higher PASI75 rates than placebo, with golimumab yielding the most favorable results (relative risk [RR]=14.02 [6.85-17.11]). Accordingly, several agents provided higher ACR20 rates than placebo, with infliximab yielding the most favorable results (RR=3.02 [1.67-4.55]). Overall, rates of SAE and AE were higher for several but not all biologic agents versus placebo, with golimumab being associated with the most favorable results for SAE (RR=0.40 [0.11-1.41]), and abatacept for AE (RR=1.00 [0.79-1.22]).

Conclusions: Efficacy and safety of biologic agents for psoriasis differ, and clinicians should bear in mind these features to maximize safety and efficacy in the individual patient.

Keywords: Meta-analysis, Mixed treatment comparison, Network meta-analysis, Plaque psoriasis, Psoriasis, Psoriatic arthritis, Systematic review.

INTRODUCTION

Psoriasis, whenever involving a sizable body surface of a patient or being associated with arthritis, represents a major cause of morbidity worldwide [1]. Despite the limited advancements in the management of this condition which occurred in prior decades, novel treatments have been tested in the last years, with very favorable results for many biologic agents with disease modifying properties [2]. These includes agents which block tumor necrosis factor-α (TNF-α), as well as anti-lymphocyte T, anti-interleukin-12/23 (IL-12/23), and anti-interleukin-17 (IL-17) agents. Clinicians wishing to decide which treatment is better, in terms of safety or efficacy, are however facing a major challenge, as most studies were placebo-controlled trials with moderate size, and few meaningfully powerful comparative effectiveness and safety trials are available [3].

Systematic reviews incorporating pairwise and network meta-analysis may successfully synthesize the evidence base on a specific clinical issue, providing precise overall and interaction effect estimates [4]. Indeed, three mixed treatment comparisons have already been reported on this topic [5-7], but were limited by the too narrow focus on a specific subset of studies, or the lack of inclusion of the many trials which have been published in the last few years. Specifically, Migliore *et al.* included four trials [6], Lin and colleagues 17 [5], and Reich *et al.* 20 [7].

We thus performed an updated and comprehensive systematic review on randomized trials focusing on biologic therapy in patients with psoriasis or psoriatic arthritis, exploiting pairwise and network meta-analytic techniques as well.

METHODS

Design

This review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses (PRISMA) guidelines [8]. All reviewing activities were performed independently by two experienced reviewers, with divergences solved after consensus.

Search

Pertinent studies were searched in MEDLINE/PubMed according to Biondi-Zoccai *et al*'s string for controlled clinical trials [9], and exploiting the following terms: abatacept; adalimumab; anakinra; briakinumab; brodalumab; certolizumab; etanercept; golimumab; infliximab; ixekizumab; psoriasis; rituximab; tocilizumab; ustekinumab (see also Appendix for the detailed strategy). In addition, CENTRAL, Google Scholar, and Scopus were searched for suitable studies. The search was last updated on September 21, 2013. No language restriction was enforced.

Selection

Initially retrieved citations were screened at the title/abstract level and then retrieved as full texts if potentially pertinent. Full reports were included if reporting on patients with psoriasis receiving biologic agents, and included in a randomized trial. Studies were excluded if not based on random allocation, duplicates, lacking details on clinical efficacy or safety outcomes, including anti-IL-17 agents (whose evidence base is still preliminary and are still under pre-registration investigation), or focusing on efalizumab (which was discontinued due to the risk of fatal brain infarctions associated with its usage) [10].

Abstraction and Validity Appraisal

Key baseline, procedural and outcome data were systematically retrieved, focusing specifically on efficacy and safety outcomes. As efficacy outcomes, we focused on the binary rates of reduction ≥75% in the Psoriasis Area and Severity Index (PASI75), and improvement ≥20% in the American College of Rheumatology core set of outcomes (ACR20), both at the longest available follow-up. As safety outcomes, we focused on serious adverse events (SAE), and adverse events (AE), both at the longest available follow-up. The internal validity of shortlisted studies was appraised focusing on design features, including study setting, blinding, and type of comparator.

Analysis

Categorical variables are described as counts or %. Pairwise meta-analysis was performed with RevMan (The Cochrane Collaboration, Copenhagen, Denmark) within a frequentist framework with the DerSimonian-Laird random-effect model, pooling risk ratios (95% confidence intervals). Conversely, network meta-analysis was performed with WinBUGS (MRC Biostatistics Unit, Cambridge, UK) within a Bayesian framework with a random-effect binomial likelihood hierarchical model, sampling effect estimates with Markov chain Monte Carlo (MCMC) methods, computing risk ratios (95% credibility intervals) and probability of being the best treatment for each agent [11]. These analyses were based on a 50,000-run training set and a 150,000-run inferential set. Convergence was appraised with the Gelman-Rubin statistic. Model fit for Bayesian inference was appraised with the deviance information criterion (DIC), comparing random-effect and fixed-effect models reported in detail by Greco *et al.* [12].

Using RevMan within a frequentist framework, kairwise heterogeneity was appraised using chi-squared test, and inconsistency with I^2. Consistency between direct estimates (which are directly based on head-to-head randomized comparisons) and indirect estimates (which rely on the exchangeability assumption) was instead appraised by comparing consistency and inconsistency models as computed with WinBUGS in a Bayesian framework [12]. Specifically, consistency models assume that no substantial variation in treatment effect between pairwise contrasts, whereas an inconsistency model does not assume underlying similarity of direct and indirect effects. Accordingly, comparing results stemming from consistency and inconsistency models is a suitable test of the exchangeability and consistency assumptions [13]. Small study effects were appraised with funnel plot inspection using RevMan within a frequentist framework.

RESULTS

Reviewing Process

From an initial set of 21,475 citations, 21,286 were excluded at the title/abstract screening stage (Figure **1**). Thereafter, 189 articles were appraised as full reports, leading to the inclusion of a total of 52 trials and 17,617 patients, including 9 different biologic agents (references of included and excluded studies are available from the corresponding author upon request). The main reason for exclusion of full reports was duplication of trial data, followed by observational design, and meta-analysis as study type.

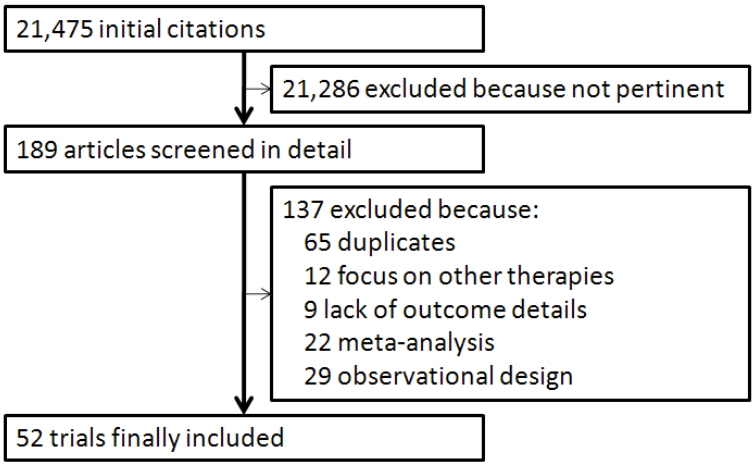


Figure 1: Review profile.

Evidence Base

The included studies compared, with variable assortments, placebo and 11 different pharmacologic agents: abatacept, acitretin, adalimumab, alefacept, briakinumab, certolizumab, etanercept, golimumab, infliximab, methotrexate, and ustekinumab (Table **1**; Figure **2**). Specifically, 1 trial (170 patients) compared abatacept versus placebo, 7 trials (2044) adalimumab versus placebo or control therapy, 1 (100) adalimumab versus etanercept versus infliximab, 1 (271) adalimumab versus methotrexate versus placebo, 2 (702) alafacept versus placebo, 2 (1645) briakinumab versus placebo, 2 (697) briakinumab versus etanercept versus placebo, 1 (317) briakinumab versus methotrexate, 1 (409) certolizumab pegol versus placebo, 8 (2144) etanercept versus placebo, 1 (60) etanercept versus acitretin, 1 (60) etanercept plus acitretin versus etanercept versus acitretin, 1 (478) etanercept plus methotrexate versus etanercept alone, 1 (41) etanercept plus methotrexate versus etanercept plus cyclosporine, 1 (405) golimumab versus placebo, 9 (2006) infliximab versus placebo, 1 (868) infliximab versus methotrexate, 1 (115) infliximab plus methotrexate versus methotrexate, 7 (3358) ustekinumab versus placebo, and 1 (903) ustekinumab versus etanercept.

Pairwise Meta-Analysis

Pairwise meta-analysis for PASI75 (Figure **3**) showed that adalimumab was significantly superior to placebo (RR=7.68 [4.27-13.80], p<0.001, I^2=67%). The same applied to alefacept (RR=2.28 [1.53-3.40],

Table 1: Key Biologic Agents Tested for the Treatment of Moderate to Severe Psoriasis or Psoriatic Arthritis in Randomized Clinical Trials

Features	Agent	Manufacturer	Route of administration	Commonly used dosages and regimens in the included studies
Anti-IL-12/23 agents	Briakinumab	Abbott	SC injection	200 mg (or 100 mg) at weeks 0 and 4 followed by 100 mg at week 8
	Ustekinumab	Centocor	SC injection	90 mg (or 45 mg) at week 0, week 4, and every 12 weeks thereafter
Anti-T-cell agents	Abatacept	Bristol Myers Squibb	SC injection	30/10 mg/kg (2 initial doses of 30 mg/kg, followed by 10 mg/kg); 10 mg/kg (or 3 mg/kg) on days 1, 15, and 29 and then once every 28 days
	Alefacept	Astellas	IM injection	15 mg qw; 10 mg qw
Anti-TNF-α agents	Adalimumab	Abbott	SC injection	80 mg eow; 80 mg loading followed by 40 mg eow; 40 mg qw; 40 mg eow
	Certolizumab pegol	UCB	SC injection	400 mg qm; 400 mg eow; 200 mg eow
	Etanercept	Amgen	SC injection	50 mg biw; 50 mg qw; 25 mg biw; 25 mg qw; 25 mg eow
	Golimumab	Centocor	SC injection	100 mg qm; 50 mg qm
	Infliximab	Centocor	IV infusion	10 mg/kg (or 5 mg/kg or 3 mg/kg) at weeks 0, 2, and 6, then q6-8w

Biw=twice weekly; eow=every other week; IM=intramuscular; IV=intravenous; q6-8w=every 6-8 weeks; qm=every month; qw=every week; SC=subcutaneous.

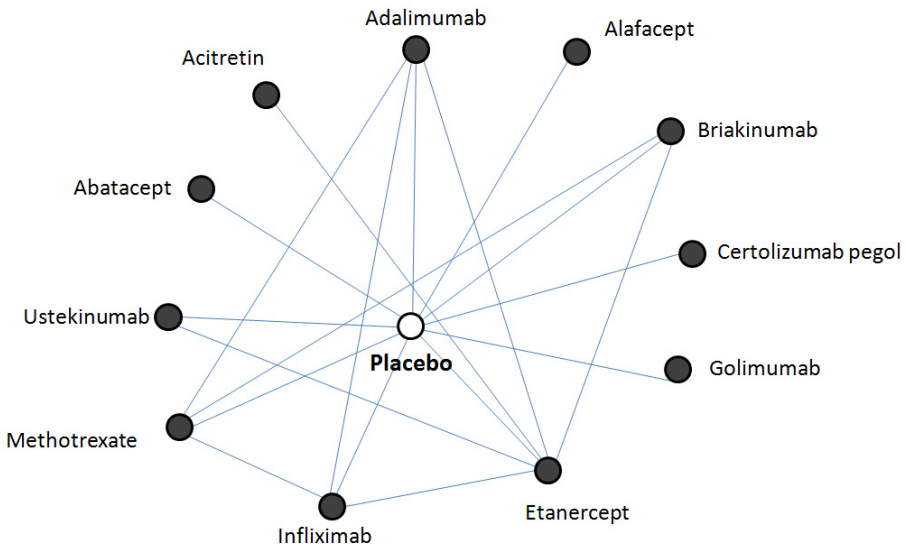


Figure 2: Evidence network.

p<0.001, I^2=0), briakinumab (RR=16.53 [11.51-23.74], p<0.001, I^2=0), etanercept (RR=7.76 [5.94-10.13], p<0.001, I^2=0), infliximab (RR=14.52 [6.95-30.34], p<0.001, I^2=59%), and ustekinumab (RR=11.00 [6.65-18.18], p<0.001, I^2=73%). However, funnel plot inspection suggested the presence of small study effects for PASI75 (Figure **4**). Pairwise meta-analysis for ACR20 (Figure **1A**) showed that adalimumab was significantly superior to placebo (RR=3.36 [2.21-5.10], p<0.001, I^2=21%). The same applied to etanercept (RR=3.39 [2.60-6.13], p<0.001, I^2=0), and infliximab (RR=4.13 [2.69-6.32], p<0.001, I^2=4%), without clear evidence of small study effects (Figure **2A**).

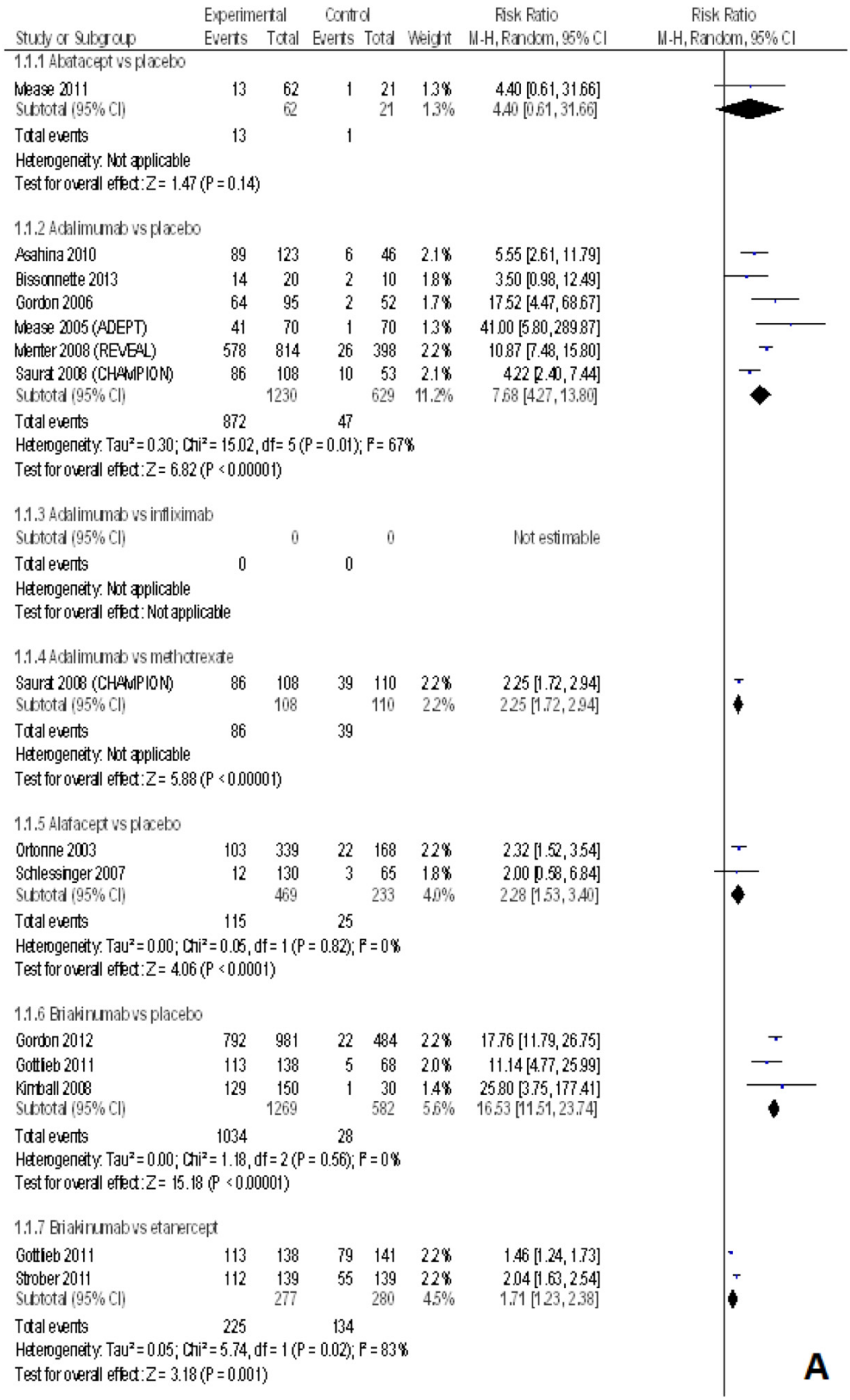
Pairwise meta-analysis for SAE (Figure **3A**) showed that adalimumab had a similar safety profile to placebo (RR=0.92 [0.52-1.63], p=0.79, I^2=0). The same applied to briakinumab (RR=1.21 [0.57-2.57], p=0.62, I^2=1%), etanercept (RR=1.21 [0.57-2.56], p=0.62, I^2=2), and ustekinumab (RR=0.74 [0.42-1.30], p=0.29, I^2=0). Conversely, infliximab was associated with an increased risk of SAE (RR=1.61 [1.14-2.25], p=0.006, I^2=0). Small study effects were not apparent at funnel plot inspection (Figure **4A**). Finally, pairwise meta-analysis for AE showed that adalimumab had a similar safety profile to placebo (RR=0.98 [0.87-1.10], p=0.75, I^2=61%) (Figure **5A**). The same applied to briakinumab (RR=1.18 [0.99-1.40], p=0.06, I^2=33%), etanercept (RR=1.07 [0.94-1.23], p=0.31, I^2=0), or ustekinumab (RR=1.03 [0.96-1.10], p=0.45, I^2=0). Conversely, AE were significantly more frequent with infliximab (RR=1.17 [1.08-1.28], p<0.001, I^2=0). Funnel plot for AE did not suggest the presence of small study effects (Figure **6A**).

Network Meta-Analysis

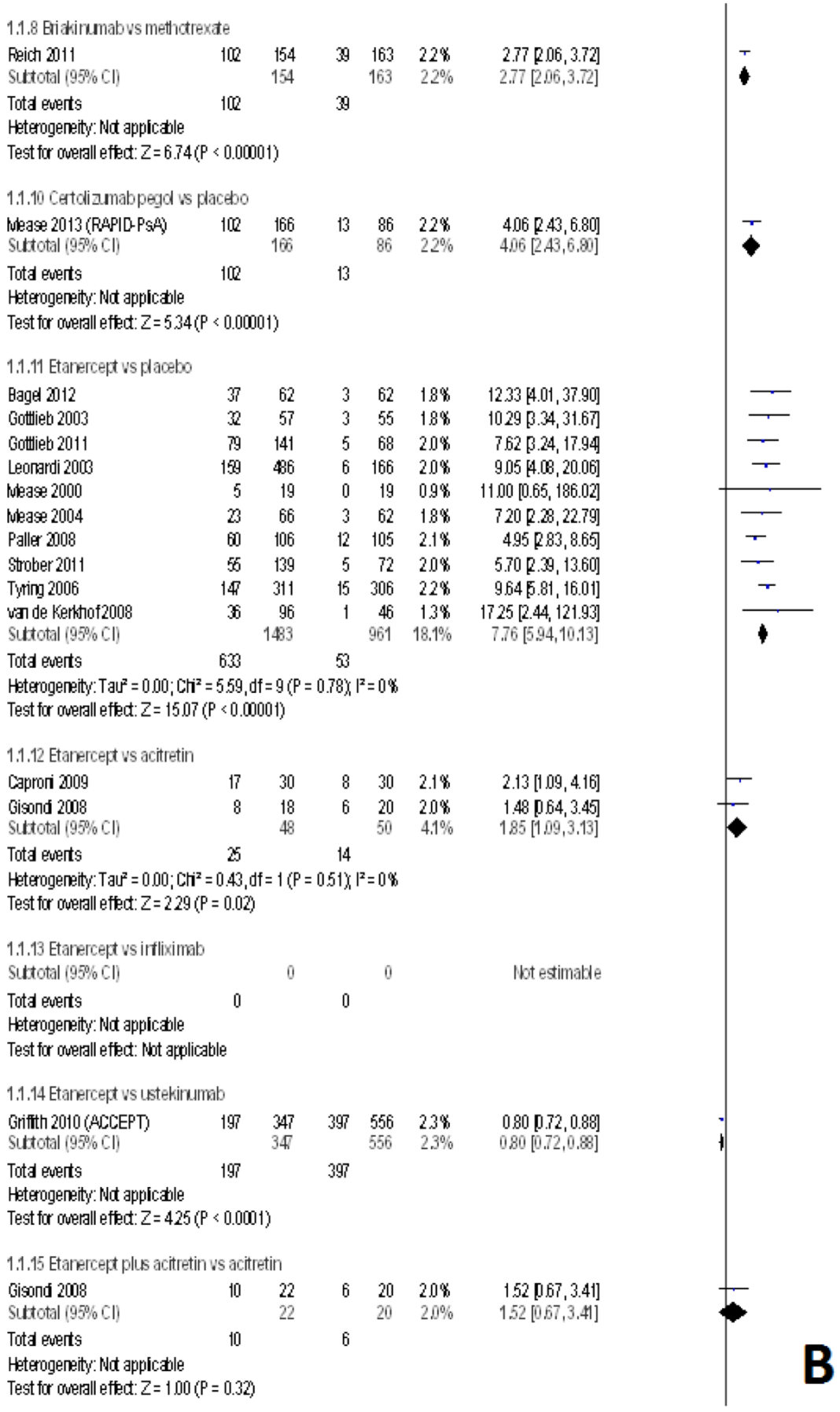
Network meta-analysis, exploiting both direct and indirect agent-level comparisons, showed that several biologic agents provided higher PASI75 rates than placebo (Table **3**), with golimumab yielding the most favorable results (RR=14.02 [6.85-17.11]). Accordingly, several agents provided higher ACR20 rates than placebo (Table **4**), with infliximab yielding the most favorable results (RR=3.02 [1.67-4.55]). Overall, rates of SAE and AE were higher for several but not all biologic agents versus placebo (Tables **5** and **6**), with golimumab being associated with the most favorable results for SAE (RR=0.40 [0.11-1.41]), and abatacept for AE (RR=1.00 [0.79-1.22]).

DISCUSSION

This review has several key implications: first, biologic therapy for moderate to severe psoriasis or psoriatic arthritis is associated with clear and clinically meaningful benefits in terms of psoriasis and arthritis burden in comparison to placebo; second, adverse events are increased, at least by some classes of biologic agents, but the overall balance is not clearly in favor of placebo given the occurrence of disease-related adverse events when the condition is not adequately controlled; third, remarkable differences in safety and efficacy profile are evident between the different classes of biologic agents and even between individual agents in the same class; thus, biologic therapy should be considered in the management of moderate to severe psoriasis or psoriatic arthritis, with class and agent choice based on the specific patient risk profile, clinical history, and goal of therapy.


Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 Abatacept vs placebo
Mease 2011 13 62 1 21 1.3% 4.40 [0.61, 31.66]
Subtotal (95% CI) 62 21 1.3% 4.40 [0.61, 31.66]
Total events 13 1
Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)
1.1.2 Adalimumab vs placebo
Asahina 2010 89 123 6 46 2.1% 5.55 [2.61, 11.79]
Bissonnette 2013 14 20 2 10 1.8% 3.50 [0.98, 12.49]
Gordon 2006 64 95 2 52 1.7% 17.52 [4.47, 68.67]
Mease 2005 (ADEPT) 41 70 1 70 1.3% 41.00 [5.80, 289.87]
Menter 2008 (REVEAL) 578 814 26 398 2.2% 10.87 [7.48, 15.80]
Saurat 2008 (CHAMPION) 86 108 10 53 2.1% 4.22 [2.40, 7.44]
Subtotal (95% CI) 1230 629 11.2% 7.68 [4.27, 13.80]
Total events 872 47
Heterogeneity: Tau² = 0.30; Chi² = 15.02, df = 5 (P = 0.01); I² = 67%
Test for overall effect: Z = 6.82 (P < 0.00001)
1.1.3 Adalimumab vs infliximab
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
1.1.4 Adalimumab vs methotrexate
Saurat 2008 (CHAMPION) 86 108 39 110 2.2% 2.25 [1.72, 2.94]
Subtotal (95% CI) 108 110 2.2% 2.25 [1.72, 2.94]
Total events 86 39
Heterogeneity: Not applicable
Test for overall effect: Z = 5.88 (P < 0.00001)
1.1.5 Alafacept vs placebo
Ortonne 2003 103 339 22 168 2.2% 2.32 [1.52, 3.54]
Schlessinger 2007 12 130 3 65 1.8% 2.00 [0.58, 6.84]
Subtotal (95% CI) 469 233 4.0% 2.28 [1.53, 3.40]
Total events 115 25
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)
1.1.6 Briakinumab vs placebo
Gordon 2012 792 981 22 484 2.2% 17.76 [11.79, 26.75]
Gottlieb 2011 113 138 5 68 2.0% 11.14 [4.77, 25.99]
Kimball 2008 129 150 1 30 1.4% 25.80 [3.75, 177.41]
Subtotal (95% CI) 1269 582 5.6% 16.53 [11.51, 23.74]
Total events 1034 28
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 15.18 (P < 0.00001)
1.1.7 Briakinumab vs etanercept
Gottlieb 2011 113 138 79 141 2.2% 1.46 [1.24, 1.73]
Strober 2011 112 139 55 139 2.2% 2.04 [1.63, 2.54]
Subtotal (95% CI) 277 280 4.5% 1.71 [1.23, 2.38]
Total events 225 134
Heterogeneity: Tau² = 0.05; Chi² = 5.74, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 3.18 (P = 0.001)
A

(Figure 3). Continued.



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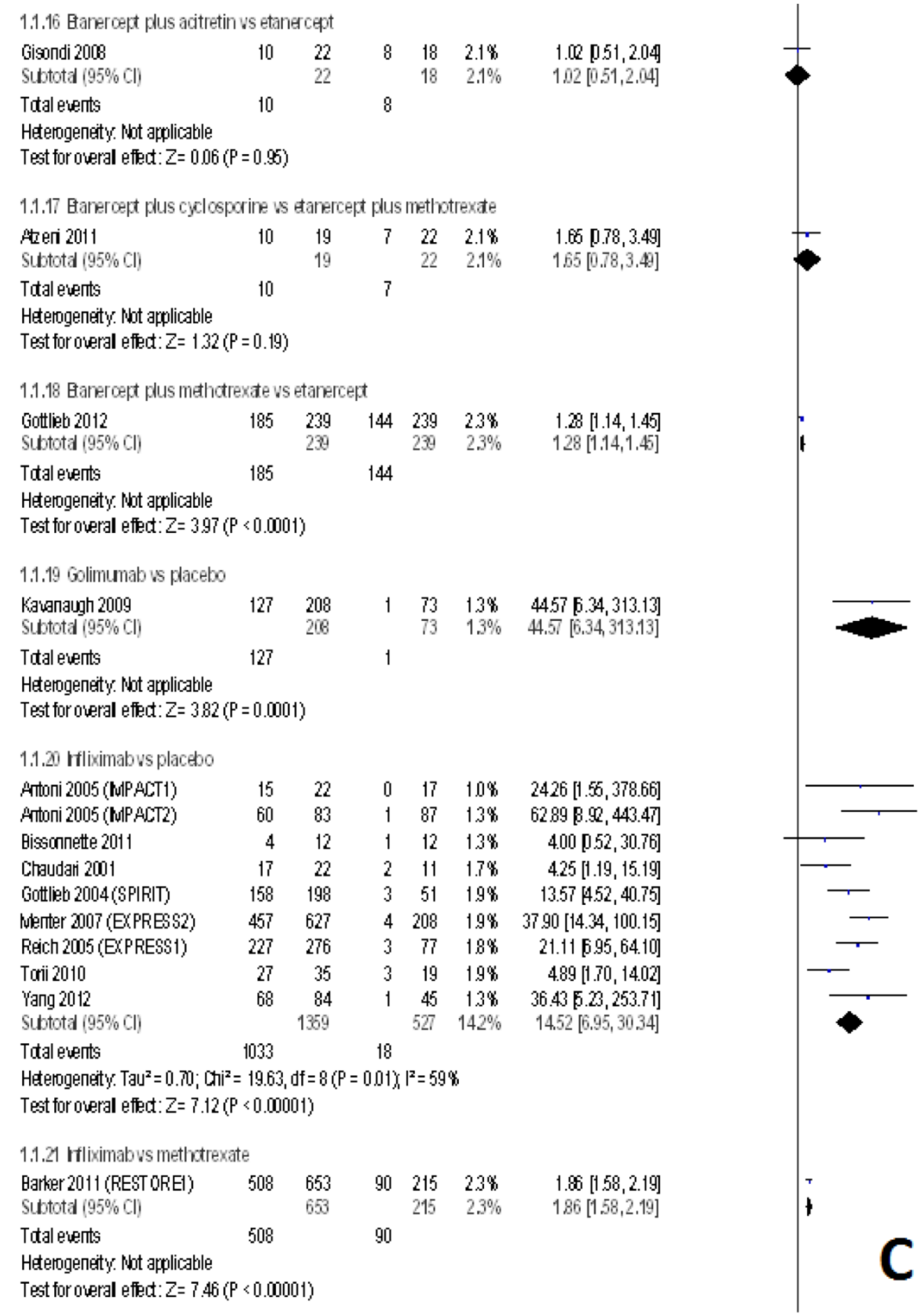

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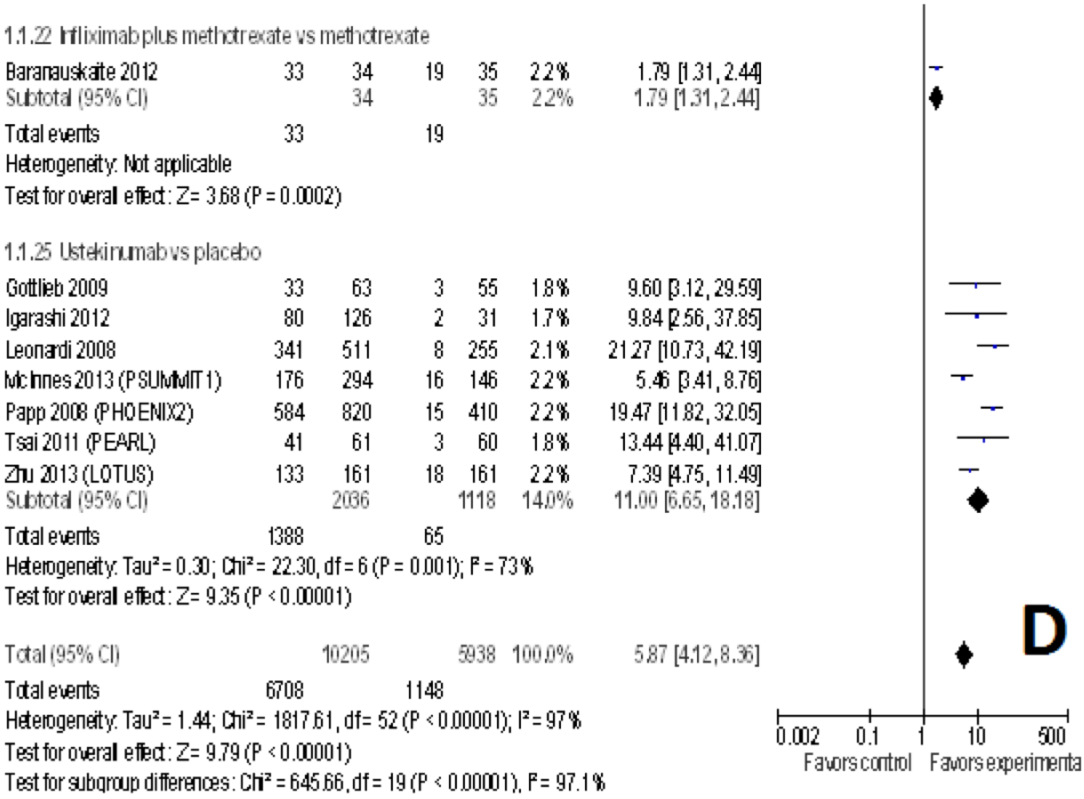

Figure 3: (panels **A**, **B**, **C**, and **D**). Forest plot for reduction ≥75% in the Psoriasis Area and Severity Index (PASI75). CI=confidence interval; df=degrees of freedom; M-H=Mantel-Haenszel.

The burden of psoriasis is very important and not limited to few developed countries. Given its chronicity and phasicity, psoriasis may prove clinically challenging, especially when associated with arthritis or involving a large part of the body surface or the nails [14]. Given the improvement in our understanding of its pathophysiology, including the preminent role of inflammation, and the setbacks of topical therapy or phototherapy in severe cases, there is an ongoing quest for effective and safe systemic therapies for psoriasis. This momentum has lead to the successful testing of several anti-inflammatory agents, and, subsequently, immune-modulating agents, typically called biologics [15].

Biologics belong to four broad categories, which correspond to the main inflammation mechanisms involved in this condition [16-19]. Agents blocking the IL-12/23 pathway, such as briakinumab and ustekinumab, anti-IL-17 agents, such as brodalumab, ixekinumab, and secukinumab, drugs which have inhibitory effects on T lymphocytes, such as abatacept and alefacept, and anti-TNF-α agents, such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Our work, which comprehensively pools the evidence on biologic agents and compare them versus placebo, acitretin, and methotrexate, has important implications for practicing physicians and patients. Under the hypothesis that each agent has, even within the same class, a unique and individual risk-benefit profile, we suggest that the most effective agent in patients with moderate to severe plaque psoriasis is golimumab, whereas the most effective one in subjects with psoriatic arthritis is infliximab. Conversely, severe adverse events were fewer with golimumab, while the occurrence of any adverse event was less likely with abatacept. However, differences between individual agents were often not large and credible. Nonetheless, decision-makers should bear in mind these agent-specific risk-benefit profiles to maximize response rates and minimize complications of systemic therapy for psoriasis.

This work is not the first in its kind, but actually builds upon prior network meta-analyses, yet substantially expanding their findings. Indeed, Lin *et al*. already showed, analyzing 17 trials on moderate to severe plaque psoriasis and 5 biologic agents, that ustekinumab was more efficacious than adalimumab, etanercept, and alefacept, but not infliximab [5].

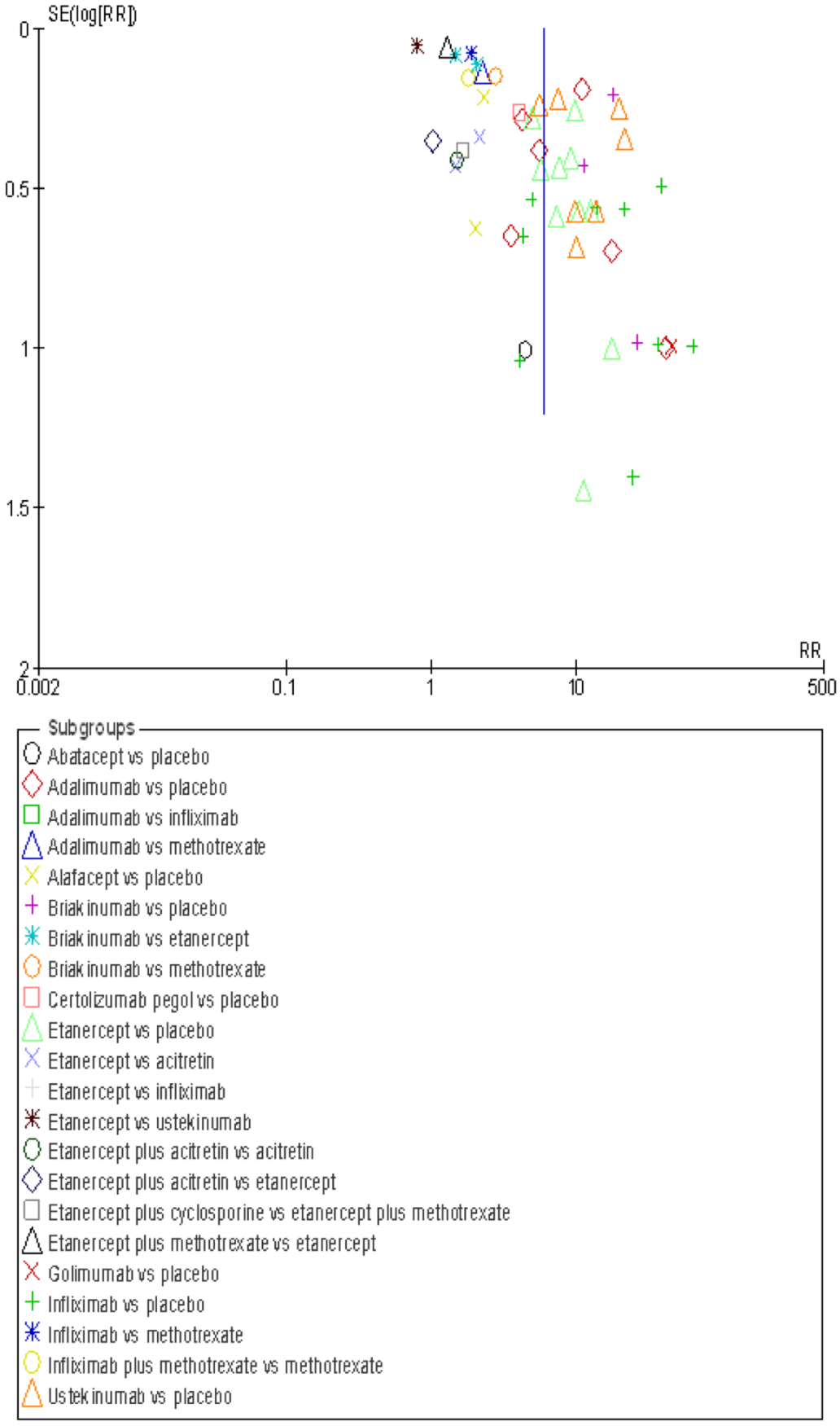

Figure 4: Funnel plot for reduction ≥75% in the Psoriasis Area and Severity Index (PASI75). RR=relative risk; SE=standard error.

Table 2: Key Features of Included Studies

First author	Acronym	Year	Agents tested	Sample size	Follow-up (weeks)
Antoni	IMPACT1	2005	Infliximab vs placebo	104	16
Antoni	IMPACT2	2005	Infliximab vs placebo	200	24
Asahina		2010	Adalimumab vs placebo	169	24
Atteno		2010	Infliximab vs etanercept vs adalimumab	100	52
Atzeni		2011	Etanercept plus methotrexate vs etanercept plus ciclosporin	41	24
Bagel		2012	Etanarcept vs placebo	124	12
Baranauskaite	RESPOND	2012	Infliximab plus methotrexate vs methotrexate	115	16
Barker	RESTORE1	2011	Infliximab vs methotrexate	868	16
Bissonnette		2011	Infliximab vs placebo	24	14
Bissonnette		2013	Adalimumab vs control therapy	30	16
Caproni		2009	Etanercept vs acitretin	60	12
Chaudhari		2001	Infliximab vs placebo	33	10
Genovese		2007	Adalimumab vs placebo	100	12
Gisondi		2008	Etanercept vs acitretin vs etanercept plus acitretin	60	24
Gordon		2006	Adalimumab vs placebo	148	12
Gordon		2012	Briakinumab vs placebo	1465	12
Gottlieb		2003	Etanercept vs placebo	112	24
Gottlieb	SPIRIT	2004	Infliximab vs placebo	249	10
Gottlieb		2009	Ustekinumab vs placebo	146	12
Gottlieb		2011	Briakinumab vs etanercept vs placebo	347	12
Gottlieb		2012	Etanercept plus methotrexate vs etanercept	478	24
Griffiths	ACCEPT	2010	Ustekinumab vs etanercept	903	12
Igarashi		2012	Ustekinumab vs placebo	158	12
Kavanaugh	GO-REVEAL	2009	Golimumab vs placebo	405	24
Kimball		2008	Briakinumab vs placebo	180	12
Krueger		2012	Ixekizumab vs placebo	46	20
Leonardi	Etanercept Psoriasis Study	2003	Etanercept vs placebo	672	12
Leonardi	PHOENIX1	2008	Ustekinumab vs placebo	766	12
Leonardi	REACH	2011	Adalimumab vs placebo	72	16
McInnes	PSUMMIT 1	2013	Ustekinumab vs placebo	615	24
Mease		2000	Etanercept vs placebo	60	12
Mease		2004	Etanercept vs placebo	205	48
Mease	ADEPT	2005	Adalimumab vs placebo	313	24
Mease		2011	Abatacept vs placebo	170	24
Mease	RAPID-PsA	2013	Certolizumab pegol vs placebo	409	24
Menter	EXPRESS2	2007	Inflximab vs placebo	835	10
Menter	REVEAL	2008	Adalimumab vs placebo	1212	16
Ortonne		2003	Alefacept vs placebo	507	14
Paller		2008	Etanercept vs placebo	211	12

(Table 2). Continued.

First author	Acronym	Year	Agents tested	Sample size	Follow-up (weeks)
Papp	PHOENIX2	2008	Ustekinumab vs placebo	1230	12
Reich	EXPRESS1	2005	Infliximab vs placebo	378	24
Reich		2011	Briakinumab vs methotrexate	317	52
Saurat	CHAMPION	2008	Adalimumab vs methotrexate vs placebo	271	16
Schlessinger		2007	Alafacept vs placebo	195	14
Strober		2011	Briakinumab vs etanercept vs placebo	350	12
Torii		2010	Infliximab vs placebo	54	14
Tsai	PEARL	2011	Ustekinumab vs placebo	121	12
Tyring		2006	Etanercept vs placebo	618	12
van de Kerkhof		2008	Etanercept vs placebo	142	12
Yang		2012	Infliximab vs placebo	129	10
Zhu	LOTUS	2013	Ustekinumab vs placebo	322	12

Table 3: Reduction ≥75% in the Psoriasis Area and Severity Index (PASI75) Expressed as Decreasing Rate Ratios for Different Biologic Agents Against Placebo, and Rate Ratios Against Best Treatment, Stemming from a 5.8% (0.2%-15.2%) Rate in the Placebo Group*

Agent	Rate ratio vs placebo	Rate ratio vs best agent (golinumab)
Golinumab	14.02 (6.85-17.11)	-
Infliximab	8.69 (6.88-10.74)	0.44 (0.01-2.71)
Briakinumab	8.87 (7.09-10.64)	0.25 (0.01-8.88)
Ustekinumab	7.39 (5.98-8.92)	0.18 (0.01-1.18)
Adalimumab	6.98 (5.19-8.88)	0.16 (0.01-1.08)
Etanercept	6.34 (5.18-7.66)	0.21 (0.01-1.68)
Abatacept	4.99 (0.93-15.77)	0.10 (0.01-3.51)
Methotrexate	4.55 (2.98-6.37)	0.09 (0.01-0.60)
Acitretin	4.05 (1.90-7.39)	0.07 (0.01-0.59)
Certolizumab pegol	3.67 (1.70-7.08)	0.06 (0.01-0.52)
Alafacept	2.16 (1.12-3.98)	0.03 (0.01-0.27)
Placebo	-	0.07 (0.06-0.15)

*Rate ratios far from 1.0 indicate credibly different rates.

Table 4: Improvement ≥20% in the American College of Rheumatology Core Set of Outcomes (ACR20) Expressed as Decreasing Rate Ratios for Different Biologic Agents Against Placebo and Rate Ratios Against Best Treatment, Stemming from a 17.4% (15.1%-19.6%) Rate in the Placebo Group*

Agent	Rate ratio vs placebo	Rate ratio vs best agent (infliximab)
Infliximab	3.02 (1.67-4.55)	-
Golinumab	2.93 (0.93-4.90)	0.94 (0.11-6.25)
Etanercept	2.84 (1.31-4.51)	0.88 (0.16-4.35)
Adalimumab	2.39 (0.97-4.01)	0.65 (0.10-2.78)
Certolizumab pegol	2.03 (0.56-4.22)	0.50 (0.06-3.13)
Abatacept	1.87 (0.45-4.25)	0.44 (0.05-3.13)
Ustekinumab	1.41 (0.56-3.09)	0.33 (0.07-1.34)
Placebo	-	0.33 (0.22-0.60)

*Rate ratios far from 1.0 indicate credibly different rates.

Table 5: Serious Adverse Events (SAE) Expressed as Increasing Rate Ratios for Different Biologic Agents Against Placebo and Rate Ratios Against Best Treatment, Stemming from a 2.4% (1.9%-2.8%) Rate in the Placebo Group*

Agent	Rate ratio vs placebo	Rate ratio vs best agent (golinumab)
Golimumab	0.40 (0.11-1.41)	-
Ustekinumab	0.75 (0.42-1.32)	1.85 (0.46-6.85)
Methotrexate	0.81 (0.35-1.87)	2.03 (0.41-8.01)
Etanercept	0.82 (0.44-1.44)	2.08 (0.47-8.33)
Adalimumab	1.00 (0.55-1.84)	2.56 (0.58-11.11)
Briakinumab	1.34 (0.68-2.60)	3.39 (0.01-10.86)
Infliximab	2.00 (1.16-3.52)	4.77 (0.01-14.81)
Abatacept	2.60 (0.37-27.52)	6.23 (0.01-37.51)
Certolizumab pegol	6.22 (2.58-14.75)	13.75 (0.01-30.75)
Placebo	-	2.50 (0.71-9.09)

*Rate ratios far from 1.0 indicate credibly different rates.

Table 6: Adverse Events (AE) Expressed as Decreasing Rate Ratios for Different Biologic Agents Against Placebo, and Rate Ratios Against Best Treatment, Stemming from a 51.8% (50.2%-53.4%) Rate in the Placebo Group*

Agent	Rate ratio vs placebo	Rate ratio vs best agent (abatacept)
Abatacept	1.00 (0.79-1.22)	-
Certolizumab pegol	1.01 (0.88-1.15)	1.01 (0.76-1.26)
Ustekinumab	1.01 (0.88-1.14)	1.01 (0.75-1.25)
Adalimumab	1.01 (0.94-1.08)	1.01 (0.78-1.22)
Methotrexate	1.01 (0.75-1.28)	1.01 (0.67-1.33)
Etanercept	1.05 (0.99-1.12)	1.06 (0.82-1.26)
Golinumab	1.06 (0.92-1.21)	1.06 (0.79-1.31)
Briakinumab	1.06 (0.99-1.13)	1.06 (0.84-1.28)
Infliximab	1.09 (1.02-1.16)	1.09 (0.86-1.30)
Placebo	-	1.00 (0.63-1.54)

*Rate ratios far from 1.0 indicate credibly different rates.

Migliore and colleagues focused instead only on anti-TNF-agents for psoriatic arthritis, including four trials with 820 patients. In this very specific setting, they reported that etanercept was the best agent in terms of rates of ACR20 [6]. Reich *et al*. pooled instead a total of 20 trials, albeit 4 of them focusing on efalizumab, which was discontinued for fatal toxicity. They suggested, in keeping with our own results, that infliximab was the drug with the most favorable efficacy profile, followed by ustekinumab, adalimumab, and etanercept [7]. Most recently, Schmitt and colleagues pooled data from 48 trials and 16,696 patients, finding that infliximab was the most effective agent for moderate-to-severe psoriasis, but limited their scope to efficacy endpoints only [20]. Finally, our findings should also be put into the cost-effectiveness context laid out in 2008 by Nelson *et al*., who suggested by pooling 14 trials that adalimumab and infliximab were the most cost-effective biologic agents for the treatment of psoriasis [21].

This work has several limitations, and shares most of the drawbacks typical of systematic reviews, pairwise meta-analyses, and network meta-analyses/mixed treatment comparisons [11, 12, 22]. In addition, we mainly relied on subjectively assessed endpoints, as both therapeutic response in plaque psoriasis or psoriatic arthritis is typically based on such outcomes. In addition, cross-over phases were excluded, limiting statistical precision and follow-up

duration [23]. Notably, differences in trial phases and follow-up durations may have confounded the overall study results. Some effect estimates were based only on few studies (for instance only 1 trial reported on golimumab). Accordingly, the robustness and external validity of our results may vary depending on the specific agent analyzed and its corresponding evidence base. Appraisal of specific and rarer adverse effects of these agents (e.g. myocardial infarction, life-threatening infection or cancer) was beyond the scope of this review [24, 25]. Finally, biologic agents can be combined with other anti-inflammatory drugs, such as methotrexate, acitretin, or cyclosporine. Other combinations include those with phototherapy or other topical treatments. Network analyses of these treatment approaches was beyond the scope of the present review and merits further investigations in the future.

In conclusion, biologic agents provide significant clinical benefits in patients with moderate to severe psoriasis or psoriatic arthritis. There are differences in the efficacy and safety profile for each agent, and clinicians should bear in mind these features to maximize safety and efficacy in the individual patient.

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CONFLICTS OF INTEREST

Dr. Biondi-Zoccai has consulted for Novartis, Origgio, Italy.

APPENDIX

MEDLINE/PubMed was searched according to the following explicit strategy: (psoriasis OR psoriatic) AND (abatacept OR adalimumab OR anakinra OR briakinumab OR brodalumab OR certolizumab OR etanercept OR golimumab OR infliximab OR ixekizumab OR rituximab OR tocilizumab OR ustekinumab) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])).

SUPPLEMENTAL DATA

The supplemental tables and figures can be downloaded from the journal website along with the article.

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