Comparative Risk-Benefit Analysis of Different Classes of Biologic Agents in Patients with Psoriasis: A Case Study on the Pros and Cons of Mixed Treatment Comparison in Synthesizing Complex Evidence Networks

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Abstract: *Background*: Several classes of biologic agents are used for the management of moderate to severe psoriasis or psoriatic arthritis. However, there is uncertainty on which, if any, individual class of biologics is superior in terms of efficacy and safety in comparison to the other classes or placebo. We thus exploited the corresponding evidence network with suitable statistical methods (mixed treatment comparison and network meta-analysis) to formally address this issue.

Methods: Randomized trials on biologic agents in psoriasis (including psoriatic arthritis) were systematically sought in several databases. We distinguished anti-tumor necrosis factor-α (TNF-α) agents, anti-T lymphocytes (T-cell) agents, anti-interleukin-12/23 (IL-12/23) agents, and anti-interleukin-17 (IL-17) agents. Endpoints of interest were the rates of ≥75% reduction in the Psoriasis Area and Severity Index (PASI75), of ≥20% improvement in the American College of Rheumatology core set of outcomes (ACR20), of serious adverse events (SAE), and of adverse events (AE) at the longest available non-cross-over follow-up. Random-effect methods were used to obtain network estimates for risk ratios (RR, with 95% credible intervals).

Results: A total of 58 trials with 18,508 patients were included, with 51% affected by psoriatic arthritis. After a median of 17 weeks since randomization into parallel groups, several classes of biologic agents provided higher PASI75 rates than placebo, with anti-IL-17 agents yielding the most favorable results (RR=9.53 [5.55-13.80]). Accordingly, several classes of biologic agents provided higher ACR20 rates than placebo, with anti-TNF-α agents yielding the most favorable results (RR=2.58 [2.12-3.15]). Overall, rates of SAE and AE were higher for several but not all biologic agents versus placebo, with anti-T-cell agents being associated with the most favorable results for both SAE (RR=0.97 [0.30-3.35]), and AE (RR=1.00 [0.80-1.22]).

Conclusions: 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 of each class, with anti-IL-17 and anti-TNF-α agents appearing most effective, and anti-T-cell agents appearing safest.

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

INTRODUCTION

The management of psoriasis has dramatically improved in terms of efficacy and effectiveness since the introduction of biologic therapy [1]. Biologic agents include those which block tumor necrosis factor-α (TNF-α) [anti-TNF-α agents), as well as those inhibiting T lymphocytes (anti-T-cell agents), anti-interleukin-12/23 (IL-12/23) agents, and anti-interleukin-17 (IL-17) agents [2]. Given the availability of several different individual agents for each of the above classes, the scholarly literature now includes several trials comparing different agents against placebo, against standard care, or against active controls [3-4].

While clinicians wishing to decide which treatment is better eventually focus on the comparative efficacy and safety of a specific molecule, they often tend to preliminarily assume that class effects are present [5]. Thus they routinely approach a management decision by also looking at the risk-benefit profile of therapeutic classes. Several research groups [6-10] have independently tried to appraise and compare individual biologics for the management of psoriasis. Conversely, there is no work hitherto dedicated to class effects of biologic agents for psoriasis.

Given the complex evidence base on this topic, a naïve approach wishing to summarize such data with a

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straightforward systematic review and pairwise meta-analysis would provide fewer quantitative estimates, of spurious precision and limited external validity [11]. Yet, tackling this apparent conundrum with the recently refined statistical methods enabling network meta-analysis and mixed treatment comparison holds the promise of a more robust and valid set of quantitative results [12-14]. Indeed, a systematic review uses explicit and established methods for evidence search, selection and appraisal. A pairwise meta-analysis combines statistically data from similar head-to-head randomized trials (e.g. 3 studies comparing treatment A and treatment B). Conversely, a network meta-analysis and mixed treatment comparison uses the whole set of clinical evidence on a specific condition and focusing on similar treatments in order to identify the treatment with the most favorable risk-benefit balance (e.g. 3 studies comparing treatment A and treatment B, 1 study comparing treatment A and treatment C, and 2 studies comparing treatment B and treatment C [11]. The key strengths of these novel statistical methods is that they can distinguish also class effect from agent-specific effects, an aspect of great importance whenever different agents within the same pharmacologic class are available.

Accordingly, assuming a prevalent class effect in this therapeutic realm, and exploiting a recent systematic review and agent-level network meta-analysis conducted by our research group on this very topic [15], we aimed to review the current evidence based and explicitly focus on the appraisal of the efficacy and safety of different classes of biologics in patients with moderate to severe plaque psoriasis or psoriatic arthritis.

METHODS

Review Design

This review and the parent one from which the present stems [15] were conducted in compliance with the Quality of Reporting of Meta-analyses (QUOROM) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16-17]. All reviewing activities were performed independently by two experienced reviewers, with divergences solved after consensus.

Database Search and Study Selection

Pertinent studies were searched in MEDLINE/PubMed online database according to the search strategy dedicated to randomized clinical trials previously reported by Biondi-Zoccai *et al.* [18]. In addition, other key online databases such as The Cochrane Library, Google Scholar, and Scopus were searched for suitable studies. The search was last updated on October 2013. No language restriction was enforced, thus enabling the inclusion of studies reported in English as well as in other languages.

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 moderate to severe psoriasis or psoriatic arthritis 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, or focusing on agents which had been discontinued before or shortly after market approval for safety issues [19].

Data Extraction

Key baseline, procedural and outcome data were systematically retrieved, focusing specifically on efficacy and safety outcomes. For the purpose of this review, we focused on 4 separate classes of 12 individual biologic agents: anti-IL-12/23 agents (briakinumab, ustekinumab); anti-IL-17 agents (brodalumab, iIxekinumab, secukinumab); anti-T-cell agents (abatacept, alefacept); anti-TNF-α agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) [2,20].

As efficacy outcomes, we focused on the binary rates of reduction ≥75% in the Psoriasis Area and Severity Index (PASI75), which is a validated endpoint for the assessment of the extent of psoriasis, and improvement ≥20% in the American College of Rheumatology core set of outcomes (ACR20), which is a validated endpoint for the assessment of the extent of arthritis, both at the longest available follow-up. As safety outcomes, we focused on serious adverse events (SAE), and adverse events (AE), which are validated endpoints in the assessment of drug safety, both at the longest available follow-up.

Statistical Analysis

Continuous variables are described as median and categorical variables as %. Pairwise meta-analysis was performed within a frequentist framework computing DerSimonian-Laird random-effect risk ratios (RR) with

95% confidence intervals [11]. Network meta-analysis and mixed treatment comparison was performed within a Bayesian framework with a random-effect binomial likelihood hierarchical model, sampling effect estimates with Markov chain Monte Carlo (MCMC) methods with Gibbs sampling, computing RR with 95% credibility intervals, and probability of being the best treatment for each agent (Pbest, which is a quantitative estimate of the posterior likelihood that a given treatment is most likely to yield the most favorable results for the specific endpoint of interest) [11,13]. Such credibility intervals can be interpreted at large in a similar fashion as confidence intervals for the purpose of clinical decision-making [21]. Analyses were based on two separate sets of computer simulations, in keeping with the MCMC method: a 50,000-run training set (with corresponding estimates being discarded) and a 150,000-run inferential set (used for inferential estimates). Convergence of the three chains stemming from different and separate initial values was appraised with the Gelman-Rubin method (which showed adequate convergence at the 50,000-run threshold. Model fit was appraised with the deviance information criterion (DIC), comparing random-effect and fixed-effect models, with choice a fixed-effect model preferred at similar DIC values for parsimony sake. Pairwise consistency (i.e. the agreement between estimates stemming from trials having the same type of comparators) was appraised with I-squared and consistency between direct and indirect estimates was appraised by comparing consistency and inconsistency models [11]. Small study effects and publication bias (i.e. the phenomenon in which small studies provide over-optimistic results, possibly due to their selective publication) were appraised with visual inspection of funnel plot (graphical plots assessing the association between effect estimates and study precision). Computations were performed with RevMan 5 (The Denmark Cochrane Center, Copenhagen, Denmark), and WinBUGS (MRC Biostatistics Unit, University of Cambridge, Cambridge, UK).

RESULTS

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 eventual inclusion of a total of 58 trials and 18,508 patients. The main reason for

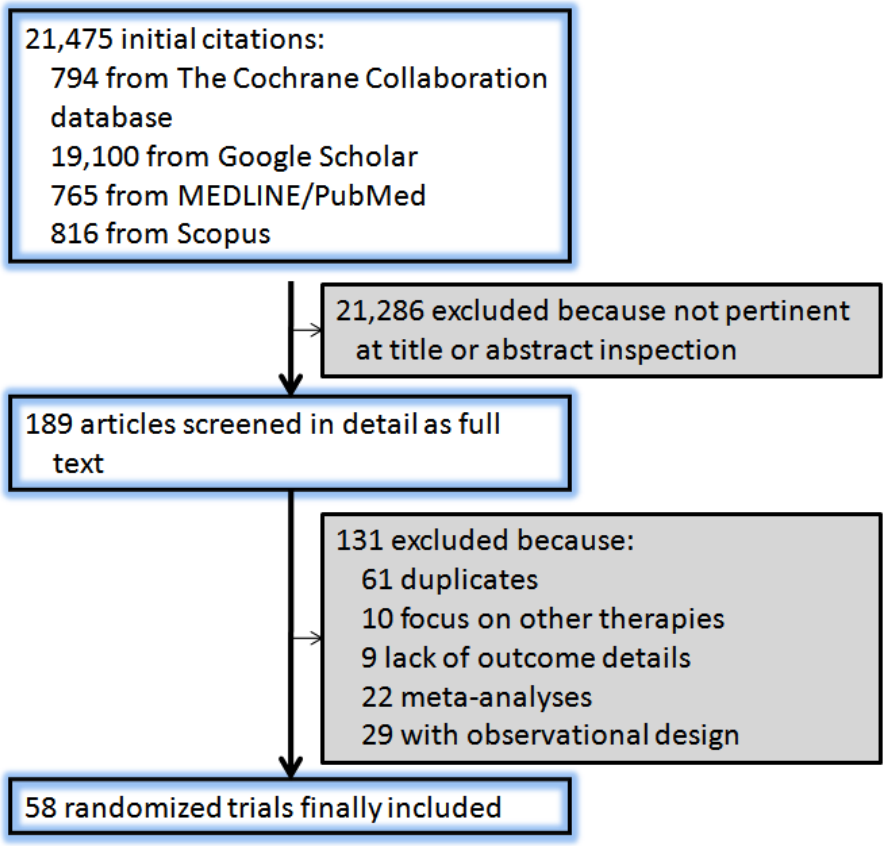


Figure 1: Review profile, disclosing the database searched with corresponding yields, number of citations excluded at the first screening stage, full texts appraised according to the selection criteria, and the number of studies finally included.

Table 1: Included Studies*

Study first author	Study acronym	Year of publication	Agent(s) tested	Sample size	Follow-up (weeks)	Patient age (y)	Psoriatic arthritis	Moderate or severe plaque psoriasis	Psoriasis duration (y)
Antoni	IMPACT1	2005	Infliximab vs placebo	104	16	45	100%	38%	11
Antoni	IMPACT2	2005	Infliximab vs placebo	200	24	47	100%	85%	8
Asahina		2010	Adalimumab vs placebo	169	24	45	23%	100%	14
Atteno		2010	Infliximab vs etanercept vs adalimumab	100	52	49	100%	NA	NA
Atzeni		2011	Etanercept plus methotrexate vs etanercept plus ciclosporin	41	24	52	100%	100%	10
Bagel		2012	Etanarcept vs placebo	124	12	40	NA	100%	14
Baranauskaite	RESPOND	2012	Infliximab plus methotrexate vs methotrexate	115	16	41	100%	62%	3
Barker	RESTORE1	2011	Infliximab vs methotrexate	868	16	43	NA	100%	NA
Bissonnette		2011	Infliximab vs placebo	24	14	54	0%	100%	NA
Bissonnette		2013	Adalimumab vs control therapy	30	16	56	NA	100%	NA
Caproni		2009	Etanercept vs acitretin	60	12	NA	NA	100%	NA
Chaudhari		2001	Infliximab vs placebo	33	10	45	NA	100%	NA
Genovese		2007	Adalimumab vs placebo	100	12	48	100%	NA	7
Gisondi		2008	Etanercept vs acitretin vs etanercept plus acitretin	60	24	54	NA	100%	21
Gordon		2006	Adalimumab vs placebo	148	12	44	28%	100%	18
Gordon		2012	Briakinumab vs placebo	1465	12	45	30%	100%	19
Gottlieb		2003	Etanercept vs placebo	112	24	47	31%	100%	21
Gottlieb	SPIRIT	2004	Infliximab vs placebo	249	10	44	31%	100%	17
Gottlieb		2009	Ustekinumab vs placebo	146	12	49	100%	85%	5
Gottlieb		2011	Briakinumab vs etanercept vs placebo	347	12	43	21%	100%	17
Gottlieb		2012	Etanercept plus methotrexate vs etanercept	478	24	44	22%	100%	17
Griffiths	ACCEPT	2010	Ustekinumab vs etanercept	903	12	45	28%	100%	19
Igarashi		2012	Ustekinumab vs placebo	158	12	46	9%	100%	16
Kavanaugh	GO-REVEAL	2009	Golimumab vs placebo	405	24	47	100%	69%	8
Kimball		2008	Briakinumab vs placebo	180	12	47	29%	100%	21
Krueger		2012	Ixekizumab vs placebo	46	20	42	NA	100%	15
Leonardi	Etanercept Psoriasis Study	2003	Etanercept vs placebo	672	12	45	NA	100%	19
Leonardi	PHOENIX1	2008	Ustekinumab vs placebo	766	12	45	34%	100%	19
Leonardi	REACH	2011	Adalimumab vs placebo	72	16	53	9%	100%	13
Leonardi		2012	Ixekizumab vs placebo	142	12	45	NA	100%	15
McInnes		2013	Secukinumab vs placebo	42	6	47	100%	NA	24
McInnes	PSUMMIT 1	2013	Ustekinumab vs placebo	615	24	48	100%	72%	4
Mease		2000	Etanercept vs placebo	60	12	45	100%	47%	10

(Table 1). Continued.

Study first author	Study acronym	Year of publication	Agent(s) tested	Sample size	Follow-up (weeks)	Patient age (y)	Psoriatic arthritis	Moderate or severe plaque psoriasis	Psoriasis duration (y)
Mease		2004	Etanercept vs placebo	205	48	47	100%	62%	9
Mease	ADEPT	2005	Adalimumab vs placebo	313	24	49	100%	44%	9
Mease		2011	Abatacept vs placebo	170	24	51	100%	21%	8
Mease	RAPID-PsA	2013	Certolizumab pegol vs placebo	409	24	47	100%	61%	8
Menter	EXPRESS2	2007	Inflximab vs placebo	835	10	44	27%	100%	18
Menter	REVEAL	2008	Adalimumab vs placebo	1212	16	45	28%	100%	18
Ortonne		2003	Alefacept vs placebo	507	14	NA	NA	100%	20
Paller		2008	Etanercept vs placebo	211	12	13	9%	100%	6
Papp	PHOENIX2	2008	Ustekinumab vs placebo	1230	12	46	24%	100%	20
Papp		2012	Brodalumab vs placebo	198	12	42	24%	100%	18
Papp		2013	Sekukinumab vs placebo	125	12	46	19%	100%	18
Reich	EXPRESS1	2005	Infliximab vs placebo	378	24	43	30%	100%	19
Reich		2011	Briakinumab vs methotrexate	317	52	44	16%	100%	19
Rich		2013	Sekukinumab vs placebo	338	12	45	25%	100%	17
Saurat	CHAMPION	2008	Adalimumab vs methotrexate vs placebo	271	16	41	20%	100%	19
Schlessinger		2007	Alafacept vs placebo	195	14	48	NA	100%	NA
Strober		2011	Briakinumab vs etanercept vs placebo	350	12	45	27%	100%	16
Torii		2010	Infliximab vs placebo	54	14	45	34%	100%	13
Tsai	PEARL	2011	Ustekinumab vs placebo	121	12	41	14%	100%	13
Tyring		2006	Etanercept vs placebo	618	12	46	34%	100%	19
van de Kerkhof		2008	Etanercept vs placebo	142	12	44	13%	100%	18
Yang		2012	Infliximab vs placebo	129	10	40	NA	100%	16
Zhu	LOTUS	2013	Ustekinumab vs placebo	322	12	NA	NA	100%	NA

*References are available from the corresponding author upon request; NA=not available or applicable.

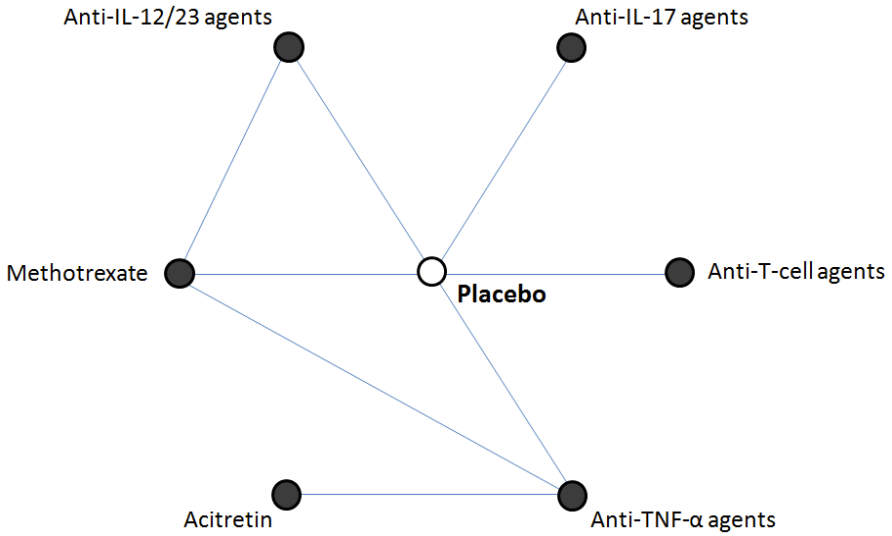
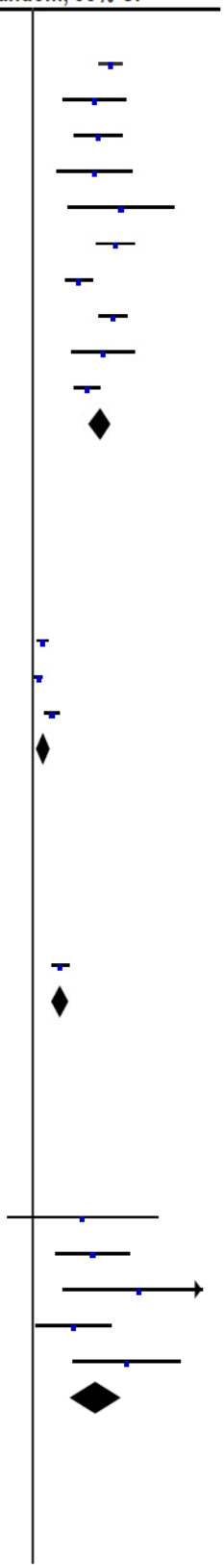


Figure 2: Evidence network. IL=interleukin. TNF=tumor necrosis factor.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Anti-IL-12/23 agents vs placebo						
Gordon 2012	792	981	22	484	2.3%	17.76 [11.79, 26.75]
Gottlieb 2009	33	63	3	55	1.9%	9.60 [3.12, 29.59]
Gottlieb 2011	113	138	5	68	2.1%	11.14 [4.77, 25.99]
Igarashi 2012	80	126	2	31	1.8%	9.84 [2.56, 37.85]
Kimball 2008	129	150	1	30	1.4%	25.80 [3.75, 177.41]
Leonardi 2008	341	511	8	255	2.2%	21.27 [10.73, 42.19]
McInnes 2013 (PSUMMIT1)	176	294	16	146	2.3%	5.46 [3.41, 8.76]
Papp 2008 (PHOENIX2)	584	820	15	410	2.3%	19.47 [11.82, 32.05]
Tsai 2011 (PEARL)	41	61	3	60	1.9%	13.44 [4.40, 41.07]
Zhu 2013 (LOTUS)	133	161	18	161	2.3%	7.39 [4.75, 11.49]
Subtotal (95% CI)		3305		1700	20.4%	12.11 [8.16, 17.97]
Total events	2422		93			
Heterogeneity: Tau² = 0.24; Chi² = 28.47, df = 9 (P = 0.0008); I² = 68%						
Test for overall effect: Z = 12.39 (P < 0.00001)						
2.1.4 Anti-IL-12/23 agents vs anti-TNF-alfa agents						
Gottlieb 2011	113	138	79	141	2.4%	1.46 [1.24, 1.73]
Griffith 2010 (ACCEPT)	397	556	197	347	2.4%	1.26 [1.13, 1.40]
Strober 2011	112	139	55	139	2.4%	2.04 [1.63, 2.54]
Subtotal (95% CI)		833		627	7.1%	1.53 [1.18, 1.97]
Total events	622		331			
Heterogeneity: Tau² = 0.04; Chi² = 15.32, df = 2 (P = 0.0005); I² = 87%						
Test for overall effect: Z = 3.26 (P = 0.001)						
2.1.7 Anti-IL-12/23 agents vs methotrexate						
Reich 2011	102	154	39	163	2.3%	2.77 [2.06, 3.72]
Subtotal (95% CI)		154		163	2.3%	2.77 [2.06, 3.72]
Total events	102		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.74 (P < 0.00001)						
2.1.8 Anti-IL-17 agents vs placebo						
Krueger 2012	11	32	0	8	1.0%	6.27 [0.41, 96.55]
Leonardi 2012	78	115	2	27	1.8%	9.16 [2.40, 34.95]
Papp 2012	104	160	0	38	1.0%	50.63 [3.22, 796.97]
Papp 2013	42	103	2	22	1.8%	4.49 [1.17, 17.16]
Rich 2013	130	271	1	67	1.4%	32.14 [4.58, 225.73]
Subtotal (95% CI)		681		162	6.9%	10.52 [4.15, 26.66]
Total events	365		5			
Heterogeneity: Tau² = 0.26; Chi² = 5.20, df = 4 (P = 0.27); I² = 23%						
Test for overall effect: Z = 4.96 (P < 0.00001)						



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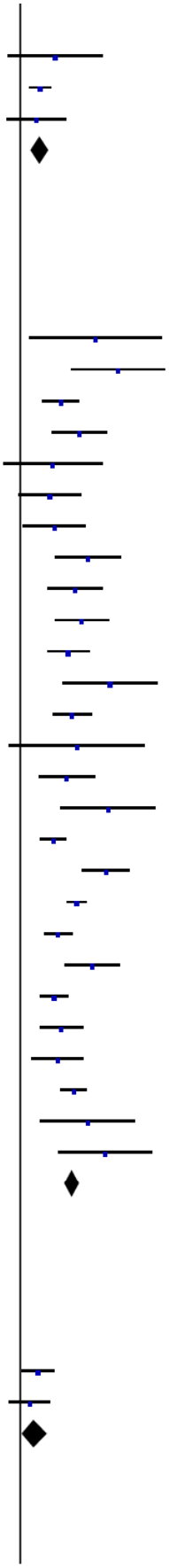

2.1.10 Anti-T-cell agents vs placebo

Mease 2011	13	62	1	21	1.4%	4.40 [0.61, 31.66]
Ortonne 2003	103	339	22	168	2.3%	2.32 [1.52, 3.54]
Schlessinger 2007	12	130	3	65	1.8%	2.00 [0.58, 6.84]
Subtotal (95% CI)		**531**		**254**	**5.5%**	**2.34 [1.59, 3.46]**
Total events	128		26			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 2 (P = 0.79); $I^2 = 0\%$

Test for overall effect: Z = 4.27 (P < 0.0001)

2.1.12 Anti-TNF-alfa agents vs placebo

Antoni 2005 (IMPACT1)	15	22	0	17	1.0%	24.26 [1.55, 378.66]
Antoni 2005 (IMPACT2)	60	83	1	87	1.4%	62.89 [8.92, 443.47]
Asahina 2010	89	123	6	46	2.1%	5.55 [2.61, 11.79]
Bagel 2012	37	62	3	62	1.9%	12.33 [4.01, 37.90]
Bissonnette 2011	4	12	1	12	1.3%	4.00 [0.52, 30.76]
Bissonnette 2013	14	20	2	10	1.8%	3.50 [0.98, 12.49]
Chaudari 2001	17	22	2	11	1.8%	4.25 [1.19, 15.19]
Gordon 2006	64	95	2	52	1.8%	17.52 [4.47, 68.67]
Gottlieb 2003	32	57	3	55	1.9%	10.29 [3.34, 31.67]
Gottlieb 2004 (SPIRIT)	158	198	3	51	1.9%	13.57 [4.52, 40.75]
Gottlieb 2011	79	141	5	68	2.1%	7.62 [3.24, 17.94]
Kavanaugh 2009	127	208	1	73	1.4%	44.57 [6.34, 313.13]
Leonardi 2003	159	486	6	166	2.1%	9.05 [4.08, 20.06]
Mease 2000	5	19	0	19	0.9%	11.00 [0.65, 186.02]
Mease 2004	23	66	3	62	1.9%	7.20 [2.28, 22.79]
Mease 2005 (ADEPT)	41	70	1	70	1.4%	41.00 [5.80, 289.87]
Mease 2013 (RAPID-PsA)	102	166	13	86	2.3%	4.06 [2.43, 6.80]
Menter 2007 (EXPRESS2)	457	627	4	208	2.0%	37.90 [14.34, 100.15]
Menter 2008 (REVEAL)	578	814	26	398	2.3%	10.87 [7.48, 15.80]
Paller 2008	60	106	12	105	2.2%	4.95 [2.83, 8.65]
Reich 2005 (EXPRESS1)	227	276	3	77	1.9%	21.11 [6.95, 64.10]
Saurat 2008 (CHAMPION)	86	108	10	53	2.2%	4.22 [2.40, 7.44]
Strober 2011	55	139	5	72	2.1%	5.70 [2.39, 13.60]
Torii 2010	27	35	3	19	2.0%	4.89 [1.70, 14.02]
Tyring 2006	147	311	15	306	2.3%	9.64 [5.81, 16.01]
van de Kerkhof 2008	36	96	1	46	1.4%	17.25 [2.44, 121.93]
Yang 2012	68	84	1	45	1.4%	36.43 [5.23, 253.71]
Subtotal (95% CI)		**4446**		**2276**	**48.8%**	**9.09 [6.79, 12.17]**
Total events	2767		132			

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 61.63$, df = 26 (P = 0.0001); $I^2 = 58\%$

Test for overall effect: Z = 14.82 (P < 0.00001)

2.1.23 Anti-TNF-alfa agents vs acitretin

Caproni 2009	17	30	8	30	2.2%	2.13 [1.09, 4.16]
Gisondi 2008	8	18	6	20	2.1%	1.48 [0.64, 3.45]
Subtotal (95% CI)		**48**		**50**	**4.3%**	**1.85 [1.09, 3.13]**
Total events	25		14			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0\%$

Test for overall effect: Z = 2.29 (P = 0.02)

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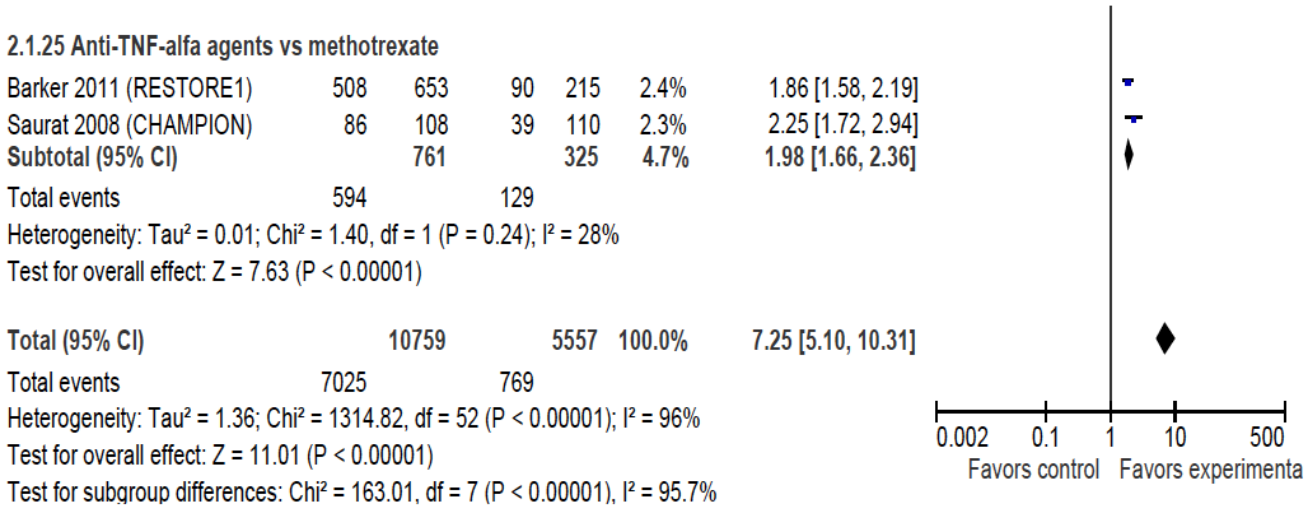


Figure 3: Forest plot for reduction ≥75% in the Psoriasis Area and Severity Index (PASI75). IL=interleukin. TNF=tumor necrosis factor.

exclusion of full reports was duplication of trial data, followed by observational design, and meta-analysis as study type.

The included studies compared, with variable assortments, placebo and 14 different pharmacologic agents (12 biologics) grouped in 5 main classes: anti-IL-12/23 agents (briakinumab, ustekinumab); anti-IL-17 agents (brodalumab, ixekinumab, secukinumab); anti-T-cell agents (abatacept, alefacept); anti-TNF-α agents (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab); and other agents (acitretin, methotrexate) (Table **1**; Figure **2**).

Pairwise meta-analyses were performed for PASI75 (Figure **3**), ACR20 (Figure **4**), SAE (Figure **5**), and AE (Figure **6**). Whereas PASI75 rates were highest with anti-IL-12/23 agents (RR=12.11 [8.16-17.97], p<0.001), ACR20 was best achieved by anti-TNF-α agents (RR=3.53 [2.86-4.36], p<0.001) and anti-T-cell agents (RR=2.13 [1.10-4.12], p=0.02). Conversely, SAE rates were not significantly increased by any class of biologics. Finally, AE were significantly more common with anti-IL-12/23 (RR=1.06 [1.00-1.13], p=0.04) or anti-TNF-α agents than with placebo (RR=1.07 [1.02-1.13], p=0.009). Overall, pairwise inconsistency was mild, and funnel plot inspection based on such data did not suggest the presence of small study effects.

Network meta-analysis, exploiting both direct and indirect class-level comparisons, showed that several classes biologic agents provided higher PASI75 rates than placebo (Table **2**), with anti-IL-17 agents yielding the most favorable results (RR=9.53 [5.55-13.80] vs placebo), but similarly favorable results for anti-IL-12/23 agents (RR=8.15 [6.77-9.58] vs placebo), and anti-TNF-α agents (RR=6.96 [5.96-8.15] vs placebo). Conversely, anti-T-cell agents proved significantly inferior to anti-IL-17 agents (RR=0.13 [0.03-0.46]). Accordingly, several classes of biologics provided higher ACR20 rates than placebo (Table **3**), with anti-TNF-α agents yielding the most promising results (RR=2.58 [2.12-3.15] vs placebo), but similarly favorable albeit non-significant trends for anti-IL-17 agents (RR=2.12 [0.59-4.65] vs placebo) and anti-T-cell agents (RR=1.86 [0.78-3.48] vs placebo). Conversely, anti-IL-12/23 agents proved significantly inferior to anti-TNF-α agents (RR=0.37 [0.17-0.86]).

Overall, rates of SAE and AE were higher for several but not all biologic agents versus placebo (Tables **4** and **5**). Excluding methotrexate, anti-T-cell agents were associated with the most favorable results for both SAE (RR=0.97 [0.30-3.35] vs placebo) and AE (RR=1.00 [0.80-1.22] vs placebo). Less favorable results were apparent for the other agents, with anti-IL-17 agents having the least favorable profile for SAE (RR=1.45 [0.48-4.99] vs placebo), and anti-TNF-α agents for AE (1.05 [1.01-1.08] vs placebo).

DISCUSSION

This review, the first to comprehensive appraise and quantify the risk-benefit profile of different classes of biologic agents in the management of moderate to severe psoriasis or psoriatic arthritis has the following main implications: a) the evidence base on this topic, despite being mainly dominated by placebo-controlled

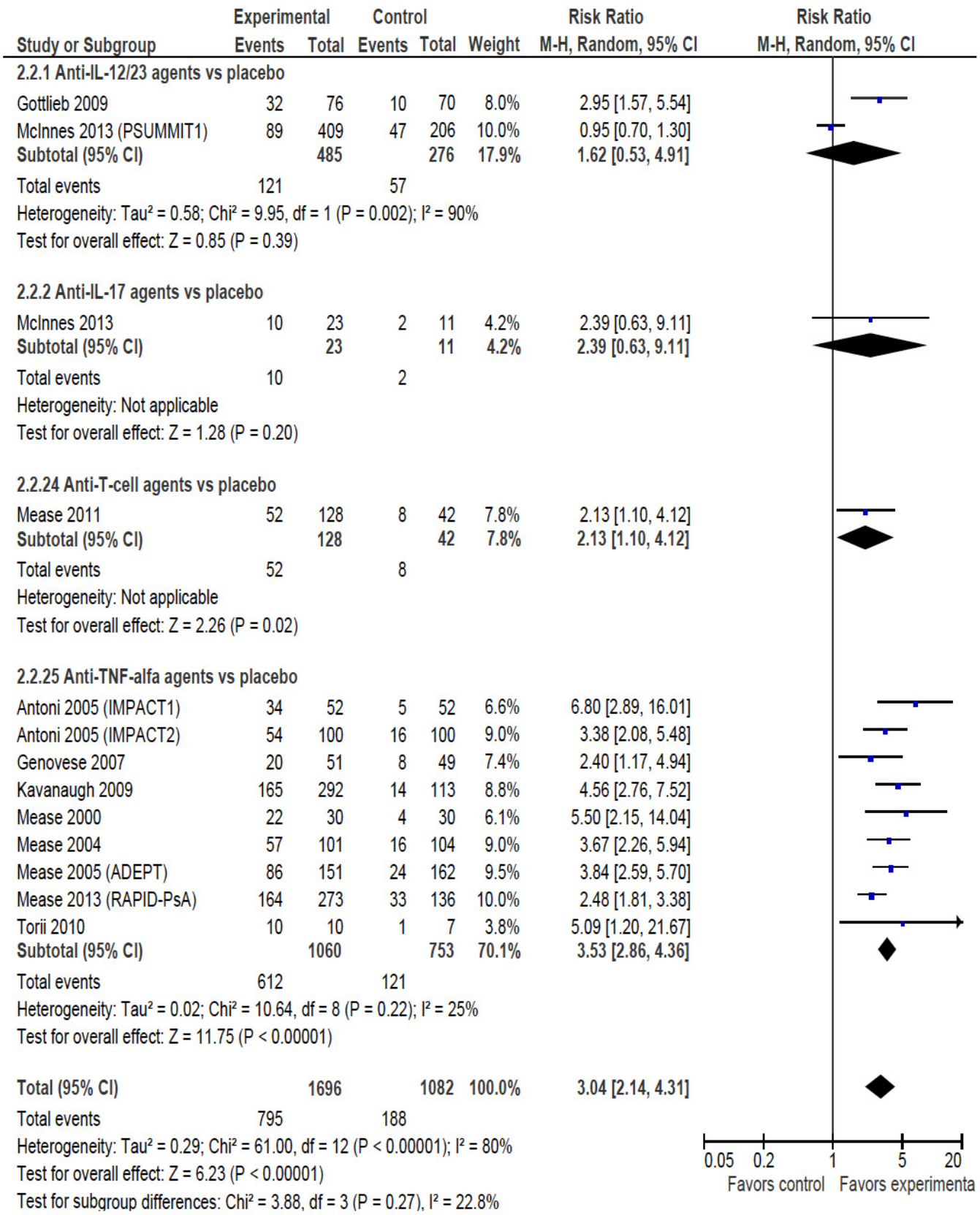
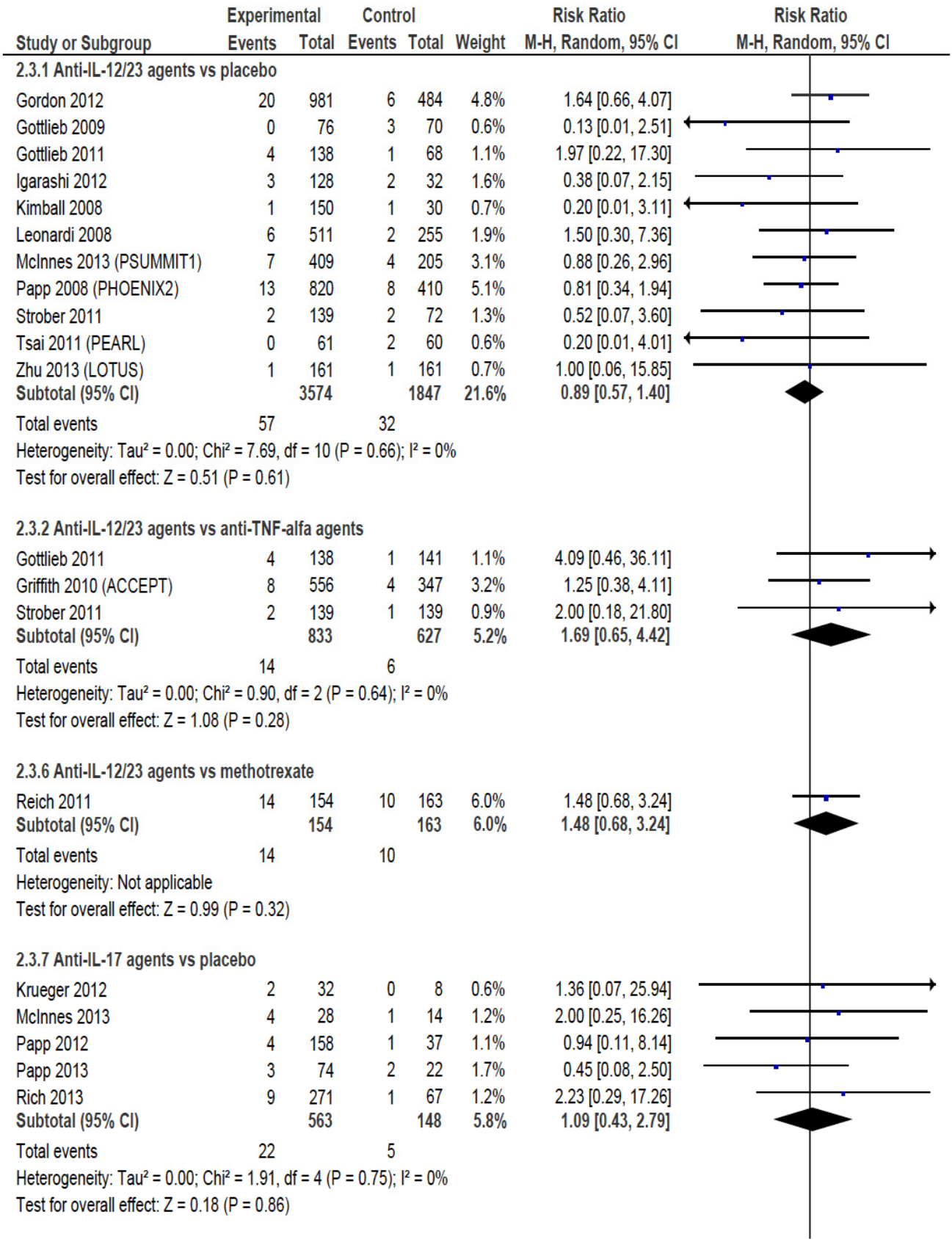


Figure 4: Forest plot for improvement ≥20% in the American College of Rheumatology core set of outcomes (ACR20). IL=interleukin. TNF=tumor necrosis factor.


Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
2.3.1 Anti-IL-12/23 agents vs placebo
Gordon 2012 20 981 6 484 4.8% 1.64 [0.66, 4.07]
Gottlieb 2009 0 76 3 70 0.6% 0.13 [0.01, 2.51]
Gottlieb 2011 4 138 1 68 1.1% 1.97 [0.22, 17.30]
Igarashi 2012 3 128 2 32 1.6% 0.38 [0.07, 2.15]
Kimball 2008 1 150 1 30 0.7% 0.20 [0.01, 3.11]
Leonardi 2008 6 511 2 255 1.9% 1.50 [0.30, 7.36]
McInnes 2013 (PSUMMIT1) 7 409 4 205 3.1% 0.88 [0.26, 2.96]
Papp 2008 (PHOENIX2) 13 820 8 410 5.1% 0.81 [0.34, 1.94]
Strober 2011 2 139 2 72 1.3% 0.52 [0.07, 3.60]
Tsai 2011 (PEARL) 0 61 2 60 0.6% 0.20 [0.01, 4.01]
Zhu 2013 (LOTUS) 1 161 1 161 0.7% 1.00 [0.06, 15.85]
Subtotal (95% CI) 3574 1847 21.6% 0.89 [0.57, 1.40]
Total events 57 32
Heterogeneity: Tau² = 0.00; Chi² = 7.69, df = 10 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
2.3.2 Anti-IL-12/23 agents vs anti-TNF-alfa agents
Gottlieb 2011 4 138 1 141 1.1% 4.09 [0.46, 36.11]
Griffith 2010 (ACCEPT) 8 556 4 347 3.2% 1.25 [0.38, 4.11]
Strober 2011 2 139 1 139 0.9% 2.00 [0.18, 21.80]
Subtotal (95% CI) 833 627 5.2% 1.69 [0.65, 4.42]
Total events 14 6
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)
2.3.6 Anti-IL-12/23 agents vs methotrexate
Reich 2011 14 154 10 163 6.0% 1.48 [0.68, 3.24]
Subtotal (95% CI) 154 163 6.0% 1.48 [0.68, 3.24]
Total events 14 10
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
2.3.7 Anti-IL-17 agents vs placebo
Krueger 2012 2 32 0 8 0.6% 1.36 [0.07, 25.94]
McInnes 2013 4 28 1 14 1.2% 2.00 [0.25, 16.26]
Papp 2012 4 158 1 37 1.1% 0.94 [0.11, 8.14]
Papp 2013 3 74 2 22 1.7% 0.45 [0.08, 2.50]
Rich 2013 9 271 1 67 1.2% 2.23 [0.29, 17.26]
Subtotal (95% CI) 563 148 5.8% 1.09 [0.43, 2.79]
Total events 22 5
Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)

(Figure 5). Continued.

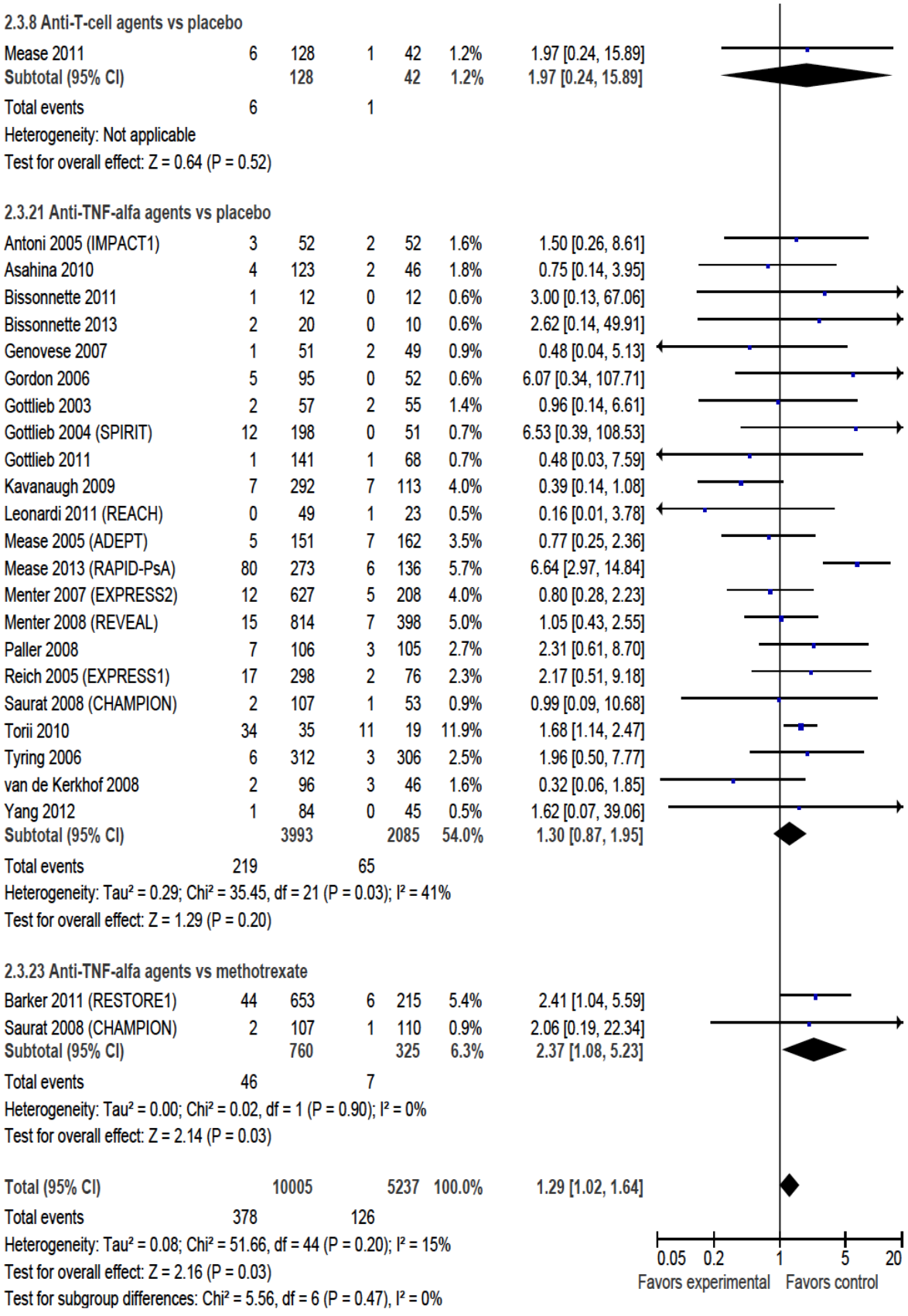
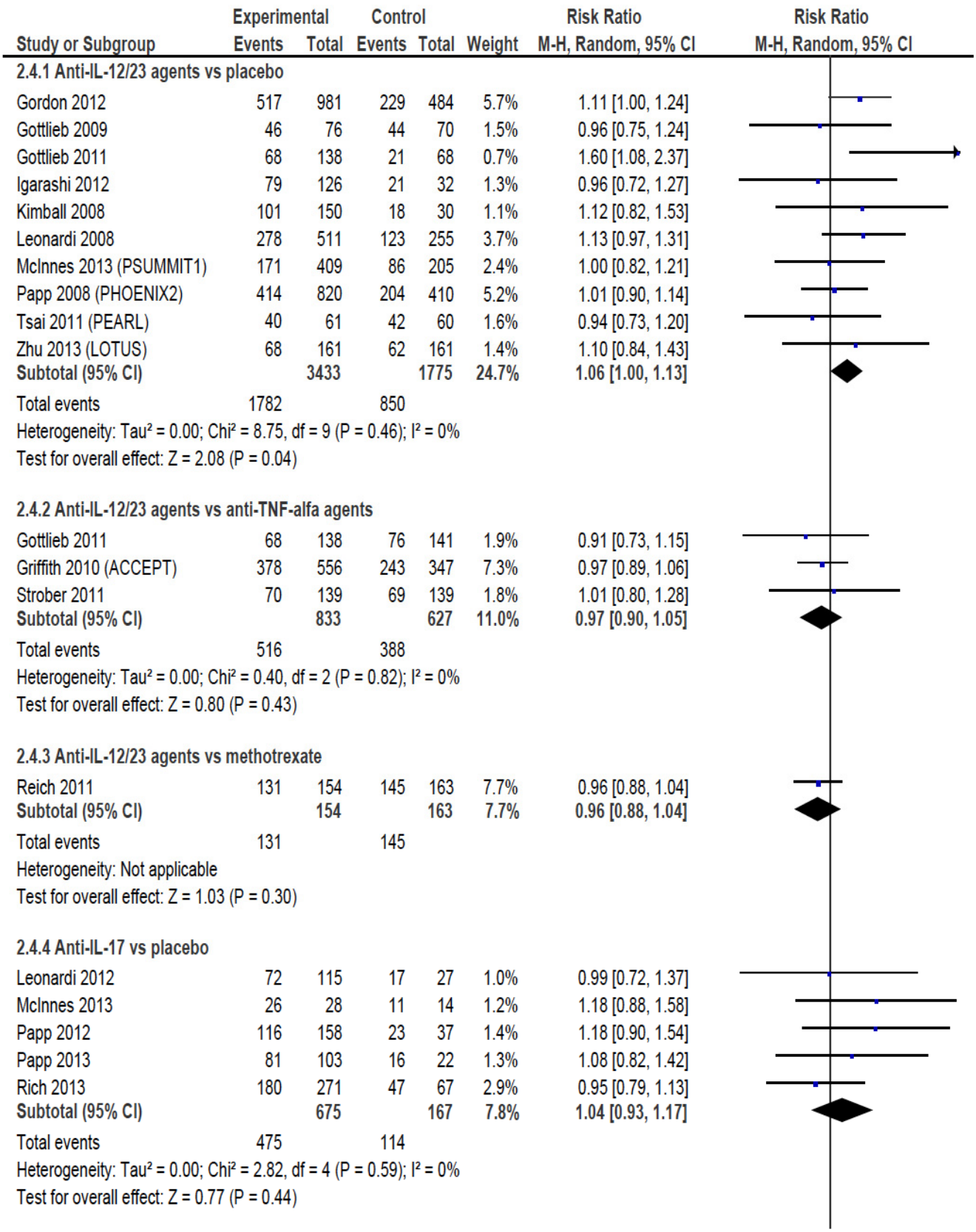


Figure 5: Forest plot for serious adverse events (SAE). IL=interleukin. TNF=tumor necrosis factor.


Experimental
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.4.1 Anti-IL-12/23 agents vs placebo
Gordon 2012 517 981 229 484 5.7% 1.11 [1.00, 1.24]
Gottlieb 2009 46 76 44 70 1.5% 0.96 [0.75, 1.24]
Gottlieb 2011 68 138 21 68 0.7% 1.60 [1.08, 2.37]
Igarashi 2012 79 126 21 32 1.3% 0.96 [0.72, 1.27]
Kimball 2008 101 150 18 30 1.1% 1.12 [0.82, 1.53]
Leonardi 2008 278 511 123 255 3.7% 1.13 [0.97, 1.31]
McInnes 2013 (PSUMMIT1) 171 409 86 205 2.4% 1.00 [0.82, 1.21]
Papp 2008 (PHOENIX2) 414 820 204 410 5.2% 1.01 [0.90, 1.14]
Tsai 2011 (PEARL) 40 61 42 60 1.6% 0.94 [0.73, 1.20]
Zhu 2013 (LOTUS) 68 161 62 161 1.4% 1.10 [0.84, 1.43]
Subtotal (95% CI) 3433 1775 24.7% 1.06 [1.00, 1.13]
Total events 1782 850
Heterogeneity: Tau² = 0.00; Chi² = 8.75, df = 9 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)
2.4.2 Anti-IL-12/23 agents vs anti-TNF-alfa agents
Gottlieb 2011 68 138 76 141 1.9% 0.91 [0.73, 1.15]
Griffith 2010 (ACCEPT) 378 556 243 347 7.3% 0.97 [0.89, 1.06]
Strober 2011 70 139 69 139 1.8% 1.01 [0.80, 1.28]
Subtotal (95% CI) 833 627 11.0% 0.97 [0.90, 1.05]
Total events 516 388
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.43)
2.4.3 Anti-IL-12/23 agents vs methotrexate
Reich 2011 131 154 145 163 7.7% 0.96 [0.88, 1.04]
Subtotal (95% CI) 154 163 7.7% 0.96 [0.88, 1.04]
Total events 131 145
Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
2.4.4 Anti-IL-17 vs placebo
Leonardi 2012 72 115 17 27 1.0% 0.99 [0.72, 1.37]
McInnes 2013 26 28 11 14 1.2% 1.18 [0.88, 1.58]
Papp 2012 116 158 23 37 1.4% 1.18 [0.90, 1.54]
Papp 2013 81 103 16 22 1.3% 1.08 [0.82, 1.42]
Rich 2013 180 271 47 67 2.9% 0.95 [0.79, 1.13]
Subtotal (95% CI) 675 167 7.8% 1.04 [0.93, 1.17]
Total events 475 114
Heterogeneity: Tau² = 0.00; Chi² = 2.82, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)

(Figure 6). Continued.

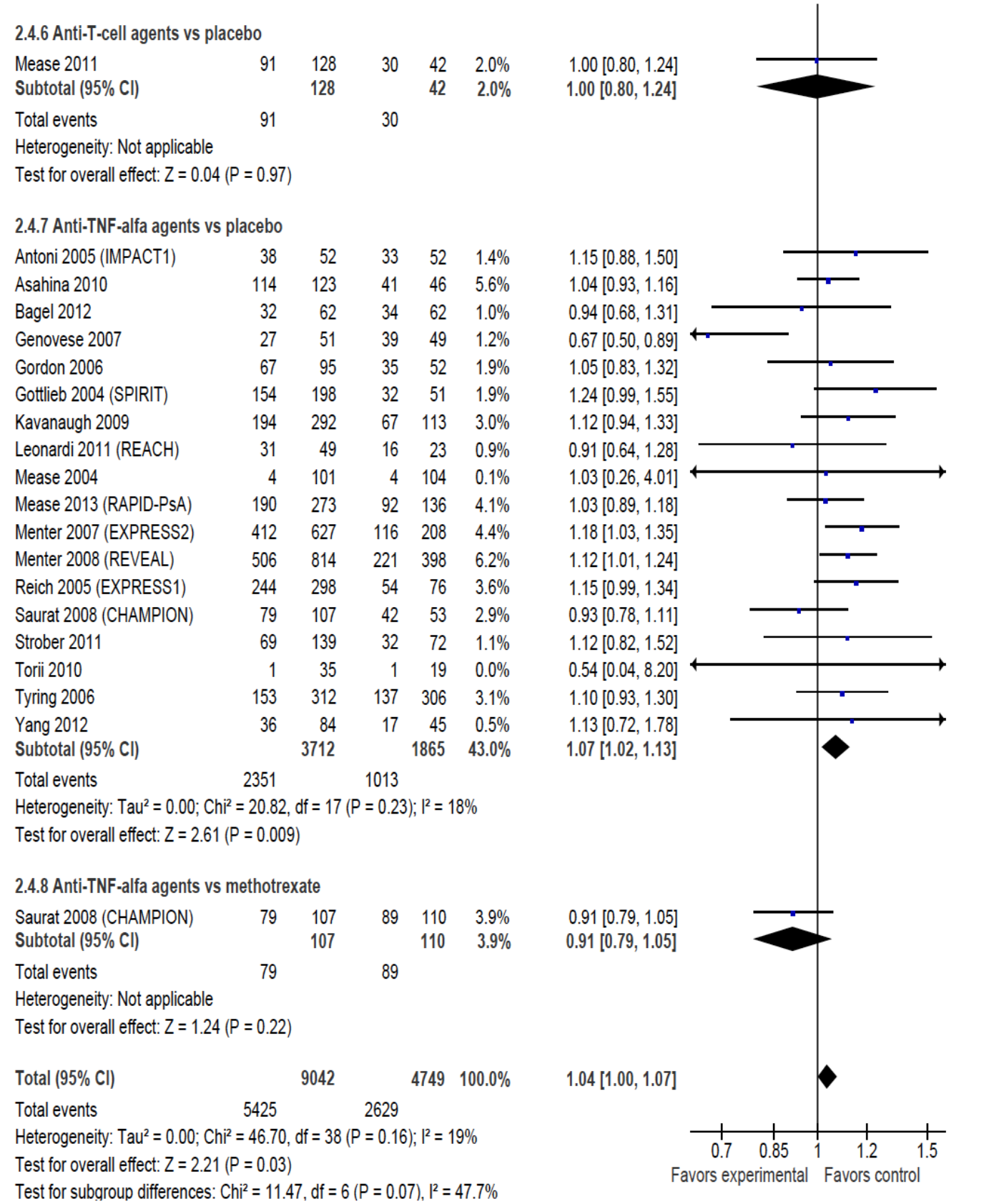


Figure 6: Forest plot for adverse events (AE). IL=interleukin. TNF=tumor necrosis factor.

Table 2: Reduction ≥75% in the Psoriasis Area and Severity Index (PASI75) expressed as decreasing rate ratios for different classes of biologic agents against placebo, rate ratios against best treatment, and probability of being best treatment, stemming from a 5.8% (0.2%-15.2%) rate in the placebo group*

Class	Rate ratio vs placebo	Rate ratio vs best class (anti-IL-17 agents)	Probability of being best
Anti-IL-17 agents	9.53 (5.55-13.80)	-	71.2%
Anti-IL-12/23 agents	8.15 (6.77-9.58)	0.76 (0.25-1.96)	25.5%
Anti-TNF-α agents	6.96 (5.96-8.15)	0.55 (0.16-1.49)	1.1%
Methotrexate	4.00 (1.30-9.00)	0.24 (0.05-1.22)	2.1%
Acitretin	3.82 (2.32-5.86)	0.23 (0.06-0.71)	<0.1%
Anti-T-cell agents	2.36 (1.17-4.59)	0.13 (0.03-0.46)	<0.1%
Placebo	-	0.11 (0.07-0.18)	0

*Rate ratios far from 1.0 indicate credibly different rates, with RR>1.0 suggesting that the agents of choice are better than placebo or the best class, and RR<1.0 suggesting that the agents of choice are worse than placebo or the best class; IL=interleukin; TNF=tumor necrosis factor.

Table 3: Improvement ≥20% in the American College of Rheumatology core set of outcomes (ACR20) expressed as decreasing rate ratios for different classes of biologic agents against placebo, rate ratios against best treatment, and probability of being best treatment, stemming from a 17.4% (15.1%-19.6%) rate in the placebo group*

Class	Rate ratio vs placebo	Rate ratio vs best class (anti-TNF-α agents)	Probability of being best
Anti-TNF-α agents	2.58 (2.12-3.15)	-	53.0%
Anti-IL-17 agents	2.12 (0.59-4.65)	0.71 (0.13-5.99)	33.8%
Anti-T-cell agents	1.86 (0.78-3.48)	0.58 (0.17-1.99)	12.6%
Anti-IL-12/23 agents	1.35 (0.79-2.32)	0.37 (0.17-0.86)	0.7%
Placebo	-	0.39 (0.32-0.42)	0

*Rate ratios far from 1.0 indicate credibly different rates, with RR>1.0 suggesting that the agents of choice are better than placebo or the best class, and RR<1.0 suggesting that the agents of choice are worse than placebo or the best class; IL=interleukin; TNF=tumor necrosis factor.

Table 4: Serious adverse events (SAE) expressed as increasing rate ratios for different classes of biologic agents against placebo, rate ratios against best treatment, and probability of being best treatment, stemming from a 2.4% (1.9%-2.8%) rate in the placebo group*

Class	Rate ratio vs placebo	Rate ratio vs best class (methotrexate)	Probability of being best
Methotrexate	0.63 (0.14-2.35)	-	55.9%
Anti-T-cell agents	0.97 (0.30-3.35)	1.56 (0.26-121.95)	22.9%
Anti-IL-12/23 agents	0.98 (0.52-1.73)	1.57 (0.42-6.25)	8.2%
Anti-TNF-α agents	1.35 (0.85-2.04)	2.20 (0.53-9.62)	0.7%
Anti-IL-17 agents	1.45 (0.48-4.99)	2.40 (0.41-172.41)	7.2%
Placebo	-	1.55 (0.43-7.14)	5.2%

*Rate ratios far from 1.0 indicate credibly different rates, with RR<1.0 suggesting that the agents of choice are better than placebo or the best class, and RR>1.0 suggesting that the agents of choice are worse than placebo or the best class; IL=interleukin; TNF=tumor necrosis factor.

trials, is sufficiently comprehensive and consistent to enable precise estimation of efficacy and safety of the different class types of biologics; b) application of network meta-analysis methods to this topic yields quantitative estimates of the relative efficacy and safety of such classes, showing that anti-IL-17 and anti-TNF-α agents appear the most effective ones, and anti-T-cell agents appear the safest ones; and c) this work, building upon a prior analysis on the very same set of data but exploiting an agent-level focus [15], provides a

Table 5: Adverse events (AE) expressed as decreasing rate ratios for different classes of biologic agents against placebo, rate ratios against best treatment, and probability of being best treatment, stemming from a 51.8% (50.2%-53.4%) rate in the placebo group*

Class	Rate ratio vs placebo	Rate ratio vs best class (methotrexate)	Probability of being best
Methotrexate	0.99 (0.88-1.10)	-	6.6%
Anti-T-cell agents	1.00 (0.80-1.22)	1.04 (0.80-1.25)	44.6%
Anti-IL-17 agents	1.02 (0.92-1.13)	1.02 (0.87-1.14)	21.3%
Anti-IL-12/23 agents	1.03 (0.99-1.07)	1.00 (0.93-1.08)	1.2%
Anti-TNF-α agents	1.05 (1.01-1.08)	1.03 (0.89-1.19)	0
Placebo	-	1.01 (0.91-1.14)	26.1%

*Rate ratios far from 1.0 indicate credibly different rates, with RR<1.0 suggesting that the agents of choice are better than placebo or the best class, and RR>1.0 suggesting that the agents of choice are worse than placebo or the best class; IL=interleukin; TNF=tumor necrosis factor.

clear example of the potential usefulness of mixed treatment comparison methods in summarizing apparently complex sets of data and guide, despite the inherent limitation of these approaches and the many assumptions, clinical decision making.

The outlook of patients with more than mild psoriasis or suffering from psoriatic complications such as arthritis has momentously changed thanks to the introduction of biologic therapy, which is based on disease modifying pharmacologic agents capable of substantial effects on the pathophysiologic mechanisms underlying this condition, while concomitantly minimizing, as much as possible toxicity [22]. The pioneering successes of the first trials on biologics in psoriasis have lead to the progressive increase in the availability of agents from the same pharmacologic class, as well as from other classes. Accordingly, while it appears evident that biologics are now a mainstay in moderate to severe psoriasis or psoriatic arthritis, it is also true that clinicians face the dilemma of choosing first the class of agents with the most favorable risk-benefit profile, and then, within that specific class, the best agent [23].

This line of thinking is based on the widespread assumption in clinical medicine and pharmacology that drugs have a class effect, with only minor differences between individual agents belonging to the same class [5]. This assumption has been challenged in several settings and is difficult to prove unless a comprehensive evidence base is available. Yet, the human mind, and, in particular, the clinician's mind relies often on this assumption, as do the research and development units of pharmacologic companies when aiming at developing a specific novel or "me-too" agent.

Several independent researchers have recently provided a comprehensive and synthetic appraisal of the risk-benefit profile of specific and individual biologic agents in the management of psoriasis. However, no formal appraisal of the presence of class effects is hitherto available, neither in our recent work nor in other similar ones. Yet, this clinical question appears interesting and scientifically important. If differences between individual biologic agents have nothing to do with the corresponding class, then hypothetically a class-level analysis will not be evident, and no significant differences will appear between the different classes or versus placebo. Conversely, if a class effect does exist, then hypothetically we should be able to demonstrate beyond random variability that a given class is superior or inferior to other classes or to placebo. This is indeed what we found, thus demonstrating that class effects are present and impact on risk and benefit of biologic therapy.

Specifically, our work shows that anti-IL-17 agents are the most promising ones when treating patients with moderate to severe psoriasis and aiming for the highest likelihood of achieving a PASI75 result (i.e. a reduction ≥75% in the Psoriasis Area and Severity Index). When the goal is instead achieving an improvement ≥20% in the American College of Rheumatology core set of outcomes in patients with psoriatic arthritis, TNF-α agents appear the most promising. Conversely, if the risks of adverse effects of biologic therapy need to be minimized, then anti-T-cell agents appear as the safest option. Clinicians might exploit this piece of evidence when initially treating a patient to choose the class of agents with the most favorable risk-benefit profile in keeping with the specific individual disease severity as well as likelihood of adverse effects. Moreover, awareness of these class effects might help in changing from an individual biologic agent to another from the same class if there are agent-specific intolerances or contraindications.

Physicians might thus move from a class to a different one depending on the response to the initial biologic therapy and changes in treatment goals. Similar findings, despite some minor differences mainly stemming from the diverse pools of included studies, have been reported by other authors, who however only focused on agent-level analyses [6-10].

From a more poignant statistical perspective, this work provides a clear example of the pros and cons of exploiting by means of mixed treatment comparison methods a complex evidence network [11,24-26]. We hereby emphasize class effects, whereas previous works mainly emphasized agent-specific effects. Both approaches may appear partial and somewhat naïve, but they both contribute in understanding and making sense of the complexity of randomized trials focusing on biologics in psoriasis. The robustness of our findings is testified by the similar results achieved at agent- and class-level analyses, by the concordance of analysis based on fixed- or random-effects methods, and by the coherent results stemming from consistent and inconsistent models [6].

Limitations of this review are substantial, and go beyond those typical of network meta-analyses and mixed treatment comparisons [11]. A key limitation is the reliance, for efficacy appraisal, on subjectively collected and measured endpoints, and, for safety appraisal, on adverse outcomes which may be too sensitively collected, thus lacking specificity and clinical relevance [27]. In addition, the prevalent star shape of the evidence network may hinder the robustness of indirect estimates for some comparisons. In addition, follow-up was limited to few months, thus limiting our inferential strength on long-term efficacy and safety results. It must also be emphasized that this work builds upon a prior agent-level meta-analysis recently published in this Journal by our group. It however provides additional results and insights and may thus help to guide clinical decision making, highlighting the pros and cons of using a class-level rather than an agent-level approach when quantifying the risk-benefit balance of biologic agents in psoriasis. Finally, the lack of simultaneous agent- and class-level effects or meta-regression adjustment for key moderators may provide spuriously precise results. Accordingly, further analyses will be necessary to corroborate our present findings when adequately powered head-to-head randomized trials have been conducted and reported.

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 class of agents, with anti-IL-17 and anti-TNF-α agents appearing most effective, and anti-T-cell agents appearing safest. Clinicians should bear in mind these features to maximize safety and efficacy of biologic therapy in the individual patient.

CONFLICTS OF INTEREST

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

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