Effect of Biologic Agents on Non-PASI Outcomes in Moderate-to-Severe Plaque Psoriasis: Systematic Review and Meta-Analyses

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ABSTRACT

Introduction: The objective of this review was to conduct a systematic review with meta-analysis and Bayesian mixed treatment comparisons (MTC) evaluating the impact of biologics on non-Psoriasis Area and Severity Index (PASI) health outcomes in patients with moderate-to-severe plaque psoriasis.

Methods: MEDLINE and Cochrane Central Register of Controlled Trials were searched from 1966 to May 2009. Citations were screened for randomized, controlled trials of biologics versus either placebo or each other in adults with moderate-to-severe plaque psoriasis and reported any of several outcomes. Traditional and Bayesian MTC meta-analyses were conducted for each endpoint using either a random- or fixed-effect model where appropriate.

Results: Thirty-eight studies met eligibility criteria. All biologics showed significant improvement in achieving a good response on the static physician’s global assessment (PGA) versus placebo while, in the MTC, differences were noted between individual drugs. In achieving a good response on the dynamic PGA, all biologics showed significant improvements over placebo, while the MTC showed significant improvements with the anti-interleukins versus anti-T cells. Relative to placebo, antitumor necrosis factor (TNF) agents and anti-interleukins showed significant improvements in the Dermatology Life Quality Index (DLQI). Compared with placebo, the anti-TNF agents showed significant improvements in both 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36) mental and physical health outcomes.
component scores, while anti-T cell agents showed no improvements. The MTC showed no differences between any biologics for either the DLQI or SF-36.

**Conclusion:** Individual biologics and classes showed consistent benefits across non-PASI health outcomes in patients with moderate-to-severe plaque psoriasis while MTC meta-analyses suggested that some differences exist.

**Keywords:** Biologics; Meta-analysis; Plaque psoriasis

**INTRODUCTION**

Psoriasis is a chronic inflammatory disorder seen in approximately 2–3% of the world’s population, affecting the skin and often joints. The most common form is plaque psoriasis, which appears as sharply demarcated, erythematous areas covered with silvery-white scale [1, 2]. The formation of psoriatic plaques involves the interplay of T cells, cytokines, and keratinocytes. The presence of activated T cells within psoriatic plaques and the response to T cell-directed therapy suggest an immunologic nature of the disease [3, 4]. Various cytokines, such as tumor necrosis factor alpha (TNFα), are also present in psoriatic lesions, and may be a target for drug therapy [5]. Both cytokines and activated T cells promote the dysregulated growth of keratinocytes, leading to patches of erythematous, scaly skin.

Although there is no cure, treatment is directed at decreasing the signs and symptoms of psoriasis and modifying the natural progression of the disease. Methotrexate and cyclosporine are systemic agents that have proven efficacy but are limited by various toxicities including liver and kidney complications [1]. Numerous other systemic biologic agents are available and are categorized into three classes: anti-T cell agents (efalizumab, which was removed from the United States market in 2009, and alefacept), anti-TNF agents (infliximab, adalimumab, and etanercept), and anti-interleukin (IL)-12/23 agents (ustekinumab and an investigational agent briakinumab) [6].

Prior meta-analyses have demonstrated the benefits of these agents on various outcomes in moderate-to-severe plaque psoriasis [7, 8]. This includes studies of the Psoriasis Area and Severity Index (PASI), a traditionally reported endpoint in this area [8]. However, none have comprehensively evaluated the impact of biologics on the physician’s global assessment (PGA) or assessments of health-related quality of life (HRQoL). Thus, the authors conducted a systematic review with meta-analysis and Bayesian mixed treatment comparisons (MTC) evaluating the impact of biologics on health outcomes, including the PGA and patient-reported HRQoL in patients with moderate-to-severe plaque psoriasis.

**METHODS**

**Search Strategy**

Two independent investigators conducted systematic literature searches of MEDLINE (1966 to May 2009) using the Cochrane Highly Sensitive and specific Search Strategy (Sensitivity and Precision Maximizing Version 2008) [9], and the Cochrane Central Register of Controlled Trials (1966 to May 2009). The following Medical Subject Heading and text keywords were used: psoriasis, plaque psoriasis, etanercept, infliximab, adalimumab, efalizumab, alefacept, ustekinumab, ABT-874 (briakinumab), T cell modulator, monoclonal...
antibody, tumor necrosis factor, biologic agent, and biologics.

**Study Selection**

Studies were included in the evaluation if they were (1) randomized, controlled trials (RCTs) of biologic agents to treat psoriasis versus placebo or each other; (2) conducted in adult patients with moderate-to-severe plaque psoriasis, usually defined as having an inadequate response to topical treatments alone and either having received prior systemic therapy or are candidates for such therapy; and (3) studies that reported efficacy data on clinical or humanistic outcomes. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram was constructed for the literature search and selection process to describe the number of citations identified, studies excluded, and studies ultimately included (Fig. 1) [10].

**Validity Assessment**

All studies were reviewed and evaluated by two reviewers with disagreement resolved by discussion. The validated Jadad scale was used to assess the methodological quality of included trials [11]. This rating scale assesses inherent controllers of bias by using the following quality assessment criteria: use of and methods for generating randomization; use of and methods for double-blinding; and description of patient withdrawals and dropouts. One point was given for each satisfied criterion. An aggregate score between 0 and 5 was calculated for each included trial (0 = weakest, 5 = strongest), with trials scoring <3 deemed to have lower methodological quality.

**Data Abstraction**

Through use of a standardized data abstraction tool, two reviewers independently collected data, with disagreement resolved through discussion or triage to a third reviewer. The following information was obtained from each trial: author identification, year of publication, study design and above-mentioned methodological quality criteria, source of study funding, study population, patient demographics, and co-morbidities.

**Study Endpoints**

The first endpoint is the PGA, which can be reported as either a static or dynamic scale [12]. There is no standard PGA, and different versions include six- or seven-point scales, which measure the severity of psoriasis. Terms such as “clear” or “excellent” (scores of 0 or 1) are used to define the clearing of psoriatic plaques from the skin, with higher scores denoting more severe disease. To measure HRQoL, two scales are used. The first is the (acute or chronic version) 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36). It measures eight domains of HRQoL (physical function, social function, pain, physical and emotional role limitation, vitality, personal perceptions of health, and emotional well-being). Normal scores have a mean of 50, with higher scores being more favorable. The second is the Dermatology Life Quality Index (DLQI), a 10-item questionnaire that assesses the impact of chronic skin conditions on HRQoL, and is frequently used in clinical trials of psoriasis [13]. Scores range from 0 to 30, with 0 representing no disease impact on HRQoL.
Statistical Analysis

Traditional meta-analysis was initially performed. For the primary analyses, only the US Food and Drug Administration (FDA)-approved doses for each agent were included (for briakinumab, the investigational doses were included). In an attempt to avoid double-counting individual agents in the analyses, when studies investigated more than one FDA-approved dose, only the highest dose was included in an analysis. This rule was not applied to either ustekinumab or briakinumab, which were not FDA-approved at the time this protocol was developed. Sensitivity analyses were also performed whereby data from all studies were included, regardless of dose. For dichotomous endpoints, weighted averages were reported as odds ratios (ORs) with associated 95% CIs using a DerSimonian and Laird random-effects model [14]. For traditional meta-analysis for continuous outcomes,
weighted averages were reported using a difference between means, with associated 95% CIs using a DerSimonian and Laird random-effects model [14].

Statistical heterogeneity was addressed using the I² statistic, which assesses the degree of inconsistency across studies and ranges from 0% to 100% with the higher percentage representing a higher likelihood of the existence of heterogeneity [15]. Visual inspection of funnel plots and Egger’s weighted regression statistics were used to assess for the presence of publication bias [16, 17]. Statistics were performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd., Cheshire, UK) and Comprehensive Meta-Analysis, Version 2 (Biostat, Englewood, NJ, USA). A P value of <0.05 was considered statistically significant for all analyses.

In addition to traditional meta-analysis, a MTC meta-analysis was conducted using previously validated WinBUGS code [18–22]. MTC methods were used to compare the different biologic agents to treat plaque psoriasis. These methods are a generalization of meta-analysis methods because they allow comparisons of agents not addressed within any of the individual trials. A random-effects model was fitted, taking into account the correlation structure induced by multi-arm trials. All MTC analyses were conducted using a Bayesian Markov chain Monte Carlo method and fitted in the freely available Bayesian Software, WinBUGS.

RESULTS

Literature Search

A total of 1,287 citations were identified through the MEDLINE, Cochrane Central, and manual reference searches (Fig. 1). Of these, 31 studies were identified describing the following comparisons (Table 1) [23–53]: alefacept versus placebo (n = 5) [23–27]; efalizumab versus placebo (n = 7) [28–34]; infliximab versus placebo (n = 6) [35–40]; adalimumab versus placebo (n = 5) [41–45]; etanercept versus placebo (n = 4) [46–49]; ustekinumab versus placebo (n = 3) [50, 51]; briakinumab versus placebo (n = 1) [53]. A total of 20 studies were included in the statistical analyses and evaluated FDA-approved doses: alefacept (n = 2) [26, 27], efalizumab (n = 4) [31–34], infliximab (n = 3) [36–38], adalimumab (n = 4) [41, 42, 44, 45], etanercept (n = 3) [46–48], ustekinumab (n = 3) [50–52], briakinumab (n = 1) [53].

PGA Static Response Rate

Sixteen RCTs evaluating seven drugs from three classes reported data on the PGA response rate using a static scale (Table 2) [23, 24, 27, 31, 33, 34, 36, 38, 42, 45–49, 51–53]. All of the RCTs were of high quality (Jadad ≥4) and ranged from 8 to 24 weeks in duration. Ten studies [31, 33, 34, 36, 38, 42, 45, 51–53] defined their endpoint using a scale of “clear” or “minimal” rating while the remaining six studies [23, 24, 27, 46, 48, 49] used a scale of “clear” or “almost clear.”

Six RCTs evaluated the anti-T cell agents with a single alefacept study [27] and three efalizumab studies [31, 33, 34] reporting results using FDA-approved doses. Seven RCTs evaluated the anti-TNF agents with two infliximab studies [36, 38], two adalimumab studies [42, 45], and two etanercept studies [46, 48] evaluating FDA-approved doses. Three RCTs evaluating the anti-IL-12/23 agents were included. Two ustekinumab studies [51, 52] reported results using the FDA-approved dose and the maximally effective dose of
Table 1  Included study characteristics

| Study, ref       | Years | Study duration (weeks) | Comparison | N    | Baseline PASI       | Jadad Score |
|------------------|-------|------------------------|------------|------|---------------------|-------------|
| **Alefacept**    |       |                        |            |      |                     |             |
| Ellis et al. [23]| 2001  | 12                     | ALA 0.025 mg/kg IV QW | 57   | 14 (4–45)            | 5           |
|                  |       |                        | ALA 0.075 mg/kg IV QW | 55   | 15 (4–45)            |             |
|                  |       |                        | ALA 0.150 mg/kg IV QW | 58   | 20 (7–33)            |             |
|                  |       |                        | Placebo    | 59   | 15 (3–72)            |             |
| Gordon et al. [24]| 2003  | 12                     | ALA 7.5 mg IV QW | 367  | 14.4–15.9            | 5           |
| Feldman et al. [25]| 2004  |                        | Placebo    | 186  | 15.1                |             |
| Finlay et al. [26]| 2003  | 12                     | ALA 10 mg IM QW | 173  | 15.1 (3.4–58.8)     | 5           |
| Lebwohlet al. [27]| 2003  | 14                     | ALA 15 mg IM QW | 168  | 13.2 (3.7–52.8)     |             |
|                  |       |                        | Placebo    | 168  | 14.3 (5.3–44.8)     |             |
| **Efalizumab**   |       |                        |            |      |                     |             |
| Papp et al. [28] | 2001  | 8                      | EFA 0.1 mg/kg IV QW | 22   | 18.2 ± 6.7          | 4           |
|                  |       |                        | EFA 0.3 mg/kg IV QW | 75   | 19.1 ± 7.3          |             |
|                  |       |                        | Placebo    | 48   | 16.2 ± 4.4          |             |
| Gordon et al. [29]| 2003  | 12                     | EFA 1 mg/kg SQ QW | 369  | 19.4 (10.1–58.7)    | 4           |
| Menter et al. [30]| 2005  |                        | Placebo    | 187  | 19.4 (11.4–50.3)    |             |
| Leonardi et al. [31]| 2005  | 12                     | EFA 1 mg/kg SQ QW | 160  | 18.6 (11.9–50.1)    | 5           |
|                  |       |                        | EFA 2 mg/kg SQ QW | 166  | 18.9 (10–55.6)      |             |
|                  |       |                        | Placebo    | 170  | 19.0 (9.6–57.6)     |             |
| Ortone et al. [32]| 2005  | 12                     | EFA 1 mg/kg SQ QW | 529  | 23.6 ± 9.7          | 5           |
| Dubertret et al. [33]| 2006  |                        | Placebo    | 264  | 23.0 ± 9.6          |             |
| Papp et al. [34] | 2006  | 12                     | EFA 1 mg/kg SQ QW | 450  | 19.1 ± 7.5          | 5           |
|                  |       |                        | Placebo    | 236  | 18.7 ± 7.0          |             |
| **Infliximab**   |       |                        |            |      |                     |             |
| Chaudhari et al. [35]| 2001  | 10                     | INF 5 mg/kg IV$^c$ | 11   | 22.1 ± 11.5         | 5           |
|                  |       |                        | INF 10 mg/kg IV | 11   | 26.6 ± 10.3         |             |
|                  |       |                        | Placebo    | 11   | 20.3 ± 5.5          |             |
| Gottlieb et al. [36]| 2004  | 10                     | INF 3 mg/kg IV$^c$ | 99   | 20 (15, 26)         | 5           |
| Feldman et al. [37]| 2005  |                        | INF 5 mg/kg IV | 99   | 20 (14, 28)         |             |
|                  |       |                        | Placebo    | 51   | 18 (15, 27)         |             |
| Reich et al. [38] | 2005  | 24                     | INF 5 mg/kg IV$^c$ | 301  | 22.9 ± 9.3          | 4           |
|                  |       |                        | Placebo    | 77   | 22.8 ± 8.7          |             |
| Study, ref     | Years | Study duration (weeks) | Comparison | N  | Baseline PASI | Jadad Score |
|---------------|-------|------------------------|------------|----|---------------|-------------|
| Menter et al. [39] | 2007  | 10                     | INF 3 mg/kg IV | 313 | 20.1 ± 7.9 | 5           |
| Feldman et al. [40] | 2008  |                         | INF 5 mg/kg IV | 314 | 20.4 ± 7.5 |             |
|               |       |                        | Placebo     | 208 | 19.8 ± 7.7 |             |
| Adalimumab    |       |                        |             |     |               |             |
| Revicki et al. [41] | 2007  | 16                     | ADA 40 mg SQ QOW | 814 | 19.0 ± 7.1 | 5           |
| Menter et al. [42] | 2008  |                         | Placebo     | 397 | 18.8 ± 7.1 |             |
| Shikiar et al. [43] | 2007  | 12                     | ADA 40 mg SQ QOW | 45  | 16.7 (5.4–39.0) \(a\) | 4           |
|               |       |                        | ADA 40 mg SQ QW | 50  | 14.5 (2.3–42.4) \(a\) |             |
|               |       |                        | Placebo     | 52  | 16.0 (5.5–40.4) \(a\) |             |
| Revicki et al. [44] | 2008  | 16                     | ADA 40 mg SQ QOW | 110 | 19.4 ± 7.4 | 5           |
| Saurat et al. [45] | 2008  |                         | Placebo     | 53  | 19.2 ± 6.9 |             |
| Etanercept    |       |                        |             |     |               |             |
| Leonardi et al. [46] | 2003  | 12                     | ETA 25 mg SQ QW | 160 | 19.3 ± 11.4 | 4           |
|               |       |                        | ETA 25 mg SQ BIW | 162 | 18.5 ± 11.5 |             |
|               |       |                        | ETA 50 mg SQ BIW | 164 | 18.6 ± 11.5 |             |
|               |       |                        | Placebo     | 166 | 18.4 ± 11.6 |             |
| Krueger et al. [47] | 2005  | 12                     | ETA 25 mg SQ BIW | 196 | 19.1 ± 8.2 | 5           |
| Papp et al. [48] | 2005  |                         | ETA 50 mg SQ BIW | 194 | 19.5 ± 8.8 |             |
|               |       |                        | Placebo     | 193 | 18.6 ± 8.6 |             |
| Van de Kerkhof et al. [49] | 2008  | 12                     | ETA 50 mg SQ QW | 96  | 21.4 ± 9.3 | 4           |
|               |       |                        | Placebo     | 46  | 21.0 ± 8.7 |             |
| Ustekinumab   |       |                        |             |     |               |             |
| Krueger et al. [50] | 2007  | 12                     | UST 45 mg SQ X1 | 64  | 19.0 ± 7.4 | 4           |
|               |       |                        | UST 45 mg SQ QW X4 | 64  | 18.9 ± 7.0 |             |
|               |       |                        | UST 90 mg SQ X1 | 64  | 18.8 ± 7.3 |             |
|               |       |                        | UST 90 mg SQ QW X4 | 64  | 19.0 ± 7.9 |             |
|               |       |                        | Placebo     | 64  | 19.9 ± 8.3 |             |
| Leonardi et al. [51] | 2008  | 12                     | UST 45 mg SQ \(X\) | 255 | 20.5 ± 8.6 | 5           |
|               |       |                        | UST 90 mg SQ | 256 | 19.7 ± 7.6 |             |
|               |       |                        | Placebo     | 255 | 20.4 ± 8.6 |             |
briakinumab (200 mg every other week) was reported in another study [53].

Each individual agent, as well as each class, showed an increase in the odds of achieving a positive response (Fig. 2) [27, 31, 33, 34, 36, 38, 42, 45, 46, 48, 51–53]. When all anti-T cell agent RCTs (OR 5.89, 95% CI 4.34–7.99) and anti-TNF agent RCTs (OR 24.27, 95% CI 15.66–37.61) were pooled, regardless of dose, slightly smaller overall effects were seen.

The MTC analysis included data from 13 trials of seven therapies in three drug classes that reported data on the PGA response rate using a static scale and included arms using the FDA-approved dose (Tables 3, 4) [27, 31, 33, 34, 36, 38, 42, 43, 46, 48, 51–53]. The placebo-based comparisons were similar to those discussed above, although generally had wider credible intervals (CrI). When the drug classes were analyzed, both the anti-TNF agents (OR 6.19, 95% CrI 2.75–12.87) and anti-IL-12/23 agents (OR 7.60, 95% CrI 3.25–18.80) were suggested to be superior to the anti-T cell agents. Pair-wise drug comparisons followed similar trends with many anti-TNF and anti-IL-12/23 agents showing superior results to the anti-T cell agents.

PGA Dynamic Response Rate

Seven RCTs evaluating three drugs from three classes reported data on the PGA response rate using a dynamic scale (Table 2) [28, 29, 31, 33, 35, 39, 50]. All of the RCTs were of high quality (Jadad ≥4) and ranged from 10 to 12 weeks in duration. All of the studies defined their endpoint using a rating of “clear” or “excellent.” Efalizumab was the only anti-T cell agent that provided data on the PGA dynamic

| Table 1 continued |
|-------------------|
| Study, ref        | Years | Study duration (weeks) | Comparison | N   | Baseline PASI | Jadad Score |
|-------------------|-------|------------------------|------------|-----|---------------|-------------|
| Papp et al. [52]  | 2008  | 12                     | UST 45 mg SQ$^c$ | 409 | 19.4 ± 6.8    | 4           |
|                   |       |                        | UST 90 mg SQ  | 411 | 20.1 ± 7.5    |             |
|                   |       |                        | Placebo     | 410 | 19.4 ± 7.5    |             |
| Briakinumab       |       |                        | BRI 100 mg SQ QOW | 30  | 20.0 ± 6.9    | 4           |
| Kimball et al. [53]| 2008  | 12                     | BRI 200 mg SQ X1 | 30  | 18.0 ± 6.7    |             |
|                   |       |                        | BRI 200 mg SQ QW X4 | 30  | 20.0 ± 7.6    |             |
|                   |       |                        | BRI 200 mg SQ QOW | 30  | 20.0 ± 6.2    |             |
|                   |       |                        | BRI 200 mg SQ  | 30  | 19.0 ± 6.3    |             |
|                   |       |                        | QW X12       | 30  | 16.0 ± 2.9    |             |

ADA adalimumab, ALA alefacept, BIW twice weekly, BRI briakinumab, EFA efalizumab, ETA etanercept, INF infliximab, IV intravenous, PASI psoriasis area and severity index, QW every week, QOW every other week, SQ subcutaneous, UST ustekinumab

a Median (range)
b Mean (range)
c At weeks 0, 2, and 6
d Median (interquartile range)
e At weeks 0, 4, then every 12 weeks

Efalizumab was the only anti-T cell agent that provided data on the PGA dynamic...
Table 2  Traditional meta-analysis results

| Comparison       | PGA-static<sup>a</sup> | PGA-dynamic<sup>a</sup> | DLQI<sup>b</sup>            | SF-36 MCS<sup>b</sup> | SF-36 PCS<sup>b</sup> |
|------------------|------------------------|-------------------------|--------------------------|------------------------|------------------------|
| ALA versus PLC   | 3.79 (1.95–7.39)       | –                       | −2.20 (−4.80 to 0.40)    | 2.18 (−1.61 to 5.97)   | 1.95 (−1.44 to 5.34)   |
| 1 RCT [27]       | 1 RCT [26]             |                         |                          | 1 RCT [26]             | 1 RCT [26]             |
| EFA versus PLC   | 8.99 (5.22–15.49)      | 10.27 (6.83–15.46)      | −3.54 (−6.52 to −0.57)   | −                      | −                      |
| 3 RCTs [31, 33, 34] | 3 RCTs [29, 31, 33] |                         |                          |                        |                        |
| Anti-T versus PLC | 7.23 (4.05–12.91)    | 10.27 (6.83–15.46)      | −2.78 (−4.74 to −0.83)   | 2.18 (−1.61 to 5.97)   | 1.95 (−1.44 to 5.34)   |
| 4 RCTs [27, 31, 33, 34] | 3 RCTs [29, 31, 33] | 2 RCTs [30, 32] |                          | 1 RCT [26]             | 1 RCT [26]             |
| INF versus PLC   | 89.87 (37.02–218.18)  | 160.47 (23.07–1,116.41) | −9.40 (−10.55 to −8.24) | 5.60 (4.13 to 7.07)    | 4.92 (2.59 to 7.25)    |
| 2 RCTs [36, 38]  | 2 RCTs [35, 39]        | 3 RCTs [37, 38, 40]     |                          | 2 RCTs [38, 40]        | 2 RCTs [38, 40]        |
| ADA versus PLC   | 31.74 (20.12–50.07)    | −                       | −6.53 (−7.11 to −5.94)   | 4.94 (0.89 to 8.94)    | 3.29 (2.28 to 4.30)    |
| 2 RCTs [42, 45]  | 2 RCTs [41, 43]        | 2 RCTs [41, 43]        |                          | 2 RCTs [38, 40]        |                        |
| ETA versus PLC   | 25.88 (14.21–47.15)    | −                       | −6.68 (−13.38 to −0.02)  | −                      | −                      |
| 2 RCTs [46, 48]  | 1 RCT [47]             |                        |                          |                        |                        |
| Anti-TNF versus PLC | 35.12 (22.71–54.31)  | 160.47 (23.07–1,116.41) | −8.42 (−10.29 to −6.54)  | 4.98 (3.40 to 6.55)    | 4.06 (2.82 to 5.29)    |
| 6 RCTs [36, 38, 42, 45, 46, 48] | 2 RCTs [35, 39] | 5 RCTs [37, 38, 40, 41, 43, 47] |                  | 4 RCTs [38, 40, 41, 43] | 4 RCTs [38, 40, 41, 43] |
| UST versus PLC   | 41.38 (21.21–80.75)    | 62.29 (14.85–261.23)    | −8.53 (−9.94 to −7.65)   | −                      | −                      |
| 2 RCTs [51, 52]  | 1 RCT [50]             | 2 RCTs [51, 52]        |                          |                        |                        |
| BRI versus PLC   | 188.5 (19.78–1,796.21) | −                       | −                        | −                      | −                      |
| 1 RCT [53]       |                        |                        |                          |                        |                        |
| Anti-IL versus PLC | 45.86 (31.40–66.99)  | 62.29 (14.85–261.23)    | −8.53 (−9.41 to −7.65)   | −                      | −                      |
| 3 RCTs [51–53]   | 1 RCT [50]             | 2 RCTs [51, 52]        |                          |                        |                        |

AD<sub>a</sub> alafacept, ALA<sub>a</sub> alefacept, DLQ<sub>i</sub>I<sub>a</sub> Dermatology Life Quality Index, EFA<sub>a</sub> efalizumab, ETA<sub>a</sub> etanercept, IL<sub>a</sub> interleukin 12/23, INF<sub>a</sub> infliximab, MTC<sub>a</sub> mixed treatment comparison, PGA<sub>a</sub> physician’s global assessment, PLC<sub>a</sub> placebo, RCT<sub>a</sub> randomized, controlled trial, SF-36<sub>a</sub> 36-item Medical Outcomes Study Short-Form General Health Survey, T<sub>a</sub> T cell, TNF<sub>a</sub> tumor necrosis factor-alpha, UST<sub>a</sub> ustekinumab

<sup>a</sup> Results presented as odds ratio (95% confidence interval)

<sup>b</sup> Results presented as weighted mean difference (95% confidence interval)
endpoint with three RCTs evaluating FDA-approved doses [28, 29, 31, 33]. Infliximab was the only anti-TNF agent that reported data on this endpoint, with two RCTs evaluating FDA-approved doses [35, 39]. Ustekinumab was the only anti-IL-12/23 agent that reported data on this endpoint [50].

Each individual agent, as well as each class, showed an increase in the odds of achieving a positive response (Fig. 3) [24, 31, 33, 35, 39, 50]. When all anti-T cell agent RCTs (OR 9.73, 95% CI 6.54–14.49) and anti-TNF agent RCTs (OR 140.58, 95% CI 39.14–504.97) were pooled, regardless of dose, similar overall effects were seen.

The MTC analysis included data from six RCTs of three therapies in three drug classes that reported data on the PGA response rate using a dynamic scale and included arms using the FDA-approved dose [29, 31, 33, 35, 39, 50]. Due to the small numbers of studies included in the analysis, many indirect comparisons yielded unreliable results (Tables 3, 4). As a class, the anti-TNF agents were suggested to be superior to the anti-T cell agents (OR 22.53, 95% CrI 2.61–206.3).

Change in DLQI from Baseline

Fifteen RCTs evaluating six drugs from three classes reported data on the change in DLQI score from baseline (Table 2) [23, 25, 26, 30, 32, 37, 38, 40, 41, 43, 47, 49–52]. All of the RCTs were of high quality (Jadad ≥4) and ranged from 10 to 24 weeks in duration. A lower score on the DLQI represents an improvement, with a score of 0
| Comparison   | PGA-static | PGA-dynamic | DLQI\(^b\)  | SF-36 MCS\(^b\) | SF-36 PCS\(^b\) |
|-------------|------------|-------------|-------------|----------------|----------------|
| ALA versus PLC | 3.92 (1.54–10.52) | – | −2.22 (−4.46 to 0.03) | 2.20 (−0.75 to 5.08) | 1.98 (−0.93 to 4.83) |
| EFA versus PLC | 9.31 (5.41–17.15) | 11.09 (3.89 to 32.46) | −3.67 (−5.70 to −1.67) | – | – |
| INF versus PLC | 104.3 (39.84–309.2) | 250.8 (39.29 to 1,814.0) | −9.41 (−10.75 to −7.92) | 5.56 (3.42 to 7.81) | 4.78 (2.78 to 7.02) |
| ADA versus PLC | 48.86 (22.83–100.6) | – | −6.67 (−8.76 to −4.99) | 4.04 (2.09 to 6.75) | 3.27 (0.96 to 5.52) |
| ETA versus PLC | 27.11 (13.53–58.9) | – | −6.77 (−6.77 to −2.76) | – | – |
| UST versus PLC | 49.24 (27.07–92.33) | \(^c\) | −8.52 (−9.54 to −7.39) | – | – |
| BRI versus PLC | 337.0 (39.34–12,970.0) | – | – | – | – |
| EFA versus ALA | 2.418 (0.76–7.46) | – | −1.52 (−4.46 to 1.37) | – | – |
| INF versus ALA | 27.05 (6.72–108.40) | – | −7.26 (−9.74 to −4.63) | 3.43 (−0.28 to 7.10) | 2.74 (−0.56 to 6.47) |
| ADA versus ALA | 12.42 (3.47–39.70) | – | −4.49 (−7.57 to −1.90) | 1.91 (−1.60 to 6.05) | 1.29 (−2.29 to 4.86) |
| ETA versus ALA | 6.89 (2.15–23.38) | – | −4.57 (−9.11 to −0.04) | – | – |
| UST versus ALA | 12.49 (3.97–38.69) | – | −6.32 (−8.74 to −3.97) | – | – |
| BRI versus ALA | 84.39 (7.94–3,677.0) | – | – | – | – |
| INF versus EFA | 11.30 (3.47–36.89) | 22.53 (2.61 to 206.3) | −5.76 (−8.14 to −3.23) | – | – |
| ADA versus EFA | 5.20 (1.94–12.64) | – | −3.13 (−5.80 to −0.46) | – | – |
| ETA versus EFA | 2.94 (1.07–7.25) | – | −3.15 (−7.51 to 1.59) | – | – |
| UST versus EFA | 5.27 (2.23–12.13) | \(^d\) | −4.84 (−7.11 to −2.60) | – | – |
| BRI versus EFA | 35.54 (3.73–1,415.0) | – | – | – | – |
| ADA versus INF | 0.47 (0.12–1.51) | – | 2.72 (0.01 to 4.80) | −1.54 (−4.41 to 1.99) | −1.49 (−4.75 to 1.37) |
| ETA versus INF | 0.26 (0.08–0.89) | – | 2.87 (−1.57 to 7.03) | – | – |
| UST versus INF | 0.47 (0.13–1.47) | \(^c\) | 0.90 (−0.98 to 2.62) | – | – |
| BRI versus INF | 3.34 (0.24–156.8) | – | – | – | – |
| ETA versus ADA | 0.56 (0.20–1.67) | – | 0.01 (−4.35 to 4.46) | – | – |
| UST versus ADA | 1.00 (0.40–2.75) | – | −1.84 (−3.80 to 0.55) | – | – |
suggesting no impact of the disease on the patients’ HRQoL scores.

Five RCTs evaluated the anti-T cell agents, with one alefacept study [26], and two efalizumab studies [30, 32] reporting results using FDA-approved doses. Seven RCTs evaluated the anti-TNF agents, with three infliximab studies [37, 38, 40], two adalimumab studies [41–43], and one etanercept study [47] reporting results using FDA-approved doses. Ustekinumab was the only anti-IL-12/23 agent that reported data on this endpoint with two studies reporting results using FDA-approved doses [50–52].

The anti-T cell agents as a class, as well as efalizumab alone significantly reduced the DLQI score from baseline (Fig. 4). No significant effect was seen with alefacept alone. Each individual anti-TNF agent, as well as the pooled class, significantly reduced the DLQI score from baseline. Similar effects were seen with ustekinumab. When all anti-T cell agent RCTs (WMD $-2.377$, 95% CI $-3.286$ to $-1.469$), anti-TNF agent RCTs (WMD $-8.03$, 95% CI $-9.24$ to $-6.81$), and anti-IL-12/23 RCTs (WMD $-7.94$, 95% CI $-8.83$ to $-7.05$) were pooled, regardless of dose, similar overall effects were seen.

The MTC analysis included data from seven RCTs of six therapies in three drug classes that reported data on the change from baseline in DLQI score and included arms using the FDA-approved dose (Tables 3, 4) [26, 30, 32, 37, 38, 40, 41, 43, 47, 51, 52]. As above, the placebo-controlled comparisons were similar between the MTC and traditional meta-analysis models. When the drug classes were compared, both the anti-TNF agents (mean difference $-7.77$, 95% CrI $-8.27$ to $-3.23$) and anti-IL-12/23 agents (mean difference $-5.37$, 95% CrI $-7.89$ to $-2.82$) reduced the DLQI to a greater extent than the anti-T cell agents. Many of the individual comparisons followed the same trend.
Eight RCTs evaluating four drugs from two classes reported data on the change in SF-36 score from baseline (Table 2) [23, 25, 26, 38, 40, 41, 43, 47]. There were two component scores examined in this category, the physical and mental component summary (PCS and MCS) scores. All of the RCTs were of high quality (Jadad ≥4) and ranged from 10 to 24 weeks in duration.

Alefacept was the only anti-T cell agent that reported data on these endpoints [23, 25, 26], with a single RCT [26] reporting results using FDA-approved doses. Five RCTs evaluated the anti-TNF agents, including infliximab [38–40], adalimumab [41, 43], and etanercept [47], all of which reported results using FDA-approved doses. No anti-IL-12/23 agent studies reported data on the SF-36 MCS or PCS.

Whereas alefacept had no significant impact on either the SF-36 MCS or PCS (Figs. 5, 6), each anti-TNF agent as well as the class significantly improved both SF-36 endpoints from baseline. When all anti-T cell agent RCTs (MCS = WMD 2.18, 95% CI –1.61 to 5.97; PCS = WMD 1.95, 95% CI –1.44 to 5.34), and anti-TNF agent RCTs (MCS = WMD 4.56, 95% CI 3.59–5.54; PCS = WMD 3.93, 95% CI 3.09–4.78) were pooled, regardless of dose, similar overall effects were seen.

The MTC analysis included data from seven trials of three therapies in two drug classes that reported data on the change in SF-36 scores (both MCS and PCS) from baseline using the FDA-approved dose (Tables 3, 4) [23, 25, 26, 38, 40, 41, 43]. No differences between individual agents or drug classes were seen in the MTC model.

### Statistical Heterogeneity/Publication Bias

Significant statistical heterogeneity was seen with the anti-T cell class for the static PGA.
analysis ($I^2 = 59.8\%$), and the anti-TNF class for the DLQI analysis ($I^2 = 84.2\%$). In each case, the statistical heterogeneity was likely due to differences in the magnitude of effect rather than directionality. All other analyses had no significant heterogeneity ($I^2 < 25\%$),
although many analyses had too few studies to formally test for its presence. Similarly, publication bias was not statistically significant in any analysis where enough studies were included for it to be tested (Egger’s $P > 0.05$ for all).

**DISCUSSION**

Overall, biologic agents were shown to be effective for improving clinical psoriasis symptoms (static and dynamic PGA), as well as measures of health-related quality of life (DLQI and SF-36). However, differences between drug classes and individual agents were seen using a MTC meta-analytic model. Although each individual agent and drug class showed significant improvements in the PGA (static and dynamic), the MTC model suggested that the anti-TNF agents and anti-IL 12/23 agents were both significantly better than the anti-T cell agents. Individual indirect drug comparisons showed similar trends. Each pharmacologic agent and drug class also showed significant improvements in the DLQI from baseline with the MTC model showing...
similar results to the PGA analysis. Studies have established that at least a five-point change in the DLQI can be considered clinically significant, indicating patients are a little better or worse [13]. Larger changes are required for more pronounced clinical improvements. Significant differences between individual agents ranged from three to seven points, and between classes from five to six points. Thus it can be debated that the differences seen equate to minimal clinical improvements in DLQI from one agent or class to the next.

Although the PASI is the outcome most commonly reported in efficacy clinical trials for biologic agents in chronic plaque psoriasis, many regulatory agencies have stressed the importance of patient-related outcome measures for their approval process [54]. Since prior meta-analyses have reported on the comparative effectiveness of biologics in patients with plaque psoriasis using PASI [8], the authors felt it was important to concentrate on other outcomes of interest, including the PGA and various HRQoL measures. This makes the information from our analyses pertinent to both practicing clinicians as well as regulatory bodies making drug coverage decisions. Moreover, studies evaluating the association between improvements in PASI with patient-related outcomes have been inconsistent [55, 56], with more recent data showing only a mild correlation [56].

Traditional meta-analyses showed that the anti-T cell agents did not have an impact on the SF-36 whereas improvements in both the MCS and PCS were seen with the anti-TNF agents. No significant effects were seen in the MTC model. These results are all intriguing, especially given that the MTC model showed similar point estimates to traditional meta-analysis for the direct placebo comparisons. This suggests that the Bayesian models used were reliable giving higher credence to the indirect comparison results.

The traditional meta-analysis results from this review are similar to those of prior published reports [7, 8, 57, 58]. Additionally, this meta-analysis is the only one to utilize Bayesian MTC methodologies to provide indirect-comparisons between agents in addition to classes on non-PASI endpoints. This allows us to estimate the comparative treatment effects of available biologics and potentially guide treatment decisions in the absence of direct studies. The prior meta-analysis by Reich and colleagues used a Bayesian hierarchical model and concluded that no differences between the biologic agents existed at 24 weeks using the PASI 50, 75, or 90 [57]. No indirect comparisons were made by class. When compared with placebo, their results suggest the largest benefit with infliximab and etanercept versus other agents such as efalizumab and alefacept on the PASI 75.

Current guidelines from the American Academy of Dermatology, published in 2008, state that either an anti-T cell or anti-TNF agent can be used when a biologic agent is indicated with no preference given to any particular agent [1]. More recently published guidelines from the Deutsche Dermatologische Gesellschaft and the Berufsverband Deutscher Dermatologen in 2011 suggest that the anti-TNF agents (particularly adalimumab or infliximab) or ustekinumab should be the biologics of first choice in patients with psoriasis [59]. The choice of which anti-TNF agent to use should be patient specific and based on clinical need. The recommendations state that patients with stable chronic plaque psoriasis could consider etanercept or adalimumab as first choice due to their ease of administration (self subcutaneous injection). Because of the relatively new status of the anti-IL 12/23 agents, particularly ustekinumab, their use is recommended to be reserved as a second-line biologic agent if anti-TNF therapy has failed or cannot be used. Our results
support these recommendations by showing that anti-TNF agents, as well as anti-IL 12/23 agents, significantly improve clinical efficacy (via the PGA) and HRQoL (via the DLQI) as compared with the anti-T cell agents in patients with moderate-to-severe plaque psoriasis. It is also worth noting that the choice of biologic of preference in some countries, such as the UK, incorporates both clinical as well as pharmacoeconomic considerations into their ranking of agents. The present study did not evaluate cost-effectiveness, and thus the authors cannot comment on this further.

The results of this meta-analysis must be interpreted cautiously as various limitations exist. Common limitations seen with traditional meta-analyses include heterogeneity and publication bias. Due to the low number of studies included in many of the analyses, statistical heterogeneity and publication bias could not be determined. A few analyses included a moderate degree of heterogeneity (I² = 50–75%). Often the differences seen were related to the magnitude of the effect rather than its direction. Thus, it is unlikely that this heterogeneity significantly altered the conclusions of this review. Differences in the included studies could have also contributed to both clinical as well as statistical heterogeneity. Studies varied by the severity of patients included (as measured by the baseline PASI score), duration of studies (ranging from 8 to 24 weeks), study quality (as assessed using the Jadad score), and inherent differences between the agents themselves. All of the studies included in this review were of high quality (Jadad ≥4), and the inclusion of only the FDA-approved doses of the drugs into the primary analyses was done in an attempt to provide a somewhat homogeneous sample.

Similar to heterogeneity, publication bias could not be assessed in many analyses due to low study numbers. When it was available, publication bias was not likely due to an Egger’s weighted regression statistic P > 0.05. The systematic nature of this literature search, in addition to the relatively tight inclusion criteria, likely lead to the lack of publication bias.

Lastly, the short-term nature of many of the studies included in this review precludes extrapolation of our results to patients requiring long-term therapy. Although estimates from the MTC meta-analysis cannot simply be assumed accurate, were considered valid due, in part, to the similar results seen in the placebo-controlled comparisons between the MTC and traditional meta-analytic models.

Various knowledge gaps have been identified by this review. It is clear that comparative effectiveness studies evaluating the impact of biologics continue to be required. When these studies are designed and carried out it should be required that measures of HRQoL are collected and reported. In addition, comparative studies should be of a sufficient duration. As previously stated, most of the studies included in this review were 8–24 weeks in duration. Some included non-randomized 52-week extension studies that provided safety and efficacy data in an observational manner. Studies of a year or more in duration should maintain randomization in order to confirm whether differences seen between groups are seen over the long term.

**CONCLUSION**

Individual biologics and classes showed consistent benefits across health outcomes in patients with moderate-to-severe plaque psoriasis while MTC meta-analysis suggested that some differences exist. This work provides an important channel in the planning of future
clinical trials aimed at defining the most efficacious biologic therapy.

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Conflict of interest. C.M.M. and J.C.C. are employed by Pfizer Inc. No other authors report significant conflicts of interest germane to this project.

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