Comparison of Adalimumab and Etanercept for the Treatment of Moderate to Severe Psoriasis: An Indirect Comparison Using Individual Patient Data from Randomized Trials

Kim A. Papp, MD, PhD1, Min Yang, MD, PhD2*, Murali Sundaram, MBA, PhD3, John Jarvis, MBA2, Keith A. Betts, PhD2, Yanjun Bao, PhD3, James E. Signorovitch, PhD2

1Probity Medical Research, and K. Papp Clinical Research, Waterloo, Ontario, Canada; 2Analysis Group Inc., Boston, MA, USA; 3AbbVie Inc., North Chicago, IL, USA

ABSTRACT

Objectives: To compare outcomes between adalimumab and etanercept in the treatment of moderate to severe plaque psoriasis.

Methods: Study groups included patients randomized to adalimumab or placebo (REVEAL and CHAMPION trials) and those randomized to etanercept or placebo (M10-114 and M10-315 trials). Week 12 outcomes were compared between patients receiving adalimumab and those receiving etanercept after adjusting for cross-trial differences in patient characteristics using propensity score weighting and after subtracting effects of placebo. Outcomes included proportion of patients achieving 75% or more, 90% or more, and 100% reductions from baseline in the Psoriasis Area and Severity Index (PASI75, PASI90, PASI100, respectively), symptom resolution (pruritus = 0; psoriatic pain = 0), lesion resolution (minimal scores for plaque signs erythema, desquamation, and induration, and by body regions head, upper limbs, trunk, and lower limbs), absence of skin-related quality-of-life impact (Dermatology Life Quality Index [DLQI] = 0), “complete disease control” (patient’s global assessment [PtGA] = 0), and adverse events. Results: After adjustment, baseline characteristics were balanced among study groups (adalimumab = 875 vs. placebo = 427; etanercept = 260 vs. placebo = 130). Compared with etanercept, adalimumab was associated with significantly better placebo-adjusted outcomes (PASI75: 62.3% vs. 42.6%; PASI90: 35.9% vs. 12.1%; PASI100: 13.1% vs. 4.9%; pruritus: 24.7% vs. 13.0%; psoriatic pain: 27.4% vs. 8.7%; DLQI: 27.7% vs. 11.7%; and PtGA: 16.4% vs. 10.6%; all p < 0.05), except for similar rates of adverse events and head-specific lesion resolution. Conclusions: Compared with etanercept, adalimumab treatment for moderate to severe plaque psoriasis was associated with greater PASI reduction, higher rates of resolution of skin signs and symptoms, and greater improvements in dermatological life quality. Keywords: adalimumab, etanercept, indirect comparison, psoriasis.

Introduction

Plaque psoriasis is a common chronic systemic illness affecting 3.2% of American adults [1] that is characterized by a combination of inflammation and epidermal thickening. This leads to red and scaly plaque lesions on the skin, which can be itchy and painful, and results in substantial impairment of physical and psychosocial functioning [2,3]. Symptoms may also lead to emotional distress, a sense of stigmatization, worry, embarrassment, and compromised health-related quality of life (HRQOL) [3–6]. Biologic therapy has significantly advanced the management of psoriasis, making complete (or almost complete) plaque clearance an achievable goal even in patients with more severe psoriasis. Two of the most commonly used biologics for psoriasis are the tumor necrosis factor (TNF) antagonists adalimumab and etanercept. In separate clinical trials, both adalimumab and etanercept demonstrated superior efficacy in the reduction of psoriasis signs and symptoms, as measured by a reduction in the...
Psoriasis Area and Severity Index (PASI) from baseline, when compared with placebo [2,3]. Both treatments demonstrated improvements in HRQOL on the basis of the Dermatology Life Quality Index (DLQI), the short form 36 health survey, and patient’s global assessment (PtGA) of psoriasis [2,4-6].

Nevertheless, to date, there has been no head-to-head randomized trial of adalimumab and etanercept for the treatment of plaque psoriasis. Comparative analyses of these two treatments have relied on indirect comparisons across separate randomized trials [7-15]. In all these studies, adalimumab has been associated with greater proportions of patients achieving more than 75% reduction from baseline in PASI (PASI75) when compared with etanercept. Nevertheless, cross-trial comparisons of treatment outcomes can be limited by differences in trial designs and patient characteristics [16-20]. For example, patients in trials of one treatment could have more severe psoriasis than patients in trials of other treatments. Previous analyses have aimed to account for such differences by comparing placebo-adjusted treatment effects across trials, either directly [7] or in the context of a network meta-analysis involving multiple trials and treatments [9,10,13]. These methods, however, do not adjust for observed all cross-trial differences in patients’ baseline characteristics, which could modify the effects of treatment versus placebo. One previous study adjusted for cross-trial differences in baseline characteristics by combining individual patient data from adalimumab trials with published aggregate data from an etanercept trial [11]. Consistent with the network meta-analyses, this study found that adalimumab was associated with a significantly greater proportion of patients achieving PASI75 compared with etanercept. Nevertheless, the aggregate nature of the published data used in previous studies precluded comparisons of outcome measures that were not reported in publications, for example, DLQI, PtGA, outcomes by body location, and resolution of signs and symptoms.

In traditional pairwise meta-analyses, the use of individual patient data is recognized as a gold criterion for comparative evidence [21,22]. The present study indirectly compares outcomes between adalimumab and etanercept on the basis of individual patient data from separate randomized, placebo-controlled trials of adalimumab [23,24] and etanercept [25,26]. The availability of patient-level data for both treatments allowed for comparisons of a broader range of outcomes than previous indirect comparisons, including PASI reduction, sign and symptom clearance, and impacts on HRQOL and safety.

Methods

Data Sources

Individual patient data drawn from the double-blind periods of four randomized, placebo-controlled phase 3 clinical trials were used in this analysis. Data from adalimumab treatment came from the phase 3 trials REVEAL (NCT00237887) [23] and CHAMPION (NCT00235820) [24]. Data from etanercept treatment came from the phase 3 trials M10-114 (NCT00691964) [25] and M10-315 (NCT00710580) [26] of an interleukin (IL) 12/23 inhibitor, biaknnumab, which included etanercept 50 mg twice weekly and placebo arms. The characteristics of the four trials are presented in Appendix Table A2 in Supplemental Materials found at dx.doi.org/10.1016/j.jval.2017.05.025.

Sample Selection

A detailed review of trial protocols was conducted to identify differences in trial designs and patient populations. As the first step toward ensuring comparability, patients from each trial were selected by imposing the strictest exclusion criteria across all four trials. In particular, patients in the CHAMPION trial were excluded if they did not meet the thresholds of a PASI score of 12 or more and physician’s global assessment of moderate or severe disease applied in the other trials. Patients with previous exposure to IL inhibitors or anti-TNFs were excluded. Adalimumab-treated and placebo-treated patients in the REVEAL and CHAMPION trials were pooled to form the REVEAL/CHAMPION patient population. Etanercept-treated and placebo-treated patients in the M10-114 and M10-315 trials were pooled to form the M10-114/M10-315 patient population.

Balancing Baseline Characteristics

Baseline characteristics were compared between the REVEAL/CHAMPION patient population and the M10-114/M10-315 patient population using t tests for continuous variables and χ² tests for categorical variables. Because imposing the most restrictive exclusion criteria across trials may not by itself result in sufficiently balanced trial populations, propensity score weighting was used to adjust for cross-trial differences in baseline characteristics [27,28]. This approach has been previously used in comparisons of nonrandomized biologic treatment groups to adjust for baseline differences [29,30].

Propensity score weighting adjusted for differences between trial populations by increasing or decreasing the relative contributions of individual patients in each trial so that, after weighting, the trials would have on average similar baseline characteristics. In this application, baseline characteristics available in all four trials were included for adjustment in a multivariable logistic regression model, with membership in REVEAL/CHAMPION or M10-114/M10-315 populations as the outcome. PASI scores were included in the model in terms of the overall PASI score. Each patient was then assigned a propensity score weight equal to his or her estimated probability of population membership on the basis of the fitted logistic regression model [28].

Propensity Score Model Fit Assessment

Availability of individual patient data from all trials allowed for a full evaluation of the propensity score model. In particular, the overlap between the propensity score distributions for patients in CHAMPION/REVEAL and M10-114/M10-315 trials was assessed. Lack of overlap would indicate the presence of extreme patients who were not well represented in trial populations and should be excluded from the comparative analyses [27]. The calibration of the propensity score model (i.e., how well the predicted probability of trial membership aligns with the observed probability) was assessed using the Hosmer-Lemeshow test and by visually comparing the observed versus the predicted membership in the CHAMPION/REVEAL trial as opposed to that in the M10-114/M10-315 trial. Poor calibration would indicate that further adjustment is needed before applying the propensity score weights [31].

Study Outcomes

Psoriasis Area and Severity Index

The PASI is the most widely used measurement for treatment efficacy in psoriasis clinical trials. It takes into account the severity of psoriasis lesions and the percentage of lesion-affected area within four body regions, and then sums the corresponding scores of weighted body regions (i.e., head 10%, upper limbs 20%, trunk 30%, and lower limbs 40%) to yield a single score ranging from 0 (no disease) to 72 (maximal disease). Specifically, the severity of lesions is captured by scoring separately for erythema (redness), induration (thickness), and desquamation (scaling) as
none (0), slight (1), moderate (2), severe (3), or very severe (4). The percentage of lesion-affected area is assigned a numeric value according to the extent of involvement within each body region (no involvement = 0; >0%–<10% = 1; 10%–<30% = 2; 30%–<50% = 3; 50%–<70% = 4; 70%–<90% = 5; and 90%–100% = 6). This allows for calculating four body region–specific PASI scores when considering all types of plaque signs within each body region (also ranging between 0 and 72) as well as three plaque sign–specific PASI scores when considering separately each type of plaque sign in the whole body (ranging between 0 and 24).

This study reported the week 12 achievement of PASI75 and PASI90, which are frequently reported in psoriasis clinical trials. In addition, PASI100 (i.e., complete plaque clearance) and plaque resolution (i.e., plaque sign–specific PASI = 0 and body region–specific PASI = 0) were studied.

Dermatology Life Quality Index
The DLQI is a widely used disease-specific questionnaire designed to assess symptoms and HRQOL impacts of skin conditions from a patient's perspective. The DLQI score ranges from 0 (no impact on quality of life) to 30 (extremely poor quality of life). Week 12 DLQI outcomes were reported in three trials but not in REVEAL, which had DLQI reported at week 16. Therefore, week 16 DLQI outcomes from REVEAL were used in the analyses along with week 12 DLQI outcomes from CHAMPION, M10-114, and M10-315. Achievement of DLQI = 0 (absence of quality-of-life impact due to skin condition) at the respective time (i.e., week 16 in CHAMPION and week 12 in the other three trials) was assessed.

Pruritus, pain, and PtGA
The severity of psoriasis-related itching was measured on a pruritus numerical rating scale, ranging from 0 (no itching) to 10 (severe itching). Psoriatic pain due to psoriasis and/or psoriatic arthritis was assessed using a visual analogue scale, ranging from 0 (minimal pain) to 100 (severe pain). The PtGA reported the level of overall psoriasis control from a patient’s perspective. The PtGA scores ranged from 0 (complete disease control) to 3 (uncontrolled disease). Rates of achievement of pruritus = 0, psoriatic pain = 0, and PtGA = 0 at week 12 were studied.

Adverse events
An adverse event (AE) was considered treatment-related if it was classified as “probably related” or “possibly related” to the treatment. Rates of treatment-related overall AEs, AEs leading to discontinuation, serious AEs, severe AEs, and infectious AEs were identified from the trials and were also studied.

Statistical Analysis
Outcomes were compared on the basis of the pre- and post-treatment differences between adalimumab versus placebo (adalimumab-placebo) and etanercept versus placebo (etanercept-placebo) (i.e., the difference in difference [32]). Specifically, unadjusted analyses were conducted using unweighted tests. After weighting, baseline characteristics of the REVEAL/CHAMPION patient population were compared with those of the M10-114/M10-315 patient population using \( \chi^2 \) tests for categorical variables and t tests for continuous variables.

All outcomes of interest were compared indirectly between adalimumab-treated patients and etanercept-treated patients after adjusting for cross-trial differences in patient characteristics using propensity score weighting and subtracting the corresponding rates of the placebo arms (i.e., adalimumab-placebo vs. etanercept-placebo). Two-sided P values of less than 0.05 were considered statistically significant. No adjustment was made for multiple testing.

Results

Sample Selection and Baseline Characteristics
A total of 875 adalimumab-treated patients and 427 placebo-treated patients formed the REVEAL/CHAMPION patient population (N = 1302); a total of 260 etanercept-treated patients and 130 placebo-treated patients formed the M10-114/M10-315 patient population (N = 390) (Table 1). Before propensity score weighting, there were significant differences in a number of baseline characteristics between patients in REVEAL/CHAMPION and those in M10-114/M10-315 (Table 2). Compared with patients in M10-114/M10-315, patients in REVEAL/CHAMPION had lower mean weight, longer mean duration of psoriasis, higher body surface area affected, higher PASI-upper limb score, worse PASI-erythema score, lower DLQI, and lower psoriasis-related pruritus. Greater proportions of patients in REVEAL/CHAMPION had concurrent joint involvement and had previous systemic treatment and phototherapy, and a lower proportion of patients had PtGA of “uncontrolled disease.” After weighting, adjustment there were no significant differences in baseline characteristics other than subscores for PASI-upper limbs (Table 2).

Unadjusted Outcome Comparisons
In unadjusted analyses, comparing outcomes for adalimumab minus placebo versus those for etanercept minus placebo without applying propensity score weights, adalimumab was associated with significantly greater rates of PASI75 (62.7% vs. 43.8%) and PASI90 (36.3% vs. 16.2%) and greater percentages of PASI improvement at weeks 4, 8, and 12 when compared with etanercept-treated patients (42.6%, 56.1%, and 60.5% vs. 24.3%, 39.6%, and 47.6%, respectively) (Table 3). Compared with etanercept, adalimumab was also associated with significantly greater rates of achieving PASI100, DLQI = 0, and psoriatic pain = 0.

In addition, adalimumab was associated with significantly greater rates of plaque sign–specific resolution (erythema: 15.4% vs. 8.5%; desquamation: 20.1% vs. 9.2%; induration: 25.8% vs. 12.1% and body region–specific plaque resolution for upper limbs (28.3% vs. 20.0%), trunk (45.3% vs. 30.8%), and lower limbs (22.1% vs. 9.2%) (all \( P < 0.05 \)). Although not statistically significant, rates of achieving PtGA = 0 (16.6% vs. 13.5%), pruritus = 0 (24.4% vs. 20.0%), and PASI-head = 0 (50.0% vs. 41.5%) were numerically greater in adalimumab-treated patients than in etanercept-treated patients. There were no statistically significant differences in rates of AEs between adalimumab and etanercept (see Appendix Table A1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.025).

Assessment of the Propensity Score Model
The distribution of propensity scores in REVEAL/CHAMPION was found to have adequate overlap with that in M10-114/M10-315 (see Appendix Figure A1a in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.05.025). When patients were stratified by deciles of the propensity scores, the mean predicted chance of being in REVEAL/CHAMPION (i.e., the propensity score) was similar to the observed chance by decile (see Appendix Figure A1b in Supplemental Materials), and the Hosmer-Lemeshow test did not detect any significant lack of calibration.
Table 1 – Sample selection flowchart.

<table>
<thead>
<tr>
<th>Selection criterion</th>
<th>Trials with adalimumab</th>
<th>Trials with etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REVEAL</td>
<td>CHAMPION</td>
</tr>
<tr>
<td>All patients</td>
<td>Adalimumab 814</td>
<td>Placebo 398</td>
</tr>
<tr>
<td>Patients with PASI ≥ 12 and PGA ≥ moderate</td>
<td>Adalimumab 814</td>
<td>Placebo 398</td>
</tr>
<tr>
<td>Patients with no previous use of anti-TNFs</td>
<td>Adalimumab 788</td>
<td>Placebo 382</td>
</tr>
<tr>
<td>Patients with no previous use of anti-IL-12s</td>
<td>Adalimumab 782</td>
<td>Placebo 380</td>
</tr>
<tr>
<td>Total pooled treatment populations</td>
<td>Adalimumab, n = 875</td>
<td>Placebo, n = 427</td>
</tr>
</tbody>
</table>

IL-12, interleukin 12; PASI, Psoriasis Area and Severity Index; PGA, physician’s global assessment; TNF, tumor necrosis factor.

* A total of 110 patients treated with methotrexate were excluded from the present study.
† A total of 138 patients treated with briakinumab were excluded from the present study.
‡ A total of 139 patients treated with briakinumab were excluded from the present study.

Propensity Score-Adjusted Outcome Comparisons

After weighting, adalimumab-treated patients continued to have significantly higher placebo-adjusted PASI75 (62.3% vs. 42.6%) and PASI90 (35.9% vs. 12.1%) response rates at week 12, and a higher mean percentage improvement in PASI at weeks 4 (42.1% vs. 18.3%), 8 (55.3% vs. 34.7%), and 12 (59.8% vs. 45.8%) than etanercept-treated patients (Table 3; all \( P < 0.01 \)). Adalimumab-treated patients were more likely to achieve sign and symptom clearance in terms of PASI100 (13.1% vs. 4.9%), DLQI = 0 (27.7% vs. 11.7%), PtGA = 0 (16.4% vs. 10.6%), psoriasis-related pruritus = 0 (24.7% vs. 13.0%), and psoriatic pain = 0 (27.4% vs. 8.7%) compared with etanercept-treated patients after adjusting for placebo (all \( P < 0.05 \)).

In addition, adalimumab was associated with significantly higher rates of achieving plaque sign-specific resolution (Fig. 1), including resolution for erythema (15.0% vs. 6.0%), desquamation (20.2% vs. 7.7%), and induration (25.4% vs. 6.7%) when compared with etanercept-treated patients after adjusting for placebo (all \( P < 0.001 \)). Adalimumab was also associated with significantly higher rates of achieving body region-specific resolution other than the head region, within which a comparable resolution rate was observed between the two treatments. The plaque resolution rates by body region were upper limbs (27.9% vs. 14.8%), lower limbs (21.5% vs. 5.7%), and trunk (44.3% vs. 26.7%) for adalimumab versus etanercept, respectively (all \( P < 0.01 \)).

Rates of treatment-related AEs were largely similar between adalimumab- and etanercept-treated patients other than treatment-related infectious AEs (2.0% vs. 7.0%; \( P = 0.041 \)) (see Appendix Table A1 in Supplemental Materials).

Discussion

Indirect comparisons play an important role in assessing the comparative efficacy of alternative treatments when no randomized head-to-head comparative trials are available, as in the case of adalimumab and etanercept for plaque psoriasis. Because biologic therapies have made complete clearance of psoriasis signs and symptoms an achievable goal, it is of value to compare these outcomes between adalimumab and etanercept, both of which are widely used for treating patients with psoriasis. This study used patient-level data from randomized, placebo-controlled trials of adalimumab and etanercept in patients with moderate to severe psoriasis to compare outcomes in terms of PASI reduction, psoriasis lesion sign and symptom clearance, safety, and patient-reported outcomes. After applying identical selection criteria to patients from each of the trials and balancing baseline characteristics across trials, adalimumab was associated with a greater likelihood of PASI reduction and sign and symptom clearance compared with etanercept.

The placebo-adjusted outcome rates found in the present study are similar to those from previous adalimumab and etanercept trials. In three separate trials of etanercept, placebo-adjusted PASI75 rates ranged between 42% and 46% [2,3,33]; the rate of 42.6% in the present study is within this range. In these same trials, the placebo-adjusted PASI90 rates ranged between 20% and 21%, which are higher than the rate of 12.1% found in the present study but still lower than the placebo-adjusted rate of 35.9% for adalimumab in the present study. The higher rates of PASI reduction in adalimumab-treated patients compared with etanercept-treated patients in the present study are consistent with previous indirect comparisons of adalimumab and etanercept [7–15]. For example, a recent network meta-analysis study including multiple adalimumab trials and etanercept trials (and other biologics) found that the estimated PASI75 response was 66.2% for adalimumab and 51.9% for etanercept; the estimated PASI90 response was 38.1% for adalimumab and 24.9% for etanercept 50 mg [13]. The low rates of serious AEs from the present study are also consistent with previous studies of etanercept and adalimumab [3,24].

Previous comparative studies did not include outcomes such as plaque resolution by body region and by types of plaque sign. Achieving plaque resolution and skin clearance is a highly...
<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Before Weighting</th>
<th>After Weighting</th>
<th>p-value</th>
<th>Before Weighting</th>
<th>After Weighting</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REVEAL/CHAMPION</td>
<td>M10-114/M10-315</td>
<td></td>
<td>REVEAL/CHAMPION</td>
<td>M10-114/M10-315</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=1302)</td>
<td>(N=390)</td>
<td></td>
<td>(N=1302)</td>
<td>(N=390)</td>
<td></td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>44.1 (13.2)</td>
<td>44.0 (13.6)</td>
<td>0.961</td>
<td>44.0 (13.2)</td>
<td>43.2 (14.1)</td>
<td>0.637*</td>
</tr>
<tr>
<td>Female (%)</td>
<td>34.1%</td>
<td>34.4%</td>
<td>0.925</td>
<td>34.5%</td>
<td>35.7%</td>
<td>0.815</td>
</tr>
<tr>
<td>White (%)</td>
<td>90.9%</td>
<td>91.8%</td>
<td>0.601</td>
<td>91.0%</td>
<td>91.8%</td>
<td>0.702</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>172.5 (10.1)</td>
<td>172.7 (10.0)</td>
<td>0.832</td>
<td>172.5 (10.1)</td>
<td>173.2 (10.8)</td>
<td>0.656</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>91.6 (23.0)</td>
<td>95.4 (24.1)</td>
<td>0.007*</td>
<td>92.5 (23.5)</td>
<td>96.0 (23.7)</td>
<td>0.210</td>
</tr>
<tr>
<td>Disease duration (y), mean (SD)</td>
<td>18.1 (11.6)</td>
<td>16.2 (12.5)</td>
<td>0.005*</td>
<td>17.7 (11.7)</td>
<td>17.6 (12.0)</td>
<td>0.897</td>
</tr>
<tr>
<td>History of Ps (%)</td>
<td>27.5%</td>
<td>23.8%</td>
<td>0.153</td>
<td>26.9%</td>
<td>29.7%</td>
<td>0.587</td>
</tr>
<tr>
<td>Duration of PsA (y), mean (SD)</td>
<td>9.3 (9.0)</td>
<td>7.9 (7.1)</td>
<td>0.092</td>
<td>9.0 (8.8)</td>
<td>7.9 (6.7)</td>
<td>0.310</td>
</tr>
<tr>
<td>Current joint involvement (%)</td>
<td>36.4%</td>
<td>18.5%</td>
<td>&lt;.001*</td>
<td>32.2%</td>
<td>37.6%</td>
<td>0.406</td>
</tr>
<tr>
<td>Psoriasis family history (%)</td>
<td>50.3%</td>
<td>47.7%</td>
<td>0.372</td>
<td>49.8%</td>
<td>49.9%</td>
<td>0.980</td>
</tr>
<tr>
<td>Previous medication history (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>94.2%</td>
<td>96.2%</td>
<td>0.139</td>
<td>94.6%</td>
<td>90.2%</td>
<td>0.331</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>52.2%</td>
<td>21.5%</td>
<td>&lt;.001*</td>
<td>45.2%</td>
<td>49.0%</td>
<td>0.496</td>
</tr>
<tr>
<td>Systemic non-biologic</td>
<td>41.5%</td>
<td>28.7%</td>
<td>&lt;.001*</td>
<td>38.4%</td>
<td>46.2%</td>
<td>0.183</td>
</tr>
<tr>
<td>Systemic biologic</td>
<td>16.3%</td>
<td>3.6%</td>
<td>&lt;.001*</td>
<td>13.4%</td>
<td>20.4%</td>
<td>0.354</td>
</tr>
<tr>
<td>BSA, mean (SD)</td>
<td>26.7 (15.9)</td>
<td>23.8 (14.3)</td>
<td>&lt;.001*</td>
<td>26.1 (15.5)</td>
<td>26.0 (14.7)</td>
<td>0.941</td>
</tr>
<tr>
<td>DLQI, mean (SD)</td>
<td>11.5 (6.7)</td>
<td>13.0 (7.0)</td>
<td>&lt;.001*</td>
<td>11.8 (6.8)</td>
<td>11.7 (6.6)</td>
<td>0.889</td>
</tr>
<tr>
<td>PASI, mean (SD)</td>
<td>19.2 (7.2)</td>
<td>18.7 (6.8)</td>
<td>0.236</td>
<td>19.1 (7.1)</td>
<td>18.9 (6.7)</td>
<td>0.640</td>
</tr>
<tr>
<td>PASI-Erythema, mean (SD)</td>
<td>6.75 (2.7)</td>
<td>6.45 (2.4)</td>
<td>0.034*</td>
<td>6.71 (2.6)</td>
<td>6.59 (2.4)</td>
<td>0.472</td>
</tr>
<tr>
<td>PASI-Induration, mean (SD)</td>
<td>6.16 (2.4)</td>
<td>6.00 (2.4)</td>
<td>0.247</td>
<td>6.13 (2.4)</td>
<td>5.88 (2.3)</td>
<td>0.171</td>
</tr>
<tr>
<td>PASI-Desquamation, mean (SD)</td>
<td>6.29 (2.5)</td>
<td>6.28 (2.5)</td>
<td>0.941</td>
<td>6.26 (2.5)</td>
<td>6.42 (2.4)</td>
<td>0.379</td>
</tr>
<tr>
<td>PASI-Head, mean (SD)</td>
<td>16.86 (11.0)</td>
<td>16.01 (13.1)</td>
<td>0.243</td>
<td>16.93 (11.1)</td>
<td>16.04 (13.5)</td>
<td>0.397</td>
</tr>
<tr>
<td>PASI-Upper Limbs, mean (SD)</td>
<td>18.50 (8.5)</td>
<td>17.21 (8.3)</td>
<td>0.008*</td>
<td>18.43 (8.4)</td>
<td>17.70 (7.8)</td>
<td>0.033*</td>
</tr>
<tr>
<td>PASI-Trunk, mean (SD)</td>
<td>16.98 (9.9)</td>
<td>17.12 (10.4)</td>
<td>0.816</td>
<td>16.85 (9.9)</td>
<td>18.08 (10.4)</td>
<td>0.101</td>
</tr>
<tr>
<td>PASI-Lower Limbs, mean (SD)</td>
<td>21.80 (9.3)</td>
<td>21.37 (9.3)</td>
<td>0.422</td>
<td>21.66 (9.2)</td>
<td>21.02 (8.4)</td>
<td>0.298</td>
</tr>
<tr>
<td>Pruritus, mean (SD)</td>
<td>6.9 (2.4)</td>
<td>7.3 (2.4)</td>
<td>0.004*</td>
<td>6.9 (2.4)</td>
<td>7.0 (2.5)</td>
<td>0.687</td>
</tr>
<tr>
<td>PtGA of uncontrolled disease (%)</td>
<td>72.1%</td>
<td>77.2%</td>
<td>0.048*</td>
<td>73.2%</td>
<td>69.5%</td>
<td>0.557</td>
</tr>
</tbody>
</table>

BSA: body surface area; DLQI: dermatology life quality index; PASI: psoriasis area and severity index; PsA: psoriatic arthritis; PtGA: patient global assessment.

*P-value < 0.05
desirable outcome in the management of moderate to severe psoriasis. In the present study, adalimumab was also found to be associated with higher rates of clearance of skin signs and symptoms, resolution of itching and pain, and absence of quality-of-life impact due to skin condition in patients with moderate to severe psoriasis. These parallel improvements in psoriasis signs and symptoms are not unexpected, given that multiple studies have linked the extent and severity of skin plaques to quality of life in patients with psoriasis (e.g., Revicki et al. [34]). To our knowledge, no previous study has compared the safety of adalimumab and etanercept in the treatment of psoriasis while adjusting for baseline differences. The present study found that the superior efficacy of adalimumab relative to etanercept is associated with a similar safety profile between the two treatments.

As the use of biologic therapy for the management of psoriasis continues to grow in clinical practice, indirect comparisons have provided comparisons of treatment strategies in the absence of head-to-head randomized trials. From a methodological standpoint, the approach used in this study, involving individual patient data from multiple trials, offers advantages beyond conventional approaches to the comparison of nonrandomized treatment groups. Conventional indirect comparisons of trial data, for example, cannot adjust for cross-trial differences in large numbers of patient baseline characteristics, but by comparing treatment effects relative to a common comparator (e.g., placebo), they may mitigate biases due to cross-trial differences that would equally impact the treatment and placebo arms [19,20]. Nevertheless, multivariate regression adjustment and propensity score–based methods applied in traditional epidemiological studies [27,31] can adjust for multiple baseline differences between treatment groups, but do not typically have a randomized placebo arm that could help indicate or account for unobserved confounding factors. By combining individual patient data from randomized, placebo-controlled trials, the present study has the advantages of traditional epidemiological studies, in adjusting for multiple baseline characteristics, along with the advantages of indirect comparisons of trial data on the basis of a common comparator group.

Several limitations of this study should be noted. One general limitation of indirect comparison studies is the loss of the benefits of randomization that may not be fully compensated for by the adjustments made. In addition, although observed differences between patient populations were balanced by

---

Table 3 - Outcomes before and after propensity score weighting.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before weighting</th>
<th>P value</th>
<th>After weighting</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REVEAL/CHAMPION</td>
<td></td>
<td>M10-114/M10-315</td>
<td></td>
</tr>
<tr>
<td></td>
<td>adalimumab-placebo</td>
<td></td>
<td>etanercept-placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M10-114/M10-315</td>
<td></td>
<td>adalimumab-placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>etanercept-placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI75 at week 12 (%)</td>
<td>62.7</td>
<td>12.0</td>
<td>&lt;0.001</td>
<td>62.3</td>
</tr>
<tr>
<td>PASI90 at week 12 (%)</td>
<td>36.3</td>
<td>16.3</td>
<td>&lt;0.001</td>
<td>35.9</td>
</tr>
<tr>
<td>% Change in PASI</td>
<td>42.6</td>
<td>24.3</td>
<td>&lt;0.001</td>
<td>42.1</td>
</tr>
<tr>
<td>Week 4</td>
<td>56.1</td>
<td>39.6</td>
<td>&lt;0.001</td>
<td>55.3</td>
</tr>
<tr>
<td>Week 8</td>
<td>60.5</td>
<td>47.6</td>
<td>&lt;0.001</td>
<td>59.8</td>
</tr>
<tr>
<td>Week 12</td>
<td>13.5</td>
<td>6.5</td>
<td>&lt;0.001</td>
<td>13.1</td>
</tr>
<tr>
<td>DLQI = 0 (no impact) (%)</td>
<td>28.1</td>
<td>16.5</td>
<td>0.004</td>
<td>27.7</td>
</tr>
<tr>
<td>PtGA = 0 (complete control) (%)</td>
<td>16.6</td>
<td>13.5</td>
<td>0.241</td>
<td>16.4</td>
</tr>
<tr>
<td>Pruritus = 0 (no itching) (%)</td>
<td>24.4</td>
<td>20.0</td>
<td>0.251</td>
<td>24.7</td>
</tr>
<tr>
<td>Psoriatic pain = 0 (no pain) (%)</td>
<td>26.6</td>
<td>15.4</td>
<td>0.025</td>
<td>27.4</td>
</tr>
</tbody>
</table>
| DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PtGA, patient’s global assessment. | * P-value < 0.05

---

Fig. 1 – Psoriasis plaque resolution rate by body region and by plaque sign. The “***” indicates a statistically significant difference. ADA-PBO, adalimumab-placebo; ETN, etanercept-placebo.
etanercept in the treatment of psoriasis. A head-to-head clinical
adds to the body of comparative evidence for adalimumab and
clearance and plaque resolution over time. The present study
pivotal trials of etanercept.
consistent with those from previous studies including those
trials described in this study; thus, other pivotal phase 3
trials of etanercept were not included in the analyses. Never-
theless, the findings from the present comparative analyses were
consistent with those from previous studies including those
pivotal trials of etanercept.

Conclusions
In this indirect comparison of treatments with adalimumab and
etanercept in patients with moderate to severe psoriasis, adali-
mumab was found to be associated with significantly higher rates of
PASI75 and PASI90 as well as with more patients having skin
clearance and plaque resolution over time. The present study
adds to the body of comparative evidence for adalimumab and
etanercept in the treatment of psoriasis. A head-to-head clinical
trial directly comparing adalimumab and etanercept is warranted
to confirm the results of the indirect comparison reported here.

Acknowledgments
We thank Evan S. Kantor, a former employee at Analysis Group Inc.,
for data analysis, and Cinzia Malteco, an employee at
Analysis Group Inc., for assistance in writing the article.
Source of financial support: Design, study conduct, and
financial support for the study were provided by AbbVie Inc.

Supplemental Materials
Supplemental material accompanying this article can be found in
the online version as a hyperlink at http://dx.doi.org/10.1016/j.
vjl.2017.05.025 or, if a hard copy of article, at www.valueinhealth
journal.com/issues (select volume, issue, and article).

References
[1] Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence
controlled trial of etanercept in psoriasis: safety, efficacy, and effect of
and health-care resource utilization in patients with psoriasis treated
with etanercept: continuous versus interrupted treatment. Value
health-related quality of life of patients with psoriasis: results of a
treatment on patient-reported outcomes: results from a phase III
clinical trial in patients with moderate to severe plaque psoriasis.
biologic treatments for psoriasis based on subjective and objective
efficacy measures assessed over a 12-week treatment period. J Am
moderate to severe plaque psoriasis: systematic review and meta-
therapies for moderate to severe psoriasis. Br J Dermatol
treatment of moderate to severe psoriasis: a network meta-analysis of
head-to-head trials: a method for matching-adjusted indirect
comparisons applied to psoriasis treatment with adalimumab or
biologic therapies for Crohn’s disease, psoriasis, and rheumatoid
[13] Signorovitch JE, Betts KA, Yan YS, et al. Comparative efficacy of
biological treatments for moderate-to-severe psoriasis: a network
meta-analysis adjusting for cross-trial differences in reference arm
[14] Lin VW, Ringold S, Devine EB. Comparison of ustekinumab with other
biological agents for the treatment of moderate to severe plaque
psoriasis: a Bayesian network meta-analysis. Arch Dermatol
safety of new biological agents targeting the interleukin-23-T helper 17
pathway for moderate-to-severe plaque psoriasis: a systematic review
[16] Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and
indirect treatment comparisons in meta-analysis of randomized
comparisons and network meta-analysis for health-care decision making:
report of the ISPOR Task Force on Indirect Treatment Comparisons Good
[21] Stewart LA, Parmar MK. Meta-analysis of the literature or of individual
[22] Stewart LA, Clarke MJ. Practical methodology of meta-analyses
(overviews) using updated individual patient data. Cochrane Working
moderate to severe psoriasis: a randomized, controlled phase III trial.
[24] Rautaharju PM, Detlie AB, Leonard CI, et al. The results of direct and
indirect comparison of adalimumab and etanercept safety and efficacy
results from the randomized controlled comparative study of adalimumab vs.
methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J
vs. etanercept and placebo in patients with moderate to severe chronic


