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

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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

Conflicts of interest: K. A. Papp is a consultant for AbbVie Inc., Akros, Alza, Amgen, Baxter, Boehringer Ingelheim, Celgene, Centocor, Cipher, Eli Lilly, Forward Pharma, Janssen, Janssen Biotech (Centocor), Medical Minds, Merck, Mitsubishi Pharma, Novartis, Pfizer, Takeda, UCB, and Vertex; is on the Speakers Bureau for AbbVie Inc., Amgen, Janssen, Merck, Novartis, and Pfizer; does clinical research for AbbVie Inc., Amgen, Anacor, Astellas, Celgene, Celtic, Dow Pharma, Eli Lilly, Galderma, Janssen, Janssen Biotech (Centocor), Merck, Novartis, and Pfizer; and is on the advisory boards of AbbVie Inc., Amgen, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen, Janssen Biotech (Centocor), Merck, Novartis, Pfizer, and UCB. Y. Bao is an employee of AbbVie Inc. and may own stock or stock options. M. Sundaram is a former employee of AbbVie Inc. and may own stock or stock options. M. Yang, K. A. Betts, and J. E. Signorovitch are employed by Analysis Group Inc. and J. Jarvis is a former employee of Analysis Group Inc., who received payment from AbbVie Inc. to assist with data analysis.

This article is dedicated in memory of Parvez Mulani (1974–2014), a colleague and friend at AbbVie Inc.

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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, briakinumab, 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 http://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 χ^2 tests for categorical variables. Because imposing the most restrictive exclusion criteria across trials may not by itself result in sufficintly 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%,