Impact of Adalimumab on Symptoms of Psoriatic Arthritis in Patients with Moderate to Severe Psoriasis: A Pooled Analysis of Randomized Clinical Trials

Philip J. Mease a  James Signorovitch b  Andrew P. Yu b  Eric Q. Wu b  Shiraz R. Gupta c  Yanjun Bao c  Parvez M. Mulani c

a Seattle Rheumatology Associates, Seattle, Wash., b Analysis Group, Boston, Mass., and c Abbott Laboratories, Abbott Park, Ill., USA

Key Words
Adalimumab  Psoriasis  Psoriatic arthritis  Comorbidities

Abstract
Background: Psoriatic arthritis often affects patients with psoriasis. Objective: To examine the effect of adalimumab on psoriatic arthritis in patients with moderate to severe psoriasis. Methods: Data from patients with psoriasis and a reported history of comorbid psoriatic arthritis in 3 randomized, placebo-controlled psoriasis trials of adalimumab were analyzed. Results: Adalimumab (n = 274) reduced the risk of psoriatic arthropathy adverse events by 75% versus placebo (1.1 vs. 4.8%; p = 0.025). Psoriasis/psoriatic arthritis-related pain was significantly reduced (–31.3 vs. –5.6 visual analog scale units; p < 0.0001). At week 16, adalimumab-treated patients were more likely to respond (56.9 vs. 4.5%; p < 0.001) and responded for a greater percentage of follow-up time (39.3 vs. 2.9%; p < 0.0001) than placebo-treated patients (regression model for PASI 75 and ACR 20 responses). Conclusion: Adalimumab treatment of moderate to severe psoriasis reduced symptoms of comorbid psoriatic arthritis.

Copyright © 2009 S. Karger AG, Basel

Introduction
Psoriasis is a chronic inflammatory disease affecting 2–3% of the US population [1]. Symptoms include itchy, painful skin lesions and substantial impairment of physical and psychosocial quality of life [2–4]. In addition, many patients with psoriasis develop psoriatic arthritis, a chronic inflammatory arthritis that causes progressive joint damage, reduced functionality and an increased mortality risk [5, 6]. Though rare in the general population [7], psoriatic arthritis affects up to 40% of patients with moderate to severe psoriasis [8], most often developing after the onset of psoriasis symptoms [9]. Patients with psoriasis who have comorbid psoriatic arthritis experience substantially increased costs of care and greater impairment of physical functioning and quality of life compared with patients with psoriasis alone [7, 10]. Because comorbid psoriatic arthritis affects a large subgroup of patients with moderate to severe psoriasis, with a distinct collection of symptoms, it is important to study the efficacy of psoriasis treatments in patients with comorbid psoriatic arthritis.

Treatment options for moderate to severe psoriasis include systemic therapy with biological agents (e.g. adalimumab, infliximab or etanercept), systemic therapy with
methotrexate, cyclosporine or oral retinoids, and phototherapy with psoralen. Methotrexate, the first available systemic therapy for psoriasis and one of the most widely prescribed [11], is also indicated for moderate to severe psoriatic arthritis. However, long-term use of methotrexate is associated with cumulative toxicities, particularly acute hematological toxicities and acute and chronic hepatotoxicity, that limit lifetime total dose [12, 13].

Biological systemic therapies for moderate to severe psoriasis, in particular the anti-tumor necrosis factor agents adalimumab and etanercept, can reduce symptoms of both psoriasis and psoriatic arthritis without the toxicities of methotrexate. Adalimumab is a fully human anti-tumor necrosis factor monoclonal antibody with demonstrated short- and long-term efficacies and safety in patients with moderate to severe psoriasis [14, 15] and psoriatic arthritis [16, 17]. In addition to reducing the signs and symptoms of psoriasis and psoriatic arthritis, adalimumab has been shown to reduce the functional and psychosocial impairments associated with both conditions [16, 18, 19]. In the REVEAL study (Randomized Controlled Evaluation of Adalimumab Every Other Week Dosing in Moderate to Severe Psoriasis Trial), patients with moderate to severe psoriasis treated with adalimumab experienced substantial reductions in psoriasis symptoms and improvements in health-related quality of life compared with placebo [19]. For patients with moderate to severe psoriatic arthritis, the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) demonstrated the efficacy of adalimumab therapy in improving health-related quality of life, inhibiting joint damage, and improving signs and symptoms of psoriatic arthritis and psoriasis [16–18]. An extended follow-up of the ADEPT cohort has shown that continued adalimumab treatment is associated with sustained inhibition of progression and joint damage and sustained improvement of skin and joint symptoms and quality of life for up to 144 weeks [17].

Although the ADEPT included patients with both psoriasis and psoriatic arthritis, active psoriasis was not required for enrollment. The goal of the present study is to describe the effect of adalimumab treatment on psoriatic arthritis-related symptoms in patients with active moderate to severe psoriasis enrolled in psoriasis trials in which psoriatic arthritis was not formally evaluated. In particular, using patient level data from randomized, placebo-controlled trials of adalimumab for the treatment of moderate to severe psoriasis and focusing on those patients with a reported history of comorbid psoriatic arthritis, this study describes the effect of adalimumab on the risk of psoriatic arthropathy adverse events, considered in this study as a surrogate for flaring psoriatic arthritis-related symptoms, the reduction of psoriasis/psoriatic arthritis-related pain, and the predicted concurrent reduction of psoriasis- and psoriatic arthritis-related symptoms.

### Methods

#### Data Sources

Patient level data were pooled from 3 clinical trials of adalimumab treatment in moderate to severe psoriasis [M02-528, Comparative Study of Humira vs. Methotrexate vs. Placebo in Psoriasis Patients (CHAMPION) and REVEAL] and from the ADEPT. Detailed descriptions of the methods and primary results of each trial have been previously published [14–16, 20]. Briefly, M02-528 was a phase II clinical trial in which patients with moderate to severe psoriasis [defined by body surface area (BSA) involvement of 5% or greater] were randomized to 12 weeks of double-blind treatment with adalimumab 40 mg every other week (e.o.w.; n = 45), adalimumab 40 mg weekly (n = 50) or placebo (n = 52). The phase III REVEAL randomized patients with moderate to severe psoriasis [defined by a Psoriasis Area and Severity Index (PASI) score ≥12, a Physician’s Global Assessment of at least ‘moderate’ and BSA ≥10%] to 16 weeks of double-blind treatment with adalimumab 40 mg e.o.w. (n = 814) or placebo (n = 398). The phase III CHAMPION randomized patients with moderate to severe psoriasis (BSA ≥10% and PASI ≥10) to 16 weeks of double-blind treatment with adalimumab 40 mg e.o.w. (n = 108) or placebo (n = 53). The CHAMPION also included a methotrexate arm (n = 110) that was not included in the present study. In all 3 psoriasis trials, patients randomized to adalimumab received a loading dose of 80 mg at baseline and a dose of 40 mg at the end of the first week, with subsequent 40-mg doses as indicated (e.o.w. or weekly). Patients in the 3 psoriasis trials were not systematically evaluated for psoriatic arthritis symptoms by a rheumatologist. The phase III ADEPT randomized patients with active moderate to severe psoriatic arthritis (systematically assessed by rheumatologists) to adalimumab e.o.w. (with a 40-mg dose at baseline and e.o.w. thereafter; no 80-mg loading dose; n = 151) or placebo (n = 162). Approximately 50% of patients in the ADEPT were receiving methotrexate at baseline and were allowed to continue use during the study. Patients in the CHAMPION and REVEAL were not permitted to use methotrexate during the study period. The ADEPT, CHAMPION and REVEAL included study visits at baseline and at weeks 4, 8, 12 and 16.

#### Statistical Methods

Analyses of patients with psoriasis pooled across M02-528, CHAMPION and REVEAL were conducted for the subgroup of patients who reported a history of psoriatic arthritis at baseline. Baseline demographic and clinical characteristics for these patients were summarized descriptively in the pooled adalimumab and placebo arms. Continuous variables were compared between treatment arms using the 2-sample Student t test; categorical variables were compared using the χ² test.
Incident worsening of psoriatic arthritis-related symptoms was identified from adverse events categorized using the Medical Dictionary for Regulatory Activities as a ‘psoriatic arthropathy’ adverse event during double-blind treatment with adalimumab (e.o.w. or weekly) or placebo in M02-528, CHAMPION and REVEAL. The cumulative incidence of psoriatic arthropathy adverse events, defined at each point of time during follow-up as the probability that a patient has experienced such an adverse event since baseline, was compared in the pooled adalimumab versus placebo arms using Kaplan-Meier estimates and the log-rank test. Patients were considered to be censored when they withdrew from the study or at the end of the double-blind treatment period (12 weeks for M02-528; 16 weeks for CHAMPION and REVEAL), whichever occurred first.

The effect of adalimumab versus placebo on the reduction of psoriasis/psoriatic arthritis-related pain was measured using a 100-point visual analog scale. Patients rated their degree of pain related to psoriasis or psoriatic arthritis during the past week on a scale from 0 (no pain) to 100 (pain as bad as it could be) in CHAMPION and REVEAL (M02-528 was excluded from this subanalysis because the pain scale was not used in this trial). Only patients with a baseline pain assessment and at least 1 postbaseline pain assessment were included in the analysis. Missing visual analog scale scores were imputed by carrying the last observation forward. Least-squares mean changes in psoriasis/psoriatic arthritis-related pain from baseline to week 16 were estimated for each treatment group and compared using an analysis of covariance model adjusted for baseline pain.

To study the concurrent effect of adalimumab on symptoms of psoriasis and psoriatic arthritis, ‘concurrent response’ was defined as achieving, at the same study visit, a 75% or greater improvement in PASI score (PASI 75) and a 20% or greater improvement in the American College of Rheumatology score (ACR 20). PASI 75 and ACR 20 responses served as the primary endpoints in the psoriasis and psoriatic arthritis trials included in this study, respectively. Data from the 2 phase III psoriasis trials, REVEAL and CHAMPION, were pooled for this subanalysis. ACR scores were not measured in the REVEAL or CHAMPION. Therefore, ACR 20 responses were predicted for patients with psoriasis who had a reported history of psoriatic arthritis in these trials by using a longitudinal logistic regression model for the odds of ACR 20 response. These data were then fit to patients from the ADEPT who had a history of psoriasis at visits in which they achieved a PASI 75 response. The full set of variables considered in building the prediction model included baseline characteristics (treatment group, age, sex, duration of psoriasis, duration of psoriatic arthritis), week of visit (separate effects of weeks 8, 12 and 16 using week 4 as the reference), baseline PASI scores and follow-up PASI scores (at weeks 4, 8, 12 and 16). Statistical significance was assessed using generalized estimating equations to account for correlations within patients across time. Only statistically significant ($p < 0.05$) predictors were retained in the model. The ability of the model to discriminate visits with versus those without concurrent response was assessed using the c-statistic, which ranges from 0.5 (no discrimination) to 1 (perfect discrimination) with a c-statistic of 0.7 indicating adequate discrimination [21].

The prediction model built from the ADEPT thus provides a predicted probability of concurrent ACR 20 response conditional on observed PASI 75 responses in the REVEAL, the mean predictive times in concurrent response, which was then compared between the adalimumab and placebo arms using a 2-sample Student t test. The adalimumab and placebo arms were also compared in terms of the predicted percentage of patients with concurrent response at week 16 using a 2-sample Student t test.

**Results**

A total of 413 patients with moderate to severe psoriasis in M02-528, CHAMPION and REVEAL reported a history of psoriatic arthritis at baseline and were considered for subsequent analyses. For this group, baseline characteristics were well balanced between those randomized to the adalimumab and placebo arms (table 1).

The cumulative incidence of psoriatic arthropathy adverse events, implying flaring psoriatic arthritis-related symptoms, was significantly less for patients treated with adalimumab compared with placebo (log-rank test $p < 0.05$; fig. 1), with psoriatic arthropathy adverse events affecting 1.1% (3 of 274) of adalimumab-treated patients compared with 4.3% (6 of 139) of placebo-treated patients (table 2). After accounting for censoring using the Kaplan-Meier method, the cumulative incidence of psoriatic arthropathy adverse events was estimated to be 1.1% for adalimumab-treated patients versus 4.8% for placebo-treated patients. Adalimumab-treated patients also experienced significantly greater reductions in psoriasis/psoriatic arthritis-related pain from baseline to week 16, with an average decrease of 31.3 versus 5.6 visual analog scale units, respectively ($p < 0.001$ for difference; table 3).

The model for concurrent response developed from the ADEPT had a c-statistic of 0.7, indicating that it was suitable for predicting concurrent responses in the ADEPT. After using the ADEPT-based model to predict the probability of concurrent response for patients achieving PASI 75 responses in the REVEAL, the mean predicted times in concurrent response were compared between treatment arms. According to the model, adalimumab-treated patients would spend a significantly greater percentage of time in concurrent response compared with placebo-treated patients (39.3 vs. 2.9%; $p < 0.0001$; table 4). Similarly, at week 16, the predicted percentage of adalimumab-treated patients with concurrent response (56.9%) was significantly greater than for placebo-treated patients (4.5%; $p < 0.0001$; table 4).
For patients with moderate to severe psoriasis and a reported history of psoriatic arthritis enrolled in randomized trials of adalimumab, adalimumab reduced existing psoriasis/psoriatic arthritis-related pain and reduced the risk of worsening of psoriatic arthropathy-related symptoms. Given the proven efficacy of adalimumab in reducing psoriatic arthritis-related symptoms for patients with moderate to severe psoriatic arthritis [16–18], the effects observed in this study are not surprising. However, this study illustrates the psoriatic arthritis-related benefits of adalimumab for patients with moderate to severe psoriasis and a reported history of psoriatic arthritis. The psoriatic arthritis-related effects of adalimumab are of particular interest in this population because numerous studies have shown that comorbid psoriatic arthritis substantially increases the physical limitations, social impairment and psychological distress of patients with psoriasis [2–4]. Management of psoriasis and comorbid psoriatic arthritis should therefore aim to control symptoms of both diseases.
In addition to describing reductions in psoriatic arthritis-related symptoms for patients with moderate to severe psoriasis and a reported history of comorbid psoriatic arthritis, this study also has demonstrated that adalimumab reduces the risk of psoriatic arthropathy adverse events, which could be associated with worsening psoriatic arthritis-related symptoms. Furthermore, patients with a reported history of psoriatic arthritis have a relatively substantial 16-week risk (almost 5%) of experiencing adverse psoriatic arthropathy-related symptoms. Because psoriatic arthropathy adverse events were reported spontaneously and classified by study investigators without systematic review by a rheumatologist, the reported events may not fully represent all adverse events related to psoriatic arthritis in the study population. Despite these limitations, the reported psoriatic arthropathy adverse events reflect a consistent assessment of adverse joint symptoms applied across randomized study arms. The finding that adalimumab treatment can significantly reduce the risk of reported psoriatic arthropathy adverse events relative to placebo treatment highlights the need for a comprehensive management of psoriasis with comorbid psoriatic arthritis, not only to reduce existing symptoms, but also to reduce the risk of worsening psoriatic arthritis-related symptoms.

This study also has shown that adalimumab treatment increased the time spent with concurrent reductions in psoriasis and psoriatic arthritis-related symptoms. Because psoriatic arthritis-related symptoms were predicted in the current study of patients with moderate to severe psoriasis, the findings are subject to some limitations. In particular, the prediction model for concurrent responses was based on patients with psoriasis in the ADEPT, where the majority of patients did not have moderate to severe psoriasis. Although the model adjusted for psoriasis severity (using the PASI score) to predict ACR 20 responses for patients with moderate to severe psoriasis in the CHAMPION and REVEAL, it could not adjust...
for psoriatic arthritis severity, which was not measured in either study. Patients in the REVEAL and CHAMPION could vary significantly from those in the ADEPT based on responsiveness to therapy as measured by PASI or ACR criteria. Because patients in the CHAMPION and REVEAL could have milder baseline psoriatic arthritis than patients in the ADEPT, the prediction model may be conservative, predicting less-than-actual concurrent response rates for the less severe psoriatic arthritis. Furthermore, adalimumab treatment in the ADEPT did not include an induction dose in the first week, making it likely that the ADEPT-based prediction model underestimated the effect of adalimumab for inducing an ACR 20 response in the CHAMPION and REVEAL (in which patients did receive an induction dose, as currently indicated for the treatment of psoriasis). Despite these limitations, which would result in underestimates of the rate of concurrent response and the effect of adalimumab, the results of this study suggest that adalimumab treatment for psoriasis can substantially increase the chances of concurrent response in the first 16 weeks of treatment. Adalimumab substantially increased the amount of time that patients with a reported history of comorbid psoriatic arthritis spent in concurrent response, even during the first 12 weeks of treatment. Because psoriatic arthritis-related symptoms are associated with substantially increased costs [10], the potential cost implications of concurrent psoriasis/psoriatic arthritis response warrant further study.

Despite the limitations of combining data across clinical trials, this study has used the existing data to conservatively explore the effects of adalimumab treatment of psoriasis on symptoms related to psoriatic arthritis. This research question was not addressed in the individual trials included in the analyses. The results of this study suggest that psoriatic arthritis-related symptoms should be considered when evaluating the benefits, risks and costs of adalimumab treatment for patients with psoriasis who have a history of psoriatic arthritis.

Acknowledgment

The authors would like to thank Arbor Communications Inc., Ann Arbor, Mich., USA, for editorial support in the development of this paper.

Conflicts of Interest

The work reported here was performed under contract with Abbott Laboratories by Analysis Group Inc. P.J.M. has received research grants and speakers’ bureau honoraria from Abbott Laboratories and has served as a consultant for Abbott Laboratories. J.S., A.P.Y. and E.Q.W. are employees of Analysis Group Inc. S.R.G., Y.B. and P.M.M. are employees of Abbott Laboratories.

References


Mease/Signorovitch/Yu/Wu/Gupta/Bao/Mulani
Adalimumab Treatment of Psoriatic Arthritis-Related Symptoms in Psoriasis


