Baseline Factors That Influence ASAS 20 Response in Patients with Ankylosing Spondylitis Treated With Etanercept

JOHN C. DAVIS, JR., DÉSIRÉE M.F.M. VAN DER HEIJDE, MAXIME DOUGADOS, JURGEN BRAUN, JOHN J. CUSH, DANIEL O. CLEGG, ROBERT D. INMAN, TODD de VRIES, and WAYNE H. TSUJI

ABSTRACT. ***Objective.*** To examine the baseline demographic and disease characteristics that might influence improvement as measured by the Assessment in Ankylosing Spondylitis Response Criteria (ASAS 20) in patients with ankylosing spondylitis (AS).

Methods. A multicenter Phase 3 study was performed to compare the safety and efficacy of 24 weeks of etanercept 25 mg subcutaneous injection twice weekly (n = 138) and placebo (n = 139) in patients with AS. The ASAS 20 was measured at multiple time points. Using a significance level of 0.05, a repeated measures logistic regression model was used to determine which baseline factors influenced response in the etanercept-treated patients during the 24-week double blind portion of the trial. The following baseline factors were used in the model: demographic and disease severity variables, concomitant medications, extra-articular manifestations, and HLA-B27 status. The predictive capability of the model was then tested on the patients receiving placebo after they had received open-label etanercept treatment.

Results. Baseline factors that were significant predictors of an ASAS 20 response in etanercept-treated patients were C-reactive protein (CRP), back pain score, and Bath Ankylosing Spondylitis Functional Index (BASFI) score. Although clinical response to etanercept was seen at all levels of baseline disease activity, responses were consistently more likely with higher CRP levels or back pain scores and less likely with increased BASFI scores at baseline.

Conclusions. Higher CRP values and back pain scores and lower BASFI scores at baseline were significant predictors of a higher ASAS 20 response in patients with AS receiving etanercept but predictive value was of insufficient magnitude to determine treatment in individual patients. (J Rheumatol 2005;32:1751–4)

Key Indexing Terms:
SPONDYLITIS PREDICTIVE FACTORS TNFR:Fc FUSION PROTEIN CLINICAL TRIAL

The Assessment in Ankylosing Spondylitis Response Criteria (ASAS 20)[1] have been validated and are generally accepted as a primary tool to measure symptomatic improvement in patients with ankylosing spondylitis (AS) in clinical trials. The ASAS 20 requires an improvement of 20% and a change of at least 10 units on a 100 mm visual analog scale (VAS) in ≥ 3 of the 4 ASAS domains, as well as the absence of worsening of the same magnitude in the remaining domain. The 4 ASAS domains include patient global assessment of disease activity, pain, function, and inflammation, and the instruments used to measure these have been described[1].

We reported results of a 24-week, randomized, double-blind, controlled trial that compared etanercept with placebo in patients with AS[2]. At week 12, ASAS 20 was achieved by 59% of patients in the group receiving etanercept and by 28% of patients in the placebo group ($p < 0.0001$). At 24 weeks, the ASAS 20 was achieved by 57% of patients in the etanercept group and by 22% of patients in the placebo group ($p < 0.0001$).

Exploratory analyses were conducted to evaluate which if any baseline variables were predictive of achieving the ASAS 20 response because it is potentially important information for clinicians when considering treatment options for patients.

From the University of California, San Francisco, California, USA; University Hospital Maastricht, The Netherlands; Hopital Cochin, Paris, France; Rheumazentrum Nordrhein-Westfalen, Herne, Germany; Presbyterian Hospital of Dallas, Texas; University of Utah Medical Center, Salt Lake City, Utah, USA; Toronto Western Hospital, Toronto, Ontario, Canada; Amgen Inc., Thousand Oaks, California, USA.

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J.C. Davis, Jr., MD, MPH, University of California; D.M.F.M. van der Heijde, MD, PhD, University Hospital Maastricht; M. Dougados, MD, Hopital Cochin; J. Braun, MD, Rheumazentrum Nordrhein-Westfalen; J. Cush, MD, Presbyterian Hospital of Dallas; D.O. Clegg, MD, University of Utah Medical Center; R. Inman, MD, Toronto Western Hospital; T. DeVries, PhD; W. Tsuji, MD, Amgen Inc.

Address reprint requests to Dr. J.C. Davis, Jr., Division of Rheumatology, University of California, 533 Parnassus Ave, Room U386, Box 0633, San Francisco, CA, 94143-0633. E-mail: jdavis@medicine.ucsf.edu

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MATERIALS AND METHODS

Trial design. This randomized, double-blind, placebo-controlled trial of etanercept in patients with AS has been reported[2]. Briefly, a total of 277 patients received twice-weekly subcutaneous injections of etanercept 25 mg (n = 138) or placebo (n = 139) for 24 weeks. Patients were required to have active disease at enrollment, defined as (1) a score of 30 mm for morning stiffness and pain (average of 2 scores on a 100 mm VAS analyzing both duration and intensity of morning stiffness); and (2) scores of 30 mm for 2 of the following 3 variables: patient global assessment (on 100 mm VAS), back pain (average of 2 VAS scores evaluating nocturnal back pain and total back pain), and the Bath Ankylosing Spondylitis Functional Index (BASFI)[3]. Efficacy evaluations were conducted at weeks 2, 4, 8, 12, and 24.

Statistical analysis. Generalized Estimating Equations for longitudinal data, described in Liang and Zeger[4] and fitted with the SAS/STAT software (version 8.2), was used to model ASAS 20 responses as a function of baseline factors accounting for the correlation between responses over time within an individual patient. This methodology is similar to logistic regression analysis accounting for correlated responses over time within a patient. A forward model building procedure, similar to that described by Agresti[5], was used to create this model. Baseline factors were added sequentially to the model until no terms were significant at the 0.05 level. Separate modeling was performed for patients receiving etanercept and placebo.

Baseline variables considered for the model included gender, race (Caucasian or non-Caucasian), site (North American versus European), HLA-B27 positive status, history of uveitis, history of antecedent bacterial dysentery, urethritis, chlamydia, or other sexually-transmitted disease, inflammatory bowel disease, history of psoriasis, presence of hip disease, use of nonsteroidal antiinflammatory drugs within 6 months, use of corticosteroids within 6 months, concomitant use of disease modifying antirheumatic drugs, age, patient global assessment (PGA), total back pain score, inflammation score [average of last 2 questions on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[6] on the duration and severity of morning stiffness], BASDAI, BASFI, disease duration, C-reactive protein (CRP), and weight. Time on drug (exposure), evaluated as a categorical variable, was also considered as a potential predictor in the model. Continuous variables other than time were included in the multivariate model fitting as continuous variables and were not included in the multivariate model fitting as categorical variables based on cuts at the median or some other categorical division.

The predictive capability of the model derived for patients treated with etanercept during the blinded portion of the trial was tested on patients who had received placebo (n = 99) after they had entered the open label period of the study and received at least 1 dose of open label etanercept. For these patients, baseline was considered the last value before the open label etanercept treatment phase. Variables from the logistic regression model derived from the forward selection algorithm for patients treated with etanercept were applied to baseline scores for each patient receiving placebo, and the predicted probability of an ASAS 20 response at weeks 4, 8, 12, and 24 of the open label study was then determined for each patient who had received placebo. If the predicted probability for a patient at the time point in question was 0.5 or higher, the patient was classified as a responder for prediction purposes; otherwise the patient was classified as a non-responder. The predicted ASAS 20 responses were compared to the actual ASAS 20 responses at each time point for each patient, and the sensitivity and specificity of the model predictions were then computed.

RESULTS

Table 1 provides estimates of odds ratios (OR) for response versus non-response for variables from the model derived using the forward selection algorithm for etanercept and placebo-treated patients. Baseline CRP, BASFI, back pain, and time were significant predictors for the etanercept-treated patients. No baseline disease factors had significant interactions with time ($p > 0.10$), indicating that a constant OR can be assumed for each baseline disease variable over the 24-week period. Baseline CRP, back pain, and site were significant predictors of placebo response, although time was not. No variable had significant interactions with time for the patients receiving placebo. Higher levels of CRP and back pain were associated with a higher likelihood of being a responder for etanercept-treated patients; however the opposite trend was true for placebo-treated patients. It should be noted that other models could have been considered for the etanercept-treated patients. Baseline CRP and BASFI were the most significant predictors of ASAS 20 response in etanercept-treated patients. The following variables were significant predictors in the presence of CRP, BASFI, and time: PGA ($p = 0.0101$), BASDAI ($p = 0.0211$), inflammation ($p = 0.0373$), and age ($p = 0.0439$). The OR estimates for the PGA, BASDAI, and inflammation were very similar to the OR for total back pain and thus models including any 1 of these variables instead of total back pain could be considered a reasonable alternative. Note that the correlations with back pain for the etanercept-treated patients were 0.69, 0.55, and 0.49 for the PGA, BASDAI, and inflammation, respectively; therefore, these measures exhibit a fairly high degree of correlation. Age was not significantly correlated with back pain ($r = -0.11$, $p = 0.21$).

The predictive capability of the model was evaluated with placebo-treated patients after they had received open label etanercept therapy for 24 weeks. As shown in Table 2, the percentages of patients who met the ASAS 20 response criteria in the open label portion were 46%, 56%, 63%, and 64% at weeks 4, 8, 12, and 24, respectively. These results are similar to the ASAS 20 response percentages observed in the double-blind portion of the trial for the etanercept-treated patients. Also as shown in Table 2, the model correctly predicted an actual ASAS 20 response of between 53% and 67% of the patients, depending on time point. The sensitivity of the model ranged between 47% and 55%, and the specificity of the model ranged between 59% and 83%. Thus, the forward model for etanercept-treated patients may be prone to misclassification bias.

To illustrate that etanercept was effective in treating patients with varying degrees of baseline disease severity, the ASAS 20 response percentages at week 24 are provided in Table 3 by the quartiles of baseline disease activity for CRP, BASFI, and total back pain. Table 3 shows that etanercept is more effective than placebo regardless of the baseline disease activity level for any of the 3 variables.

DISCUSSION

Results from the 24-week, placebo-controlled, double-blind segment of this study suggest that back pain, BASFI, and CRP are predictive factors of ASAS 20 response to etanercept treatment and that site, back pain, and CRP are predictive factors for ASAS 20 response in placebo-treated

Table 1. Model of ASAS 20 responses in patients in etanercept group (n = 138) and placebo group (n = 139) based on the forward selection algorithm. Time was included in the model fit for etanercept-treated patients and was a significant predictor of an ASAS 20 response (p = 0.0043). Time was not a significant predictor for placebo response (p = 0.1790).

Treatment Group	Baseline Variable	OR (95% CI)	p
Etanercept	CRP	1.66 (1.36, 2.02)	< 0.0001
	BASFI	0.96 (0.94, 0.98)	< 0.0001
	Back pain	1.03 (1.01, 1.04)	0.0024
Placebo			
	Site, EU vs NA	0.36 (0.16, 0.85)	0.0263
	CRP	0.87 (0.77, 0.98)	0.0365
	Back pain	0.98 (0.96, 0.99)	0.0046

BASFI: Bath Ankylosing Spondylitis Functional Index; CI: confidence interval; CRP: C-reactive protein, mg/dl.

Table 2. Sensitivity and specificity of the logistic regression model predictions after administration of open label etanercept to patients in the original placebo group (n = 99).

Week	ASAS 20 Responders, %	Predicted Correctly, %	Sensitivity, %	Specificity, %
4	46	67	48	83
8	56	65	55	77
12	63	53	48	59
24	64	56	47	72

Table 3. ASAS 20 response percentages at week 24 of the double-blind portion of the trial by quartiles for baseline CRP, BASFI, and back pain.

Variable	Level	Placebo n/N (%)	Etanercept n/N (%)
*CRP	0.009–0.35	10/36 (28)	15/34 (44)
	0.36–1.04	7/36 (19)	18/33 (55)
	1.05–3.03	9/32 (28)	18/37 (49)
	3.04–14.17	5/35 (14)	27/34 (79)
BASFI	4.3–39.1	13/35 (37)	21/35 (60)
	39.2–53.4	6/26 (23)	26/43 (60)
	53.5–70.0	9/39 (23)	17/30 (57)
	70.1–97.7	3/39 (8)	14/30 (47)
Back pain	0–50	11/32 (34)	18/40 (45)
	51–64	12/36 (33)	19/31 (61)
	65–78	4/39 (10)	25/42 (60)
	79–100	4/32 (13)	16/25 (64)

* Normal ≤ 1 mg/dl.

patients. Interestingly, low levels of CRP and back pain were associated with higher levels of ASAS 20 response in the placebo group, while the opposite was observed in patients receiving etanercept.

Identification of baseline back pain and BASFI as predictors of ASAS 20 response is not surprising since both are components of the ASAS response criteria and are not independent variables. This finding is likely an artifact of the response criteria rather than an indication of the nature of AS or the effect of etanercept in this disease; however, the direction of the response for back pain was different in the etanercept group compared to the placebo group. In contrast, the acute phase reactants, CRP and erythrocyte sedimentation rate (ESR), are not elements of the ASAS 20, yet CRP is identified as a predictor of response. This finding may reflect the pathology of AS and its possible response to treatment with etanercept. This is of particular interest because although acute phase reactants such as CRP and ESR may correlate with peripheral disease activity, they usually do not reflect axial activity.

While back pain, BASFI, and CRP have been identified as predictors of an ASAS 20, they are imperfect predictors and may not be practical for routine clinical use in identifying candidates likely to respond to treatment. In fact, 52% of the patients in the etanercept arm who had a normal baseline CRP met the ASAS 20 at week 24. Also, the predictive capability of the model in etanercept-treated patients was evaluated in patients in the initial placebo group who were treated with etanercept in the open label segment and was found to have low specificity, indicating that the model was imperfect in predicting response. Although these results may have implications for clinical research and further research needs to be performed, clinicians should not withhold treatment based on these variables alone. Until further results are available, clinical guidelines that have been proposed for the initiation of anti-tumor necrosis factor therapy for patients with AS should be followed[7].

In exploratory analyses of various baseline variables in a study of etanercept in patients with AS, baseline total back pain, CRP, and BASFI were significant predictors of an ASAS 20 response. Higher total back pain and CRP values and lower BASFI scores at baseline were all associated with a higher chance of being a responder on the ASAS 20. Sensitivity and specificity of the model, when averaged over

all time points, were about 50% and 73%, respectively, when evaluated on a separate cohort of patients independent from the cohort used in the model building.

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