Effectiveness, Safety, and Predictors of Good Clinical Response in 1250 Patients Treated with Adalimumab for Active Ankylosing Spondylitis

MARTIN RUDWALEIT, PASCAL CLAUDEPIERRE, PAUL WORDSWORTH, EDUARDO LOZA CORTINA, JOACHIM SIEPER, MARTINA KRON, ROBERTO CARCERERI-DE-PRATI, HARTMUT KUPPER, and SONJA KARY

ABSTRACT. ***Objective.*** We evaluated the effectiveness and safety of adalimumab in a large cohort of patients with active ankylosing spondylitis (AS) and identified clinical predictors of good clinical response.

Methods. Patients with active AS [Bath AS Disease Activity Index (BASDAI) ≥ 4] received adalimumab 40 mg every other week in addition to their standard antirheumatic therapies in a multinational 12-week, open-label study. We used 3 definitions of good clinical response: 50% improvement in the BASDAI (BASDAI = 50), 40% improvement in the ASsessments of SpondyloArthritis International Society criteria (ASAS40), or ASAS partial remission. Response predictors were determined by logistic regression with backward elimination (selection level 5%).

Results. Of 1250 patients, 1159 (92.7%) completed 12 weeks of adalimumab treatment. At Week 12, 57.2% of patients achieved BASDAI 50, 53.7% achieved ASAS40, and 27.7% achieved ASAS partial remission. Important predictors of good clinical response (BASDAI 50, ASAS40, and partial remission) were younger age ($p < 0.001$), and greater C-reactive protein (CRP) concentration ($p \leq 0.001$), HLA-B27 positivity ($p \leq 0.01$), and tumor necrosis factor (TNF) antagonist naivety ($p < 0.001$).

Conclusion. Adalimumab was effective in this large cohort of patients with AS, with more than half of patients achieving a BASDAI 50 or ASAS40 response and more than a quarter of patients reaching partial remission at Week 12. Younger age, greater CRP concentrations, HLA-B27 positivity, and TNF antagonist naivety were strongly associated with BASDAI 50, ASAS40, and partial remission responses. ClinicalTrials.gov identifier: NCT00478660. (J Rheumatol First Release March 1 2009; doi:10.3899/jrheum.081048)

Key Indexing Terms:
ADALIMUMAB ANKYLOSING SPONDYLITIS EXTRAAXIAL ARTHRITIS
PREDICTOR TUMOR NECROSIS FACTOR ANTAGONIST

Ankylosing spondylitis (AS) belongs to a group of interrelated spondyloarthritides that present as chronic inflammatory disorders and share common features, such as inflammation of the sacroiliac joints and/or other spinal structures, extraaxial arthritis (primarily of the lower limbs), and enthesitis, and have a strong association with HLA-B27. The prevalence of AS is 0.55% among the European white population, with twice as many men as women affected[1,2].

Most patients experience the first symptoms in their second or third decades of life. The first line of pharmacologic defense is a nonsteroidal antiinflammatory drug (NSAID). Among disease-modifying antirheumatic drugs (DMARD), only sulfasalazine and methotrexate have demonstrated at least some therapeutic effect (i.e., limited effect on extraaxial arthritis but no effect on spinal inflammation)[3-5]. Tumor necrosis factor (TNF) antagonists, including the TNF-receptor construct etanercept and the monoclonal antibodies infliximab and adalimumab, have markedly improved the therapeutic options for patients with active AS[6-14].

Few studies of patients with AS have addressed the question of whether certain clinical characteristics predict clinical response to TNF antagonist therapy[14,15]. The safety and efficacy of adalimumab, the first available fully human anti-TNF monoclonal antibody, for the treatment of patients with

From Charité–University Medicine Berlin, Campus Benjamin Franklin, Berlin, Germany; AP-HP, Henri Mondor Albert Chenevier, Créteil, and Université Paris XII, Créteil, France; Nuffield Orthopaedic Centre, Oxford, United Kingdom; Hospital de Navarra, Pamplona, Spain; and Abbott GmbH & Co. KG, Ludwigshafen, Germany.

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M. Rudwaleit, MD; J. Sieper, MD, Charité–University Medicine Berlin, Campus Benjamin Franklin; P. Claudepierre, MD, AP-HP, Henri Mondor Albert Chenevier and Université Paris XII; P. Wordsworth, MD, Nuffield Orthopaedic Centre; E.L. Cortina, MD, Hospital de Navarra; M. Kron, PhD; R. Carcereri-de-Prati, MD; H. Kupper, MD; S. Kary, MD, Abbott GmbH & Co. KG.

Address reprint requsts to Dr. M. Rudwaleit, Charité, Campus Benjamin Franklin Hospital, Medical Department I, Rheumatology, Hindenburgdamm 30, 12200 Berlin, Germany.
E-mail: martin.rudwaleit@charite.de

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AS were demonstrated in 2 randomized, controlled clinical trials[11,16,17]. In addition to the 2 pivotal trials of adalimumab for the treatment of AS, a Phase IIIb clinical trial, the Review of Safety and Effectiveness With Adalimumab in Patients With Active Ankylosing Spondylitis (RHAPSODY), was completed. Our objective for the RHAPSODY trial was to collect data on adalimumab effectiveness and safety in more than 1200 patients from 15 European countries in an open-label design that allowed inclusion of patients with the typical characteristics of AS eligible for anti-TNF therapy in daily rheumatologic practice. In addition, we determined predictors of good clinical response to adalimumab using established definitions of at least a 50% improvement in the Bath AS Disease Activity Index (BASDAI 50)[18,19], at least a 40% improvement in the ASsessments of SpondyloArthritis International Society response criteria (ASAS40), and the ASAS partial-remission response[20,21]. We also compared the identified predictors across the 3 definitions of good clinical response.

MATERIALS AND METHODS

Patients. Adults at least 18 years of age with AS according to the 1984 modified New York criteria for ankylosing spondylitis[22] for at least 3 months and active disease defined by a BASDAI score ≥ 4[23] despite treatment with at least 1 NSAID were eligible for this multinational clinical study. Patient enrollment followed national guidelines for TNF antagonist use for the treatment of AS if the national guidelines were more strict, for example, requiring failure of more than 1 NSAID before initiating a TNF antagonist. Continuing treatment with NSAID (including cyclooxygenase-2 inhibitors), glucocorticoids (≤ 10 mg/day prednisolone equivalent at maximum), and/or DMARD other than alkylating agents (i.e., chlorambucil, cyclophosphamide) was allowed provided the dosage was not increased during the study. Treatment with NSAID and/or glucocorticoids and topical treatment for AS-related uveitis and/or psoriasis could be tapered beginning at Week 2 at the physician's discretion. Preexisting stable dosages of analgesic drugs were allowed provided no dosage change occurred throughout the study period and administration was interrupted at least 24 hours before a study visit, except for those patients who were receiving a continuous maintenance dosage regimen of an analgesic drug.

Exclusion criteria encompassed current pregnancy or breastfeeding; any persistent or severe infection within 30 days of baseline; treatment during the past 2 months with infliximab or during the past 3 weeks with etanercept or any previous treatment with adalimumab; systemic use of glucocorticoids equivalent to > 10 mg/day prednisolone within 28 days before or at screening, intraarticular injections or infiltrations of extraaxial joints and tendons within 28 days before or at screening, or intraarticular injections of sacroiliac joints ≤ 14 days before screening; a history of rheumatic disorder other than AS; any uncontrolled medical condition (e.g., uncontrolled diabetes mellitus, unstable ischemic heart disease); history or signs of demyelinating disease; active tuberculosis (TB) or histoplasmosis; malignancy (except for completely treated squamous or basal cell carcinoma); positive serology for hepatitis B, hepatitis C, or human immunodeficiency virus; and infections requiring hospitalization or intravenous treatment with antibiotics within 30 days or oral treatment with antibiotics within 14 days before enrollment. All patients were screened for active or latent TB infection. Patients diagnosed with latent TB infection were treated with isoniazid or alternative regimen before the first adalimumab injection.

Independent ethics committees in all 15 countries where the study was conducted provided approval for each of the 211 participating centers. The principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice were applied throughout the study. Each patient provided written informed consent before any study-related procedures were performed.

Study design. Patients subcutaneously self-administered adalimumab 40 mg (Abbott Laboratories, Abbott Park, IL, USA) every other week in addition to their preexisting antirheumatic treatment for a core study period of 12 weeks. An extension period through Week 20 was planned for all patients with symptomatic uveitis within the past 12 months before study entry. The extension period through Week 20 was optional for patients who had benefited from study medication if adalimumab was not commercially available for the treatment of AS after 12 weeks of treatment. The presence of active AS was carefully evaluated in each patient. Based on previous radiographs, investigators documented the presence or absence of advanced ankylosis at baseline, defined as structural damage in at least 50% of the spine in more than 2 spinal segments[24].

The presence of extraaxial symptoms or AS-related diseases was also determined at baseline. Specifically, patients were evaluated for symptomatic extraaxial arthritis based on a tender joint count of 46 joints and a swollen joint count (SJC) of 44 joints; symptomatic enthesitis was assessed using the Maastricht AS Enthesitis Score[25] and additional examination of the fascia plantaris. The Physician's Global Assessment for psoriasis was used to evaluate symptomatic psoriasis. Investigators documented a history of uveitis before and/or at baseline if an ophthalmologic report was provided. A history of inflammatory bowel disease (IBD) was determined by patient report, including whether or not the patient had symptomatic IBD at baseline.

Evaluations for effectiveness and safety occurred at Weeks 2, 6, 12, and 20, as applicable. Observed data at Week 12 were used for all analyses of effectiveness. For comparison with efficacy results in randomized controlled trials and for sensitivity analysis, we imputed missing observations with the last observation carried forward (LOCF) and also with nonresponder imputation (NRI). Safety data were analyzed based on the complete treatment period of each patient. Measures of effectiveness included the ASAS20 and ASAS40, defined as improvement of at least 20% and 40%, respectively, in at least 3 of the 4 domains of the ASAS20 criteria, as follows: (1) inflammation (morning stiffness, 0–10 point scale measured by the mean of BASDAI questions 5 and 6); (2) total back pain on a 0–100 mm visual analog scale (VAS); (3) function assessed by the 0–10 point Bath AS Functional Index (BASFI)[26]; and (4) patient's global assessment of disease activity on a 0–100 mm VAS, with no deterioration in the remaining domain[21]. Additional measures of effectiveness were ASAS 5/6 response, defined as at least 20% improvement in at least 5 of 6 ASAS assessment criteria using C-reactive protein (CRP) serum concentration as the acute-phase reactant and the Bath AS Metrology Index (BASMI) for metrology[27], ASAS partial remission (value < 2 on a 0–10 point scale in each of the 4 ASAS20 domains), BASDAI 50[19], and the BASFI (0–10 point scale)[26]. In addition, we summarized adverse events (AE) reported from the time of first adalimumab injection until 70 days (5 serum half-lives) after the last adalimumab injection.

Statistical analysis. We included all patients who received at least 1 adalimumab injection in the analyses. Endpoints at Week 12 were BASDAI 50, ASAS40, and ASAS partial remission. Continuous variables that were included in the analysis as possible predictors of good clinical response (i.e., BASDAI 50, ASAS40, ASAS partial remission responses) were age (years), duration of AS (years), BASFI (0–10), BASDAI (0–10), CRP (mg/dl), erythrocyte sedimentation rate (ESR, mm/h), BASMI (0–10), morning stiffness (0–10, mean of questions 5 and 6 of the BASDAI), physician's global assessment of disease activity (0–100 mm VAS), patient's global assessment of disease activity (0–100 mm VAS), and total back pain (0–100 mm VAS). Categorical variables (yes vs no) that were included in the analysis as possible predictors of good clinical response were male sex; HLA-B27 positivity; presence of advanced AS; current symptoms of extraaxial arthritis (defined as SJC ≥ 1), enthesitis (≥ 1 inflamed enthesis in Maastricht AS Enthesitis Score and/or fascia plantaris), IBD, and skin psoriasis and history of at least 1 episode of uveitis; prior TNF antagonist ther-

apy; and ongoing systemic use of ≥ 1 NSAID, of ≥ 1 DMARD, or of ≥ 1 glucocorticoid (≤ 10 mg/day prednisolone equivalent). We analyzed the categorical baseline factors descriptively for response versus nonresponse according to BASDAI 50, ASAS40, and ASAS partial remission criteria, whereas we evaluated the linearity of effects of continuous variables on the logit of the response graphically (data not shown). To identify potential predictors of good clinical response, crude odds ratios (OR) with 95% confidence intervals (95% CI) and p values based on chi-square tests were calculated. Afterwards, important predictors of good clinical response were identified by logistic regression with backward elimination (selection level 5%). ESR was not considered for variable selection because of a strong correlation with CRP. Only the results of the final model, including OR, 95% CI, and p values are presented. Crude OR are not shown because of the abundance of data (data available on request). The predictive value of the model was evaluated by calculation of the area under the receiver-operating characteristics curve for each of the 3 outcomes of good clinical response. Data were analyzed using SAS version 8.2 (SAS Inc., Cary, NC, USA). All values presented are mean ± SD unless otherwise noted.

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RESULTS

Patient disposition, withdrawals, and adalimumab treatment duration. A total of 1250 patients were enrolled at 211 centers in 15 European countries between March 2006 and March 2007. Up to Week 12, 91 (7.3%) patients discontinued prematurely; of the 1250 enrolled patients, 13 (1.0%) withdrew because of unsatisfactory therapeutic effect and 54 (4.3%) withdrew because of at least 1 AE. Throughout the complete 20-week treatment period, 115 (9.2%) of 1250 patients withdrew, including 66 (5.3%) who discontinued because of at least 1 AE and 21 (1.7%) who discontinued because of unsatisfactory therapeutic effect. Additional reasons for premature discontinuation were withdrawal of consent, protocol violation, loss to followup, or other. The mean adalimumab treatment duration was 15 weeks (median 12 wks).

Patient characteristics at baseline. The patients enrolled in this study had active disease indicated by a BASDAI of 6.3 ± 1.4. Of the 1250 patients, 1098 (87.8%) had a history of treatment with at least 2 NSAID. The majority of patients were white (97.1%), male (71.3%), and positive for HLA-B27 (82.1%). Additional baseline characteristics of the patient sample were age 44 ± 11.4 years; duration of AS 11 ± 9.8 years; BASFI 5.4 ± 2.2; BASMI 4.1 ± 2.3; morning stiffness 6.6 ± 2.1; serum CRP 2.0 ± 2.4 mg/dl; total back pain 62 ± 23 mm; physician's global assessment of disease activity 61 ± 17 mm; and patient's global assessment of disease activity 66 ± 21 mm. Of the 1250 patients, 330 (26.9%) had advanced AS (information was missing for 23 patients), 281 (22.5%) had peripheral arthritis (SJC ≥ 1), and 686 (54.9%) had enthesitis (≥ 1 inflamed enthesis). At baseline, 59 (4.7%) patients reported symptomatic IBD, 108 (8.6%) had symptomatic psoriasis, and 274 (21.9%) had a history of at least 1 uveitis episode. A history of prior TNF antagonist therapy (etanercept and/or infliximab) was documented in 326 (26.1%) patients. At baseline, 929 (74.3%) patients were receiving NSAID, 323 (25.8%) were receiving DMARD, and 169 (13.5%) were receiving glucocorticoids. Six patients reported continuous maintenance analgesic treatment with fentanyl or buprenorphine patches.

Effectiveness. At Week 12, 69.9% of the 1250 patients achieved ASAS20 and 53.7% achieved ASAS40 responses. The BASDAI 50 response rate was 57.2%. ASAS 5/6 criteria were fulfilled by 58.0% of patients, and 27.7% of patients experienced ASAS partial remission at Week 12. The 12-week results were similar when missing observations were imputed using the LOCF method and somewhat lower when NRI was used. For example, the BASDAI 50 response, ASAS40 response, and partial remission rates based on the most conservative NRI calculation were 55.1%, 50.6%, and 26.1%, respectively. The onset of adalimumab effectiveness was rapid, with approximately 30% of patients achieving a BASDAI 50 or ASAS40 response at Week 2 (i.e., after the first adalimumab injection; Figure 1). The mean changes from baseline to Week 12 were BASDAI –3.3 ± 2.3 (0–10); BASFI –2.2 ± 2.3 (0–10); morning stiffness –3.7 ± 2.7 (0–10); CRP –1.4 ± 2.5 (mg/dl); physician's global assessment of disease activity –37 ± 22 (0–100 mm VAS); patient's global assessment of disease activity –35 ± 30 (0–100 mm VAS); and total back pain –33 ± 28 (0–100 mm VAS).

Safety. Adalimumab was generally well tolerated during this short-term treatment period. Overall, 685 (54.8%) patients reported at least 1 AE. The AE were predominantly mild. Serious AE were documented in 43 (3.4%) patients, including serious infections in 5 (0.4%) patients. No cases of serious opportunistic infection or tuberculosis were reported. One 34-year-old male patient (0.1%) with a medical history of decreasing visual ability before enrollment had a serious optic neuritis. No deaths, malignancies, lupus or lupus-like reactions, or serious allergic reactions were documented.

Predictors of good clinical response. In the analyses of each individual predictor, the BASDAI 50 response rates, ASAS40 response rates, ASAS partial-remission rates in patients of various ages, CRP concentrations, HLA-B27 positivity, and TNF antagonist naivety are illustrated in Figure 2. Sex, treatment with glucocorticoids, extraaxial arthritis, enthesitis, IBD, and psoriasis had no important influence on good clinical response at Week 12 across all 3 response measures, whereas all other possible predictors indicated important effects in at least 1 of the endpoints (data not shown).

In the next step, we investigated the ensemble of all variables (except for ESR because of a strong correlation with CRP) by logistic regression with backward elimination to simultaneously assess the effects of the predictors on good clinical response. Younger age, a greater CRP concentration, HLA-B27 positivity, and TNF antagonist naivety were strongly associated with achievement of good clinical response (Table 1). In addition to these 4 important factors, patients with a lower baseline BASFI were more likely to

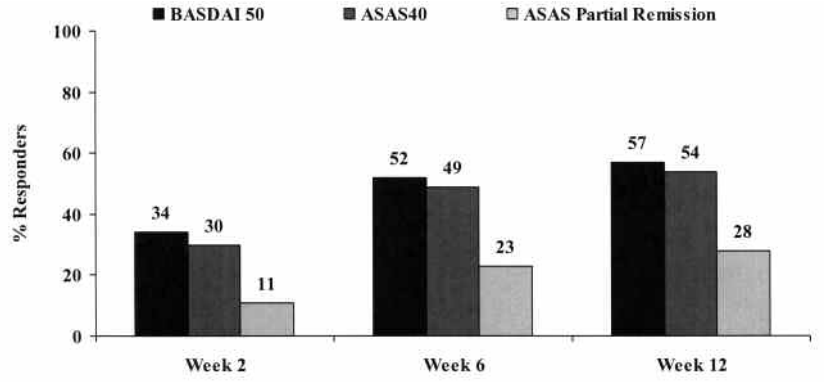

Figure 1. Fifty percent improvement in BASDAI 50, 40% improvement in ASAS40, and ASAS partial remission response rates over time (N = 1250; observed values).

achieve both BASDAI 50 and ASAS partial remission. Better mobility at baseline as measured by the BASMI was also strongly associated with partial remission. A lower baseline total back pain score was associated only with achievement of BASDAI 50. Morning stiffness, physician's global assessment of disease activity, patient's global assessment of disease activity, and, in contrast to the analysis of single variables, treatment with glucocorticoids were identified by logistic regression as additional important predictors only for an ASAS40 response (Table 1).

The area under the receiver-operating characteristics curve was 0.72, 0.74, and 0.77 for the final models of predictor identification for BASDAI 50, ASAS40, and ASAS partial remission, respectively. The profile of predictors for each of the 3 outcomes was similar with minor changes in OR when the 3 outcomes were based on LOCF values. For the BASDAI 50 response, 2 additional predictors were identified using the LOCF values: BASDAI (OR 1.13, 95% CI 1.00–1.26, p = 0.041) and use of steroids (OR 0.68, 95% CI 0.47–1.00, p = 0.048). Because NRI includes patients with good response who discontinue from a study for reasons other than nonresponse, the predictor analyses were not performed based on NRI values.

Predictors of good clinical response in TNF antagonist-naive patients. We repeated the analyses for the subset of 924 TNF antagonist-naive patients. The logistic regression with backward elimination included the same possible predictors at baseline that were used for the complete study population, with the exception of prior TNF antagonist therapy. The logistic regression identified a profile of important predictors for BASDAI 50, ASAS40, and ASAS partial remission responses that was very similar to the profile of predictors for all 1250 patients; younger age, greater CRP serum concentration, and HLA-B27 positivity were strongly associated with BASDAI 50, ASAS40, and ASAS partial remission, respectively. A lower BASFI and a lower BASMI had an important influence only on ASAS partial remission. Baseline glucocorticoid treatment and physician's global assessment of disease activity had no important influence on ASAS40 response in TNF antagonist-naive patients, whereas the influence of morning stiffness and patient's global assessment of disease activity remained clinically relevant. In addition, the influence of total back pain on BASDAI 50 response remained important, and we identified psoriasis as another predictor of good clinical response (data not shown).

Finally, we evaluated the baseline values for the 4 common predictors as well as BASFI and BASMI in those 13 patients who prematurely discontinued adalimumab through Week 12 because of lack of effectiveness and who thus had not been included in the predictor analyses. By comparison with baseline characteristics in ASAS40 responders and ASAS20 nonresponders, patients with unsatisfactory response to adalimumab displayed the pattern of baseline characteristics consistent with our final models of predictors of good clinical response (Table 2).

DISCUSSION

Our study is the largest prospective clinical trial of adalimumab for the treatment of AS. Although there is a limitation in the open-label uncontrolled study design for the evaluation of adalimumab effectiveness, the large number of patients with active AS who had a clinical profile that reflects typical patients treated by rheumatologists enabled us to evaluate the effectiveness of adalimumab in daily clinical practice. The disease characteristics at baseline of the patients enrolled in this study, including mean BASDAI of 6.3, mean BASFI of 5.4, mean AS duration of 11 years, and a history of insufficient treatment with at least 2 NSAID in 87.8% of the patients, mirror the profile of patients with AS who are considered eligible for TNF antagonist therapy[19,28,29]. These baseline clinical characteristics are also similar to the baseline characteristics of patients with AS in previous randomized controlled trials of adalimumab[11,16] apart from the exclusion of prior TNF antagonist therapy in the pivotal trials. Overall, at Week 12, the ASAS20 response rate of 69.9%, the ASAS40 response rate of 53.7%, and the BASDAI 50 response rate of 57.2% of patients in this open-

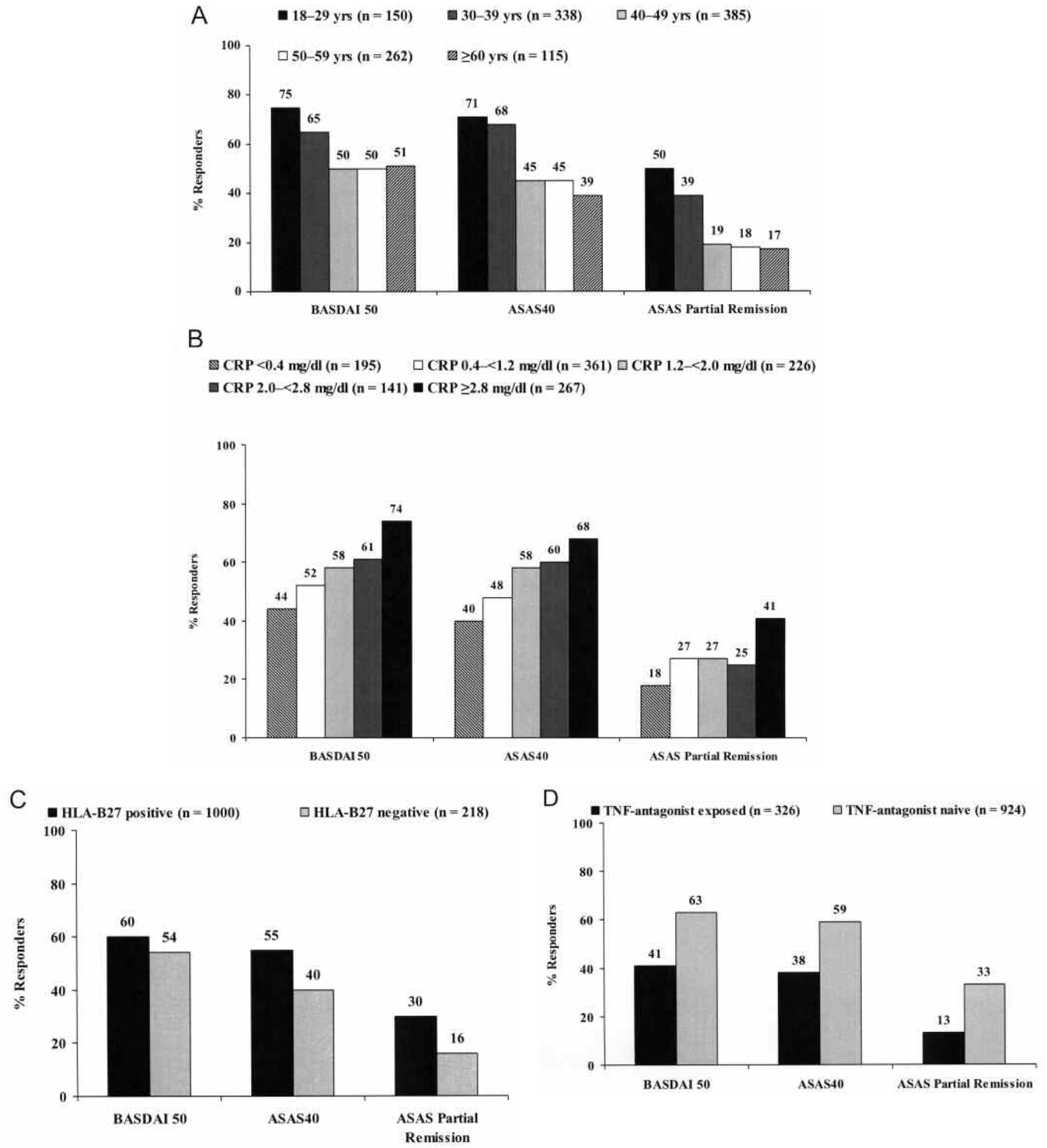

Figure 2. Week 12 BASDAI 50, ASAS40, and ASAS partial remission response rates by age (A); by baseline serum CRP concentration (reference value 0.4 mg/dl) (B); by HLA-B27 positivity (C); and by TNF antagonist naivety (D). All data are observed.

label trial are somewhat greater than the corresponding response rates reported for randomized controlled trials of TNF antagonists for the treatment of patients with AS[8,10,11,13]. Because demonstration of adalimumab efficacy was not the objective of this study, we used observed values whereas the efficacy results of randomized controlled trials are conservatively calculated using NRI. By comparison, the therapeutic response rates based on NRI in this large uncontrolled study were similar to those reported for randomized controlled trials.

Table 1. Results of logistic regression with backward elimination for a major clinical response to adalimumab at week 12 as defined by BASDAI 50, ASAS40, and ASAS partial remission.

Predictors	BASDAI 50 OR (95% CI)	p	ASAS40 OR (95% CI)	p	ASAS Partial Remission OR (95% CI)	p
Age, yrs	0.97 (0.96–0.98)	< 0.001	0.96 (0.95–0.97)	< 0.001	0.96 (0.95–0.97)	< 0.001
HLA-B27-positive vs negative	1.77 (1.25–2.49)	0.001	1.60 (1.12–2.28)	0.009	2.20 (1.40–3.45)	< 0.001
Prior TNF antagonist therapy*	0.35 (0.26–0.48)	< 0.001	0.32 (0.24–0.44)	< 0.001	0.32 (0.21–0.47)	< 0.001
CRP, mg/dl	1.23 (1.15–1.32)	< 0.001	1.17 (1.09–1.25)	< 0.001	1.20 (1.12–1.28)	< 0.001
BASFI, 0–10	0.89 (0.83–0.96)	0.003	—	—	0.77 (0.72–0.83)	< 0.001
BASMI, 0–10	—	—	—	—	0.91 (0.85–0.99)	0.019
Total back pain, 0–100 mm VAS	0.99 (0.98–1.00)	0.012	—	—	—	—
Morning stiffness, 0–10	—	—	1.11 (1.04–1.20)	0.004	—	—
Physician global assessment of disease activity, 0–100 mm VAS	—	—	0.99 (0.98–1.00)	0.016	—	—
Patient global assessment of disease activity, 0–100 mm VAS	—	—	1.02 (1.01–1.02)	< 0.001	—	—
Use of glucocorticoids*	—	—	0.67 (0.45–1.00)	0.048	—	—

* Yes versus no, selection level, 0.05. AS: ankylosing spondylitis, ASAS40: Assessment in Spondyloarthritis International Society 40% response, BASDAI 50: Bath AS Disease Activity Index 50% response, BASFI: Bath AS Functional Index, BASMI: Bath AS Metrology Index, CRP: C-reactive protein, TNF: tumor necrosis factor, VAS: visual analog scale.

Table 2. Predictive variables at baseline in ASAS40 responders, ASAS20 nonresponders, and patients who discontinued because of lack of adalimumab effectiveness.

Predictors	ASAS40 Responders, n = 633	ASAS20 Nonresponders, n = 264	Patients Who Discontinued Because of Lack of Effectiveness, n = 13
Age, yrs, mean ± SD	41.3 ± 11.2	47.5 ± 11.4	45.8 ± 12.4
CRP, mg/dl, mean ± SD*	2.3 ± 2.6	1.6 ± 2.3	1.5 ± 1.9
HLA-B27-positive, %	83	74	69
Prior TNF antagonist therapy, %	18	42	46
BASFI (0–10), mean ± SD	5.4 ± 2.1	5.4 ± 2.5	6.6 ± 2.2
BASMI (0–10), mean ± SD	3.9 ± 2.2	4.5 ± 2.4	4.5 ± 2.1

* Reference value 0.4 mg/dl. ASAS20: Assessment in Spondyloarthritis International Society 20% response, ASAS40: Assessment of Spondyloarthritis International Society 40% response, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, CRP: C-reactive protein, TNF: tumor necrosis factor.

In parallel with evaluating the safety and effectiveness of adalimumab, we also analyzed predictors for achieving good clinical response as defined by BASDAI 50, ASAS40, and ASAS partial remission. The study provided an excellent database to identify predictors for good clinical response, which can be generalized for widespread use in daily rheumatologic practice. The multiple logistic regression of the 1250 patients revealed that the likelihood to experience a good clinical response, measured by BASDAI 50, ASAS0, or ASAS partial remission, is decreased per year of age and increased per mg/dl of CRP concentration. The OR in these 2 continuous variables had very narrow confidence intervals and very low p values. We arbitrarily excluded ESR and not CRP from the regression model because of the strong correlation of these 2 acute-phase reactants; thus presumably an elevated ESR is also associated with a better chance of good clinical response. Among the categorical variables (yes vs no), HLA-B27 positivity and TNF-antagonist naivety were additionally identified as strong predictors of good clinical response across all 3 definitions of good response. The chance of a BASDAI 50 response is higher in patients with lower functional disability (as assessed by the BASFI) and lower total back pain at baseline, although the total back pain score is not specific for inflammatory back pain. Thus, these results are largely in accord with a previous predictor evaluation in 99 patients with AS from 2 randomized controlled trials of etanercept and infliximab[15]. In that previous predictor analysis, shorter disease duration, younger age, greater CRP concentration, and a lower baseline BASFI were strong predictors of a BASDAI 50 and ASAS40 response; a greater baseline BASDAI had some additional effect.

The number of patients in the previous study[15] was relatively small; however, data were collected in randomized, placebo-controlled trials, whereas this uncontrolled study comprises more than 1000 patients. Because age and disease

duration were closely related in the previous study, the authors arbitrarily decided to use disease duration instead of age for the multiple regression analysis. In our study population, age and AS duration were not strongly correlated based on a visual evaluation of scatterplots (data not shown). In the logistic regression, disease duration was not a strong predictor of BASDAI 50, ASAS40, or partial remission. The difference in the results of the 2 predictor analyses could reflect a chance finding in the previous study or, alternatively, illustrate difficulties in estimating disease duration in AS[30].

ASAS40 was another endpoint of our predictor analyses. In addition to the 4 common factors that predicted a BASDAI 50, ASAS40, or a partial remission response, morning stiffness (from the BASDAI) and both physician's and patient's global assessment of disease activity had some predictive effect on ASAS40. Of note, morning stiffness and patient's global assessment of disease activity are also domains of the ASAS response criteria, so that patients with high baseline values have a better chance of a greater relative improvement. In another study, Davis and colleagues[31] identified CRP, BASFI, and back pain as predictors of an ASAS20-defined clinical response by using generalized estimating equations and also described some effect of age. Direct comparisons between the studies are somewhat restricted because of different endpoints (ASAS40 or BASDAI 50 vs ASAS20), different statistical methods, and different study designs (open-label clinical trial vs placebo-controlled clinical trial). Despite these differences, the results reported by Davis and colleagues[31] are consistent with our findings.

We performed the first predictor analysis for ASAS partial remission and this criterion requires achievement of a state of very low disease activity (i.e., a score of < 2 in each of the 4 ASAS domains) compared with the relative improvement required by the ASAS40 response criteria. The logistic regression for predictors of partial remission revealed a pattern of important clinical characteristics that was nearly identical to the predictors identified in the logistic regression for the BASDAI 50, as follows: younger age, greater CRP concentration, lower baseline BASFI, HLA-B27 positivity, and naivety of another TNF antagonist were the most important factors for both measures of clinical response [i.e., these were the predictive factors with the odds ratios that were clearly different from 1 (with the most stable estimate and the lowest p values)] with some additional effect of a lower BASMI on a partial remission response.

The profile of predictors remained consistent when logistic regression was performed only for patients who had not received prior TNF antagonist therapy. In addition, the pattern of predictors was stable when missing values were imputed using LOCF data. Of note, this study is the first to show an important additional predictive effect of HLA-B27 on the prediction of good clinical response; a similar weak trend had been found in a previous analysis but failed to reach statistical relevance because of the small sample size[15].

The majority of patients with active AS responded well to adalimumab therapy. Treatment with adalimumab was well tolerated. In this large study we identified 4 common factors (younger age, greater CRP concentrations, HLA-B27 positivity, and TNF antagonist naivety) that were strongly associated with BASDAI 50, ASAS40, and ASAS partial remission response. Patients with lower BASFI had a better chance for BASDAI 50 and ASAS partial remission responses.

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