Predictors of Clinical Remission under Anti-tumor Necrosis Factor Treatment in Patients with Ankylosing Spondylitis: Pooled Analysis from Large Randomized Clinical Trials

Xenofon Baraliakos, Andrew S. Koenig, Heather Jones, Annette Szumski, David Collier, and Eustratios Bananis

ABSTRACT. ***Objective.*** Investigate the role and relation of disease duration of different factors for achieving clinical remission with anti-tumor necrosis factor (TNF) treatment in patients with active ankylosing spondylitis (AS).

Methods. Data pooled from 4 large (n = 1281) clinical trials were used to compare disease duration subgroups for placebo or sulfasalazine (SSZ) versus etanercept (ETN), which, in turn, were analyzed by age of diagnosis ≤ 40 versus > 40 years, HLA-B27 status, and baseline C-reactive protein (CRP) ≤ upper limit of normal (ULN) versus > ULN using chi-square tests, and ANCOVA. The primary efficacy measure was Assessments of SpondyloArthritis international Society (ASAS) partial remission (PR) after 12 weeks of treatment. Also analyzed were Bath AS Disease Activity Index and Functional Index, AS Disease Activity Scores, and ASAS response rates.

Results. Overall, a larger percentage of patients achieved ASAS-PR with ETN versus SSZ or placebo. More patients with ≤ 2-year disease duration treated with ETN experienced partial remission (34%) versus longer disease duration (30%, 27%, and 22% for > 2–5, > 5–10, and > 10 yrs, respectively; all $p < 0.05$). In the subgroup of patients with both disease duration ≤ 2 years and aged ≤ 40 years at diagnosis, the treatment response was even more pronounced. Similar results were seen in HLA-B27–positive patients in the disease duration ≤ 2-year subgroup. Overall, patients with high CRP at baseline had better treatment responses compared with patients with normal CRP.

Conclusion. Treatment response under anti-TNF treatment with ETN at 12 weeks was greatest among patients with disease duration ≤ 2 years and even more pronounced in subgroups of patients ≤ 40 years old or HLA-B27–positive at diagnosis. (J Rheumatol First Release June 15 2015; doi:10.3899/jrheum.141278)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS EARLY MEDICAL INTERVENTION
ETANERCEPT SULFASALAZINE PLACEBO

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Ankylosing spondylitis (AS) is a rheumatic disorder characterized by chronic inflammatory back pain and may have various additional features, including peripheral symptoms such as enthesitis[1]. Regardless of the presentation, this form of arthritis can result in substantial disability[1,2,3]. AS typically presents early in adulthood (< 40 yrs of age) with symptoms often appearing in the second and third decades of life[4]. Although the causes of AS are unknown, the strongest genetic contributor to AS is the MHC class I molecule HLA-B27. AS is one of a spectrum of diseases classified as spondyloarthropathy by their clinical features and prognostic factors[5].

The overall therapeutic options for patients with AS have been limited during previous decades. The Assessment of SpondyloArthritis international Society (ASAS) and the European League Against Rheumatism recommendations[6] for managing AS include guidance on nonpharmacologic and pharmacologic treatment. Pharmacologic treatment begins

with administration of nonsteroidal antiinflammatory drugs (NSAID), especially in those patients with persistent disease activity. For patients with predominantly axial symptoms, in the case of unsatisfactory response to NSAID, treatment with tumor necrosis factor (TNF) blockers is the only alternative[7]. TNF inhibitors, including etanercept (ETN), have demonstrated a rapid and good response in patients with axial AS[6,8], and longterm treatment results are now available[9,10]. As an alternative or additional treatment, sulfasalazine (SSZ) is the only disease-modifying antirheumatic drug that has shown some efficacy in selected patients with AS, albeit only those who presented with peripheral symptoms[11].

Only 1 pooled analysis from randomized clinical trials has demonstrated a strong association between younger age, greater C-reactive protein (CRP) levels, HLA-B27 positivity, and previous exposure to anti-TNF therapy with good clinical response in patients with active AS[12]. Overall, however, there is a paucity of published articles that address treatment of established AS at early stages after diagnosis, although in 1 recent study of patients with AS from 2 randomized controlled trials, patients with < 4 years of disease showed a significantly better improvement in patient-reported outcomes than did patients with longer disease duration[13].

While other previous reports have failed to identify any association between disease duration and clinical response to anti-TNF therapy[14,15], these studies have been largely observational in nature and therefore more prone to bias and confounding than analyses conducted in a well-controlled population in randomized clinical trials.

In an attempt to fill the knowledge gap, we pooled data from 4 active- or placebo-controlled clinical trials that treated patients with AS with ETN. The objective of this exploratory posthoc analysis of pooled studies was to investigate the relationship between disease duration and treatment effect on clinical outcomes in an AS population on background NSAID treatment that received anti-TNF therapy, SSZ, or placebo.

MATERIALS AND METHODS

Patients. Data from 4 clinical trials included patients (n = 1281) with AS who received ETN 50 mg weekly, SSZ 3 g daily (maximum), or placebo. Details have been published elsewhere and are outlined in Figure 1[16,17,18,19]. These trials were selected because we had access to individual patient data and they were all randomized placebo/active-controlled studies with a large number of different country investigator centers with no limitation of disease duration in the trials' exclusion criteria.

Study design. All 4 studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice guidelines. In addition, all local regulatory requirements were followed, and in particular those affording greater protection to the safety of trial participants. All patients signed an informed consent form that was reviewed and approved by an independent ethics committee or institutional review board. All 4 studies were initiated prior to the US Food and Drug Administration Amendments Act of 2007 and no registration was required; however, 3 of the 4 trials are posted on clinicaltrials.gov (Study 311 = NCT00421915, Study 402 = NCT00247962, Study 314 = NCT00418548), and the other study is not, having been conducted prior to current legislation, but the extension study is posted (Study 16.0037 = NCT00356356).

The pooled data from the selected studies were stratified into 4 disease duration categories (≤ 2, > 2–5, > 5–10, and > 10 yrs). These cutoff values were based on clinical relevance as well as providing patient groups large enough for meaningful analysis. Data were further stratified by HLA-B27 status at baseline (positive or negative), baseline CRP [≤ upper limit of normal (ULN) or > ULN], and age (≤ 40 or > 40 yrs) at diagnosis. Our study used the patient's age at diagnosis (the age when the first symptoms manifested were not recorded in the 4 trials included in the pooled dataset). Stratification was performed on each treatment group separately.

Endpoints. The main efficacy endpoint was partial remission as defined by ASAS20 at Week 12 of treatment. Additional efficacy endpoints included the proportions of patients who achieved ≥ 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50), achieved ASAS improvement of 20% (ASAS20), achieved major improvement of ≥ 2 units in the Ankylosing Spondylitis Disease Activity Score (including CRP; ASDAS-CRP), and achieved ASDAS inactive disease (ASDAS < 1.3). Also examined were changes in mean scores from baseline to Week 12 for Bath AS Functional Index (BASFI), ASDAS-CRP, physician's global assessment (PGA), serum CRP concentration, modified Schober test, and occiput-to-wall measurement.

Statistical methods. All randomized patients were included in baseline analyses, whereas all randomized patients who received ≥ 1 dose of treatment and had data for Week 12 were included in the Week 12 analyses (modified intent-to-treat population, observed cases). As a result of missing data regarding their date of diagnosis, 2 patients (1 receiving ETN, 1 receiving SSZ) were not included in these disease duration analyses[16]. To test for significant disease duration effect, categorical baseline characteristics were analyzed using chi-square tests whereas continuous baseline characteristics were analyzed using 1-way ANOVA. At Week 12, continuous outcomes were analyzed in ANCOVA models with baseline values, study, and disease duration categories as predictors in which disease duration was analyzed as an ordered predictor as well as a nominal predictor. Categorical outcomes were analyzed using Cochran-Mantel-Haenszel (CMH) test of general association in which disease duration was treated as nominal, and also analyzed using CMH test of non-zero correlation (i.e., trend test), in which disease duration category was analyzed as ordered. These analyses were repeated by subgroups for age ≤ 40 versus > 40 years at diagnosis, HLA-B27–positive versus –negative, and baseline CRP ≤ ULN versus > ULN according to the laboratory cutoff as provided in the studies. Univariate analyses were performed on each baseline predictor for Week 12 ASAS partial remission (ASAS-PR); these included continuous (i.e., age of diagnosis, CRP, AS disease duration) and dichotomous predictors (age of diagnosis ≤ 40 vs > 40 yrs; CRP ≤ ULN vs > ULN; disease duration ≤ 2, 2 to ≤ 5, 5 to ≤ 10, > 10 yrs; HLA-B27 positivity vs negativity). Two stepwise regression analyses were performed on these baseline predictors for Week 12 ASAS-PR. One analysis included all variables to determine whether continuous or dichotomous variables were better in predicting response while the other analysis included only dichotomous predictors, to determine whether they gave similar conclusions as for the continuous predictors.

RESULTS

From the 4 pooled studies, data from 1281 patients were analyzed (Table 1). The percentage of patients in each disease duration category ranged from 17% (> 2-yrs to 5-yrs category) to 37% (> 10-yrs category). At baseline, greater age, lower age at diagnosis, elevated BASFI, larger modified Schober measurement, and larger occiput-to-wall measurement were significantly correlated with higher disease duration categories ($p < 0.05$; Table 1).

A larger percentage of patients responded to anti-TNF

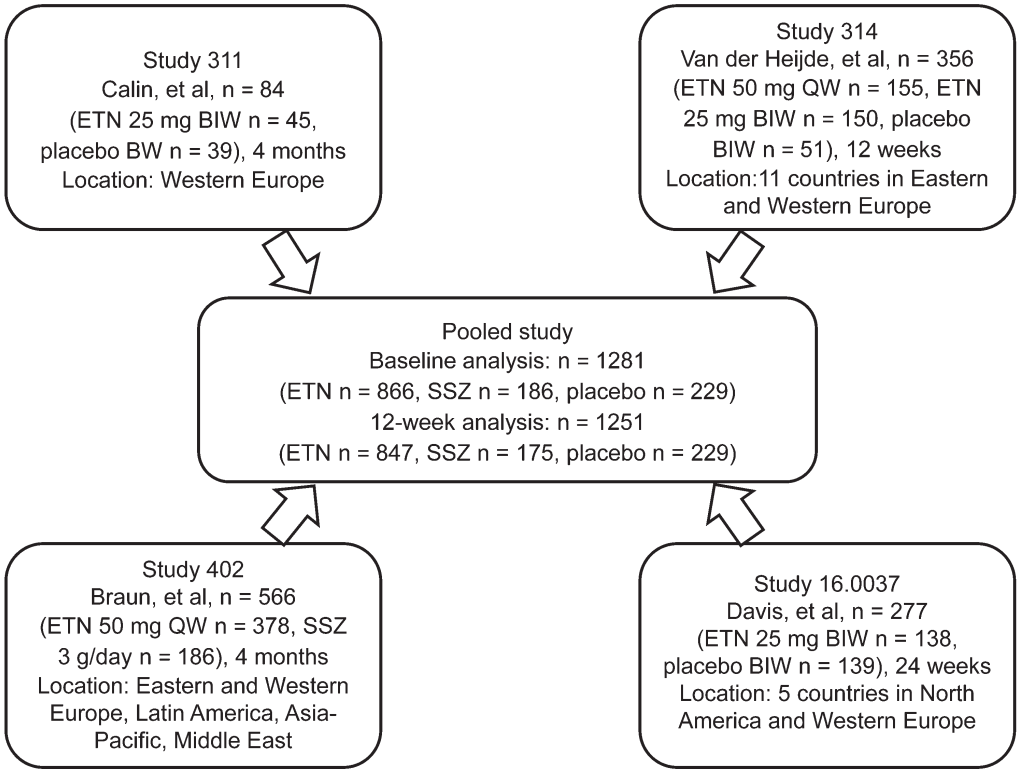

Figure 1. Study design. BIW: twice weekly; ETN: etanercept; QW: once weekly; SSZ: sulfasalazine.

Table 1. Baseline characteristics by duration of disease state. Values are mean (95% CI) unless otherwise noted.

Characteristics	≤ 2 Yrs, n = 351	> 2 to 5 Yrs, n = 219	> 5 to 10 Yrs, n = 243	> 10 Yrs, n = 468
Male, n (%)	247 (70.4)	152 (69.4)	191 (78.6)	367 (78.4)
Age at baseline, yrs	36.9 (35.8–38.1)*	37.9 (36.4–39.4)*	39.5 (38.1–40.9)*	46.6 (45.8–47.5)*
Age at diagnosis, yrs	36.3 (35.1–37.4)*	34.6 (33.1–36.1)*	32.2 (30.8–33.6)*	28.0 (27.2–28.8)*
AS duration, yrs	0.7 (0.6–0.7)*	3.3 (3.2–3.5)*	7.3 (7.2–7.5)*	18.6 (18.0–19.2)*
HLA-B27–positive, n (%)	264 (75.2)	173 (79.0)	203 (83.5)	397 (84.8)
ASDAS-CRP score	3.6 (3.6–3.7)	3.7 (3.6–3.8)	3.7 (3.6–3.8)	3.7 (3.7–3.8)
BASDAI score	58.9 (57.2–60.6)	61.0 (58.8–63.1)	58.4 (56.5–60.3)	60.3 (58.8–61.9)
BASFI score	53.4 (51.3–55.6)*	54.8 (52.1–57.6)*	55.8 (53.3–58.2)*	59.3 (57.5–61.1)*
CRP, mg/l	18.4 (16.1–20.6)	18.0 (15.5–20.4)	20.5 (17.6–23.3)	18.9 (16.8–21.1)
Modified Schober test	7.9 (7.4–8.4)*	8.8 (8.2–9.5)*	9.0 (8.4–9.6)*	9.2 (8.8–9.7)*
OWD	4.4 (3.8–4.9)*	3.9 (3.2–4.6)*	5.4 (4.6–6.1)*	7.2 (6.5–7.8)*
PGA	59.5 (57.7–61.3)	59.5 (57.4–61.7)	57.8 (55.6–60.0)	59.8 (58.3–61.3)

* $p \leq 0.001$ from 1-way ANOVA where disease duration categories are treated as nominal. AS: ankylosing spondylitis; ASDAS: AS Disease Activity Score; CRP: C-reactive protein; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Disease Functional Index; OWD: occiput-to-wall distance; PGA: physician's global assessment.

treatment with ETN compared with SSZ or placebo in almost all disease duration categories for all continuous and categorical outcomes (Figure 2; Supplementary Table 1, available online at jrheum.org). Shorter disease duration was associated with greater response in the ETN group, with the shortest disease duration group (≤ 2 yrs) showing the best response, and this was significant for Week 12 ASAS20, modified Schober test, PGA (Supplementary Table 1, available online at jrheum.org), and partial remission (Figure 2A). Further, when patients receiving ETN were subdivided into age ≤ 40 years at diagnosis, this trend in disease duration was even more pronounced for these outcomes (Figures 2B and Figure 3; Supplementary Table 2, available online at jrheum.org). A higher proportion of patients achieved ASDAS inactive disease with ETN versus SSZ and placebo, and a greater treatment response was shown in patients who were ≤ 40 years at diagnosis, HLA-B27–positive, and CRP ≤ ULN (Figure 3; Supplementary Table 1, available online at

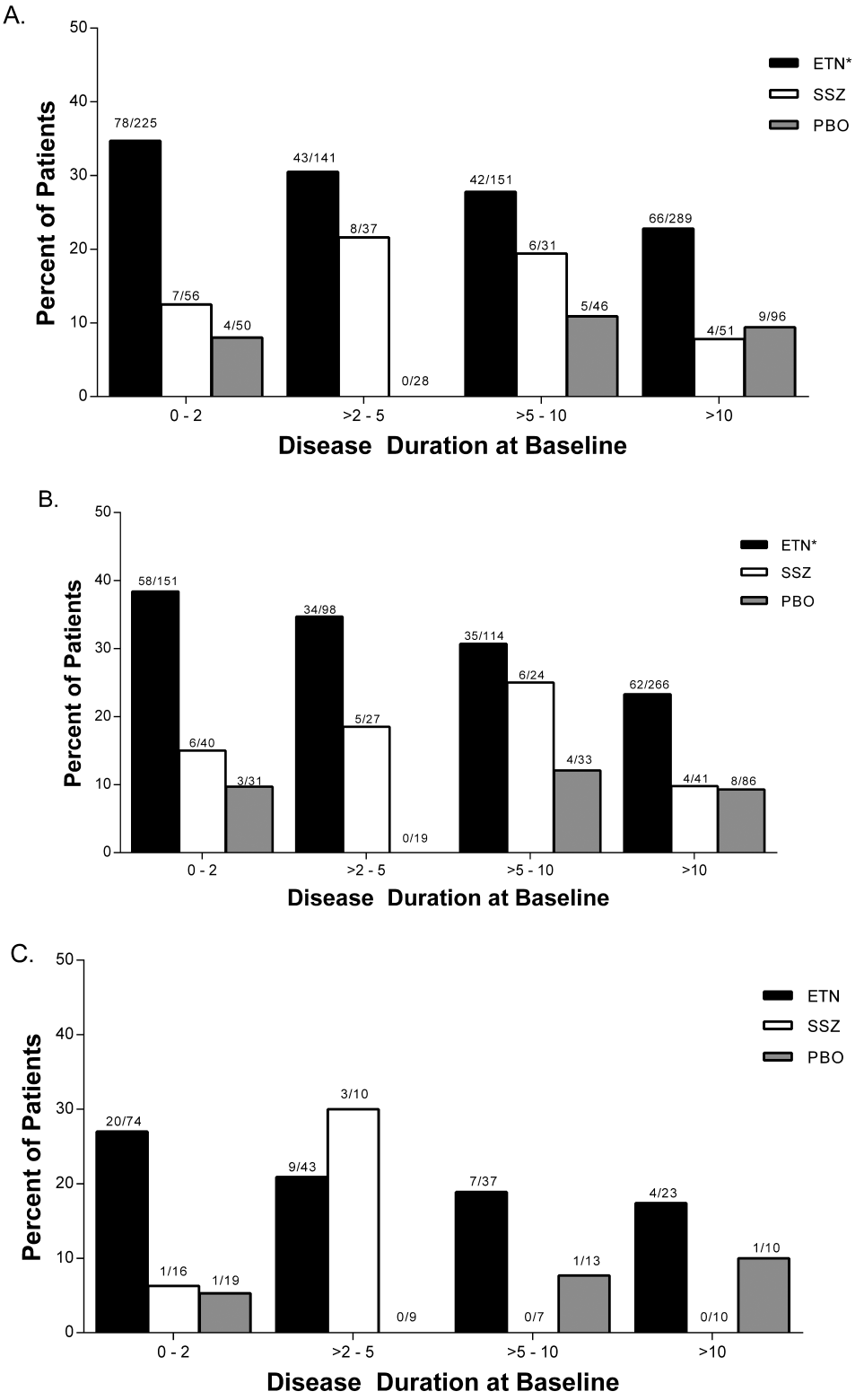

Figure 2. Partial remission across disease duration categories at Week 12 in (A) all patients, (B) patients ≤ 40 years old at diagnosis, and (C) patients > 40 years old at diagnosis. * $p \leq 0.05$ for disease duration categories analyzed as non-ordered, nominal using CMH test of general association and as ordered (trend) using CMH test of non-zero correlation. n/N values are shown above each bar. CMH: Cochran-Mantel-Haenszel; ETN: etanercept; SSZ: sulfasalazine; PBO: placebo.

			0–2 years, n/N (%)	>2–5 years, n/N (%)	>5–10 years, n/N (%)	>10 years, n/N (%)
ETANERCEPT	≤40 years at diagnosis	ASAS20*†	121/151 (80.1%)	73/97 (75.3%)	89/114 (78.1%)	176/266 (66.2%)
		BASDAI50*†	99/151 (65.6%)	69/98 (70.4%)	72/114 (63.2%)	146/226 (54.9%)
		ASDAS Δ≥2	61/151 (40.4%)	43/98 (43.9%)	54/113 (47.8%)	106/266 (39.8%)
		ASDAS Inactive Disease <1.3	46/151 (30.5%)	24/98 (24.5%)	29/113 (25.7%)	58/266 (21.8%)
	>40 years at diagnosis	ASAS20*†	50/74 (67.6%)	26/43 (60.5%)	19/37 (51.4%)	15/23 (65.2%)
		BASDAI50	38/74 (51.4%)	20/43 (46.5%)	12/37 (32.4%)	13/23 (56.5%)
		ASDAS Δ≥2	20/74 (27.0%)	13/43 (30.2%)	10/37 (27.0%)	6/23 (26.1%)
		ASDAS Inactive Disease <1.3	15/74 (20.3%)	6/43 (14.0%)	6/37 (16.2%)	4/23 (17.4%)
	HLA-B27+	ASAS20*†	141/176 (80.1%)	83/111 (74.8%)	96/130 (73.8%)	168/251 (66.9%)
		BASDAI50†	116/176 (65.9%)	75/112 (67.0%)	77/130 (59.2%)	139/251 (55.4%)
		ASDAS Δ≥2	70/176 (39.8%)	49/112 (43.8%)	58/129 (45.0%)	98/251 (39.0%)
		ASDAS Inactive Disease <1.3	55/176 (31.3%)	26/112 (23.2%)	30/129 (23.3%)	60/251 (23.9%)
	HLA-B27–	ASAS20	28/45 (62.2%)	15/28 (53.6%)	12/21 (57.1%)	20/33 (60.6%)
		BASDAI50	21/45 (46.7%)	14/28 (50.0%)	7/21 (33.3%)	17/33 (51.5%)
		ASDAS Δ≥2	10/45 (22.2%)	7/28 (25.0%)	6/21 (28.6%)	13/33 (39.4%)
		ASDAS Inactive Disease <1.3	6/45 (13.3%)	4/28 (14.3%)	5/21 (23.8%)	1/33 (3.0%)
	Baseline CRP≤ULN	ASAS20	72/100 (72.0%)	37/61 (60.7%)	37/60 (61.7%)	72/117 (61.5%)
		BASDAI50†	60/100 (60.0%)	33/62 (53.2%)	29/60 (48.3%)	54/117 (46.2%)
		ASDAS Δ≥2	16/100 (16.0%)	12/62 (19.4%)	12/59 (20.3%)	14/117 (12.0%)
		ASDAS Inactive Disease <1.3*†	33/100 (33.0%)	15/62 (24.2%)	11/59 (18.6%)	20/117 (17.1%)
	Baseline CRP>ULN	ASAS20†	99/125 (79.2%)	62/79 (78.5%)	71/91 (78.0%)	118/171 (69.0)
		BASDAI50	77/125 (61.6%)	56/79 (70.9%)	55/91 (60.4%)	104/171 (60.8%)
		ASDAS Δ≥2	65/125 (52.0%)	44/79 (55.7%)	52/91 (57.1%)	98/171 (57.3%)
		ASDAS Inactive Disease <1.3	28/125 (22.4%)	15/79 (19.0%)	24/91 (26.4%)	42/171 (24.6%)
SULFASALAZINE	≤40 years at diagnosis	ASAS20	23/40 (57.5%)	12/27 (44.4%)	16/24 (66.7%)	24/41 (58.5%)
		ASDAS Δ≥2	3/40 (7.5%)	4/27 (14.8%)	2/24 (8.3%)	3/40 (7.5%)
	>40 years at diagnosis	ASAS20	5/16 (31.3%)	5/10 (50.0%)	4/7 (57.1%)	4/10 (40.0%)
		ASDAS Δ≥2	0/16 (0.0%)	0/9 (0.0%)	1/7 (14.3%)	0/10 (0.0%)
PLACEBO	≤40 years at diagnosis	ASAS20	15/31 (48.4%)	3/19 (15.8%)	10/33 (30.3%)	24/86 (27.9%)
		ASDAS Δ≥2	2/31 (6.5%)	1/19 (5.3%)	3/33 (9.1%)	8/86 (9.3%)
	>40 years at diagnosis	ASAS20	7/19 (36.8%)	1/9 (11.1%)	4/13 (30.8%)	2/10 (20.0%)
		ASDAS Δ≥2	1/19 (5.3%)	0/9 (0.0%)	0/13 (0.0%)	1/10 (10.0%)

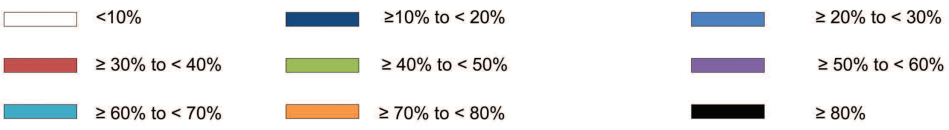

Figure 3. Proportions of patients in various patient subgroups who achieved ASAS20, BASDAI 50, ASDAS-CRP change ≥ 2, and ASDAS inactive disease < 1.3 at Week 12 across disease duration categories. * $p \leq 0.05$ for disease duration categories analyzed as non-ordered, nominal using CMH test of general association and † as ordered (trend) using CMH test of non-zero correlation. SSZ treatments were not significant in these analyses. ASAS: Assessments in Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; CMH: Cochran-Mantel-Haenszel; SSZ: sulfasalazine; ULN: upper limit of normal.

jrheum.org). Although this was not significant across disease duration categories (except for CRP ≤ ULN), patients with AS ≤ 2 years had a higher response than those with longer disease duration.

Even though no significant differences in improvement were observed across disease duration categories for Week 12 outcomes in ASDAS-CRP, BASDAI, BASFI, and BASDAI50 in the overall population (Supplementary Table 1, available online at jrheum.org), in the subgroup of patients who were aged ≤ 40 years at the time of diagnosis and treated with ETN, shorter disease duration resulted in significantly better responses for these endpoints (Figure 3; Supplementary Table 2, available online at jrheum.org). Patients aged > 40 years old at diagnosis performed worse than patients aged ≤ 40 across all disease duration categories, and also showed no significant trends in disease duration (Figures 2C and Figure 3; Supplementary Table 2, available online at jrheum.org).

Disease duration effects were marginally significant for SSZ (in CRP and modified Schober test) and placebo

(ASAS20, BASFI; Supplementary Table 1, available online at jrheum.org), but when analyzing by age at diagnosis, HLA-B27 status, or baseline CRP category, the only relationship to remain significant was with CRP in the SSZ group (data shown only for age at diagnosis). The smaller sample sizes in these treatment arms and subcategories may have resulted in a lack of power to detect significant differences.

Patients who were HLA-B27–positive and treated with ETN had better improvement in outcomes for each disease duration category compared with patients who were HLA-B27–negative (Figure 3 and Figure 4). For ETN, the subgroup of HLA-B27–positive patients in the shorter disease duration categories had significantly better responses for most outcome measures [$p < 0.05$ for disease duration categories analyzed as ordered (trend)], including ASAS20, BASDAI 50, and ASAS-PR (Figure 3), as well as modified Schober test and PGA (data not shown).

Analysis of each baseline variable in univariate models for ASAS-PR at Week 12 demonstrated similar results for the continuous and dichotomous version of that predictor. Stepwise regression analysis of all predictors, included as both continuous and dichotomous, showed that in addition to treatment and HLA-B27 (positive vs negative), AS disease duration and age at diagnosis as continuous variables were better predictors of ASAS-PR in patients treated with ETN than their dichotomous counterparts. A similar analysis of dichotomous predictors showed that disease duration categories (i.e., ≤ 2, 2 to ≤ 5, 5 to ≤ 10, > 10 yrs) and age of diagnosis (≤ 40 vs > 40 yrs) were the best predictors of Week 12 ASAS-PR [in addition to treatment and HLA-B27 status (positive vs negative)].

Patients with baseline CRP ≤ ULN treated with ETN had either a significantly decreasing (e.g., in BASDAI 50, ASDAS inactive disease < 1.3, partial remission, BASDAI, PGA) or numerically decreasing response (e.g., in ASAS20, ASDAS change ≥ 2.0, BASFI) across increasing disease

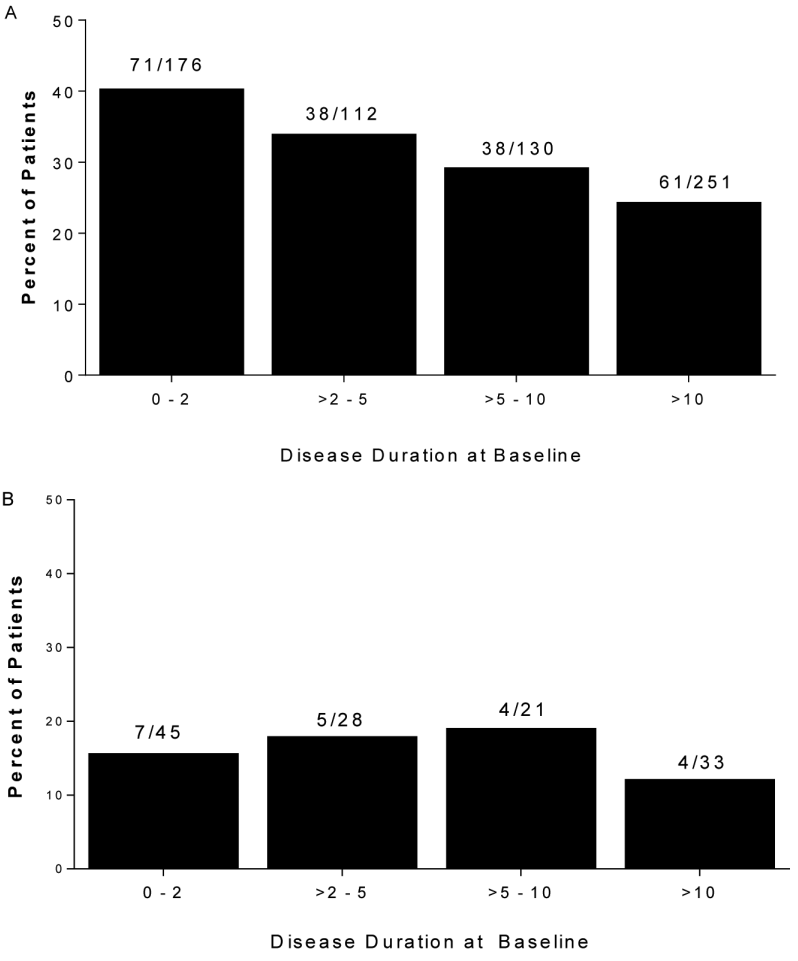

Figure 4. Partial remission in patients receiving ETN across disease duration categories at Week 12 in (A) HLA-B27+ patients*†, (B) HLA-B27– patients. * $p \leq 0.05$ for disease duration categories analyzed as non-ordered, nominal using CMH test of general association and † $p < 0.01$ as ordered (trend) using CMH test of non-zero correlation. n/N values are shown above each bar. ETN: etanercept; CMH: Cochran-Mantel-Haenszel.

duration categories, with the earliest disease duration category (≤ 2 yrs) having the most pronounced response (Figure 3; only data for ASAS20, BASDAI 50, ASDAS change ≥ 2.0, and ASDAS inactive disease < 1.3 presented). This trend was also seen for ASAS20 in patients receiving ETN who had baseline CRP > ULN, but not for other outcomes. Even so, patients with baseline CRP > ULN had better responses across all disease duration categories than those with baseline CRP ≤ ULN (with the exception of ASDAS inactive disease < 1.3), with the ≤ 2-year category having the smallest response advantage in CRP > ULN compared with CRP ≤ ULN (indicating that outcomes were similar between CRP ≤ ULN vs > ULN within the ≤ 2-yr category) and > 10 having the greatest response advantage. However, for ASDAS change ≥ 2.0, 3 times as many patients in CRP > ULN responded as patients in CRP ≤ ULN, regardless of disease duration category (Figure 3).

DISCUSSION

In our study, our analyses of pooled data from 4 large trials of patients with AS provided a basis to explore the possible relationships of disease duration with anti-TNF treatment response in AS outcomes overall and by age at diagnosis, HLA-B27 status, and baseline CRP as predictive factors for the best possible response (ASAS-PR) to anti-TNF treatment for AS. The results are the first report on this topic in such a large number of patients and also represent the first analysis of a population treated with anti-TNF, an active-comparator, or placebo in controlled studies. This dataset included agents such as SSZ and background NSAID, which are considered active treatments in this disease[6,7].

Overall, the results showed that earlier intervention in the spectrum of AS disease with ETN is better for various clinical outcomes. There were very few outcomes in which disease duration effects were seen for the SSZ and placebo groups because the population sizes may have been too underpowered to draw conclusions. Of the interventions evaluated, ETN treatment in patients with disease duration ≤ 2 years had the highest treatment response.

While previous studies have established younger age at baseline (i.e., at study enrollment) to be predictive of the response to anti-TNF therapy in AS[12,21,22], our analyses are the first, to our knowledge, to demonstrate that patients who were aged ≤ 40 years at the time of diagnosis had better treatment response and a more pronounced disease duration trend than those who were older than 40 years at the time of diagnosis. The current findings also support previous evidence from a large pooled analysis of clinical trial data with adalimumab that HLA-B27 status and baseline CRP may also play a role in treatment outcomes[12]; in addition, we observed that some assessments had more pronounced disease duration trends with positive HLA-B27 or baseline CRP ≤ ULN.

Regardless of the time from diagnosis, ETN was more effective in patients with active AS compared with SSZ or placebo in the presence of background NSAID. This is in line with previous data that showed weak initial evidence that younger age at baseline and shorter disease duration can be predictive of treatment outcomes in AS[13]. However, the data presented here suggest that younger age at diagnosis and shorter disease duration are both important factors when considering treatment options. Our study used the age at which patients were diagnosed rather than the age at which first symptoms manifested. This timepoint was chosen because symptom data were not available. Future studies should examine treatment efficacy as a function of disease onset.

The data from this analysis demonstrated that greater improvement in physical function (BASFI) occurred in patients receiving ETN who had shorter disease duration relative to those with longer disease duration and better overall than those who had received other treatments (but statistically significant only in the ETN-treated group aged ≤ 40 yrs at diagnosis and HLA-B27–positive). Similar results were seen for the disease activity measures, BASDAI, ASDAS-CRP, modified Schober test, and PGA for this age at diagnosis and HLA-B27 subgroups as well as baseline CRP ≤ ULN. These data support previous findings that showed BASFI correlates with disease activity[23].

Our data from the current pooled analysis also supported previous findings that spinal mobility and function are likely impaired by inflammation during the first 3 years of AS, but are made worse by a combination of inflammation and irreversible structural damage that may occur as the disease progresses[24]. It is worth noting that impaired function owing to irreversible structural damage would result in an inability to achieve ASAS-PR. Although ETN has been shown to improve inflammation, there is currently no treatment available that has been shown to reverse structural damage in AS; thus, irrespective of treatments, rates of partial remission would likely decrease with longer disease duration.

As a result of a lack of efficacy with axial disease, treatment of AS with SSZ is only partly recommended by the ASAS/European League Against Rheumatism guidelines, especially in patients with peripheral manifestations[6,7]. Data from the current analysis suggest that SSZ may help selected patients, but the small number of patients in the SSZ arm was too low to draw conclusions. However, our data support the recommendations that patients who do not adequately respond to NSAID therapy should be treated with a TNF inhibitor[7], and also suggest that treatment with ETN early in the disease should be considered.

Limitations of this posthoc analysis include that none of the studies were primarily designed to examine the effect of age at diagnosis or disease duration on treatment outcomes and that there was no predefined protocol for this pooled analysis. These studies used the New York Criteria and not the ASAS classification criteria; thus, "early" is related to AS

only, and not to other classifications of related spondyloarthropathy conditions. In addition, the studies collected data on duration since diagnosis of AS, but not on duration since symptom onset; thus, the true disease duration may not be known for many patients and may be subject to recall bias. Nevertheless, the latter limitation represents the situation in daily routine where information about symptom onset is unclear and where onset of diagnosis is what is recorded most accurately on clinical records prior to treatment initiation with anti-TNF treatment. Although our data distinguish between categories of disease duration, the analyses herein did not specify patients with and without spinal radiographic manifestations of disease; thus, it was not possible to estimate whether treatment with ETN had an effect on the radiographic progression in patients with active AS if initiated shortly after diagnosis. Although SSZ has been historically used to treat AS, current guidelines bluntly state that SSZ is rather ineffective in treating axial disease alone[6,7] and recommend it mainly in treating additional peripheral symptoms. However, the data in the 4 pooled studies did not clearly distinguish between peripheral and axial symptoms in AS.

Results of this exploratory analysis suggest that earlier intervention of AS in the course of disease is a preferred option. Intervention with ETN at early stages was associated with better clinical outcomes than intervention started later in the course of the disease and/or treatment with SSZ or NSAID alone. Further research, including prospective clinical trials targeting these outcomes, is necessary to confirm this beneficial effect of early intervention in patients with established AS, but also in those in the nonradiographic stage of axial spondyloarthritis.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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