

Remission in Nonradiographic Axial Spondyloarthritis Treated with Anti-tumor Necrosis Factor- α Drugs: An Italian Multicenter Study

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ABSTRACT. Objective. To investigate the possibility of achieving partial remission (PR) in patients with non-radiographic axial spondyloarthritis (nr-axSpA) versus ankylosing spondylitis (AS) treated with anti-tumor necrosis factor (TNF)- α antagonists, such as adalimumab (ADA), etanercept (ETN), and infliximab (IFX), in a real clinical practice setting. The Assessment of SpondyloArthritis international Society (ASAS) 20, ASAS40, and Ankylosing Spondylitis Disease Activity Score were also calculated. **Methods.** A retrospective study was conducted in patients with axSpA treated with ADA, ETN, and IFX from 2000 to 2013. All patients fulfilled the ASAS or the modified New York criteria. PR was reached when the score was < 20 mm (on a visual analog scale of 0–100 mm) in each of these domains: (1) patient global assessment, (2) pain, (3) function, and (4) inflammation. **Results.** A total of 321 patients with axSpA were treated. Among them, 62 were nr-axSpA while the remaining 259 were AS. Log-rank test to compare survival curves showed that the probability of obtaining PR in nr-axSpA and AS during treatment with anti-TNF- α was not significantly different. At 12 weeks of exposure to the first anti-TNF- α drug, PR was achieved in 7 patients with nr-axSpA (11.3%) and in 68 patients with AS (26.2%). **Conclusion.** Our results, obtained from clinical practice, showed that PR is an achievable target of anti-TNF- α treatment in nr-axSpA. The PR rate, as a reliable indicator of sustained effectiveness, is similar in nr-axSpA and in AS. (J Rheumatol First Release Dec 15 2014; doi:10.3899/jrheum.140811)

Key Indexing Terms:

NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS
REMISSION

ANKYLOSING SPONDYLITIS
ANTI-TNF- α DRUGS

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The authors have received honoraria from Abbott; Bristol Meyer Squibb; Merck, Sharp & Dome; Pfizer; UCB pharma; and Roche to attend scientific meetings.

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Accepted for publication October 16, 2014.

The Assessment of SpondyloArthritis international Society (ASAS) has validated classification criteria for patients with axial spondyloarthritis (axSpA)¹, including nonradiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS). Patients with nr-axSpA and those with AS have comparable, but not identical, clinical manifestations and burden of disease, requiring treatment irrespective of the presence of radiographic damage^{2,3}.

Randomized clinical trials with tumor necrosis factor (TNF)- α antagonists such as infliximab (IFX), etanercept (ETN), adalimumab (ADA), and certolizumab pegol (CZP) for the treatment of nr-axSpA have been performed^{4,5,6,7,8}. In these studies, the ASAS criteria were applied, but partial remission (PR) has been considered as primary endpoint in only 1 randomized controlled trial study including about 60% of patients who met the modified New York criteria for AS⁵. Moreover, to our knowledge, direct comparison among TNF- α blockers has not been reported in nr-axSpA.

The primary objective of our retrospective study was to investigate the possibility of achieving PR in nr-axSpA as opposed to patients with AS treated with TNF- α antagonists, such as ADA, ETN, and IFX, in a real clinical practice setting. Secondary endpoints were the proportion of patients

in both groups achieving the ASAS20, ASAS40, and Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease.

MATERIALS AND METHODS

Study design. A retrospective study was conducted in 6 Italian secondary referral rheumatology centers (Rome, Campobasso, Milan, Padua, Potenza, and Reggio Emilia) involved in the research studies of SpA. Subjects' written consents were obtained according to the Declaration of Helsinki, and the design of our work was approved by the local ethics committee (Sapienza, University of Rome). We collected data on the efficacy of TNF- α blockers on axSpA and on the safety of patients treated with them, after a minimum of 6 months of followup from June 2000 to September 2013. All patients fulfilled the ASAS¹ or the modified New York criteria⁹ for the classification of axSpA or AS, respectively.

ADA (40 mg every other week) and ETN (25 mg twice/weekly or 50 mg/weekly) were given subcutaneously; IFX was administered intravenously at 3–5 mg/kg at weeks 0, 2, and 6, and then every 6–8 weeks, although the treating physician could increase or decrease this dose or schedule when warranted.

At the time of initiation and during the followup of anti-TNF- α treatment, the patients' data were collected, including age, sex, diagnosis, disease duration, extraarticular manifestations [i.e., uveitis, inflammatory bowel diseases (IBD), psoriasis], Bath AS Metrology Index (BASMI)¹⁰, Bath AS Disease Activity Index (BASDAI)¹¹, Bath AS Functional Index (BASFI)¹², patient visual analog scale (VAS) on global disease activity spinal pain (0–100 mm), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), clinical pattern (axial, peripheral arthritis, enthesitis, dactylitis), swollen (out of 66) and tender (out of 68) joints, as well as radiological and/or magnetic resonance imaging (MRI) data recorded as positive/negative for sacroiliac joints as only short-tau inversion recovery sequences [New York criteria/bone marrow edema (BME)].

PR was reached when the score was < 20 mm (on a VAS of 0–100 mm) in each of the following 4 domains: (1) patient global assessment (in the last week), (2) pain (spinal pain), (3) function (measured by the BASFI), and inflammation (mean of intensity and duration of morning stiffness, from the BASDAI)^{13,14}.

The association of PR with the main variables was studied. In particular, the values of age (\leq or $>$ 40 yrs), disease duration (\leq or $>$ 10 yrs), CRP (low \leq 0.6, moderate 0.7–1.9, high \geq 2 mg/dl), and BASFI (low \leq 4.5, moderate 4.6–6.4, high \geq 6.5) were categorized according to Vastesaeger, *et al*¹⁵.

The discontinuation reasons were classified as lack of response, adverse events, or other. The definition of failure for inefficacy was based on clinical evaluation according to the ASAS/European League Against Rheumatism management recommendations in AS¹⁶.

The ASAS20, ASAS40, and ASDAS inactive disease were also calculated and expressed as proportion of patients achieving these outcome measures in the 2 groups.

Details of past and present antirheumatic therapies were also recorded, such as disease-modifying antirheumatic drugs, corticosteroids, nonsteroidal antiinflammatory drugs (NSAID), or analgesics, and current comorbidities.

Statistical analysis. Categorical variables were analyzed by chi-square test with Yates correction or Fisher's exact test. Kaplan-Meier survival curves were plotted to determine the rates of PR during the treatment with anti-TNF- α drugs (ADA, ETN, or IFX). In the Kaplan-Meier survival curves calculation, we entered time until the subject was "censored" or the "event" occurred. The differences between survival curves were determined by the log-rank test. The ASAS PR was explored using OR (lower and upper 95% CI) of outcome relative to the main variables.

OR was interpreted as 1.5 to 1 as weak association, 2.5 to 1 as moderate association, 4 to 1 strong association, and 10 to 1 very strong association¹⁷.

The results were expressed as median (25–75 percentile). P values < 0.05 were considered significant.

RESULTS

From June 2000 to September 2013 (range of followup 6–142 mos), a total of 321 patients with axSpA were treated, including nr-axSpA (n = 62) and AS (n = 259). The baseline characteristics of these groups of patients are shown in Table 1. Sex, disease duration, and values of ESR, CRP, BASMI, and BASFI were significantly different.

The number of patients with elevated CRP and ESR, as well as numbers with positive or negative MRI, are reported in Appendix 1.

At 12 weeks of exposure to the first anti-TNF- α drug, PR was achieved in 7 patients with nr-axSpA (11.3%) and in 68 patients with AS (26.25%, p = 0.067). During the followup, PR was achieved in 33 patients with nr-axSpA (53.2%) and in 147 AS (50.9%) after a median interval of 6 (3–11) and 4 (3–6) months, respectively. The median duration of PR in nr-axSpA and in AS was 34 (15–60) and 32 (12–56) months, respectively. PR was lost in 24.2% of patients with nr-axSpA (8/33) and 20.4% in AS (30/147) after a median interval of 13 (3.2–44.2) and 12 (7.7–24.2) months, respectively.

Table 1. The main demographic and clinical features of patients with axSpA (n = 321) at baseline and treated with TNF- α blockers (ADA = 57, ETN = 87, IFX = 177).

Characteristics	AS, n = 259	nr-axSpA, n = 62
Male, %	75	50*
Age, yrs (median)	43 (34.0–53.5)	46.5 (36.3–53.7)
Disease duration, mos (median)	96 (36–189)	36 (12.5–69)*
Articular manifestations, %		
Axial	100	100
Peripheral arthritis	50.5	58
Enthesitis	35	29
Extraarticular manifestations, %		
Uveitis	17.3	8
Psoriasis	13.1	19.3
IBD	10.8	6
BASDAI (median)	6 (4.9–7.5)	5.2 (4.1–6.6)
BASFI (median)	5.8 (4.2–7.5)	4.3 (2.7–5.3)*
BASMI (median)	3 (2–4.9)	1 (1–3)*
HLA-B27+, %	64.9	58.3
ESR, mm/first h (median)	30 (17–44)	21 (13–33)*
CRP, mg/dl (median)	1.4 (0.8–2.6)	0.6 (0.1–1.2)*
Concomitant treatment at baseline, %		
DMARD	31.6	30.9
Prednisone intake	25.8	14.5
NSAID intake	76.8	53.2*
Anti-TNF- α therapy, %		
ADA	18.3	16.1
ETN	28.9	16.1
IFX	52.8	67.8**

* p < 0.01. ** p < 0.05. axSpA: axial spondyloarthritis; TNF: tumor necrosis factor; ADA: adalimumab; ETN: etanercept; IFX: infliximab; AS: ankylosing spondylitis; nr-axSpA: nonradiographic axSpA; IBD: inflammatory bowel disease; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; BASMI: Bath AS Metrology Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

The Kaplan-Meier life-table for PR during treatment with TNF- α blockers in nr-axSpA (n = 62) and AS (n = 259) is shown in Figure 1. Log-rank test to compare survival curves showed that the probability of obtaining PR in nr-axSpA and AS during treatment with anti-TNF- α was not significantly different.

However, there was no indication of clinically relevant differences between the different TNF- α because of the small sizes of the groups treated with ADA and ETN.

During treatment with anti-TNF- α drugs, PR was significantly associated with the absence of peripheral arthritis, enthesitis, and psoriasis at baseline in patients with AS, but not in nr-axSpA.

The overall rate of discontinuation after the first anti-TNF- α drug was 11.2% (n = 7) in nr-axSpA and 18.5% (n = 48) in AS. In particular, lack of response was observed in 7/7 of patients with nr-axSpA and 30/48 of AS, while adverse events occurred in none of the patients with nr-axSpA and 18/48 of patients with AS (p < 0.03).

Figure 2 and Figure 3 report all data regarding the proportion of PR, the ASDAS inactive disease, ASAS20, and ASAS40. In particular, the proportion of the ASAS20 in patients with nr-axSpA with BME was statistically different from those without (Figure 3A), while no statistically significant differences were found between the 2 groups when compared for the CRP levels at baseline (Figure 3B). Finally, when BME was present at MRI scan, this was associated with the response to the treatment (Table 2).

DISCUSSION

The concept of disease remission plays a relevant role in the management of axSpA, including both nr-axSpA and AS. Remission should consider different aspects of the disease, such as clinical disease activity (including articular and extraarticular manifestations/associated diseases, such as uveitis, psoriasis, or IBD), objective inflammation (i.e., raised CRP or active inflammation on MRI), function, and

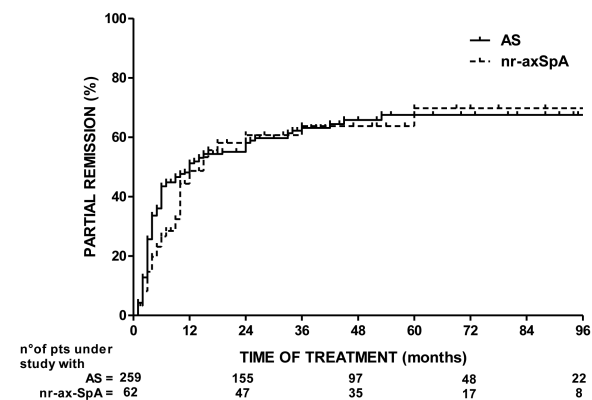


Figure 1. Kaplan-Meier life-table for partial remission during treatment with TNF- α blockers in patients with nr-axSpA (n = 62) and AS (n = 259). TNF: tumor necrosis factor; nr-axSpA: nonradiographic axial spondyloarthritis; AS: ankylosing spondylitis.

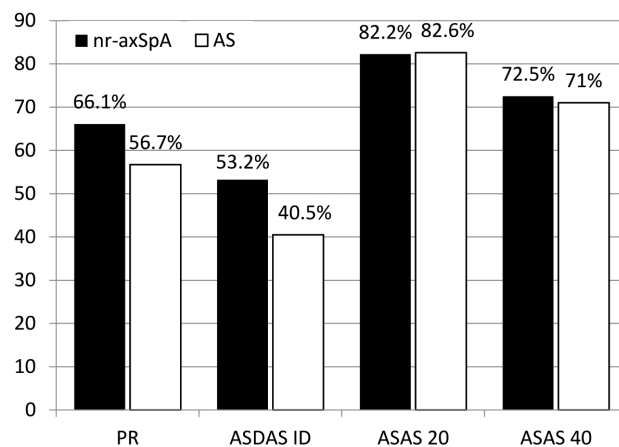
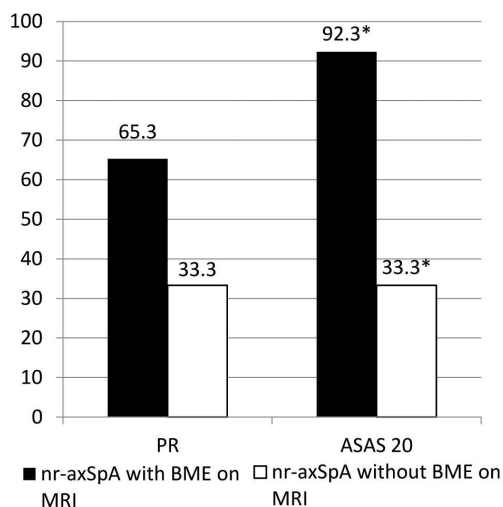


Figure 2. PR, ASDAS inactive disease, ASAS20, and ASAS40 response in AS (n = 259) and nr-axSpA (n = 62). All differences were not statistically significant. PR: partial remission; ASDAS ID: the Ankylosing Spondylitis Disease Activity Score inactive disease; ASAS: the Assessment of SpondyloArthritis international Society; nr-axSpA: nonradiographic axial spondyloarthritis; AS: ankylosing spondylitis.

structural damage. PR could be considered as the term normally used owing to the lack of a definition of the difference between complete clinical remission and a status of low disease activity. The ASAS definition of PR considers 4 domains (patient global assessment, pain, physical function, and inflammation) for defining PR¹⁸. This composite measure, giving a dichotomous result of absence or presence of PR, has been validated among expert opinion and in clinical trials in AS¹⁸. A PR rate, usually around 20% to 40% for active therapy versus 5% for placebo groups, regardless of which biologic agent is used, has been reported in AS¹⁸. Anti-TNF- α clinical trials in axSpA, including nr-axSpA, showed that ADA, CZP, ETN, and IFX were efficacious even though a direct comparison was not performed^{4,5,6,7,8}. In fact, in studies with mixed population (nr-axSpA and AS), PR was achieved in 55.6% of patients treated with IFX at 16 weeks⁴ (vs 12.5% placebo), in 61.9% of IFX-treated patients (at 28 weeks⁵ vs 35.3% naproxen), and in 23.4% of CZP-treated patients at 12 weeks⁸ (vs 2.7% placebo). In studies including only nr-axSpA, PR was achieved in 16% of ADA-treated patients at 12 weeks⁷ (vs 5.3% placebo), and in 50% of ETN-treated patients at 48 weeks⁶ (vs 19% sulfasalazine).

In our real-life study, we confirmed the usefulness of anti-TNF- α therapy in nr-axSpA with no significant difference in the probability curve of obtaining PR among all anti-TNF- α drugs. It is likely that our longterm followup allowed us to detect the achievement of PR in a larger group of patients. In fact, at 12 weeks of exposure to the first anti-TNF- α drug, the PR rate was 14.5% and continued to increase (to 53.2%) after a median interval of 6 months (3–11 mos). The results obtained in nr-axSpA were similar

3A



3B

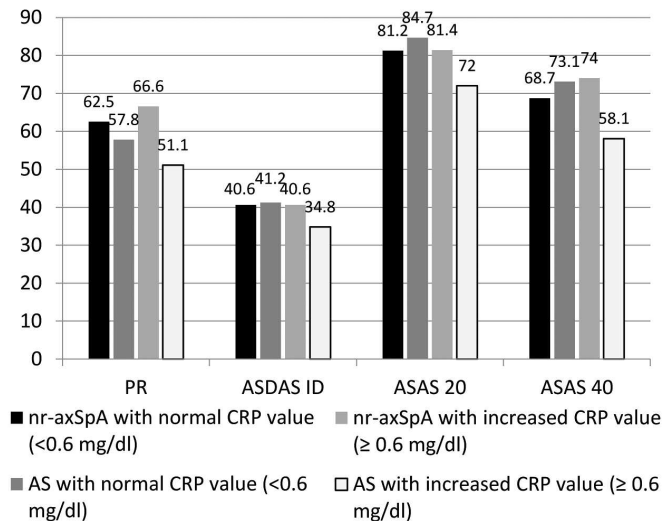


Figure 3. A. PR and ASAS20 rate in nr-axSpA with and without BME at MRI assessment. * $p < 0.05$. B. Percentage of all outcome measures between nr-axSpA ($n = 62$) and AS ($n = 259$) with or without normal CRP levels at baseline. All differences were not statistically significant. PR: partial remission; ASAS: the Assessment of SpondyloArthritis international Society; nr-axSpA: nonradiographic axial spondyloarthritis; BME: bone marrow edema; MRI: magnetic resonance imaging; AS: ankylosing spondylitis; ASDAS ID: the Ankylosing Spondylitis Disease Activity Score inactive disease; CRP: C-reactive protein.

Table 2. ASAS20 and PR when assessed by CRP, ESR, and BME on MRI. Values are OR (95% CI).

Variables	ASAS 20	PR
CRP low vs high	1.01 (0.27–3.78)	1.01 (0.69–1.48)
ESR low vs high	0.80 (0.31–2.06)	0.52 (0.18–1.5)
BME on MRI, present vs absent	25 (3.38–134.6)*	3.77 (0.75–18.8)

* $p < 0.05$. ASAS: Assessment of Spondyloarthritis international Society; PR: partial remission; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BME: bone marrow edema; MRI: magnetic resonance imaging.

to those observed in patients with AS, as shown by the probability curve of obtaining PR (Figure 1), confirming previous results with ETN¹⁹. Nevertheless, at 12 weeks, the PR rate was less in nr-axSpA than AS. This result could be explained by the evidence that nr-axSpA had a lower level of CRP at baseline than those of patients with AS. Moreover, our study showed that, when comparing low versus high CRP values at baseline, no differences were found in both nr-axSpA and AS. These results are not in keeping with previous studies showing that CRP is 1 predictor of response resulting from anti-TNF- α and conventional therapy in various AS subpopulations¹⁵ and with randomized controlled trials showing a good response in patients with abnormal CRP and/or MRI^{7,8}. On the other hand, when evaluating PR in both groups by baseline high CRP levels (> 2 mg/dl), a statistically significant association was found (data not shown) confirming those previous data. Moreover, our study showed that PR, during treatment with anti-TNF- α drugs,

was significantly associated with the absence of peripheral arthritis, enthesitis, and psoriasis at baseline in patients with AS, but not in nr-axSpA.

Few studies have addressed whether certain clinical/laboratory characteristics were associated with clinical response to TNF- α antagonist therapy in patients with AS^{15,20,21,22,23,24}. Nevertheless, there are no data about different patterns of articular involvement (i.e., peripheral arthritis, enthesitis) or extraarticular manifestations (i.e., IBD, uveitis, psoriasis) as being predictors of response during anti-TNF- α treatment in nr-axSpA. These results suggest that different patterns of articular involvement and extraarticular manifestations seem to have a minor effect on the disease course in nr-axSpA.

Despite a similar burden of disease²⁵, we found that sex, disease duration, and values of ESR, CRP, BASFI, and BASMI were significantly different between the nr-axSpA and AS groups. In particular, we found in nr-axSpA a lower prevalence of men and lower CRP levels than in patients with AS, in accordance with previous studies^{2,25,26}.

These results, obtained from clinical practice, showed that PR is an achievable target of anti-TNF- α treatment in nr-axSpA. The PR rate, as a reliable indicator of sustained effectiveness, is similar in nr-axSpA and AS. It also showed that the response peak occurs after a median period of 6 months. Despite the retrospective design of our real-life study, which is a possible limitation, CRP is the most relevant variable associated with PR in nr-axSpA, as well as in AS. These results are in keeping with the European Medicine Agency's indications for the use of anti-TNF- α

drugs in patients with severe axSpA, who have no evidence in the radiographs of AS but have objective signs of inflammation, and who have not responded adequately or are intolerant to NSAID²⁷.

ACKNOWLEDGMENT

Prof. Antonio Spadaro took part in the writing of this paper. He died on May 13, 2014. We dedicate this manuscript to Prof. Spadaro, who was a scientist and a respected and beloved physician of the Sapienza University of Rome.

REFERENCES

1. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
2. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondylarthritis Inception Cohort. *Arthritis Rheum* 2009;60:717-27.
3. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum* 2008;58:1981-91.
4. Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum* 2009;60:946-54.
5. Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondylarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. *Ann Rheum Dis* 2014;73:101-7.
6. Song IH, Hermann K, Haibel H, Althoff CE, Listing J, Burmester G, et al. Effects of etanercept versus sulfasalazine in early axial spondylarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis* 2011;70:590-6.
7. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondylarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815-22.
8. Landewé R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondylarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis* 2014;73:39-47.
9. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
10. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol* 1994;21:1694-8.
11. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286-91.
12. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281-5.
13. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001;44:1876-86.
14. Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:1438-44.
15. Vastesaeger N, van der Heijde D, Inman RD, Wang Y, Deodhar A, Hsu B, et al. Predicting the outcome of ankylosing spondylitis therapy. *Ann Rheum Dis* 2011;70:973-81.
16. Braun J, van der Berg R, Baraliakos X, Boehm H, Burgos Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011;70:896-904.
17. Rosenthal JA. Qualitative descriptors of strength of association and effect size. *J Soc Serv Res* 1996;21:37-59.
18. Zochling J, Braun J. Remission in ankylosing spondylitis. *Clin Exp Rheumatol* 2006; 24 Suppl 43:S88-92.
19. Song IH, Weiß A, Hermann KG, Haibel H, Althoff CE, Poddubnyy D, et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis* 2013;72:823-5.
20. Davis JC, van der Heijde D, Braun J, Dougados M, Cush J, Clegg D, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis* 2005;64:1557-62.
21. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:665-70.
22. Rudwaleit M, Claudepierre P, Wordsworth P, Cortina EL, Sieper J, Kron M, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol* 2009;36:801-8.
23. Braun J, Rudwaleit M, Kary S, Kron M, Wong RL, Kupper H. Clinical manifestations and responsiveness to adalimumab are similar in patients with ankylosing spondylitis with and without concomitant psoriasis. *Rheumatology* 2010;49:1578-89.
24. Spadaro A, Lubrano E, Marchesoni A, D'Angelo S, Ramonda R, Addimanda O, et al. Remission in ankylosing spondylitis treated with anti-TNF- α drugs: a national multicentre study. *Rheumatology* 2013;52:1914-9.
25. Kiltz U, Baraliakos X, Karakostas P, Igelmann M, Kalthoff L, Klink C, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res* 2012;64:1415-22.
26. Ciurea A, Scherer A, Exer P, Bernhard J, Dudler J, Beyeler B, et al. Tumor necrosis factor α inhibition in radiographic and nonradiographic axial spondylarthritis: results from a large observational cohort. *Arthritis Rheum* 2013;65:3096-106.
27. European Medicines Agency. European public assessment reports. [Internet. Accessed November 6, 2014.] Available from: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

APPENDIX 1. CRP, ESR, and presence of BME at baseline in nr-axSpA and AS. All values are n (%).

Variables	nr-axSpA, n = 62	AS, n = 259
CRP < 0.6 mg/dl	29 (46.8)	43 (16.6)
CRP ≥ 0.6 mg/dl	33 (53.2)	216 (83.4)
ESR < 16 mm/h	39 (62.9)	199 (76.8)
ESR ≥ 16 mm/h	23 (37.1)	60 (23.2)
Presence of BME on MRI	25 (73.5)	—
Absence of BME on MRI	9 (26.5)	—

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BME: bone marrow edema; nr-axSpA: nonradiographic axial spondyloarthritis; AS: ankylosing spondylitis; MRI: magnetic resonance imaging.