

Concise report

Non-radiographic axial spondyloarthritis patients without initial evidence of inflammation may develop objective inflammation over time

Xenofon Baraliakos¹, Joachim Sieper², Su Chen³, Aileen L. Pangan⁴ and Jaclyn K. Anderson⁴

Abstract

Objectives. In patients with active axial spondyloarthritis (axSpA), inflammation in the SIJ or spine on MRI, an elevated CRP level or both are considered useful objective assessments for disease activity and initiation of TNF antagonists. The aim of this *post hoc* analysis of the randomized, double-blind ABILITY-1 study (NCT00939003) was to assess changes in objective inflammation over time.

Methods. Patients with non-radiographic axSpA (nr-axSpA) were randomized to receive adalimumab 40 mg every other week or placebo for 12 weeks in ABILITY-1. MRIs were performed at baseline and week 12; CRP was measured every 4 weeks.

Results. Of 94 placebo-treated ABILITY-1 patients, 29 (30.9%) had a normal MRI of the SIJs and spine, 57 (60.6%) had normal CRP and 20 (21.3%) had a normal MRI of the SIJs and spine and a normal CRP at baseline. After 12 weeks of placebo, 9/29 (31.0%) patients subsequently developed inflammation on MRI, 14/57 (24.6%) patients developed elevated CRP and 10/20 (50.0%) patients developed a positive MRI and/or elevated CRP through week 12.

Conclusions. Patients who have clinically active disease but who lack objective evidence of inflammation initially may benefit from subsequent retesting for inflammation to guide treatment.

Key words: anti-TNF, spondyloarthritis, magnetic resonance imaging, inflammation

Rheumatology key messages

- Non-radiographic axial SpA patients may lack quantifiable signs of inflammation even with high disease activity.
- Non-radiographic axial SpA patients without initial objective evidence of inflammation may subsequently develop positive MRI and/or elevated CRP.
- Monitoring of patients with clinically active non-radiographic axial SpA can inform treatment decisions.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that predominantly affects the axial skeleton, with inflammation in the spine and SIJs; the estimated global prevalence is ~1% [1]. Axial SpA includes both non-

radiographic axSpA (nr-axSpA) and AS (radiographic axSpA), which are differentiated by the absence or presence, respectively, of radiographic damage in the SIJs. Patients with axSpA may suffer from pain, fatigue, stiffness and functional impairment, which contribute to a poor quality of life [2].

Although most tools for disease measurement used in patients with axSpA are subjective in nature, objective evidence of inflammation in patients with clinically active disease may be assessed non-invasively through observation of bone marrow oedema in the axial skeleton on MRI and elevated CRP levels [3]. In addition to the status of high disease activity as defined by a BASDAI ≥ 4 and expert opinion for active disease in patients with

¹Rheumazentrum Ruhrgebiet Herne, Ruhr-University, Bochum, Germany, ²Department of Gastroenterology, Infectiology, and Rheumatology, Charité Universitätsmedizin Berlin, Berlin, Germany, ³Data and Statistical Sciences and ⁴Immunology Clinical Development, AbbVie Inc., North Chicago, IL, USA

Submitted 6 May 2016; revised version accepted 27 February 2017

Correspondence to: Xenofon Baraliakos, Rheumazentrum Ruhrgebiet, Ruhr-University Bochum, Claudiusstr. 45, 44649 Herne, Germany. E-mail: baraliakos@me.com

established AS, patients with nr-axSpA also need to have objective evidence of inflammation as measured by MRI or serum acute phase reactant levels (CRP) when considering them as candidates for anti-TNF therapy [4].

TNF antagonists can suppress bone inflammation in patients with axSpA [5–7]. However, it is also known that in patients with AS treated with anti-TNF therapy, bone marrow oedema may persist or arise in new locations [8]. In contrast, little is known about the degree of natural fluctuation in imaging (MRI) and lab (CRP) inflammation markers in patients who do not receive anti-TNF therapy [9, 10].

The ABILITY-1 study demonstrated that adalimumab was effective in patients with nr-axSpA who had active disease despite treatment with NSAIDs or who were intolerant to or had a contraindication for NSAIDs [5]. Adalimumab was subsequently approved in many countries for the treatment of patients with nr-axSpA, most of which require objective evidence of inflammation as measured by a positive MRI result and/or elevated CRP level. In this *post hoc* analysis, biologic-naïve patients allocated to the placebo arm of the ABILITY-1 study who had clinically active disease but a normal MRI result for the SIJs and spine and/or normal CRP at baseline were assessed for development of a positive MRI and/or elevated CRP over time.

Methods

Study design and patient population

ABILITY-1 was a phase 3, multicentre, randomized, double-blind study in patients with active nr-axSpA [5]. Patients were randomized to receive adalimumab 40 mg every other week or placebo for 12 weeks, followed by open-label adalimumab for up to an additional 144 weeks. This was a *post hoc* analysis of the patients who received placebo during the first 12 weeks of ABILITY-1. Enrolled patients were ≥ 18 years of age with active nr-axSpA classified using the Assessment of SpondyloArthritis international Society (ASAS) criteria. Active disease was defined as total back pain ≥ 4 on a 0- to 10-cm visual analogue scale and a BASDAI score ≥ 4 on a 0-10 scale. Patients also must have had an inadequate response or intolerance to ≥ 1 NSAID or a contraindication for NSAIDs; no changes in NSAID use were permitted during the first 24 weeks of the study. Key exclusion criteria were a diagnosis of AS as defined by the modified New York criteria, past or present diagnosis of psoriasis or PsA, and prior exposure to biologic therapy. Approval of an institutional ethics review board and voluntary written informed patient consent were obtained prior to study procedures.

Assessments

The primary outcome for this *post hoc* analysis was the development of objective signs of inflammation in biologic-untreated nr-axSpA patients with clinically active disease but with normal MRI for the SIJs and spine or normal CRP at baseline. This was assessed among

placebo-treated patients at week 12, at the end of the placebo-controlled period.

CRP levels were measured every 4 weeks from baseline to week 12, and levels above the laboratory-defined upper limit of normal were considered to be elevated. MRI of the SIJs and spine were performed at baseline and week 12. MRIs were independently scored after all patients had reached week 12 by two central readers who were blinded to treatment and time point, with adjudication by a third central reader in the case of a discrepancy (6% of the MRIs at week 12 of ABILITY-1 required adjudication). The Spondyloarthritis Research Consortium of Canada (SPARCC) method was used for scoring the SIJs (0–72) and the SPARCC 6-discvertebral unit method was used for scoring the spine (0–108). SPARCC scores were based on the presence of bone marrow oedema representing inflammation. A positive MRI result was defined as SPARCC MRI score ≥ 2 for either the SIJs or spine.

Statistical methods

The number of patients who developed objective evidence of inflammation, as measured by MRI and/or CRP level, was determined. The association of baseline variables with the change from no objective evidence of inflammation at baseline to having MRI or CRP evidence of inflammation through week 12 was determined using Fisher's exact test. Baseline variables evaluated included HLA-B27 status, age, sex, duration of axSpA symptoms, nicotine use, number of SpA features, past history of positive MRI results in the SIJs and elevated CRP level before study enrolment.

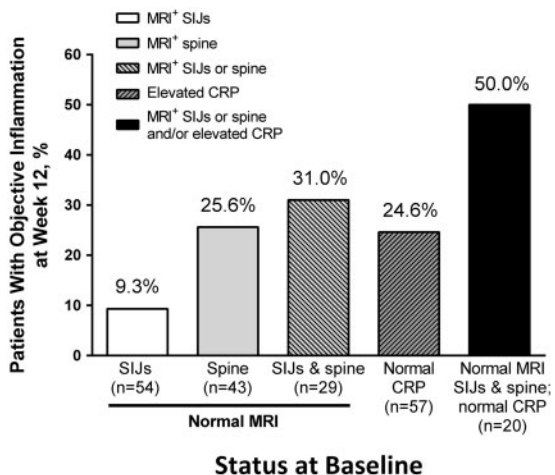
Results

Patients without objective inflammation at baseline

Of the 94 placebo-treated patients in ABILITY-1, 29 had a normal MRI result for the SIJs and spine at baseline, 57 had a normal CRP level at baseline and 20 had both a normal MRI of the SIJs and spine and a normal CRP level at baseline (Fig. 1). These 20 patients were predominantly women (65%) and white (95%), and had a mean age of 38 years; most (95%) reported inflammatory back pain (supplementary Table S1, available at *Rheumatology* Online). One patient had a missing baseline MRI and a normal CRP; thus, his baseline inflammation status was undetermined.

In the double-blind treatment period, among the 29 patients who had a normal MRI result for both the SIJs and the spine at baseline, 9 (31.0%) had a positive MRI result in either the SIJs or spine at week 12 (Fig. 1). Among 54 patients who had a normal MRI result for the SIJs at baseline, 5 (9.3%) had a positive MRI result for the SIJs at week 12, whereas, among 43 patients who had a normal MRI result for the spine at baseline, 11 (25.6%) developed a positive MRI result for the spine at week 12. Of the 57 patients with a normal CRP level at baseline, 14 (24.6%) developed an elevated CRP level at ≥ 1 time point from weeks 4 to 12; only 3 of these 14 patients reported AEs that might reasonably explain CRP elevation

Fig. 1 Development of objective inflammation in placebo treated patients without baseline inflammation during 12 weeks



Development of objective evidence of inflammation in patients with nr-axSpA during 12 weeks of placebo treatment, by subgroup. MRI was repeated at week 12 and CRP was repeated every 4 weeks through week 12. MRI⁺: positive MRI; nr-axSpA: non-radiographic axial spondyloarthritis.

(flu-like symptoms, viral syndrome and sinusitis). Persistence of CRP elevation was variable among patients with elevated post-baseline CRP levels (supplementary Fig. S1, available at *Rheumatology* Online). Of the 20 patients who had a normal MRI result for both the SIJs and spine and a normal CRP level at baseline, 10 (50.0%) had a positive MRI result for either the SIJs or spine, and/or an elevated CRP level at ≥ 1 post-baseline time point through week 12.

Predictors of subsequent inflammation in patients without objective inflammation at baseline

Among the 20 patients without signs of inflammation (normal MRI result for the SIJs and spine and normal CRP) at baseline, there were no statistically significant predictors for subsequent development of objective signs of inflammation (positive MRI result or elevated CRP). However, those who were female, aged <40 years, and who had a longer duration of symptoms were more likely to develop objective inflammation by week 12, although these trends were not significant. The mean duration of symptoms was 10.2 years for patients who subsequently developed inflammation by week 12 and 6.2 years for patients who did not develop inflammation by week 12.

Patients with objective inflammation at baseline

Among patients with either a positive MRI result for the SIJs and/or spine or elevated CRP levels at baseline, 91.8% (67/73) had a positive MRI result for the SIJs

and/or spine and/or had elevated CRP levels post-baseline through week 12; 69.9% (51/73) had a positive MRI result for the SIJs and/or spine, 60.3% (44/73) had elevated CRP levels and only 8.2% (6/73) no longer had objective evidence of inflammation during the 12 weeks (Table 1). In patients with both a positive MRI result for the SIJs and/or spine and elevated CRP levels at baseline, all patients continued to demonstrate objective inflammation through week 12.

Discussion

Prior studies have established that anti-TNF therapies can reduce CRP levels [5, 11–13] and suppress bone marrow inflammation (assessed via MRI) [5–7] in patients with axSpA. Less is known about the natural course of inflammation in patients not treated with an anti-TNF agent. However, the German Spondyloarthritis Inception Cohort (GESPIC) study reported spontaneous changes in both disease activity and CRP over a 2-year period in a limited number of anti-TNF-untreated patients [9], and results from the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) study demonstrated that clinical disease activity is longitudinally associated with inflammatory lesions of the SIJs in a mostly anti-TNF-untreated patient population [10]. This study demonstrated that in biologic-naïve patients with clinically active nr-axSpA, localized inflammation in the bone and systemic inflammation as measured by CRP may change during the natural course of the disease. Patients in our study had clinically active disease despite background and prior treatments that included NSAIDs and, in a few patients, DMARDs, with most patients receiving concomitant NSAIDs. In this sub-analysis, 50% of patients who had no objective signs of inflammation at baseline developed a positive MRI result and/or elevated CRP during 12 weeks of placebo treatment. No significant predictors for development of bone marrow oedema on MRI or CRP elevation were identified in this small population and further studies are needed to elucidate predictors.

Inflammation may be present in bone, but not at a sufficient threshold for imaging to reflect bone marrow oedema or to register systematically as elevated acute phase reactants. Patients who have clinically active disease may lack a positive MRI result because the level of bone marrow oedema is below the limit of detection, as evidenced by a study that demonstrated the presence of inflammation on bone biopsy when imaging was negative [14]. However, given its invasive nature, bone biopsy is not a feasible option for determining the appropriate treatment for patients with axSpA in daily practice.

Current treatment recommendations state that patients with active disease who have failed NSAIDs and have either elevated serum acute phase reactant levels or imaging results (such as radiographs demonstrating rapid progression or MRI scans indicating inflammation) may be considered as candidates for treatment with anti-TNF agents [4]. However, there is a lack of formal guidelines for MRI or CRP monitoring frequency in patients with axSpA [4]. CRP monitoring is inexpensive, easily obtained and

TABLE 1 Changes in SIJs and spine MRI and CRP values in patients initially receiving placebo

Baseline status	Status post-baseline through week 12, n (%)			
	CRP elevated	MRI ⁺	MRI ⁺ and/or CRP elevated	MRI ⁻ and CRP normal
MRI ⁻ and CRP normal (n = 20)	4 (20.0)	8 (40.0)	10 (50.0)	10 (50.0)
MRI ⁺ and/or CRP elevated (n = 73)	44 (60.3)	51 (69.9)	67 (91.8)	6 (8.2)
Both MRI ⁺ and CRP elevated (n = 25)	24 (96.0)	19 (76.0)	25 (100)	0
MRI ⁺ only (n = 61)	34 (55.7)	48 (78.7)	56 (91.8)	5 (8.2)
CRP elevated only (n = 37)	34 (91.9)	22 (59.5)	36 (97.3)	1 (2.7)

Patients received placebo for 12 weeks. MRI status is for the SIJ and/or the spine. MRI⁺: positive MRI; MRI⁻: normal MRI.

performed routinely in patients with rheumatic disease. In clinical practice, MRI may be inaccessible and/or cost prohibitive, especially when considering serial examinations; however, the use of this imaging tool may be warranted when considering long term biologic therapy for patients. Because inflammation may be absent at one time point but present later, periodic monitoring of patients with clinically active nr-axSpA is reasonable to assist with treatment decisions. Although CRP was measured every 4 weeks and MRI was repeated at week 12 in this clinical study, this frequency does not reflect usual clinical practice and physicians should use their best judgment to determine timing of repeated evaluations.

A key aspect of this sub-analysis was the evaluation of patients with clinically active disease who initially did not have objective signs of inflammation by either MRI or CRP; this study is important because such patients may be excluded from future clinical trials that will likely enrol only patients with objective inflammation at baseline (i.e. those who are more likely to show a response to a study drug). Furthermore, CRP elevation in axSpA has been demonstrated to be the best predictor of both clinical response [5, 15] and radiographic progression [16, 17]. A limitation of the current study is small sample size; therefore, these results should be interpreted with caution and confirmed in larger observational studies. Additionally, elevated CRP levels attributed to disease-related inflammation in this study may result from other causes (i.e. infection) that must be ruled out in practice.

We have demonstrated that objective signs of inflammation in patients with clinically active nr-axSpA can change during the natural course of the disease. Thus, patients with clinically active disease but without objective inflammation at one time point may benefit from subsequent retesting for inflammation to guide treatment.

Acknowledgements

Medical writing support was provided by Katherine Groschwitz, PhD, and Tiffany Brake, PhD, of Complete Publication Solutions, LLC (North Wales, PA) and

was funded by AbbVie. AbbVie funded the study (NCT00939003), contributed to its design, and was involved in the collection, analysis and interpretation of the data, and in the writing, review and approval of the publication.

Funding: This work was supported by AbbVie Inc., North Chicago, IL, USA.

Disclosure statement: X.B. has received consulting and/or speaker's fees from AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Janssen, Merck Sharp & Dohme Corp, Novartis, Pfizer, Sandoz and Union Chimique Belge (UCB). J.S. has received research funds, consulting fees and/or speaker's fees from AbbVie, Merck, Pfizer and UCB. J.K.A., A.L.P. and S.C. are employees of AbbVie and hold and/or stock options.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

- 1 Akkoc N. Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review. *Curr Rheumatol Rep* 2008;10:371-8.
- 2 Boonen A, Sieper J, van der Heijde D *et al.* The burden of non-radiographic axial spondyloarthritis. *Semin Arthritis Rheum* 2015;44:556-62.
- 3 Sieper J, Rudwaleit M, Baraliakos X *et al.* The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1-44.
- 4 van der Heijde D, Sieper J, Maksymowych WP *et al.* 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011;70:905-8.
- 5 Sieper J, van der Heijde D, Dougados M *et al.* Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-

- controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815–22.
- 6 Braun J, Landewe R, Hermann KG *et al.* Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. *Arthritis Rheum* 2006;54:1646–52.
 - 7 Lambert RG, Salonen D, Rahman P *et al.* Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2007;56:4005–14.
 - 8 Maksymowych WP, Morency N, Conner-Spady B, Lambert RG. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. *Ann Rheum Dis* 2013;72:23–8.
 - 9 Poddubnyy D, Haibel H, Braun J, Rudwaleit M, Sieper J. Brief report: Clinical course over two years in patients with early nonradiographic axial spondyloarthritis and patients with ankylosing spondylitis not treated with tumor necrosis factor blockers: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheumatol* 2015;67:2369–75.
 - 10 Navarro-Compan V, Ramiro S, Landewe R *et al.* Disease activity is longitudinally related to sacroiliac inflammation on MRI in male patients with axial spondyloarthritis: 2-years of the DESIR cohort. *Ann Rheum Dis* 2016;75:874–8.
 - 11 van der Heijde D, Kivitz A, Schiff MH *et al.* Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006;54:2136–46.
 - 12 Davis JC Jr, van der Heijde D, Braun J *et al.* Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;48:3230–6.
 - 13 van der Heijde D, Dijkmans B, Geusens P *et al.* Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;52:582–91.
 - 14 Gong Y, Zheng N, Chen SB *et al.* Ten years' experience with needle biopsy in the early diagnosis of sacroiliitis. *Arthritis Rheum* 2012;64:1399–406.
 - 15 Arends S, Brouwer E, van der Veer E *et al.* Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011;13:R94.
 - 16 Poddubnyy D, Rudwaleit M, Haibel H *et al.* Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011;70:1369–74.
 - 17 Rudwaleit M, Haibel H, Baraliakos X *et al.* The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009;60:717–27.