Resolution of Inflammation Following Treatment of Ankylosing Spondylitis Is Associated with New Bone Formation

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ABSTRACT. ***Objective.*** To test the hypothesis that in patients with ankylosing spondylitis (AS) a vertebral corner inflammatory lesion (CIL) visible on magnetic resonance imaging (MRI) that completely resolves following treatment with anti-tumor necrosis factor-α (TNF-α) agents is more likely to develop into a *de novo* syndesmophyte visible on a radiograph as compared to a vertebral corner with no CIL.

Methods. Fifty patients with AS, who had MRI at baseline and at followup (mean 19.2 months), and spinal radiography at baseline and after 2 years, were followed prospectively. A persistent CIL was defined as being present on both MRI, while a resolved CIL was defined as present at baseline MRI and completely disappeared at followup MRI. Two readers read the MRI independently, and analyses were done for areas with agreement (concordant reads) and for individual reads.

Results. For patients receiving anti-TNF therapy (n = 23), new syndesmophytes developed more frequently from vertebral corners where a CIL had completely resolved on followup MRI (42.9% on concordant reads) as compared to vertebral corners where no CIL was demonstrable on either the baseline or followup MRI (2.4%; $p < 0.0001$). Results from individual readers showed similar differences. For patients receiving standard treatment (n = 27), the same pattern, although nonsignificant, was observed (20% vs 3.3%; $p = 0.16$) on concordant reads, as well as on individual reads.

Conclusion. Our study of AS spines documents that MRI findings predict new bone formation on radiograph. Demonstration of an increased likelihood of developing new bone following resolution of inflammation after anti-TNF therapy supports the theory that TNF-α acts as a brake on new bone formation. Because the number of new syndesmophytes was low, further study is necessary to make firm conclusions. (First Release April 1 2011; J Rheumatol 2011;38:1349–54; doi:10.3899/jrheum.100925)

Key Indexing Terms:
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Magnetic resonance imaging (MRI) demonstrates bone marrow edema in the sacroiliac joints and spine as a characteristic feature of active inflammation in patients with ankylosing spondylitis (AS)[1,2]. In the spine, inflammation is primarily seen at the anterior and posterior vertebral corners, i.e., the location where syndesmophytes develop. This has led to the hypothesis that inflammation leads to new bone formation in patients with AS. Three studies have demonstrated a positive association between vertebral corner inflammation on baseline MRI and subsequent development of new syndesmophytes on radiographs 2 years later in patients treated with tumor necrosis factor-α (TNF-α) inhibitor[3,4,5]. The conclusion was based on baseline MRI examination of patients recruited to clinical trials of anti-TNF therapy while we also reported data from 1 followup MRI evaluation in testing the hypothesis that persistent inflammation at vertebral corners was more likely to lead to new syndesmophytes[4]. Surprisingly, the converse was observed. Inflammation that completely resolved on followup MRI was more prone to develop into syndesmophytes as compared to persistent inflammation in patients taking anti-TNF therapy[4]. This observation may be explained by TNF-α inducing Dickkopf-1 (DKK-1), a protein that downregulates the Wnt signaling pathway that directs osteoblast formation from mesenchymal precursor

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cells[6]. Inhibition of TNF-α would then lead to reduced DKK-1 and thereby enhanced Wnt signaling, leading to formation of new bone. Further, it has been shown that osteoblast differentiation induced by bone morphogenetic protein (BMP-2), which is also upregulated by Wnt signaling, is attenuated by DKK-1 and DKK-2[7]. Consequently, 1 prediction of this hypothesis is that new syndesmophytes are more likely to develop after resolution of inflammation induced by anti-TNF agents.

Our purpose was to examine the relationship between the course of MRI inflammation and the subsequent development of new syndesmophytes in an observational cohort of patients with AS receiving anti-TNF therapy or standard treatment with nonsteroidal antiinflammatory drugs (NSAID) and physical modalities. In particular, we aimed to test the hypothesis that a CIL visible on MRI that completely resolves following treatment is more likely to develop into a *de novo* syndesmophyte than a vertebral corner that demonstrates no inflammation on MRI.

MATERIALS AND METHODS

Patients. Our study comprised 50 patients with AS according to the modified New York criteria[8]. The patients were recruited consecutively to an observational cohort of patients with AS who were evaluated systematically according to a standardized protocol including clinical, laboratory, and imaging investigations[9]. Radiography was conducted at baseline and after 2 years and included anteroposterior and lateral views of the lumbar spine and a lateral view of the cervical spine. MRI was conducted at baseline and repeated prior to the 2-year radiographic followup. The patients were assessed clinically with the Bath AS Disease Activity Score[10], the Bath AS Functional Index (BASFI)[11], the patient's global assessment, total back pain, nocturnal back pain, and C-reactive protein. Twenty-three patients began TNF-α inhibitor therapy and 27 patients continued standard therapy such as NSAID and/or physical therapy.

Imaging. All the MRI was performed with 1.5 Tesla systems (Siemens, Erlangen, Germany) using appropriate surface coils. Sagittal spine sequences were obtained with 3–4 mm slice thickness, and 11–15 slices were acquired. Sequence measurements were (1) T1-weighted spin-echo [repetition time (TR) 517–618 ms, echo time (TE) 13 ms]; and (2) short-tau inversion recovery [STIR; TR 3000–3170 ms, inversion time (TI) 140 ms, TE 38–61 ms]. Field of view was 380–400 mm and matrix was 512 × 256 pixels. The spine was imaged in 2 parts: the upper half, comprising the entire cervical and most of the thoracic spine; and the lower half, comprising the lower portion of the thoracic spine and the entire lumbar spine.

MRI definitions. Standardized definitions of active and structural spinal lesions observed on MRI in patients with AS have been developed by the Spondyloarthritis Research Consortium of Canada as well as an international working group of rheumatologists and radiologists from Canada and Denmark[12,13,14,15]. The MRI readings were based on these definitions. A vertebral corner inflammatory lesion (CIL) is defined as an increased STIR signal at a vertebral corner that is present in at least 1 sagittal slice, which includes the spinal canal[12,16], where the bone marrow signal in the center of the vertebra, if normal, constitutes the reference for designation of normal signal[17]. A CIL was defined as being completely resolved if it was recorded as being present at baseline and then absent after the introduction of therapy[4]. A CIL was defined as being persistent if it was recorded as being present on baseline and followup MRI[4].

Evaluation of images. Each MRI and radiograph was assigned a unique computer-generated number ensuring that readers were blinded to patient demographics and treatment. The assessments were performed on dedicated work stations using imaging software (Merge eFilm, Milwaukee, WI, USA), and with standardized viewing conditions. MRI and radiographs were coded in chronological order but a random number assignment ensured that they were read independently. On MRI, the anterior vertebral corners of the cervical (C2 lower to Th1 upper) and lumbar (Th12 lower to S1 upper) spines were independently evaluated by 2 readers for presence/absence of CIL and for changes in these (resolved, persistent, and new CIL). Concordant assessments were identified after completion of all reads. Anterior vertebral corners on radiographs of the cervical (C2 lower to Th1 upper) and lumbar (Th12 lower to S1 upper) spines were evaluated independently by 2 readers, who scored the images individually, with disagreements resolved by a third reader. The thoracic spine was excluded from the assessment because of inadequate visualization on radiographs[18].

Ethics. The study was approved by the local ethical committee and performed in compliance with the Helsinki Declaration. Written informed consent was obtained from each patient before any study-related procedure was performed.

Statistical analysis. The primary analysis focused on concordant data between 2 readers, as recommended[4]. Vertebral corners that already demonstrated radiographic syndesmophytes or ankylosis at baseline were excluded. We compared the proportion of new syndesmophytes developing at each anterior vertebral corner that demonstrated a completely resolved CIL or a persistent CIL versus a vertebral corner that was normal by imaging at baseline and at followup MRI. Patient characteristics were compared with unpaired t-test and proportions with the Pearson chi-squared or Fisher's exact test. A $p < 0.05$ was considered statistically significant. Statistics were analyzed in SPSS version 13 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics are presented in Table 1. All patients were followed at the Department of Rheumatology, University of Alberta, Edmonton, Canada. Anti-TNF therapy was initiated according to the discretion of the attending rheumatologist but only after failure of 2 NSAID. Patients starting anti-TNF agents (n = 23) were treated with either infliximab 3 or 5 mg/kg (n = 11), etanercept 25 mg twice a week (n = 10), or adalimumab 40 mg every other week (n = 2), and had NSAID on demand and physical therapy, while patients in the standard therapy group (n = 27) were treated only with NSAID and physical therapy. Baseline data on 18 patients receiving anti-TNF agents and 23 receiving standard therapy has been described[4], while the followup data that has since become available have not been presented previously. In addition, a different reader pair independently assessed the MRI scans in our current study[3]. Followup MRI and radiographs were done a mean of 19.2 and 27.4 months from baseline, respectively. There were no significant differences between the 2 cohorts except that anti-TNF-treated patients had significantly higher baseline scores for BASFI ($p = 0.046$).

Development of new syndesmophytes. The total number of anterior vertebral corners assessed in patients starting anti-TNF therapy was 552 and in patients continuing standard therapy was 648. Radiographic data were unavailable for 83 (15.0%) and 25 (3.9%) anterior vertebral corners in patients treated with TNF-α inhibitors and standard therapy, respectively, primarily because of lack of visualization of

Table 1. Patient characteristics stratified according to therapy. Results are given as mean (SD), except where indicated.

Characteristics	TNF-α Inhibitor Therapy, n = 23	Standard Therapy, n = 27	p
Sex (male:female)	18:5	25:2	NS
Age, yrs	40.4 (12.1)	40.3 (13.4)	NS
Disease duration, yrs	18.2 (11.4)	15 (10)	NS
BASDAI (0-10)	5.1 (2.0)	5.0 (2.3)	NS
BASFI (0-10)	4.7 (2.3)	3.2 (2.8)	0.046
Patient global (0-10)	5.2 (2.7)	4.5 (2.9)	NS
Total back pain (0-10)	5.6 (2.8)	5.1 (2.4)	NS
Nocturnal back pain (0-10)	5.7 (2.7)	4.6 (2.5)	NS
C-reactive protein (mg/dl)	15.8 (15.1)	8.3 (13.4)	NS
No. new syndesmophytes	0.52 (0.8)	0.70 (1.4)	NS
Baseline mSASSS	14.5 (16.1)	10.0 (12.1)	NS
mSASSS change	1.4 (1.9)	1.5 (3.1)	NS

TNF: tumor necrosis factor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

the lower part of the cervical spine. Further, 96 (17.4%) and 67 (10.3%) vertebral corners demonstrated radiographic syndesmophytes or ankylosis at baseline in patients treated with TNF-α inhibitors and standard therapy, respectively. These vertebral corners were excluded from all analyses.

At baseline, patients starting anti-TNF therapy had a higher number of CIL [mean 1.4 (SD 1.53)] as compared to patients receiving standard therapy [0.85 (1.8); p = 0.26; Table 2] although this was not statistically significant.

During the study, ≥ 1 new syndesmophyte was detected in 8 of 23 patients (34.8%) treated with TNF-α inhibitors and in 9 of 27 patients (33.3%) receiving standard therapy (Table 3). Patients receiving anti-TNF therapy developed new syndesmophytes in 12 of 373 (3.2%) vertebral corners [mean per patient 0.52 (SD 0.9)], while patients continuing standard therapy developed new syndesmophytes in 19 of 556 (3.4%) vertebral corners [0.70 (SD 1.4)].

Association between CIL at baseline and development of new syndesmophytes. New syndesmophytes developed more frequently from vertebral corners that had a CIL at baseline as compared to vertebral corners without a CIL (Table 3). In patients starting anti-TNF therapy, new syndesmophytes developed in 3 of 18 (16.7%) vertebral corners with a CIL at baseline as compared to 7 of 307 (2.2%) vertebral corners without a CIL at baseline (p = 0.01). Similar data were recorded in patients continuing standard therapy where syndesmophytes arose from 3 of 20 (15.0%) vertebral corners with a CIL at baseline as compared to 16 of 494

Table 2. Descriptive data on the number of corner inflammatory lesions (CIL) recorded in the anterior cervical and lumbar spine at baseline and at followup MRI. Results are given for concordant and individual reads.

	Concordant Reads		First Reader		Second Reader	
CIL Data	TNF-α Inhibitor Therapy n = 23	Standard Therapy n = 27	TNF-α Inhibitor Therapy n = 23	Standard Therapy n = 27	TNF-α Inhibitor Therapy n = 23	Standard Therapy n = 27
Baseline MRI (total no. spinal sites)	474	599	552	648	552	648
Total number (%) of CIL	32 (6.8)	23 (3.8)	86 (15.6)	62 (9.6)	56 (10.1)	33 (5.1)
No. CIL per patient						
Mean (SD)	1.4 (1.53)	0.85 (1.81)	3.74 (2.63)	2.30 (2.30)	2.43 (1.97)	1.22 (1.91)
Median (IQR)	1 (0–2)	0 (0–1)	3 (2–5)	2 (1–3)	2 (1–3.5)	1 (0–1.5)
Range	0–6	0–9	0–10	0–10	0–7	0–9
Followup MRI						
Total number of CIL	11	16	53	49	25	22
CIL per patient						
Mean (SD)	0.48 (1.20)	0.59 (1.45)	2.30 (2.48)	1.81 (2.06)	1.09 (2.17)	0.81 (1.66)
Median (IQR)	0 (0–0)	0 (0–1)	1 (0–4)	1 (0.5–2)	0 (0-2)	0 (0–1)
Range	0–5	0–7	0–10	0–8	0–10	0–7
No. completely resolved CIL	14	7	42	22	44	20
No. new CIL	1	3	9	9	13	9

IQR: interquartile range; MRI: magnetic resonance imaging; TNF-α: tumor necrosis factor-α. First reader: PC; second reader: SJP.

Table 3. Development of new syndesmophytes on radiographs of anterior cervical and lumbar spine in 50 patients with AS treated with TNF-α inhibitors or standard therapy. Data are from concordant and individual reads and show number (%) of anterior vertebral corners associated with the presence or absence of new syndesmophytes.

	TNF-α Inhibitor Therapy, n = 23 New Syndesmophytes at Followup			Standard Therapy, n = 27 New Syndesmophytes at Followup		
	Yes	No	p*	Yes	No	p*
Concordant Reads						
Baseline MRI						
Vertebral corner with CIL	3 (16.7)	15 (83.3)	0.01†	3 (15.0)	17 (85.0)†	0.03†
Vertebral corner without CIL	7 (2.2)	300 (97.7)		16 (3.2)	478 (96.8)	
Followup MRI						
Completely resolved CIL	3 (42.9)	4 (57.1)	0.0009††	1 (20.0)	4 (80.0)††	0.16††
Persistent CIL	0(0)	4 (100)	0.76**	0 (0)	10 (100)	0.56**
No CIL	7 (2.4)	287 (97.6)		16 (3.3)	469 (96.7)	
New CIL at followup		1			3	
First reads						
Baseline MRI						
Vertebral corner with CIL	4 (7.5)	49 (92.5)	0.08†	3 (5.8)	49 (94.2)†	0.43†
Vertebral corner without CIL	8 (2.5)	312 (97.5)		16 (3.2)	488 (96.8)	
Followup MRI						
Completely resolved CIL	4 (15.4)	22 (84.6)	0.009††	2 (10.6)	17 (89.5)††	0.14††
Persistent CIL	0 (0)	27 (100)	0.40**	1 (3.0)	32 (97.0)**	0.95**
No CIL	8 (2.6)	303 (97.4)		16 (3.2)	481 (96.8)	
New CIL at followup		9			7	
Second reads						
Baseline MRI						
Vertebral corner with CIL	4 (12.9)	27 (87.1)	0.01†	3 (10.0)	27 (90.0)	0.08†
Vertebral corner without CIL	8 (2.3)	334 (97.7)		16 (3.0)	510 (97.0)	
Followup MRI						
Completely resolved CIL	4 (15.4)	22 (84.6)	0.007††	2 (11.1)	16 (88.9)	0.12††
Persistent CIL	0 (0)	5 (100)	0.73**	1 (7.6)	12 (92.3)	0.35**
No CIL	8 (2.4)	327 (97.6)		16 (3.1)	502 (96.9)	
New CIL at followup		7			7	

*Pearson chi-squared test. †Compared to vertebral corners without a CIL baseline. ††Comparison of new syndesmophytes developing in vertebral corners with a CIL that has completely resolved on followup MRI vs those vertebral corners with no CIL on either baseline or followup MRI scan. **Comparison of new syndesmophytes developing in vertebral corners with a CIL that is present on both baseline and followup MRI vs those vertebral corners where there is no CIL on either MRI scan. CIL: corner inflammatory lesions; MRI: magnetic resonance imaging; TNF-α: tumor necrosis factor-α. Reader 1: PC; Reader 2: SJP; standard therapy included NSAID and physical therapy.

(3.2%) vertebral corners without a CIL at baseline (p = 0.03). Analysis of individual data from 1 reader confirmed these results in the anti-TNF treatment group (12.9% vs 2.3%; p = 0.01) but not the standard therapy group (10.0% vs 3.0%; p = 0.08), while data from another reader did not show a significant association (anti-TNF group: 7.5% vs 2.5%, p = 0.08; standard therapy group: 5.8% vs 3.2%, p = 0.43).

Associations between CIL at followup and development of new syndesmophytes. In patients starting anti-TNF therapy, new syndesmophytes developed more frequently at those vertebral corners where a CIL had completely resolved on followup MRI [3 (42.9%)] as compared to those vertebral corners where no CIL was demonstrable on either baseline or followup MRI [7 (2.4%); p < 0.0009; Table 3]. The same finding was observed in patients continuing standard therapy, although it was less striking than in patients treated with anti-TNF therapy [1 (20%) vs 16 (3.3%); p = 0.16]. In both patient cohorts, concordant data did not demonstrate a single vertebral corner that evolved into a new syndesmophyte where a CIL was persistently demonstrable on both baseline and followup MRI. Analysis of data from individual readers confirmed the association between completely resolved CIL and the development of new syndesmophytes [both readers: 4 (15.4%)] as compared to vertebral corners without CIL at baseline [PC: 8 (2.6%), p = 0.009; SJP: 8 (2.4%), p < 0.007] in patients starting anti-TNF therapy, while this association was not found in patients receiving standard therapy [PC: 2 (10.5%) vs 16 (3.2%), p = 0.14; SJP: 2 (11.1%) vs 16 (3.1%), p = 0.12].

DISCUSSION

We have tested the hypothesis that complete resolution of inflammation following anti-TNF therapy is associated with the development of new radiographic syndesmophytes in patients with AS. Vertebral corners with completely resolved inflammation on followup MRI were more prone to develop into new syndesmophytes as compared to verte-

bral corners with no baseline inflammation, while no differences were found between vertebral corners with persistent inflammation as compared to vertebral corners with no baseline inflammation. While this appeared to be evident regardless of treatment, this association was significant only in patients who received anti-TNF therapy.

In a previous report[4] that included data from patients with AS receiving anti-TNF therapy in phase III clinical trials, our finding that complete resolution of inflammation was associated with new syndesmophytes was unexpected and ran counter to our study hypothesis that syndesmophytes would develop at sites of persistent inflammation. In our current study, comprising an unrelated observational cohort, we show that vertebral corners where inflammation completely resolves on MRI are indeed more prone to develop new syndesmophytes as compared to vertebral corners with persistent or no inflammation, despite MRI evaluation being performed by 2 readers other than the ones in the previous cohort[4]. In particular, we have demonstrated that vertebral corners with persistent inflammation do not appear to develop new syndesmophytes. Consequently, these results support the TNF-brake hypothesis, in which TNF-α upregulates DKK-1, a major negative regulator of osteoblastogenesis through the Wnt signaling pathway[4]. Reduced levels of active TNF due to anti-TNF therapy may therefore not only promote resolution of inflammation but also enhance osteoblastogenesis because of downregulation of DKK-1.

The higher frequency of CIL at baseline and of completely resolved CIL in patients treated with TNF-α inhibitors but without excess development of syndesmophytes as compared to patients receiving standard therapies might appear to be contradictory with the TNF-brake hypothesis. Moreover, data from phase III trials of anti-TNF therapy have not demonstrated any overall difference in radiographic progression, as measured with the Modified Stoke AS Spinal Score, as compared to historical controls receiving standard therapy[19,20,21]. The results from the clinical trials can be reconciled with the data and conclusions from our study by first considering that lesions in AS evolve from early inflammatory lesions with features of synovial and/or subchondral marrow inflammation that may include erosive changes, followed by reparative processes that include fat infiltration, cartilage metaplasia, and the formation of new bone through endochondral ossification[22,23,24]. Lesions at all these stages of evolution may be present simultaneously in the individual patient with established AS who is characteristic of patients recruited to phase III trials of anti-TNF therapy. It may be possible that very early inflammatory lesions resolve completely without any sequelae if anti-TNF therapy is introduced before signaling pathways leading to reparative processes, especially new bone formation, have been triggered[25]. On the other hand, once a lesion has become more advanced and reparation is well under way, introduction of anti-TNF alleviates inflammation but now accelerates reparation and new bone formation through its effects on DKK-1 and other regulatory molecules. For an individual patient, the overall development of new bone during anti-TNF therapy may therefore depend on the balance between the number of early and more mature inflammatory lesions.

The focus on the assessment of lesions that are concordantly detected by 2 readers is in our view important in studies using MRI to detect these lesions as compared to focusing on individual reader data, which, as in this analysis, may show discrepancy. This reflects the fact that inflammatory lesions at vertebral corners can be small and/or demonstrate only a slight alteration in signal intensity on STIR sequences. Reliable assessment of lesions in the cervical spine is particularly difficult because of the small size of the vertebrae and the large field of view, which is currently standard for MRI in spondyloarthritis. In addition, phase-encoding artefact constitutes a significant limitation in the reliable assessment of inflammatory lesions in the anterior vertebral corners of the lumbar spine. Specifically, MRI is subject to physiological motion artefacts, so that flowing blood in the inferior vena cava and the abdominal aorta may cause spurious signal that mimics anterior vertebral corner inflammatory lesions in the lumbar spine.

The necessity to focus on concordant data, especially reliable detection of resolution of inflammation, together with the small number of new syndesmophytes, limits the sample size available for analysis and constitutes a limitation of our study, so the results should be interpreted with caution. Moreover, the small sample size precludes the consideration of potential confounders previously shown to influence disease progression in the spine of patients with AS, especially baseline radiographic damage.

The majority of new syndesmophytes develops at sites without inflammation on baseline and followup scans and this may well point to noninflammatory pathways of new bone formation, as pointed out by others[26]. However, it is important to note that MRI has limited sensitivity for the detection of spinal inflammatory lesions evident on histopathology[1], with only about half of such lesions being evident on STIR MRI. In addition, MRI scans limited to 1 or 2 timepoints can only reflect a limited snapshot of events that may evolve rapidly with time.

We tested and confirmed the hypothesis that vertebral corners with resolved inflammation on MRI were more likely to develop into new syndesmophytes as compared to vertebral corners with no inflammation. The results support a biomolecular model in which TNF-α suppresses bone formation through upregulation of DKK-1 in established inflammatory lesions where bone signaling pathways mediated by Wnt, BMP, and possibly other proteins are activated during the course of inflammation. An important prediction of the model that should now be tested is that anti-TNF ther-

apy used very early in the course of SpA will prevent new bone formation by abrogating inflammation prior to activation of bone signaling pathways.

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