Health and imaging outcomes in axial spondyloarthritis

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Chapter 6

MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a tumour necrosis factor inhibitor

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ABSTRACT

Objectives

To investigate the relationship between MRI inflammation and measures of clinical disease activity as well as treatment responses in patients with ankylosing spondylitis (AS) treated with a tumour necrosis factor inhibitor.

Methods

MRI at baseline (n=221), 24 (n=158) and 102 weeks (n=179) were scored for inflammation/ activity (MRIa, Berlin scoring system). Treatment responses according to the AS disease activity score (ASDAS), Bath AS disease activity index (BASDAI) and assessment of spondyloarthritis 20 (ASAS20) criteria were calculated. For each treatment response criterion, subgroups of responders and non-responders changes in MRIa scores were compared.

Results

Higher baseline ASDAS and C-reactive protein (CRP) values were associated with higher baseline MRIa scores and with greater decreases in MRIa scores at follow-up. ASDAS and CRP improvements correlated with MRIa improvement. Stronger correlations were observed for CRP. Differences in MRIa change scores between responders and non-responders were greater when subgroups were defined according to ASDAS response than according to BASDAI or ASAS20 response.

Conclusion

MRIa correlates better with CRP than with other measures of disease activity. By including both CRP and patient-reported outcomes in its formula, ASDAS has the advantage of providing combined information on objective and subjective measures. As a status and response measure ASDAS better reflects the spinal inflammatory disease process in AS than other composite measures.

INTRODUCTION

The contribution of MRI to our understanding of spondyloarthritis including ankylosing spondylitis (AS) is indisputable. MRI can be used to detect inflammatory lesions of the spine and sacroiliac joints, and spinal MRI is currently considered a powerful tool to document treatment effects by detecting improvement, persistence or new onset of spinal inflammation in AS.[1]

The relationship between MRI inflammation and measures of clinical disease activity, including the recently developed AS disease activity score (ASDAS),[2–4] is incompletely understood. Our aim was to investigate the relationship between MRI inflammation and measures of clinical disease activity as well as treatment responses in patients with AS treated with a TNF inhibitor.

METHODS

Patients and assessments

A random 80% sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) database was used for this analysis. Details of the ASSERT study have been published previously.[5,6] Briefly, ASSERT was a 24-week randomized controlled trial comparing infliximab monotherapy and placebo in patients with active AS, with an open extension until 102 weeks with all patients on infliximab.

MRI (T1-weighted before and after gadolinium, and short tau inversion recovery) at baseline, week 24 and week 102 were scored by two independent readers using the AS spinal MRI activity (ASspiMRI-a) score[7] that assesses 23 vertebral units of the entire spine (C2 to S1). For this analysis, ASspiMRI-a scores were re-coded using the Berlin modification[8] in order to exclude erosions from the scores. The two-way random model, absolute agreement type and average measures intraclass correlation coefficients for the Berlin re-coded MRI activity (MRIa) scores were 0.90 (baseline), 0.47 (24 weeks), 0.66 (102 weeks), 0.86 (24 weeks change) and 0.88 (102 weeks change).

The Bath AS disease activity index (BASDAI),[9] the C-reactive protein (CRP) version of the ASDAS[2–4] and individual BASDAI and ASDAS questions were used as measures of disease activity. At 24 and 102 weeks, three response criteria were calculated: ASDAS clinically important improvement (ASDAS response),[4] BASDAI 50% improvement and/or absolute change of 2 units on a 0–10 scale (BASDAI response)[1] and the assessment of spondyloarthritis 20 response (ASAS20 response).[1]

Statistical analysis

Analyses were performed for all patients at baseline (n=221), for changes in the infliximab group at 24 weeks (n=158) and for changes in all patients at 102 weeks (n=179). Spearman correlation coefficients were determined to assess the relationships between MRIa scores and disease activity measures, namely ASDAS, BASDAI and individual components of BASDAI and ASDAS (including CRP).

At 24 and 102 weeks, for each treatment response criterion (ASDAS, BASDAI and ASAS20 response), responders and non-responders were identified and changes in MRIa scores over time were compared among these responder subgroups using four statistical approaches:

The standardised mean difference (SMD) - the SMD (difference of the group means divided by the pooled SD of the group means) was used to assess the discriminatory capacity of changes in MRIa with respect to subgroups of patients with and without a clinical response. The SMD is unitless and the higher the absolute value, the greater the discriminatory capacity.

The difference in the standardised response mean (ΔSRM) between responders and non-responders - the SRM for each subgroup was calculated as the change between the mean follow-up and baseline MRIa score divided by the SD of the change score. The SRM is a measure of responsiveness and the ΔSRM was used to compare the performance of different response criteria with regard to changes in MRIa; the higher the absolute value of ΔSRM, the better the performance.

The F-score and p value of a two-sided analysis of variance on van der Waerden normal scores was used as an additional measure of discrimination; the higher the F-score, the greater the discriminatory capacity.

The area under the receiver operating characteristic (AUC) curve and its 95% CI were used to assess the discriminatory ability of changes in MRIa scores on clinical response according to the various criteria; the higher the AUC, the better the discriminatory ability.

RESULTS

Correlation analysis

At baseline, ASDAS (r=0.16, p=0.016) and CRP (r=0.28, p<0.001) correlated weakly with MRIa scores. Similarly, changes in ASDAS (r=0.22, p=0.006 at 24 weeks; r=0.23, p=0.002 at 102 weeks) and changes in CRP (r=0.25, p=0.002 at 24 weeks; r=0.32, p<0.001 at 102 weeks) correlated with changes in MRIa scores. Higher baseline ASDAS

and CRP values were associated with greater decreases in MRIa scores (ASDAS: r=−0.14, p=0.076 at 24 weeks; r=−0.15, p=0.044 at 102 weeks; CRP: r=−0.25, p=0.002 at 24 weeks; r=−0.31, p<0.001 at 102 weeks). None of the associations described for CRP and ASDAS were consistently present for BASDAI, individual BASDAI questions and patient global (table 1).

Performance of the various response criteria with regard to changes in MRIa

Differences in MRIa change scores between responders and non-responders were greater when subgroups were defined according to the ASDAS response criterion than when subgroups were defined according to the BASDAI or ASAS20 response criteria (table 2). All statistical approaches showed consistent results, with higher absolute values (modulus) for SMD, F-scores, ΔSRM and AUC when responders and non-responders were defined according to the ASDAS response criterion, in comparison with the BASDAI or ASAS20 response criteria. Differences between the various response criteria were small, especially comparing the ASDAS and BASDAI response, but more pronounced at 102 weeks than at 24 weeks (table 2).

DISCUSSION

This study shows that MRIa correlates better with CRP than with other measures of disease activity. MRIa also correlates with ASDAS, a discriminatory instrument for assessing AS disease activity that includes patient-reported outcomes and CRP levels.[2-4] Improvement in MRIa correlated with improvements in CRP and ASDAS, and a greater improvement in spinal inflammation was seen for those with higher CRP or ASDAS values at baseline. The other measures of disease activity, namely BASDAI, individual BASDAI questions and patient global, did not correlate with MRIa.

Our data are supported by recent observations from the MRI substudy of the golimumab trial in AS,[10] in which in the combined active group (75 patients) there was a significant correlation between ASDAS and ASspiMRI-a change scores at week 14 (r=0.35), and between baseline ASDAS and changes in ASspiMRI-a at both week 14 (r=−0.30) and week 104 (r=−0.33). Baseline CRP levels also correlated with baseline ASspiMRI-a (r=0.38) and with changes from baseline to weeks 14 and 104 in ASspiMRI-a (r=−0.30 and −0.33, respectively); moreover, changes from baseline to weeks 14 and 104 in CRP levels significantly correlated with changes in ASspiMRI-a (r=0.45 and 0.38, respectively). Regarding response criteria, the golimumab study only investigated the ASAS20 response, which was not significantly associated with ASspiMRI-a change scores. Similarly to our and previous reports,[11-13] in this study there were no consistent correlations between MRIa and other disease activity measures, namely BASDAI, total

Table 1. Spearman correlation coefficients (and p values) between measures of disease activity and MRIa score

	MRIa score		
	Baseline (n=221)	**Change from baseline to week 24 (n=158)***	**Change from baseline to week 102 (n=179)***
CRP			
Baseline	0.28 (<0.001)	−0.25 (0.002)	−0.31 (<0.001)
Change from baseline to week 24/week 102	NA	0.25 (0.002)	0.32 (<0.001)
ASDAS			
Baseline	0.16 (0.016)	−0.14 (0.076)	−0.15 (0.044)
Change from baseline to week 24/week 102	NA	0.22 (0.006)	0.23 (0.002)
BASDAI			
Baseline	−0.09 (0.174)	0.12 (0.132)	0.14 (0.063)
Change from baseline to week 24/week 102	NA	0.14 (0.090)	0.14 (0.057)
Patient global			
Baseline	−0.02 (0.759)	−0.02 (0.816)	0.02 (0.837)
Change from baseline to week 24/week 102	NA	0.10 (0.196)	0.12 (0.116)
BASDAI Q1—fatigue/tiredness			
Baseline	−0.08 (0.216)	0.08 (0.351)	0.08 (0.289)
Change from baseline to week 24/week 102	NA	0.11 (0.179)	0.18 (0.015)
BASDAI Q2—axial pain			
Baseline	−0.01 (0.877)	−0.02 (0.716)	0.01 (0.892)
Change from baseline to week 24/week 102	NA	0.21 (0.009)	0.18 (0.019)
BASDAI Q3—joint pain/swelling			
Baseline	−0.18 (0.008)	0.17 (0.033)	0.21 (0.004)
Change from baseline to week 24/week 102	NA	0.00 (0.976)	−0.05 (0.518)
BASDAI Q4—discomfort to touch			
Baseline	0.00 (0.983)	0.10 (0.237)	0.02 (0.797)
Change from baseline to week 24/week 102	NA	0.06 (0.436)	0.12 (0.098)
BASDAI Q5—intensity of morning stiffness			
Baseline	−0.08 (0.227)	0.11 (0.179)	0.13 (0.078)
Change from baseline to week 24/week 102	NA	0.10 (0.201)	0.12 (0.099)
BASDAI Q6—duration of morning stiffness			
Baseline	−0.05 (0.490)	0.09 (0.264)	0.10 (0.175)
Change from baseline to week 24/week 102	NA	0.07 (0.380)	0.11 (0.135)
BASDAI Q5/6—morning stiffness (inflammation)			
Baseline	−0.08 (0.262)	0.12 (0.121)	0.14 (0.064)
Change from baseline to week 24/week 102	NA	0.11 (0.171)	0.14 (0.063)

*Data are shown for the all patients at baseline, for changes in the infliximab group at 24 weeks (placebo-controlled phase of the ASSERT trial) and for changes in all patients at 102 weeks (open extension phase of the ASSERT trial); the corresponding follow-up change score in each clinical/laboratory variable was used to calculate the correlation coefficient with MRI change scores.

ASDAS, ankylosing spondylitis disease activity score; ASSERT, AS Study for the Evaluation of Recombinant Infliximab Therapy; BASDAI, Bath ankylosing spondylitis disease activity index; CRP, C-reactive protein; MRIa, MRI activity; NA, not applicable; Q, question.

Table 2. Measures of discrimination and responsiveness for changes in MRIa score according to different types of treatment response

	MRIa score													
	Change from baseline to week 24 (n=158)*							Change from baseline to week 102 (n=179)*						
	Mean (SD)	**Median (IQR)**	**SRM**	**ΔSRM**	**SMD**	**F-score (p value)†**	**AUC (95% CI)**	**Mean (SD)**	**Median (IQR)**	**SRM**	**ΔSRM**	**SMD**	**F-score (p value)†**	**AUC (95% CI)**
ASDAS response‡														
No	−2.3 (4.0)	−1 (−4, 0)	−0.56	–	–	–	–	−2.3 (4.1)	−1 (−5, 0)	−0.57	–	–	–	–
Yes (Δ ≥1.1)	−4.3 (4.8)	−3 (−8, 0)	−0.90	−0.34	−0.45	6.4 (0.012)	0.63 (0.54, 0.72)	−5.0 (5.0)	−4 (−8, −1)	−0.99	−0.42	−0.56	13.8 (<0.001)	0.66 (0.58, 0.75)
BASDAI response‡														
No	−2.6 (4.3)	−1 (−4, 0)	−0.60	–	–	–	–	−3.1 (4.7)	−1 (−5, 0)	−0.66	–	–	–	–
Yes (Δ≥50% and/or Δ≥2)	−4.3 (4.7)	−3 (−8, 0)	−0.91	−0.31	−0.37	5.4 (0.022)	0.61 (0.52, 0.70)	−4.7 (4.9)	−4 (−8, −1)	−0.96	−0.30	−0.32	5.2 (0.023)	0.61 (0.52, 0.70)
ASAS20 response‡														
No	−3.1 (4.7)	−2 (−5, 0)	−0.66	–	–	–	–	−3.2 (4.7)	−2 (−6, 0)	−0.68	–	–	–	–
Yes (ASAS20)	−4.0 (4.6)	−2 (−8, 0)	−0.88	−0.22	−0.19	1.5 (0.221)	0.56 (0.47, 0.65)	−4.6 (4.9)	−3 (−8, −1)	−0.93	−0.25	−0.29	4.8 (0.030)	0.59 (0.49, 0.69)

ASAS20 response criterion is based on four independent domains: spinal pain, physical function measured by the Bath ankylosing spondylitis functional index, patient global assessment and inflammation measured as the mean of the last two BASDAI questions (severity and duration of morning stiffness); ASAS20 treatment response is defined as improvement of 20% or greater and 1 unit or greater (range 0–10) in at least three of the four above domains, and no worsening of 20% or greater and 1 unit or greater in the remaining fourth domain. BASDAI response is defined by at least 50% improvement or absolute improvement of at least 2 units on a 0–10 scale. ASDAS response is defined by an improvement of at least 1.1 units in ASDAS.

*Data are shown for the infliximab group at 24 weeks (placebo-controlled phase of the ASSERT trial) and for all patients at 102 weeks (open extension phase of the ASSERT trial). †Results from analysis of variance on van der Waerden normal scores. ‡Percentage of patients achieving a response at 24 weeks: ASDAS response, 69%; BASDAI response, 64%; ASAS20 response, 61%. Percentage of patients achieving a response at 102 weeks: ASDAS response, 73%; BASDAI response, 70%; ASAS20 response, 68%.

ASSERT, AS Study for the Evaluation of Recombinant Infliximab Therapy; ASDAS, ankylosing spondylitis disease activity score; AUC, area under the receiver operating characteristic curve; BASDAI, Bath ankylosing spondylitis disease activity index; SMD, standardised mean difference; SRM, standardised response mean.

back pain and morning stiffness.

Other previous studies provided conflicting or inconsistent results and were limited by the small numbers of patients, short follow-up time (or cross-sectional nature) and frequently only lumbar spine and/or sacroiliac joint MRI assessment.[14-17] We found weak to moderate correlations between CRP/ASDAS and MRIa scores. Therefore, these clinical and laboratory measures cannot be used to replace MRI assessment of spinal inflammation, which has become an important tool in the diagnosis, management, monitoring and prognosis of patients with axial spondyloarthritis. Nevertheless, in this respect, ASDAS performs better than BASDAI because it is more capable of measuring spinal inflammation and changes in spinal inflammation than BASDAI.

A limitation of our study is that it was a clinical trial cohort involving rather severe and active patients. It would be of interest to investigate these relationships in patients with earlier and less severe disease status or in a mixed cohort of patients. However, we have analysed the largest cohort of patients to date (158–221 patients) and explored a large number of disease activity measures and response criteria. Such a broad and detailed analysis has never been reported. Furthermore, and in contrast to the majority of previous studies,[14-16] we included MRIa assessment of the entire spine; importantly, it has been reported that spinal inflammatory lesions are more frequent in the thoracic spine.[17,18]

In summary, in a large population of AS patients treated with infliximab, baseline levels and improvements in spinal inflammation correlated with baseline levels and improvements in ASDAS and CRP, but not with various other subjective measures of disease activity. By including both CRP and patient-reported outcomes in its formula, ASDAS has the advantage of providing combined information on objective and subjective measures. As a status and response measure ASDAS better reflects the spinal inflammatory disease process in AS than BASDAI. This study strengthens the construct validity of ASDAS and provides further evidence that ASDAS may be a useful tool for monitoring patients with axial spondyloarthritis.

REFERENCES

1. 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.
2. Lukas C, Landewe R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.
3. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–18.
4. Machado P, Landewe R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47–53.
5. 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.
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. Braun J, Baraliakos X, Golder W, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum 2003;48:1126–36.
8. Haibel H, Rudwaleit M, Brandt HC, et al. Adalimumab reduces spinal symptoms in active ankylosing spondylitis: clinical and magnetic resonance imaging results of a fifty-two-week open-label trial. Arthritis Rheum 2006;54:678–81.
9. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
10. Braun J, Baraliakos X, Hermann KG, et al. Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo- controlled GO-RAISE study. Ann Rheum Dis 2012;71:878–84.
11. 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.
12. Sieper J, Baraliakos X, Listing J, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. Rheumatology (Oxford) 2005;44:1525–30.
13. Baraliakos X, Brandt J, Listing J, et al. Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. Arthritis Rheum 2005;53:856–63.
14. Aydin SZ, Bennett A, Emery P, et al. Disease activity assessment by ASDAS doesn't predict sacroiliac inflammation with MRI in axial SpA [abstract]. Arthritis Rheum 2010;62(Suppl. 10):524.
15. Pedersen SJ, Sorensen IJ, Hermann KG, et al. Responsiveness of the Ankylosing Spondylitis Disease Activity Score (ASDAS) and clinical and MRI measures of disease activity in a 1-year follow-up study of patients with axial spondyloarthritis treated with tumour necrosis factor alpha inhibitors. Ann Rheum Dis 2010;69:1065–71.
16. Xu M, Lin Z, Deng X, et al. The Ankylosing Spondylitis Disease Activity Score is a highly discriminatory measure of disease activity and efficacy following tumour necrosis factor-alpha inhibitor therapies in ankylosing spondylitis and undifferentiated spondyloarthropathies in China. Rheumatology (Oxford) 2011;50:1466–72.
17. Konca S, Keskin D, Ciliz D, et al. Spinal inflammation by magnetic resonance imaging in patients with ankylosing spondylitis: association with disease activity and outcome parameters. Rheumatol Int Published Online First: 11 Dec 2011. PMID: 22159818.
18. Baraliakos X, Landewe R, Hermann KG, et al. Inflammation in ankylosing spondylitis: a systematic description of the extent and frequency of acute spinal changes using magnetic resonance imaging. Ann Rheum Dis 2005;64:730–4.