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Follow-up and prognostic value using magnetic resonance imaging in patients with spondyloarthritis treated with biologic agents

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ABSTRACT

Early diagnosis and assessment of the response to treatment in patients suffering from spondyloarthritis have always been challenging due to the lack of imaging techniques able to demonstrate spinal and sacroiliac inflammation.
The last 2 years have seen important advances in the use of magnetic resonance imaging (MRI) for the study of spondyloarthritis. The possibility of quantification of inflammatory lesions using different scoring systems allows not only an early diagnosis, but the assessment of the response to several therapeutic agents, especially those known as "biological therapies."
A number of randomized controlled trials of anti-tumor necrosis factor agents have been published showing regression of inflammatory lesions in MRI. This review discusses briefly the techniques and scoring systems used and all the evidences that exist about assessing treatment in spondyloarthritis.

Monitorización y valor pronóstico por resonancia magnética de los tratamientos biológicos en las espondiloartritis

Palabras clave:
Resonancia magnética
Espondiloartritis
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RESUMEN

El diagnóstico precoz y la respuesta al tratamiento en los pacientes con espondiloartritis han supuesto, desde siempre, un reto dada la escasez de técnicas de imagen que demostrasen, de manera cuantitativa, la inflamación en columna y articulaciones sacroilíacas.
Durante los últimos 2 años se han llevado a cabo importantes avances en el uso de la resonancia magnética (RM) para el estudio de las espondiloartritis. La posibilidad de cuantificar la inflamación que ocurre en estos pacientes mediante la utilización de diferentes sistemas de puntuación permite no sólo llevar a cabo el diagnóstico de forma precoz, sino además valorar la respuesta de los pacientes con espondiloartritis a diferentes agentes terapéuticos, en especial a las nuevas terapias biológicas.
Se han publicado varios ensayos controlados con dichos fármacos que muestran la disminución de las lesiones inflamatorias en RM. Esta revisión se centra, brevemente, en las técnicas y los sistemas de puntuación de RM utilizados, así como en los datos aportados por dichos estudios, que valoran la respuesta al tratamiento con terapias biológicas mediante las imágenes de RM.

Introduction

In the past few years, early diagnosis and evaluation of response to treatment in spondyloarthritis has been undergoing very important changes due to the introduction of magnetic resonance (MR) as an imaging technique in these patients.

Osteomuscular affection in spondyloarthritis can be of 2 types: produced by inflammatory changes and structural changes that follow the former.

Traditionally, in order to diagnose and classify patients with suspected spondyloarthritis, sacroiliac and spinal column joint x-rays have been the first choince. These x-rays allow for the clear detection of structural changes while, in order to detect active inflammation, MR is becoming the technique of choice,[1] after having demonstrated that it can show inflammatory changes at an early stage.[2,3]

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The use of MR has meant an incredible improvement in the evaluation of patients with spondyloarthritis, given its capacity to perform an early diagnosis at an early stage and the possibility it offers of detecting active inflammation (something that cannot be detected in a trustworthy manner using clinical or laboratory data). In addition, it allows for the measurement of spinal inflammation, making MR an ever more present tool used in the design of clinical trials of new therapeutic agents.[4] This review centers on the role that MR can have in the evaluation of response to treatment through biologic therapy in patients with spondyloarthritis.

Technique

Sacroiliac joints are usually studied in MR using a semicoronal plane, oriented through the long axis of the sacral bone. This allows for the visualization of the cartilage component of the joint, which presents a convex form with its apex oriented antero-inferiorly. Occasionally, the sacroiliac joints can be studied in the axial plane, oriented in a perpendicular manner to the transaxial sections described above, allowing to study ligament structures of the postero-superior portion of the joint.

The spine is generally studied in a sagital plane, and can be divided into 2 segments: one, superior, including the cervical spine and the dorsal vertebrae, (generally C1-T10) and the inferior one, which includes the last dorsal vertebrae and the lumbar vertebrae (T10-S2).

Currently there are 4 types of sequences for the study of patients with spondyloarthritis.[5] A T1 potentiated sequence (used to evaluate structural changes and obtain images that serve as an anatomical guide), A T2 FSE sequence with fat suppression, a STIR (*short tau inversion recovery*) sequence or a T1 sequence with fat suppression and the administration of paramagnetic contrast. These last three are the ones that will demonstrate inflammatory changes, either by manifesting bone marrow edema (T2 and STIR) or by showing an increase in vascularization that occurs in areas with inflammation.

Inflammatory findings appear in the form of hyper intense lesions in the T2 and STIR with paramagnetic contrast (Figure 1). The sacroiliac joint affection can be unilateral at the beginning (predominantly on the iliac side of the joint), and then become bilateral and affect the sacral sector.

Signs on the spine are usually located in the cervico-thoracic and thoraco-lumbar transition zones, and affect the vertebral body as well as posterior vertebral elements and even the intervertebral disc.

Figure 1. Inflammatory affection of the spine. Hyperintensity can be seen on the STIR sequence and gadolinium-enhanced T1, affecting multiple vertebral bodies of the thoracic spine.

Scoring system

The development of different systems that, through the use of MR, allow for the quantification of inflammation has been an interesting advance in the study of patients with spondyloarthritis. Thanks to them it is possible to evaluate change in inflammatory activity produced after the administration of determined therapeutic agents.

Currently, there are several systems which have been described for sacroiliac joints, both to evaluate the activity of sacroilitis as for determining the structural abnormalities found.

There are six methods recognized by OMERACT for the evaluation of inflammatory sacroiliac lesions: MISS, Leeds, Aarhus, SPARCC systems, and two initiatives proposed by Sieper-Rudwaleit and Hermann-Bollow.[6] Only the system developed in Aarhus has been published in a complete form, while MISS and SPARCC have appeared in abstract form. The rest remain unpublished. Of all of them, some use contrast (gadolinium) sequences, while other only use STIR sequences. Scores vary from a general form for the whole joint to a detailed joint quadrant score using several scans. Changes in scores through time and the capacity for discrimination of the scoring methods among patients have almost never been nvestigated.[6] Intra-observer agreement was shown to be good or excellent, while between observers it was poor to moderate except in the case of the SPARCC system in which it was very good. In general, all of the observations were based on a limited number of images and readers and were obtained only in centers in which the systems were developed.

To evaluate the activity of the inflammatory process in the spine, 4 methods have been proposed so far: SPARCC, Leeds, Berlín and ASSpiMRI-a (Table).[7,8] Of those, only ASSpiMRI-a uses gadolinium in a standardized form. The Berlin method is based on the ASSpiMRI-a, modified through the elimination of the use of gadolinium and not including erosions as part of the final score of each vertebral unit. These two methods score all of the vertebrae from C2 to S1, while the Leeds system includes only lumbar vertebrae and the SPARCC, only the 6 worse affected discovertebral units. Only the SPARCC and ASSpiMRI-a systems provide data regarding their effectiveness. For both methods, intra and interobserver agreement was good to excellent.[6]

In general, there is little information on reproducibility, effectiveness and sensitivity to change of all of these scoring methods (both in the sacroiliac joints as in the spine). The methods that evaluate inflammatory change seem to be more useful than those that evaluate structural change, and the capacity of MR to detect the latter has even been recently called into question.[6]

Evaluation of response to treatment

Without a doubt, the introduction of what is now referred to as "biologic therapy" in the past years, with drugs that specifically inhibit cytokine pathways (for example, Tumor Necrosis Factor alpha [TNFα] antagonists) has extraordinarily modified the therapeutic management of the spondyloarthritidies.[9] There are threeactive antagonists of TNFα on whom studies have been performed: adalimumab, etanercept, and infliximab, with abundant evidence supporting the effectiveness of these agents in improving signs and symptoms of ankylosing spondylitis.[10–12] In addition, recent data indicates that these drugs can also have disease modifying activity from a structural standpoint as well.[9]

Infliximab has demonstrated to be clinically effective for ankylosing spondylitis.[13]

Baraliakos et al[14] evaluated the radiological progression in the cervical and lumbar spine in patients with ankylosing spondylitis treated with both infliximab as well as conventional therapy. 41 patients from the first clinical randomized trial on the use of

Table
Technical characteristics of the scoring systems evaluating spinal activity

Method	Sequences	Plane	Thickness	Score by	Segments	Degrees	Interval
SPARCC	T1 SE. STIR	Sagital	3–4 mm (12 cuts in total)	Discovertebral unit divided into 4 quadrants	6 units that show more significant alterations in STIR. Evaluate three consecutive scans for each lesion	12 due to the presence of edema in a discovertebral unit; extra points for intensity and depth	0–108
Leeds	T2 SPIR	Sagital		Vertebral body spinous process, interapophiseal joints paraspinal soft tissue	5 lumbar vertebrae	Number of lesions	
Berlin (Sieper-Rudwaleit)	STIR	Sagital	Sagital	Vertebral unit	23 vertebral units (C2/C3-L5/S1)	Bone marrow edema (0-3)	0–69
ASSpiMRI-a	STIR. T1 after gadolinium			Vertebral unit	23 vertebral units (C2-S1)	Bone marrow edema	(0–6)

infliximab in patients with ankylosing spondylitis[15] were compared with 41 patients selected randomly from a German cohort of ankylosing spondylitis (GESIC) who underwent conventional therapy. Cervical and lumbar spine radiographs were obtained and scored using the mSASSS system. In the first measurement, the group taking infliximab had mean disease duration larger than the group on conventional therapy and increased results on the mSASSS score.

Two years later, the mean mSASSS score in the infliximab group had not changed while the other group had considerably worsened. Based on this study, the authors concluded that treatment with infliximab improves the radiographic prognosis in a period of 2 years, compared to conventional therapy. Unfortunately, this study did not provide evidence on the capacity to modify the disease from a structural standpoint, due to differences in disease duration and severity between both groups, as well as its diminished capacity to detect subtle structural changes present on simple x-rays.[9]

In another recent study, 266 patients with active ankylosing spondylitis were randomly assigned to 2 groups, one that received infliximab and the other one that received placebo at weeks 0, 2 and 6 and then every 6 weeks.[16] Baseline characteristics of both groups were similar regarding BASDAI and BASFI. Both groups underwent studies through MR with T1 sequences before and after gadolinium and spinal STIR at weeks 0 and 24. Two readers who were unaware of treatment and the temporal sequence of the images, evaluated them using the ASSpiMRI-a scoring system. In the baseline studies, approximately 80% of patients presented activity in at least one area, demonstrated through MR. After 24 weeks of treatment, the group that received infliximab showed a larger improvement on the ASSpiMRI-a than the placebo group. Patients treated with infliximab showed almost complete resolution of the spinal inflammation.

Sieper et al[16] communicated data from a cohort of 20 patients with active ankylosing spondylitis in whom MR was performed. Of these 20 patients, 9 received infliximab every 6 weeks for 2 years and were compared to 11 patients who received placebo for 3 months and infliximab for the remaining 21 months. All of them were scored by a single reader who was unaware of treatment and temporal sequence, using the ASSPiMRI-a system. At 3 months, there was a reduction in spinal activity in subjects undergoing treatment with infliximab and not so in the placebo group. In the same manner, after 2 years, all of the patients had improved their scores on the ASSpiMRI-a. This study proved that treatment with infliximab improved activity measurements, even when there was evidence that showed a tendency for worsening of chronicity scores. In addition, there was no correlation between the clinical parameters and the MR images, although the statistical power was poor due to the small size of the sample.

Marzo-Ortega et al[17] studied the effects of infliximab infusions compared to placebo sed for 30 weeks in 42 patients with active ankylosing spondyilitis who had received treatment with methotrexate. BASDAI and BASFI scores were similar in both groups at the beginning. MR images of the sacroiliac and spinal joints were obtained at weeks 0 and 30 and scored according to a system previously described.[18] The image readers were unaware of the patients' clinical characteristics. After 30 weeks of treatment, patients with infliximab had a larger resolution of the lesions when compared to those on placebo, even if there were no differences in the number of new lesions in both groups. There was a statistically significant relationship between the degree of improvement in the BASDAI and the number of lesions that were resolved in each patient during treatment.

Etanercept has demonstrated its efficacy for the treatment of ankylosing spondylitis.[18,19] As is the case with infliximab, it has been recently published that it is able to structurally modify the disease.[20] In this study, 19 patients received subcutaneous etanercept twice a week for 48 weeks and 21 patients received a placebo for 6 months followed by etanercept. At baseline, the BASDAI scores were somewhat increased in the etanercept group. MR was performed at the beginning and after 12, 24, and 48 weeks and each patient was scored using the ASSpiMRI-a system. In the group that was treated with etanercept there was a considerable improvement which was also seen in the placebo group once they started treatment with etanercept. Correlation between the changes in BASDAI and ASSpiMRI-a was not significant.

More information on the treatment with etanercept derives from a trial done in 26 patients with ankylosing spondylitis treated with etanercept for 2 years compared to 16 patients receiving placebo.[21] In this case, the mean ASSpiMRI-a score also improved in patients treated with etanercept, as well as the clinical parameters that, alas, did not correlate with improvement of the MR scores. Other studies with smaller series have also shown a tendency to improve aspects such as enthesitis and sacroilitis.[18]

Adalimumab was also shown to be a clinically effective therapeutic agent in patients with ankylosing spondylitis.[12] In a recent study,[22] 15 patients with non-steroidal anti-inflammatory drug resistant ankylosing spondylitis received adalimumab for 52 weeks: MR was performed on the patients and scored using the ASSpiMRI-a system (for the spine) and according to a scoring system proposed by the authors (the sacroiliac joints images). In both cases, the scores were reduced after treatment with adalimumab. However, the sample size was very small and significant differences were observed. Additionally the absence of a control group precludes the possibility of obtaining definite conclusions.

In another study,[3] a baseline MR was performed in 13 patients with ankylosing spondylitis, using the ASSpiMRI-a system. After 6 months of treatment with adalimumab, the MR was repeated. All

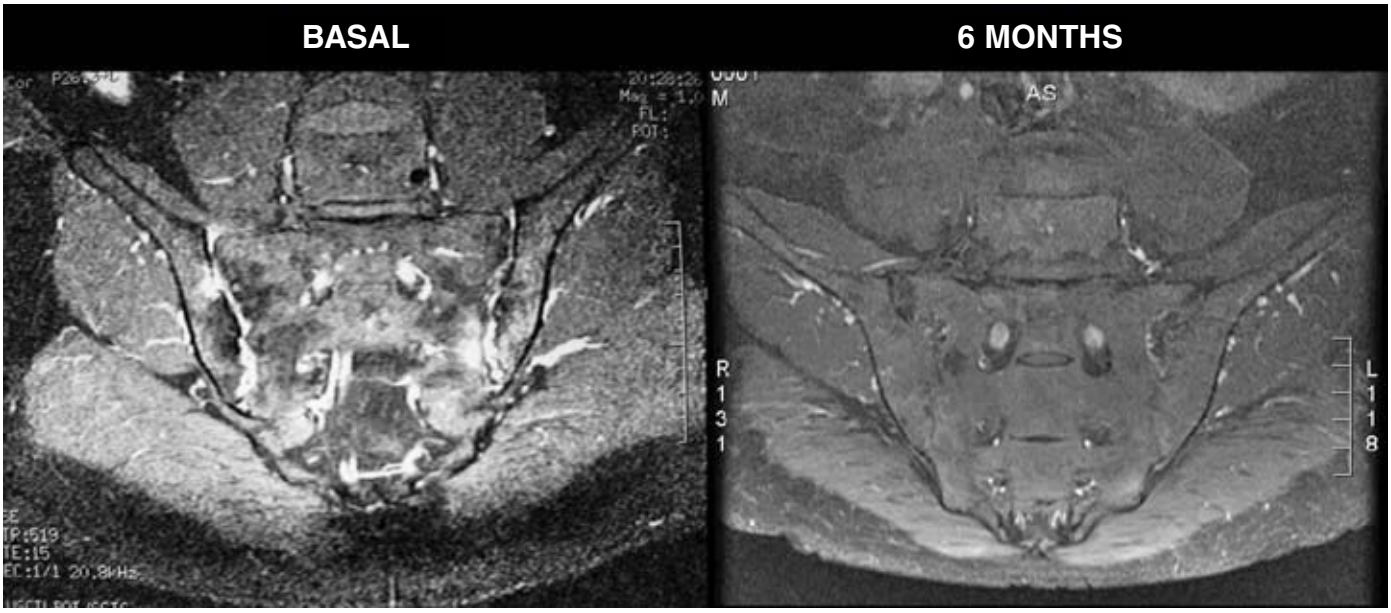

Figure 2. Response to treatment with adalimumab. Bilateral sacroilitis seen in a magnetic resonance image which disappears after 6 months of treatment with adalimumab.

of the patients showed improvement in the ASSpiMRI-a scores and the inflammatory images in the sacroiliac joints (Figure 2).

Prognosis

As has been stated up to this point, MR has shown to be particularly useful for demonstrating the presence of early spondyloarthritis and can predict the development of radiological changes and significant sacroilitis with 2-3 years of anticipation with respect to x-rays.[23] This indicates that MR could be employed for early diagnosis, before developing radiographic changes and could possibly be included in future classification criteria for spondyloarthritis. However, the cost/effectiveness relationship of this technique has not been yet evaluated in this context.[24]

There is very little data that shows a correlation between the inflammatory changes in the MR and the clinical and laboratory data that have been classically used to evaluate the prognosis of spondyloarthritis.[17] The occasional presence, in small quantities, of residual inflammation in the images taken after treatment, as well as the little agreement seen between clinical activity and MR inflammation and the absence of long-term studies that evaluate the progression of the inflammatory lesions and their transformation into structural lesions an ankylosis forces us to be prudent and await for further information to be able to include MR as a method of prognostic value in spondyloarthritis.

Conclusions

MR is a very important advance in the diagnosis of spondyloarthritis. Currently, its larger use lies in its capacity to perform an early diagnosis that saves years in the diagnosis of spondyloarthritis. The capacity of MR for quantifying inflammation is of great help when evaluating response to treatment with biologic therapy; however, it is necessary to perform long-term studies to demonstrate the cost/efficacy relationship of this technique.

References

1. Baraliakos X, Braun J. Magnetic resonance imaging in spondyloarthropathies. Joint Bone Spine. 2006;73:1-3.
2. Braun J, Golder W, Bollow M, Sieper J, van der Heide D. Imaging and scoring in ankylosing spondylitis. Clin Exp Rheumatol. 2002;20:178-84.
3. Martos JM, Carrasco JA, Cano A, Martínez M. Diagnóstico y valoración de la respuesta al tratamiento mediante resonancia magnética en la espondilitis anquilosante. Radiología. 2007;493:177-81.
4. Maksymowych WP, Landewé R. Imaging in ankylosing spondylitis. Best Pract Res Clin Rheumatol. 2006;20:507-19.
5. Zochling J, Baraliakos X, Hermann KG, Braun J. Magnetic resonance imaging in ankylosing spondylitis. Curr Opin Rheumatol. 2007;19:346-52.
6. van der Heijde D, Landewé R, Hermann KGA, Jurik AG, Maksymowych WP, Rudwaleit M. Application of the OMERACT filter to scoring methods for magnetic resonance imaging of the sacroiliac joints and the spine. Recommendations for a research agenda at OMERACT 7. J Rheumatol. 2005;32:2042-7.
7. Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Williams M, Stone M. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis Rheum. 2005;53:703-9.
8. Braun J, Baraliakos X, Golder W, Brandt J, Rudwaleit M, Listing J. MRI examinations of the spine in patients with ankylosing spondylitis, before and alter successful therapy with infliximab. Evaluation of a new scoring system. Arthritis Rheum. 2003;48:1126-36.
9. Manadan AM, James N, Block JA. New therapeutic approaches for spondyloarthritis. Curr Opin Rheumatol. 2007;19:259-64.
10. Brandt J, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J. Succesful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. Arthritis Rheum. 2000;43:1346-52.
11. Brandt J, Khariouzov A, Listing J, Haibel H, Sörensen H, Grassnickel L. Six-month results of a double-blind placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum. 2003;48:1667-75.
12. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J. ATLAS Study Group. 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.
13. Nikas SN, Alamanos Y, Voulgari PV, Pliakou XI, Papadopoulos CG, Drosos AA. Infliximab treatment in ankylosing spondylitis: an observational study. Ann Rheum Dis. 2005;64:940-2.
14. Baraliakos X, Listing J, Rudwaleit M, Brandt J, Sieper J, Braun J. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumor necrosis factor alpha antibody infliximab. Ann Rheum Dis. 2005;64: 1462-6.
15. Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet. 2002;359:1187-93.
16. Sieper J, Baraliakos X, Listing J, Brandt J, Haibel H, Rudwaleit M. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 years of treatment with the anti-tumor necrosis factor infliximab. Rheumatology (Oxford). 2005;44:1525-30.
17. Marzo-Ortega H, McGonagle D, Jarrett S, Haugeberg G, Hensar E, O'Connor P. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis. 2005;64:1568-75.

18. Marzo-Ortega H, McGonagle D, O'Connor P, Emery P. Efficacy of etanercept in the treatment of entheseal patology in resistant spondyloarthropathy: a clinical and magnetic resonance imaging study. Arthritis Rheum. 2001;44:2112-7.
19. Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. Ann Rheum Dis. 2006;65:379-84.
20. Baraliakos X, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum. 2005;52:1216-23.
21. Rudwaleit M, Baraliakos X, Listing J, Brandt J, Sieper J, Braun J. Magnetic resonance imaging of the spine and sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloartrhtis during treatment with etanercept. Ann Rheum Dis. 2005;64:1305-10.
22. Haibel H, Rudwaleit M, Brandt HC, Grozdanovic Z, Listing J, Kupper H. 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.
23. Oostven J, Prevo R, Den Boer J, van de Laar M. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. J Rheumatol. 1999;26:1953-8.
24. Zochling J, Brandt J, Braun J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. Rheumatology (Oxford). 2005;44: 1483-91.