MRI predicts response to anti-TNF in ankylosing spondylitis

Evaluation of: Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J: MRI in predicting a major clinical response to anti-TNF treatment in ankylosing spondylitis. *Ann. Rheum. Dis.* 67(9), 1276–1281 (2008). Ankylosing spondylitis is a common inflammatory arthritis affecting young people that causes significant morbidity and work instability. MRI is increasingly being used in the diagnosis of ankylosing spondylitis and preradiographic ankylosing spondylitis/axial spondyloarthropathy, in disease assessment and in assessment of response to treatment. Anti-TNFs have been demonstrated to elicit a dramatic and sustained response in many patients with ankylosing spondylitis; however, not all patients have a major clinical response (as measured with the Bath Ankylosing Spondylitis Disease Activity Index 50). In addition, the anti-TNF drugs are expensive, have potential side effects and treatment is likely to be long term. Therefore, it is essential to identify predictors of response to anti-TNF in ankylosing spondylitis. Rudwaleit and colleagues are the first to identify the extent of inflammatory lesions on spinal MRI as a predictor of response to anti-TNF. Patients with a high Berlin MRI spinal score (≥11) have an increased likelihood ratio (LR: 6.7) of a major clinical response. In combination with other predictors of response, C-reactive protein levels of 40 mg/l or more and disease duration of more than 10 years give a probability of having a major response to anti-TNF of 99.1%. These findings allow clinical, serological and radiological factors to be used, either individually or in combination, to predict response to anti-TNF.

KEYWORDS: ankylosing spondylitis ■ anti-TNF ■ MRI ■ response to treatment

Alexander N Bennett[1,2] & Paul Emery[1†]

[†]Author for correspondence:
[1]Academic Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, Chapel Allerton Hospital, Chapel Town Road, Leeds LS7 4SA, UK
Tel.: +44 113 392 4884;
Fax: +44 113 392 4991;
p.emery@leeds.ac.uk
[2]Defence Medical Rehabilitation Unit, Headley Court, Surrey, UK

Rudwaleit and colleagues have recently reported on the role of MRI in predicting response to anti-TNF [1]. Ankylosing spondylitis (AS) is the archetypal axial spondyloarthropathy (SpA). SpA occurs in 0.2–1% of the general population and in 5% of chronic back pain sufferers [2]. AS typically affects young patients in the second and third decades of life [3,4], and causes significant morbidity and work instability [5–7].

For a diagnosis of AS to be made, the modified New York criteria must be fulfilled which includes radiographic sacroiliitis [8], and it is well recognized that this often only occurs after many years of symptoms [9,10]. MRI is able to detect sacroiliitis and inflammatory spinal lesions consistent with AS much earlier than conventional radiography. Therefore, MRI is frequently used in AS diagnosis to assess disease activity by quantifying inflammatory lesions in the spine and sacroiliac joints (SIJs), and to assess response to treatment. In addition, owing to the long delay in the development of characteristic and diagnostic radiographic features in AS, MRI is being used to diagnose AS early [11,12].

Until recently, the mainstay of treatment in AS has been NSAIDs and physiotherapy. However, in recent years, new biologic drugs, in particular the anti-TNF drugs, have proven to be extremely efficacious in the symptomatic treatment of AS, both in the short and longer term [13–18] and have revolutionized AS treatment. Anti-TNFs have also been shown to be efficacious in early disease [19,20]. Clinical markers of disease activity including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), C-reactive protein (CRP) and MRI lesion scores have all been shown to improve considerably after anti-TNF therapy [13–15,17,18]. However, although overall treatment response to anti-TNF in AS is very good in general, some patients do fail to respond, and of the responders some respond better than others [21]. Therefore, it is critical, as with any new treatment, but particularly in the case of the very expensive anti-TNF drugs, to identify predictors of response to enable the treatment to be used in the most judicious way. Therefore, this paper by Rudwaleit and colleagues on MRI predicting major clinical response to anti-TNF is a very welcome and important addition to the literature.

Overview

Rudwaleit and colleagues systematically scored MRI scans of the whole spine and SIJs in patients from two previous randomized, controlled trials

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of anti-TNF in AS [13,15]. Of the 99 patients from the two studies, 62 patients had baseline pretreatment MRI available for assessment (spine: n = 46; SIJ: n = 42; both sites: n = 26), as MRI scans were not part of the original protocol. Major clinical response was defined as an improvement by at least 50% of the initial BASDAI 50 after 12 weeks of treatment. Scoring was by the Berlin MRI spine score [22], which has been validated by Outcome Measures in Rheumatology (OMERACT [ON, Canada]) [23–25]. Disease duration and CRP levels were also analyzed as predictors of major clinical response.

The results demonstrated that a major clinical response was associated with a high Berlin MRI spine score of 11 or higher (likelihood ratio [LR]: 6.7), a disease duration of less than 10 years (LR: 4.2) and a CRP of over 40 mg/l (LR: 3.4). A BASDAI 50 response after 12 weeks of therapy with anti-TNF was found in 54.3% of patients (25/46) with MRI scans of the spine. A positive MRI with a score of 1 or more did not differentiate between responders (84%) and nonresponders (62%; p = 0.1). Interestingly, four of 12 patients (33.3%) with negative scans had a major clinical response.

However, the extent of inflammatory lesions in the spine was significantly higher (Berlin spine score: 7.2) in responders compared with nonresponders (2.9; p = 0.04). Univariate analyses revealed the Berlin MRI spine score to be a significant predictor of response, as was disease duration. However, on multivariate analysis with adjustment for disease duration, the strongest possible confounder, the Berlin spine score was not a significant predictor of a major clinical response.

Interestingly, the results also demonstrated that there was no significant correlation between the extent of active inflammatory lesions in the spine and BASDAI, morning stiffness, global pain, patient global (patient visual analogue scale of disease activity), doctor global (doctor visual analogue scale of disease activity), CRP or erythrocyte sedimentation rate, nor with the extent of active lesions in the SIJs.

Critique of paper

In this paper, Rudwaleit and colleagues have addressed an extremely important clinical question that is relevant to all clinicians treating SpA. With the increasing use of anti-TNF drugs and their associated variable response [1,21], high costs and potential (but rare) side effects [16], it is of great importance that predictors of response are identified. MRI is being increasingly used to diagnose axial SpA early [11,12,26–28], and MRI of inflammatory spinal and SIJ lesions have been demonstrated to improve with anti-TNF treatment [15,17,18,29]. Inflammatory SpA lesions on MRI, one of the few objective measures of disease activity in SpA patients, are a logical marker of disease to use as a predictor of response to anti-TNF.

The results of the study demonstrate that extent of MRI lesions in the spine (Berlin Score ≥ 11 [range: 0–69]), CRP of 40 mg/l or more and disease duration of less than 10 years predict response to anti-TNF. The results of the study are interesting and extremely useful, but a few methodological points need to be taken into consideration. The Berlin scoring system [22,30] that is used in the study does not include posterior elements. This may be of significance as two groups recently identified posterior element lesions as being very common in SpA [31,32], and inclusion of posterior element lesions may have altered the study findings significantly. The methods section does not detail any reliability scores for the two named scorers who, as a pair, scoring by consensus, have not previously been published. In addition, details regarding the MRI techniques used and the section of the spine scanned are also lacking from the methods section. The paper implies that all three sections (cervical, thoracic and lumbar) were scanned, but it does not detail if this was in all of the 46 patients with spinal scans. This could be of significance as the thoracic spine is the most common place in the spine to develop lesions in SpA [33], and if this was excluded, again, it could have a significant effect on results.

Rudwaleit and colleagues have already shown that lower BASFI, elevated CRP and shorter disease duration are clinical predictors of a good response [21], and the latter two predictors were confirmed in this study. MRI is a relatively expensive investigation, which is not available to all rheumatologists and patients worldwide. It is not recommended for an MRI scan to be performed before treatment in the Assessment in Ankylosing Spondylitis (ASAS) international consensus statement on the use of anti-TNF in AS [34], and therefore, it is debatable as to what extra information using MRI as a predictor of response gives over disease duration, BASFI and CRP.

The results revealed that 33.3% of patients with normal MRI scans had a major clinical response. This raises the possibility of there being clinically active inflammation that is below the threshold for detection on MRI but is still clinically symptomatic. This could at least partly explain the lack of

correlation between BASDAI, the main clinical tool of disease activity assessment, and the MRI lesion findings.

Also of note is that the significance of the extent of inflammatory spinal lesions by the Berlin score, as a predictor by univariate analysis, was lost once the important cofounder disease duration was adjusted for. This begs the question – is the extent of MRI lesions just a surrogate marker for the duration of disease? In which case, does an expensive MRI scan add any predictive value above and beyond recording and using disease duration as a predictor? The inflammatory lesions in the SIJ were certainly found to be more extensive in earlier disease and, although it was not statistically significant, there was also a tendency for patients with shorter duration of disease to have more active spinal inflammation.

Thanks to excellent work by Rudwaleit and his colleagues, we now have several predictors of response that, in isolation or in combination, provide the clinician with a likelihood or probability of response to treatment at the point of assessment. However, given that as many as 33.3% of patients with normal MRI still have a major clinical response to anti-TNF, is it ethical to deny a patient with active, symptomatic disease as per BASDAI and the visual activity score, but with long duration of disease, a high BASFI, a low CRP and a normal MRI, anti-TNF treatment based on probability, when a 3-month trial of the drug could be given to assess definite response?

Until overwhelming evidence is available as to which patients will not develop a major clinical response as defined by a BASDAI 50 response, patients with active disease should be allowed a 3-month trial of a potential life-changing treatment with the drug to determine this.

However, as Rudwaleit and colleagues have previously advocated [27,30], an approach that combines likelihood ratios of clinical factors for response, to develop an overall probability of response leads to a much more powerful predictive tool. A high Berlin MRI spinal score (≥11) (LR: 6.7) in combination with other predictors of response, such as CRP being 40mg/l or more (LR: 3.4) and disease duration of less than 10 years (LR: 4.2), gives an impressively high probability of a major response to anti-TNF of 99.1%.

In conclusion, Rudwaleit and colleagues have again answered another important question in the management of AS. They have now identified both clinical, serological and radiological predictors of response for a disease of young people that affects their quality of life and work status, and anti-TNF agents that can have dramatic effects on patients' symptoms and employment [5,35,36], but importantly, this is very expensive and treatment is likely to be long term [37]. A combined approach of radiological, clinical and serological predictors of response is extremely useful in identifying SpA patients with a very high likelihood of having a good response to anti-TNF treatment.

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Executive summary

- Rudwaleit and colleagues have demonstrated clearly that MRI is a useful tool for predicting response to anti-TNF in ankylosing spondylitis.
- Ankylosing spondylitis patients with a high Berlin MRI spinal score (≥11) have an increased likelihood ratio (6.7) of having a major clinical response to anti-TNF treatment.
- A high MRI score in combination with other predictors of response, such as a CRP of 40 mg/l or more and disease duration of less than 10 years, gives a probability of having a major response to anti-TNF in ankylosing spondylitis of 99.1%.
- However, ankylosing spondylitis patients with no inflammatory lesions on MRI scan still had a major clinical response to anti-TNF in 33% of cases.
- A combined approach of using radiological, clinical and serological predictors of response is recommended in identifying spondyloarthropathy patients who have a very high likelihood of response to anti-TNF treatment.

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