



Editorial

Anti-TNF therapy in Ankylosing Spondylitis (AS). Is it possible to suspend treatment?

La terapia anti-TNF en la espondilitis anquilosante (EA). ¿Es posible suspender el tratamiento?

Jordi Gratacos Masmitja* and Mireia Moreno Martinez-Losa

Hospital de Sabadell, Institut Universitari UAB, Sabadell, Barcelona, Spain

From the therapeutic point of view, biological therapy (specifically, anti-TNF therapy) has been the most important event in spondyloarthritis treatment in the last decade. In patients with established ankylosing spondylitis (AS) (according to NY 1986 criteria), active and refractory to conventional therapy, anti-TNF therapy achieves a good clinical response. However, only 20%-30% present an excellent response, considering "excellent response" as that defined by the criteria on partial remission established by the Assessment of Spondyloarthritis International Society (ASAS), in which the patient would be apparently asymptomatic.¹⁻³ When anti-TNF therapy is administered to patients with a scarcely developed condition (pre-radiological stage), it is important to highlight that the percentage who manifest an excellent response (ASAS partial remission) is of about 40%-50%, and thus significantly superior to that observed in patients in whom the disease is more established.^{4,5} These data suggest that, as is the case with rheumatoid arthritis (RA), early administration of treatment is essential to obtain a consistent, prolonged response. The new ASAS group classification criteria for axial and peripheral forms could be of great importance in establishing an early diagnosis and treatment that improves the therapeutic expectations of those patients.⁶ However, are these data sufficient to consider the possibility of discarding biological therapy in patients with AS?

From a logical point of view, it could be thought that suspending the treatment systematically for all patients is not an adequate option, given that only 40%-50% of patients in the early stages and 20%-30% in advanced stages present a consistent clinical response (ASAS partial remission). Various studies have analysed the consequences of systematic suspension of treatment on AS patients; the results, independently of which anti-TNF drug was being used and treatment duration, showed clinical reactivation in the short-medium term in up to 75% of cases after 6 months and in over 90% after 12 months.^{7,8} When the factors associated with reactivation were analysed, it

was observed, as expected, that the degree of clinical activity at the time of treatment suspension, especially measured through C-reactive protein (CRP), as well as age and disease evolution time were important factors in the onset of reactivation.⁸ Furthermore, Breban et al⁹ compared treatment with infliximab on-demand versus treatment following the drug specifications on the technical datasheet on patients with active AS. They observed that patients with on-demand treatment presented a significantly lower clinical response (27% vs 7%, ASAS partial remission) compared to the group with regulated treatment, which seemed to discourage the on-demand therapeutic alternative. However, in clinical practice, there are numerous patients with AS who present an excellent clinical response (apparent clinical remission), in whom it is possible to adjust the treatment (reduce doses and/or extend the drug administration period) without this having any repercussions on the good clinical response shown by these patients; in some cases, treatment can even be interrupted for a certain period. When analysing the possible causes of this dissociation between results obtained in therapeutic trials and clinical practice, it is possible to observe that the patients included in these trials were ones with a very evolved disease (the average period of evolution was 14 years), with a considerable degree of disability, and that treatment was systematically suspended, independently of the degree of clinical remission. In this regard, the published data suggests that interrupting treatment in all patients, or even in the majority, with a good clinical response is not an acceptable option. However, this assertion does not rule out the possibility of contemplating the interruption of treatment in patients who present a real clinical remission. Evaluating this alternative is especially interesting considering recent studies showing that the reintroduction of anti-TNF therapy in patients with AS safely achieves levels of therapeutic response similar to those initially observed before the interruption.^{7,10}

Nevertheless, is it possible to define clinical remission in a patient with AS?

There is only one validated definition for remission, although it is partial (ASAS partial remission). Patients who meet these criteria are practically asymptomatic, but these criteria were obtained from the results of five therapeutic trials with NSAIDs, that is, with a drug considered only for symptomatic treatment of the disease. That is

*Corresponding author.

E-mail address: jgratacosmas@gmail.com (J. Gratacos Masmitja).

why objective variables such as RCP or outcome variables were not included, making the definition of true remission more difficult. Clinical remission could be defined as absence of signs and symptoms, as well as absence of disease progression (no functional impairment and no progression of structural damage), all during an acceptable period of time (a minimum of 6 months).¹¹ This definition implies two concepts differing from the ASAS partial remission definition. The first is the concept of progression remission and the second maintains that state for a certain time before considering a remission. However, this concept of remission creates a number of problems in the case of AS: variability in assessing inflammatory activity, irregularity in evaluating manifestations (especially extra-articular ones) and difficulty in predicting structural damage progression.

Subjective variables are generally used in the assessment of inflammatory activity. Objective variables such as CRP or ESR have low sensitivity, especially in axial forms, and they only present a discreet correlation with the other clinical variables used, as well as with outcome variables. Recently the ASAS group has published a new composite index for assessing the inflammatory activity in spondyloarthritis (ASDAS), in which clinical variables and biological variables are combined and weighted.¹² The preliminary data with this new scale are especially good, and levels of activity including remission criteria have already been established.¹³ However, more data are necessary before the effectiveness of this clinical assessment tool can be definitely established for the prediction of structural damage and especially in the definition of the concept of remission.

The assessment of extra-articular manifestations, especially the presence of enthesitis, constitutes a real clinical challenge. Enthesitis is one of the distinctive clinical signs of the spondylitis family; for many investigators, it is also the principal inflammatory lesion in AS. The presence of enthesitis has also been related to activity, as well as to outcome measures that determine the level of patient disability and quality of life, even though its clinical evaluation is controversial and contradictory. There are different clinical assessment scales, such as the MANDEL index, the MASES index, the modified MASES index (which includes the assessment of plantar fasciitis), and the more recent SPARCC index (Canadian Group of Spondylitis Research).¹⁴ There is also the BASDAI scale, which is the main scale in the clinical assessment of these patients. It largely reflects enthesitis activity (especially in its Question 4), but none of these instruments has been accepted by OMERACT (International Consensus Conference on Outcome Measures in Rheumatology) as a definitive instrument for determining enthesitis activity in patients with AS. The OMERACT expert group only considers it necessary to reflect the clinically evident presence of enthesitis or lack thereof, without needing any instrument in its quantification. However, diverse studies have recently defined the inflammatory activity at the enthesitis level from the ultrasound point of view (echo Doppler). Approximately 30% of enthesitis cases confirmed through ultrasound were not accompanied by clinical manifestations and, therefore, were undetectable in routine clinical evaluation.¹⁵ In this regard, a simple clinical evaluation of enthesitis appears to have insufficient sensitivity, which makes establishing real clinical remission more difficult. However, there are no data that allow us to establish the real clinical importance of enthesitis undetectable in ultrasound in the general concept of activity in this disease. From a logical point of view, it could be said that in clinical practice the BASDAI index along with collecting clinically evident enthesitis are probably sufficient, leaving ultrasound for doubtful cases. This is especially true if, in the near future, ultrasound can confirm in clinical practice the reliability of results obtained from different studies.

Finally, predicting the progression of structural damage is even more difficult. A simple ultrasound of the pelvis and spinal column is the method employed to assess structural damage in patients with AS. There are different radiographic assessment scales, although none of them allow predicting the evolution of structural damage;

in fact, the radiographic changes observed are definitive changes that irreversibly worsen structural damage in patients with AS. The recent progress of nuclear magnetic resonance (NMR) allows acute inflammatory lesions to be visualised, and has therefore represented a great advancement in the early diagnosis of spondyloarthritis. However, its use in monitoring and prognosis is still controversial. Maksymowych et al¹⁶ found an association between the acute lesions observed by NMR and the progression of vertebral ankylosis. However, the low sensitivity of NMR in detecting lesions in everyday clinical practice (particularly in the posterior segment of the column) and the apparent dissociation between improvement of the NMR-observed lesions in patients treated with anti-TNF therapy and the progression of vertebral ankylosis^{17,18} have raised doubts about the usefulness of NMR as a tool for predicting outcome measures and, consequently, as an instrument to establish the clinical remission of these patients.

One could conclude that clinical remission in patients with AS following biological treatment should be represented by an absence of signs and symptoms in any location, along with the absence of disease progression during a certain period (approximately 6 months) long enough to establish its persistence over time. The new instruments for assessing disease activity (the Ankylosing Spondylitis Disease Activity Score, ASDAS), the introduction of ultrasound (to assess the enthesitis), and the NMR in some cases can be of great use in establishing the concept of true clinical remission.

To conclude, in my opinion we could say that:

- The systematic interruption of biological treatment in patients with AS is not a recommendable option, not even in patients with a good clinical response, given that it is usually accompanied by a nearly constant clinical reactivation in the short term.
- There is no validated definition of clinical remission in patients with AS. A hypothetical definition of remission in these patients should include the absence of signs and symptoms of the disease in any location, associated with no disease evolution during a period of time sufficient to establish its persistence in time.
- It is possible to consider adjusting the treatment (change of dose and/or period of administration) in patients with AS who have shown clinical remission (as defined previously). Furthermore, treatment could be temporarily interrupted if this clinical remission were to become established. This option is especially interesting, given that the reintroduction of anti-TNF treatment is safe and effective when there is disease recurrence.

References

1. Brandt J, Listing J, Haibel H, Sørensen H, Schwegig A, Rudwaleit M, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. *Rheumatology (Oxford)*. 2005;44:342-8.
2. Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet*. 2002;359:1187-93.
3. Van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, 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.
4. Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum*. 2009;60:946-54.
5. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum*. 2008;58:1981-91.
6. Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2009;68:18-24. Epub 2008 Jul 14.
7. Brandt J, Listing J, Haibel H, Sørensen H, Schwegig A, Rudwaleit M, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. *Rheumatology (Oxford)*. 2005;44:342-8.

8. Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis Res Ther.* 2005;7:R439-44.
9. Breban M, Ravaud P, Claudepierre P, Baron G, Henry YD, Hudry C, et al. Maintenance of infliximab treatment in ankylosing spondylitis: results of a one-year randomized controlled trial comparing systematic versus on-demand treatment. *Arthritis Rheum.* 2008;58:88-97.
10. Baraliakos X, Listing J, Rudwaleit M, Brandt J, Alten R, Burmester G, et al. Safety and efficacy of readministration of infliximab after longterm continuous therapy and withdrawal in patients with ankylosing spondylitis. *J Rheumatol.* 2007;34:510-5. Epub 2007 Feb 1.
11. Zochling J, Braun J. Remission in ankylosing spondylitis. *Clin Exp Rheumatol.* 2006;24(Suppl 43):S88-92.
12. Pedersen SJ, Sørensen IJ, Hermann KG, Madsen OR, Tvede N, Hansen MS, et al. Responsiveness of the Ankylosing Spondylitis Disease Activity Score (ASDAS), and clinical and magnetic resonance imaging measures of disease activity in a 1 year follow-up study of patients with axial spondyloarthritis treated with TNF-alpha inhibitors. *Ann Rheum Dis.* 2009. Epub ahead of print.
13. Van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2009;68:1811-8. Epub ahead of print.
14. Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, et al. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis.* 2009;1:948-53. Epub 2008 Jun 4.
15. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum.* 2003;48:523-33.
16. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Østergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. *Arthritis Rheum.* 2009;60:93-102.
17. Van der Heijde D, Landewé R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum.* 2008;58:1324-31.
18. Van der Heijde D, Salonen D, Weissman BN, Landewé R, Maksymowych WP, Kupper H, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther.* 2009;11:R127. Epub 2009 Aug 24.