Remission and possible discontinuation of biological therapy in axial spondyloarthritis

J. Braun[1], J. Sieper[2]

[1]*Rheumazentrum Ruhrgebiet, Herne, and Ruhr-Universität Bochum, Germany;*
[2]*Dept. of Rheumatology, Campus Benjamin Franklin, Universitätsmedizin Charité, Berlin, Germany.*

Jürgen Braun, MD, Prof.
Joachim Sieper, MD, Prof.

Please address correspondence to:
Prof. Jürgen Braun,
Rheumazentrum Ruhrgebiet,
Landgrafenstraße 15,
44652 Herne, Germany.
E-mail:
j.braun@rheumazentrum-ruhrgebiet.de

Received on August 16, 2013; accepted in revised form on August 22, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 78): S33-S36.

Key words: axial spondyloarthritis, classification, remission, treatment discontinuation

Competing interests: none declared.

ABSTRACT

Remission has not been a major topic in ankylosing spondylitis (AS) in recent years but there is now increasing interest in analogy to rheumatoid arthritis (RA). RA and AS are chronic inflammatory disease with more differences than similarities. New classification criteria for axial spondyloarthritis (axSpA) have recently added patients with so called non-radiographic axSpA to the spectrum, hereby including earlier disease stages without structural changes. Therapeutic strategies include non-steroidal anti-inflammatory agents (NSAIDs) and biologics, mainly anti-TNF agents. Both work rather well for signs and symptoms, and possibly also for structure modification. Discontinuation of anti-TNF agents has been a major topic in RA in the last 2 years. In axSpA there has been less enthusiasm because early reports have been rather discouraging. However, no prospective controlled trials have been performed. This is a clear unmet need which should be addressed in future trials.

Introduction

This review addresses different topics in relation to data concerning anti-TNF therapy in patients with ankylosing spondylitis (AS). This includes the discussion of remission rates, reasons for discontinuation, retention rates, switching, and the influence of clinical parameters on the response to therapy.

There has been recent interest in remission in AS, analogous to an extensive literature concerning remission in rheumatoid arthritis (RA) (1, 2). Both, RA and AS, are chronic inflammatory disease with some similarities, but more differences (3). New classification criteria have recently added to the spectrum of disease that is now named axial spondyloarthritis (axSpA); the subset that has now been added to AS is non-radiographic axSpA, which implies that, in contrast to AS, no structural changes are present on radiographs of the sacroiliac joints (4, 5). In addition criteria for peripheral SpA and SpA in general have been proposed (6).

Remission is not only an indication of successful management of the disease by the rheumatologist, but also a possible reason to discontinue medical therapy or to lower the dosage – an approach that has recently been shown to be efficacious in some patients with moderate RA (7).

Remission

When talking about remission in axSpA, including AS, there is need to first identify the tool used to assess the patient. More than a decade ago, the Assessment of SpondyloArthritis international Society (ASAS) developed improvement criteria and also criteria for what has been called partial remission – a disease state where, on a 0–10 scale the items pain, function, patient global assessment and morning stiffness (as a proxy for inflammation) all have a value of less than or equal to 2 (or, alternatively, ≤20 mm on a VAS between 0 and 100) (8). The most frequently used disease activity measure in AS is currently the BASDAI (9), and the BASDAI cut-off of 4 has been used in the vast majority of clinical trials ever since that measure was applied initially in an anti-TNF clinical trial (10). Until now, no remission criterion has been proposed or applied by using a BASDAI cut-off. The most recently proposed tool for the measurement of disease activity, the ASDAS, which was developed on a data-driven basis, has garnered considerable interest (11). The ASDAS has been designed to differentiate clearly between inactive disease *versus* low, moderate and high disease activity (12).

Thus, tools are available to define partial remission and inactive disease, but clear criteria for remission have yet to be proposed. Nevertheless, most ex-

perts would probably accept that both the ASAS criteria for partial remission and the ASDAS definition of inactive disease are close to what conceptually would be understood when talking about "remission", *i.e.* absence of disease activity.

The major differences between the ASAS partial remission and the ASDAS inactive disease criteria are the following: ASAS partial remission criteria do also include the achievement of good function. Thus, it is difficult for patients with advanced structural damage to meet these criteria even if disease activity parameters such as pain and stiffness have improved substantially.

Function is not included in ASDAS, but C-reactive protein (CRP) is, and has a rather strong weight in the ASDAS formula. Elevated CRP serum levels have not only been shown to nicely predict a major clinical response to TNF-blocker therapy, as was also found in a recent study (13), but they are also predictive of radiographic progression in both the sacroiliac joints (14) and the spine (15). However, it has not yet been shown that such progression can be prevented when the CRP is normalised by a therapeutic intervention. Taken together, the ASDAS inactive disease criterion may well become the preferred one for the definition of remission for patients with axSpA in the future.

In RA, criteria used for remission do leave some space for limited remaining disease activity (16). The advantage of criteria for remission rather than improvement criteria is that they describe an absolute disease status, rather than the percentage of change which depends on the initial value (17).

Partial remission can be achieved in AS by non-steroidal anti-inflammatory agents (NSAIDs) and anti-TNF-α agents. The magnitude of the proportion of responders has varied substantially in the literature. In the original publication for which the data of some NSAID trials had been pooled (8), only a minority of patients met criteria for partial remission after 6 and 12 weeks of therapy. Only a few years later, the introduction of the TNF blockers changed the picture, and partial remission rates between 20–30% were seen in those clinical trials (18, 19). Thereafter it became clear that disease activity, CRP, MRI, and disease duration were relevant items for the prediction of response to anti-TNF therapy (20). Discontinuation of these biological agents has not been successful in several trials after 3 years (21) and after 1 year (22).

It seems clear that very well-selected young patients with a short disease duration respond especially well to anti-TNF treatment (23).

There is only one study in which NSAIDs and anti-TNF agents have been directly compared. In this recent controlled study with axSpA patients, infliximab plus naproxen has been prospectively compared to naproxen alone (24, 25). After 28 weeks, the remission rate was slightly above 60% in the combination group but also about 35% in the naproxen-only group. Higher remission rates have not been reported in any other trial with axSpA patients for both types of drugs.

A retrospective study (13) recently reported remission rates in patients with AS in daily clinical care, reflecting the interest of Italian rheumatologists in long-term follow-up studies (26-29). The demographic measures suggest that the included patients had established disease (mean age 44 years); however, the disease duration of "only" 8 years and the relatively low prevalence of HLA B27 (65%) raise questions about the nature of this group. Remission rates reported after 12 weeks (27% in partial remission) are consistent with trial data, and they were similar for all anti-TNF drugs available in this period of time: infliximab (INF), etanercept (ETN) and adalimumab (ADA).

On follow-up, as expected, patient numbers decreased and the percentage of patients in partial remission increased – this is due to the fact that the patients who do not respond or who do not tolerate the treatment are no longer under care. This phenomenon is also frequently observed in open label extension studies of clinical trials (30, 31). The retrospective study under discussion began with 283 patients, but only 163 patients remained after 7 months – and >50% of these were in partial remission (13). Of interest, the time period for which partial remission was documented was almost 3 years (range 12–57 months), and about 20% of these patients lost this favourable health state after a mean of 12 months. As expected, the probability of obtaining partial remission with other anti-TNF-α agents was not significantly different among the drugs administered in this study.

Retention rates and switching

In this study (13), the overall rate of discontinuation after the first anti-TNF-α agent was almost 20% of which 13% discontinued due to lack or loss of response and 7% due to an adverse event. The rate of partial remission in the patient group starting a second anti-TNF-α drug was slightly above 40%, higher than in most previous studies (32-37). However, the general trend does clearly suggest that switching to another anti-TNF agent is beneficial in a relatively high percentage of patients with AS, although the probability of obtaining partial remission with a second anti-TNF-α agent was significantly lower than with the first anti-TNF-α agent. On the background that the subgroups with the different agents became rather small, patients switching to ETN (n=23) compared to patients remaining on therapy with a monoclonal antibody (n=10) had significantly higher rates of partial remission (56.5% *vs*. 10%). Similar tendencies have been previously reported but no controlled data are available. There are two issues related to the question of switching to another compound: 1) is the response to anti-TNF agents with another mode of action (monoclonal antibodies *vs*. the soluble receptor) superior to the alternative of simply sticking to the same category? and 2) does this have anything to do with the reported potential immunogenicity (38, 39) of these agents? A third possibility can be that a patient is in a different phase of disease of activity and/or has absence of relevant psycho-socio-economic stressors, *e.g.* family or financial issues that interfere with response – human beings and clinical status are not identical over time.

Factors influencing the response to anti-TNF therapy

Most studies concerning prediction of response to anti-TNF therapy have reported that young age, short disease duration, high CRP levels and spinal inflammation detected by magnetic resonance imaging (MRI) predict a favourable or even a major clinical response (17, 40). Also, reaching partial remission early has been recently identified as being predictive of even very long-term outcomes (31).

In the study chosen to be discussed here (13), the probability of obtaining partial remission was significantly lower in patients with enthesitis or psoriasis or low levels of CRP at baseline. While the significance and the influence of CRP as a marker in SpA is quite established (41), the influence of having psoriasis is questionable (42). The predictive value of having enthesitis seems to differ in relation to the measuring tool applied and whether the enthesitis is rather localised (43) or more diffuse, potentially even resembling widespread pain as reported in patients with fibromyalgia (44).

Taken together, in patients with established AS we have seen good remission and retention rates with the TNF blockers, and the response to anti-TNF-therapy and some of the factors that may have an influence on response are well known. A relatively high remission rate in daily clinical practice is reassuring that anti-TNF therapy is effective in these patients with relatively longstanding disease, and we do know that it likely will be better in patients in earlier stages of axSpA (21). The best switching strategy remains to be established, but it may well be that changing the mode of action of the TNF blocker is more beneficial. The potential value of frequent testing for anti-drug antibodies in daily practice remains to be shown. A possible differential effect of the anti-TNF agents (for example, regarding the different dosages used) on the skin of patients with psoriasis and psoriatic arthritis also has not been convincingly demonstrated. In the case of other extra-articular manifestations, such as colitis in IBD and anterior uveitis, the situation in more clear (45)

Finally, psoriasis and enthesitis clearly improve with anti-TNF therapy. By contrast, widespread pain possibly related in part to a coexisting fibromyalgia is likely to respond less well or not at all to therapeutic strategies directed against TNF-α. The most important goal is to obtain and maintain a good response – clearly more important than reduction or discontinuation of anti-TNF agents, as reviewed in this supplement. Nevertheless, there remains hope that very early interventions in SpA may also allow for drug-free remission – at least for limited periods of time in certain patients.

References

1. VAN DER HEIJDE D, KLARESKOG L, LANDEWÉ R *et al*.: Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 3928-39.
2. HØRSLEV-PETERSEN K, HETLAND ML, JUNKER P *et al*.; OPERA STUDY-GROUP: Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial. *Ann Rheum Dis* 2013 Mar 7 [Epub ahead of print].
3. BRAUN J, SIEPER J, PINCUS T: A systematic comparison between rheumatoid arthritis and ankylosing spondylitis: an introduction. *Clin Exp Rheumatol* 2009; 27 (Suppl. 55): S1-2.
4. RUDWALEIT M, LANDEWÉ R, VAN DER HEIJDE D *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009; 68: 770-6.
5. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
6. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011; 70: 25-31.
7. SMOLEN JS, NASH P, DUREZ P *et al*.: Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013 Jan 16 [Epub ahead of print].
8. ANDERSON JJ, BARON G, VAN DER HEIJDE D, FELSON DT, DOUGADOS M: Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001; 44: 1876-86.
9. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
10. BRANDT J, HAIBEL H, CORNELY D *et al*.: Successful treatment of active ankylosing spondylitis with the anti-TNF-α monoclonal antibody infliximab. *Arthritis Rheum* 2000; 43: 1346-52.
11. LUKAS C, LANDEWÉ R, SIEPER J *et al*.; ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY: Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 18-24.
12. VAN DER HEIJDE D, LIE E, KVIEN TK *et al*.; ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY (ASAS): ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 1811-8.
13. SPADARO A, LUBRANO E, MARCHESONI A *et al*.: Remission in ankylosing spondylitis treated with anti-TNF-α drugs: a national multicenter study. *Rheumatology* 2013 July 22 [Epub ahead of print].
14. PODDUBNYY D, RUDWALEIT M, HAIBEL H *et al*.: Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011 Aug; 70: 1369-74.
15. PODDUBNYY D, HAIBEL H, LISTING J *et al*.: Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. *Arthritis Rheum* 2012; 64: 1388-98.
16. WECHALEKAR MD, LESTER S, PROUDMAN SM *et al*.: Active foot synovitis in patients with rheumatoid arthritis: applying clinical criteria for disease activity and remission may result in underestimation of foot joint involvement. *Arthritis Rheum* 2012; 64: 1316-22.
17. DOUGADOS M: Status versus changes, onset of action, and sustainability - how do we define and present these concepts in clinical trial reports in rheumatology ? *Bull NYU Hosp Jt Dis* 2011; 69: 111-5.
18. BRAUN J, BRANDT J, LISTING J *et al*.: Treatment of active ankylosing spondylitis with infliximab – a double-blind placebo controlled multicenter trial. *Lancet* 2002, 359: 1187-93.
19. DAVIS JC JR, VAN DER HEIJDE D, BRAUN J *et al*.; AND THE ENBREL ANKYLOSING SPONDYLITIS STUDY GROUP: Recombinant human TNF receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; 48: 3230-6.
20. RUDWALEIT M, SCHWARZLOSE S, HILGERT ES, LISTING J, BRAUN J, SIEPER J: Magnetic Resonance Imaging (MRI) in predicting a major clinical response to anti-TNF-treatment in ankylosing spondylitis. *Ann Rheum Dis* 2007 Nov 15 [Epub ahead of print].
21. BARALIAKOS X, LISTING J, BRANDT J *et al*.: Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treat-

ment with infliximab. *Arthritis Res Ther*. 2005; 7: R439-44.
22. SONG IH, ALTHOFF CE, HAIBEL H *et al*.: Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. *Ann Rheum Dis* 2012; 71: 1212-5.
23. BARKHAM N, KEEN HI, COATES LC *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.
24. SIEPER J, LENAERTS J, WOLLENHAUPT J *et al*.: Double-blind, placebo-controlled, 28 week trial of efficacy and safety of infliximab plus naproxen versus naproxen alone: results from the infliximab as first-line therapy in patients with early, active axial spondyloarthritis *Arthritis Rheum* 2012; 61 (Suppl.): abstract 1365.
25. SIEPER J, LENAERTS J, WOLLENHAUPT J *et al*.: changes in active inflammatory lesions assessed by MRI: results of the infliximab as first-line therapy in patients with early active axial spondyloarthritis. *Arthritis Rheum* 2012; 61 (Suppl.): abstract 779.
26. CANTINI F, NICCOLI L, BENUCCI M *et al*.: Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. *Arthritis Rheum* 2006; 55: 812-6.
27. CONTI F, CECCARELLI F, MAROCCHI E *et al*.: Switching tumour necrosis factor alpha antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period. *Ann Rheum Dis* 2007; 66: 1393-7.
28. OLIVIERI I, SCARANO E, PADULA A, D'ANGELO S, CANTINI F: Switching tumor necrosis factor alpha inhibitors in HLA-B27-associated severe heel enthesitis. *Arthritis Rheum* 2007; 57: 1572-4.
29. SPADARO A, PUNZI L, MARCHESONI A *et al*.: Switching from infliximab or etanercept to adalimumab in resistant or intolerant patients with spondyloarthritis: a 4-year study. *Rheumatology* (Oxford) 2010; 49: 1107-11.
30. HELDMANN F, BRANDT J, VAN DER HORST-BRUINSMA IE *et al*.: The European Ankylosing Spondylitis Infliximab Cohort (EASIC): a European multicentre study of long term outcomes in patients with ankylosing spondylitis treated with infliximab. *Clin Exp Rheumatol* 2011; 29: 672-80.
31. BARALIAKOS X, LISTING J, FRITZ C *et al*.: Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis after 8 years - early clinical response predicts long-term outcome. *Rheumatology* (Oxford) 2011; 50: 1690-9.
32. COATES LC, CAWKWELL LS, NG NWF *et al*.: Real life experience confirms sustained response to long-term biologics and switching in ankylosing spondylitis. *Rheumatology* 2008; 47: 897-900.
33. DELAUNAY C, FARRENQ V, MARINI-PORTUGAL A, COHEN JD, CHEVALIER X, CLAUDE-PIERRE P: Infliximab to etanercept switch in patients with spondyloarthropathies and psoriatic arthritis: preliminary data. *J Rheumatol* 2005; 32: 2183-5.
34. PRADEEP DJ, KEAT AC, GAFFNEY K, BROOKSBY A, LEEDER J, HARRIS C: Switching anti-TNF therapy in ankylosing spondylitis. *Rheumatology* (Oxford) 2008; 47: 1726-7.
35. LIE E, VAN DER HEIJDE D, UHLIG T *et al*.: Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. *Ann Rheum Dis* 2011; 70: 157-63.
36. PACCOU J, SOLAU-GERVAIS E, HOUVENAGEL E *et al*.: Efficacy in current practice of switching between anti-tumour necrosis factor-α agents in spondyloarthropathies. *Rheumatology* (Oxford) 2011; 50: 714-20.
37. DADOUN S, GERI G, PATERNOTTE S, DOUGADOS M, GOSSEC L: Switching between tumour necrosis factor blockers in spondyloarthritis: a retrospective monocentre study of 222 patients. *Clin Exp Rheumatol* 2011; 29: 1010-3.
38. VINCENT FB, MORAND EF, MURPHY K, MACKAY F, MARIETTE X, MARCELLI C: Antidrug antibodies (ADAb) to TNF-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis* 2013; 72: 165-78.
39. VAN SCHOUWENBURG PA, RISPENS T, WOLBINK GJ: Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* 2013; 9: 164-72.
40. VASTESAEGER N, VAN DER HEIJDE D, INMAN RD *et al*.: *Ann Rheum Dis* 2011; 70: 973-8.
41. BRAUN J, BARALIAKOS X: Spondyloarthropathies: The disease process in axial SpA: what can biomarkers tell us? *Nat Rev Rheumatol* 2011; 8: 8-10.
42. BRAUN J, RUDWALEIT M, KARY S, KRON M, WONG RL, KUPPER H: Clinical manifestations and responsiveness to adalimumab are similar in patients with ankylosing spondylitis with and without concomitant psoriasis. *Rheumatology* (Oxford). 2010; 49: 1578-89.
43. DOUGADOS M, COMBE B, BRAUN J *et al*.: A randomised, multicentre, double-blind, placebo-controlled trial of etanercept in adults with refractory heel enthesitis in spondyloarthritis: the HEEL trial. *Ann Rheum Dis* 2010; 69: 1430-5.
44. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011; 38: 1113-22.
45. BRAUN J, VAN DEN BERG R, BARALIAKOS X *et al*.: 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011; 70: 896-904.