Remission and possible discontinuation of biological therapy in axial spondyloarthritis

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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 spondyloarthritides (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). 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-
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... 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 favorable 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

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