Biologics in the treatment of rheumatoid arthritis and ankylosing spondylitis

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.**ABSTRACT**

There are clear differences in the clinical picture and in the pathogenesis between rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Biologic agents targeting TNF-α are efficacious in both diseases, with some tendency to work even better in spondyloarthritides (SpA) on a clinical basis. However, anti-TNF therapy was shown to inhibit radiographic progression in RA but not in AS. This is probably due to the outstanding difference in pathogenesis: while in RA osteodestructive lesions such as erosions predominate, AS patients will rather develop osteoproliferative changes such as syndesmophytes. There is some evidence that anti-TNF agents may show longterm efficacy and acceptable safety profiles over 5–10 years. There are some differences between the agents.

Whether the recent developments of targeted therapies in RA with agents such as rituximab, abatacept and tocilizumab will also work for AS is unknown at present.

The differences in the clinical picture and in the pathogenesis between rheumatoid arthritis (RA) and ankylosing spondylitis (AS) have been adressed elsewhere in this supplement. With respect to therapeutic strategies, there are also and especially differences in the affected structures: while the synovium is a critical target in RA, it is rather the bone and the entheses in AS. The axial skeleton is the most important musculoskeletal structure in AS, in RA involvement of many joints of the hand and feet is most characteristic.

Clearly, the treatment options for RA and AS have experienced significant changes over the past decade. However, it needs to be stressed that conventional DMARDs and systemic corticosteroids work differently in RA and AS. NSAIDs are first choice in the treatment of AS but only adjuvants in RA. Thus, the efficacy of biologic therapy is relatively more important in the management of AS. First comparisons in registries indicate a better efficacy and retention rates in AS (1, 2). However, a central problem in these comparisons is the different dosage of infliximab in RA (3mg/kg) *vs*. AS (5mg/kg). On the other hand, there is much more information available in RA since many more agents are approved, many more studies have been conducted, and more data are therefore provided.

The importance of TNF-α as a centrally important cytokine in the pathogenesis of RA and AS has been stressed by experimental data showing the down-regulation of IL-1 and other pro-inflammatory cytokines by infliximab in in vitro synovial cell cultures (3), the up-regulation of TNF-α and TNF-α receptors in the rheumatoid synovium (4) and in the sacroiliac joints (5, 6), and the improvement of arthritis by TNF blockers in animal models even in established disease (7, 8).

Subsequently, an initial open-label and later randomized placebo-controlled trial using infliximab as a single agent in RA, demonstrated a significant and substantial improvement of signs and symptoms of rather severely affected patients (9, 10). When other anti-TNF agents such as etanercept and adalimumab were tested in clinical trials in RA patients, it soon became clear that TNF antagonists were especially more effective when combined with the established 'anchor' DMARD methotrexate (11-13). More recently, it was demonstrated that other combinations of biologics with DMARDs are also efficacious in treating RA (14, 15).

Again, the situation is different in AS: DMARDs and specifically methotrexate do not show any, and this includes no additional effect, on axial symptoms of AS patients (16-18). Whether DMARDs, alone or in combination

with biologics are more efficacious in peripheral arthritis is a matter of ongoing discussion.

TNF blockers were shown to inhibit radiographic progression in RA (19, 20). Recent observations in RA patients being treated with infliximab showed a dissociation between the (absent) clinical response and a definite inhibition of radiographic progression, this phenomenon is as yet not completely understood (21).

Again, the situation in AS is completely different. One problem is that there are no placebo controlled trials – therefore, a historical cohort (OASIS) was used for comparisons (22, 23). The other one is that in contrast to RA where osteodestructive changes are seen we are dealing with osteoproliferative changes and new bone formation in AS. Using the radiographic scoring system mSASSS to quantify radiographic structural changes in AS patients treated with TNF blockers no influence on radiographic progression after 2 years and 4 years was observed (24).

The treatment of AS patients with TNF antagonists was first performed in Berlin. Initially infliximab was used (24), later etanercept (26), and finally adalimumab (27) and golimumab (28). After the pilot study (29) a national multicenter investigator driven trial was conducted that demonstrated a significant improvement of disease activity, function, spinal mobility and quality of life in comparison to controls (24), this study was the basis of approval of infliximab for active AS in Europe. All following studies showed the same: a persistent clinical response with an acceptable safety profile (30-32). Similar data with TNF antagonists were obtained in RA (33, 34).

Discontinuation of anti-TNF therapy in an established clinical situation, even in patients in clinical remission, was usually be followed by a flare of the disease (35). However, single patients may stay in remission for longer periods of time (36).

The influence on other disease manifestations of SpA such as uveitis and colitis associated with chronic inflammatory bowel diseases has also been tested, some differences between the agents were reported (37, 38).

Fig. I. A systematic comparison between rheumatoid arthritis and ankylosing spondylitis – therapy with biologics.

	RA established	AS established	RA early	AS/SpA early
Anti-TNF therapy				
Infliximab	+++	+++	+++	+++
Etanercept	+++	+++	+++	ND
Adalimumab	+++	+++	+++	+++
Golimumab	+++	+++		ND
Certolizumab	+++	ND	ND	ND
Anti-B-cell therapy				
Rituximab	++	(+) ?	ND	ND
Ofatumumab	++	ND	ND	ND
Anti-BAFF	+	ND	ND	ND
Anti-T-cell therapy				
Anti-CD 4	+	ND	ND	ND
Abatacept	++	study ongoing	ND	ND
Anti-IL-1 therapy				
Anakinra	+	(-) ?	ND	ND
Anti-IL-6 therapy				
Tocilizumab	+++	ND	+++	ND

TNF antagonists such as adalimumab may even reduce signs and symptoms of patients with active AS with total spinal ankylosis (39). However, it is also clear that older age, longer disease duration, more structural damage and decreased function are associated with poorer responses to anti-TNF therapy (40).

Nevertheless, the other end of the spectrum deserves even more interest.

In RA the importance of early and intensive therapy, tight control and rapid adaptations of therapy if necessary are supported by an number of carefully conducted trials, and this was shown with and without biologics (42-46).

In contrast, in AS the time to diagnosis is still in the range of several years. However, two recent studies have been conducted in early disease (47, 48). The classification and diagnosis of early axial spondyloarthritis has recently been facilitated by validation of a new criteria set that includes MRI and x-rays as important imaging tools and HLA B27 in the absence of that evidence (49). On the basis of the new treatment paradigm of early 'aggressive' therapy, adalimumab and infliximab were effective to reduce clinical and imaging evidence of increased disease activity in patients with early axial spondyloarthritis as determined by MRI (47, 48).

Clinical experience tells that a significant proportion of patients do not respond to TNF antagonists (primary non-response) or efficacy is lost over time (secondary non-response). This is the clinical situation when the question of switching to another TNF blocker or a different biologic comes into place. RA patients who failed one TNF antagonist or even a second one may still be successfully treated with another one (50-52). Similar data have also been obtained in AS patients (53, 54), However, for both diseases placebo-controlled trials are needed before definite conclusions can be drawn.

All three TNF antagonists might exhibit some immunogeneicity. This has been specifically reported for the chimeric antibody infliximab but also for adalimumab, less so for etanercept (55). Therefore, one of the reasons why a combination of TNF antagonists with DMARDs such as methotrexate may be superior with regard to clinical efficacy as compared to monotherapy, could be the suppression of human anti-chimeric or anti-infliximab antibodies (HACAs or AIAs). The overall percentage of patients developing antibodies seems to be rather small. Although combination therapy is of no proven benefit for AS patients, it is of interest whether such antibodies influence clinical efficacy. Indeed, it was recently shown that in AS high levels of serum trough infliximab showed some correlation to the clinical response (56). However, another study reported a highly heterogeneous

responsiveness to anti-TNF treatment among individual AS patients and low or high circulating infliximab concentrations rather failed to explain treatment success or failure (57).

New TNF-α inhibitors have recently been introduced into the treatment of RA: Golimumab, a human anti-TNF monoclonal antibody (58), Certolizumab pegol, a PEGylated tumor necrosis factor inhibitor (59), and furthermore, Tocilizumab, a humanized antibody against the IL-6 receptor (60). Tocilizumab has even worked better than methotrexate in RA when these drugs were compared as monotherapies (61). The latter two have not yet been tested in treatment trials with AS patients. The only non anti-TNF biologic that has been tested in AS to date was anakinra (62,63) which did not work very well.

Similarly, B or T cell targeted therapies, which have been successfully applied in RA patients (64, 65) have not yet been used in trials in AS patients.

With regard to the anti-inflammatory activity, there are no major differences using TNF antagonists in both diseases. There are some signals from the clinical trials that infliximab might be used in AS patients with higher doses as in RA to achieve acceptable clinical responses. Likewise, in both diseases a comparable and acceptable safety profile has been observed even over long treatment periods. Differences might exist regarding the risk of tuberculosis and the appearance of HAMAs and HAQAs especially in patients on monotherapy with the monoclonal anti-TNF antibodies.

Applying early and intensive therapy, tight control and rapid adaptations of therapy are necessary. The treatment goal in AS should be similar as for RA to go for remission of the disease. For RA it was shown, for AS it still seems possible to prevent structural damage if therapy starts early enough.

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