Commentary

Tumor necrosis factor-α blockade in ankylosing spondylitis: a potent but expensive anti-inflammatory treatment or true disease modification?

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Abstract

Blocking tumor necrosis factor-α either with monoclonal antibodies or with soluble receptor constructs has been proven to be effective with an acceptable safety profile in patients with rheumatoid arthritis, and more recently also in the diseases belonging to the spondyloarthropathy concept. Nevertheless multiple questions still remain unresolved especially concerning longer-term treatment. Data from a recent manuscript by Baraliakos and colleagues seem to indicate that at least for the vast majority of ankylosing spondylitis patients treatment with infliximab can not be withdrawn, if one wants to control disease activity in a continuous way. Although still unproven, this might be of crucial importance with regard to structure modification and prevention of ankylosis in this chronic inflammatory disorder.

A few years ago, rheumatologists treating patients with ankylosing spondylitis (AS) had to accept the fact that the only goal of their proposed treatment was to alleviate pain and stiffness. Disease modification, let alone 'cure' of the disease, was an unrealistic endpoint. The advent of so-called 'biological' therapies at the end of the second millennium provoked a therapeutic breakthrough seldom witnessed in the field of rheumatology. Inhibition of tumor necrosis factor-α (TNF-α) proved highly efficacious, with an acceptable safety profile in the chronic treatment of rheumatoid arthritis. Not only did the therapy turn out to alleviate signs and symptoms, but it also improved greatly the quality of life of the patients, and was shown to significantly retard the structural damage that is typical of this chronic inflammatory disorder. In the field of spondyloarthropathies (SpA), a group of diseases that present rheumatologically mainly with spondylitis, pauci-articular peripheral arthritis and enthesopathy, there is conclusive short-term evidence for the efficacy of TNF-α blockade, both with infliximab and etanercept. Nevertheless, several questions remain with regard to the use of these biological therapies in SpA.

First, long-term data on safety and efficacy of these compounds are scarce. More specifically, for infliximab, which has to be given by way of an intermittent intravenous perfusion, we still have no definitive knowledge of the optimal re-treatment strategy (dose and interval), especially with regard to cost-effectiveness.

Second, almost no information is available on the optimal duration of this type of treatment: should it be continued for as long as the patient benefits from the treatment without obvious side effects, or is there a time point after which discontinuation can be safely considered? Should one stop the therapy abruptly or is gradual tapering (either in dose or re-treatment interval) more appropriate? Is 'on-demand' treatment safe and feasible; if so, what should the threshold be before re-treatment can be considered?

Third, do these biological agents hold the promise of true disease modification (meaning retardation or arrest of progressive and irreversible structural damage) or is the treatment merely blocking inflammation efficiently without interfering with the underlying pathophysiological mechanisms that for example lead to ankylosis in AS?

An interesting addition to our knowledge of TNF-α blockade with infliximab in AS has been provided in a recent article by Baraliakos and colleagues [1], who provide preliminary answers to some of the questions raised above. The authors followed a cohort of 42 AS patients who were initially treated in a randomized placebo-controlled trial [2] and afterwards

AS = ankylosing spondylitis; SpA = spondyloarthropathies; TNF = tumor necrosis factor.

received open-label treatment with infliximab. All patients were re-treated with infliximab at a dose of 5 mg/kg body weight every 6 weeks. After completing the third year of continuous treatment, patients gave consent to stop infliximab treatment. They were followed regularly to monitor closely a possible relapse of the disease, in which case they were re-treated. From their experience we can deduce some practical consequences.

Definitive cessation of anti-TNF-α treatment with infliximab was not possible in this patient group. Relapse was observed in 41 of 42 cases: the mean time to relapse was 17.5 weeks. However, re-treatment seemed to be safe and effective (resulting in clinical improvement similar to the state before withdrawal in all patients), giving the opportunity in selected cases to interrupt the treatment. The authors also looked at variables that might be able to predict a longer disease-free interval. AS patients in partial remission as defined by the Assessments in Ankylosing Spondylitis (ASAS) Working Group criteria [3] had a mean time to relapse of 21.3 weeks, whereas patients not in remission experienced on average a relapse after 15.4 weeks. Low levels of C-reactive protein at the time of withdrawal were also associated with longer flare-free periods.

The present data indicate that, at least in most AS patients, continuous treatment with infliximab, and probably also with other TNF-α-blocking agents, remains necessary to control signs and symptoms of this disease in a continuous manner. It might be possible that this conclusion only holds true in the case of long-standing disease and that there remains a specific window of opportunity, probably at an early disease stage, in which this type of immunomodulation might more definitively influence the outcome of the disease. Specific studies will be necessary to address this issue, but undoubtedly this type of exercise will need to be preceded by the development of a consistent case definition of 'early disease'. As long as AS is only classifiable when radiographic sacroiliitis is present at least in stage 2 on both sides, it seems obvious that at that moment irreversible damage has been inflicted, and probably the immune system will have reached a point of chronic stimulation that cannot be switched off by merely blocking one cytokine.

Another interesting point is whether a continuous control of signs and symptoms in the long term translates into true disease modification or prevention of structural damage and ankylosis. Although the data certainly cannot be extrapolated, preliminary evidence suggests that continuous therapy with non-steroidal anti-inflammatory drugs seems to be superior to 'on-demand' treatment in terms of retardation of radiographic progression [4]. This brings us to another difficult question, which is how to define 'disease modification' in AS. One might look at this from three viewpoints: clinical data, radiographic data (either conventional radiographs or newer modalities), and finally data from the evaluation of target tissues such as the synovial membrane.

From a clinical point of view, probably the best available tool reflecting the potential to halt the disease is the evaluation of the axial metrology. Classically, one evaluates the Bath Ankylosing Spondylitis Metrology Index (BASMI) [5] or one of its components. With regard to infliximab, clear improvements in the BASMI have been observed in both open [6,7] and placebo-controlled studies [2], although sometimes the number of patients included in the subgroup of AS was too low to reach statistical significance [8]. Alternatively, one might evaluate the effect of a drug on the consequences of ankylosis and/or destruction by looking at the improvement of a functional index (BASFI) [9], with the caveat, of course, that function is probably only well correlated with structural damage in the later stages of the disease, whereas in the first years inflammation might be the driving force. Invariably, a major improvement in the BASFI has been reported in all studies with infliximab.

Imaging data, especially by conventional radiographs, are considered the 'gold standard' tool for assessing disease modification. However, these data are not yet available. Moreover, with regard to radiological evaluation, there are two important limitations. First, radiographic progression is typically slow in AS, often necessitating an interval of at least 2 years between successive images to permit the detection of a meaningful difference. Second, a comparison with placebo over this period is not realistic, given the impressive short-term clinical results, thus necessitating the use of historical cohorts as a comparison. To overcome these limitations, new imaging modalities such as magnetic resonance imaging have been proposed; however, the question remains whether magnetic resonance imaging provides information on the destruction or repair of the structural tissue rather than on the inflammatory process occurring in the bone tissue and at the site of the enthesis.

Whereas clinical measurements might be relatively insensitive for assessing structure-modifying capacities, and radiological evaluations require longer-term follow-up, it is tempting to hypothesize that the evaluation of biological immuno-modulation by TNF-α blockade might provide additional evidence for a disease-modifying effect in SpA. In this context it should be seen not only as inhibition of bone and cartilage destruction but more broadly as modulation of tissue histology rather than just downregulation of inflammation. The major drawback of histopathological evaluations in AS is that most tissues targeted by the disease are not easily accessible for biopsy sampling (uvea, axial skeleton, sacroiliac joints, and enthesis). With regard to peripheral joint inflammation, the feasibility of repeated synovial biopsy sampling has led to several studies of SpA [10,11]. As well as a significant reduction in the number of macrophages and polymorphonuclear cells in the sublining layer and an impaired expression of vascular cell adhesion molecule-1, suggesting that infliximab acts on synovitis in SpA by reducing the influx of inflammatory cells, there was a

decrease in the hypervascularity typical of SpA and a reduction of the synovial lining hyperplasia, indicating that infliximab also modulates the structural synovial characteristics of the disease. In another study [12], synovial matrix metalloproteinases were significantly downregulated by treatment with infliximab. Because matrix metalloproteinases are involved in neovascularization, matrix degradation, and cartilage and bone destruction, the observed effect might support the concept that TNF-α blockade could influence structural damage in the long term. These and other mechanisms of tissue remodelling might become unique short-term biomarkers that could predict the long-term effect of new treatment modalities on the structural damage in SpA.

Competing interests

The author(s) declare that they have no competing interests.

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