Treatment of active spondyloarthropathy with infliximab, the chimeric monoclonal antibody to tumour necrosis factor α

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The spondyloarthropathies (SpA) are a group of chronic autoimmune disorders of the joint.1 Entities belonging to this group are ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis related to inflammatory bowel diseases such as Crohn’s disease (CD) and ulcerative colitis, and arthritis associated with acute anterior uveitis. Patients who fulfil the European Spondyloarthropathy Study Group (ESSG) classification criteria,2 but who do not belong to one of the subtypes described above are termed undifferentiated spondyloarthropathy.3

This common rheumatic condition has a global prevalence of 0.5–1%, with, however, important racial and geographical differences and a clear male predominance. Juveniles as well as adults can be affected by one of the diseases included in the SpA group. All the diseases in this group have common clinical, radiological, and genetic features. The typical hallmarks of this disease group are sacroilitis, spondylitis, peripheral arthritis, and enthesitis. The spondylitis typically affects the insertion of the collateral ligaments with syndesmophyte formation and the zygapophysial joints. The peripheral arthritis is asymmetrical and mainly affects the legs. The synovitis may be self limiting or chronic with joint destruction. Enthesitis, mostly localised at the Achilles tendon and plantar fascia is also typical for this disease entity.

A specific feature, mostly seen in psoriatic arthritis or inflammatory bowel disease, is dactylitis, where different small joints on one finger or toe are affected. In an important number of cases, subclinical gut inflammation with pathological findings resembling CD can be found, its presence ranging from 25 to 75% depending upon the type of SpA.4 Some of these patients (undifferentiated SpA with histological evidence of chronic gut inflammation) may eventually develop overt CD at a five years’ follow up.5 In repeat ileocolonoscopy studies, clinical remission of articular symptoms was consistently associated with normalisation of gut histology, whereas persistence of locomotor inflammation was usually associated with persistence of gut inflammation.6

Although few studies of SpA have been made, chronic autoimmune arthritis is not a benign disease. Multiple studies on long term outcomes have shown that the quality of life of the patients can be severely compromised. Moreover, several factors are responsible for a high cost to society of patients with chronic arthritis: (a) the chronic intake of drugs; (b) the monitoring of side effects; (c) the need for physiotherapy to try to maintain adequate mobility; (d) the eventual requirement for orthopaedic surgery to correct deformities or replace destroyed joints; and (e) the work disability resulting from the loss of anatomical and functional integrity.

Therapeutic options in patients with SpA are limited. Nearly all patients take non-steroidal anti-inflammatory drugs for control of pain and stiffness. However, their use is sometimes limited by major side effects and drug interactions. The only disease modifying agent that has been shown to be useful for SpA is sulfasalazine: the drug has a proven beneficial effect on gastrointestinal symptoms in inflammatory bowel disease7; although it has also been found to have a favourable effect on articular symptoms in patients with SpA, this effect appears to be modest for peripheral arthritis and enthesitis, and nearly imperceptible for spondylitis.8,9 In patients with PsA, methotrexate has become the most widely used treatment.10 Although cyclosporin has a proven effect on skin disease in psoriasis,11 the only data in PsA come from a one year prospective trial which compared cyclosporin with methotrexate, and showed that both treatments were effective12; however, no double blind, placebo controlled trials were performed with this agent in PsA.

Recently, the use of biological treatments that block tumour necrosis factor α (TNFα) has opened new perspectives for the treatment of patients with SpA. Infliximab (Remicade, Centocor, Malvern PA, USA) is a chimeric anti-TNFα monoclonal IgG1 antibody, neutralising the soluble cytokine as well as blocking the membrane bound cytokine.14 Infliximab has been approved by the health authorities in the United States (FDA) and Europe (EMEA) for treatment of resistant moderate to severe CD and CD with fistulas, and for treatment resistant rheumatoid arthritis (RA), another form of chronic autoimmune arthritis. In both diseases the effect of TNFα blockade with infliximab has been well documented.15–19

However, studies with infliximab in inflammatory bowel disease have not evaluated the effect on associated rheumatological manifestations, such as spondylitis, synovitis, or enthesitis, in patients with concomitant SpA. From a clinical point of view, we observed a fast and significant improvement of articular as well as axial inflammation in four patients with SpA associated with CD treated with infliximab.10 The observations in these patients suggested that refractory joint manifestations in CD might be a potential indication for infliximab.
treatment, and warranted further investigation of the therapeutic potential of TNFα blockade in patients with other subtypes of SpA. Moreover, observations in polyarticular PsA suggested that TNFα blockade had a beneficial effect on articular symptoms and skin disease. Few data exist on the expression of TNFα in joints of patients with SpA; however, in sacroiliac joint biopsy specimens from patients with AS, an abundant TNFα message could be found by in situ hybridisation.

**Pilot studies with infliximab in spondyloarthropathy**

Based on the data described above, a pilot study was set up to evaluate the efficacy of TNFα blockade with infliximab in patients with different subtypes of active SpA; this was an open label study in 21 patients who received a loading dose regimen of three infusions of infliximab (5 mg/kg) at weeks 0, 2, and 6. All patients had longstanding, treatment resistant disease. Active disease was defined by the presence of active synovitis, tendinitis, or dactylitis or significant inflammatory pain of the spine. All the measured variables (global disease activity, peripheral arthritis assessments, axial disease assessments, and skin disease) improved significantly, with most parameters reaching statistical significance already at day 3. During this pilot trial, the beneficial effect was maintained up to day 84 (six weeks after the third infusion). In this study, no significant adverse events were seen. Minor side effects, such as nausea, dizziness, headache, and fatigue, were reported, but none of these caused interruption or discontinuation of the treatment. After the initial loading dose all patients entered into a maintenance regimen protocol consisting of an infusion of 5 mg/kg infliximab every 14 weeks.

This study aimed at determining whether repeated infusions would effectively and safely maintain the observed effect. Of the 21 patients, 19 completed the one year follow up for efficacy; two patients changed to another dosing regimen after week 12 owing to partial lack of efficacy. However, these patients were included in the safety analysis. By giving repeated infusions, a sustained significant decrease of all disease manifestations was seen. Before retreatment, recurrence of symptoms was seen in 3/19 (16%) at week 20, in 13/19 (68%) at week 34, and in 15/19 (79%) at week 48. This may indicate that an interval of 14 weeks is too long to obtain adequate disease control. However, no loss of efficacy was seen after retreatment.

A major concern with TNFα blockade is the occurrence of infections or malignancies. In this one year follow up study 12 infectious episodes were noted: eight patients had an episode of self limiting upper respiratory tract infection, whereas in four patients the infections (one otitis media, one vaginal candidiasis, one tooth abscess, and one pyelonephritis) required antibiotic or antifungal treatment. None of these infections were life threatening, nor did they require admission to hospital. No malignancies were reported.

During the one year follow up 12 patients (57%) developed antinuclear antibodies; in four of these patients (19%) antibodies to double stranded DNA (anti-dsDNA) were detected by the *Crithidia luciliae* assay. However, no lupus-like symptoms were seen. This is consistent with the data in RA, where the incidence of antinuclear antibodies and anti-dsDNA after treatment with infliximab is respectively 53% and 14%.

Simultaneously, successful treatment with infliximab in 11 patients with AS was reported in an open label German study: 10 patients improved significantly, beginning as early as one day after the initial infusion. Benefits persisted for six weeks after the third and final dose. One patient withdrew after the first dose because of skin rash.

**Evaluation of biological end points in patients with spondyloarthropathy treated with infliximab**

With the arrival of new targeted biological treatments, such as TNFα blockade, there is a need to explore, beside the clinical evaluation, specific immunological targets, such as the impact of the treatment on the T cell cytokine profile, and on the synovial inflammation. In the above described pilot study peripheral blood mononuclear cells were obtained in 20 patients with SpA and compared with those of 15 healthy controls and 19 patients with RA. After stimulation with phorbol myristate acetate/ionomycin, the intracellular cytokines interleukin (IL)2, IL4, IL10, and interferon γ (IFNγ) were determined in CD3+ T cells and in CD3+/CD56+ natural killer (NK) T cells by flow cytometry. At baseline the percentage of T cells positive for IFNγ and IL2 was decreased in patients with SpA compared with healthy controls, while IL10 was increased. Treatment with infliximab induced a significant and persistent increase in IFNγ and IL2, resulting in values comparable with those of healthy controls. From these data, it seems that before treatment, patients with SpA have an impaired T helper 1 (Th1) cytokine profile compared with healthy controls and patients with RA. TNFα blockade with infliximab induced restoration of the Th1 cytokines, resulting in a normal cytokine balance.

Over recent years, histopathology of the synovial membrane has become an important tool to address new challenges in autoimmune arthritis. A major breakthrough has been the development of needle arthroscopy. This technique, which can be safely performed in an outpatient setting, allows serial synovial biopsy specimen sampling without altering the synovial features by the procedure itself.

In eight patients with treatment resistant SpA who were treated with infliximab at weeks 0, 2, and 6, synovial biopsy specimens were obtained at weeks 0, 2, and 12. Histological analysis indicated that the synovial lining layer thickness tended to decrease, with a significant reduction of CD55+ synoviocytes at week 12. In the sublining layer, vascularity was reduced at week 12, with a decreased endothelial expression of vascular cell adhesion molecule-1. The number
of neutrophils and CD68+ macrophages in the sublining layer was decreased at weeks 2 and 12, whereas the CD20+ lymphocytes (B cells) and plasma cells were clearly increased. Although these preliminary data need to be confirmed in a larger cohort, they suggest distinct immunomodulatory mechanisms of TNFα blockade in SpA, and confirm the clinical improvement in the peripheral arthritis, seen in these patients.

Comparison of infliximab with placebo in spondyloarthropathy

In view of the substantial improvement seen in open label trials with infliximab in different subtypes of SpA, the paraclinical observations on the T cell cytokine profile and the synovial histology before and after anti-TNFα treatment, and the very limited therapeutic options for patients with severe SpA, further exploration of TNFα blockade with infliximab in patients with active SpA was imperative. Recently, we concluded that the comparison of infliximab with placebo in patients with different subtypes of active SpA (Van den Bosch et al, unpublished data). In this study, carried out at one centre, 40 patients who fulfilled the ESSG criteria and had active disease, were randomly allocated to receive a loading dose regimen (weeks 0, 2, and 6) of 5 mg/kg infliximab (n=20) or placebo (n=20). The primary end points of this study were the improvement of the patient and doctor's assessment of global disease activity on a 100 mm visual analogue scale at week 12 (six weeks after the third infusion). Both variables improved significantly in the infliximab group in comparison with the baseline value; no improvement was seen in the placebo group. As early as week 2, and sustained up to week 12, there was a highly statistically significant difference between the values for these two end points in the infliximab versus the placebo group. Moreover, in most of the other assessments of disease activity (laboratory measures, assessments of specific peripheral and/or axial disease), significant improvements were seen in the infliximab group when compared with the baseline value as well as when compared with placebo. One severe drug related adverse event occurred: a patient developed a diffuse infectious syndrome, with high fever and general malaise, which was found to be disseminated tuberculosis.

Conclusion

These data indicate that TNFα has a prominent role in the pathogenesis and the disease manifestations of SpA, and that blockade of this cytokine is highly effective in reducing signs and symptoms in this disease group. They suggest that, for the first time, there may be an effective therapeutic option for patients with severe SpA. However, the recurrence of tuberculosis seen in one patient treated with infliximab, necessitates strict inclusion criteria. Moreover, longer term experience and follow up are needed to determine the optimal maintenance regimen (dose and interval) and to detect possible long term side effects.


