
Anti-tumour necrosis factor (TNF)- α therapy in undifferentiated spondyloarthropathy

S. Schnarr, J.G. Kuipers, H. Zeidler

Hannover Medical School, Department of Internal Medicine, Division of Rheumatology, University of Hannover, Germany.

Please address correspondence to:

S. Schnarr, MD, Hannover Medical School, Department of Internal Medicine, Division of Rheumatology, Carl-Neuberg-Strasse 1, D-30625 Hannover, Germany. E-mail: schnarr.sebastian@mh-hannover.de

Clin Exp Rheumatol 2002; 20 (Suppl. 28): S126-S129.

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Key words: Undifferentiated spondyloarthropathy, tumour necrosis factor, infliximab, etanercept, adalimumab.

ABSTRACT

The cytokine tumour necrosis factor (TNF)- α plays a major role in the spinal inflammatory process of spondyloarthropathy. In contrast to rheumatoid arthritis, disease modifying antirheumatic drugs have not been proved effective against inflammation and progressive ankylosis. Initial studies on TNF α inhibitors in ankylosing spondylitis are promising and raise the question as to whether early stages of the disease, mostly classified as "undifferentiated spondyloarthropathy" (uSpA), should also be treated with TNF α inhibitors. This article summarizes the preliminary results of 11 uSpA patients in 4 different trials treated with TNF α inhibitors.

Introduction

The concept of spondyloarthropathy, introduced by Moll *et al.* in 1974 (1), puts together several separate diseases which have in common clinical, radiological and genetic features such as inflammation of the spine especially sacroiliitis, peripheral arthritis predominantly of the lower limbs, enthesitis, the association with the MHC class I antigen HLA-B27 and aggregation within families.

Facilitated by this evolving concept and due to the variety of signs and symptoms and the heterogeneity of presentation, severity and disease course, especially in family- and follow-up-studies of patients with early or abortive disease it was recognized that many cases did not fulfil criteria for established diseases such as the modified New York criteria for ankylosing spondylitis (2). Two new sets of criteria, the European Spondyloarthropathy Study Group (ESSG) criteria and the multiple entry criteria diagnosing spondyloarthropathies (AMOR criteria) have been proposed to encompass the whole clinical spectrum of spondyloarthropathies (3, 4). These criteria

offer the advantage to reflect the whole spectrum of spondyloarthropathies: both the well-defined disorders ankylosing spondylitis, reactive arthritis, psoriatic arthritis with involvement of the spine, and ulcerative colitis and Crohn's disease with spondyloarthritis but also the otherwise unclassified spondyloarthropathies which have in common some clinical features however do not fulfil the criteria e.g. for definite AS (5). Although these criteria lack somewhat sensitivity for early or milder forms of the disease they are useful also in daily practice for diagnosis of spondyloarthropathy (6).

Early diagnosis of undifferentiated spondyloarthropathy (uSpA) or generally speaking of patients not fulfilling definite criteria of AS is of considerable relevance to minimize the significant health burden of this disease. Mau *et al.* described that almost 60% of patients originally classified as uSpA will go on to develop ankylosing spondylitis (AS) within a 10-years follow up (7). Furthermore in a recent study on the prognosis of uSpA Sampaio-Barros *et al.* demonstrated that after a 2-years follow-up 10% of the uSpA-patients already had developed AS and that buttock pain and positive HLA-B27 were associated with progression (8). This illustrates, that uSpA is not a distinct entity but may be rather a manifestation of early AS at least in some patients. Effective therapeutic strategies both for relief of symptoms but also for prevention of the development of definite AS is therefore urgently needed in patients with undifferentiated spondyloarthropathy.

Therapeutic options in uSpA

Nonsteroidal anti-inflammatory drugs (NSAID) and physiotherapy are the cornerstones of treatment of axial involvement (9). However NSAID use is sometimes limited by major side effects. Furthermore a considerable per-

centage of patients do need analgesics in addition for control of spinal pain. The only disease-modifying agent that has been demonstrated to be useful in spondyloarthropathies is sulfasalazine, which has a proven beneficial effect on peripheral arthritis but has not been shown to modify signs and symptoms of spinal involvement (10). Until recently there was no DMARD therapy available proved to be effective against spinal inflammation, which is considered to be the underlying cause of progressive ankylosis.

With tumour necrosis factor-(TNF) being present in sacroiliac joint biopsy specimens from AS-patients with active sacroiliitis (11) and the dramatic improvement of spinal inflammation in AS by TNF- α -inhibiting therapy (12) this cytokine has been regarded also a promising target for anti-inflammatory therapy in other spondyloarthropathies. Moreover, uSpA may progress to AS in a considerable percentage, no treatment has been available so far to prevent this progression and currently available therapy is not sufficient to relieve the pain and stiffness in some uSpA patients. Altogether, the evaluation of TNF- α -inhibiting therapy in these patients is therefore urgently needed.

Meanwhile 3 TNF inhibiting drugs are available: infliximab is a chimeric monoclonal IgG-1 antibody capable of neutralizing soluble and membrane-bound TNF. Infliximab is approved by the US food and drug administration (FDA) and by the European Agency for the Evaluation of Medicinal Products (EMA) for the treatment of severe rheumatoid arthritis (RA; in combination with methotrexate) and fistulating forms of Crohn's disease. Etanercept is a fusion molecule of two soluble p75-TNF-receptors and the Fc-domain of IgG-1. In contrast to infliximab, which has to be administered intravenously, etanercept can be injected subcutaneously and is also approved for the treatment of active RA. The third drug, adalimumab (D2E7), is a fully human anti-TNF- α -antibody, which is at present being studied in RA patients. FDA approval is expected in 2003. None of these agents is approved for the treatment of spondyloarthropathies until now.

Published data on TNF α -inhibition in uSpA

The first study on TNF inhibition in spondyloarthropathies including uSpA patients was published in 2000 by van den Bosch *et al.* (13). Twenty-one patients with different subtypes of spondyloarthropathies (AS n = 10, psoriatic arthritis n = 9, uSpA n = 2) received 5 mg/kg infliximab at weeks 0, 2, and 6 in an open pilot study. No DMARDs but low dose corticosteroids (10 mg) and NSAIDs were allowed in stable dosage throughout the study. The 2 patients with uSpA were 39 and 58 years old, both male, and had a disease duration of 3 and 18 years, respectively. Both individuals had peripheral arthritis but no axial night pain or morning stiffness. The authors summarize, that all measured outcome variables (patient's global assessment, number of swollen joints, pain score, and c-reactive protein) significantly improved after the first infusion. The analysis is not shown for the diagnostic subgroups but the authors affirm, that there were no differences in response between the groups. The response was maintained throughout the study for three months. At the 65th annual scientific meeting of the American College of Rheumatology the authors presented the one year follow up data (14): one uSpA patient had to increase the infliximab dosing regimen due to a partial lack of efficacy. The second uSpA patient and 18 patients with other spondyloarthropathies completed the one year follow up with 5 mg/kg given every 14 weeks. The authors conclude that all these patients maintained a significant improvement of all disease manifestations over 12 months. No serious adverse events occurred during the study. Three infection episodes (pyelonephritis, otitis media, tooth abscess) were observed. Minor events were nausea, dizziness, headache, fatigue, diarrhoea, palpitations, burning eyes. Twelve patients (57%) developed antinuclear antibodies, 4 (19%) antibodies against double stranded-DNA within one year, no patient had signs of a lupus-like syndrome.

Later on, the same authors published histologic findings in 8 patients of this

study at baseline, week 2, and week 12 (15). Included was one patient with uSpA but the authors again present only cumulative data. The clinical improvement after 2 weeks was in all patients accompanied by reduced expression of VCAM-1 and diminished neutrophil and macrophage counts. Additionally, histology showed decreased vascularity and normalisation of the thickened synovial lining layers after 12 weeks. Surprisingly, plasma cells and CD20+ B-cells were significantly increased after 12 weeks of TNF- α -inhibition which is contrary to observations in RA patients. These data illustrate, that histologic and immunologic changes are detectable in the synovium of SpA patients corresponding to clinical improvement under TNF blockade. In September 2001 Marzo-Ortega and co-workers published the first descriptive longitudinal study of 10 SpA patients treated with 25 mg etanercept twice weekly for 6 months (16). All patients had active inflammatory back pain and peripheral arthritis (n=7) or enthesitis (n = 9). Seven patients were diagnosed having AS, 2 as enteropathic arthritis, and 1 as uSpA. Sulfasalazine and corticosteroids had to be stopped 4 weeks prior study entry, 4 patients were allowed to maintain a stable dosage of methotrexate. Again, the authors do not show data of individual patients but all clinical outcome parameters (joint counts, lumbar flexion, pain score, enthesiopathy score, Bath ankylosing spondylitis disease activity index [BASDAI] (17), Bath ankylosing spondylitis functional index [BASFI] (18), patient's and physician's global assessment) improved significantly after 6 months. Additionally, MRI scans showed improved or resolved enthesial lesions in 86%, diminished or resolved subchondral edema of the sacroiliac joints in 60%, and improvement of spinal lesions in 100%. Interestingly, the authors point out that the only patient with uSpA and a disease duration of 8 months remained in clinical remission more than 9 months after stopping etanercept which could be an indication for the great potential of TNF- α -inhibition especially in early diseases. No adverse events were seen throughout the

whole study. This study suggests that TNF -inhibition with etanercept is strongly effective and safe in SpA and that clinical improvement can be visualized in many cases by resolving MRI pathology.

In January 2002 Brandt *et al.* were the first to publish 6 patients with severe uSpA treated with infliximab in a dosage of 3 mg/kg (n = 3) and 5 mg/kg (n = 3) at weeks 0, 2, and 6. Mean disease duration was 6.2 years, all patients had inflammatory back pain and peripheral arthritis, 2 patients had enthesitis. Corticosteroids and DMARDs had been withdrawn 6 weeks before study entry. All patients significantly improved concerning disease activity (BASDAI), pain score, and functional index (BASFI). Changes in metrology index [BASMI] (19) and C-reactive protein levels were not statistically significant. Spinal symptoms, peripheral arthritis and enthesitis improved equally. Although the power of the study is limited by the small number of patients, the higher dosage group showed a more substantial improvement of BASDAI, BASFI, and pain score than the low dosage group. Besides one case of uncomplicated diarrhoea no adverse events had been observed. The authors conclude that TNF blockade with infliximab is an efficient and well tolerated treatment of uSpA and that a dosage of 5 mg/kg seems superior to 3 mg/kg.

Recently van den Bosch *et al.* published the first double-blind placebo controlled trial of infliximab in active SpA (20). They included 40 patients randomly assigned to 5 mg/kg infliximab in week 0, 2, and 6 or placebo. Low dose corticosteroids (≤ 10 mg prednisolone per day) and NSAID were allowed throughout the study but DMARDs had to be stopped 4 weeks prior to study entry. The verum group consisted of patients with AS (n = 9) psoriatic arthritis (n = 9) and uSpA (n = 2). The 2 uSpA patients had a disease duration of 2 years each, both had peripheral arthritis and one had axial night pain. Patient's and physician's global assessment, pain score, CRP and ESR levels significantly improved in the infliximab group from week one onwards compared to the placebo group. Peripheral

arthritis assessed by morning stiffness, joint pain, tender and swollen joint count, and axial disease assessed by morning stiffness, spinal pain, BASDAI, BASFI, and Dougados Functional Index (DFI) (21), improved significantly under TNF inhibition until week 12 compared to baseline and all these changes except for the swollen joint count and DFI score were statistically significant compared to the placebo group. The presented data are not split for the diagnostic subgroups so that a detailed analysis of the 2 uSpA patients is not possible. During the study 2 serious adverse events occurred: one patient developed tuberculosis, a second one septic arthritis of a knee joint after needle arthroscopy. Both patients were withdrawn from the trial. The rate of minor adverse events was not statistically significant between the two treatment arms. As supposed from earlier studies this first placebo-controlled trial could confirm the excellent efficacy of infliximab in spondyloarthropathy.

In summary, 11 patients with uSpA have been treated with TNF blocking agents in clinical trials so far. This small number provides partial evidence that TNF inhibition is effective in controlling spinal inflammation, peripheral arthritis and enthesitis even if other DMARD therapies have failed before. As only one patient was followed over one year no statement can be made about long term efficacy. Comparative studies of different TNF-blockers are lacking as well as dosage finding studies. Large placebo controlled trials with long term follow up of patients are needed to investigate if inhibition of proinflammatory cytokines will maintain structural integrity of joints and spine. Presumably, these data will be first available for the treatment of AS. As the diagnostic SpA subgroups did not show significant differences to anti-TNF -treatment so far, these results will pave the way for future treatment of uSpA. Since TNF-inhibition is an expensive therapy it will be a future challenge to identify uSpA subgroups at high risk for functional disability in which early TNF-inhibition may be cost-effective. Talking about the chances of anti-cytokine

therapy one should not disregard potential risks namely infections. In the studies cited above few serious adverse events occurred. However, worldwide over 200 cases of tuberculosis are described under infliximab and, less frequently, under etanercept therapy (<http://www.fda.gov>). Precise precautions according to the manufacturer's instructions should be undertaken to identify patients with latent Tb-infection who are at high risk for reactivation. However, FDA and EMEA affirmed that TNF inhibitors have an excellent risk-benefit relation and hopefully they will prove to be the first real "disease modifying" drugs in the treatment of spondyloarthropathies.

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