Treatment of spondyloarthropathies with antibodies against tumour necrosis factor α: first clinical and laboratory experiences

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Drug treatment of patients with spondyloarthropathies (SpA), especially ankylosing spondylitis (AS) has limited capacity.[1] Pain but not disease activity can be reduced by non-steroidal anti-inflammatory drugs (NSAIDs), in severe cases very high doses are needed.[2] By examination of sacroiliac biopsy specimens we have shown that, in correlation to disease activity assessed by magnetic resonance imaging (MRI), T cells and macrophages[3] and tumour necrosis factor α (TNFα) mRNA[4] and protein (fig1) but no bacterial DNA[5] is present in these joints that are pathognomonically involved in AS.[6] Furthermore, anti-TNFα monoclonal antibodies (mAb) have recently been shown to be efficacious in Crohn's disease[7]—a disease that is strongly linked to AS because more than 60% of AS patients have clinically often silent gut lesions resembling Crohn's colitis.[8] Furthermore, in another chronic inflammatory rheumatic disease, rheumatoid arthritis (RA), anti-TNF treatment has proved efficacious and even seems to prevent joint damage.[9]

TNFα is a cytokine that is mainly produced by monocytes and macrophages and to a lesser degree by T cells. There are two specific receptors, a 55 kDa and a 75 kDa present on many cell types. TNFα mediates inflammatory and immunoregulatory activities. Effects on cells such as lymphocyte activation and fibroblast proliferation, on mediators such as other cytokines like interleukin 1(IL1), IL6 and IL8, chemokines, prostaglandins, metalloproteinases, on the vasculature by promoting angiogenesis and on upregulation of adhesion molecules and transendothelial migration of leucocytes are well described. In in vitro and in animal models TNFα causes fever, pain and cachexy, mobilises calcium from bone and induces apoptosis (for review see Beutler[10]). All theses mechanisms are proinflammatory but, moreover, TNFα has important physiological functions in immune responses against pathogens and may contribute to suppression of autoimmunity and malignancy.[11] Blocking of these functions might lead to undesired side effects.

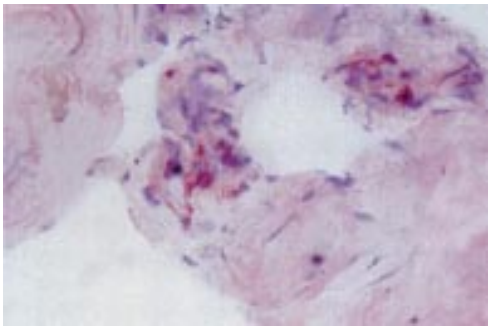

Figure 1 Immunohistological examination of a sacroiliac biopsy specimen obtained by computed tomography guided biopsy of a 23 year old patient with ankylosing spondylitis, four years disease duration, with inflammatory back pain grade 6 on a visual analogue scale (0–10). The red staining indicates a mononuclear cell positive for TNFα (APAAP staining technique).

Infliximab, a chimeric human murine monoclonal anti-TNFα neutralising antibody of IgG1κ isotype (Infliximab, cA2, Remicade, Essex/Centocor), was used for the first time in Berlin[12] and later also in a study from Ghent/Belgium[13] to treat AS patients. There are other agents acting against TNFα such as a TNFα 75 kDa receptor IgG1 fusion protein (Etanercept, Enbrel, Wyeth/Immunex), which proved effective in RA patients who were not sufficiently treated with methotrexate alone.[14] It is unclear whether Etanercept works in Crohn's disease but it seems to work in other SpA (see below).

In the Berlin study, 11 patients who fulfilled the 1984 modified New York criteria for AS were included.[12] All patients were in an acute phase with high disease activity and severe pain quantified by the evaluated outcome parameter Bath AS Disease Activity Index (BASDAI, 15) and a Visual Analogue Scale (VAS) for spinal pain. Patients were included in the study if they had a BASDAI score > 4 plus a VAS score for pain > 4. Ten patients were male, one female, mean age 36 (27–56) years with a median disease duration (date of first symptoms) of 5 (0.5 –13) years. Five patients had relevant radiological changes of the spine with three or more syndesmophytes and/or fusions of vertebrae. Ten patients were HLA B27 positive. The study drug infliximab was infused intravenously in a dose of 5 mg/kg at three time points (week 0, 2 and 6). Disease modifying antirheumatic drugs (DMARDs) and corticosteroids had been withdrawn four weeks before the study started. Patients who were allowed to take NSAIDs had to record the daily dose. The following end points were assessed: the BASDAI, the Bath AS functional index (BASFI), a 10 cm VAS for spinal pain, the Bath AS metrology index (BASMI), quality of life as measured by the short form (SF)36 instrument, C reactive protein (CRP) and IL6 serum levels. Patients returned for follow up assessments every two

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weeks until week 8 and then every four weeks until the final visit at week 24.

The female patient had to be withdrawn from the study eight days after the first infusion because of a generalised rash. The remaining 10 patients experienced dramatic improvement starting already on the first day after the first infusion. The median improvement of BASDAI was 70% after four weeks, 9 of 10 improved > 50%. The immediately occurring effects persisted for more than six weeks after the third infusion in 10 of 11 patients. The median duration of improvement before the BASDAI reached 80% of the pretreatment value was 9.5 weeks after the third infusion (range 3–14 weeks). The first subjective symptoms were reported after a median of six weeks (range 1–14 weeks). One patient, after constantly active disease over two years, is in permanent remission for to date 16 weeks, one had an early relapse three weeks after the third infusion. In the direct comparison between day 0 and day 43 all parameters showed a statistically significant improvement (median of scores and values for day 1, day 28 and 43): BASDAI from 6.5 to 2.8 (p=0.001) and 1.7 (p=0.002); BASFI from 5.3 to 2.0 (p=0.002) and 2.0 (p=0.002); BASMI from 3.0 to 1.0 (p=0.031) and 1.0 (p=0.008); VAS for pain from 7.8 to 2.0 (p=0.002) and 1.3 (p=0.002) and CRP from 15.5 mg/l to normal range (< 6 mg/l) at day 15 (p=0.006) and day 43 (p=0.004) respectively; this was similar for IL6 (median before 12.7 ng/l, 4 and 12 weeks after treatment < 5ng/l; 6 of 11 patients had increased levels).

The quality of life measurements showed clear improvement in physical and also social concepts. Two patients had peripheral arthritis of knee and ankle that disappeared two days after the first infusion. The patients used less than 50% of the NSAID dose taken before; five patients completely stopped taking NSAIDs. After a follow up of 10 months, eight patients are still in the study as two more patients were withdrawn because of significant infusion reactions that were easy to handle but did not permit further treatment with infliximab. To minimise such effects it has to be studied whether methotrexate or azathioprine have to be added to this treatment. Of note, methotrexate is used by a relatively high number of rheumatologists in AS,[16] although there is little evidence that it is efficacious: not a single controlled study has been performed to date.

The actual situation is that the remaining eight patients would like to receive infliximab about every sixth week because they do not want to wait until the symptoms come back. There is no clear indication of a lack of effect so far.

In the first three months, 5 of 11 patients developed uncomplicated infectious episodes and continued the study: two tonsillitis, two sinusitis (all requiring antibiotic treatment) and one herpes labialis. Some weeks later another patient developed diarrhoea and *Salmonella enteritidis* was grown from his stool; antibiotic treatment with ciprofloxacin stopped the symptoms and stool cultures have remained negative thereafter. Taken together, there seems to be a slight increase of infections in patients treated with infliximab in doses > 3 mg/kg. However, there is no indication that this represents a serious concern.

Similarly, in the Belgian study[13] spinal pain in 7 of 11 AS patients improved significantly at two and six weeks after anti-TNFα treatment given as an induction treatment at week 0, 2 and 6; CRP values became normal after treatment. Together 18 SpA patients with peripheral arthritis were treated, mostly successful on a six weeks basis. The AS patients were older and had a longer disease duration compared with the Berlin study.[17]

These open studies suggest that infliximab is efficacious in the treatment of active AS. The results of the study provide some evidence that TNFα blockade is effective in AS; this seems to be true also in other SpAs. In the Belgian study eight patients with psoriasis were treated with infliximab. Peripheral joint and skin symptoms ameliorated significantly after 7 and 14 days. In another open study[18] six patients with severe psoriatic arthritis under treatment with methotrexate (15–25 mg/week) received additional treatment with infliximab. All patients developed quick and persistent improvement of joint and skin symptoms.

A randomised study with Enbrel in addition to methotrexate has been performed in a randomised controlled trial in patients with psoriatic arthritis with a very good efficacy.[19] Thus, blockade of TNFα seems to be also effective in patients with severe psoriatic arthritis.

Undifferentiated spondyloarthropathy (uSpA) is the most or the second most frequent SpA subset.[20 21] It is remarkable that no treatment study dealing with this condition has ever been performed to date. The two uSpA patients of the Belgian study[13] improved similarly to the other SpA. This is in accordance with our experience in three cases with active uSpA. Of note, this included a patient with multilocular enthesitis who significantly improved after infliximab. In conclusion, anti-TNF treament seems to be efficacious also in other SpA subsets with active disease.

There are some interesting effects and partly unexpected findings of anti-TNF treatment on laboratory parameters. Feldmann *et al* measured increased TNFα serum concentrations while both soluble TNF receptor levels remained unchanged or increased. However, measuring serum TNFα is difficult (only 50% of the RA patients treated had increased levels) because the half life is short and the TNF measured in that study was not in its bioactive state,[22] which might indicate that immune complexes of soluble TNF and infliximab were measured.

The changes in the TNFα secretion capacity and in T cell counts after treatment with infliximab in AS patients were recently investigated in our laboratory using FACS technology allowing for intracellular cytokine secretion on a single cell level. Unexpectedly we found an increased TNFα secretion capacity of peripheral blood mononuclear (PBM) cells after

treatment in six patients: the percentage of CD3+ TNFα producers increased from a mean of 5.6% at baseline to 9.9% at week 2 after non-specific stimulation with PMA/Ionomycin; one example is shown in figure 2. Similarly, we found a stronger interferon γ (IFNγ) secretion after infliximab compared with pretreatment values, which, of interest, had been similarly reported in RA.[23] Furthermore we have performed experiments to examine the antigen specific cytokine secretion using the G1 domain of the main proteoglycan, aggrecan, which was reported to induce spondylitis in a mouse model.[24] Also here we found evidence of a rather increased IFNγ secretion after stimulation with recombinant G1 (kindly provided by Y Zhang, Toronto, Canada) after infliximab treatment.

However, the TNF secretion capacity of PB CD4+ and CD8+ T cells was recently reported to be reduced in AS patients and in HLA B27 positive healthy controls as compared with HLA B27 negative normal persons by our group.[25] Further experiments suggested that especially the CD8+ subset of experienced effector cells was found to be reduced in HLA B27+ AS patients. This might well not be a real contradiction because it possibly shows that the cytokine pattern of PBM cells is just the reverse of what is happening in the gut, the synovium or in the joints. Accordingly, in patients with acute enteritis we found the lowest TNF secretion while normal healthy people produced the highest amounts.[26] Thus, low TNF secretion of PB cells might represent active regulatory suppression in order to prevent damage at other sites or it might be attributable to the fact that effector cells had left the previously inflamed sites. Furthermore, there might be an influence of TNF polymorphisms.[25 27–29] However, these findings have been rather controversial and it is unclear how the polymorphisms relate to secretion capacity.

There is also a discrepancy regarding total lymphocyte counts after treatment with infliximab. Paleolog *et al*[30] reported rather an increase of lymphocyte counts but others found a lower count after infliximab in RA patients.[31] In our study (see above) PBMCs of six AS patients were examined before, one and two weeks after a single infusion of 5 mg/kg cA2. Cells were stimulated with PMA/Ionomycin for six hours, Brefeldin A was added and cells were fixed. FACS analysis was performed by staining for surface CD3. The median total lymphocyte count remained largely unchanged (median from 2.2/nl initially to 2.0/nl) and the relative percentage of CD3+ T cells decreased slightly (median from 1.4/nl at baseline to 0.8/nl) at week 2 after treatment, respectively. Taken together, these results indicate rather a decrease of the total number of T cells and an increase of the T cell TNFα secretion capacity after anti-TNFα treatment in AS patients. However, we still know little about the possible influence of anti-TNF treatment on T cells and it remains also unclear whether TNFα surface expression plays a part in AS and in treatment with infliximab. There are some arguments for an influence of infliximab on T cells in Crohn's disease.[32]

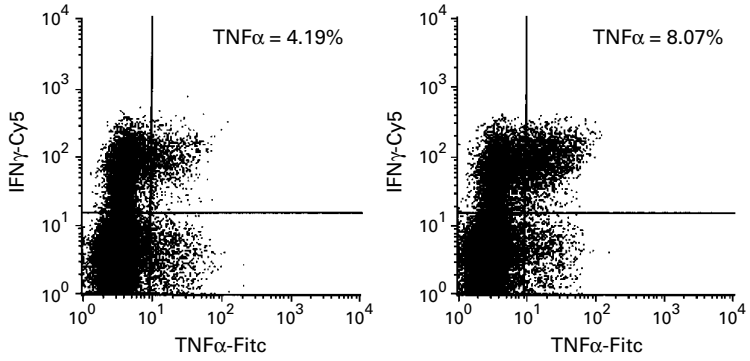

Figure 2 Flow cytometry showing intracellular secretion of TNFα of CD4+ T cells before (left) and one week after treatment with infliximab (right) in a 27 year old patient with ankylosing spondylitis.

On the basis of these discussed results we do not think that a definitive conclusion can be drawn regarding the effect of anti-TNF treatment on a possible TH1/TH2 bias in SpA. In ReA we have reported on a stronger TH2[33] and a weaker TH1 response[34] at the site of inflammation compared with RA and Lyme disease. We have speculated that this cytokine pattern might facilitate bacterial persistence. However, acute ReA has a relatively good prognosis and only 10–20% of the patients, mostly the HLA B27 positive ones, develop ReA over several years. Thus, there are clear differences between the SpA and certainly between different disease stages in SpA. The efficacy of anti-TNF in some severe SpAs certainly argues against a strong systemic TH2 bias in active and severe disease.

Is there an indication for expensive anti-TNF treatment in SpA? Is the course of disease in SpA severe enough to justify costly interventions? There are rapidly progressing severe courses of AS[35] and it is well known that the majority of the burden of disease develops in the first 10 years.[36 37] This would argue for early treatment. However, there is limited knowledge on prognostic factors in SpA.[38] The total burden of disease in AS is incompletely defined but a significant percentage of young AS patients has a chronic recurrent course of disease resulting in significant disability.[39] There is still a significant diagnostic delay of five years and more and there are almost no studies on AS patients with a disease duration of < 10 years. Although studying radiographic progression in AS seems to be difficult,[40] we aim for preventing wide spread spinal ankylosis—an essential factor for disability in AS. Modern imaging techniques such as MRI are promising new tools as activity and outcome parameters in AS.[41] (Figure 3). In the Berlin infliximab pilot study we observed improvement of inflammatory spinal lesions after infliximab in a rather small number of patients.[12] As part of a grant by the German Ministery of Research and Technology (BMFT) we hope to be able to also include evaluation of spinal MRI in a large inception cohort study with several hundred patients[42]

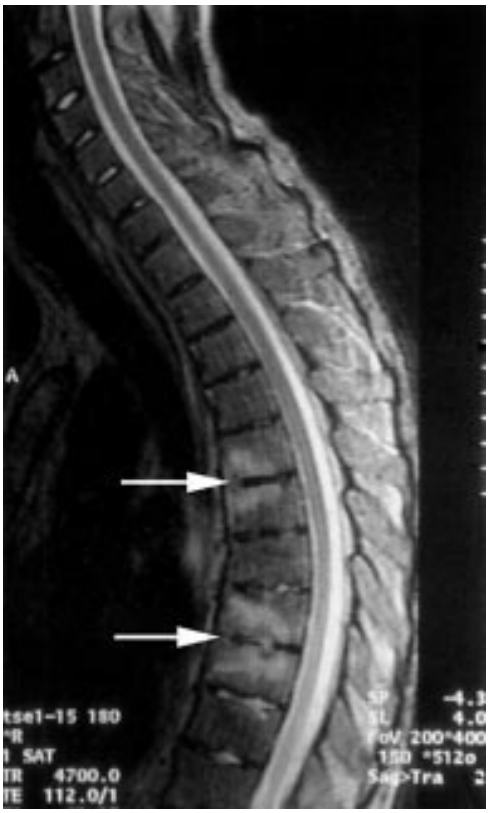

Figure 3 Magnetic resonance imaging (turbo spin echo sequence) of the spine in a 27 year old patient with ankylosing spondylitis, disease duration 12 years, inflammatory back pain grade 5 on a visual analogue scale (0–10), showing severe spondylitis/spondylodiscitis in the thoracic spine at the levels TH 5/6 and TH 8/9.

performed together with other German centres with expertise in SpA.

In summary, treatment directed against TNF*α* seems to work not only in RA and Crohn's disease but also in AS and other SpA. However, controlled trials need to be performed to compare the effects with a standard treatment regimen and demonstrate the advantages. As we do not have significant long term experience we do not know about long term side effects. Because of the high costs of treatment we need to study minimal dose requirements but should also think about the possibility of high dose induction treatment that might be even more effective (20 mg/kg was probably the highest dose ever tried but no more than 10 mg/kg has been used in studies). It is also unclear, whether we have to treat regularly and we have to find out about the optimal intervals? In the randomised controlled trial on AS now planned in Berlin we will treat every sixth week after the induction phase. Initially we should probably treat only very severely affected patients. Later we might also think about very early treatment to interrupt inflammation as soon as possible and prevent cartilage damage to occur.

If the present promising results can be confirmed we have, for the first time, a very effective therapeutic option in severe SpA. This could become a major breakthrough in the treatment of this group of diseases. In AS there might even be hope for prevention of progressive ankylosis by effective suppression of inflammation.

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