EXTENDED REPORT

Repeated infusions of infliximab, a chimeric anti-TNFα monoclonal antibody, in patients with active spondyloarthropathy: one year follow up

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Background: In a pilot study, the anti-tumour necrosis factor α monoclonal antibody, infliximab, induced a rapid and significant improvement in global, peripheral, and axial disease manifestations of patients with active spondyloarthropathy.
Objective: To determine whether repeated infusions of infliximab would effectively and safely maintain the observed effect.
Methods: Safety and efficacy of a maintenance regimen (5 mg/kg infliximab every 14 weeks) was evaluated using the measurements reported in the pilot study. 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, they are still being followed up for safety analysis.
Results: After each re-treatment a sustained significant decrease of all disease manifestations was observed. Before re-treatment, symptoms recurred in 3/19 (16%) at week 20, in 13/19 (68%) at week 34, and in 15/19 (79%) at week 48. No withdrawals due to adverse events occurred. Twelve minor infectious episodes were observed. Twelve patients (57%) developed antinuclear antibodies; in four of them (19%) anti-dsDNA antibodies were detected. However, no lupus-like symptoms occurred.
Conclusion: In this open study of infliximab in patients with active spondyloarthropathy, the significant improvement of all disease manifestations was maintained over a one year follow up period without major adverse events. Although recurrence of symptoms was noted in a rising number of patients before each re-treatment, no loss of efficacy was observed after re-treatment.

The group of spondyloarthropathies (SpA) comprises related chronic autoimmune disorders of the joint with common clinical, radiological, and genetic characteristics.[1] Entities belonging to this group are ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), undifferentiated SpA (uSpA),[2] arthritis associated with inflammatory bowel disease, and acute anterior uveitis. Juveniles as well as adults can be affected by one of the diseases in the group of SpA. This common rheumatic condition has a global prevalence of 0.5–1%, with, however, important racial and geographical differences and a clear male predominance. Quality of life may be severely compromised by pain and loss of anatomical and functional integrity. The actual therapeutic options for the management of the SpA are still limited and often unsatisfactory. Non-steroidal anti-inflammatory drugs and physiotherapy are considered the cornerstone of the treatment of AS.[3 4] Patients with peripheral disease manifestations may benefit from sulfasalazine.[5–7] For PsA, different disease modifying treatments have been suggested to be efficacious, including sulfasalazine,[8] methotrexate,[9 10] and cyclosporin.[11]

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[12] that has been shown to be efficacious in treatment resistant Crohn's disease[13 14] and rheumatoid arthritis (RA).[15 16] We noted a significant improvement in articular as well as axial disease manifestations in four patients with Crohn's disease with associated SpA, treated with infliximab.[17] In patients with poly-articular PsA, a clinically significant benefit with infliximab as well as with other TNFα blocking agents was shown.[18 19] In view of these observations we designed an open label trial with infliximab to investigate the therapeutic potential of TNFα blockade in the different subtypes of SpA.[20] In this pilot study the effect of a loading dose regimen of three infusions of 5 mg/kg infliximab was evaluated over 12 weeks. The treatment induced a rapid and significant improvement in global, peripheral, and axial disease manifestations in all 21 patients, without major side effects. Simultaneously, successful treatment of active AS was also reported in an open label trial of 11 patients.[21] All patients of the initial open label trial[20] were re-treated every 14 weeks with an infusion of 5 mg/kg infliximab. In this paper we report the safety and efficacy of this maintenance regimen.

PATIENTS AND METHODS

Study design

This study was an extension protocol of the initial 12 week pilot study.[20] The study design consisted of an induction regimen of three infusions of infliximab (5 mg/kg) at weeks 0, 2, and 6, followed by a maintenance regimen every 14 weeks with the same dose. The study protocol, the information for the patients, and the consent form were approved by the ethics committee of Ghent University Hospital. All patients enrolled in the trial signed an informed consent form before any study related procedure.

Patient selection criteria

Patients with active SpA, fulfilling the European Spondylarthropathy Study Group criteria for SpA,[22] were enrolled in the

Abbreviations: ANA, antinuclear antibodies; AS, ankylosing spondylitis; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthropathies; TNFα, tumour necrosis factor α; uSpA, undifferentiated spondyloarthropathy; VAS, visual analogue scale

Table 1 Demographic and descriptive characteristics of the study group. Values are given as median and range

	Total (n=21)	AS (n=3)	AS + PA (n=7)	PsA (n=9)	uSpA (n=2)
Age (years)	49 (26–73)	33 (26–65)	44 (28–59)	49 (30–73)	48 (39–58)
Sex (M/F)	17/4	3/0	6/1	6/3	2/0
Disease duration (years)	17 (1–42)	15 (9–40)	17 (10–33)	19 (1–42)	15 (3–28)
Swollen joint count (0–66)	3 (0–12)	0	2 (1–4)	9 (1–12)	9 (8–10)
Axial morning stiffness (min)	–	90 (60–120)	90 (30–240)	–	–
Axial night pain (0–3)	–	3 (2–3)	3 (1–3)	–	–
Sedimentation rate (mm/1st h)	44 (10–101)	26 (10–74)	44 (10–101)	27 (13–51)	60 (29–92)
C reactive protein (mg/l)	46 (7–290)	55 (29–64)	92 (7–290)	34 (7–61)	61 (30–91)
HLA-B27 (+/–)	14/5	3/0	6/1	4/3	1/1

AS, ankylosing spondylitis; AS + PA, ankylosing spondylitis with peripheral arthritis; PsA, psoriatic arthritis; uSpA, undifferentiated spondyloarthropathy.

initial trial. Patients with AS were classified according to the modified New York criteria.[23] Disease modifying drugs were not allowed during the study.

Concurrent drugs

During this extension study, efforts were made to keep the dose and schedule of non-steroidal anti-inflammatory drugs or prednisolone, or both, stable; however, modifications were allowed at the discretion of the treating rheumatologist.

Drug administrations

Infliximab at a dose of 5 mg/kg in 250 ml NaCl 0.9% was prepared by the hospital pharmacy. The total dose was given over a period of at least two hours. Aseptic procedures were used during the preparation and administration of the study drug. Patients were re-treated every 14 weeks (weeks 20, 34, and 48).

Clinical evaluation

Evaluation of efficacy was performed at weeks 20, 22, 28, 34, 36, 42, 48, and 50 using the same measurements as reported in the open pilot study.[20 24–28] In addition, patients were asked at each visit about recurrence of symptoms, including occurrence of night pain, morning stiffness, pain in peripheral joints, or axial pain.

Safety evaluation

During the infusion the patient was monitored for adverse effects, and vital parameters (blood pressure, pulse, temperature) were measured. At each visit patients were asked about side effects, and routine laboratory tests were performed, which consisted of a full blood count with white blood cell differentiation, and biochemical screening, including electrolytes, urea, creatinine, total protein, liver function tests, and urine analysis. Furthermore, screening for antinuclear antibodies (ANA) by indirect immunofluorescence on HEp-2 cells and, when positive, additional testing for anti-double stranded DNA antibodies (anti-dsDNA) by the *Crithidia luciliae* assay test was performed on each visit. ANA and anti-dsDNA were considered positive in a patient when present on at least two occasions.

Statistical analysis

Results were presented as the median and range. Significance of the change from baseline was measured by the Wilcoxon signed ranks test ($p<0.05$).

RESULTS

Table 1 shows the demographic and descriptive characteristics of the 21 patients who were enrolled in the pilot study.[20] Three patients were classified as having AS with only axial involvement, seven with AS and peripheral arthritis, nine with PsA, and two with uSpA. Of the nine patients with PsA, one also fulfilled the modified New York criteria for AS.

Nineteen patients completed the one year follow up for efficacy. Two patients (one patient with PsA, one with uSpA) changed to another dosing regimen with infliximab owing to partial lack of efficacy. One patient with uSpA had a disease flare at week 12 (patient global assessment of disease activity on a 100 mm visual analogue scale (VAS) 73 mm, four swollen joints, C reactive protein (CRP) 217.6 mg/l). After re-treatment with infliximab (5 mg/kg) at week 16, the patient's disease remained stable, but the swollen joint count and the CRP did not improve. Because there was a new relapse at week 20, it was decided to give infliximab monthly (weeks 22, 26, 30, 34, 38, 42, 46, 50). Moreover as this patient had had a partial response to methotrexate, it was decided to add methotrexate to the infliximab regimen. With this regimen the disease symptoms were adequately controlled (at week 52: VAS global patient score 2 mm, four swollen joints, CRP 5.1 mg/l).

The other patient, with polyarticular PsA, had a disease flare at week 16 (VAS global patient score 88 mm, six swollen joints, CRP 49.3 mg/l). After re-treatment with infliximab (5 mg/kg) at week 18 the patient's disease remained stable, but the swollen joint count and CRP did not improve. Because there was a new relapse at week 30, it was decided to give infliximab monthly (weeks 30, 34, 38, 42, 46, 50), which controlled the disease symptoms adequately (at week 52: VAS global patient score 3 mm, three swollen joints, CRP 20.8 mg/l). However, these two patients remained in the follow up for safety evaluation.

Efficacy evaluation

Global (n=19) and peripheral (n=16) assessments were performed at weeks 20, 22, 28, 34, 36, 42, 48, and 50, and were compared with the baseline value. Axial assessments (n=11) were carried out at weeks 20, 34, 48, and 50. Table 2 summarises the results (data for weeks 28 and 42 are not shown). At week 50 a significant decrease ($p\leq0.05$) for all variables was observed, comparable with the effect seen at week 12. When the global assessments were analysed at different times, this significant decrease was maintained for all variables, except for erythrocyte sedimentation rate (ESR) and CRP at week 48, immediately before the third re-treatment, reflecting a trend towards relapse in some patients. A similar trend was noted for morning stiffness of the spine, spinal pain assessed by the patient on a VAS, and the Dougados functional index.

Figure 1 shows the evolution over this one year period for patient global assessment (100 mm VAS), CRP (mg/l), swollen joint count, and spinal pain assessment (100 mm VAS).

When patients were asked about recurrence of symptoms, reflecting a possible disease relapse, 3/19 (16%) patients reported recurrence of symptoms at week 20, 13/19 (68%) reported a relapse at week 34, and 15/19 (79%) reported a relapse at week 48. However, two weeks after each re-treatment, at weeks 22, 36, and 50, none of the 19 patients reported such disease manifestations. The moment of recurrence of symptoms varied, though for most of these patients (3/3 at week 20, 12/13 at week 34, and 12/15 at week 48) symptoms occurred between weeks 10 and 14 after re-treatment. Nevertheless, none of them reported a full relapse comparable with baseline symptoms.

Table 2 Global, peripheral, and axial assessments at baseline, and at weeks 12, 20, 22, 34, 36, 48, and 50

	Baseline	Week 12	Week 20	Week 22	Week 34	Week 36	Week 48	Week 50
Global assessment	(n=21)	(n=21)	(n=19)	(n=19)	(n=19)	(n=18)	(n=19)	(n=19)
Patient global (0–100)	57 (27–100)	10 (1–73)***	10 (0–94)***	6 (0–34)***	24 (1–97)***	5.5 (0–41)***	22 (2–95)*	14 (2–47)***
Patient pain (0–100)	70 (23–100)	10 (1–86)***	14 (1–96)***	8 (1–37)***	29 (1–100)***	7.5 (1–37)***	26 (2–100)*	15 (1–60)***
Doctor global (0–100)	57 (12–79)	10 (5–75)***	14 (1–38)***	14 (1–32)***	20 (1–60)**	10 (5–23)***	21 (7–73)*	12 (4–20)***
ESR (mm/1st h)	44 (10–101)	4 (2–68)***	7 (2–30)***	5 (2–15)***	17 (1–91)**	5 (1–25)***	26 (1–97) NS	6 (1–28)***
CRP (mg/l)	46 (7–290)	6 (0–155)***	6 (0–64)***	3 (0–9)***	22 (0–204)**	2.8 (0–15.5)***	25.7 (0–253.7) NS	3.7 (0–26.7)***
Peripheral assessment	(n=18)	(n=18)	(n=16)	(n=16)	(n=16)	(n=15)	(n=16)	(n=16)
Morning stiffness (min)	90 (10–300)	5 (0–60)***	10 (0–300)**	–	25 (0–120)*	–	25 (0–120)**	7.5 (0–90)***
Pain peripheral joints (0–100)	75 (20–99)	12 (0–84)***	15 (4–31)***	–	28 (0–80)***	–	34 (1–91)*	11.5 (1–34)***
Tender joint count (0–68)	6 (1–18)	0 (0–5)***	1 (0–6)***	0.5 (0–5)***	0.5 (0–8)***	0 (0–4)***	1 (0–12)*	0 (0–4)***
Swollen joint count (0–68)	3.5 (1–12)	0 (0–7)***	0 (0–9)**	0 (0–10)***	0 (0–12)***	0 (0–6)***	0 (0–9)*	0 (0–6)***
Axial assessment	(n=11)	(n=11)	(n=11)		(n=11)		(n=11)	(n=11)
Night pain (0–3)	3 (1–3)	1 (0–1)**	1 (0–2)*	–	1 (0–3)*	–	1 (0–3)*	0 (0–1)**
Morning stiffness (min)	90 (30–240)	5 (0–120)**	12.5 (0–120)**	–	15 (0–120)*	–	60 (0–120) NS	10 (0–200)*
Pain spine (0–100)	57 (4–95)	11 (1–60)**	15.5 (3–62)**	–	17 (0–81)*	–	22 (1–88) NS	10 (1–65)**
BASDAI (0–100)	62.5 (28.8–82.4)	11.3 (1.2–44.0)**	15.9 (1–61.7)**	–	26 (2.8–46.7)**	–	42.1 (2.7–91.6)*	11.2 (3.9–40.3)**
BASFI (0–100)	77.5 (9.9–94.2)	22.3 (1.0–63.2)**	36.8 (1–74.4)**	–	37.9 (4.7–73.7)**	–	45.6 (5.8–75.3)*	17.9 (3.9–63.9)**
Dougados functional index (0–40)	21 (7–31.5)	8.5 (0.5–21.0)**	13.25 (1–26)**	–	12.5 (1.5–23.5)**	–	15 (3.5–24.0) NS	9 (2.5–20.5)*
Spinal pain (0–3)	2 (0–3)	0 (0–2)*	0 (0–3)*	–	0.5 (0–3) NS	–	0 (0–3) NS	0 (0–3)*
BASMI (0–10)	5 (3–9)	5 (1–9)*	4.5 (1–9)*	–	5 (1–8)**	–	5 (1–8)*	4.5 (2–8)*
Occiput to wall (cm)	12 (3.7–21.5)	7.7 (2.5–22.0)**	9 (3.5–21)*	–	8.5 (3.8–21)*	–	8.5 (4–20)*	10 (2.5–20)*
Chest expansion (cm)	1.8 (1.5–3.2)	3.8 (1.7–5.5)**	3.5 (1.7–5.5)**	–	3.2 (1.5–5.6)**	–	4.5 (1.8–5.5)**	4.5 (2.0–6.0)**
Fingers to floor (cm)	24 (5.5–38.0)	15 (0–20.3)**	10.5 (0–33.8)**	–	15.6 (7.2–36.5)**	–	17.5 (0–31)*	17.4 (0–31)*
Dougados articular index (0–30)	6 (1–15)	0 (0–4)**	0.5 (0–4)**	–	2 (0–11)*	–	1.5 (0–8)**	0 (0–4)**

Values are given as median (range). *p≤0.05, **p≤0.01, ***p≤0.001, NS, not significant (determined by Wilcoxon signed ranks test compared with baseline).

All variables (global, peripheral, and axial) were evaluated in the different subgroups—namely, AS, AS with peripheral arthritis, PsA, and uSpA (data not shown). All the subgroups responded in the same way to the maintenance treatment with infliximab.

Severity of psoriatic skin involvement was initially evaluated in eight patients with PsA, using the PASI index. The marked improvement in the PASI score noted throughout the three month study was not maintained over the one year follow up, even though there was a trend at weeks 20 and 34. The evolution of the median score (range) for baseline, weeks 20, 34, 48, and 50, respectively, was as follows: 0.72 (0.12–15.8), 0.10 (0.04–3.62), 0.11 (0.02–2.56), 1.79 (0.02–4.80), and 0.92 (0.00–2.4).

Safety evaluation and adverse drug reactions

No patients were withdrawn from the study owing to adverse events. Infliximab infusions were well tolerated. During the one year follow up one mild self limiting, infusion related adverse event was observed. Nineteen of the 21 patients had an adverse event. Minor events comprised nausea (n=3), dizziness (n=2), headache (n=2), fatigue (n=3), palpitations (n=1), and transient epigastric pain (n=3). One patient with PsA developed eczema of hands and feet. Another patient had an episode of erosive lichen of the mouth mucosa, which disappeared after local treatment. In total, 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 antimycotic treatment. None of these infections were life threatening, nor did they require admission to hospital. No malignancies were reported. Laboratory tests performed at week 50 indicated a significant increase in serum aspartate aminotransferase (median score at baseline 17 U/l (range 12–36), median score at week 50, 28 U/l (range 13–53), $p<0.001$) and serum alanine aminotransferase (median score at baseline 21 U/l (range 7–55), median score at week 50, 35 U/l (range 12–83), $p\leq0.001$), but these median values were still in the normal range. Moreover, these laboratory findings were not clinically significant. A significant increase in haemoglobin was found at week 50 (median score at baseline 132 g/l (range 101–159), median score at week 50, 148 g/l (range 133–161), $p\leq0.001$) compared with baseline. Initially, nine (42%) patients had a normocytic normochromic anaemia; however, after one year's maintenance treatment the haemoglobin level and packed cell volume had normalised in all patients.

During the one year follow up 12/21 (57%) patients developed ANA; in four of these patients (19%) anti-dsDNA were detected. However, no abnormalities in peripheral blood count or complement nor any symptoms suggestive for lupus-like syndromes occurred.

DISCUSSION

In this study we report the safety and efficacy of a maintenance regimen of 5 mg/kg infliximab every 14 weeks in patients with active SpA. The patients included in this extension protocol were initially treated with three infusions of infliximab in a 12 week open label pilot study[20]: after this loading dose regimen, a rapid and significant improvement in global, peripheral, and axial disease manifestations was seen, without major side effects.

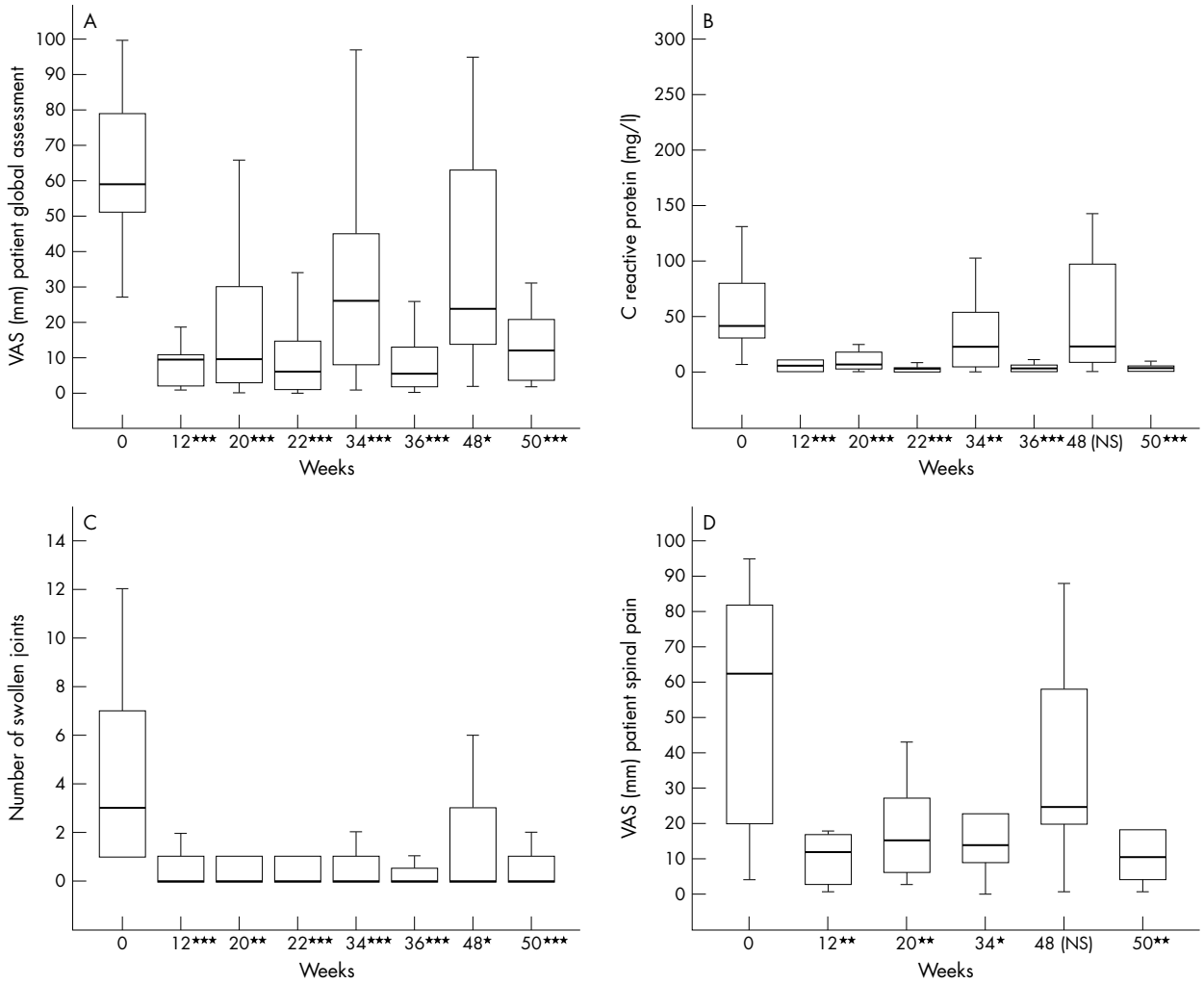

Figure 1 Evolution of patient assessments over time. The box plots show the median value (horizontal line) and range (first to third quartiles in boxes) of the chosen parameter (y axis) over time (weeks). Significance (p) was calculated by the Wilcoxon signed ranks test: *p≤0.05, **p≤0.01, ***p≤0.001, NS, not significant. (A) Patient global assessment (100 mm VAS); (B) C reactive protein (mg/l); (C) swollen joint count; (D) spinal pain assessment (100 mm VAS).

From this one year follow up study the following conclusions can be reached. Firstly, a statistically significant decrease of global, peripheral, and axial disease manifestations was seen after one year of treatment in the 19 evaluated patients. Two patients changed to another dosing regimen owing to partial lack of efficacy of the drug. Improvements in BASMI, chest expansion, fingers to floor, and occiput to wall distance in the group of patients with AS, paralleled global improvement of the disease activity in these patients. It is unclear if this improvement in spinal metrology is an indication of an effect on the progressive axial ankylosis which is typical for AS. This study was designed to evaluate the clinical efficacy of infliximab in SpA, and not to evaluate the effect on ankylosis in AS: therefore one cannot draw conclusions from this small subgroup. In order to detect such a structural improvement, homogeneous patient groups, adequate sample size, and sensitive outcome measurements, including radiological assessments evaluated over longer periods, are mandatory.[29] During this one year follow up study, general wellbeing was furthermore shown by the fact that a statistically significant increase was found for body weight, as well as for body mass index (data not shown). In addition, in this patient cohort, 42% had a normocytic normochromic anaemia at baseline, probably reflecting severe chronic inflammatory disease, which can be deduced from the patient demographics. Patients had longstanding disease with high ESR, CRP, and marked inflammatory symptoms. After one year's maintenance treatment with infliximab, anaemia was no longer present. A comparable effect, of a dose dependent increase in haemoglobin levels after only four weeks' treatment, has been reported in patients with RA.[30] Whether the beneficial effect of infliximab on haemoglobin in our patients reflects the reduction in their disease activity or a possible direct effect of infliximab on erythropoiesis, has yet to be determined.[31]

Secondly, recurrence of symptoms, such as axial night pain, morning stiffness, or synovitis, was reported by three patients (16%) at week 20, 13 patients (68%) at week 34, and 15 patients (79%) at week 48, with the moment of recurrence between 10 and 14 weeks after re-treatment. This relapse was furthermore documented by the fact that ESR, CRP, axial morning stiffness, and axial pain assessed by the patient, were no longer statistically significant when compared with baseline, immediately before the third re-treatment, at week 48. Together with observations made in other open label studies,[32 33] these results indicate that a maintenance regimen of 5 mg/kg infliximab every 14 weeks could not control the inflammatory disease activity continuously. Adjustment of the maintenance regimen seems warranted; however, it is not clear whether this should be achieved by increasing the dose or shortening the interval between doses.

Thirdly, re-treatment of patients whose symptoms recurred induced an improvement comparable with the response seen after the induction scheme reported in the 12 week pilot study. All variables of disease activity were again significantly improved two weeks after every re-treatment.

Fourthly, the treatment with infliximab in this patient group was shown to be safe and the infusion procedure was generally well tolerated. Only one mild self limiting infusion reaction was seen, and no major infectious episodes or malignancies occurred. Previous studies indicate that treatment with TNFα inhibitors, such as infliximab, can induce the development of ANA in patients with RA.[34] So far no data on the occurrence of such antibodies in patients with SpA treated with infliximab have been reported: here, up to 12/21 (57%) patients developed ANA; in four of them (19%) anti-dsDNA antibodies were also detected. However, no significant laboratory changes in peripheral blood count or complement occurred in these patients; no patients developed proteinuria, nor where there any other lupus-like symptoms. The overall frequency of autoantibodies is comparable with the data reported in RA.[34] However, we have to remember that the background for developing such antibodies—in RA versus SpA—is different. Occurrence of ANA in RA is not considered unusual and a prevalence up to 60% has been seen[35]; in SpA and AS, however, only scarce data are available, showing a prevalence ranging from 11.4% to 19.1%.[36 37] In these studies a bias attributed to the use of sulfasalazine is likely. A retrospective analysis of a patient group with SpA disclosed a prevalence of 8% ANA positive patients before sulfalsalazine treatment with no anti-dsDNA antibodies detected. After two to five years of sulfasalazine treatment, the incidence rose to 24% and 4%, respectively for ANA and anti-dsDNA antibodies.[38]

In conclusion, this one year open pilot study suggests that infliximab is a safe and effective drug in the treatment of SpA. Regardless of the fact that these data need further confirmation in ongoing double blind, placebo controlled trials, the extent of the clinical improvements, their consistency throughout the study group, the parallel changes in laboratory indices of inflammation, and the maintenance of this therapeutic effect over one year, are encouraging. Further accurate follow up of this patient group is mandatory for the optimisation of the maintenance regimen and for the evaluation of longer term safety with regard to infections, malignancies, and the occurrence of ANA.

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REFERENCES

1 **Wright V**. Seronegative polyarthritis – a unified concept. Arthritis Rheum 1978;21:618–33.
2 **Zeidler H**, Mau W, Khan MA. Undifferentiated spondyloarthropathies. Rheum Dis Clin North Am 1992;18:187–202.
3 **Kraag G**, Stokes B, Groh J, Helawa A, Goldsmith C. The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis – a randomised controlled trial. J Rheumatol 1990;17:228–33.
4 **Dougados M**, Gueguen A, Nakache JP, Velicitat P, Veys EM, Zeidler H, *et al*. Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal inflammatory drug trial. Rheumatology (Oxford) 1999;38:235–44.
5 **Dougados M**, van der Linden S, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, *et al*. Sulfasalazine in the treatment of spondylarthropathy: a randomised, multicenter, double-blind, placebo-controlled study. Arthritis Rheum 1995;38:618–27.
6 **Clegg DO**, Reda DJ, Weisman MH, Blackburn WD, Cush JJ, Cannon GW, *et al*. Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1996;39:2004–12.
7 **Clegg DO**, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo in the treatment of axial and peripheral articular manifestations of the seronegative spondyloarthropathies. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1999;42:2325–9.
8 **Clegg DO**, Reda DJ, Meijas E. Cannon GW, Weisman MH, Taylor T, *et al*. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1996;39:2013–20.
9 **Willkens RF**, Williams HJ, Ward JR, Egger MJ, Clements PJ, Cathcart ES, *et al*. Randomised, double-blind placebo controlled trial of low dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984;27:376–81.
10 **Cuellar ML**, Espinoza LR. Methotrexate use in psoriasis and psoriatic arthritis. Rheum Dis Clin North Am 1997;23:797–809.
11 **Spadaro A**, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. Clin Exp Rheumatol 1995;13:589–93.
12 **Knight DM**, Trinh H, Le J, Siegel S, Shealy D, McDonough M, *et al*. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993;30:1443–53.
13 **Targan SR**, Hanauer SB, Van Deventer SJ, Mayer L, Present DH, Braakman T, *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–35.
14 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–405.
15 **Kavanaugh AF**. Anti-tumor necrosis factor-α monoclonal antibody therapy for rheumatoid arthritis. Rheum Dis Clin North Am 1998;24:593–614.
16 **Maini RN**, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, *et al*. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552–63.
17 **Van den Bosch F**, Kruithof E, de Vos M, De Keyser F, Mielants H. Crohn's disease associated with spondyloarthropathy: effect of TNF-α blockade with infliximab on the articular symptoms. Lancet 2000;356:1821–2.
18 **Antoni C**, Dechant C, Lorenz H, Olgivie A, Kalden-Nemeth D, Kalden J, *et al*. Successful treatment of severe psoriatic arthritis with infliximab [abstract]. Arthritis Rheum 1999;42(suppl):A1801.
19 **Mease PJ**, Goffe BS, Metz J, Vanderstoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385–90.
20 **Van den Bosch F**, Kruithof E, Baeten D, De Keyser F, Mielants H, Veys EM. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor α (infliximab) in spondyloarthropathy: an open pilot study. Ann Rheum Dis 2000;59:428–33.
21 **Brandt J**, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J, *et al*. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor α monoclonal antibody infliximab. Arthritis Rheum 2000;43:1346–52.
22 **Dougados M**, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, *et al*. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218–27.
23 **van der Linden S**, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York Criteria. Arthritis Rheum 1984;27:361–8.
24 **Garrett S**, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath ankylosing spondylitis disease activity index. J Rheumatol 1994;21:2286–91.
25 **Calin A**, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, *et al*. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath ankylosing spondylitis functional index. J Rheumatol 1994;21:2281–5.
26 **Dougados M**, Gueguen A, Nakache JP, Nguyen M, Mery C, Amor B. Evaluation of a functional index and an articular index in ankylosing spondylitis. J Rheumatol 1988;15:302–7.
27 **Jenkinson TR**, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS metrology index. J Rheumatol 1994;21:1694–8.
28 **Fredriksson T**, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978;157:238–44.
29 **Spoorenberg A**, De Vlam K, van der Heijde D, de Klerk E, Dougados M, Mielants H, *et al*. Radiological scoring methods in ankylosing spondylitis: reliability and sensitivity to change over one year. J Rheumatol 1999;26:997–1002.
30 **Elliott MJ**, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, *et al*. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344:1105–10.
31 **Davis D**, Charles PJ, Potter A, Feldmann M, Maini RN, Elliott MJ. Anaemia of chronic disease in rheumatoid arthritis: in vivo effects of tumour necrosis factor α blockade. Br J Rheumatol 1997;36:950–6.

32 **Dechant C**, Antoni C, Wendler J, Ogilvie ALJ, Lueftl M, Lorenz HM, *et al*. One year outcome of patients with severe psoriatic arthritis treated with infliximab [abstract]. Arthritis Rheum 2000;43(suppl):A212.
33 **Brandt J**, Haibel H, Reddig J, Sieper J, Braun J. Anti-TNF-α treatment of patients with severe ankylosing spondylitis – a one year follow up [abstract]. Arthritis Rheum 2000;43(suppl):A208.
34 **Charles PJ**, Smeenk RJ, De Jong J, Feldmann M, Maini RN. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor α. Arthritis Rheum 2000;43:2383–90.
35 **Blackburn WD**, Chatham WW. Laboratory findings in rheumatoid arthritis. In: Koopman W, ed. *Arthritis and allied conditions*. Philadelphia: Lippincot Williams and Wilkins, 2001:1202–22.
36 **Brandt J**, Rudwaleit M, Eggens U, Mertz A, Distler A, Sieper J, *et al*. Increased frequency of Sjögren's syndrome in patients with spondyloarthropathy. J Rheumatol 1998;25:718–24.
37 **Prohaska E**, Neumuller J, Partsch, Eberl R. Antinuclear antibodies in ankylosing spondylitis. Wien Klin Wochenschr 1980;92:876–9.
38 **De Keyser F**, Mielants H, Praet J, Goemaere S, Veys EM. Changes in antinuclear serology in patients with spondylarthropathy under sulphalazine treatment. Br J Rheumatol 1993;32:521.