Successful Short Term Treatment of Severe Undifferentiated Spondyloarthropathy with the Anti-Tumor Necrosis Factor-α Monoclonal Antibody Infliximab

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ABSTRACT. ***Objective.*** Tumor necrosis factor-α (TNF-α) has been detected in sacroiliac joints of patients with spondyloarthropathies (SpA). Anti-TNF-α therapy has been efficacious in patients with active ankylosing spondylitis (AS) and psoriatic arthritis. Similar to these SpA subtypes, therapeutic options in undifferentiated SpA (uSpA) are also limited. We tested the efficacy of the monoclonal anti-TNF-α antibody infliximab in patients with active and severe uSpA in an open observation trial.

Methods. Six patients with uSpA were treated with 3 infusions of infliximab in a dosage of 3 (n = 3) or 5 mg/kg (n = 3) at Weeks 0, 2, and 6. The total observational period was 12 weeks. The Bath AS Disease Activity Index (BASDAI), the Functional Index (BASFI), pain on a visual analog scale, the Bath AS Metrology Index (BASMI), and quality of life (SF-36) were assessed before, during, and after therapy.

Results. Significant improvement at Day 1 after the first infusion lasting until Week 12 was reported by 5/6 patients. Improvement of ≥ 50% in all activity, function, pain, and swollen joint scores was observed in the patients taking 5 mg/kg. The 3 mg/kg dose was less effective, resulting in ≥ 15% improvement in outcome variables. Peripheral arthritis, enthesitis, and spinal symptoms improved equally. C-reactive protein dropped in 4 patients. Health related quality of life increased. No serious side effects or infections occurred.

Conclusion. These observations suggest that anti-TNF-α therapy has significant short term efficacy in patients with severe uSpA. (J Rheumatol 2002;29:118–22)

Key Indexing Terms:
THERAPY
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The European Spondylarthropathy Study Group (ESSG) classification criteria[1] for spondyloarthropathies (SpA) have introduced the concept of undifferentiated SpA (uSpA). uSpA seems to be among the most frequent SpA subsets[2]. The disease may run a severe course and a significant percentage of such patients may develop ankylosing spondylitis (AS) later[3]. No disease modifying antirheumatic drug (DMARD) therapy has been approved for AS to date. The data for sulfasalazine are somewhat contradictory, with more positive results in patients with peripheral joint involvement[4]. However, data on sulfasalazine in SpA are limited in early and active disease. Methotrexate has not been properly tested in SpA to date. In contrast to rheumatoid arthritis (RA), systemic therapy with prednisolone seems to have limited efficacy in most patients with SpA and is rarely used. However, this has not been properly investigated. For patients with uSpA no therapy studies have been performed. There is a clear need for studying and developing more effective drugs in SpA.

Using computed tomography guided sacroiliac biopsies we have shown that tumor necrosis factor-α (TNF-α) mRNA and protein — but no DNA — of reactive arthritis associated bacteria is present in inflamed sacroiliac joints of patients with SpA[5]. In an open pilot study we have recently shown that anti-TNF therapy is effective in patients with severe AS with relatively short disease duration[6]. This result was confirmed in a Belgian study with 11 AS patients who had a longer disease duration[7]. In this study spinal and peripheral joint symptoms improved in 21 SpA patients including 8 with psoriatic arthritis (PsA) and 2 with uSpA. The efficacy of anti-TNF-α therapy has been documented in 60 PsA patients using etanercept, another biologic agent directed against TNF-α[8]. Randomized controlled trials are currently under way to prove the efficacy of infliximab and etanercept in AS. Taken together, there is some evidence that TNF-α plays an important pathogenetic role in SpA. However, there is a need to study the therapeutic efficacy of these compounds in different SpA subsets and dis-

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ease manifestations. As well, knowledge about proper dosage, treatment intervals, and comedication is also limited. We describe first experiences in 6 uSpA patients with severe disease refractory to conventional therapy.

MATERIALS AND METHODS

Study medication. The study drug infliximab (cA2, Remicade®) is a human/mouse neutralizing chimeric monoclonal antibody (Mab) of the IgG1κ isotype (Centocor, Malvern, PA, USA) with specificity and high affinity ($Ka = 10^{10}$/mole) for TNF-α[9]. Drug preparation and administration was as described[6]. The medication was provided by Essex Pharma, Munich, Germany, on the basis of treating therapy resistant cases with informed consent. Two different dosages in 3 patients each were used to determine whether the administration of 3 infusions of cA2 at 3 and 5 mg/kg per dose has a similarly beneficial effect on the course of severe uSpA. The first patient received the 5 mg/kg dose, the second the 3 mg/kg dose, and so on.

Patients. There are no validated outcome measures for uSpA to date. Nevertheless, due to its clinical and immunological similarity to uSpA the core set of endpoints in AS[10] seemed most suitable to measure the benefit of anti-TNF-α therapy in uSpA. All 6 patients met the ESSG criteria for SpA[1], but no differentiated subset could be diagnosed. Only those patients were treated who had severe and active disease lasting > 6 months as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[11] score ≥ 4 and by a visual analog scale (VAS) pain score ≥ 4 on 2 occasions with at least 3 days in between despite therapy with nonsteroidal antiinflammatory drugs (NSAID). Health related quality of life assessments were regularly performed using the validated SF-36 questionnaire[12]. All but one patient had formerly been treated with sulfasalazine. This therapy had been stopped due to either lack of effect or side effects.

All examinations were performed before, during, and after therapy. Information on morning stiffness (duration, severity), occurrence of anterior uveitis (number of episodes, duration), and number of inflamed peripheral joints was obtained. Outcome measures were quantified by evaluated measurement tools: the BASDAI, a 10 cm VAS for pain, the Bath AS Functional Index (BASFI)[13], and the Bath AS Metrology Index (BASMI)[14]. Routine blood tests were performed and patients were screened for HLA-B27 (standard microlymphocytotoxicity test), rheumatoid factor (nephelometry; normal < 40 kU/l), antinuclear antibodies (immunofluorescence; normal < 1:320), and C-reactive protein (CRP, nephelometry; normal < 6 mg/l). The erythrocyte sedimentation rate (ESR, normal ≤ 15 mm/h) was conventionally determined. All patients had radiographs of the sacroiliac joints. The vertebral column or other joints with signs of inflammation were radiographed when appropriate.

Patients were not pregnant, had no previous exposure to murine or chimeric Mab, had no history of a chronic or serious recent infection or history of malignancy, and had no significant abnormalities of clinical relevance in the clinical examination. Disease modifying antirheumatic drugs (DMARD) or other immunosuppressants and oral corticosteroids had been withdrawn at least 6 weeks before screening, mostly due to inefficacy. Patients were allowed to take NSAID as needed but they were asked to record the daily dosage.

All assessments were taken prior to entering the observational period and at Weeks 2, 6, and 12. Adverse events were recorded.

Statistical analysis. Wilcoxon's rank sum test was used to determine the significance of the differences of outcome measures.

RESULTS

Six patients with uSpA received infliximab. The patients' characteristics are shown in Table 1. The median age was 36 years (range 19–49) and the median disease duration was 6.2 years (range 1.2–15). Four patients had elevated CRP values; in 3, this had been documented several times over at least one year.

All patients had inflammatory back pain in the sacroiliac region before treatment with infliximab; 2 also had inflammatory pain in the cervical spine and one in the whole vertebral column. No AS relevant changes were found in radiographic assessments of symptomatic regions of the spine. Four of 6 patients had unilateral sacroiliitis (grade II). One radiographically negative patient had active sacroiliitis revealed by magnetic resonance image (MRI). Three patients had oligoarthritis and 3 polyarthritis of the peripheral joints. Two patients had additional enthesitis in the feet.

All 6 patients were available for followup. One had an uncomplicated infectious diarrhea and another had one episode of atopic dermatitis (xerosis cutis). Five of 6 patients showed dramatic improvement starting as soon as one day after the first infusion. One patient (Patient 5) treated with the lower dosage (3 mg/kg) of infliximab had only partial improvement of her complaints of inflammatory back pain and polyarthritis. The analysis of disease activity (by BASDAI) and functional disability (BASFI) and the VAS values for pain led to a more substantial response in the group of patients treated with 5 mg/kg compared to the 3 mg/kg group (Figure 1). In detail (all values are given in ranges), the BASDAI (Figure 1a) in the 5 mg/kg group was 7.0–7.6 before and 0.7–2.7 six weeks after the third infusion. In the 3 mg/kg group the BASDAI was 7.7–8.6 before and 1.7–7.8 after treatment. The functional index (Figure 1b) also improved in all but one patient: the BASFI values had decreased in the 5 mg/kg group from 7.0–7.6 to 0.8–2.7 and in the 3 mg/kg group from 6.7–8.5 to 0.8–8.4. Pain on VAS improved in the 5 mg/kg group from 7.1–7.7 to 0.8–2.6 and in the 3 mg/kg group from 5.1–9.0 to 1.2–8.1.

The median of the metrology index (BASMI) in all 6 uSpA patients without severe involvement of the spine declined moderately from 2.0 (range 2.0–5.0) to 1.5 (range 1.0–5.0). Spinal symptoms (Figure 1c), peripheral arthritis (Figure 1d) and enthesitis improved equally. The median number of swollen joints was reduced by more than 70% from 4.5 (range 2–13) at baseline to 0.0 (range 0–4) after treatment. In 2 patients of the 3 mg/kg group the single component of the BASDAI joint pain and swelling improved only slightly upon treatment, whereas a reduction of the number of swollen joints was observed. Also, in 2 patients enthesitis improved upon anti-TNF-α treatment. No patient had established uveitis within the observation period. Five of 6 patients were able to stop intake of NSAID during the observation period, whereas one reduced the dosage to < 50% of the baseline amount.

Median CRP levels dropped from 18.4 (range < 6–120) mg/l before therapy to < 6 (range < 6–16) mg/l at Week 12. Calculation of significant differences between baseline and followup visits for both dosage groups was not possible because of the small number of patients. Taking both groups together, improvement between baseline and Week 6 was statistically significant ($p < 0.05$) for all outcome variables despite the BASMI values and CRP levels.

Table 1. Characteristics of the 6 patients with uSpA treated with infliximab.

	Patient					
	1	2	3	4	5	6
Age/sex	40 F	33 M	20 M	19 M	47 F	49 M
Dosage of infliximab, mg/kg	5	5	3	3	3	5
IBP	+	+	+	+	+	+
Disease duration, yrs	4.3	9.0	1.2	3.0	15.0	8.0
Arthralgias	+	–	–		+	–
Arthritis	Oligoarthritis	Polyarthritis	Polyarthritis	Oligoarthritis	Polyarthritis	Oligoarthritis
Sacroiliitis*	Grade 2, left	Grade 2, right	Grade 2, right	Grade 0; MRI: sacroiliitis, right	Grade 0	Grade 2, left
Enthesitis	Achilles tendon bilateral	–	Plantar aponeurosis bilateral		–	–
HLA-B27	+	–	+	+	+	+
Other features	Stiffness of the neck	–	–	Psoriasis in first-degree relatives		AS in first-degree relatives
DMARD	SSZ, MTX AZA, MTX + SSZ	SSZ, MTX, AZA, HCQ, Mycophenolate	–	MTX, SSZ	MTX, SSZ	SSZ
Prednisolone, mg/day	7.5–15	–		–	16	–
Other therapies	Local radiation of both Achilles tendons	–	Radiosynoviorthesis of the right knee	–	Synovectomy of tendons of the right hand	–

IBP: inflammatory back pain, SSZ: sulfasalazine, MTX: methotrexate, AZA:azathioprine, HCQ: hydroxychloroquine. *Radiographic grading according to the modified New York criteria[20].

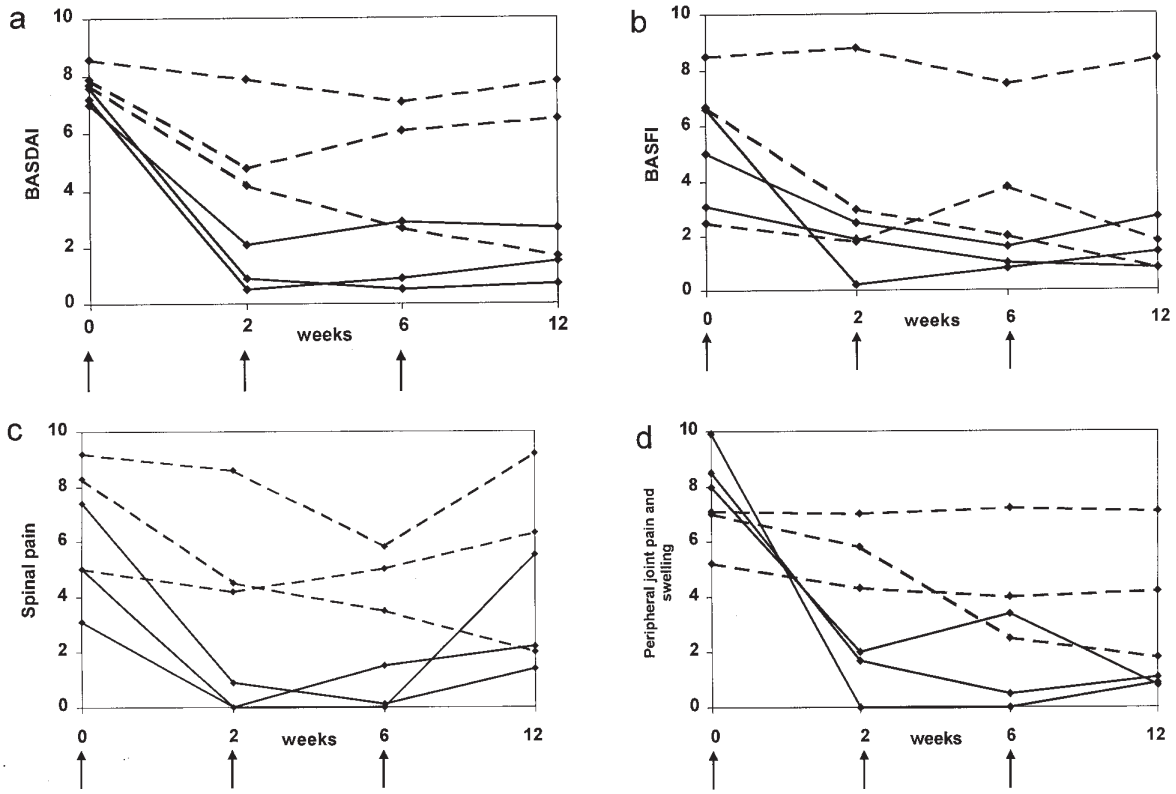

Figure 1. a. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); b. Bath Ankylosing Spondylitis Functional Index (BASFI); and 2 single components of the BASDAI: c. spinal pain, and d. peripheral joint pain and swelling, before, during, and after treatment with 3 mg/kg (broken lines) and 5 mg/kg (solid lines) infliximab. Each line represents the course of an Index or a single BASDAI component value in an individual patient. Arrows indicate dates of infusion.

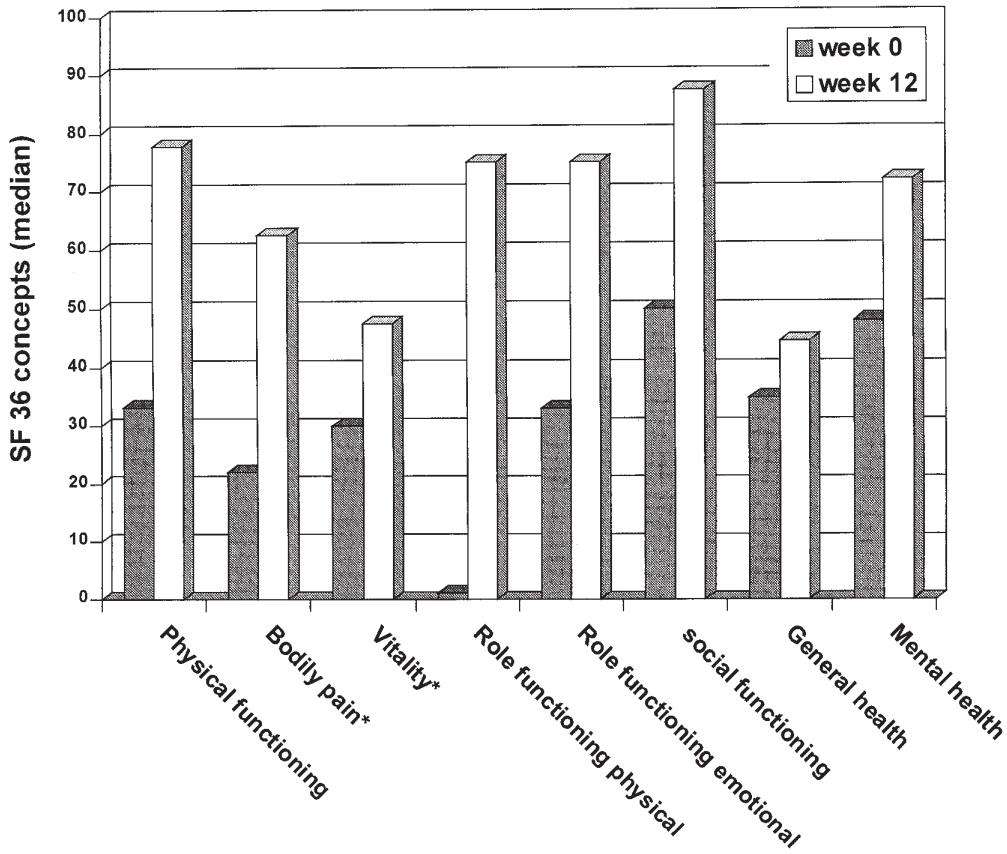

Figure 2. Improvement of global health assessment measures assessed by the SF-36 before and after 12 weeks of treatment with infliximab in 6 patients with uSpA. Values are median scores on a 0–100 transformed scale, 100 indicating the best health. *Differences between median values of Week 12 versus Week 0 were statistically significant ($p < 0.05$, Wilcoxon rank sum test).

Improvement of all 8 SF-36 items assessed at baseline and at Week 12 was noted; the differences between Weeks 0 and 12 were significant ($p < 0.05$) for the items "bodily pain" and "vitality" (Figure 2).

DISCUSSION

These data on a limited number of patients suggest (1) that infliximab is also effective in uSpA, and (2) that a dosage of infliximab of 5 mg/kg may be more effective than 3 mg/kg for this indication. A positive effect on 2 patients with uSpA has also been reported in a study from Belgium[7], in which SpA patients with a longer disease duration compared to our first study[6] were treated with infliximab in a dosage of 5 mg/kg.

USpA is the second most frequent SpA subset following AS. Its prevalence has been estimated between 2.0%[15] and 0.7%[16]. Similarly to reactive arthritis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease, 30–50% of patients with uSpA are at risk to develop AS in the further course of the disease[3]. Besides a small pilot study on sulfasalazine from our group (unpublished data) no controlled study in uSpA has been performed to date. Our data indicate that patients with severe uSpA respond to infliximab therapy similarly to patients with relatively early AS[6]. We do recognize that it is unusual that data on the efficacy of a biological agent are presented for this SpA subset before conventional DMARD or corticosteroid therapy has been established for uSpA.

As expected from clinical experience but not from the published RA studies[17], the higher 5 mg/kg dose was more effective than the lower 3 mg/kg dose. Nevertheless, the 3 mg/kg dose was also effective in 2 out of 3 patients. There might well be a difference between the efficacy of infliximab in RA and in uSpA. However, there are patients with RA who do better taking infliximab 5 mg/kg. In the future, the optimal dose and the interval between treatments may well be determined on an individual trial and error basis. This clearly needs further study.

These data on the efficacy of infliximab in uSpA are important concerning short term efficacy, but they do not allow conclusions for longterm effects. However, since it is known that a significant percentage of patients with uSpA develop AS over time it becomes possible that this transition can be prevented by early and consequent anti-TNF therapy. Longterm studies are needed to prove this hypothesis.

However, similarly to RA[17], not all patients with SpA seem to respond. While it seems logical that patients with long-

standing AS with a fused spine have limited benefit from such therapy there are phenomena that remain unexplained. One of our uSpA patients had clear benefit for his enthesitis, but the back symptoms did not improve. This patient had a normal CRP. Since we have mostly treated SpA patients with elevated CRP levels, we cannot say much about those with active disease and normal CRP — who do exist in significant numbers[18]. However, with regard to the clear effects of infliximab on CRP and interleukin 6 levels[2,17], it may be that the patient subset with normal CRP levels does not respond in the same way.

We observed no relevant side effects in the small number of patients reported here, who were followed over a relatively short time. In general, there is no evidence for an increased prevalence of infections[19], but, very rarely, cases of tuberculosis have been reported. Nevertheless, although there is still limited experience with this therapy in SpA (about 300 patients have now been treated worldwide), we feel the benefits of anti-TNF therapy justify a small risk. This discussion will be important to have with our patients as well.

Having tested the BASDAI in a study of sulfasalazine in uSpA (unpublished data), we were confident this disease activity index could also be used for uSpA, because the 2 main and most common symptoms of SpA, inflammatory back pain and peripheral arthritis of the lower limbs, are also common in uSpA[2] and they are a central part of the BASDAI.

Therapy directed against TNF-α seems to hit a critical target in SpA. Further studies should clarify whether transition to AS can be prevented by consequent antiinflammatory treatment strategies. The optimal dose might have to be individually determined.

REFERENCES

1. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria of the classification of spondyloarthropathy. Arthritis Rheum 1991;34:1218-72.
2. Brandt J, Bollow M, Häberle J, et al. Studying patients with inflammatory back pain and arthritis of the lower limbs clinically and by magnetic resonance imaging: many, but not all patients with sacroiliitis have spondyloarthropathy. Rheumatology 1999; 38:831-6.
3. Mau W, Zeidler H, Mau R, et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. J Rheumatol 1988;7:1109-14.
4. Dougados M, van der Linden S, Leirisalo-Repo M, et al. Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. Arthritis Rheum 1995;38:618-27.
5. Braun J, Bollow M, Neure L, et al. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. Arthritis Rheum 1995;38:499-505.
6. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. Arthritis Rheum 2000;43:1346-52.
7. 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 alpha (infliximab) in spondyloarthropathy: an open pilot study. Ann Rheum Dis 2000;59:428-33.
8. Mease PJ, Goffe BS, Metz J, Vander Stoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385-90.
9. Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993;30:1443-53.
10. Van der Heijde D, Bellamy N, Calin A, Dougados M, Khan MA, van der Linden S. Preliminary core sets for endpoints in ankylosing spondylitis. J Rheumatol 1997;24:2225-9.
11. Garrett S, Jenkinson TR, Kennedy LG, Whitelock HC, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis. The Bath AS Disease Activity Index. J Rheumatol 1994;21:2286-91.
12. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
13. Calin A, Garrett S, Whitelock HC, et al. A new approach to defining functional ability in ankylosing spondylitis. The Bath AS Functional Index. J Rheumatol 1994;21:2286-91.
14. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett S, Calin A. Defining spinal mobility in ankylosing spondylitis. The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8.
15. Boyer GS, Lanier AP, Templin DW. Prevalence rates of spondyloarthropathies, rheumatoid arthritis, and other rheumatic disorders in an Alaskan Inupiat Eskimo population. J Rheumatol 1988;15:678-83.
16. Braun J, Bollow M, Remlinger G, et al. Prevalence of spondylarthropathies in HLA B27-positive and -negative blood donors. Arthritis Rheum 1998;41:58-67.
17. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
18. Spoorenberg A, van der Heijde D, de Klerk E, et al. Relative value of erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. J Rheumatol 1999;26:980-4.
19. Gershon S, Wise RP, Niu M, Siegel J. Postlicensure reports of infection during use of etanercept and infliximab [abstract]. Arthritis Rheum 2001;44 Suppl: 2857.
20. 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.