Successful Short Term Treatment of Patients with Severe Undifferentiated Spondyloarthritis with the Anti-Tumor Necrosis Factor-α Fusion Receptor Protein Etanercept

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ABSTRACT. ***Objective***. Anti-tumor necrosis factor-α (TNF-α) therapy has been successfully used in patients with active ankylosing spondylitis (AS) and other subtypes of spondyloarthritis (SpA). Treatment options for patients with severe forms of undifferentiated spondyloarthritis (uSpA), a rather frequent SpA subset, are limited. In this open study we examined the efficacy of the TNF-α receptor fusion protein etanercept in patients with uSpA.

Methods. Ten patients classified to have uSpA according to modified European Spondylarthropathy Study Group criteria in a severe and active stage of disease were included in the study and received etanercept in a dosage of 25 mg two times a week for 12 weeks, followed by an observation period of 12 weeks. The following outcome variables were used: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Functional Index (BASFI), pain on a numerical rating scale, disability by the Funktionsfragebogen Hannover (FFbH), a validated questionnaire to assess functional disability, and quality of life (Medical Outcome Study Short Form-36, SF-36). The primary outcome variable was defined as ≥ 50% improvement of the BASDAI.

Results. Treatment with etanercept resulted in a ≥ 50% regression of disease activity in 60% (95% CI 31–83%) of the patients. The mean BASDAI at baseline of 6.1 (range 3.7–9.2) dropped significantly to 3.5 at Week 12 (0.8–8.7; p = 0.01). Function, spinal pain, peripheral arthritis, enthesitis, quality of life, and acute phase reactants improved similarly. The FFbH improved from 62.8% to 69.7%. After cessation of anti-TNF therapy, 4 out of 8 patients relapsed after an average of 4.5 weeks (range 3–6). Two patients went into longstanding remission. No severe adverse events or major infections were observed.

Conclusion. This study strongly suggests that treatment with etanercept has short term efficacy in patients with active and severe uSpA. Since it is known that 30–50% of uSpA patients develop AS over time, it will be important to study whether this can be prevented by anti-TNF-α therapy. (J Rheumatol 2004;31:531–8)

Key Indexing Terms:
ETANERCEPT TUMOR NECROSIS FACTOR-α
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Through the use of the European Spondylarthropathy Study Group (ESSG) classification criteria[1] for spondyloarthritides (SpA) the concept of undifferentiated SpA (uSpA) has been introduced. USpA seems to be among the most frequent SpA subsets[2]. The disease may run a severe course, and a significant percentage of patients may later develop ankylosing spondylitis (AS)[3]. No disease modifying antirheumatic drug (DMARD) therapy has been approved for AS to date. The data for sulfasalazine are somewhat contradictory but indicate benefit for patients with peripheral joint involvement[4]. No data on sulfasalazine therapy for patients with uSpA have been published. Although often used, methotrexate has not been properly studied in SpA. In contrast to its use in rheumatoid arthritis (RA), systemic therapy with prednisolone seems to have limited efficacy in most patients with SpA. However, this question has not been

properly investigated. In general, there are few studies of patients with uSpA. Only one recent small study with infliximab, the chimeric monoclonal antibody against tumor necrosis factor-α (TNF-α), has been published[5].

Using computed tomography-guided sacroiliac (SI) biopsies, we have shown that TNF-α mRNA and protein[6] but not DNA of reactive arthritis-associated bacteria are present in inflamed sacroiliac joints of patients with SpA[7]. Moreover, anti-TNF-α therapy with the other established TNF-α blocking agent infliximab has also been approved for treatment of Crohn's disease (CD), which is closely linked to SpA[8]; also joint symptoms of patients with CD have been found to improve on infliximab therapy[9]. Taken together, there is some evidence that TNF-α plays an important pathogenetic role in SpA.

Anti-TNF-α therapy with etanercept, a dimeric fusion protein of the human 75 kDa (p75) TNF receptor linked to the Fc portion of human IgG1 (Enbrel, Immunex, Seattle, WA, USA), was shown to be very effective in RA[10]; however, RA is pathogenetically distinct from SpA. As recently shown in randomized controlled trials from different groups, therapy with etanercept[11,12] and infliximab[13] is very efficacious in active AS, the prototype of the SpA. Limited evidence concerning the efficacy of TNF-α blocking agents in uSpA patients has been published recently: one small open study with 6[5] and 2 patients treated with infliximab[14], the latter as part of a study with several different SpA subtypes. Only one uSpA patient has been reportedly treated with etanercept to date[15]. Clearly, there is a need to study the therapeutic efficacy of anti-TNF-α therapy in uSpA. We report our experience with etanercept treatment of 10 patients with severe active uSpA.

MATERIALS AND METHODS

Patients and study protocol. This open national multicenter trial was designed to investigate whether the administration of etanercept 25 mg twice weekly is effective in active uSpA. Only patients fulfilling the modified ESSG criteria for SpA[1] were included. Thus, patients with inflammatory back pain (IBP[16]) and/or peripheral arthritis predominantly in the lower limbs plus at least one additional minor criterion were included. To this list, the additional criterion of HLA-B27 positivity was added as a modification. Other differentiated SpA subsets such as AS were excluded. Patients had to have severe and active disease > 6 months as defined by pain ≥ 4 by a numerical rating scale (NRS, 0–10) despite therapy with maximally tolerated doses of nonsteroidal antiinflammatory drugs (NSAID). Patients were excluded if they had had active tuberculosis within the previous 3 years, serious infections within the previous 2 months, a history of lymphoproliferative disease or other malignancies in the past 5 years, multiple sclerosis or related disorders, or showed current signs or symptoms of severe disease. The study was approved by the local ethical committee, and patients gave written informed consent before participation.

DMARD and oral corticosteroids were withdrawn at least 4 weeks before inclusion into the study because of limited efficacy. NSAID intake was allowed but this could not be increased over the dosage at baseline; any reduction in dosage was recorded.

Of the 20 patients screened 10 were excluded due to low disease activity, failure to fulfil ESSG criteria, or comorbidity such as previous infection. Patients were enrolled over 4 months between March and July 2001. After the main initial treatment period of 12 weeks, patients were followed up further until Week 24. During the observation period outcome assessments were performed every 3 weeks.

Study medication. Patients received etanercept 25 mg twice weekly by subcutaneous administration during the first 12 weeks of the study. The 25 mg dose was obtained using 10 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine per vial. Three vials were reconstituted with 1 ml of bacteriostatic water. Then the reconstituted drug was drawn up into 2 syringes with equal volumes (1.25 ml each) to be given at 2 different injection sites.

Clinical response. The following validated questionnaires were filled out by the patients every 3 weeks: the Bath Ankylosing Spondylitis Activity Index (BASDAI; 6 questions relating to fatigue, spinal pain, peripheral arthritis, enthesitis and morning stiffness, both quantitatively and qualitatively, assessed on a NRS) to measure disease activity[17]; the Bath AS Functional Index (BASFI; 10 questions about daily life functions) to measure physical function[18]; and NRS to measure spinal pain and patient's and physician's global assessment, rating from 0 to 10 (10 = very bad and 0 = very good). The Bath AS Metrology Index (BASMI[19]) used to grade mobility of spine and hip was measured in each patient by the same rheumatologist. Enthesitis was assessed as reported[13]. Health related quality of life assessments were performed at baseline and every 6 weeks until Week 30 using the Medical Outcome Study Short Form-36 (SF-36)[20]. The individual subscales of the survey were grouped into physical- and mental-component summary scores, each of which was assigned as mean ± SD of 50 ± 10 on the basis of US population data[20]. The scoring algorithm of the Medical Outcome Trust[21] was used to check and calculate the SF-36 as well as for the handling of single missing items in this questionnaire. To assess disability in patients with the leading symptom of peripheral arthritis the Hannover Functional Ability Questionnaire (Funktionsfragebogen Hannover; FFbH), a German questionnaire to measure functional disability in RA patients, which correlates well with the Health Assessment Questionnaire disability index (HAQ[22]), was completed every 6 weeks. Occurrence of anterior uveitis (number of episodes) and number of inflamed peripheral joints were recorded. Routine blood tests were performed and patients were screened for HLA-B27 (standard microlymphocytotoxicity test).

As primary endpoint of the study an improvement of disease activity of 50% between baseline and Week 12, measured by BASDAI, was chosen. The secondary outcome variables analyzed were improvements in: NRS for spinal pain, BASFI, BASMI, SF-36, FFbH, serum C-reactive protein (CRP, nephelometry; normal ≤ 15 mg/l), and erythrocyte sedimentation rate (ESR, normal ≤ 15 mm/h).

Further, we investigated the time to relapse after cessation of etanercept treatment. Only patients who reached at least a 20% improvement of the NRS values for pain compared to baseline after 3 month treatment with etanercept were used to define the time until relapse occurred. The definition for the time until patients relapsed was the time between the end of the treatment period and the first visit at which an increase of at least 2 points in the NRS for pain (range 0–10) was noted compared to the last value at the end of the treatment period.

Radiographic evaluation. All patients had radiographic assessments of the SI joints. Radiography of the spine was performed only in the presence of appropriate clinical symptoms. Magnetic resonance imaging (MRI) including use of gadolinium-DTPA of the spine and SI joints was only performed after informed consent if patients were symptomatic at these sites.

Statistical analysis. All results are based on the data of the 10 patients included in the study. The "last observation carried forward" method was applied. The Wilcoxon rank sum test was used for statistical analysis of the data.

RESULTS

Ten patients with uSpA were included in the study and received at least one dose of the study drug etanercept.

Patient characteristics are shown in Table 1. The mean age was 39.3 years (range 31–58) and the mean disease duration was 5.9 years (range 1–31). Four patients had elevated CRP values at baseline (> 10 mg/l). Six patients had inflammatory back pain (IBP) in the SI region or at the lumbar spine; one additionally had IBP in the cervical spine, and 2 patients in the whole vertebral column, prior to etanercept treatment. No AS-typical changes were found in radiographic assessments of symptomatic regions of the spine. Two patients had unilateral sacroiliitis (grade II). Out of 9 patients with IBP 5 had an additional oligoarthritis of the lower limbs and 4 isolated IBP without peripheral arthritis. One patient had polyarthritis of the peripheral joints without spinal symptoms. Five patients had active sacroiliitis as detected by MRI, 4 of these had IBP located to the SI region. Seven patients with IBP of the vertebral column were MRI negative. Most patients with peripheral arthritis and/or enthesitis had been previously treated with intraarticular corticosteroids.

Nine patients were available for followup until Week 24. One patient dropped out after 6 weeks because of a nonserious adverse event.

Treatment with etanercept resulted in a ≥ 50% regression of disease activity (assessed by BASDAI) in 60% of the patients [95% confidence interval (CI) 31–83%]. The mean BASDAI, which was 6.1 (range 3.7–9.2) at baseline, fell significantly to 3.5 at Week 12 (range 0.8–8.7; p = 0.01). Six patients showed substantial improvement as early as one week after the first injection (> 20% regression of disease activity as assessed by BASDAI).

For the more detailed analyses, patients were divided into 3 subgroups with isolated IBP (n = 4), IBP and peripheral arthritis (n = 5), and peripheral arthritis without axial disease (n = 1) at baseline. In patients with isolated IBP the mean disease activity (BASDAI) decreased from 6.0 (range 3.7–9.1) to 5.0 (range 1.2–8.4) at Week 12. This rather limited response is due to 2 patients who did not show improvement, whereas the remaining 2 were BASDAI 50% responders. In patients with IBP and peripheral arthritis the mean BASDAI decreased from 6.4 (range 3.8–8.0) to 2.8 (range 0.8–6.1) and in the only patient with isolated peripheral polyarthritis the BASDAI also improved markedly from 5.0 to 1.2.

Looking at the whole group of patients again, the functional index (BASFI) improved by at least 20% in all but 2 patients (the 2 BASDAI 50% nonresponders, see above). The mean BASFI values decreased significantly from 5.7 (range 2.1–9.5) to 3.7 (range 0.2–9.9) at Week 12 (p =

Table 1. Baseline characteristics of patients with undifferentiated spondyloarthritis.

Patient	Age/sex	Disease Duration, yrs	IBP	Peripheral Arthritis*	Enthesitis*	Uveitis*	Family History†	HLA-B27	MRI	SI Joint X-rays#	Previous Treatment
1	37M	4.3	Lumbar and thoracic spine	—	–	–	—	+	Spine Neg. SIJ Neg.	Grade 1 bilateral	SSZ
2	42M	5.4	Lumbar spine	—	–	+	Uncertain	+	Spine and SIJ Neg.	Grade 1 bilateral	Pred
3	35M	1.0	Whole spine	Oligoarthritis	+	–	–	+	Bilateral sacroiliitis; spine Neg.	Grade 1 right, Grade 2 left	SSZ, MTX, Pred
4	31M	4.5	Thoracic spine	Oligoarthritis	–	–	–	+	Bilateral sacroiliitis; spine Neg.	Grade 0	SSZ, MTX, Pred
5	34M	1.6	Whole spine	—	–	–	Uncertain	+	ND	Grade 2 left	SSZ
6	33M	1.4	SI and lumbar spine	—	–	–	Uncertain	+	ND	Grade 1 bilateral	SSZ
7	48M	31.3	Whole spine	Oligoarthritis	+	+	–	+	Spine and SIJ Neg.	Grade 1 bilateral	SSZ, MTX, Pred
8	38F	3.4	SI and lumbar spine	Oligoarthritis	+	–	AS in 2nd degree relative	+	Sacroiliitis right; spine Neg.	Grade 1 bilateral	SSZ
9	32M	0.6	Lumbar and thoracic spine	Oligoarthritis	+	–	AS in 1st degree relative	+	Bilateral sacroiliitis; spine Neg.	Grade 1 bilateral	—
10	44M	1.5	—	Polyarthritis	+	+	–	+	Bilateral sacroiliitis; spine Neg.	Grade 1, right	SSZ, MTX, Pred

* Manifestations could be previous or current; peripheral arthritis: 68 joints assessed; enthesitis: 12 enthesitic regions assessed. # Grading by modified New York criteria[31]. † Presence in first-degree or second-degree relatives of any of the following: ankylosing spondylitis, psoriasis, acute uveitis, reactive arthritis, inflammatory bowel disease. IBP: inflammatory back pain; SI: sacroiliac, SSZ: sulfasalazine; MTX: methotrexate; Pred: oral prednisolone, SIJ: sacroiliac joints; MRI: magnetic resonance imaging; ND: not done.

0.006). Mean pain values assessed on a NRS improved from 7.5 (range 5–10) to 3.9 (range 1–9; p = 0.006). Disability as measured with the FFbH decreased from 62.8% (range 36.1–91.7) to 69.7% (range 33.3–97.2; p = 0.02), indicating improvement of function.

Of interest, spinal mobility (BASMI) in all 10 uSpA patients without severe involvement of the spine improved from 3.5 (range 0–7) to 1.8 (range 0–6; p = 0.008).

Similarly, spinal symptoms, peripheral arthritis (Figure 1), and enthesitis improved. The mean number of swollen joints was reduced by 47% from 1.7 (range 0–7) at baseline to 0.8 (range 0–6) after treatment as well as the single component of the BASDAI joint pain and swelling (Figure 1). Also, enthesitis improved from a mean number of affected sites at baseline of 2.6 (range 0–8) to 0.8 (range 0–6). Two patients had at least one episode of uveitis before treatment. One patient had established uveitis at Week 1 of treatment.

Nine of 10 patients were treated with NSAID at baseline. One was unable to take NSAID because of GI side effects, but he had taken corticosteroids prior to the trial. Three of 9 patients were able to stop intake of NSAID during the study, whereas one reduced the dosage to < 50% of baseline.

Four patients had elevated CRP levels at baseline (> 10 mg/l). These normalized in all 4 until Week 12. Mean CRP levels dropped from 36.1 (range 0.0–177.0) mg/l before therapy to < 6 (range < 6–9.4; p = 0.125) mg/l. ESR levels also decreased significantly (p = 0.02; Table 2).

Between baseline and Week 12, the physical component score as assessed by the SF-36 improved due to etanercept. The difference between baseline and Week 12 reached statistical significance (p = 0.004). No improvement was seen in the mental component score during 12 weeks of treatment (Table 2).

Followup. Eight of 10 patients improved on the pain scale by at least 20%, and their data were used to estimate the time to relapse after cessation of treatment. The remaining 2 patients were excluded from this analysis because they had dropped out before the end of the treatment period due to a non-serious adverse event (see below) (n = 1) and due to lack of response (n = 1).

After cessation of treatment 4 of 8 patients (50%) relapsed within 3 months, and 3 patients (37.5%) relapsed later. The mean time until relapse that occurred during the followup period of 3 months was 4.5 weeks (range 3–6).

Two patients went into a longstanding remission: one was a 42-year-old man (Patient 2, Table 1) with 6 year disease duration and IBP partly controlled by NSAID, with sacroiliitis detected by MRI 2 years before baseline, who showed recent evidence of reduced spinal mobility with a cervical rotation of 60° and chest expansion of 2.5 cm; no radiographic change was found at baseline and acute phase reactants were normal; he remained in complete remission for 21 months before signs and symptoms recurred. The second patient was a 44-year-old man (Patient 10, Table 1) with a disease duration of 19 months who had chronic polyarthritis and enthesitis; he had strongly elevated acute phase reactants over several months (ESR 100 mm/h and CRP 177 mg/l). He remains in complete remission now, 20 months after initiation of therapy with etanercept. The 6 patients who relapsed have been included in a 2-year, open-extension phase of the trial. These data will be reported at a later time.

Adverse events. There were no serious adverse events in this study, but some minor adverse events occurred: one patient dropped out due to edema, sweating, and weight gain (3 kg) after 6 weeks of treatment. This was considered to be possibly related to etanercept. Two patients in the etanercept group had an injection site reaction. Minor uncomplicated infections of the upper respiratory tract occurred in 4 patients. One patient had diarrhea due to an uncomplicated infection with *Salmonella enteritidis*. Other adverse events occurred only in single patients and were classified as mild to moderate.

DISCUSSION

Our data from an open label study of 10 patients suggest that etanercept is effective in a majority of patients with undifferentiated spondyloarthritis. This information can be regarded as comparatively novel, since to date only one patient with uSpA treated with etanercept has been described in a small open British study[15]. The results of our study are in agreement with the data from 2 recent randomized controlled trials of etanercept in AS in 40[11] and 30[12] patients, respectively. Etanercept proved efficacious in patients with active AS allowed to continue treatment with NSAID throughout the studies, but therapy with DMARD and steroids was only possible in one of the studies[11]. Positive results were also reported in a different SpA subset, psoriatic arthritis (PsA), in which the efficacy of etanercept has been clearly demonstrated[23], and etanercept has been approved for this indication in North America and Europe.

The positive effect on signs and symptoms of SpA was similar when the other available anti-TNF-α agent, infliximab, was given to uSpA patients in Berlin[5] and similarly to SpA patients in Spain[24], France[25], and Belgium[26]. Infliximab was also proven to be efficacious in AS in a recent controlled multicenter trial[13]. Infliximab is now approved for AS in Europe.

In the present trial, we report that the various disease manifestations of patients with uSpA[2] respond equally well to therapy with etanercept: moreover, anti-TNF-α treatment with etanercept improved IBP as well as peripheral arthritis and enthesitis. Similarly, disability and quality of life improved as assessed by established instruments.

Because of our experience with the BASDAI in early studies of sulfasalazine and azathioprine[27] and infliximab in uSpA[5] and in the German cohort with different SpA subsets

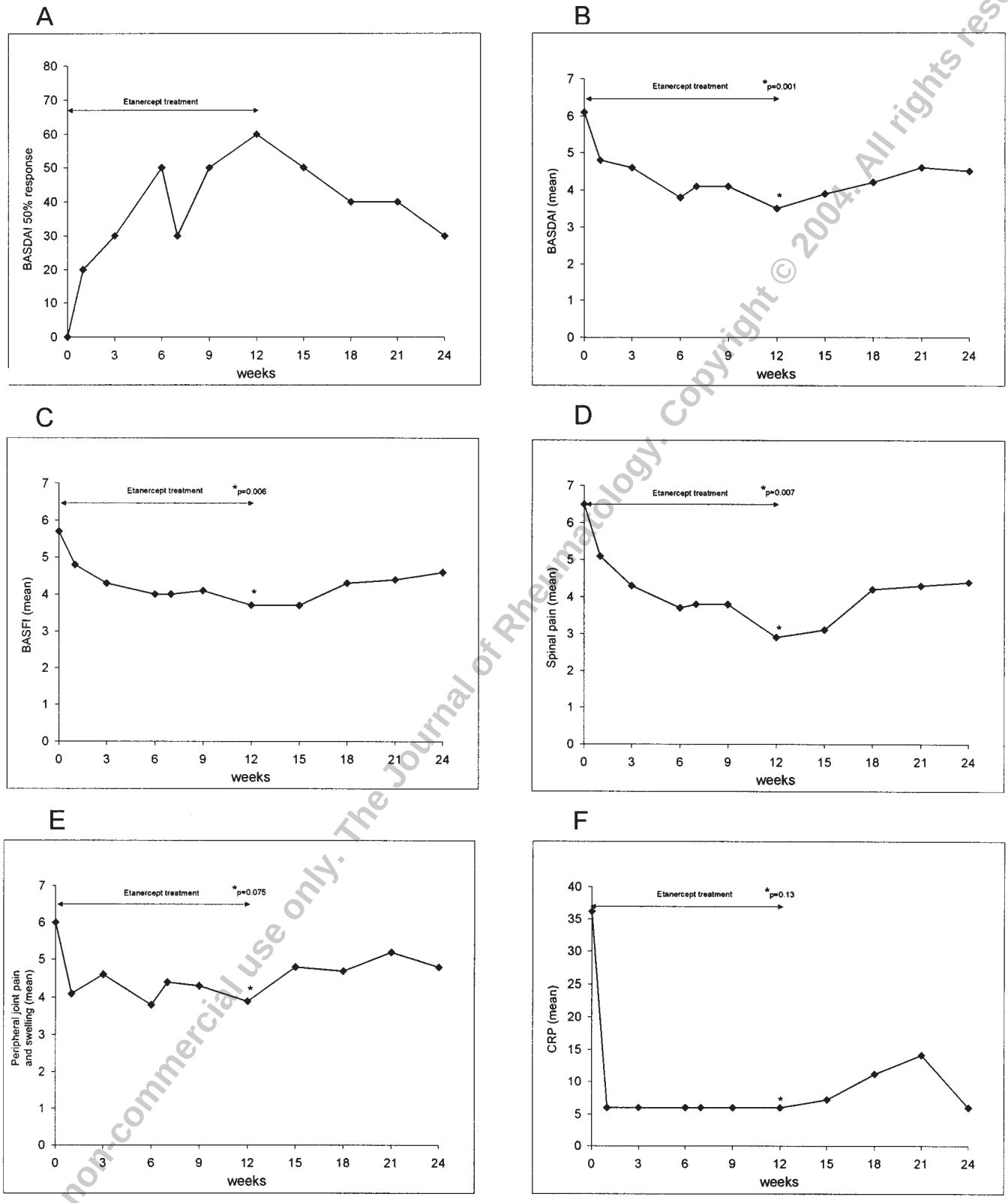

Figure 1. A. Patients with uSpA responding to treatment measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) on an improvement level of 50%. B. BASDAI. C. Bath Ankylosing Spondylitis Functional Index (BASFI). D and E. Two single components of the BASDAI: spinal pain (D) and peripheral joint pain and swelling (E). F. CRP before, during, and after treatment with 25 mg etanercept twice weekly.

Table 2. Comparison of outcome variables before and after one and 12 weeks of treatment with etanercept in patients with active uSpA.

	Week 0	Week 1	p*	Week 12	p*
BASDAI	6.1 (3.7–9.2)	4.8 (1.7–9.6)	0.01	3.5 (0.8–8.7)	0.01
BASFI	5.7 (2.1–9.5)	4.8 (0.7–9.7)	0.03	3.7 (0.2–9.9)	0.01
FFbH	62.8 (36.1–91.7)	ND		69.7 (33.3–97.2)	0.02
BASMI	3.5 (0–7)	2.5 (0–7)	0.19	1.8 (0–6)	0.01
NRS for IBP	6.5 (3–10)	5.1 (1–10)	0.016	2.9 (0–9)	0.007
No. of swollen joints	1.7 (0–7)	1.7 (0–7)	1.0	0.8 (0–6)	0.34
No. of enthesitic sites	2.6 (0–8)	1.5 (0–6)	0.13	0.1 (0–1)	0.06
CRP, mg/l	36.1 (0.0–177.0)	< 6 (< 6–8.0)	0.13	< 6 (< 6–9.4)	0.13
ESR, mm/h	34.6 (2–100)	25.9 (2–90)	0.02	10 (1–28)	0.02
Health related quality of life					
Physical component score	27.4 (23.6–34.4)	ND		42.4 (25.1–59.2)	0.004
Mental component score	42.9 (22.9–57.8)	ND		40.7 (27.1–59.1)	0.57

Values are the mean (range). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; FFbH: questionnaire for function ability (Funktionsfragebogen Hannover); BASMI: Bath Ankylosing Spondylitis Metrology Index; NRS: numerical rating scale; IBP: inflammatory back pain; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ND: not done; * week 1 or 12 vs week 0, by Wilcoxon rank sum test.

(unpublished data), we were confident that this disease activity index could be used as an outcome measure for uSpA: the 2 main and most common symptoms of SpA, IBP and peripheral arthritis of the lower limbs, which are reportedly also common in uSpA[2], are a central part of the BASDAI. However, no formal validation of the BASDAI in uSpA has been performed to date, nor of the other measures BASFI and BASMI.

USpA is the second most frequent SpA subset after AS. The prevalence of uSpA has been estimated between 0.7%[28] and 1.3%[29]. The main difference between uSpA and AS is the absence in uSpA of radiographic evidence of sacroiliitis > grade 2 bilateral. However, uSpA is similar to reactive arthritis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease, in that 30–50% of patients with uSpA are at risk to develop AS[3]. Other than our pilot study of infliximab in uSpA[5] no controlled study in uSpA has been performed to date. Our data indicate that etanercept is as effective as infliximab in patients with severe and active uSpA, and the response to infliximab is similar to that of patients with AS[13,30].

Our data on etanercept in uSpA are mainly relevant for the short term efficacy of this drug, but they do not allow conclusions about longterm effects. However, since it is known that a significant percentage of patients with uSpA will develop AS over time and since recent data from MRI analyses in AS have supported that spinal inflammation is suppressed by infliximab[31], transition to AS may be prevented by early and consequent anti-TNF-α therapy. However, longterm studies are needed to prove this hypothesis.

Seven patients with IBP of the spine were MRI negative. Since the clinical diagnosis of IBP[16] has limited specificity, we cannot completely exclude that the origin of the back pain in these patients was mechanical rather than SpA. On the other hand, SpA patients may have back pain of the inflammatory type without specific findings on MRI. It is unlikely that spinal MRI is 100% sensitive. For example, inflammation of the zygapophyseal joints is not routinely assessed by MRI[32], and these joints are not part of a recently proposed scoring system for spinal MRI[33].

The question of which patients with AS should be considered for anti-TNF treatment has recently been discussed and recommendations published[34]. There are currently no recommendations for uSpA. The diagnostic situation in uSpA differs from AS in that uSpA patients are classified on a more clinical basis (Patients 1 and 2, Table 1) without a potentially more objective confirmation by imaging. Two patients in this trial had been diagnosed solely on a clinical basis (both patients had normal CRP). Both were clear responders, with BASDAI levels of 1.6 and 1.2 after 12 weeks. However, recent data in AS have suggested that patients with low CRP levels respond less often and less well to anti-TNF therapy with infliximab[35]. Clearly, more experience is needed to be able to come to definite conclusions on these issues.

Additional important information can be derived from this trial due to the careful recording of patients' experiences after discontinuation of therapy. In order to do this systematically, we had to define relapse. On the basis of our experience and in correlation with the inclusion criterion for disease activity we chose a deterioration of ≥ 2 points on the NRS for pain to indicate a relapse. However, this cutoff needs to be further validated. In our study it proved quite useful since we observed that 50% of patients relapsed after a mean of 4.5 weeks. The remainder of the patients relapsed

some weeks later, but, importantly, in 2 of them long-standing remission of at least 20 months was induced by 3 months of treatment with etanercept. This is in accord with our previous pilot study with infliximab in AS[30], where one of 10 patients stayed in remission for at least one year after 3 infusions. This experience is also backed by recent results from France[25], in which 48 patients with AS were treated 6 weeks with infliximab: after 6 months 28% of patients had not had relapse. In addition, in the recent randomized controlled trials 21% of the patients were in partial remission after 12 weeks of treatment[13]. Thus, it seems possible that about 10%–20% of patients with SpA go into remission after a short course of treatment with biologics. Further trials are necessary to confirm these preliminary results. Our data underline that discontinuation of anti-TNF-α therapy may be tried in a subset of patients that needs to be defined.

Thus, anti-TNF-α therapy combined with etanercept is very likely to be useful for patients with active undifferentiated spondyloarthritis.

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