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Efficacy of Etanercept in the Treatment of the Entheseal Pathology in Resistant Spondylarthropathy

A Clinical and Magnetic Resonance Imaging Study

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***Objective*. To determine the effect of tumor necrosis factor α (TNFα) blockade with etanercept on the clinical manifestations of resistant spondylarthropathy (SpA) and on axial and peripheral entheseal lesions using magnetic resonance imaging (MRI).**

***Methods*. We performed a descriptive longitudinal study of 10 SpA patients, all of whom had active inflammatory back pain and peripheral involvement. Patients were treated with 25 mg subcutaneous etanercept twice weekly for 6 months. Clinical assessments included entheseal count, visual analog scale (VAS) scores for spinal pain during the day and night, VAS scores for entheseal pain, the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire. MRI scans of sacroiliac (SI) joints, the lumbar spine, and affected peripheral joints were performed using a 1.5T scanner employing T1-weighted, T2-weighted fat-suppressed (FS), and T1-weighted FS postgadolinium sequences at baseline and at 6 months. Enthesitis and associated osteitis were scored semiquantitatively in pre- and posttreatment scans.**

***Results*. There was a statistically significant improvement in all clinical and functional parameters ($P = 0.008$ for VAS spinal pain score during the day and for VAS spinal pain score during the night, $P = 0.008$ for the BASFI, and $P = 0.005$ for the BASDAI) as well as in quality of life ($P = 0.005$ for the ASQoL) at 6 months. Nine patients had a total of 44 MRI-detectable entheseal lesions. These were seen in the SI joints in 6 patients (n = 15 lesions), in the lumbar or cervical spine in 9 patients (n = 22 lesions), and in peripheral joints in 5 patients (n = 7 lesions). Overall, 86% of MRI-detected entheseal lesions either regressed completely or improved. No new lesions developed.**

***Conclusion*. These findings suggest that TNFα blockade with etanercept is markedly effective in controlling the clinical manifestations of SpA that is resistant to disease-modifying antirheumatic drugs. This is associated with marked improvement of enthesitis and associated osteitis pathology as determined by MRI.**

The spondylarthropathies (SpA) are a heterogeneous group of diseases characterized by entheseal and synovial involvement of both axial and peripheral skeleton. Inflammation at ligament, tendon, and capsular insertions, or enthesitis, is the hallmark of these diseases, and is the primary lesion in ankylosing spondylitis (AS), their most common clinical subgroup (1). On magnetic resonance imaging (MRI), diffuse bone edema or osteitis is seen at all sites of entheseal involvement in SpA (2,3). This is in contrast to rheumatoid arthritis (RA), in which synovitis is the primary joint abnormality.

While disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine and methotrexate, are useful in RA, evidence is lacking for comparable efficacy in SpA. Recently, tumor necrosis factor α (TNFα) blockade has been proven to be extremely efficacious in RA, and preliminary studies with infliximab have also shown considerable promise in SpA (4,5). However, while these therapies are effective in

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suppressing synovitis (6), it is unclear what effect, if any, this has on active enthesopathy and associated osteitis. The aims of this study were 2-fold: first, to assess in SpA the clinical efficacy of the recombinant human receptor etanercept; and second, to use MRI to investigate the impact of etanercept on enthesitis and associated osteitis in both the axial and peripheral skeleton.

PATIENTS AND METHODS

Patients and study protocol. The study was designed as a 24-week, single-center, open-label trial and had approval by the local ethics committee. All patients gave written informed consent. Eligible patients were adults of ages 18–65 years with a diagnosis of SpA according to the European Spondylarthropathy Study Group criteria (7). All had active axial and peripheral involvement defined, respectively, by back pain according to the criteria of Calin et al (8) and the presence of peripheral arthritis or enthesitis. Patients had failed to respond to nonsteroidal antiinflammatory agents and to at least 1 DMARD. Six patients who were receiving a stable dose of methotrexate for at least 4 weeks before the screening visit were allowed to continue this medication throughout the study period. Corticosteroids and sulfasalazine were discontinued 1 month before the beginning of the study. Exclusion criteria included pregnancy and known significant concurrent medical disease. Patients were treated with 25 mg subcutaneous etanercept twice weekly for 6 months.

Assessments of efficacy and outcome. *Clinical parameters*. For outcome parameters, we evaluated a core set of end points that included the visual analog scale (VAS) scores for spinal pain during day and night, the VAS scores for patient's and physician's global disease assessment, the enthesseal count of clinically accessible entheses, scores on the Bath Ankylosing Spondylitis Functional Index (9), and scores on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (10). Item number 4 from the BASDAI, considered to represent a VAS for enthesopathy, was reanalyzed independently.

Counts of 68 tender joints and 66 swollen joints were performed by a trained metrologist. Functional assessments included the Schober test for lumbar flexion performed by the same observer (HMO) at baseline, 12 weeks, and 24 weeks. The quality-of-life instrument used was the Ankylosing Spondylitis Quality of Life questionnaire (11).

Patients were examined every 4 weeks, at which time routine laboratory tests were performed, including a complete blood cell count, levels of urea and electrolytes, liver function tests, and C-reactive protein level. HLA–B27 type and rheumatoid factor and antinuclear antibody (ANA) positivity were assessed at baseline, and the assessment for ANA was repeated at weeks 12 and 24.

MRI. Scans were performed at baseline and at 24 weeks using a commercially available 1.5T Gyroscan ACS NT (Philips, Best, The Netherlands).

Systematic scanning of the sacroiliac (SI) joint and lumbar spine was performed in all patients. We performed T1-weighted turbo spin-echo (TSE) and T2-weighted spectral presaturation with inversion recovery (SPIR) (fat-suppressed [FS]) coronal oblique sequences as well as a T1 fast field echo SPIR post–gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA; volume of 1.5 mm^3) sequence of the SI joints and a T2 SPIR sagittal sequence of the lumbar spine. In the case of 2 patients with symptoms in the cervical spine, T2 SPIR sagittal sequences of this area were also performed.

MR parameters were as follows: an SE sequence with T1-weighted images (repetition time [TR] 908 msec, time to echo [TE] 14 msec, matrix 192/256, field of view [FOV] 320 mm, slice thickness 4.0 mm, slice gap 0.3 mm, number of signals averaged [NSA] 3, and acquisition time 2 minutes 56 seconds) was used for the SI joints. T2 TSE/FS acquisition parameters were as follows: for the SI joints, TR 2,125 msec, TE 120 msec echo train length, matrix 252/512, FOV 320 mm, slice thickness 4.0 mm, slice gap 0.4 mm, NSA 3, and acquisition time 2 minutes 54 seconds; and for the spine, TR 1,327 msec, TE 120 msec, FOV 320 mm, slice thickness 4.0 mm, slice gap 0.4 mm, matrix 247/512, NSA 4, and acquisition time 2 minutes 29 seconds.

For peripheral joints, coronal and sagittal T1, T2 FS, and T1 FS post–Gd-DTPA sequences were performed in a selected symptomatic joint in 7 patients. Parameters varied depending on the joint examined.

Definitions. MRI enthesitis was defined on T2 FS images as bone edema (identified by high or intermediate marrow signal) and/or soft tissue edema (high signal in the extracapsular connective tissues) adjacent to entheses. Joint effusion was defined as homogeneous high signal on T2 FS sequences. Synovitis was defined as intraarticular enhancement on the T1-weighted FS post–Gd-DTPA images.

MRI scoring. Two experienced observers, one a musculoskeletal radiologist (POC) and the other a rheumatologist (DMG), both of whom were blinded to the patients' clinical characteristics and to the chronology of scanning, scored paired scans independently. Randomization was undertaken using random numbers. A number of areas were systematically analyzed per joint. In the SI joints, 4 quadrants were assessed: right upper, left upper, right lower, and left lower. Each quadrant was subdivided into ilial and sacral aspects. In the spine, lesions were classified as present within the vertebrae or in the paraspinal soft tissues. In the peripheral joints, bone and soft tissue lesions were recorded depending on the joint examined. At baseline, all features were recorded as present or absent, and the total number of lesions per area scanned (SI, spine, and peripheral joints) was counted. To assess the degree of change between scans after therapy, paired scoring was performed for every lesion using a semiquantitative scale (-3 = resolution, -2 = moderate improvement, -1 = mild improvement, 0 = no improvement, 1 = mild deterioration, 2 = moderate deterioration, 3 = severe deterioration).

Statistical analysis. Variables are presented as the median, unless stated otherwise. Wilcoxon's matched pairs signed rank test was used to measure the significance of the change from baseline. P values less than 0.05 were considered significant.

RESULTS

The demographic details of the patients are shown in Table 1. Diagnoses included AS (n = 7), Crohn's spondylitis (n = 2), and undifferentiated SpA

Table 1. Summary of patient demographics and clinical and functional assessments at baseline and at 24 weeks*

	Baseline	Week 24	P†
Age, mean (range) years	37 (26–51)		
Men, %	90		
Disease duration, mean (range) years	12 (0.6–34)		
HLA–B27 positive, %	80		
Receiving methotrexate, %	60		
CRP level, mg/dl	43.5	15	0.025
EMS, minutes	120	2.5	0.008
Tender joint count (0–68 joints)	6	0	0.046
Swollen joint count (0–66 joints)	0.5	0	0.043
Schober test for lumbar flexion, cm	3.75	4.65	0.005
VAS scores (0–100-mm scale)			
Spinal pain during day	63.5	10	0.008
Spinal pain during night	71.5	4	0.008
Enthesopathy	62	3	0.008
Patient's global assessment of disease activity	70	3	0.005
Physician's global assessment of disease activity	60.5	3	0.005
BASFI score (0–10)	7.05	4.35	0.008
BASDAI score (0–10)	6.25	1.3	0.005
ASQoL score (0–18)	14	3	0.005

* Except where indicated otherwise, values are the median. CRP = C-reactive protein; EMS = early morning stiffness; VAS = visual analog scale; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASQoL = Ankylosing Spondylitis Quality of Life questionnaire.
† All values were significant ($P < 0.05$) by Wilcoxon's matched pairs signed rank test.

(uSpA; n = 1). All 10 patients had active axial disease and 7 patients had active peripheral joint disease involving 3 knee joints, 2 hip joints, and 2 hand joints on the day of scanning. Nine patients (90%) had evidence of clinical enthesitis at several discrete sites, including the costochondral joints (5 patients), sternum (3 patients), cervical spine (2 patients), thoracic spine (7 patients), and lumbar spine (2 patients). Of note, all clinically symptomatic entheseal sites that were scanned in the spine (n = 4) demonstrated entheseal inflammatory changes on MRI at baseline, which improved both clinically and on MRI following scanning.

Clinical outcomes. All standard clinical and quality-of-life outcome measures that were monitored improved significantly in all patients (Table 1). Enthesitis resolved completely in 7 patients and improved in the other 2 patients. This response was sustained up to the end of the study period (24 weeks). No adverse side effects were seen in any of the patients at any time during the study. One of the patients (the only woman in the cohort) who had a history of uveitis had a flare of unilateral uveitis during the study period and required local treatment.

MRI results. Consensus was required in 2 patients for 4 lesions**.** Nine patients had a total of 44 MRI-detectable entheseal lesions (in the SI joints [n = 15] in 6 patients, in the lumbar or cervical spine [n = 22] in 9 patients, and in peripheral joints [n = 7] in 5 patients). Overall, 38 MRI-detected entheseal lesions (86%) either resolved completely (score of −3) or improved (score of −2 or −1).

Findings in the SI joints. Nine of 10 patients were available for analysis, since 1 patient was excluded due to technical failure of the scan (failure of FS). Three patients were clinically asymptomatic and had no MRI-detectable inflammatory change. Six patients, all symptomatic, had active osteitis (subchondral edema) with a total of 15 lesions (Table 2). Appearances were symmetric in 4 patients and asymmetric in 2 patients, with the sacrum being the most commonly affected area (11 lesions). At followup, improvement was seen in 60% of the lesions, with complete resolution in 3 patients (6 lesions). One patient had partial improvement (graded −1; n = 3 lesions), and the remaining 2 patients were unchanged (n = 6 lesions).

Findings in the spine. Nine patients had a total of 22 active lesions in the spine (Table 2). Vertebral body lesions included Romanus lesions (n = 11), end-plate

Table 2. Summary of the scoring results of magnetic resonance imaging lesions at the different sites assessed before and after treatment with etanercept*

		Week 24			
	Baseline	Resolution	Improvement	No change	New lesions
Sacroiliac joint	15	6 (40)	3 (20)	6 (40)	0
Spine	22	17 (77)	5 (23)	0	0
Peripheral joints	7	4 (57)	3 (43)	0	0
Total†	44	27 (61)	11 (25)	6 (14)	0

* Values are the number (%) of lesions.
† A total of 38 lesions (86%) either resolved completely (score of −3) or improved (score of −2 or −1). A total of 6 lesions (14%) remained unchanged (score of 0).

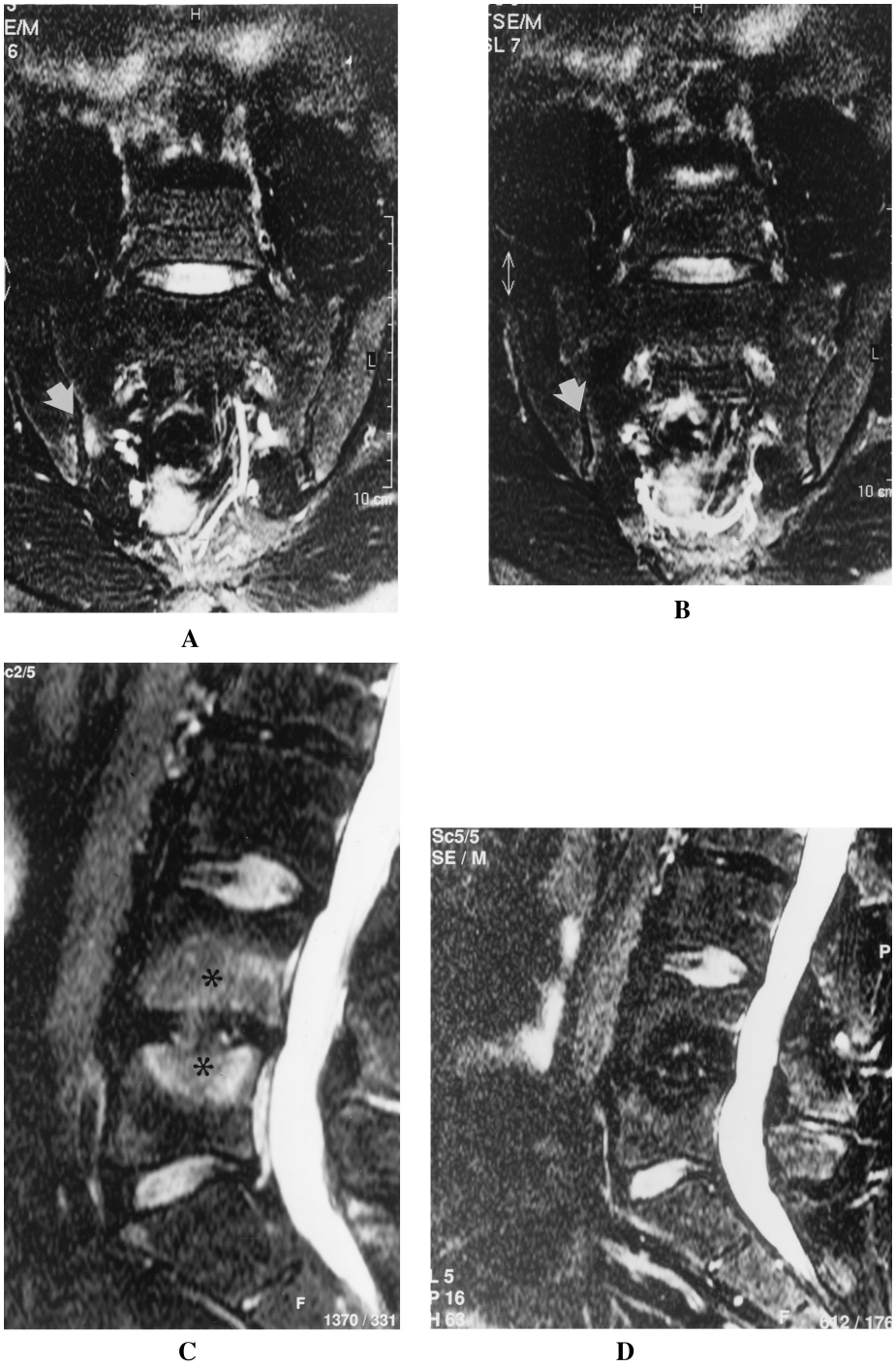
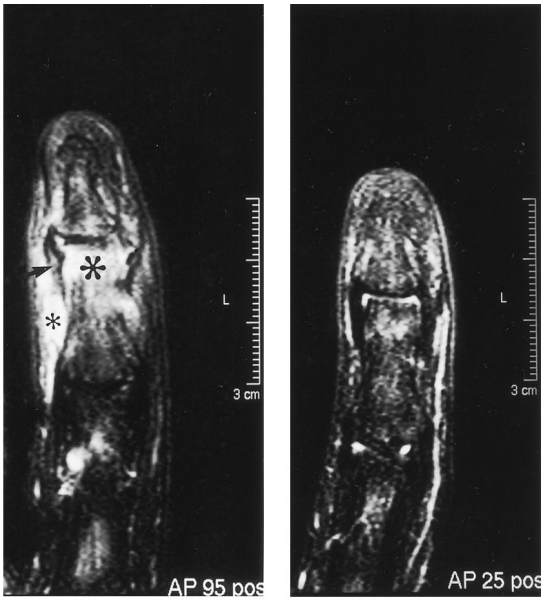


Figure 1. T2-weighted fat-suppressed (FS) coronal oblique magnetic resonance image of the sacroiliac (SI) joints of a patient with undifferentiated spondylarthropathy **A**, before, and **B**, after treatment with etanercept, showing resolution of bone edema in the inferior aspect of the right SI joint (**white arrows**). **C,** T2-weighted FS sagittal sequence of the lumbar spine of a patient with Crohn's-related spondylitis showing end-plate edema of the L4 inferior and L5 superior vertebral bodies (**black asterisks**). **D,** Followup scan after treatment with etanercept shows complete resolution of the edema.



A B

Figure 2. T1-weighted fat-suppressed post-gadolinium coronal sequence of the left second distal interphalangeal joint of a patient with undifferentiated spondylarthropathy. **A,** Appearance at baseline, before treatment with etanercept. There is extensive subcutaneous edema (**small black asterisk**) and bone marrow edema (**large black asterisk**) with inflammatory change within the collateral ligament (**black arrow**). **B,** The same joint after 6 months of treatment with etanercept, showing marked improvement of all the features described.

edema (n = 4) (Figure 1C), and spinous process edema (n = 3). Soft tissue inflammatory change was seen in or around facet joints (2 lesions) or related to ligamentous disease in the interspinous area (2 lesions). All spinal lesions improved following therapy. Seventeen lesions (77%) disappeared completely (score of −3), while the remaining 5 lesions (23%) showed moderate or mild improvement (score of −2 and −1, respectively). No new lesions developed.

Findings in the peripheral joints. Joints of the knee (3 joints), hip (2 joints), and hand (2 joints, including the distal interphalangeal and proximal interphalangeal joints) were examined. The only abnormalities demonstrable in the hip joint scans were low-grade synovitis and enthesitis at the psoas insertion in 1 patient. In the remaining cases, the most common abnormalities were semimembranous insertion enthesitis, posterior capsule insertion edema in the lateral tibia and femur, and diffuse subchondral edema in the tibial plateau in the knee. Capsular insertion edema, bone marrow edema, and subcutaneous edema were present in the hand joints (Figure 2). There was improvement in enthesitis and osteitis at all sites assessed. Synovitis was present in the 3 scanned knee joints (moderate in 2 joints, severe in 1 joint). Synovitis was also seen in the hand joints. There was marked improvement in all joints (from moderate to mild in 2 joints and from severe to moderate in 1 joint).

Positive clinical response was sustained for a median of 12 weeks (range 3–16 weeks) after discontinuation of etanercept. One patient (with uSpA) still has remission of disease at 9 months without any therapy. Interestingly, resolution of this patient's back pain correlated with complete regression of bone edema on his spine MRI (Figure 1D). Seven patients started taking etanercept again, 3 of whom had MRI evidence of subclinical disease (entheseal and synovial) at 24 weeks despite significant clinical improvement.

DISCUSSION

The aim of the present study was to assess the clinical efficacy of etanercept in SpA and to determine its effect on enthesitis and associated osteitis. All patients showed a dramatic clinical response, with complete regression or improvement of enthesitis and associated osteitis as shown on MRI. These findings support the idea that TNFα blockade is not only effective in suppressing synovitis, but is also efficacious in the primary SpA-associated pathology.

As has been shown with other commercially available anti-TNFα compounds (4,5), response was prompt and sustained throughout the study period. Moreover, there was a marked improvement in mobility outcomes, such as the modified Schober test for lumbar spine flexion, which correlated with resolution of MRI abnormalities, suggesting that there is room for functional improvement more than 10 years after disease onset. Clinically, etanercept was well tolerated and showed no evidence of significant toxicity. Most of our patients had flares of disease 8–12 weeks after stopping the drug, much the same as has been seen in RA patients. One patient's disease remains in remission more than 9 months after stopping etanercept. Interestingly, this patient (diagnosed as having uSpA) had a disease duration of only 8 months, which suggests the potential for major disease modification in this subgroup of patients with early disease.

The pathogenesis of SpA is poorly understood, and treatment options are often the same as those for RA. Conventional therapies are generally less efficacious in SpA than in RA, due mostly to their effect in synovial structures (12). There is little evidence that

these therapies alter disease progression in SpA. The identification of TNFα messenger RNA and protein (13) in sites of entheseal involvement, such as the SI joints, suggests that this is a novel target in SpA. However, unlike RA, in which these agents act in the synovium, the site of action in SpA has not been identified. This study shows that the good clinical response seen in these patients is mirrored by the regression of MRI changes, confirming the role of TNFα at the different sites of disease in SpA.

To the best of our knowledge, there are no reports of regression of the enthesitis pathology in SpA with DMARD therapies. Previous histologic studies have confirmed that MRI-determined bone edema correlates with an osteitis and with enthesitis (14,15). It has also been suggested that these lesions are the forerunners of severe bone destruction or new bone formation that is evident in SpA (16). It is therefore possible that by switching off the diffuse osseous pathology, TNFα blockade could prevent complications of SpA, such as mutilating arthritis. The concept that MRI could be used to determine whether a therapy has disease-modifying activity in SpA awaits formal assessment in controlled trials. Such trials would determine whether regression of changes seen on MRI prevents the development of ankylosis and bone damage.

In conclusion, this study shows that etanercept has considerable promise in treating patients with previously DMARD-refractory SpA. The marked clinical efficacy of this therapy is associated with improvement and with regression of the enthesitis- and osteitis-associated pathology. This suggests that biologic therapy is not only useful for treating synovitis, but is also useful for treating the distinct enthesitis-associated bone pathology. Longitudinal studies of early disease will answer the question of whether these therapies constitute true long-term disease modifiers in SpA.

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