

Prolonged Efficacy of Etanercept in Refractory Enthesitis-Related Arthritis

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ABSTRACT. *Objective.* For many children enthesitis-related arthritis (ERA) causes substantial morbidity, and conventional treatments frequently offer limited efficacy. Tumor necrosis factor- α (TNF- α) has been found to play a central role in the spondyloarthritides. We investigated the longterm efficacy of the TNF fusion protein etanercept in the treatment of patients with ERA refractory to disease modifying antirheumatic drug (DMARD) therapy.

Methods. Eight patients with active, inflammatory ERA were treated in an open-label pilot trial of twice weekly subcutaneous injections (dosing range of 25 to 37.5 mg twice weekly, 0.2–0.8 mg/kg/dose) of etanercept for 2 years. Outcome measures included duration of morning stiffness, active joint count, hemoglobin, and erythrocyte sedimentation rate (ESR). Patients were permitted concomitant nonsteroidal antiinflammatory drugs (NSAID) and DMARD at stable doses.

Results. Treatment with etanercept resulted in significant improvement in active joint count, hemoglobin, and ESR in all 8 patients within 2 months. Additionally, all patients noted increased mobility and overall well being. Improvement in morning stiffness did not achieve statistical significance. One patient was lost to followup after completing one year of the study. The remaining 7 patients had sustained statistically significant efficacy for active joint count, hemoglobin, and ESR throughout the entire 2-year trial. All patients tolerated etanercept with no side effects.

Conclusion. Despite limited power, these results indicate that etanercept provided a rapid clinical response in our cohort of patients with refractory ERA, who achieved sustained efficacy over a 2-year period. (J Rheumatol 2004;31:2055–61)

Key Indexing Terms:

ENTHESITIS-RELATED ARTHRITIS

JUVENILE ANKYLOSING SPONDYLITIS
ETANERCEPT

Enthesitis-related arthritis (ERA)¹, also previously termed juvenile ankylosing spondylitis (JAS), is a chronic inflammatory arthritis of the axial and peripheral skeleton, often accompanied by enthesitis, with a strong genetic association to the HLA-B27 antigen. In children and adolescents disease onset is frequently characterized by peripheral joint disease alone, and axial skeleton symptoms are often absent. In JAS, axial and sacroiliac joint disease involvement is a late feature, occurring most frequently after 5–10 years of disease duration². However, longterm functional disability can be quite substantial due to peripheral joint disease.

As many as 20–40% of patients with JAS/AS experience a moderately or severely persistent disease course with a high risk for permanent disability; these patients often have a particularly poor response to conventional immunosup-

pressive therapies^{3–5}. Arthritis of the hip, which is more prevalent among younger patients, is a major prognostic marker for poor disease outcome; juvenile onset patients without hip involvement do not typically have more severe disease^{6–8}.

Tumor necrosis factor- α (TNF- α) is an important mediator of the pathophysiologic events sustaining chronic JAS. The synovia of patients with juvenile spondyloarthritis are characterized by the presence of TNF- α and TNF- β and various cell lines expressing TNF receptors (p55 and p75)⁹. Higher TNF p75 receptor staining in synovial tissue has been described in juvenile spondyloarthritis compared to patients with polyarticular juvenile rheumatoid arthritis (RA) enrolled in the same study⁹. Synovial tissue TNF- α mRNA expression correlated well with these histochemical findings, and TNF- α expression was particularly marked in the patients with juvenile spondyloarthritis. Similarly, elevated TNF- α expression in the synovium of the peripheral^{10–12} and sacroiliac joints^{13–15} and high amounts of TNF- α messenger RNA at the sacroiliac joints¹⁶ have been described in adult patients with AS, strongly suggesting that TNF- α is central to the pathogenesis of spondyloarthritis at the effector level.

Etanercept has been established as a safe and efficacious medication for children with treatment-resistant polyarthritis (juvenile idiopathic arthritis/polyarticular juve-

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nile RA)^{17,18}. Etanercept is a recombinant fusion protein that combines 2 extracellular human p75 TNF-receptors with the Fc domain of a human immunoglobulin (IgG₁) and effectively neutralizes TNF- α and lymphotoxin- α before binding to its receptors.

Reports of studies using TNF- α inhibitors, either etanercept or infliximab, for AS describe statistically significant improvements within 2–12 weeks after commencing therapy. However, there is no experience with TNF- α inhibitors in ERA. Two studies using etanercept in randomized, double-blind, placebo-controlled trials have reported efficacy, one for 4 months with a 6-month open-label extension, the other a multicenter trial with a 6-month treatment duration^{19,20}. Another etanercept study was a double-blind, placebo-controlled multicenter trial with initial randomization to treatment or control groups for 6 weeks, followed by all subjects receiving treatment for a total of 3 months, and a 6-month observational phase after etanercept withdrawal²¹. Several infliximab studies have shown remarkable efficacy, including 4 open-label trials^{22–25} and a 3-month multicenter, placebo-controlled trial followed by a one-year open-label extension^{26,27}.

In this open-label pilot study we assessed whether etanercept would diminish disease activity and if it would provide sustained efficacy in a cohort of 8 children and adolescents with refractory ERA over a 2-year period. Our hypotheses were that etanercept would diminish the clinical disease activity in this ERA cohort and that it would have sustained efficacy with prolonged use. This ERA study is the first trial in a juvenile population to test these hypotheses.

MATERIALS AND METHODS

Patients. The cohort's baseline characteristics are summarized in Table 1. Each patient fulfilled diagnostic criteria for ERA, Amor criteria, and European Spondylarthropathy Study Group criteria for spondylarthropathy^{1,28,29}.

The study was approved by the institutional review board of Children's Hospital Central California. We obtained written informed consent in English or Spanish. Etanercept was supplied via prescription, and each patient's own medical insurance(s) covered pharmaceutical costs. Immunex Corporation, Amgen Inc., and Wyeth-Ayerst Pharmaceuticals were not involved in the study design, data collection, statistical analysis, or manuscript preparation; these functions were completed by the authors.

Our inclusion criteria were the diagnosis of ERA, active synovitis in one or more joints despite the use of at least one DMARD, prolonged morning stiffness, and an elevated ESR. All patients were taking stable concomitant medications for a month prior to enrolling in the study. No patient was taking corticosteroids, and no intraarticular injections were used for a year prior to starting etanercept; no patient received intraarticular injections during the 2-year study period. Exclusion criteria were any diagnosis other than ERA, any patient who had a first or second-degree relative with psoriasis confirmed by a dermatologist, a history of recurrent infections, or a serious, uncontrolled and clinically significant systemic disorder (hepatic, renal, neurologic, endocrine, cardiac, gastrointestinal, or hematologic).

Because of the paucity of peripheral or axial joint disease in ERA, neither the American College of Rheumatology core criteria nor the Bath

Table 1. Baseline patient characteristics (n = 8).

Characteristic	Result
Males, %	88
Ethnicity, %	
Mexican	88
Caucasian	12
HLA-B27 positive, %	88
Age, yrs	15.9 \pm 4.5
Disease duration, yrs	4.4 \pm 5.4
Peripheral joint disease involvement, %	100
Enthesitis, %	50
Concomitant medications, %	—
NSAID	88
DMARD	100
Corticosteroids	0
Combination therapy	75
Bilateral hip joint prostheses, %	12
Radiographic progression of disease, %	38
Steinbrocker class, n (%)	—
I	0
II	5 (63)
III	2 (25)
IV	1 (12)

AS Disease Activity Index have been validated in ERA or JAS, as these juvenile diseases are typified by the presence of enthesitis and the relatively few peripheral compared to axial joints involved. Due to these limitations, we selected these outcome measures: regression of joint disease activity by at least 50% and improvement in ESR, morning stiffness, and any baseline anemia. We did not use the Childhood Health Assessment Questionnaire for serial evaluation, nor did we examine serial radiographs in our patient series during the remainder of the study.

Protocol. All 8 patients received etanercept 25 mg subcutaneously twice weekly initially, in addition to their prestudy entry medication regimen. Three patients were allowed a dose increase while on the study to a maximum of 37.5 mg twice weekly to assess for improved efficacy; thus, the dosing range was 0.2–0.8 mg/kg/dose twice per week. Five of 8 patients received concomitant methotrexate (MTX) during the study. Two pediatric rheumatologists each followed 4 patients at their respective centers and completed every history and physical examination assessment. All 8 patients completed a one-year course of etanercept. Seven of 8 patients completed the 2-year course of etanercept, as one patient discontinued the study after 14 months due to loss of followup.

Statistical analysis. Statistical methods used were the repeated measures analysis of variance for tests of between-subjects effects (morning stiffness, ESR, hemoglobin, and active joint count) and a 2-tailed t test for equality of the means.

RESULTS

Table 2 summarizes the clinical and laboratory data. Eight patients, 7 male and one female, average age 15.9 years (range 12–25) with ERA onset at a mean age of 11.5 years (range 8–16) and mean disease duration 4.5 years (range 1.2–17.5), were enrolled in the study and followed for 2 years. Seven patients were of Mexican and one patient was of Northern European ethnicity. Seven of 8 patients were HLA-B27 positive; one male patient was HLA-B27 negative. All 8 subjects had persistent synovitis [including 6 (75%) with active hip disease] and elevated ESR, and 6 had anemia prior to etanercept treatment. Four of the 8 patients

Table 2. Clinical and laboratory data summary.

	0	2	4	6	9	12	15	18	21	24
Morning stiffness, mean min (SD)	175 (265)	6.4 (11.8)	4.3 (7.9)	2.9 (7.6)	0 (0)	1.9 (5.3)	0 (0)	2.5 (5)	0 (0)	0 (0)
Mean joint count (SD)	8.1 (3.9)	3.6 (3.0)	1.9 (1.4)	1.7 (1.5)	0.8 (0.5)	0.6 (1.1)	1.0 (0.9)	0.5 (0.6)	0.6 (0.5)	0.3 (0.5)
Hemoglobin, mean g/l (SD)	113 (16.4)	123 (16.9)	126 (13.6)	136 (14.4)	142 (10.8)	138 (13.7)	137 (14.5)	141 (7.6)	131 (5.5)	134 (14.0)
ESR, mean mm/h (SD)	64 (30)	37 (36)	17 (12)	20 (20)	10 (5.3)	12 (11)	16 (18)	12 (4.3)	21 (31)	33 (46)

SD: standard deviation.

(50%) had active enthesitis. All 8 had refractory disease, with prolonged morning stiffness and a poor sense of well being. Despite maximal therapy with multiple NSAID and MTX in all patients, and the prior or concomitant use of other DMARD [including cyclosporine A (CSA; $n = 2$), sulfasalazine ($n = 7$), oral prednisone ($n = 3$), tacrolimus ($n = 1$), plaquenil ($n = 1$), chlorambucil ($n = 1$), azathioprine ($n = 1$)] in 7/8 patients, all 8 patients continued to have persistent synovitis. Four of 8 patients used combination DMARD therapy, that is, the use of one of the following medications in addition to NSAID and MTX: sulfasalazine, CSA, or tacrolimus. Before starting etanercept one patient had bilateral total hip replacement due to advanced, antecedent hip disease.

Three of the 8 patients (38%) had radiographic disease progression at baseline, including bilateral hip and other peripheral joint space narrowing, hip joint erosions, and sacroiliac sclerosis varying in severity from mild to severe. Another 2 patients had concomitant joint sclerosis (one mild, one severe and multifocal, including sacroiliac joint). The patient with the longest disease duration (17.5 years) had additional joint space narrowing in numerous other joints (noted 1.8 years before starting etanercept) and moderate osteoporosis of his lumbar spine by dual-energy x-ray absorptiometry. He had used oral prednisone for 8 years before study entry, and notably was one of the juvenile spondyloarthropathy patients described in the study of

synovial TNF expression in juvenile patients reported by Grom, *et al*⁹.

Outcome measures. Figures 1–4 illustrate the normalization of the patients' duration of morning stiffness, decreased active joint count and ESR, and increased hemoglobin. By month 2, all 8 patients (100%) experienced a significant reduction in their active joint counts ($p = 0.009$), which was sustained throughout the 2-year study period ($p = 0.008$) for the remaining 7 subjects. ESR improved significantly by 2 months ($p < 0.0001$), as did hemoglobin levels ($p = 0.007$), and both remained stable over time for the remaining 7 subjects throughout the 2-year study period ($p < 0.0001$ for ESR and $p = 0.007$ for hemoglobin). All patients reported decreased fatigue and an enhanced sense of well being. Enthesitis present in 4 subjects at study onset resolved in all 4 within 2 months after etanercept had been started. At baseline, Steinbrocker classification of these 8 patients was as follows: 5 patients with class II (63%), 2 with class III (25%), and one patient with class IV (12%). After completing 2 years of etanercept treatment, 5 of the remaining 7 patients improved their status: 4 patients became class I (50%), one became and one maintained class II (25%), and one maintained class III (12%). The one patient who discontinued the study had no anemia, a normal ESR, no morning stiffness, and an active joint score of zero from 6 months until his loss to followup at 14 months; his Steinbrocker classification had improved from class II to class I.

Reduction in the duration of morning stiffness, a patient-reported, nonparametric measurement, did not achieve statistical significance by 2 months ($p = 0.109$) nor during any specific time interval of the study, including the 2-year point ($p = 0.14$). Notably, 2 of the 8 patients reported "all-day" stiffness (10 hours) at baseline, with reductions at 2 months to 30 minutes of morning stiffness. However, all patients reported a clinically appreciable reduction in their morning stiffness. The experience of just one or 2 outlying patients in such a small cohort can skew the statistical results of such a measurement (the standard deviation was 265 minutes at baseline and 11.8 minutes at 2 months).

Medication reductions. Table 3 summarizes baseline and end of trial medications used by each patient. The average reduction in MTX dosing was 10%. One patient discon-

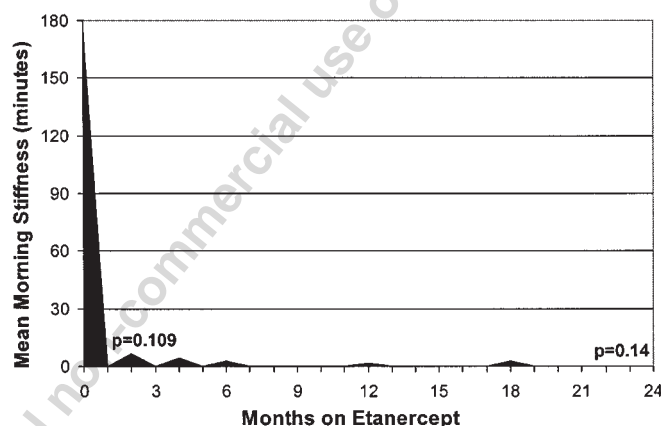


Figure 1. The duration of morning stiffness decreased markedly within the first 2 months of etanercept administration.

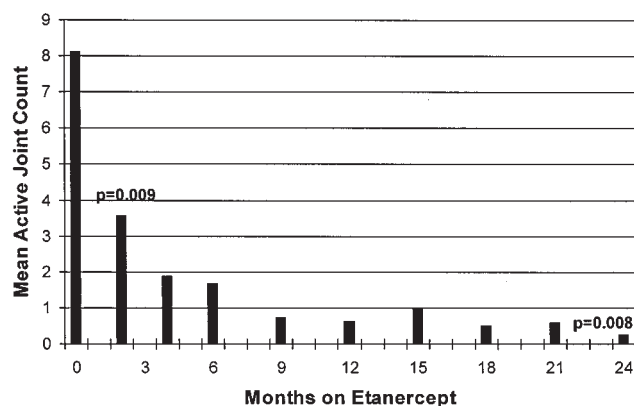


Figure 2. The active joint count decreased markedly by 2 months, improved further after 6 months, and was maintained for 2 years.

tinued CSA use at month 9 of the study. Three of the patients had such dramatic improvement that their etanercept doses were decreased to once per week rather than twice per week at months 20 ($n = 2$) and 21 ($n = 1$). This approach of decreasing etanercept was temporally associated with a progressive rise in the ESR over the study's last 3 months. One of these 3 patients experienced transient enthesitis and mild unilateral ankle arthralgia that spontaneously resolved in less than a week. Another patient was able to discontinue etanercept after being in sustained remission for more than one year, but flared roughly 2 months after discontinuation of etanercept. After restarting the drug twice weekly, he remains well controlled.

Except for mild injection site reactions, all patients tolerated etanercept therapy without adverse effects. We did not observe laboratory abnormalities, significant infections or lupus-like symptoms. We did not perform routine assessment for antinuclear antibody or double-stranded DNA antibody formation after the initiation of etanercept treatment.

DISCUSSION

Our aim was to assess the efficacy of etanercept in a cohort of patients with refractory enthesitis-related arthritis and to determine if such efficacy would remain sustained over a prolonged interval of 2 years. We observed remarkable efficacy of etanercept in a small cohort of severely affected patients with refractory ERA. All patients had severe, unremitting disease; 7/8 patients had failed at least one prior DMARD. Clinical and laboratory responses were swift — disease amelioration followed in an equally rapid fashion, including a marked reduction in both morning stiffness and active synovitis within the first 2 months after introduction of etanercept treatment. This experience is similar to the published results of TNF- α inhibitors in adults with AS. Statistical significance was achieved for decreased active joint count, resolution of anemia, and decreased ESR by month 2; these effects had a durable response over the 2-year study period and treatment was safe. After 2 years of treatment, Steinbrocker classification status improved for 5 of 7 patients (71%); additionally, the one patient lost to followup improved his status to normal by one year of the study.

This open-label pilot study has several limitations. The study had very limited power due to its sample size; it will at best show a large effect. Morning stiffness was reported and compared as a nonparametric measurement, likely skewed by the experience of 2 “outlying” patients in our small cohort. Patients were asked about their degree of fatigue, joint mobility, and overall well being, and subjective responses were recorded instead of using a functional questionnaire. All patients responded that they experienced marked improvement. Spinal measurements, although assessed (data not shown), have not been included in our report, as these data do not adequately reflect the advanced extent of peripheral disease in these patients. Compliance with etanercept injections was confirmed only by direct questioning. Sample bias

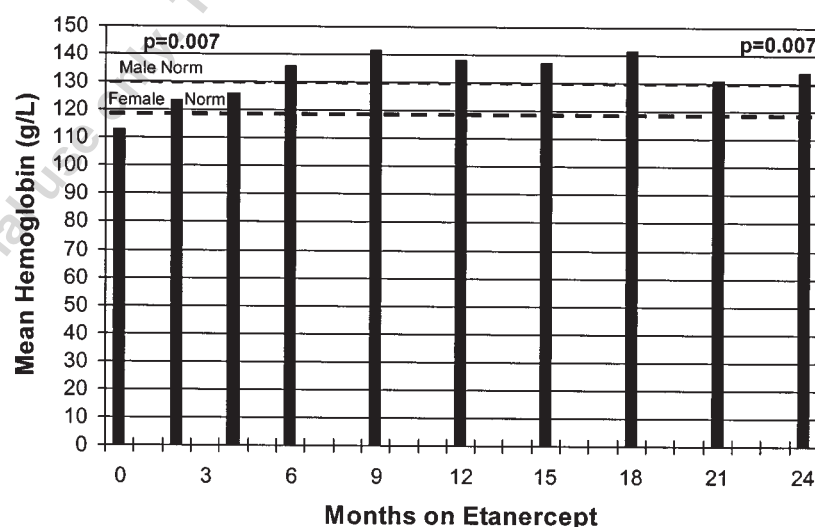


Figure 3. A statistically significant increase in hemoglobin occurred by 2 months, with a sustained effect for the 2-year study duration. Normal values varied by sex (broken lines).

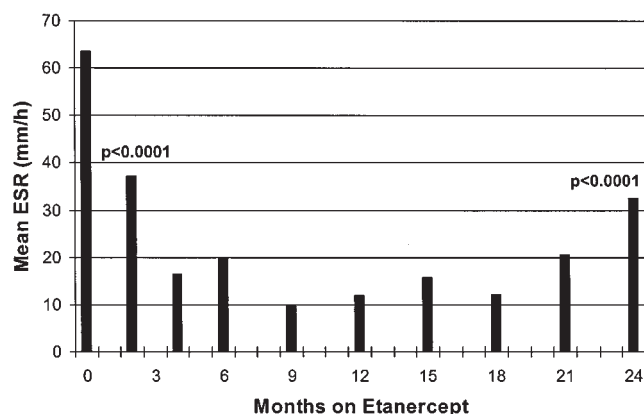


Figure 4. The Wintrobe ESR reveals an initial trend toward normal (10 mm/h) by 9 months; substantial reduction occurred during the initial 4 months. A progressive rise over the 2-year duration of the study was temporally associated with a taper of etanercept dose in 3 patients.

of the choice of ERA subjects was toward those patients with evidently severe, refractory disease. Thus, conclusions regarding the applicability of these study results to a broader ERA population may not be valid.

Although this was only a small selected cohort of patients with refractory disease, the disease course in most of these children emphasizes that patients with JAS often have worse

functional outcomes compared to adults with AS (Steinbrocker functional classes III and IV)^{30,31}. Patients with JAS have predominantly lower limb involvement, resulting in nearly 60% having moderate to severe limitations by 10 years of disease duration³². Although an open-label design, our ERA study is the first trial in a juvenile population with refractory disease to describe sustained statistically significant efficacy of etanercept for a 2-year period.

In adult patients with AS treated with etanercept for 3 months, etanercept appears to achieve its effects by preferentially binding soluble TNF- α without suppressing T cell function. In other studies of a similar population treated with infliximab for 3 months, infliximab neutralizes TNF- α , but it also appears to decrease T-helper-1 cell function and the T cell production of TNF- α ^{16,33}. Further, CD4+ T cell TNF- α and interferon- γ production increase after etanercept treatment, while infliximab treatment decreases both CD4+ and CD8+ T cell production of these cytokines^{16,34}. This may explain why there is an increased frequency of tuberculosis and other intracellular microbial infections requiring intact T cell function in patients treated with infliximab. Regarding these infection risks, etanercept may be a safer choice than infliximab. Three of our patients (38%) had improvement in their disease measures after increasing their

Table 3. Medications and Steinbrocker classification at baseline and at end of trial.

Patient	Baseline	End of Trial (2 yrs)
1	Indomethacin (3 mg/kg/day) MTX (32.5 mg/wk IM) CSA (6.5 mg/kg/day) Steinbrocker II	Indomethacin (2.1 mg/kg/day) MTX (20 mg/wk SQ) Etanercept 37.5 mg biw (0.8 mg/kg) Steinbrocker I
2	Tacrolimus (0.2 mg/kg/day) MTX (22.5 mg/wk IM) No NSAID due to history of tubulointerstitial nephritis Steinbrocker III	Tacrolimus (0.2 mg/kg/day) MTX (17.5 mg/wk PO) Etanercept 32.5 mg biw (0.5 mg/kg) Steinbrocker II
3	Naproxen (20 mg/kg/day) MTX (35 mg/wk SQ) Steinbrocker II	Naproxen (19 mg/kg/day) MTX (25 mg/wk SQ) Etanercept 37.5 mg biw (0.6 mg/kg) Steinbrocker II
4	Indomethacin (3 mg/kg/day) MTX (37.5 mg/wk SQ) Steinbrocker II	Lost to followup at 14 months (Steinbrocker I at 1 year)
5	Naprosyn (16 mg/kg/day) MTX (20 mg/wk PO) Steinbrocker II	Etanercept 25 mg qwk (0.6 mg/kg) Steinbrocker I
6	Naprosyn (13 mg/kg/day) MTX (15 mg/wk PO) Steinbrocker II	Naprosyn (11 mg/kg/day) Etanercept 25 mg biw (0.4 mg/kg) Steinbrocker I
7	Naprosyn (18 mg/kg/day) MTX (20 mg/wk PO) Steinbrocker IV	Etanercept 25 mg qwk (0.3 mg/kg) Steinbrocker I
8	Indomethacin (3.3 mg/kg/day) Sulfasalazine (27 mg/kg/day) MTX (10 mg/wk PO) Steinbrocker III	Ibuprofen (10 mg/kg/day) Prednisone (10 mg/day) MTX (25 mg/wk PO) Etanercept 25 mg biw (0.9 mg/kg) Steinbrocker III

etanercept dose from 25 mg to 37.5 mg twice weekly, at months 10, 13, and 22, respectively. We hypothesize these higher doses may be required to neutralize the observed upregulated CD4+ T cell TNF- α production noted during *in vitro* studies of adult patients with AS.

Our patient population is skewed toward identifiable ethnic and geographic risk factors known to contribute to the variation in ERA disease severity. In the Mexican Mestizo population, AS develops in 28–54% of patients before the age of 16 years^{35,36}. Regarding putative “severity” genes, a significantly higher prevalence of DRB1*08 was found in Mexican patients with JAS compared to a control group of well, unrelated Mexican Mestizo³⁷. Although we did not perform HLA Class II allelic subtyping, these findings are relevant to our study’s geographic region, where 36–39% of the juvenile population is Hispanic³⁸, of which 72–86% is Mexican³⁹.

The trend of increasing ESR and early flare in those patients who decreased or discontinued their etanercept dosing in the last part of the study suggests that etanercept is not a disease modifying, but rather a disease remitting agent. We feel that a larger trial of etanercept in ERA should be initiated to validate our findings. Given the prolonged mean duration of disease severity in this small group (4.4 ± 5.4 years), and the advancing joint disease present in patients refractory to multiple prior and concomitant medications, etanercept merits consideration for a controlled trial in this population. Although we did not do so, assessment by serial radiographs or magnetic resonance imaging would be useful data to include in a prospective trial of etanercept, which could also determine if early intervention with etanercept could prevent radiographic disease progression in ERA.

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REFERENCES

- Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban 1997. *J Rheumatol* 1998;25:1991-4.
- Burgos-Vargas R, Vazquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. *Arthritis Rheum* 1995;38:835-44.
- Flato B, Aasland A, Vinje O, Forre O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. *J Rheumatol* 1998;25:366-75.
- Garcia-Consuegra Molina J, Merino Munoz R, Fernandez Revuelta S, Soler Balda C. Juvenile spondyloarthropathies: descriptive study of 40 patients. *An Esp Pediatr* 1998;48:489-94.
- Amor B, Santos RS, Nahal R, Listrat V, Dougados M. Predictive factors for the longterm outcome of spondyloarthropathies. *J Rheumatol* 1994;21:1883-7.
- Brophy S, Calin A. Ankylosing spondylitis: interaction between genes, joints, age at onset, and disease expression. *J Rheumatol* 2001;28:2283-8.
- Claudepierre P, Gueguen A, Ladjouze A, et al. Features associated with juvenile onset of spondyloarthropathies in North Africa. *Rev Rhum Engl Ed* 1996;63:87-91.
- Calin A, Elwood J. The relationship between pelvic, spinal and hip involvement in ankylosing spondylitis — one disease process or several? *Br J Rheumatol* 1988;27:393-5.
- Grom AA, Murray KJ, Luyrink L, et al. Patterns of expression of tumor necrosis factor α , tumor necrosis factor β , and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondylarthropathy. *Arthritis Rheum* 1996;39:1703-10.
- 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.
- Heilig B, Pezzutto A, Lukoschek M, Hunstein W. Expression of TNF receptors in rheumatoid arthritis and ankylosing spondylitis. *Z Rheumatol* 1993;52:383-9.
- Gratacos J, Collado A, Filella X, et al. Serum cytokines (IL-6, TNF- α , IL-1 β and IFN- γ) in ankylosing spondylitis: a close correlation between IL-6 and disease activity and severity. *Br J Rheumatol* 1994;33:927-31.
- Braun J, Grolms M, Sieper J. Three-colour flow cytometric examination of CD4/CD45 subsets reveals no differences in peripheral blood and synovial fluid between patients with reactive arthritis and rheumatoid arthritis. *Clin Exp Rheumatol* 1994;12:17-22.
- Braun J, Bollow M, Sieper J. Radiologic diagnosis and pathology of the spondyloarthropathies. *Rheum Dis Clin North Am* 1998;24:697-735.
- Ohashi K, Hara M, Kawai R, et al. Cervical discs are most susceptible to beta 2-microglobulin amyloid deposition in the vertebral column. *Kidney Int* 1992;41:1646-5.
- Zou JX, Braun J, Sieper J. Immunological basis for the use of TNF α -blocking agents in ankylosing spondylitis and immunological changes during treatment. *Clin Exp Rheumatol* 2002;20 Suppl 28:S34-7.
- Lovell DJ, Giannini EH, Reiff A, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003;48:218-26.
- Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763-9.
- Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α . *N Engl J Med* 2002;346:1349-56.
- Davis JC Jr, van der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;48:3230-6.
- Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003;48:1667-75.
- Breban M, Vignon E, Claudepierre P, et al. Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. *Rheumatology Oxford* 2002;41:1280-5.
- Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor α monoclonal antibody infliximab. *Arthritis Rheum* 2000;43:1346-52.
- Stone M, Salonen D, Lax M, Payne U, Lapp V, Inman R. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. *J Rheumatol* 2001;28:1605-14.
- Temekonidis TI, Alamanos Y, Nikas SN, et al. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study.

- Ann Rheum Dis 2003;62:1218-20.
26. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;359:1187-93.
 27. Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. *Arthritis Rheum* 2003;48:2224-33.
 28. Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondylarthropathies. *Rev Rhum Mal Osteoartic* 1990;57:85-9.
 29. Amor B, Dougados M, Listrat V, et al. Evaluation of the Amor criteria for spondylarthropathies and European Spondylarthropathy Study Group (ESSG). A cross-sectional analysis of 2,228 patients. *Ann Med Interne* 1991;142:85-9.
 30. Calin A, Elswood J. The natural history of juvenile-onset ankylosing spondylitis: a 24-year retrospective case-control study. *Br J Rheumatol* 1988;27:91-3.
 31. Garcia-Morteo O, Maldonado-Cocco JA, Suarez-Almazor ME, Garay E. Ankylosing spondylitis of juvenile onset: comparison with adult onset disease. *Scand J Rheumatol* 1983;12:246-8.
 32. Horneff G, Burgos-Vargas R. TNF- α antagonists for the treatment of juvenile-onset spondyloarthritides. *Clin Exp Rheumatol* 2002;20 Suppl 28:S137-42.
 33. Baeten D, Kruithof E, Van den Bosch F, et al. Immunomodulatory effects of anti-tumor necrosis factor alpha therapy on synovium in spondylarthropathy: histologic findings in eight patients from an open-label pilot study. *Arthritis Rheum* 2001;44:186-95.
 34. Zou J, Rudwaleit M, Brandt J, Thiel A, Braun J, Sieper J. Down-regulation of the nonspecific and antigen-specific T cell cytokine response in ankylosing spondylitis during treatment with infliximab. *Arthritis Rheum* 2003;48:780-90.
 35. Jimenez-Balderas FJ. Cuadro clinico de al espondilitis anquilosante en el caucasop y en el mestizo mexicano. *Rev Mex Rheumatol* 1989;4:17.
 36. Burgos-Vargas R, Naranjo A, Castillo J, Katona G. Ankylosing spondylitis in the Mexican mestizo: patterns of disease according to age at onset. *J Rheumatol* 1989;16:186-91.
 37. Maksymowych WP, Gorodezky C, Olivo A, et al. HLA-DRB1*08 influences the development of disease in Mexican Mestizo with spondyloarthropathy. *J Rheumatol* 1997;24:904-7.
 38. U.S. Census Bureau, P145H. Sex by age (Hispanic or Latino) [49] — Universe: Hispanic or Latino population. Data Set: Census 2000 Summary File 3 (SF 3) — Sample Data. 2000. [Cited July 15, 2004]. http://factfinder.census.gov/servlet/DTTable?_bm=y&-context=dt&-ds_name=DEC_2000_SF3_U&-mt_name=DEC_2000_SF3_U_P145H&-CONTEXT=dt&-tree_id=403&-all_geo_types=N&-geo_id=05000US06019&-geo_id=05000US06037&-format=&-_lang=en
 39. Census of Population and Housing, 2000 [California]: Hispanic or Latino by specific origin. Summary File 1 [on-line data file]/prepared by the California Digital Library, Oakland, California: [producer and distributor]. 2001. [Cited May 31, 2004]. <http://countingcalifornia.cdlib.org/matrix/c118.html>