Case Report

Radiologic Improvement of Juvenile Idiopathic Arthritis-Enthesitis-Related Arthritis Following Anti-Tumor Necrosis Factor-α Blockade with Etanercept

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ABSTRACT. Children with juvenile spondyloarthropathy, classified as enthesitis-related arthritis (ERA) under the International League of Associations for Rheumatology classification of juvenile idiopathic arthritis, usually experience both arthritis and enthesitis. Treatment with anti-tumor necrosis factor-α (TNF-α) agents has resulted in dramatic clinical improvement. Radiologic imaging methods useful in the detection, diagnosis, and grading of arthritis and enthesitis include magnetic resonance imaging and ultrasonography. We describe the serial radiologic improvements of arthritis and enthesitis in a child with ERA in response to treatment with the anti-TNF-α agent etanercept. (J Rheumatol 2006;33:1186–8)

Key Indexing Terms:
JUVENILE SPONDYLOARTHROPATHY
COLOR POWER DOPPLER
TUMOR NECROSIS FACTOR-α
MAGNETIC RESONANCE IMAGING
ENTHESITIS RELATED ARTHRITIS
ETANERCEPT

The juvenile spondyloarthropathies (SpA), referred to as enthesitis-related arthritis (ERA) under the International League of Associations for Rheumatology classification of juvenile idiopathic arthritis, are characterized by both arthritis and enthesitis beginning in a child younger than 16 years of age. Standard antirheumatic therapy provides symptomatic relief but generally does not alter disease progression[1-3]. One promising therapy is directed against tumor necrosis factor-α (TNF-α), which has been observed at sites of synovitis and enthesitis in children with SpA. Clinical and laboratory improvement in patients with juvenile SpA treated with etanercept, a fusion protein of the p75 TNF-receptor and human Fc IgG1, has been reported[4,5]. Results of radiologic imaging studies following treatment have not been reported in juvenile SpA or ERA.

Conventional radiographs are limited to the assessment of advanced disease and lack the ability to quantify inflammation or provide clarification of whether the changes seen on radiographs arise from active inflammation or from healing (i.e., new bone formation). Both magnetic resonance imaging (MRI) and ultrasonography (US) show promise in the detection, diagnosis, and grading of arthritis and enthesitis.

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To our knowledge, this case report is the first to document and characterize the serial radiologic improvements of arthritis and enthesitis in a child with ERA treated with the anti-TNF-α agent etanercept.

CASE REPORT

A 13.5-year-old boy was diagnosed with ERA at the age of 7 years; he was HLA-B27-positive and negative for antinuclear antibodies and rheumatoid factor. His mother and maternal grandfather both had adult onset ankylosing spondylitis (AS) and a maternal aunt had rheumatoid arthritis (RA). His disease course included both arthritis (thumbs, metatarsalphalangeal joints, ankles, knees, midfoot, subtalars) and enthesitis (insertion of patellar, Achilles and plantar fascia tendons). Despite therapy with nonsteroidal antiinflammatory drugs (naprosyn, indomethacin), corticosteroids (intraarticular joint injections, intravenous pulse methylprednisolone), 14 months of methotrexate (MTX), 10 months of sulfasalazine (SSZ), and 12 months of bisphosphonate (alendronate) as well as combination therapy (MTX + SSZ + alendronate), he had persistent arthritis (left knee and right ankle) and severe enthesitis (knees and feet).

Following screening tests to exclude tuberculosis (PPD skin test, chest radiograph), etanercept 0.4 mg/kg subcutaneously twice a week was prescribed to manage his refractory disease activity. His other concurrent medications included indomethacin, MTX, and alendronate. SSZ was discontinued at the start of etanercept. He was improved 2 weeks after etanercept was started, with clinical resolution of his arthritis and enthesitis and normalization of inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) by 6 weeks. Alendronate was stopped at 1 month, indomethacin at 5 months, and his MTX dose was reduced. He has now been followed for over 24 months and has remained asymptomatic while taking etanercept and tapering doses of MTX. He has tolerated the etanercept well, without adverse events other than one initial injection site reaction.

Before starting and at 6 weeks, 6 months, 1 year, and 2 years after starting therapy with etanercept, imaging was performed with multisequence MRI examination of the knees (Figure 1) and ankles (Figure 2) before and after contrast administration. Imaging sequences were acquired in supine position with an extremity coil using a 1.5 T CV/i MRI magnet (General Electric, Milwaukee, WI, USA). The MRI protocol included sagittal T1, inversion recovery gradient-echo and postcontrast fat suppressed T1-weighted spin-echo imaging of both

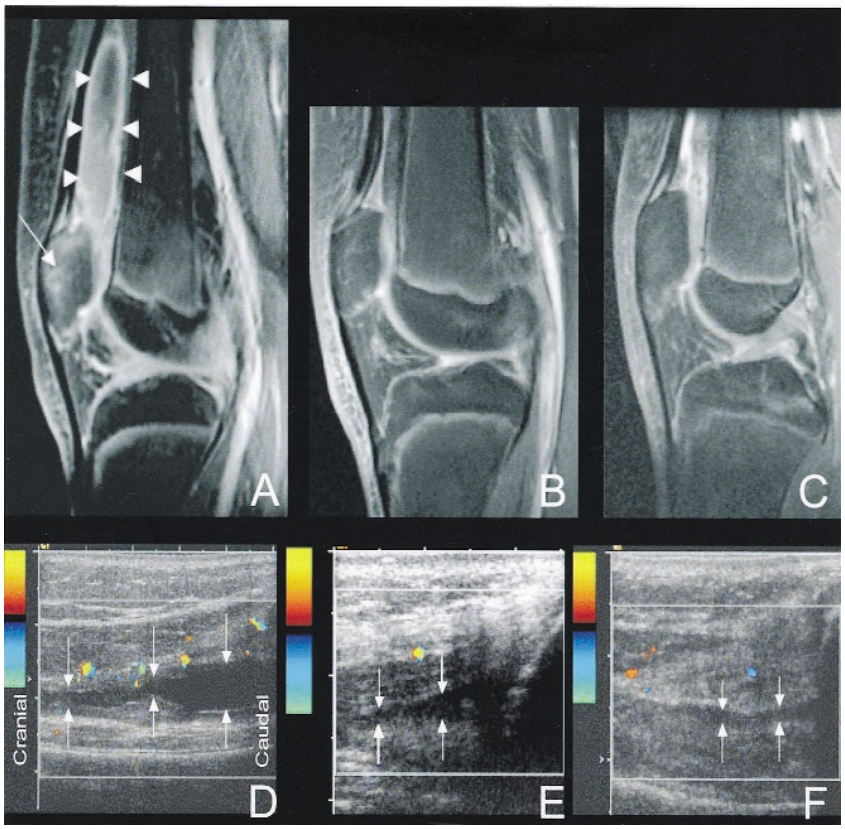

Figure 1. Panels A–C: sagittal fat-suppressed T1-weighted MR images of the left knee following contrast administration: (A) prior to, (B) at 6 weeks, and (C) 2 years after starting etanercept. At baseline (A), there is increased enhancement of the superior aspect of the patella (quadriceps tendon insertion, arrow) in keeping with enthesitis. The patellar enhancement (arrowheads in A) is distinctly better by 6 weeks (B) and fully normalized and sustained at 2 years (C). Sagittal color Doppler sonograms (D–F) of the suprapatellar bursa of the left knee were obtained (D) at baseline, (E) after 6 months, and (F) after 1 year of therapy. Moderate joint effusion (arrows) and synovial hyperemia (color pixels) are seen on the image acquired at baseline (D). A remarkable interval reduction in the amount of joint effusion (arrows) and synovial hyperemia is visible in subsequent ultrasound images obtained (E) after 6 months and (F) after 1 year of therapy. Panel D represents the superior and mid aspects of the suprapatellar bursa, panels E and F the inferior aspect of the bursa.

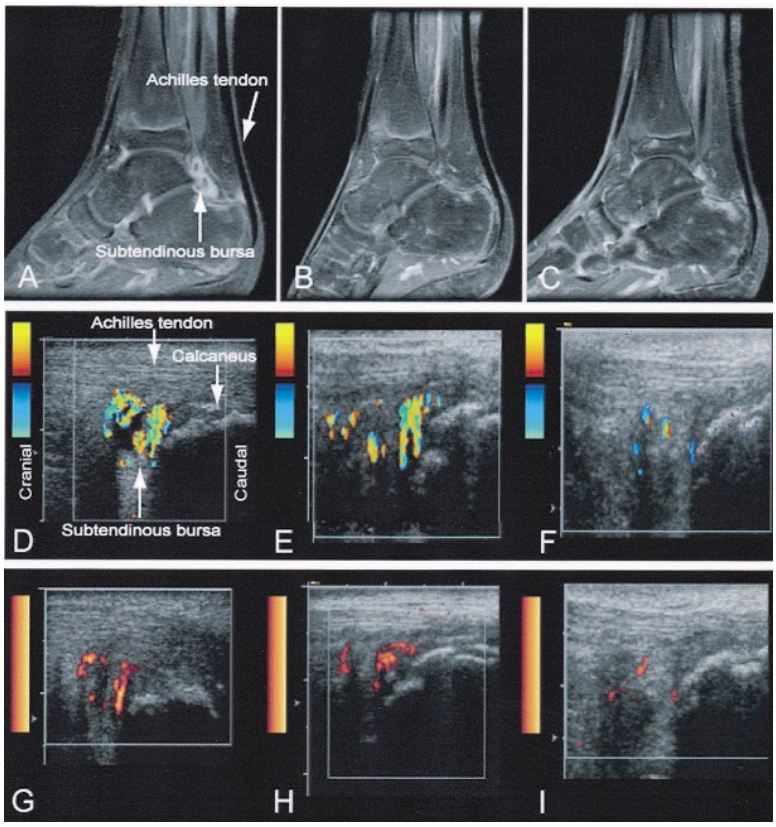

Figure 2. Panels A–C represent sagittal T1-weighted MR images of the right ankle following contrast administration (A) before, (B) at 6 months, and (C) 1 year after starting etanercept. Enhancing thickened synovitis at the tibiotalar and subtalar joints is seen at baseline (A). At 6 months, improvement with minimal residual synovitis enhancement and some enhancement in the superior aspect of the posterior calcaneus is visible (B). The 1-year followup imaging shows complete resolution of synovitis (C). Color (D–F) and power (G–I) Doppler sonograms of the posterior aspect of the right ankle are shown at baseline (D, G) and 6 months (E, H) and 1 year (F, I) after start of therapy. Although significant improvement of joint effusion at the posterior recess of the ankle is visible within the first 6 months, persistent synovial hyperemia is still seen at 6 months (E, H). Significant reduction in the degree of synovial hyperemia of the ankle is seen on color (F) and power (I) Doppler sonography only 1 year after the start of therapy.

ankles and knees. Real-time grey-scale and color power Doppler US examination was performed of knee (Figure 1) and ankle (Figure 2) regions using 8 and 15 MHz linear-array probes (Sequoia Systems, Acuson; Mountain View, CA, USA) for specific evaluation of synovium, joint fluid, and enthesitis.

Figure 1 shows the sequence of enthesitis and arthritis changes of the patient's left knee over time: panels A–C represent contrast-enhanced T1-weighted MR images, while D–F illustrate the temporal changes of the knee arthritis with color Doppler US. Figure 2 shows the interval improvement of the tibiotalar and subtalar synovitis of the right ankle following therapy on contrast-enhanced T1-weighted MR (A–C) and color (D-F) and power (G–I) Doppler images.

DISCUSSION

Our patient experienced a rapid and sustained clinical improvement from etanercept therapy, with a reduction in his active joint count, tender entheseal count, inflammatory markers, and concomitant antirheumatic medications. As in patients with AS, this is in keeping with the response seen in patients with juvenile SpA treated with anti-TNF-α agents[4,5]. This is supported by our US and MRI findings.

MRI has become the gold standard imaging modality in the detection of synovitis and enthesitis and quantification of synovial volume, which improves the assessment of disease activity and response to treatment. As contrast-enhanced MRI is capable of detecting very early and subclinical stages of synovitis and sacroiliitis in juvenile SpA[6], it is reassuring that our patient demonstrated radiologic remission of synovitis on MRI that was sustained at the 2-year followup. Further, fat-suppressed MRI, used by Marzo-Ortega, *et al*[7] to show improvement of peripheral enthesitis in response to anti-TNF-α agents in adult AS, was also successful in documenting, for the first time, improvement and disease remission of enthesitis in a child with juvenile SpA following treatment with etanercept.

Ultrasound may be user-dependent, but in the hands of a skilled operator, Doppler US has shown potential in detecting rheumatic lesions and evaluating treatment responses. Although the intensity of the color signals within the synovium in adult RA joints has been reported to decrease rapidly following treatment with etanercept[8], no US studies are available in juvenile SpA or ERA. While similar improvement was noted in the temporal evaluation of our patient's knee, color and power Doppler US revealed persistent synovial hyperemia in the ankle joint at 6 months of therapy, in spite of the minimal evidence of synovitis on MRI and the apparent clinical remission of disease activity. This indicates that the comparative assessment of color power Doppler US, MRI, and clinical findings merits further investigation in juvenile SpA.

Finally, grey-scale US has been shown to be more sensitive than clinical examination in the detection of enthesitis in AS[9]. US findings indicating improvement of peripheral enthesitis in response to anti-TNF-α agents in adult patients with AS have been reported by D'Agostino, *et al*[10]. With our patient, entheseal changes over time were depicted better by MRI compared with grey-scale US.

Overall, MRI remains the gold standard imaging modality in confirming disease activity, documenting subclinical disease, monitoring treatment efficacy, and discriminating between acute and chronic changes. Disadvantages of MRI include higher costs, longer examination time, requirement for sedation in young children, and, when gadolinium is used, the risk of allergic reaction to contrast agents compared to conventional radiography or US. Interestingly, US was reported to be slightly more sensitive in detecting the early changes of enthesopathy in adults with AS compared with MRI[11], which supports the color and power Doppler findings of ankle synovitis in our report. Clearly, the choice of imaging modality in detecting disease activity and monitoring treatment responses in children with ERA will rest on a number of factors including rheumatologic lesions involved (enthesitis, arthritis, or both), examination time required (i.e., need for sedation in a child), and availability and cost of radiologic imaging modalities.

Our patient with refractory synovitis and enthesitis improved both clinically and radiologically with etanercept. In keeping with radiologic improvements seen in adult patients with AS treated with anti-TNF-α agents, this is the first report documenting the radiologic improvements in a child with ERA. Further prospective studies are required to determine the optimal radiologic imaging techniques for detection and documentation of arthritis and enthesitis, which are necessary for examining the longterm outcomes of anti-TNF-α blockade in children with ERA.

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