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Case Report

The novel use of combined IL-1 and IL-6 inhibition in a patient with severe, aggressive, erosive, systemic-onset juvenile idiopathic arthritis

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Abstract

Systemic-onset juvenile idiopathic arthritis (SoJIA) is a form of juvenile idiopathic arthritis (JIA) that typically presents with prominent systemic features and accounts for approximately 10–15% of children with JIA. Pro-inflammatory cytokine pathways are thought to be involved in its pathogenesis, including interleukin-1 (IL-1) and interleukin-6 (IL-6), and laboratory tests demonstrate a prominent inflammatory response with high CRP and ferritin levels. We present a case of severe, aggressive, erosive SoJIA in a 17-year-old male resistant to multiple biologic therapies treated with a novel combination of IL-1 and IL-6 blockade along with subcutaneous methotrexate.

Keywords: Juvenile Idiopathic Arthritis, biologic therapy, systemic-onset

Introduction

Systemic-onset juvenile idiopathic arthritis (SoJIA) is a form of juvenile idiopathic arthritis (JIA) typically presenting with prominent systemic features (i.e., quotidian fever, rash, lymphadenopathy, and serositis) and accounts for approximately 10-15% of children with JIA (1). Pro-inflammatory cytokine pathways are thought to be involved in its pathogenesis, including IL-1 and IL-6, and laboratory tests demonstrate a prominent inflammatory response with high CRP and ferritin levels. Patients with SoJIA are at a risk of developing macrophage activation syndrome (MAS). We present a case of severe, aggressive, erosive SoJIA in a 17-year-old male successfully treated with a novel combination of IL-1 and IL-6 inhibition.

Case Presentation

A 7-year-old Caucasian male was diagnosed in 2004 with SoJIA after being referred to a pediatric rheumatology department with a 3-week history of fever, arthralgia, and rash. Other diagnoses such as infection and malignancy were excluded. The patient was seronegative for ANA, RF, and anti-CCP antibodies and was initially treated with intravenous (IV) methylprednisolone (3×1 g infusions). He was started on oral methotrexate (MTX) (10 mg weekly, increasing to 20 mg weekly) in combination with oral prednisolone (reducing dose from 60 mg daily. In September 2006, he was still symptomatic, despite starting subcutaneous (SC) MTX (20 mg weekly) and oral prednisolone (15 mg OD); therefore, he was started on etanercept (25 mg SC, twice a week). Between September 2006 and July 2012, despite the combination of SC MTX (20 mg weekly) and SC etanercept (25 mg, twice a week), his disease continued to be active, and he required oral prednisolone (60 mg daily), repeated intra-articular (IA) steroid injections, and pulses of IV methylprednisolone (repeated 1 g infusions). In July 2012, etanercept was switched to IV infliximab (titrating up to 5 mg/kg every 8 weeks), but his disease continued to be active. In April 2014, he presented with a severe flare of his arthritis, and infliximab was switched to IV tocilizumab (8 mg/kg, every 4 weeks). Despite this, he developed further active arthritis affecting his left hip and right ankle. A pelvic radiograph demonstrated severe erosive disease of the left hip (Figure 1), and an MRI scan confirmed the active disease. In November 2014, tocilizumab was switched to SC adalimumab (40 mg, fortnightly).

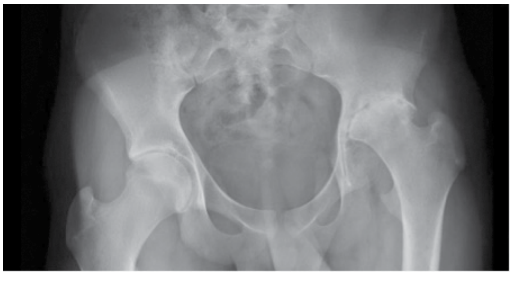

Figure 1. Plain radiograph of the pelvis demonstrating severe erosive arthritis of the left hip

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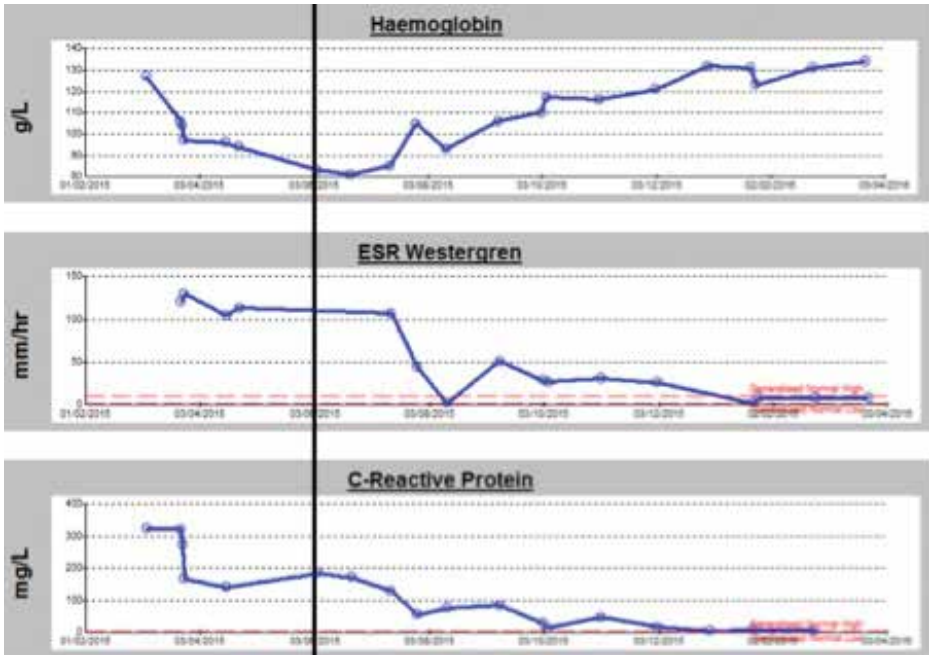

Figure 2. Laboratory results (vertical line demonstrates the addition of IV tocilizumab in June 2015)

He continued on SC MTX (between 10 and 20 mg weekly based on tolerability) the course of his treatment.

He transitioned from the pediatric to the to the adult rheumatology department at the age of 17 years and continued to have the active disease manifested by fever, rash, myalgia, elevated inflammatory marker levels, and erosive arthritis. His CRP level rose to 325 mg/L, and he was admitted for further IV methylprednisolone. Adalimumab was switched to100 mg daily of SC anakinra. On review in the outpatient clinic, many of his systemic features (such as fever, rash, and fatigue) had improved with the combination of SC anakinra and MTX, but his inflammatory marker levels were still very high (CRP, 185 mg/L and ferritin, 1374 µg/L); he had developed anemia of chronic disease (Hb, 8.1 g/dL) and had active arthritis in his right knee requiring further IA injections. In June 2015 (age, 17 years), after discussion with colleagues and a special funding request, IV tocilizumab (1 mg/kg, monthly) was added to SC anakinra (100 mg OD) and SC MTX (10 mg weekly). The tocilizumab dose was increased after several months to 2 mg/kg monthly based on his response and inflammatory marker levels (Figure 2).

Discussion

We presented a 17-year-old patient with SoJIA resistant to multiple biologic therapies currently being treated with the novel combination of IL-1 and IL-6 inhibition along with SC MTX. Previously, neither biologic drug combined with MTX had been effective in this patient. Because of concerns about potential risks associated with combination biologic therapies, tocilizumab was started at a very low dose and titrated upward according to the response. Attempts were made to reduce the frequency of anakinra injections to every other day to minimize the potential risks of infection, but this proved unsuccessful with a relapse of fever and rash. Due to the potential increased risk of infection due to combination biologic therapy, we have been particularly vigilant for any signs of infection, but fortunately, after 15 months of therapy thus far, the treatment response has been good and there have been no complications. The dose of tocilizumab currently required to control systemic symptoms is 2 mg/kg, with normalization of inflammatory marker levels and anemia of chronic disease. Furthermore, there have been no further flares of arthritis or systemic features of the disease. Our aims of treatment were to suppress the patient's systemic symptoms, prevent flares of his arthritis with consequent erosive disease, and normalize his inflammatory response (and associated complications such as anemia of chronic disease, MAS, and amyloidosis).

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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