Treating Systemic Juvenile Idiopathic Arthritis: Now and In the Future

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Medication use patterns in systemic juvenile idiopathic arthritis (sJIA) are changing gradually and reflect significant treatment variability. Data from recent Phase 3 clinical trials of 2 biologic inhibiting agents, tocilizumab and canakinumab, may prompt further changes in treatment choices in the future, as these 2 agents show impressive response rates [Yokota S et al *Lancet* 2008; De Benedetti F et al. *Arthritis Rheum* 2010; De Benedetti F et al. *Arthritis Rheum* 2011; Brunner HI et al. ACR 2012 Abstract 759].

sJIA is difficult to treat, as patients are often refractory to conventional antiarthritis therapies such as methotrexate and tumor necrosis factor (TNF) inhibitors, and many sJIA patients have been corticosteroid-dependent, said Yukiko Kimura, MD, Joseph M. Sanzari Children's Hospital at Hackensack University Medical Center, Hackensack, New Jersey, USA, in her overview of current sJIA practices. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is examining how pediatric rheumatologists are treating sJIA. The research network has 304 members from 92 sites in the United States and Canada. A survey was conducted in April 2010 regarding treatment choices of CARRA pediatric rheumatologists that had a 46% response rate. It revealed that corticosteroid-containing regimens were the most common choice of treatment, followed by methotrexate and an interleukin (IL)-1 inhibitor [DeWitt EM et al. *Arthritis Care Res (Hoboken)* 2012]. The least popular choices in 2010 were IL-6 inhibitors, TNF inhibitors, and calcineurin inhibitors. Dr. Kimura noted that these results were obtained prior to the approval of tocilizumab (an IL-6 receptor inhibitor) for the treatment of sJIA.

For initial therapy, respondents were most likely to choose prednisone and intravenous pulse corticosteroids followed by methotrexate. For refractory patients (defined as those who did not respond after 3 months of therapy), an IL-1 inhibitor and an IL-6 inhibitor gained popularity. However, more recent surveys and data have shown a shift in treatment patterns.

CARRA established a prospective registry of pediatric rheumatic diseases that began collecting data in May 2010. As of November 2012, more than 8000 patients from 60 US sites have been enrolled in the registry. Dr. Kimura examined which medications the 418 patients with sJIA who had enrolled in the registry had ever used during their disease course. More than 80% had ever taken corticosteroids, more than 70% had been on methotrexate, ~60% a TNF inhibitor, and ~50% an IL-1 inhibitor.

However, looking at current use, the CARRA registry data show that the use of biologics, especially IL-1 and IL-6 inhibitors, has increased over the past 3 years, accompanied by a decrease in the use of disease-modifying anti-rheumatic drugs (DMARDs). In addition, over time more clinicians have started using a biologic as monotherapy for treatment of sJIA, and fewer are using only a DMARD.

Ronald Laxer, MD, The University of Toronto and The Hospital for Sick Children, Toronto, Ontario, Canada, discussed recent data with IL-1 and IL-6 inhibiting agents. Data regarding anakinra, a recombinant molecule that competitively binds the IL-1 receptor site to prevent signal transduction, show an excellent early response is particularly effective in some patients and may reduce the need for corticosteroids. However, anakinra may be less effective in some patients. Of those who do respond, there is sometimes a loss of response over time [Quartier P et al. *Ann Rheum Dis* 2011]. It also seems to be less effective in younger patients and in those with polyarthritis [Pascual V et al. *J Exp Med* 2005; Gattorno M et al. *Arthritis Rheum* 2008; Lequerré T et al. *Ann Rheum Dis* 2008; Nigrovic PA et al. *Arthritis Rheum* 2011].

Canakinumab is a humanized monoclonal antibody given subcutaneously once every 4 weeks. It acts by binding IL-1β in the circulation to prevent its binding with the receptor. Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. Dr. Laxer said canakinumab and tocilizumab have each been studied in short-term, randomized clinical trials demonstrating rapid response with acceptable safety in the short term.

Tocilizumab

Data from a 12-week randomized placebo-controlled study of tocilizumab versus placebo demonstrated superiority for the primary endpoint of an adapted American College of Rheumatology (aACR) pediatric 30 (Ped30) combined with absence of fever at 12 weeks (85.3% vs 24.3%; $p<0.0001$) [De Benedetti F et al. *Arthritis Rheum* 2010]. Secondary endpoint responses of an aACR50/70/90 were also significantly greater in the tocilizumab group (85.3% vs 10.8%, 70.7% vs 8.1%, and 37.3% vs 5.4%, respectively; $p<0.0001$ for all).

Longer-term data provide insights into efficacy over time. For tocilizumab, a 2-year open-label follow-up showed continuing increases in the aACR Ped30/50/70/90 responses over time [De Benedetti F et al. ACR 2011 Abstract L12]. Sixty percent of tocilizumab recipients were able to stop steroids by Week 104 of the study.

Canakinumab

An aACR Ped30 at Day 15 was the primary endpoint of a 4-week randomized, placebo-controlled study of canakinumab given as a single subcutaneous dose [Ruperto N et al. *Pediatr Rheumatol* 2011]. In total, 83.7% of the canakinumab group reached the primary endpoints versus 9.8% of the placebo group ($p<0.0001$). Canakinumab was also superior for the secondary endpoints of aACR Ped50 (67.4% vs 4.9%) and aACR Ped100 (32.6% vs 0.0%; both $p<0.001$). aACR Ped30/50 responses with canakinumab remained significantly higher than with placebo at Day 29 (79.1% vs 9.8%, and 76.7% vs 4.9%, respectively; $p<0.001$ for both) [Brunner HI et al. ACR 2012 Abstract 759]. The data suggest that a response to canakinumab may occur earlier than with tocilizumab.

Thirty-two week open-label data with canakinumab revealed an ACR30 response in 76% of patients, an ACR70 in 63%, and an ACR100 in 34% [Quartier et al. *Ann Rheum Dis* 2012].

In the short-term studies, there were 4 serious adverse events (AEs) in 3 patients randomized to tocilizumab (varicella, septic arthritis, and urticarial/angioedema) [De Benedetti F et al. *Arthritis Rheum* 2011], and 2 serious AEs in patients randomized to canakinumab (varicella and macrophage activation syndrome), although Dr. Laxer noted high rates of AEs among the placebo groups in both trials and that 2 serious AEs occurred in the placebo group of the canakinumab trial [Ruperto N et al. *Pediatr Rheumatol* 2011].

Early Use of Biologics

Very early use of biologics is advocated by Timothy Beukelman, MD, MSCE, University of Alabama at Birmingham, Birmingham, Alabama, USA, who said that steroid-sparing therapy should be a goal of treatment for patients with systemic arthritis. AEs such as Cushing's syndrome, growth suppression, and impaired glucose tolerance are common with glucocorticoids and perhaps even anticipated. Methotrexate is often used as a steroid-sparing therapy, but its efficacy in this regard and its utility in resolving systemic features is questionable [Woo P et al. *Arthritis Rheum* 2000]. In fact, the ACR 2011 Recommendations for the Treatment of JIA state that methotrexate is "inappropriate for initial management of patients with active fever and without arthritis" [Beukelman T et al. *Arthritis Care Res (Hoboken)* 2011].

On the other hand, early interventions with IL-1 and IL-6 inhibiting agents for systemic JIA are nearing what Dr. Beukelman referred to as a "magic bullet." The typical ACR response at 3 months in randomized controlled trials of biologics for the treatment of rheumatoid arthritis is ACR20 in approximately 60% of patients, ACR50 in approximately 40%, and an ACR70 in approximately 20%. In an open-label phase of a randomized, controlled trial of etanercept for the treatment of polyarticular JIA, the ACR70 response was 36% [Lovell DJ et al. *N Engl J Med* 2000].

In contrast, the ACR70 response at 3 months in the blinded phase of a clinical trial of tocilizumab for the treatment of sJIA was 71% [De Benedetti F et al. *Arthritis Rheum* 2010], and in an open-label extension of this study, the ACR70 response improved to 87% at 12 months [De Benedetti F et al. *Arthritis Rheum* 2011]. A similar ACR70 response of 62% was achieved with canakinumab at 8 months (during glucocorticoid taper) in an open-label phase for the treatment of sJIA [Brunner HI et al. ACR 2012 Abstract 759].

A notion that IL-1 inhibition is not a good target for synovitis in sJIA is not substantiated by the data, according to Dr. Beukelman. Anakinra improved the number of active joints versus placebo at 1 month in a clinical trial of 24 patients [Quartier P et al. *Ann Rhuem Dis* 2011], and in a clinical trial of canakinumab, the median number of active joints decreased from 10 to 1 during the first 2 months of open-label use in 177 patients [Brunner HI et al. ACR 2012 Abstract 759].

In clinical trials of sJIA with a polyarticular course and without active systemic features, typical ACR30 responses at 12 to 16 weeks with the older biologic agents (anakinra, etanercept, and abatacept) are in the range of 65% to 75% [Lovell DJ et al. *N Engl J Med* 2000; Ruperto N et al. *Lancet* 2008; Ilowite N et al. *Clin Rheumatol* 2009]. Data are absent with cankinumab on JIA with polyarticular course without systemic features, while the data with tocilizumab have shown ACR70 responses of 88.5% (ages 2 to 5; n=26), 88.1% (ages 6 to 12; n=42), and 85.7% (ages 13 to 17; n=35) at 52 weeks [De Benedetti F et al. *Arthritis Rheum* 2011].