Editorial

Response of Systemic Onset Juvenile Rheumatoid Arthritis to Etanercept: Is the Glass Half Full or Half Empty?

Although systemic juvenile rheumatoid arthritis (JRA) is the least common form of JRA, it is often the most challenging to manage. Twenty-five to 35% of systemic patients will develop severe, erosive arthritis and extraarticular complications, including life threatening serositis or macrophage activation syndrome; however, it is difficult to identify at onset those patients with poor prognoses, making treatment decisions challenging[1-3]. Despite the ever-expanding body of evidence about the safety and efficacy of agents in polyarticular JRA, results may not be generalizable to all systemic onset JRA (soJRA) because only select patients with soJRA (those with a polyarticular course but without significant systemic features) are included in these studies. The current standard of care is to use methotrexate (MTX) and etanercept as second and third line agents in this disease; it can be argued that efficacy has not been proven for either of these therapies.

The data on effectiveness of MTX in soJRA are contradictory. A collaborative study between Russia and the USA regarding the effectiveness of MTX in JRA found no difference in response rates among the different subtypes, with an overall response rate of 60–89%; however, the number of systemic patients receiving the dose that was found to be effective was only 9 (20%)[4]. Woo, *et al* did not find MTX to be effective treatment using the JRA core set in systemic patients[5]. In comparison, Ruperto, *et al* in their open label uncontrolled study of over 600 patients with JRA treated with MTX 10 mg/m^2/week found that the systemic subset receiving a standard dose of MTX had a response rate of 80%[6]. In another uncontrolled study, al-Sewairy and colleagues found 89% of soJRA patients had significant improvement in their joint count, functional class, and systemic features[7].

In this issue of *The Journal*, Kimura and colleagues assessed the response of a cohort of patients with soJRA to etanercept[8]. The conclusion of the authors is that children with soJRA do not respond as well to etanercept as those with other forms of JRA, an observation that we have also made in our patients, but not proven systematically. As nicely reviewed by the authors there is growing evidence that soJRA patients' response to etanercept is less predictable when compared to other polyarticular JRA patients. In the studies quoted, when the systemic onset polyarticular course subgroup is examined separately, more soJRA patients taking etanercept had a disease flare and/or poor response versus other JRA subgroups. In addition to the studies reviewed by Kimura, *et al*, Takei, *et al* treated 5 nonresponders to conventional doses of etanercept with "high dose" (0.8 mg/kg/week); 2 who appeared to respond to the higher dose treatment had soJRA, suggesting that dose modifications may be needed with etanercept in active soJRA[9]. Additionally the German etanercept registry included 66 patients with soJRA who were evaluated according to the JRA core set. At 12 months only 24% of soJRA patients had a 70% response rate compared to 54% of the other subtypes, and 14 (21%) patients had discontinued treatment owing to lack of efficacy[10].

Interpretation of the studies is difficult because there are no prospectively validated response criteria in soJRA, nor any that incorporate systemic features such as fever, rash, anemia, pericarditis, or macrophage activation syndrome — known complications of the disease. The most used response criteria in the USA have been the JRA core set, a modification of the American College of Rheumatology (ACR) response criteria consisting of 6 response variables[11]. An ACR Pediatric 30 response represents a 30% improvement from baseline in at least 3 of the 6 response criteria without a worsening of > 30% in one of the remaining response criteria. Even when data for the complete JRA core set are available, this instrument is likely to be relatively insensitive to improvement in systemic onset JRA. Further, these response criteria have not been validated in

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prospective studies in this disease. The paper by Kimura, *et al* can therefore be criticized on these grounds alone. Unfortunately this is the state of the art; currently there are no validated or accepted measures of disease activity, nor response/flare criteria in soJRA.

Their study design has several other weaknesses, many of which are acknowledged by the authors themselves. The study results were based on a standardized questionnaire sent to USA pediatric rheumatologists regarding systemic JRA patients and their response to etanercept. Less than one-quarter of the pediatric rheumatologists in the USA contributed to the data set. Selection bias for either positive or negative results may have influenced the outcome. The data were collected retrospectively and are therefore subject to ascertainment bias. The inclusion criteria were broad. Response was calculated as an average percentage decrease in a modified JRA core set and somewhat arbitrarily was characterized as excellent (> 70% change from baseline), good (50–70%), fair (30–50%), and poor (30%). Further, there was a *post hoc* combination of response groups owing to small numbers in 2 groups that may make any statistical interpretation invalid.

The rationale for using etanercept in soJRA patients is that tumor necrosis factor-α (TNF-α) is a pivotal proinflammatory cytokine in this disease. Studies on the role of TNF-α and other cytokines in soJRA have yielded conflicting results. During periods of intense systemic activity as occur with fever, high serum levels of soluble interleukin 2 receptor (sIL-2R)[12,13], IL-6[13,14], IL-1 receptor antagonist (IL-1Ra)[15], and soluble tumor necrosis factor receptor (sTNFR)[12,13] are present in soJRA; however IL-1ß and TNF-α[13,15] levels are not increased when other inflammatory markers are raised, suggesting that the role for TNF-α, particularly in association with systemic activity, is questionable.

However there is growing evidence to suggest that in active soJRA the driving proinflammatory cytokine is IL-6[14] rather than TNF-α. Increased serum levels of IL-6 have been correlated with the fever present in patients with active soJRA[16,17]. Further, polymorphisms in the 5′ flanking region of IL-6 are seen more frequently in patients with soJRA who lacked the protective CC allele (which is associated with low secretion of IL-6), in comparison to control patients[18]. Indeed small open-labeled trials directed at abrogating the IL-6 response using a humanized anti-IL-6 receptor monoclonal antibody (MRA) have been very encouraging, with complete remission reported in 10 out of 11 soJRA patients[19].

Recently anecdotal reports have appeared regarding the excellent response of soJRA patients to anakinra (IL-1RA). To date at least 4 studies would support its use in soJRA[20–23]. In the reported 21 soJRA patients treated with IL-1RA, all responded with normalization of inflammatory markers, and prednisone dose was significantly tapered or discontinued in all. Many of these patients had failed etanercept. Trials are anticipated to begin shortly for both MRA and IL-1 inhibitor in soJRA.

There is much work still to be done in the rarer pediatric rheumatic illnesses. The formation of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) provides a structural basis for collaborative studies in these illnesses and the means to offer consensus in the development of outcome measures needed for clinical trials. Until these are in place, observational studies such as provided by Kimura, *et al* provide the evidence to guide pediatric rheumatology practice. Whether one views the glass as half full (as many as 50% of children respond to etanercept), or half empty (only about one-half of children respond), may be influenced by the outcomes of future biologic therapy trials.

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