Published in final edited form as:

Arthritis Rheumatol. 2019 July ; 71(7): 1030–1033. doi:10.1002/art.40867.

A Bullseye for Children with Systemic Juvenile Idiopathic Arthritis

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Can we cure patients with systemic juvenile idiopathic arthritis (sJIA)? This was once an inconceivable question in pediatric rheumatology because children with sJIA were traditionally among the most difficult patients to manage and their outcomes were dismal. Unlike other forms of chronic inflammatory arthritis of childhood, sJIA is characterized by a dramatic onset with spiking fevers, evanescent rash, arthritis, and systemic inflammation. The course of the disease is variable with 40–50% of patients following a more favorable monophasic course (1). The remaining children who go on to develop long-standing disease fare much worse. The arthritis of sJIA is often resistant to non-biologic disease-modifying antirheumatic drugs (DMARDs) and even TNF inhibitors (2, 3). Historically, children with chronic manifestations of sJIA had the worst functional outcomes and highest rates of prosthetic joint replacements of all JIA subtypes (4, 5). Caring for children with sJIA in the pre-biologic era engendered a sense of frustration, sadness, and regret in many pediatric rheumatologists who were left to watch helplessly as patients were ravaged by disease that could be managed only with unacceptably high doses of glucocorticoids.

Improved outcomes in sJIA were slow to materialize until the advent of IL-1 and IL-6 blockade. In 1991, De Benedetti *et al* identified increased serum IL-6 levels in sJIA patients, which surge in the peripheral blood before fever spikes (6). Pascual and colleagues demonstrated an IL-1 β signature in sJIA and showed clear clinical improvement in 9 patients treated with recombinant IL-1 receptor antagonist (rIL-1RA) (anakinra) (7). These landmark discoveries laid the foundation for using cytokine blockade in sJIA. The pivotal role of IL-1 and IL-6 in driving the acute, systemic symptoms of sJIA is well documented. Treatment with rIL-1RA in new-onset sJIA patients results in a near immediate resolution of systemic symptoms (fever and rash) in the vast majority of patients (greater than 80%) (8). Despite these remarkable results, sJIA patients were traditionally treated first with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and non-biologic DMARDs. Biologic medications such as anakinra and tocilizumab were typically reserved for patients with severe and/or refractory disease (9). Patients who ultimately received cytokine-directed therapy as second-line treatment had improved outcomes compared to historical patient cohorts but attainment of inactive disease (ID) remained elusive, and glucocorticoid dependence was still commonplace. In a randomized controlled trial of rIL-1RA in sJIA patients with chronic and refractory disease, 58% and 42% of patients achieved modified ACRPedi 50 and 70 responses, respectively, at 1 month. At 12 months, in the open extension

phase of the trial, only 30% of patients had achieved ID, and over 60% still required glucocorticoids (10). Similarly, in a randomized controlled trial of an IL-6 receptor-blocking monoclonal antibody (tocilizumab) in sJIA patients with greater than 6 months of disease, 71% achieved an JIA ACR 70 response rate at 12 weeks (11). In the open extension phase, 32% of patients had ID, and 48% of patients continued to need glucocorticoids.

In 2011, Nigrovic and collaborators reported on a small number of new-onset sJIA patients (n=10) who received first-line rIL-1RA monotherapy with remarkable outcomes (8). Eight of these 10 patients achieved ID and required no additional medications, including no glucocorticoids. This finding in a small number of patients led to the hypothesis that there may be a window of opportunity at the onset of sJIA to treat with initial IL-1 blockade and prevent chronic and severe disease (12). In 2014, Vastert and colleagues, who had been trialing a similar first-line rIL-1RA approach in a prospective single-center series, published very similar findings in 20 children with sJIA (13). Children enrolled in this single center prospective cohort study were treated according to a prescribed algorithm starting with NSAIDs and rapidly escalating to anakinra, first at 2mg/kg/day and then at higher doses. If disease continued despite high-dose anakinra, glucocorticoids or other biologics were started. Similar to the results reported by Nigrovic *et al*, 85% of patients achieved ID disease within 1 year, including 65% on rIL-1RA monotherapy, without exposure to corticosteroids (13). Children who achieved ID for 3 months entered a medication tapering procedure in which rIL-1RA was weaned to every other day dosing for one month and then stopped. In total, 8/20 patients (40%) were able to stop medications.

In this issue of *Arthritis & Rheumatology*, ter Haar and colleagues report on the long-term outcomes of 42 children with sJIA who were managed according to this treat-to-target strategy over a median time of 5.8 years. Unlike the prior manuscript, the current study includes patients with arthritis or arthralgias in the setting of a clinical picture indicative of sJIA. By 1 month, 60% of patients had achieved ID on rIL-1RA, as defined by modified Wallace criteria. At 1 year, 76% achieved this milestone with most on rIL-1RA monotherapy (67% of all patients). Thirty-three patients with ID tapered medications, and 22 (52% of all patients) were able to come off medications within the first year. Twenty-five patients were followed for 5 years; at last follow-up, 95% had ID and 72% were off medications. Importantly, only one-third of patients required glucocorticoids to achieve ID. None of the sJIA patients exhibited growth impairment from steroid dependence or active systemic inflammatory disease. Remarkably, a majority of patients reported a normal quality of life with no pain. Predictors of ID at 1 year included an elevated neutrophil count at baseline ($>9 \times 10^9/L$, sensitivity 0.91, specificity 0.8) and achievement of ID within 1 month of starting therapy. Neutrophils at baseline is the first biomarker to be identified in sJIA that predicts response to treatment.

While the present study by ter Harr and colleagues is not a randomized controlled trial (RCT), it does present the greatest amount of evidence to date on the efficacy of first-line rIL-1RA therapy and a treat-to-target approach in sJIA. The following findings presented in the paper are of particular interest: the swift attainment of disease control, the high rates of ID with rIL-1RA monotherapy, and the substantial proportion of patients who were able to taper off medications quickly. The authors demonstrated a rapid induction of ID with initial

IL-1RA therapy, which has been reported by others (3, 8, 10). By 1 month, a majority of patients had achieved ID. In addition, the rates of ID at long-term follow-up were high compared to historical accounts. In the present study, 76% of patients had ID at 1 year, and a stunning 95% of patients had attained this goal at last follow-up. For comparison, prior RCTs with rIL-1RA and anti-IL-1 β (canakinumab) demonstrated ID in approximately 30% of patients (10, 14). Of course, these RCTs were conducted with patients who had longstanding and refractory disease, and the comparison to a prospective study in patients with new-onset disease is not entirely equitable. There are more comparable inception cohort studies that report on sJIA outcomes in the biologic era, but these did not employ first-line IL-1 blockade and a treat-to-target approach. These studies reported ID rates ranging from 24–72% at long-term follow-up (2–3 years), a lower proportion of patients than in the current study (3, 15). It is all the more remarkable that these high rates of ID were attained with relatively low glucocorticoid use, although the proportion of patients who required glucocorticoid treatment in the present study was not substantially lower than those reported in recent cohort studies (3, 15). As for tapering of therapy, the authors employed a relatively rapid and early medication reduction protocol, which was well tolerated. Medications were tapered after 3 months of ID, and the median time to taper for the 33/42 patients who achieved ID was only 3.7 months. Subsequently, IL-1RA dosing frequency was decreased to every other day for 1 month and then stopped. A majority of patients did well with this tapering regimen, and at last follow-up, 72% were in remission and off medications. Compared to historical reports on sJIA disease course in which 60% of patients had chronically active disease, this is a truly remarkable finding (1). Further, ter Haar *et al* identified markers that predict a response to rIL-1RA, which include elevated neutrophil count and response to rIL-1RA therapy within one month. Patients with persistent arthritis at 1 month were unlikely to attain ID at a year and required additional therapies. Thus, the results of this study provide valuable information to clinicians regarding when patients should be switched to alternate therapies, which is relatively quickly if there is not a robust response to rIL-1RA.

Four of 42 patients developed macrophage activation syndrome (MAS) while on IL-1RA (9.5% of all patients), a rate that is not substantially lower than prior reports. An infectious trigger could be identified in 3 of these 4 patients. One child with MAS developed pulmonary hypertension and CNS involvement and died despite treatment with rIL-1RA, canakinumab, methotrexate, and prednisone. This is the only mortality and report of pulmonary disease in the study. The pathophysiology driving pulmonary complications in sJIA is unknown and may be secondary to the underlying disease, immunosuppression, infections, or a combination of all of these factors. It has been reported in patients taking glucocorticoids, cyclosporine, IVIG, tocilizumab, and anti-IL-1 agents (16). It is unclear if treatment with rIL-1RA increases the risk of pulmonary disease above other treatments for sJIA and this will need to be monitored prospectively.

In total, the study by ter Haar and colleagues suggests that first-line IL-1 blockade in new onset sJIA patients with a treat-to-target strategy results in rapid attainment of ID at higher rates than previously reported. A substantial proportion of patients treated with this approach were “cured,” meaning in remission and off medications at long-term follow-up. This represents a paradigm shift in the classic approach to treatment in pediatric rheumatology.

Instead of gradually escalating therapy from NSAIDs to non-biologic DMARDs to biologic agents in order to attain disease control, sJIA patients should be treated immediately with anti-cytokine therapy.

While the results of the current study are exciting for pediatric rheumatologists, patients, and families, these findings must be interpreted with some caution. The study conducted by ter Haar *et al* was a single center, prospective cohort study and not a multi-center RCT; therefore, bias, generalizability, and lack of a control group are concerns. In addition, the authors defined sJIA as patients with arthritis or arthralgias. In sJIA, overt arthritis can often present weeks to months or even years after the onset of systemic symptoms. Accordingly, including patients without arthritis is in keeping with what is done in a real-world clinical setting, consensus treatment guidelines, and adult Still's disease (17, 18). Further, the Pediatric Rheumatology International Trials Organization (PRINTO) has gone as far as to suggest revising the classification criteria for sJIA to remove arthritis as a necessary criterion (19). Yet, many historical case series and cohorts have restricted their definition of sJIA to patients with objective arthritis. Thus, there is a theoretical concern that the patient population in this report is biased towards individuals with milder or monophasic disease, which may explain the favorable results. To address these concerns, the clinical characteristics and laboratory values of arthritis and non-arthritis patients at baseline were presented, and there were no statistically significant differences between the two groups. The authors also presented the outcomes of arthritis and non-arthritis patients separately. Indeed, patients without arthritis were more likely to achieve ID (100% with ID at 1 year) than the patients with arthritis (68% with ID at 1 year), indicating that there could be a difference between these two groups. Consequently, these results need to be interpreted within the context of the inclusion criteria used for the study.

The treat-to-target approach employed by ter Haar and colleagues in this issue of *Arthritis & Rheumatology* has hit its mark. In a once-debilitating disease, children with sJIA in this study had excellent outcomes, including rapid attainment of ID at high rates with preserved quality of life and limited glucocorticoid use. Further work is now needed to confirm these results in larger, multi-site studies. It will also be of interest to determine whether other cytokine-directed therapies such as anti-IL-6 agents can produce a similar effect. Importantly, the biologic basis for the remarkable response to early rIL-1RA treatment is not understood. Future translational studies are needed to explore the mechanism underlying this phenomenon. The response to rIL-1RA was not universal. The authors are the first to identify markers predictive of response (neutrophilia) and non-response (lack of ID at 1 month of treatment); however, additional biomarkers are needed to risk stratify patients in order to start alternative therapies early. The work of ter Haar and collaborators has provided a glimpse into a future without chronic sJIA; however, we must continue to build on the foundation provided by the current study with rigorous clinical and translational investigation to make this vision a reality.

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