Early Aggressive Therapy for Patients with Juvenile Idiopathic Arthritis: Are We There Yet?

This is an extremely exciting time in the field of pediatric rheumatology. Advances in understanding the pathogenesis of juvenile idiopathic arthritis (JIA) have led to novel treatments with resultant marked improvements in patient outcomes, as is eloquently summarized in a review by Lovell and colleagues1.

Critical to the study of these new therapies has been the development of standardized outcome measures. These are not only relevant to research studies but also assist in making treatment decisions in clinical practice. The definition of improvement by the American College of Rheumatology (ACR) core set response criteria2 and more recently, criteria of inactive disease and remission, both on and off medication, have been developed and adopted by the ACR3 (Table 1). Application of these standardized outcome measures has greatly facilitated the reporting and generalizing of study results, as well as allowed comparison of results between trials.

Earlier studies, in the “prebiologics era,” used differing measures for reporting remission and classifying patients; and the length of followup varied. As a result, it was extremely difficult to compare results between studies. A Canadian multicenter retrospective cohort study reported that 10 years following diagnosis of juvenile rheumatoid arthritis4, the probability of remission (defined as 2 years without taking medication) was 37% in patients with systemic disease, 47% in oligoarthritis, 23% in rheumatoid factor (RF)-negative polyarthritis, and 6% in RF-positive polyarthritis5. This is in contrast to a multicenter retrospective cohort study (Italy and the United States) in which, after a median of 7.7 years post-JIA diagnosis (similar categories considered as above), 40% of patients were in remission (defined as 6 months without taking medication). However, at 2 years without medications (the more rigid criteria defined by Oen, et al5), only 28% of patients were in remission6. Overall, in cohort studies reported in the prebiologic era, patients had poor outcomes with little chance of remission, particularly patients with more severe polyarthritis.

Outcome studies reported more recently in the biologics era, using the ACR definitions for clinical inactive disease (CID) and clinical remission while not taking medication (CR), report significantly better outcomes. Ringold, et al7 reported a retrospective polyarticular JIA cohort study (28% RF-positive, 104 children) of patients followed for a median of 27.4 months (range 6–77). Eighty percent of patients achieved CID at a median time of 7.6 months after initiation of treatment; 37% received anti-tumor necrosis factor (TNF) therapy, 11.5% within their first 6 months of care. Forty-seven percent achieved clinical remission while taking medication, none achieved CR, and 20% never achieved CID. The investigators of the ReACCh-Out study (Canadian Research in Arthritis in Canadian Children emphasising Outcomes) report on the prospective inception cohort of newly diagnosed patients (< 6 mos) with all subtypes of JIA. Of the data from 1104 patients, the probabilities of attaining an active joint count of 0 exceeded 70% within 2 years in all JIA categories, except for RF-positive polyarthritis (48%). The probability of attaining CR (completely without medications for 12 months and no active disease) within 5 years was 46–57% across JIA categories except for patients with polyarthritis (0% RF-positive, 14% RF-negative). The probability of starting anti-TNF was 11.1% in the RF-positive polyarthritis patients within the first 6 months of care8.

There is no debate regarding the efficacy of anti-TNF-α therapy for patients with polyarticular JIA. A recent review reports increasing use over the last decade9. The optimal timing of introduction and withdrawal of these medications is not known. Unique in its design, the Trial of Early Aggressive Therapy (TREAT) in JIA studied the effect of early introduction of etanercept (ETN) plus prednisolone (PSL) and methotrexate (MTX) compared to MTX alone on the attainment of CID at 6 months10. Eighty-five patients

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with polyarticular JIA < 12 months’ duration were studied in this prospective, randomized, double-blind, placebo-controlled trial.

Patients received either MTX 0.5 mg/kg/week (maximum 40 mg) subcutaneously (SC), ETN 0.8 mg/kg/week (maximum 50 mg) SC, and PSL 0.5 mg/kg/day (maximum 60 mg) orally and tapered to 0 mg by 17 weeks (arm 1); or MTX (same dosage as arm 1), ETN placebo, and PSL placebo (arm 2). The study design limited the time for the patient taking placebo; if subjects failed to meet an intermediate endpoint of 70% improvement according to ACR Pediatric criteria at 4 months, they entered the open-label ETN/MTX/PSL arm. By 6 months, CID had been achieved in 17 of 42 patients (40%) in arm 1 and 10 of 43 patients (23%) in arm 2 (chi-squared = 2.91, p = 0.088).

After 12 months, clinical remission while taking medication (CRM) was achieved in 9 patients in arm 1 and 3 patients in arm 2 (p = 0.053). The trial failed to meet its primary endpoint (attainment of CID at 6 mos); the authors note this was potentially explained by the overly ambitious goal of 60% CID in the MTX/ETN/PSL arm as well as higher (potentially more effective) doses of MTX used. Importantly, CID was induced in 32% of patients by 6 months and in 66% by 12 months in this severely affected group of patients. The TREAT study participants were the most severely affected patients with polyarthritis, compared to the patients reported by Ringold, et al7 and Guzman, et al8, and this difference explains the lower proportion of TREAT patients attaining CID and CRM.

In this issue of The Journal, Wallace, et al report on an open-label extension phase of the TREAT trial11. Data from 76% (48/63) of eligible patients were reported, with a mean observation period of 39 months (range 24–54): Fifty percent of patients spent more than half their followup in CID; 88% of patients achieved CID at one or more study visits, 54% achieved CRM, but 12% never achieved CID. Forty-three of 48 patients in the extension study were receiving MTX and ETN and only 5 were taking MTX alone. Interestingly, baseline active joint counts and duration of symptoms prior to treatment did not correlate with proportion of time in CID. This is in contrast to the original 6-month trial that reported an OR for achieving CID of 1.324 for each month earlier that a patient was treated10.

One of the main concerns with the TREAT trial design is the use of prednisone (0.5 mg/kg/day to a maximum of 60 mg/day) with ETN and MTX. The study did not address the potential effect on outcomes of early prednisone use (tapered off by 4 mos). A provocative editorial in The Journal earlier this year argued that even short-term use of steroids in pediatric patients is unacceptable and can have side effects such as infection and affect self-image, growth, metabolism, and bone structure12.

Despite the growing body of literature on longterm safety in the use of biologics, the risks of potential serious longterm side effects (e.g., malignancy) are relatively unknown13,14,15,16,17, and certainly in the short term, serious infections are possible18.

The TREAT extension study reported intermediate 2-year outcomes on a severely affected group of patients with aggressively treated polyarticular JIA with superior outcomes.

Early aggressive therapy was similarly evaluated in newly diagnosed patients with polyarticular JIA in the ACUTE-JIA trial reported by Tynjala, et al19. This was a 54-week open-label trial of 60 patients randomized to 1 of 3 treatment arms: infliximab plus MTX (TNF); MTX, sulfasalazine, and hydroxychloroquine (COMBO), or MTX (MTX) alone. The primary endpoint was 75% improvement according to the ACR Pediatric criteria, achieved in 100% receiving TNF, 65% in the COMBO group (95% CI

Table 1. ACR definitions of clinical inactive disease and clinical remission for JIA. From: Wallace, et al, Arthritis Care Res 2011;63:929-36; with permission.

<table>
<thead>
<tr>
<th>Condition/disease</th>
<th>Definition</th>
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<tr>
<td>Clinical Inactive Disease (CID)</td>
<td>All 6 conditions must be met:</td>
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<tr>
<td>No joints with active arthritis</td>
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<tr>
<td>No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributed to JIA</td>
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<tr>
<td>No active uveitis</td>
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<tr>
<td>ESR or CRP level (or both if tested) within normal limits for the laboratory where tested, or, if elevated, not attributed to JIA</td>
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<tr>
<td>Physician’s global assessment of disease activity score as lowest possible on whichever scale is used</td>
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<tr>
<td>Duration of morning stiffness &lt; 15 min</td>
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| Clinical Remission on Medication (CRM) | Satisfaction of the definition of clinical inactive disease for at least 6 continuous months while on therapy for JIA |

| Clinical Remission Off Medication (CR) | Satisfaction of the definition of clinical inactive disease for at least 12 continuous months while off all therapy for JIA |

ACR: American College of Rheumatology; JIA: juvenile rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
and analysis, will be critical to understanding which patients should receive early biologic treatment, as well as how early treatment should be started.

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