Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis

Written by Maria Vinall

The Trial of Early Aggressive Treatment in Juvenile Idiopathic Arthritis [TREAT JIA; NCT00443430] addressed whether aggressive treatment, initiated early in the course of polyarticular juvenile idiopathic arthritis (JIA), can induce clinical inactive disease (CID) within 6 months. CID was defined as no active arthritis; no fever, rash, serosotis, splenomegaly, or generalized lymphadenopathy that was attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate (ESR); and physician's global assessment of disease activity score of 0. Secondary objectives included the proportion of subjects who achieved clinical remission on medication (CRM) at 12 months (defined as CID for 6 continuous months on medication), serious adverse events, and change in ACR pediatric core set variables. Trial results were presented by the principal investigator of TREAT JIA, Carol Wallace, MD, Seattle Children's Hospital and University of Washington School of Medicine, Seattle, Washington, USA.

TREAT JIA was an NIH-NIAMS-funded, randomized, prospective, multicenter (15 sites), double-blind, placebo-controlled trial in children aged 2 to 16 years with rheumatoid factor (+) or (-) polyarticular JIA of <12 months duration. Subjects were randomized 1:1 to methotrexate (MTX) 0.5 mg/kg/week SQ (40 mg max)+etanercept (ETN) 0.8 mg/kg/week SQ (50 mg max)+prednisolone 0.5 mg/kg/day (60 mg max) tapered to 0 by 17 weeks (Arm 1; n=42) or methotrexate (same dose as Arm 1)+placebo etanercept and placebo prednisolone (Arm 2; n=43). All subjects also received daily NSAIDs and folate (1 mg). Participants were followed for 12 months. Subjects who failed to achieve at least an ACR pediatric 70 improvement after 4 months on therapy and those who did not achieve CID by 6 months received open-label treatment as in Arm 1. An intent-to-treat approach was used for efficacy analyses.

Eighty-five subjects were enrolled (median age 11.1 years; 75% female). Baseline characteristics showed that participants had an average of 5 months of symptoms before study entry with active disease, according to median values of ACR pediatric core variables (physician's global assessment of disease activity 7.5; parent global assessment of well-being 5.5; ESR 33; number of joints with arthritis 19; number of joints with limited motion 11.5, C-HAQ 1.1). Sixty-nine percent were ANA+ and 36% were RF+. Baseline characteristics did not differ between treatment groups, with the exception of a significantly higher number of active joints and ESR in Arm 2 (p=0.018 and 0.017, respectively), but they were not associated with response to treatment.

The trial did not meet its primary endpoint. At 6 months, CID was achieved in 40% of subjects in Arm 1 and 23% in arm 2 (p=0.088). Overall, however, CID was achieved by 32% of subjects—a high percentage, given the stringent CID definition that was considered. The only variable that was predictive of CID at 6 months was disease duration at baseline, with the odds of achieving CID increasing by 1.32 for each month earlier treatment was started after onset of symptoms (p=0.011).

At 4 months, 30 of 42 subjects (71%) in Arm 1, and 19 of 43 subjects (44%) in Arm 2 achieved an ACR pediatric 70 improvement (p=0.011). All six ACR pediatric core variables showed significant improvement by 6 months in both arms (all p values <0.001). By 12 months, 12 subjects (14%) achieved CRM (9 remained in Arm 1 and 3 remained in Arm 2 throughout the study; p=0.053). Safety did not differ between the two arms. There were three serious adverse events: pneumonia (Arm 1), psychosis (open-label), and septic joint (open-label). All events resolved.

Although this trial failed to achieve its primary endpoint, Dr. Wallace noted that the results demonstrate that it is possible to achieve CID by 6 months and CRM by 12 months in a meaningful proportion of patients with severe polyarticular JIA using early and aggressive treatment. These data suggest that there is indeed a "window of opportunity" to treat severe JIA early in the disease course. While MTX that was given subcutaneously was fully effective for some patients, the combination of MTX, prednisolone, and ETN showed a trend to provide a more complete and durable response without increased risk for serious adverse events.

Reduced CV Risk with Use of MTX and TNF-α Inhibitors in Patients with RA

Written by Debra Gordon, MS

Patients with rheumatoid arthritis (RA) who did not have preexisting coronary artery disease (CAD) and used methotrexate (MTX) for at least 24 months or a tumor necrosis factor (TNF) antagonist for at least 40 months were significantly less likely to develop cardiovascular disease (CVD) than those who did not use MTX or anti TNF therapy, according to researchers from Geisinger Medical Center in Danville, Pennsylvania, USA.

Lead researcher Rasa Bozaite-Gluosniene and her colleagues worked with electronic health records

for 1718 adult RA patients with at least 2 outpatient encounters and no prevalent CVD for their analysis to assess the impact of medication exposure over time. The primary outcome was CVD defined as CAD, any cardiac revascularization procedure, stroke or transient ischemic attack (TIA), peripheral artery disease (PAD), abdominal aortic aneurysm (AAA), or cardiac revascularization procedures.

Median follow-up was 3.4 years, and the median age was 57 years. One-third of participants had used an anti TNF-α (n=588); 62% (n=1119) had used MTX.

The researchers identified 127 cases of incident CVD, confirmed by chart review: 48 cases of CAD, primarily myocardial infarction, unstable angina, or revascularization; 45 strokes or TIAs; and 34 cases of PAD or AAA.

Among patients who were taking MTX, the case rate for CAD per 1000 patient-years was 14.6 (10.6 to 20.1) versus 23.2 (18.8 to 28.5) in nonusers, translating into a 37% risk reduction (incidence rate ratio=0.63; 0.42 to 0.93). The median exposure to MTX was 22 months, with the risk of CVD falling as the duration of MTX use increased. Patients with 23 months or more of exposure experienced a 72% reduction in risk (p<0.001).

The incidence rate for CAD per 1000 person-years was 37.5 for nonusers versus 17.6 for users of MTX. The hazard for incident CAD in MTX users was 0.54 (95% CI, 0.37 to 0.77; p=0.001) compared with nonusers. For patients who were taking MTX for more than 24 months, the hazard for incident CAD was 0.33 (95% CI, 0.22 to 0.50; p<0.001). The incident rate for CAD per 1000 person-years was 32.1 in TNF-α inhibitor users versus 11.8 for nonusers. Among the TNF-α inhibitor users, the hazard for incident CAD was 0.54 (95% CI, 0.30 to 0.95; p=0.03) compared with nonusers. In patients who were taking TNF-α inhibitors for more than 24 months, the hazard was 0.24 (95% CI, 0.12 to 0.51; p<0.001). Patients who took the drugs for more than 35 months had a 93% reduced risk of CAD (0.01 to 0.52; p=0.010). Median TNF-α exposure was 17 months.

Study limitations included the observational design and limited information on smoking status, family history of CVD, level of physical activity, and use of aspirin. The study presenters concluded that the use of MTX or TNF-α inhibitors can provide some protection against CVD in patients with RA.

TENDER Trial 2-Year Outcomes Show Long-Term Benefits of Tocilizumab in sJIA

Written by Rita Buckley

Fabrizio De Benedetti, MD, PhD, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, presented efficacy and safety results from A Randomized, Placebo-Controlled Study to Evaluate the Effect of Tocilizumab (TCZ) on Disease Response in Patients With Active Systemic Juvenile Idiopathic Arthritis (sJIA), With an Open-Label Extension to Examine the Long-Term Use of Tocilizumab [TENDER; NCT00642460].

In the TENDER trial, 112 patients aged 2 to 17 years with active, refractory sJIA (≥ 6 months; inadequate response to previous anti-inflammatory drugs [NSAIDs] and oral corticosteroids [oral CS]) were randomly assigned 2:1 to TCZ (n=75; 8 mg/kg if body weight ≥30 kg; 12 mg/kg if body weight <30 kg) or placebo (n=37) every 2 weeks for 12 weeks in Part 1. All patients received open-label TCZ in Part 2 (to 104 weeks). Stable doses of NSAIDs and methotrexate were continued, with oral CS tapering permitted according to predefined criteria.

The data were cut for each ongoing patient at the Week 104 infusion, based on date of randomization, with baseline in the longer-term extension considered the first dose of TCZ.

At the data cutoff (May 31, 2011), 61 patients had received at least 104 weeks of treatment; 32 of the ongoing patients had not yet reached 104 weeks of TCZ treatment; and 20 withdrew, including 1 at Week 104 (safety, 9; insufficient therapeutic response, 5; other nonsafety issues, 6).

Main baseline characteristics included mean disease duration of 5.2 years, mean active joint count of 19.8, and presence of fever (temperature ≥37.5°C in the past 7 days) in 43% of patients. High proportions of those who were treated with TCZ achieved JIA ACR 70/90 responses and maintained these responses over time (Table 1). Mean joint counts decreased over time. By Week 104, 55% of patients had 0 active joints and 31% had inactive disease status. In those patients who were taking oral CS at baseline, 60% was able to discontinue the drugs by Week 104 (Table 1); mean oral CS dose decreased from 0.30 mg/kg/day at baseline to 0.04 mg/kg/day at Week 104.