Title of Project: Start Time Optimization of Biologics in Polyarticular JIA

Comparative Effectiveness of Childhood Arthritis & Rheumatology Research Alliance Consensus Treatment Plans for Polyarticular JIA

ClinicalTrials.gov identifying number: NCT02593006

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Primary Analyses for STOP-JIA

The key exposures for this study are the 3 Consensus Treatment Plans (CTPs) for treating new-onset pediatric juvenile idiopathic arthritis.

- Biologic first
- Early combination (of methotrexate and biologic)
- Step up (early use of methotrexate and addition of a biologic if needed)

The primary endpoint is clinically inactive disease (CID) at one year. Covariates that may be associated with both CTP choice and outcome will be used to develop propensity scores measuring the probability to be assigned to each of the 3 strategies. At the time of study planning, these covariates included

- disease severity at diagnosis as measured by the physician global assessment component of the American College of Rheumatology (ACR) pediatric core set
- the Juvenile Disease Activity Score (JADAS; a composite measure of disease activity)
- patient age
- sex
- disease duration prior to enrollment
- insurance status
- JIA category

Before the study began, there was an expectation that the smallest group (biologic first) would comprise approximately 100 patients, and that there would be relatively small differences in baseline characteristics between patients starting the 3 CTPs. With these expectations, it would have been feasible - with minimal dropping of participants - to implement 1:1:1 matching across the 3 CTPs, based on a multinomial or other model that generates predicted probabilities for receiving each CTP. This analysis would have made use of most of the sample.

During accrual, it became apparent that the allocation to the three CTPs was in the approximate ratio 65%:25%:10% (for CTPs step up : early combination : biologic first). There was also a larger than expected differences in baseline variables between patients receiving these 3 CTPs, so the original analysis plan was modified to use propensity scores to generate inverse probability of treatment weights (IPTW) for each subject and to use these weights in between-CTP comparisons of outcomes.

Aim 1

Primary outcome: compare the proportion of patients with CID at 1 year between the 3 treatment approaches.

- Construction of a generalized boosted model (using the twang package in R) from the covariates listed above - and others found to be associated with both CID and CTP assignment - to produce propensity scores (PS) for each subject to begin his or her own assigned CTP at baseline.
- Make PS-adjusted pairwise comparisons between CTPs using inverse probability-weighted comparisons.

Methods for handling missing data: If the primary outcome, CID at one year, is missing in more than 5% of participants, we will use multiple imputation with all these sources of information in the imputation model:

- partial data on the components of CID at 12 months
- earlier assessments (at months 3, 6 and 9) within a patient
- treatment group
- Baseline, JADAS, MD global score, parent global score, and number of active Joints

Twenty imputed datasets will be created and estimates of the relative treatment effects (from IPTW models) between treatment strategies and their uncertainty will be averaged over the results from the twenty imputed datasets to produce point estimates and confidence intervals that reflect both the variability in the observed data and the variability due to uncertainty in the missing values.

Aim 2

The analyses will use PROMIS measures of mobility and pain interference collected at baseline and at routine visits (3, 6, 9 and 12 months) throughout the year of follow-up.

The analysis, we will examine scores over the period of baseline to one year using the IPTW approach in a linear mixed effects models and assess differences between CTPs in change over time in PROMIS® measures through the time-by-CTP interaction. Random effects will be included for individual and time will be treated as a categorical variable. The model with the best-fitting correlation structure will be used to make inferences about the time-CTP interaction.