Predictive factors for Histologic Healing, Transmural Healing and Endoscopic Remission in Children Receiving Anti-TNF for Crohn's Disease

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Introduction: With 25% of new Crohn's disease (CD) diagnoses occurring in childhood and the significant, long-term impact that disease complications have on the pediatric population, the need for effective treatment methods remains critical. Despite the remarkable clinical response that children with CD have to the anti-TNF biologics, infliximab and adalimumab, the rate of endoscopic, histologic, and transmural healing is low and remains difficult to determine which patients will achieve these desired outcomes based on pre-treatment predictors. This study sought to determine if any pre-treatment demographic or biomarker metrics were predictive of endoscopic, histologic, or transmural outcomes in a pediatric CD cohort treated with the anti- TNF biologics.

Methods: In a multicenter observational study, anti-TNF naïve patients starting either infliximab or adalimumab provided longitudinal biospecimens (blood and stool) for one year. After one year, patients had a follow up colonoscopy and an optional research-only abdominal MRI. Clinical remission (CR) was assessed with the weighted pediatric Crohn's disease activity index (wPCDAI) <12.5 and off steroids. Endoscopic healing (EH) was defined as a Simple Endoscopic Score Crohn's disease (SES-CD) <3. Histologic healing (HH) was defined as a Global Histologic Disease Activity Score (GHAS) <2 for both the ileum and colon. Transmural healing (TH) was defined as simplified Magnetic Resonance Index of Activity (sMARIA) <2 for all sections of bowel. We evaluated pre-treatment demographics and biomarkers as predictors for EH, HH, TH and EH+TH using both an univariate ($p<0.1$) and multivariate regression. A priori predictors included steroid use at start of anti-TNF, age at diagnosis, age at start of anti-TNF, CD location, CD behavior, perianal disease behavior, weight z-score, BMI z-score, anti-TNF biologic, hemoglobin, platelets, ESR, CRP, serum albumin, fecal calprotectin, neutrophil CD64 ratio (nCD64), and wPCDAI.

Results: Of the 80 patients enrolled, the median age was 14.1 years (10.9-16.1), 42.5% female, and 88.8% white. Sixty-three patients started infliximab and 17 started adalimumab. The median days to start anti-TNF was 23 days (7-41).

We found the total rate of CR was 85% (68/80), EH was 52.9% (36/68), HH was 40.1 (13/32), TH was 54.5% (24/44) and combination of EH and TH was 33.3% (14/42). HH data is currently preliminary as histology scoring is still underway. We found those achieving the desired outcomes had a significantly lower fecal calprotectin and nCD64 at both month3 and year1. Patients achieving the desired outcomes were also found to have significantly higher drug trough levels at month3.

In our univariate analysis, we found significant pre-treatment predictors of EH to be PCDAI>30, wPCDAI>40, ESR<20 mm/h, and fecal calprotectin<2300 µg/g. Significant pre-treatment predictors of HH were PCDAI<30, fecal calprotectin<2300 µg/g, and fecal calprotectin<2500 µg/g with perianal phenotype found to be a significant negative predictor of HH. Significant pre- treatment predictors of TH were weight z-score>-0.6, BMI z-score>-1.2, and albumin>3.8 g/dL. Pre-treatment Entocort was found to be a significant negative predictor of TH. Significant predictors of EH+TH were found to be weight z-score>-0.6, BMI z-score>-1.2, and ESR<20mm/h, with age at diagnosis found to be a significant negative predictor.

Conclusions: Pre-treatment factors affecting positive outcomes for pediatric CD patients were found and indicate that pre-treatment biomarkers and patient demographics can be useful in predicting treatment outcomes for patients starting anti-TNF biologics. Drug levels, fecal calprotectin, and nCD64 at three months of treatment were also found to be predictive of patient outcomes after one year of treatment and may be useful in predicting a patient's long-term outcomes of anti-TNF biologic therapy.

The Medical Student Summer Research Program (MSSRP) at the University of Cincinnati is funded by the National Institute of Diabetes and Digestive Kidney Diseases grant T35 DK060444.