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Methotrexate Polyglutamates as Biomarkers of Treatment Response in IBD vs. JIA

Ryan Morrow
rpmorrow@cmh.edu

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Submitting/Presenting Author (must be a trainee): Ryan Morrow
Primary Email Address: rpmorrow@cmh.edu

□ Resident/Psychology Intern (≤ 1 month of dedicated research time)
XX Resident/Ph.D/post graduate (> 1 month of dedicated research time)
□ Fellow

Primary Mentor (one name only): Dr. Valentina Shakhnovich
Other authors/contributors involved in project: Ashley Sherman, Mara Becker, Ryan Funk

IRB Number: 14100454

Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
Performed a retrospective chart review of patients enrolled under the current IRB project. Reviewed current literature in both Gastroenterology and Rheumatology with regards to use of methotrexate polyglutamates as a tool for therapeutic response, therapeutic drug monitoring, and drug compliance. Participated in data analysis and interpretation and preparation of the manuscript stemming from this work. Next steps include writing a research protocol for a larger, longitudinal study aimed at investigating the role of methotrexate polyglutamates monitoring in treatment response to methotrexate therapy in IBD and JIA.

Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words

Background:
Methotrexate (MTX) is an immunomodulator used for the treatment of inflammatory bowel disease (IBD) and juvenile idiopathic arthritis (JIA). After administration, inside blood cells, methotrexate undergoes addition of glutamate to form methotrexate polyglutamates (MTX-Glu), classified based on the number (n) of the glutamate side-chains with up to six glutamates ($MTX\text{-}Glu_n$). MTX-Glu show promise as potential biomarkers of systemic exposure to MTX and may have clinical utility for prediction of therapeutic response.

Objectives/Goal:
The aim of this investigation was to compare MTX-Glu disposition in IBD vs. JIA. The clinical utility of MTX-Glu is being explored in adult rheumatology and gastroenterology literature, with sparse information in pediatric literature. Our goal was to assess the relationship between MTX-Glu and therapeutic response in children receiving MTX for IBD and JIA.

Methods/Design:
Cross sectional study of 27 children (5-21 years; 45% female) with IBD or JIA, receiving combination maintenance therapy with infliximab (IFX) and MTX. At the time of MTX-Glu measurements in erythrocytes (HPLC/MS), IFX serum trough concentrations were measured by an

established gene-reporter assay (ARUP Laboratories), and disease activity (Remission vs. Active) determined via 1) agreement on Physician Global Assessment by two pediatric gastroenterologist for IBD, or 2) JADAS-71 score for JIA, with scores >3.8 indicative of active disease. Given the variability in clinically prescribed drug dosing, and age and size of children, all data were adjusted ($_{adj}$) for mg/kg drug received and interval since drug administration. Spearman's correlation (ρ), Wilcoxon Rank Sum tests, and multivariable logistic regression analyses were used to compare parameters of interest in children with Remission vs. Active Disease (SAS; $\alpha<0.05$). Unless otherwise specified, data are reported as Median (Interquartile Range).

Results:

For patients with IBD (90% Crohn's disease), Total $_{adj}$MTX-Glu was significantly higher in Remission [211 (126, 299), n=9) vs. Active Disease [126 (62, 212), n=10], p=0.03. $_{adj}$MTX-Glu$_1$ [109 (53, 120) vs. 37 (0, 50), p=0.008] and $_{adj}$MTX-Glu$_2$ [62 (39, 72) vs. 24 (13, 38), p=0.01] were also significantly higher in Remission vs. Active Disease, with the two study groups comparable for age and disease duration (both p=0.9). Controlling for IFX dose, interval and trough level in a multivariable logistic regression, differences in MTX-Glu between Remission and Active Disease remained significant for $_{adj}$MTX-Glu$_1$ and $_{adj}$MTX-Glu$_2$ (short chain MTX-Glu; p≤0.04) and approached significance for Total $_{adj}$MTX-Glu (p=0.06). For patients with JIA, no statistically significant differences were noted in Total $_{adj}$MTX-Glu, or individual short chain or long chain ($_{adj}$MTX-Glu$_{3, 4, 5}$) MTX-Glu in Remission (n=5) vs. Active Disease (n=3).

Conclusions:

Adjusted for mg/kg MTX received, total and short chain MTX-Glu were significantly higher in patients with IBD in disease remission vs. active disease, independent of age, disease duration, or IFX dose, interval or trough, suggesting that MTX-Glu may be important determinants of disease response to MTX. We did not observe differences in dose-adjusted MTX-Glu in children with JIA in disease remission vs. active disease; however, this may be secondary to small sample size (n=8). Larger longitudinal studies of MTX-Glu in MTX mono- and combo-therapy are indicated in pediatric autoimmune disorders.