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### Methotrexate Polyglutamates and the Potential Role in Pediatric Inflammatory Bowel Disease

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## **Methotrexate Polyglutamates and the Potential Role in Pediatric Inflammatory Bowel Disease**

**Submitting/Presenting Author (must be a trainee): Ryan Morrow**

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**Fellow**

**Primary Mentor (one name only): Dr. Valentina Shaknovich**

**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 Rheumatology and Gastroenterology 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.

### **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). Inside the cell, methotrexate undergoes addition of glutamic acids to form methotrexate polyglutamates (MTX-Glu), classified based on the length of the glutamate side-chain as MTX-Glu<sub>1</sub> through 6. MTX-Glu show promise as potential biomarkers of systemic exposure to MTX and may have clinical utility for prediction of therapeutic response, therapeutic drug monitoring, and dose titration.

#### **Objectives/Goal:**

The clinical utility of MTX-Glu is being explored in adult rheumatology and gastroenterology literature, with sparse information in children and no information in children with IBD. This gap in knowledge is problematic as methotrexate is becoming a more widely-used immunomodulator in the treatment of pediatric IBD. Our goal was to assess the relationship between MTX-Glu and therapeutic response in children receiving MTX for IBD.

#### **Methods/Design:**

Cross sectional study of 21 children (5-21 years; 90% Crohn's disease) receiving maintenance therapy with infliximab (IFX) and MTX (i.e., no changes in dose or interval of either drug for  $\geq 2$  IFX

infusion cycles). At the time of MTX-Glu assessment, via measurement of erythrocyte MTX-Glu<sub>1-6</sub> concentrations by HPLC/MS, IFX concentrations were measured by an established gene-reporter assay (ARUP Laboratories) and disease activity (Remission vs. Active) determined by agreement on Physician Global Assessment by two pediatric gastroenterologists. Given variability in clinical dosing and age and size of children enrolled, all data were adjusted (<sub>adj</sub>) for mg/kg and interval since drug received. Spearman's correlation ( $\rho$ ), Wilcoxon Rank Sum tests and multivariable logistic regression analysis were used to compare parameters of interest in children with Remission vs. Active disease (SAS;  $\alpha=0.05$ ); data reported as Median (IQR), unless otherwise specified.

### **Results:**

MTX doses ranged 5-25mg weekly (81% oral) and, as expected, MTX Glu<sub>tot</sub> positively correlated with mg/kg MTX received ( $\rho=0.5$ ,  $p=0.02$ ). <sub>adj</sub>MTX-Glu<sub>tot</sub> was significantly higher in Remission (n=11) vs. Active (n=10); 211 (126, 299) vs. 126 (62, 212),  $p=0.04$ . Short chain <sub>adj</sub>MTX-Glu<sub>1</sub> 103 (47, 120) vs. 37 (0, 50) and <sub>adj</sub>MTX-Glu<sub>2</sub> 60 (29, 72) vs. 24 (13, 38) were also significantly higher ( $p=0.01$  and  $0.02$ , respectively) in Remission vs. Active. Although differences in IFX trough ( $p=0.4$ ) and <sub>adj</sub>trough ( $p=0.25$ ) were not statistically significant in Remission vs. Active disease, even after incorporating <sub>adj</sub>trough into a multivariable logistic regression model, the differences in <sub>adj</sub>MTX-Glu<sub>1</sub> ( $p=0.03$ ) and <sub>adj</sub>MTX-Glu<sub>2</sub> ( $p=0.04$ ) remained significant between study groups. The two study groups were comparable for age 16.0 (13.0, 17.0) vs. 14.5 (9.0, 19.5) and disease duration 2.5 (1.8, 5.2) vs. 3.8 (1.0, 4.7); both  $p=0.9$ .

### **Conclusions:**

Total methotrexate polyglutamate levels correlate with MTX dose and appear to reflect systemic MTX exposure. Total and short chain MTX-Glu were significantly higher in patients with disease remission, independent of patient age, disease duration, or concomitant IFX therapy. These results demonstrate a potential role for MTX-Glu as markers of disease response to MTX. Although the cross-sectional design and small sample size in the present study could not identify minimum MTX-Glu levels associated with therapeutic response, larger longitudinal studies may identify a meaningful threshold for MTX therapeutic drug monitoring.