Genetic Variation in Drug Transporter explains Side Effects in Pediatric Inflammatory Bowel Disease

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Antibodies neutralize biologic treatment needed for IBD

- Inflammatory bowel disease (IBD) includes two chronic diseases that cause swelling of the intestines
  - Crohn’s disease and ulcerative colitis
  - Affects 1.6 million Americans (1 in 200 people)

- IBD is commonly treated with a combination of a biologic agent (ex. Infliximab) & an immunosuppressive agent

- Infliximab monotherapy causes high immunogenicity
  - Anti-drug antibodies (ADA) form against Infliximab
    - Infusion reactions
    - Shorter duration of response
MTX transport influenced by SLCO1B1 pharmacokinetics

• Methotrexate (MTX):
  – Acts as an immunosuppressant
  – Reduces immunogenicity of infliximab
  – Increases levels of free infliximab
• MTX causes nausea and liver toxicity
• SLCO1B1 transports MTX from blood to liver (→ kidney for excretion)
• The *5 & *15 reduced function alleles have been associated with:
  – Delayed MTX clearance
  – Increased side effects in adults
**Objective:** Evaluate whether \textit{SLCO1B1} alleles are associated with MTX-induced nausea and intolerance in children with inflammatory bowel disease

**Hypothesis:** Reduced function \textit{SLCO1B1} alleles will result in MTX intolerance
Methods

- Retrospectively analyzed 278 patients < 19 years of age who were prescribed MTX for IBD at Cincinnati Children’s Hospital
- 202 patients had banked DNA and were genotyped for 3 SLCO1B1 single nucleotide polymorphisms (SNPs)
  - rs2306283
  - rs11045819
  - rs4149056
- Diplotypes were determined by combining the SNPs into the *1a, *1b, *4, *5, *14, and *15 alleles
- Nausea and intolerance were abstracted from clinician notes
- Prescriptions and demographics were extracted from the medical record
- Regression and chi-square analyses were used with a p < 0.05 being statistically significant
Our Patient Cohort

- The cohort was 69.8% male and 89.1% white with the median age of 16.04 (±3.9) years
- 51.7% of patients experienced MTX intolerance
  - Adverse drug reaction
  - Elevated liver enzymes
- 34.2% of patients experienced MTX-induced nausea
- 53.5% of patients discontinued MTX

<table>
<thead>
<tr>
<th>SLCO1B1 alleles</th>
<th>n = 404, n (%)</th>
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<tbody>
<tr>
<td>*1a (A-C-T)</td>
<td>209 (51.7%)</td>
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<tr>
<td>*4 (A-A-T)</td>
<td>0 (0%)</td>
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<tr>
<td>*5 (A-C-C)</td>
<td>8 (4.0%)</td>
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<tr>
<td>*14 (G-A-T)</td>
<td>59 (14.6%)</td>
</tr>
<tr>
<td>*15 (G-C-C)</td>
<td>50 (12.4%)</td>
</tr>
<tr>
<td>*1b (G-C-T)</td>
<td>69 (17.1%)</td>
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Nausea is associated with \textit{SLCO1B1} diplotype

![Graph showing the association between \textit{SLCO1B1} diplotype and nausea frequency. The graph indicates increased function and clearance for decreased exposure and decreased function and clearance for increased exposure. The data is fitted by multivariate general linear regression, with a p-value of 0.006. The diplotypes included are: *14/*14, *14/*1b, *14/*1a, *14/*1b/*1b, *1a/*1b/*1a, *1a/*1a/*14/*15, *5/*14, *1b/*15/*1a/*15, *1a/*5, *15/*15, *15/*5. The sample sizes for each diplotype vary from 4 to 62.]
SLCO1B1 *15 carriers reported an increase in MTX-induced nausea

\[ p = 0.032 \]

Chi-squared test for trend
Initiation with antiemetic reduced nausea in *15 carriers

Fisher's Exact Test

$p = 0.14$

- Started with ondansetron
- Did not start with ondansetron

<table>
<thead>
<tr>
<th>Frequency of reported nausea (%)</th>
<th>Zero</th>
<th>At least one</th>
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<tbody>
<tr>
<td>n=25</td>
<td>n=124</td>
<td></td>
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<tr>
<td>n=15</td>
<td></td>
<td>n=38</td>
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Conclusion

• Our data demonstrates that $SLCO1B1*15$ allele is associated with MTX-induced nausea in pediatric patients with IBD

• Our study suggests that patients with at least one $*15$ allele could benefit from:
  • A dose reduction of MTX to reduce exposure
  • Initiating MTX treatment with concurrent ondansetron to reduce nausea
Limitations & Future Directions

Limitations:
• The retrospective nature of our study may have resulted in under-reported rates of nausea, d/c, and intolerance
• Adherence to medications was not able to be assessed

Future Directions:
• Look upstream at MTX metabolite levels in the blood
• Submitting a paper in Clinical and Translational Science by the end of the month
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• Ramsey Lab
References

Feel free to contact me with any questions!

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