TPMT TESTING IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

WHY IS TPMT TESTING IMPORTANT?

- Detection of individuals with low thiopurine methyltransferase (TPMT) activity who are at risk for excessive myelosuppression or severe hematopoietic toxicity when taking thiopurine drugs
- Detection of individuals with hyperactive TPMT activity who have therapeutic resistance to thiopurine drugs and may develop hepatotoxicity if treated with these drugs

WHICH TESTS ARE AVAILABLE AND WHEN SHOULD I ORDER THEM?

<table>
<thead>
<tr>
<th>WHEN TO ORDER</th>
<th>PRIOR TO INITIATION OF THERAPY*</th>
<th>AFTER INITIATION THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENOTYPING ASSAY</td>
<td>Prior to initiation of therapy to predict risk of toxicity</td>
<td>After initiation of therapy to optimize therapy and identify elevated metabolite concentrations that may result in toxicity</td>
</tr>
<tr>
<td>(MAYO ID: GTPMT)</td>
<td>After therapy is initiated if patient was not previously tested and toxicity is encountered</td>
<td>As needed for dose changes, flare-up, signs of toxicity, or suspicion of non-compliance</td>
</tr>
<tr>
<td>ACTIVITY ASSAY</td>
<td>Prior to initiation of therapy to predict risk of toxicity</td>
<td>In patients that do not respond to therapy as expected</td>
</tr>
<tr>
<td>(MAYO ID: TPMT3)</td>
<td></td>
<td><strong>Recommended Timepoints</strong>:</td>
</tr>
<tr>
<td>METABOLITE MONITORING ASSAY</td>
<td></td>
<td>4 weeks after starting treatment to ensure patient compliance and to look for early risk of toxicity</td>
</tr>
<tr>
<td>(MAYO ID: FPMET)</td>
<td></td>
<td>12-16 weeks (after TGN metabolites have reached steady-state)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annually</td>
</tr>
</tbody>
</table>

*The current literature does not clearly demonstrate one of these tests to be superior over the other; therefore, both tests are offered and the clinical practice at Mayo Clinic supports either testing approach.

ADVANTAGES

- Can identify patients at risk of toxicity and start them on a reduced dose or alternate therapy
- Test is not impacted by other medications
- DNA is stable/specimen is less sensitive to transport conditions
- Can adjust/optimize dose during course of therapy
- Can monitor impact of additional drugs (i.e. allopurinol) added during course of therapy

Initiation of thiopurine therapy for IBD

Has patient had RBC transfusion within past 6 weeks?*

OR

Does patient have low hematocrit or reticulocytosis?

OR

Is patient uremic?

NO

Has patient had RBC transfusion within past 6 weeks?

YES

NO

Is patient a bone marrow transplant recipient?

NO

YES

Pre-transplant specimen required

TPMT genotype testing

TPMT phenotype or genotype testing

TPMT Activity: hyperactive

(phenotype testing only)

Consider alternative medications**

Normal dose and monitoring

Reduce dose and monitor appropriately

Consider reduced dose and monitor appropriately

Consider alternative medications

OR

Drastically reduce dose and monitor carefully

4 weeks after treatment initiation

12-16 weeks after treatment initiation

Annually, or as needed for dose changes, flare-up, signs of toxicity, suspicion of non-compliance, lack of response

TPMT Metabolite Monitoring

6-TGN 235-450 pmol/8x10^8 RBC

Low/absent 6-TGN and 6-MMP

Low 6-TGN and high 6-MMP

High 6-TGN and low 6-MMP

High 6-TGN and 6-MMP

Continue therapy and monitoring

Noncompliance/underdosing

Consider allopurinol and drastic dose reduction

Dose reduction and close monitoring

Refactory: consider alternative medication

*Presence of donor DNA in products may influence genotyping results; however, genotype typically reverts to recipient within 6 weeks after a transfusion.

**Patients with high TPMT activity cannot achieve therapeutic levels with thiopurine drugs and prescribing higher doses may cause hepatotoxicity.

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