THE ROLE OF DRUG MONITORING IN INFLAMMATORY BOWEL DISEASE

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DISCLOSURES
- I have the following financial disclosures
  - Abbvie

OBJECTIVES
- 1. Understand the goals of TPMT testing and thiopurine metabolite monitoring in clinical care
- 2. Recognized the association between infliximab levels and clinical outcomes in UC and Crohn's disease
- 3. Interpret anti-TNF antibody levels and apply to patient care

PATIENT
- 16 y/o male with moderate/severe ileocolonic Crohn's disease
  - Mercaptopurine maintenance therapy (1 mg/kg dose)
- 6-TG level at 4 weeks subtherapeutic
  - Leukopenia with dose escalation
- Infliximab initiated
  - Good response initially, but develops breakthrough symptoms
  - Increased to 10 mg/kg q 6 weeks, no improvement
  - Transitioned to adalimumab

QUESTIONS
- Can therapeutic drug monitoring
  - Predict complications of mercaptopurine therapy?
  - Lead to optimization of medical therapy?
  - Prevent loss of response to anti-TNF therapy?
  - Improve patient outcome?

TPMT TESTING
- Goals: Minimize adverse effects, maximize clinical response
  - Prevent leukopenia, aggressively dose patients
- Polymorphisms in TPMT influence response
  - Normal/high activity (80-86%)
    - High TPMT may shunt to 6-MMPN
  - Low activity (10-14%)
    - Predictor of response and remission
  - Deficient (0.3%-0.6%)

Dubinsky et al. Gastroenterology 2000;118:705
Augenlicht et al. Aliment Pharmacol Ther 2008;28:973
Benkov et al. JPGN 2013;56:333
LIMITATIONS OF TESTING

• Myelosuppression occurs in patients with normal TPMT activity
  – 41 patients with leukopenia or thrombocytopenia
  – 30 (73%) normal TPMT alleles
  – 11 (27%) TPMT alleles associated with low activity
• No association of TPMT activity and hepatotoxicity
• Cannot predict other complications
• Cost effective?
  – Screening more cost effective than dose escalation based on lack of response

METABOLITE MONITORING

• Advantages:
  – Optimization of dose
  – Monitoring of noncompliance
  – Early identification of nonresponders
• Limitations:
  – Cost?
  – Over-interpretation of results

Patients with 6-TGN level above 230-260 more likely to be in remission (OR 3.3)

METABOLITE-DIRECTED ALGORITHM

<table>
<thead>
<tr>
<th>6-TGN</th>
<th>6-MMP</th>
<th>Interpretation</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic</td>
<td>Normal/High</td>
<td>Refractory, appropriately dosed</td>
<td>Change therapy</td>
</tr>
<tr>
<td>Low</td>
<td>Low/Normal</td>
<td>Underdosed, Noncompliant</td>
<td>Increase dose</td>
</tr>
<tr>
<td>High</td>
<td>Normal/High</td>
<td>Refractory, overdosed</td>
<td>Change therapy</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>6-MMP shunter</td>
<td>Change therapy or add allopurinol</td>
</tr>
</tbody>
</table>

63 patients with active IBD:
Therapeutic levels both metabolites: 41%
Noncompliance: 10%
Underdosed: 29%
High levels both metabolites: 11%
Shunters: 10%

Algorithm +: 87% (40 of 46) improved
Algorithm -: 18% (3 of 17) improved

CONSENSUS RECOMMENDATIONS

• TPMT testing is recommended before initiation of thiopurines
  – Homozygous recessive or low TPMT activity avoid thiopurines
  – TPMT testing does not predict all cases of leukopenia
• Role for metabolite testing to determine adherence or guide dose changes in patients with active disease
• Routine testing has no role in patients who are doing well on acceptable dose of thiopurines
LOSS OF RESPONSE TO ANTI-TNF THERAPIES

IFX TROUGH LEVELS -- PEDIATRIC IBD

IFX TROUGH LEVELS -- PEDIATRIC IBD

IFX CONCENTRATION AND OUTCOME IN ULCERATIVE COLITIS

IFX CONCENTRATION AND OUTCOME IN ULCERATIVE COLITIS

SERUM IFX TROUGH AND COLECTOMY IN UC
IFX TROUGH LEVEL AND OUTCOME

<table>
<thead>
<tr>
<th>Trough level</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable</td>
<td>Clinical remission, CRP, endoscopic remission¹</td>
</tr>
<tr>
<td>&gt; 3.5 ug/ml</td>
<td>Sustained response²</td>
</tr>
<tr>
<td>&gt; 3 ug/ml</td>
<td>Sustained response²</td>
</tr>
<tr>
<td>&gt; 5.6 mg/l</td>
<td>Lower CRP²</td>
</tr>
<tr>
<td>Undetectable</td>
<td>Loss of response²</td>
</tr>
</tbody>
</table>

⁴Lamblin et al. J Crohn’s and Colitis 2012;334
⁵Drobe et al. Gastroenterology 2011;279

DRUG CONCENTRATION AND OUTCOMES

• Adalimumab
  – Serum concentration > 5 ug/ml predicted normal CRP and remission of Crohn’s disease⁶
  – Level of 3 ug/ml discriminated between presence and absence of inflammation²
  – Low concentrations (median 2.5 ug/ml) associated with drug discontinuation³

• Certolizumab Pegol
  – Week 8 and week 54 certolizumab levels correlated with endoscopic remission⁶

EFFECT OF ATI ON LOSS OF RESPONSE

DURATION OF RESPONSE BASED ON ATI LEVELS

ANTI-TNF DRUG/ANTIBODY LEVELS AND OUTCOME
ANTI-TNF DRUG/ANTIBODY LEVELS AND OUTCOME

Patients with adequate drug levels

P = .022 (Log rank test)

Months since intervention

REACTIVE TESTING

- Avoids dose intensification in those who will not benefit from more drug
- Allows targeted dose escalation in those whose loss of response is due to low drug concentration
- Directs patients with non-TNF driven disease to other therapeutic options

IS REACTIVE TESTING IS COST EFFECTIVE?

- Compared to empiric dose escalation for secondary loss of response
  - Reactive testing yielded similar QALYs
  - Similar rates of remission and response
  - Reactive testing was less expensive
  - Lower use of high-dose biologics
  - Greater time off biologics

REACTIVE TESTING ALGORITHM

<table>
<thead>
<tr>
<th>Secondary loss of response (disease activity confirmed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic drug concentration</td>
</tr>
<tr>
<td>ADA negative</td>
</tr>
<tr>
<td>Low level</td>
</tr>
<tr>
<td>High level</td>
</tr>
<tr>
<td>Change drug class or surgery</td>
</tr>
<tr>
<td>Dose escalate</td>
</tr>
<tr>
<td>Consider dose escalation, addition of immunomodulator, or change anti-TNF</td>
</tr>
<tr>
<td>Change to different anti-TNF</td>
</tr>
</tbody>
</table>

SUMMARY

- There is a positive association between biologic trough levels and clinical response
- Evidence supports a role for drug monitoring in patients who have lost response to anti-TNFs
- Proactive monitoring may help optimize response
  - More research needed regarding optimal trough level and timing of testing