Role of Therapeutic Drug Monitoring (TDM) in Managing IBD

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Objectives

- Review drug monitoring for immunomodulators
- Review drug monitoring for biologics
- Understand the difference and data supporting reactive versus proactive TDM
- Understand how to interpret results with respect to management of IBD patients
- Recognize and differentiate between TDM Assays
Therapeutic Drug Monitoring (TDM)

- TDM: old concept with progressive use in IBD

- Drug is absorbed, distributed, metabolized, eliminated by the body

- Monitor blood concentration

- Effect: What does the drug do to the body?
IBD Drugs:
What can we monitor?

- Thiopurines
- Methotrexate
- Biologics
  - TNF inhibitors- infliximab, adalimumab, certolizumab
  - Integrin inhibitors- natalizumab, vedolizumab
  - IL-12, IL-23 inhibitor- ustekinumab
Metabolism of Thiopurines

- **Azathioprine** $\rightarrow$ **6MP** $\rightarrow$ **6TGN**

**TPMT**

**6MMPR**

- **Bone marrow suppression** $\geq 450$
- **Therapeutic** $\geq 230-260$

**Hepatotoxicity** $\geq 5700$
Remission linked to 
\[6\text{TGN} \geq 230-260\]

Those with \(6\text{TGN} \geq 230-260\) had 3x higher likelihood of remission.

Remission rates: Over threshold 62%, below threshold 36%

Osterman M. Gastroenterology 2006
Role of Thiopurines Preventing Antibodies to TNF inhibitors

Thiopurines prevent antibodies and increase TNFi drug concentrations
Goal 6TGN of ≥125 may be adequate
If 6TGN <125 more likely to have Abs to IFX
Methotrexate Levels

- Can check RBC methotrexate polyglutamate
- Systematic review of RA patients
  - 13 studies, 8 showed association of higher levels and lower disease activity
  - High levels required to produce meaningful clinical improvement
  - Limitation: SE with higher doses
- Not much data in IBD though limited data suggest possible inverse relationship between the drug levels and efficacy but directly correlates with SE

Brooks AJ. Therapeutic Drug Monitoring 2007
Monitoring TNF inhibitors

- **Why is it important?**
  - Response to first anti-TNF agent is most promising
  - Optimize from the beginning so better outcomes
  - Higher drug levels with no Abs translates to mucosal healing and better rates of remission

- **What information can we get from the assay?**
  - Drug levels: Enough drug?
  - Antibodies: Present or not?
  - Switch within or outside class of biologic
Higher IFX Levels
Longer remission and Better endoscopy scores

105 CD patients
Prospective cohort in moderate to severe Crohn’s disease
Median follow up: 88 weeks

Maser EA. Clin Gastroenterol Hepatol 2006
Undetectable IFX trough levels
Higher rates of colectomy

115 patients with moderate to severe UC
Median follow up 13.9 months
Detectable IFX levels associated with higher remission rates
Detectable IFX levels associated with endoscopic improvement
Vedolizumab Levels: Response and Remission better with higher trough levels
Reactive vs Proactive TDM

- **Reactive TDM:**
  - Measure with loss of response
  - Measure with infusion reactions
  - Better directs care and prevents unnecessary drug exposure in those unlikely to respond to more TNFi\(^1\)
  - More cost-effective than standard of care \(^2-4\)

- **Proactive TDM:**
  - Optimize dosing to allow for best changes to prevent loss of response
  - Preliminary data (TNFi):
    - Approach can improve efficacy and potentially cost-effectiveness \(^4,5\)
    - May help guide re-introduction of drug holiday \(^6,7\)
    - May help discontinuation of TNFi in those achieving deep remission \(^8\)

1. Papamichail K, Cheifetz A. Frontline Gastroenterol 2016
2. Steenholdt C. Gut 2014
3. Velayos FS. Clin Gastroenterol Hepatol 2013
5. Vaughn BP. Inflamm Bowel Dis 2014
6. Vande Casteele N. Gastroenterology 2015
## Reactive: Treatment Algorithm in patients with Symptoms During TNFi

<table>
<thead>
<tr>
<th>Trough Anti-TNF agent Concentration</th>
<th>Interpretation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable</td>
<td><strong>Active disease</strong></td>
<td>TNFi not useful</td>
</tr>
<tr>
<td></td>
<td><strong>Inactive disease</strong></td>
<td>IBD is controlled</td>
</tr>
<tr>
<td>Undetectable</td>
<td><strong>Antibodies positive</strong></td>
<td>Antibodies could decrease TNFi levels</td>
</tr>
<tr>
<td></td>
<td><strong>Antibodies negative</strong></td>
<td>Bioavailability or pharmacokinetic problem</td>
</tr>
</tbody>
</table>
When to monitor?

**FIGURE 5.** Time points for drug level determination.

- **During Induction + First year**
  - Evidence for week 6, 14, 30 and 54 (for IFX)

- **Maintenance**
  - Clinical response
  - Loss of response
  - Mucosal Ulceration
  - Elevated Biomarkers (CRP/FC)

- **No need for drug levels evaluation**
- **Determine drug levels**

All assays available for drug levels evaluation are accurate, however for each patient, drug levels should be always measured with the same assay.
Reactive TDM: Algorithm for Loss of Response with TNFi

Symptoms concerning for response loss

1. **Trough >5-10**
   - Endoscopy shows active inflammation: Switch to drug with different MOA
   - Endoscopy shows no inflammation: Rule out other Causes

2. **Trough <5**
   - Antibodies high: Switch within class
   - No or low Abs: Optimize same anti-TNF - decrease interval, increase dose, add immunomodulator

Adapted from JF Colombel
Humira Antibodies

ADA Abs even more important
Aim for ADA level at least 5 but possibly as high as 10

Baert F. Gut 2015
MTX or AZA make low-level Abs go away
Proactive: Monitoring drugs to optimize infliximab maintenance

Retrospective cohort of patients in clinical remission, single practice
- Optimized IFX dose to trough 5-10 ug/mL (n=48)
- No optimization of IFX (n=78)

OPTIMIZING DOSE INCREASED LIKELIHOOD OF REMAINING ON IFX UP TO 5 YRS

Vaughn BP. Inflamm Bowel Dis. 2014
TAXIT: Prospective (Proactive) RCT Trough level Adapted InfliXIImab Treatment

Proactive Target IFX concentration 3-7 ug/mL = less need for rescue therapy and higher rate of drug concentration compared to clinically based dosing

During initial optimization phase dose escalation in CD patients with suboptimal IFX concentration significantly increased the number of patients in clinical remission with an associated decrease in CRP levels.

Vande Casteele N. Gastroenterology 2015
Roles of **Proactive** TDM

- **De-escalate if supra-therapeutic drug:**
  - Dose reduction, interval prolongation and/or withdrawal of IMM to allow us to maximize safety and cost-effectiveness
  - 15% of patients stopped or de-escalated IFX therapy based on TDM without any negative impact on long term outcomes\(^1\)
  - 27% in TAXIT trial underwent dose-escalation with significant reduction of treatment costs without deterioration of remission rates\(^2\)
  - 90% of patients with trough >8 ug/mL who de-escalated IFX to target concentration of 3-7 ug/mL were in deep remission after 8 mos\(^3\)
  - 80 patients with IBD in clinical remission- TDM based de-escalation approach was superior to blind adjustments of IFX therapy based on symptoms and CRP\(^4\)

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1. Vaughn BP. Inflamm Bowel Dis 2014
2. Vande Casteele N. Gastroenterology 2015
3. Paul S. Aliment Pharmacol Ther 2015
Roles of **Proactive** TDM

- **De-escalate by IMM withdrawal**
  - Drug retention similar between patients in clinical remission on mono- or combo-therapy who had IFX concentration $\geq 5$ ug/mL meaning optimized mono-therapy is possible\(^1\)
  - Patients receiving combination therapy if IFX trough $>5$ ug/mL at time of IMM discontinuation have decreased risk for dose escalation, IBD surgery, loss of response to drug\(^2\)
  - After combo-therapy for 6 mos no clear benefits\(^3\)

- **TNFi needs to be discontinued due to response other than loss of response or adverse event**
  - Low or undetectable drug concentration at time of discontinuation associated with sustained remission after TNFi withdrawal\(^4,5\)
  - Rest-starting TNFi after drug holiday showed that absence of IFX Abs and detectable IFX trough after the first dose is associated with fever infusion reactions and better long-term response\(^5\)

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1. Vaughn BP. Inflamm Bowel Dis. 2014
2. Drobne D. Clin Gastroenterol Hepatol 2015
3. Van Assche G. Gastroenterology 2008
**TDM Assays: US available**

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug-tolerant</th>
<th>Anti-drug Ab</th>
<th>Labs using commercial kits or in-house developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>No</td>
<td>Ug/mL</td>
<td>Miraca</td>
</tr>
<tr>
<td>HMSA</td>
<td>Yes</td>
<td>U/mL</td>
<td>Prometheus</td>
</tr>
<tr>
<td>ECLIA</td>
<td>Yes</td>
<td>Ng/mL</td>
<td>Lab Corp/Esoterix Janssen</td>
</tr>
<tr>
<td>SRA-L-MS/MS</td>
<td>Yes</td>
<td>U/mL</td>
<td>Mayo Clinic</td>
</tr>
</tbody>
</table>

ELISA: enzyme-linked immunosorbent assay, HMSA: homogeneous mobility shift assay
ECLIA: electro-chemiluminescence immunoassay
SRA LC-MS/MS: Selective Reaction Monitoring Liquid Chromatography Mass Spectrometry/Mass Spectrometry

Of note: Mayo clinic: own in-house IFX levels/abs, sends ADA levels/abs to Esoterix and all others to Miraca; interfaces with epic

- Chose drug-tolerant assay if you need to make clinical decision based on Ab results
- If just dose adjusting and optimizing levels earlier on in treatment then all assays appropriate
- Positive antibodies mean different things based on assay being used—so don’t stop drug due to positive antibodies alone
Limitations of TDM

- Out-of-pocket costs and health reimbursement issues related to testing and optimization of drug
- Time lag from collecting serum sample to the results of the test
- Accurate interpretation and application of the results based on assay used
- Optimal timing of serum sampling
- Need more prospective long-term data for all biologics during maintenance and induction therapy
Conclusions

- TDM based treatment strategy will likely be emerging as a standard of care but we have to overcome limitations.

- Studies show that adequate drug concentrations and improved clinical outcomes and objective measures of inflammation.

- Reactive TDM directs care in patients losing response to TNFi and more cost-effective than empiric dose escalation.

- Proactive TDM may prove event more effective to optimize biologic therapies and treatment.
"I stopped taking the medicine because I prefer the original disease to the side effects."