Therapeutic Drug Monitoring in IBD

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Objectives

• Review non-biologic drug monitoring
• Update on biologic drug monitoring
• Understand REactive and PROactive therapeutic drug monitoring (TDM)
• Learn about practical tools to help with performing TDM
What is therapeutic drug monitoring?

Drug → Dose → PK → Blood concentration → PK-PD → Effect

- Drug is absorbed, distributed, metabolized and eliminated by the body
- Blood concentration
- What the drug does to the body

Therapeutic Drug Monitoring

This is NOT a new concept

- Nomogram for once daily gentamicin dosing
- 1995!
- We were all very good at this as interns

Drugs we can monitor

- Thiopurines
- Methotrexate
- Biologics
  - Anti-TNFs
  - Vedolizumab
  - Ustekinumab

Thiopurine Metabolism

Higher remission rates if above goal 6-TGN

Patients with 6-TGN levels above threshold of 230-260 had a 3x odds of being in remission

Remission rates
Over threshold = 62%
Below threshold = 36%

What about if using thiopurines only to prevent antibodies to anti-TNF?

- To help prevent antibodies against and optimize drug concentrations of biologics
- Full dose may NOT be needed
- Goal 6-TGN lower
  - 6-TGN of ≥125 may be adequate
- If lower than 125, more likely to have antibodies against infliximab
Can we (do we) check methotrexate levels?

- We can - red blood cell methotrexate polyglutamate
- Systematic review for rheumatoid arthritis 2015
  - 13 studies, 8 showed association between higher levels and lower disease activity
  - Relatively large increases in concentrations required to produce a meaningful clinical change
  - Potentially useful, may be limited by dose-related adverse events
- Little work in IBD: inverse relationship between drug level and efficacy – but direct correlation with adverse events


Anti-TNFs – why monitor?

- Get it right the 1st time
  - 1st anti-TNF is our best shot
  - Earlier we are successful the better
- What are we looking for?
  - Not enough drug
  - Antibodies
  - Wrong drug class

Does it really matter?

- Pretty convincing data that higher drug levels (and lack of antibodies) are associated with better remission rates and mucosal healing
- Across all biologics (not just anti-TNF)
- Not convincing prospective data (yet) to make routine TDM for biologics obvious, but...
- Sure does make sense

Higher Infliximab Concentration is Associated with Longer Remission and Better Endoscopy Scores

- 105 CD patients, prospective cohort in moderate-severe CD
- Median follow-up: 88 weeks

Undetectable trough level of IFX in UC associated with colectomy

- 115 patients with moderate to severe UC, median f/u 13.9 mo
- Efficacy
  - Detectable serum IFX was associated with
    - Higher remission rates (69% vs. 15%; \(P<0.001\))
    - Endoscopic improvement (76% vs. 28%; \(P<0.001\))


Vedolizumab response and remission higher with higher trough concentrations

Sandborn WJ et al. NEJM 2013
-active monitoring

- **REactive drug monitoring**: our norm. Wait until something bad happens (e.g., loss of response, infusion reaction) then try to fix it

- **PROactive drug monitoring**: optimize dosing to maximize chance of and prevent loss of response

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**When to monitor?**

Adapted from Silva-Ferreira F. et al. Inflamm Bowel Dis 2016.
Reactive Testing for Loss of Response with anti-TNF

Symptoms suggesting loss of response

- Trough levels > 5-10
- Trough levels < 5

Switch to drug with different mode of action (non-anti-TNF)

Endoscopy shows no inflammation

Rule out complication; consider treating IBS symptoms

- Antibodies high >8 mg/L equivalents
  - Switch within class
- Antibodies low <8 mg/L equivalents
  - Optimize with same anti-TNF (decrease interval, increase dose, add immunomodulator)

Making low-level antibodies go away

Patient 1: Start MTX

Patient 2: Start AZA

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Adapted from JF Colombel

Ben Horin S, Clin Gastroenterol Hepatol 2013
Prospective therapeutic drug monitoring to optimize infliximab maintenance therapy in IBD

- Retrospective cohort of patients in clinical remission, single physician practice
  a. Infliximab dose optimization to trough concentrations 5–10 µg/mL (n=48)
  b. No infliximab dose optimization (n=78)

![Graph showing probability of infliximab effectiveness over weeks with optimized and non-optimized doses]

\[ p = 0.0006 \]

![Graph showing probability of infliximab effectiveness over weeks with different trough levels]

\[ p < 0.0001 \]

\[ p = 0.6 \]

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**TAXIT**

Prospective controlled Trough level Adapted infliXImab Treatment

Clinically based (CB) and trough level based (LB) groups

![Bar graph showing percentage of patients in clinical remission]

62.3% (n=122) for CB group and 64.3% (n=126) for LB group

\[ p = 0.79 \]

![Line graph showing relapse-free survival over maintenance phase]

LogRank \( p = 0.0038 \)
Breslow \( p = 0.0058 \)
Corey A. Siegel, MD, MS

**BUT...TAXIT diluted their benefit due to design**

- **Screening**
- **Randomization**
- **Optimization phase** (n weeks)
- **Maintenance phase** (52 weeks)
- **Primary end point**

**IFX dosing based on clinical symptoms & CRP**

**Randomized 1:1**

**LB Group**
- IFX dosing based on **IFX TL** (3-7 µg/mL)

**CB Group**
- IFX TL within optimal interval

**IFX maintenance therapy** → **Stable clinical response**

**Dosing based on IFX TL** (3-7 µg/mL)

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**Biologic assay options in the US**

- Different technology, different cost
- Pretty similar except one MAJOR difference
  - Prometheus (Anser) – able to confidently measures drug concentration AND antibody independently
  - Others (LabCorp, Mayo Labs, Miraca) have unclear significance of the antibody result

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Choice of Assay

- If concerned about antibody production and making a decision based on antibody being absent or present (and value) → drug-tolerant assay (e.g., Prometheus)
- If dose adjusting, tweaking trough levels, optimizing early → all assays appropriate
  - **But be warned**: all antibodies are not created equal, so don’t stop drug based on antibody alone because we simply don’t know what they mean

Which drugs, which assay?

<table>
<thead>
<tr>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Vedolizumab</th>
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<tbody>
<tr>
<td>LabCorp</td>
<td>LabCorp</td>
<td>Miraca</td>
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<tr>
<td>Mayo</td>
<td>Miraca <em>(also CZP)</em></td>
<td>Prometheus*</td>
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*drug-tolerant assay

**We just don’t know yet what certolizumab or vedolizumab levels should be**
Use same assays for biosimilars?

- All 69 anti-Remicade positive patients also positive for anti-Remsima ATI
- All 56 control anti-Remicade negatives also negative for anti-Remsima ATI

Ben-Horin S, presented at UEGW 2014

A tool to help you in the clinic

Anti-TNF optimizer

Found at: www.BRIDGeIBD.com

Accessible on all devices (smart phones, tablets and computers)

Melmed et al, CGH 2016
Take Home Points

- Don’t forget to optimize thiopurines
- REactive drug monitoring helps, but risks waiting until drug has failed
- Data lacking to strongly support PROactive drug monitoring, but it sure makes sense
- This is what I do:
  - Check trough after induction (week 14 for IFX, week 8 for ADA) and dial in the dose
  - Aim for goal trough drug concentration > 5, 10 even better (but not always attainable)
  - Low threshold to recheck levels and optimize dose, preserve a drug for as long as possible