Drug Level Monitoring in IBD

Corey A. Siegel, MD, MS
Director, Dartmouth-Hitchcock IBD Center
Associate Professor of Medicine, Geisel School of Medicine at Dartmouth

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 → Blood concentration → Effect

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

PK → PK-PD

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

AZA → 6-MP → 6-TGN
TPMT

6-MMPR

Hepatotoxicity
(≥ 5700)

Bone Marrow
Toxicity
(≥ 450)

Clinical
Efficacy
(≥ 230-260)

Higher remission rates if above goal 6-TGN

![Graph showing odds ratio and 95% CI for different studies.]

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
  - At least moderate potential for bias in all 8 of these studies
  - 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
- Sure does make sense though

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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

- Vedolizumab Trough Concentration (\( \mu g/mL \)):
  - First Quartile: 0 to <15.2
  - Second Quartile: 15.2 to <24.0
  - Third Quartile: 24.0 to <33.8
  - Fourth Quartile: 33.8 to 142.0

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

When to monitor?

![Diagram showing when to monitor for drug levels during induction, maintenance, loss of response, mucosal ulceration, and elevated biomarkers.](image)

All assays available for drug levels evaluation are accurate, however for each patient, drug levels should be always measured with the same assay.
Reactive Testing for Loss of Response with anti-TNF

Symptoms suggesting loss of response

- **Trough levels > 5-10**
  - Endoscopy shows active inflammation
  - Switch to drug with different mode of action (non-anti-TNF)

- **Trough levels < 5**
  - Antibodies high >8 mg/L equivalents
  - No or low antibodies <8 mg/L equivalents
  - Optimize with same anti-TNF (decrease interval, increase dose, add immunomodulator)
  - Endoscopy shows no inflammation
  - Rule out complication: consider treating IBS symptoms
  - Switch within class

Adapted from JF Colombel

Antibodies may be even more important for adalimumab

Any antibodies may be bad for adalimumab, aim for drug concentrations of at least 5, maybe 10 to prevent them from developing

High ATA = above ATA cutoff of 1.7 U/ml
Detectable ATA = below cutoff, but non-zero unquantifiable number returned
No ATA = zero ATA value

Making low-level antibodies go away

![Graphs showing concentration of antibodies over time]

Patient 1: MTX started, antibodies decrease.
Patient 2: AZA started, antibodies increase.

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
  - Infliximab dose optimization to trough concentrations 5–10 µg/mL (n=48)
  - No infliximab dose optimization (n=78)

![Graphs showing probability of remaining on infliximab]

Dose optimization increases probability of remaining on infliximab up to 5 years

p = 0.0006

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**TAXIT**

Prospective controlled Trough level Adapted infliXImab Treatment

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

![Graph showing clinical remission and maintenance phase](image)

BUT...TAXIT diluted their benefit due to design

IFX maintenance therapy -> Stable clinical response

Dosing based on IFX TL (3-7 µg/mL)

Optimization phase (n weeks)

Randomization

Screening

Primary end point

IFX dosing based on clinical symptoms & CRP

Randomized 1:1

Maintenance phase (52 weeks)

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


ACG 2016

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Patient in remission on maintenance IFX therapy

**ATI Positive**
- High level ATI (>15ug/ml)
  - • Change to different anti-TNF
  - • If failed multiple anti-TNFs change class
  - • Consider surgery
- Low level ATI (<15ug/ml)
  - • Increase dose
  - • Add on IMM

**ATI Negative**
- High IFX concentration
  - • Reduce dose
  - • If at 5mg/kg, extend interval
- Therapeutic IFX concentration
  - • Continue IFX dose and interval
  - • Consider re-check in 6-12 months
- Low IFX concentration
  - • Undetectable level: increase dose to 7.5mg/kg and consider next dose at 4 or 6 weeks
  - • Low concentration: increase IFX by 50 – 100mg

### 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
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>
</tr>
<tr>
<td>Mayo</td>
<td>Miraca (also CZP)</td>
<td>Prometheus</td>
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<td>Miraca</td>
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<tr>
<td>Prometheus</td>
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*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
Anti-TNF Optimizer

- Which drug is your patient taking?
- What is the drug concentration?
- What is the antibody level?
- What is the clinical scenario?
  - Responding to therapy
  - Primary non-response (never worked)
  - Secondary loss of response (drug worked and then stopped working)

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