The Role of Therapeutic Monitoring in IBD
Minimizing anti-TNF Failures

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How we can Optimize Drug Therapy in IBD

- Choosing therapies based on prognosis as well as severity
- Utilizing validated objective endpoints of disease control
- Understanding therapy risk in the context of disease risk
- Adjusting therapies serially until endpoints are achieved
- Optimizing therapies to match disease severity and inflammatory burden
DRUG LEVELS AND EFFICACY: UNDERSTANDING EXPOSURE RESPONSE RELATIONSHIP
Higher Serum Infliximab Concentration is Associated with Longer Remission and Better Endoscopy Score in Patients with Crohn’s Disease

- Study design: prospective cohort in moderate-severe CD
- N=105
- Median follow-up: 88 weeks
- Efficacy
  - Infliximab concentrations were positively correlated with the interval of clinical remission and change in endoscopic score

Proportion of UC Patients Achieving Clinical Remission by Serum IFX Concentration: ACT 1 and 2

At wks 8, 30 and 54, the proportion of patients achieving clinical remission increased with increasing quartiles of IFX concentrations.

<table>
<thead>
<tr>
<th>IFX Conc. (% patients)</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 8</strong></td>
<td></td>
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</tr>
<tr>
<td>26.3% (&lt;21.3μg/mL)</td>
<td>37.9% (≥21.3-&lt;33μg/mL)</td>
<td>43.9% (≥33-&lt;47.9μg/mL)</td>
<td>43.1% (&gt;47.9μg/mL)</td>
<td>P=0.0504</td>
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<tr>
<td><strong>Week 30</strong></td>
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<tr>
<td>14.6% (&lt;0.11μg/mL)</td>
<td>25.5% (≥0.11-&lt;2.4μg/mL)</td>
<td>59.6% (≥2.4-&lt;6.8μg/mL)</td>
<td>52.1% (&gt;6.8μg/mL)</td>
<td>P&lt;0.0001</td>
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<tr>
<td><strong>Week 54</strong></td>
<td></td>
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</tr>
<tr>
<td>21.1% (&lt;1.4μg/mL)</td>
<td>55.0% (≥1.4-&lt;3.6μg/mL)</td>
<td>79.0% (≥3.6-&lt;8.1μg/mL)</td>
<td>60.0% (&gt;8.1μg/mL)</td>
<td>P=0.0066</td>
<td></td>
</tr>
</tbody>
</table>

Reinisch W et al. Gastroenterology 2014
Trough adalimumab levels are higher in patients with mucosal healing.

![Graph showing Trough level of ADA (μg/mL) with MH and No MH categories.]

- MH: 6.5 μg/mL
- No MH: 4.2 μg/mL

*P* < 0.005

UNDERSTANDING THE DRIVERS OF PHARMACOKINETIC (PK) OF BIOLOGICS
# Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Presence of ADAs</th>
<th>Impact on Pharmacokinetics</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Decreases serum mAbs</td>
</tr>
<tr>
<td></td>
<td>• Threefold-increased clearance</td>
</tr>
<tr>
<td></td>
<td>• Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of IS</td>
<td>• Reduces formation</td>
</tr>
<tr>
<td></td>
<td>• Increases serum mAbs</td>
</tr>
<tr>
<td></td>
<td>• Decreases mAb clearance</td>
</tr>
<tr>
<td></td>
<td>• Better clinical outcomes</td>
</tr>
<tr>
<td>High baseline TNF-α</td>
<td>• May decrease mAbs by increasing clearance</td>
</tr>
<tr>
<td>Low albumin</td>
<td>• Increases clearance</td>
</tr>
<tr>
<td></td>
<td>• Worse clinical outcomes</td>
</tr>
<tr>
<td>High baseline CRP</td>
<td>• Increases clearance</td>
</tr>
<tr>
<td>Body size</td>
<td>• High BMI may increase clearance</td>
</tr>
<tr>
<td>Gender</td>
<td>• Males have higher clearance</td>
</tr>
</tbody>
</table>

mAB, monoclonal antibody; ADA, antidrug antibody

Anti-drug antibodies are associated with shorter infusion intervals and lower drug levels

**Infliximab in CD**

- **Antibodies against infliximab**
  - Undetectable
  - 1.7-7.9 µg/ml
  - 8.0-20.0 µg/ml

**Adalimumab in CD**

- **Median ADA (µg/ml)**
  - Week 4: 6.1 (n=53), 2.1 (n=9)
  - Week 12: 8.9 (n=37), 0.6 (n=8)
  - Week 24: 8.8 (n=30), 0.1 (n=8)
  - Week 54: 11.1 (n=46), 0.02 (n=3)
  - Therapy: 5.8 (n=30), 0.05 (n=10)

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*Baert F. et al NEJM 2003;348:601-8*

*Karmiris K. Gastroenterology 2009;137:1628–1640*
Transient vs sustained ATI

IFX discontinuation due to loss of response and/or hypersensitivity

Rapid IFX clearance: Mechanism of Non Response in UC

Fecal Loss of Infliximab (IFX) As a Cause of Lack of Response in Severe Inflammatory Bowel Disease

• Aim:
  • To determine if fecal loss of IFX contributes to failure of response to induction therapy in severe colitis

• Methods:
  • Fecal samples collected within first 14 days following 1st IFX infusion (5mg/kg)
  • Nonresponse: Cessation or intensification of therapy within 3 months

• Results:
  • 11 patients (8 UC, 3 CD); all with colonic disease
  • Compared to responders, non-responders to IFX had:
    • Higher fecal IFX concentration at day 1 (P=0.02)
    • Lower serum IFX concentration at day 14 (P=0.03)

• Conclusion: Fecal loss of infliximab may contribute to primary non-response in severe IBD colitis

Accelerated Infliximab Rescue Reduces Early Colectomy Rate in Acute Severe UC

- Retrospective study of induction IFX 5mg/kg in patients who required hospitalization for acute severe, steroid-refractory UC
- No difference in colectomy rate during IFX maintenance

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Median Induction (Days)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Dosing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 0, 2, and 6</td>
<td>35</td>
<td>43</td>
<td>Early colectomy (n=13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluid collections (n=6)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Wound infections (n=4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DVT/PE (n=1)</td>
</tr>
<tr>
<td><strong>Accelerated Dosing</strong></td>
<td></td>
<td>24.5</td>
<td>Early colectomy (n=1)</td>
</tr>
<tr>
<td>Week 0, then 2\textsuperscript{nd} and 3\textsuperscript{rd} infusion when indicated by physician determined by clinical need</td>
<td>15</td>
<td></td>
<td>Respiratory tract infection (n=1)</td>
</tr>
</tbody>
</table>

Gibson et al. *Clin Gastroenterol Hepatol* 2014
COMBINATION THERAPY VS. OPTIMIZED MONOTHERAPY
SONIC: Immunogenicity Results at Week 30
Impact of combination therapy

Adding immunomodulator to revert immunogenicity

Infliximab anti-infliximab antibodies (ATI)

Concentration (mcg/ml)

Weeks

Start MTX

Start 6-MP

Start AZA

Ben Horin S, Clin Gastroenterol Hepatol 2013
Higher 6-TGN Levels are Associated with Higher Infliximab Trough Levels in Patients on Combination Therapy

- Cross-sectional study of 72 patients on combination therapy
- 6TGN levels (but *not* thiopurine dose or lymphocyte count) correlated with IFX levels (rho:0.466, p<0.001)
- 6TGN > 125 pmol/8 x 10^8 RBC predicted higher IFX levels – ROC: 0.82, p=0.002
- 6TGN < 125 pmol/8 x 10^8 RBC predicted higher likelihood of ATIs – OR: 1.3, 95% CI 2.3 – 72.5, p<0.01

Yarur A et al. DDW 2014, Abstract 788
THERAPEUTIC DRUG MONITORING IN CLINICAL PRACTICE
How to interpret and manage loss of response: REACTIVE APPROACH

Symptoms suggesting loss of response

Trough levels detectable
- Endoscopy shows active inflammation
  - Switch to drug with different mode of action (non-anti-TNF)
- Endoscopy shows no inflammation
  - Rule out stenosis; consider treating IBS symptoms (mebeverine, otilonium,...)

Trough levels undetectable
- Antibodies high >8 mg/L equivalents
  - Switch within class
- No or low antibodies <8 mg/L equivalents
  - Optimize with same anti-TNF (decrease interval, increase dose, add immunomodulator)
Optimizing Maintenance Therapy: PROACTIVE MONITORING

Week 14 IFX Level by Week 54 Persistent Remission Status

Singh N et al IBD journal 2014;10:1708-13
Prospective therapeutic drug monitoring to optimise infliximab maintenance therapy in IBD

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

- Evaluated probability of remaining on infliximab, for up to 5 years

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

Taxit: Distribution of drug levels in IBD patients with durable response (n=275)

**Infliximab trough level (TLI)**
- undetectable TLI
- TLI < 3 μg/ml
- 3 μg/ml < TLI < 7 μg/ml
- TLI > 7 μg/ml

Receive too much drug? Can they be de-escalated?
- 26%

Receive not enough drug? Should they be escalated?
- 21%

Receive no drug? Can they be stopped?
- 9%

The Future of Individualized Dosing
With the use PK Dashboards

Dubinsky MC et al DDW 2015
The Future of Individualized Dosing  
With the use PK Dashboards  
**FAST CLEARANCE PREDICTED DOSING**

<table>
<thead>
<tr>
<th>Dose Interval</th>
<th>Next Dose</th>
<th>Dose (mg)</th>
<th>Dose (mg/kg)</th>
<th>Dose (vials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Wk</td>
<td>09-14</td>
<td>880.4</td>
<td>22.9</td>
<td>8.8</td>
</tr>
<tr>
<td>3 Wk</td>
<td>09-08</td>
<td>287.6</td>
<td>7.49</td>
<td>2.9</td>
</tr>
<tr>
<td>2 Wk</td>
<td>08-31</td>
<td>87.2</td>
<td>2.27</td>
<td>0.9</td>
</tr>
<tr>
<td>1 Wk</td>
<td>08-24</td>
<td>21.8</td>
<td>0.569</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Dubinsky MC et al DDW 2015
Therapeutic Drug Monitoring for Anti-TNFα

- Measurable drug level associated with improved response outcomes
- Anti-drug antibodies (ADA) associated with decreased efficacy
- ADA and drug levels can help guide treatment decisions
- Optimized monotherapy with proactive monitoring may be an effective and safer option
- Restarting drug after holiday is possible
- Individualized and dashboard guided dosing is closer than we think