Optimizing the treatment of IBD through use of therapeutic drug monitoring

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Conflict of Interest Disclosure

Adam S. Cheifetz

I disclose the following financial relationships with commercial entities that produce health care-related products or services relevant to the content I am planning, developing, or presenting:

<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
<th>Content Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen</td>
<td>Consulting</td>
<td>IBD</td>
</tr>
<tr>
<td>Abbvie</td>
<td>Consulting</td>
<td>IBD</td>
</tr>
<tr>
<td>Takeda</td>
<td>Consulting</td>
<td>IBD</td>
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<tr>
<td>Pfizer</td>
<td>Consulting</td>
<td>IBD</td>
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<tr>
<td>Miraca</td>
<td>Consulting/Research</td>
<td>IBD</td>
</tr>
<tr>
<td>Ferring</td>
<td>Consulting</td>
<td>GI / preps</td>
</tr>
<tr>
<td>AMAG</td>
<td>Consulting</td>
<td>Iron deficiency</td>
</tr>
</tbody>
</table>
Goals

1) Review how we can optimize the use of biologics
2) Describe the role of therapeutic drug concentration monitoring (TDM) with biologics
3) Discuss reactive vs. TDM
4) Learn potential benefits for proactive TDM
Optimizing the Treatment of IBD

• Treat deeper (mucosal healing)
• Treat earlier
• Treat more effectively
Optimizing Treatment of IBD

- Optimizing biologics
  - Induction regimen and maintenance dosing
  - Combination therapy with immunomodulator
  - Earlier use of biologics
- Therapeutic drug concentration monitoring (TDM)
  - Reactive testing of drug concentration and antibodies
    - Better directs care and more cost-effective
  - Proactive TDM – improves outcomes and cost-effective
When and why to do TDM?

• Proactive TDM
  • During maintenance
    • Improves clinical scores and markers of inflammation (CRP)
    • Decreases need for rescue therapy
    • Prolongs duration of infliximab with less infliximab discontinuation
    • Decreases IBD-related hospitalizations and surgeries, serious infusions reactions, ATI and treatment failure when compared with reactive TDM
    • Cost-effective
  • Proactive TDM following reactive TDM is better than reactive TDM alone
  • Optimized (biologic) monotherapy
  • When stopping immunomodulator (in combination with anti-TNF)
  • During induction
**American Gastroenterological Association (AGA) Guidelines on TDM**

**Table 3. Summary of Recommendations of the American Gastroenterological Association Clinical Guidelines for Therapeutic Drug Monitoring in Inflammatory Bowel Disease**

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence. Comment: Table 4 summarizes suggested trough concentration for anti-TNF therapy, for patients with active IBD on maintenance therapy. Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough concentrations for induction therapy are uncertain.</td>
<td>Conditional recommendation</td>
<td>Very low quality</td>
</tr>
<tr>
<td>In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring.</td>
<td>No recommendation</td>
<td>Knowledge gap</td>
</tr>
</tbody>
</table>
### Consensus statement on TDM in IBD by Australian IBD Consensus working group

<table>
<thead>
<tr>
<th>Statement</th>
<th>Acceptance (%)</th>
<th>EL</th>
<th>RG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenarios when TDM of anti-TNF agents should be performed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management</td>
<td>100</td>
<td>II</td>
<td>C</td>
</tr>
<tr>
<td>2. TDM can inform clinical decision-making in patients with primary nonresponse</td>
<td>100</td>
<td>III2</td>
<td>C</td>
</tr>
<tr>
<td>3. TDM should be performed in patients with secondary loss-of-response to guide clinical decision-making</td>
<td>100</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>4. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management</td>
<td>90</td>
<td>IV</td>
<td>D</td>
</tr>
<tr>
<td>5. Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have TDM along with other investigations to help guide this decision</td>
<td>100</td>
<td>III2</td>
<td>C</td>
</tr>
</tbody>
</table>

- Includes:
  - Proactive TDM at the end of induction
  - Proactive TDM in clinical remission if results are likely to impact management
BRIDGe (Rand panel): When should drug concentration and antibody testing be performed?

- **Appropriate to perform testing**
  - At the end of induction, primary non-response
  - Secondary non-response
  - During maintenance, responding
  - Restarting after drug holiday (before 2\textsuperscript{nd} infusion)

- **Uncertain to perform testing**
  - At the end of induction, in responders
Episodic therapy is associated with high rates of antibodies to infliximab and shorter duration of response

- 125 consecutive refractory CD patients
- On-demand / episodic infliximab treatment, mean 3.9 infusions (range 1–17)
- Antibodies to infliximab (ATI) in 61% patients
- Relative risk of infusion reaction with higher ATI titer: 2.4 (p<0.001)

$\text{ATI} = \text{Antibodies to infliximab}$
$\text{IFX} = \text{infliximab}$

---

Immunogenicity of infliximab is decreased with maintenance therapy and combination therapy (ACCENT I)

ATI = Antibodies to infliximab

573 patients with Crohn’s disease

- 5 mg/kg Infliximab maintenance
- 10 mg/kg Infliximab maintenance

- Without IM (n=382)
- With IM (n=152)

Episodic strategy:
- 38 patients with ATI (%)
- Without IM: 38
- With IM: 16.1

- Without IM: p=0.003
- With IM: p=NS

p=0.003 for the difference between ATI in episodic strategy.

p=NS for the difference between ATI in Infliximab maintenance.

We still haven’t fully optimized anti-TNFs Crohn’s disease

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=110)</th>
<th>5mg/kg (n=112)</th>
<th>10mg/kg (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission at 30 weeks, %</strong></td>
<td>21</td>
<td><strong>39</strong></td>
<td>45</td>
</tr>
<tr>
<td><strong>Median time to LOR, wk</strong></td>
<td>19</td>
<td>38</td>
<td>&gt;54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=170)</th>
<th>Every other week (n=172)</th>
<th>Weekly (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission at 26 weeks, %</strong></td>
<td>17</td>
<td><strong>40</strong></td>
<td>47,47</td>
</tr>
<tr>
<td><strong>Remission at 56 weeks, %</strong></td>
<td>12</td>
<td>36</td>
<td>41,41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=101)</th>
<th>Certolizumab pegol (n=112)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Remission at 26 weeks, %</strong></td>
<td>26</td>
<td><strong>42</strong></td>
<td>.01</td>
</tr>
</tbody>
</table>

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Non anti-TNF drug concentrations correlate with outcome: Cohort studies and post-hoc analysis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Concentration</th>
<th>Clinical outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD (Reinisch CGH 2015)</td>
<td>IFX</td>
<td>&gt;3</td>
<td>Mucosal healing</td>
<td>Post hoc analysis of SONIC</td>
</tr>
<tr>
<td>CD (Cornillie GUT 2014)</td>
<td>IFX</td>
<td>&gt;3.5</td>
<td>Sustained response</td>
<td>Post hoc analysis of ACCENT I</td>
</tr>
<tr>
<td>CD (Bortlik JCC 2013)</td>
<td>IFX</td>
<td>&gt;3</td>
<td>Sustained response</td>
<td>Week 14 or 24 trough</td>
</tr>
<tr>
<td>CD (Yarur APT 2017)</td>
<td>IFX</td>
<td>&gt;10.1</td>
<td>Fistula healing</td>
<td>HMSA</td>
</tr>
<tr>
<td>CD (Ward APT 2011)</td>
<td>IFX</td>
<td>&gt;5.7</td>
<td>Normal FC</td>
<td>ELISA</td>
</tr>
<tr>
<td>UC (Papamichael APT 2018)</td>
<td>IFX</td>
<td>&gt;7.5</td>
<td>Endoscopic healing</td>
<td>&gt;10.5 μg/ml for histologic healing</td>
</tr>
<tr>
<td>UC (Adedogun Gastro 2010)</td>
<td>IFX</td>
<td>&gt;2.4</td>
<td>Clinical response</td>
<td>Post hoc analysis of ACT I and II</td>
</tr>
<tr>
<td>CD/UC (Yanai CGH 2015)</td>
<td>IFX</td>
<td>&gt;3.8</td>
<td>Failed to respond to increase in IFX or change to another anti-TNF</td>
<td>Population was patients with LOR</td>
</tr>
<tr>
<td>CD/UC (Ungar CHG 2016)</td>
<td>IFX</td>
<td>&gt;6.8</td>
<td>Normal CRP</td>
<td>ELISA</td>
</tr>
<tr>
<td>CD/UC (Yarur CGH 2015)</td>
<td>IFX</td>
<td>&gt;8.3</td>
<td>Mucosal healing</td>
<td>HMSA</td>
</tr>
<tr>
<td>CD/UC (Roblin IBD 2017)</td>
<td>IFX</td>
<td>&gt;4.9</td>
<td>Clinical remission, normal CRP and normal FC</td>
<td>Normal FC (&lt;50 mg/g)</td>
</tr>
<tr>
<td>CD/UC (Papamichael CGH 2017)</td>
<td>IFX</td>
<td>&lt;3.5</td>
<td>Treatment failure</td>
<td>&lt;1.8 μg/ml for ATI formation</td>
</tr>
<tr>
<td>CD/UC (Brandse IBD 2017)</td>
<td>IFX</td>
<td>&lt;3</td>
<td>ATI formation</td>
<td>ELISA</td>
</tr>
<tr>
<td>CD (Zittan JCC 2016)</td>
<td>ADA</td>
<td>&gt;8.1</td>
<td>Mucosal healing</td>
<td>HMSA</td>
</tr>
<tr>
<td>CD/UC (Ungar CGH 2016)</td>
<td>ADA</td>
<td>&gt;6.6</td>
<td>Normal CRP</td>
<td>&gt;7.1 μg/ml for mucosal healing</td>
</tr>
<tr>
<td>CD/UC (Roblin CHG 2014)</td>
<td>ADA</td>
<td>&gt;4.9</td>
<td>Mucosal healing</td>
<td>ELISA</td>
</tr>
<tr>
<td>CD/UC (Yarur IBD 2016)</td>
<td>ADA</td>
<td>&gt;7.8</td>
<td>Histologic remission</td>
<td>HMSA</td>
</tr>
<tr>
<td>CD (Vande Casteele APT 2018)</td>
<td>CZP</td>
<td>&gt;13.8</td>
<td>Normal FC</td>
<td>Pooled data from 9 clinical trials</td>
</tr>
<tr>
<td>UC (Adedogun JCC 2017)</td>
<td>GOL</td>
<td>&gt;1.4</td>
<td>Clinical remission</td>
<td>Post hoc analysis of PURSUIT</td>
</tr>
<tr>
<td>CD/UC (Jacoub APT 2018)</td>
<td>VEDO</td>
<td>&gt;18</td>
<td>Mucosal healing</td>
<td>Week 6 concentrations</td>
</tr>
<tr>
<td>CD (Adedogun Gastro 2018)</td>
<td>USTE</td>
<td>&gt;1.4</td>
<td>Clinical remission</td>
<td>Pooled data from UNITI-1/2 and IM-UNITI</td>
</tr>
</tbody>
</table>

Higher drug concentrations are associated with better outcomes

Undetectable / low drug concentrations are associated with loss of response and antibodies
Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Impact on Pharmacokinetics</th>
</tr>
</thead>
</table>
| **Presence of anti-drug antibodies** | • Decreases serum drug concentration  
• Threefold-increased clearance  
• Worse clinical outcomes |
| **Concomitant use of immunomodulator** | • Reduces formation of anti-drug Ab  
• Increases serum drug concentration  
• Decreases drug clearance  
• Better clinical outcomes |
| **High baseline TNF** | • May decrease serum drug concentration by increasing clearance |
| **Low albumin** | • Increases clearance  
• Worse clinical outcomes |
| **High baseline CRP** | • Increases clearance |
| **Body size** | • High BMI may increase clearance |
| **Gender** | • Males have higher clearance |

mAB, monoclonal antibody; ADA, antidrug antibody
Reactive TDM
(Secondary non-response)

• Better directs care
• More cost effective than empiric dose escalation
# Measurement of IFX Concentration and ATI

Test results impacted treatment in 73% of patients

<table>
<thead>
<tr>
<th>Subtherapeutic IFX</th>
<th>Dose escalation</th>
<th>Complete or partial response - 86%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtherapeutic IFX</td>
<td>Switch anti-TNF</td>
<td>Response - 33%</td>
</tr>
<tr>
<td>Therapeutic IFX</td>
<td></td>
<td>No evidence of active inflammation in 62% of the patients</td>
</tr>
<tr>
<td>ATI positive</td>
<td>Switch anti-TNF</td>
<td>Response - 92%</td>
</tr>
<tr>
<td>ATI positive</td>
<td>Dose escalation</td>
<td>Response - 17%</td>
</tr>
</tbody>
</table>
Reactive testing algorithm

Secondary loss of response
(disease activity confirmed)

- Therapeutic anti-TNF concentration
  - ADA negative: Dose escalate
  - ADA positive: Consider dose escalation, addition of immunomodulator or change anti-TNF

- Sub-therapeutic concentration
  - Low level: Change to different anti-TNF
  - High level: Change drug class or surgery

ADA = anti-drug antibody

Adapted from Papamichail and Cheifetz, JCC 2016
Reactive testing is cost effective and more appropriately directs care

- Compared to empiric dose escalation for secondary loss of response\(^1\)
  - 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

\(^1\)Velayos et al. *Clin Gastroenterol Hepatol* 2013;11:654-666
Proactive TDM  
(During maintenance, responding)

- Improves clinical scores and markers of inflammation (CRP)
- Decreases need for rescue therapy
- Prolongs duration of infliximab with less infliximab discontinuation
- Decreases IBD-related hospitalizations and surgeries, serious infusions reactions, ATI and treatment failure when compared with reactive TDM
- Cost-effective
Therapeutic drug monitoring – Proactive monitoring

- Commonly performed in other situations
  - Cyclosporine, tacrolimus in solid organ transplantation
  - Cyclosporine and tacrolimus use in UC
  - Vancomycin and gentamycin in sepsis
- Therapeutic window
  - High concentrations can result in increased toxicity
  - Low concentrations result in lack of efficacy
  - Biologics – low concentrations result in immunogenicity*

Proactive testing in IBD: TAXIT

- **Trough level Adapted infliximab Treatment (TAXIT) trial.**
- **Patients:** Infliximab maintenance therapy with stable clinical response
- **All** patients underwent infliximab **dose optimization** to trough level of 3-7ug/ml
- **Randomized to:**
  - Infliximab dosing based on clinical symptoms and CRP
  - Infliximab dosing based on trough concentration
- **Primary outcome:** Clinical remission at 1 year
Dose escalation for Crohn’s improved disease control (symptoms and CRP)

Most patients with UC were in remission with normal CRP
TAXIT: Primary endpoint - 1 year after optimization:
No difference in (clinical and biological) remission rates between concentration and clinically dosed groups

Issues:
- All patients were initially optimized
- Only 1 year follow-up
- Sub-therapeutic window

Secondary endpoints favor dosing to infliximab concentration
- Less patients needed rescue therapy (7% vs. 17.3%; p=0.004)
- Less patients had undetectable trough concentrations (OR 3.7; p<0.001)
- Similar cost between both groups
  - 25% underwent dose de-escalation
Proactive TDM study group

• Retrospective cohort (TDM vs. control)
• Typical protocol for infliximab proactive dose optimization

- IFX undetectable
  - No or low ATI -> Increase IFX by 2.5mg/kg
  - High ATI -> Stop IFX

- IFX < 5ug/ml (detectable)
  - Increase IFX by 50-100mg (if no/low ATI)

- IFX 5–10ug/ml
  - No change

- IFX > 10ug/ml*
  - Decrease dose if > 5mg/g or
    Increase interval if at 5mg/kg

* On 2 occasions

Proactive therapeutic concentration monitoring and dose optimization results in a longer duration of infliximab and less discontinuation than standard of care.

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>TCM</th>
<th>No TCM</th>
</tr>
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<tbody>
<tr>
<td>48</td>
<td>34</td>
<td>78</td>
</tr>
<tr>
<td>34</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>10</td>
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<tr>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

P = 0.0006*
Less infliximab discontinuation in the proactive TDM group

\[ p = 0.009^* \]

Reasons for infliximab discontinuation

<table>
<thead>
<tr>
<th>Reason</th>
<th>Optimized</th>
<th>Not Optimized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing IBD symptoms</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Drug induced lupus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>High antibody (ATI) level</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute infusion reaction</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Delayed infusion reaction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other (unrelated to infliximab)*</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

73% of controls underwent dose escalation; ¾ increased IFX 10mg/kg

Median IFX dose increase was 100mg (range 50 - 200mg) in TDM group

14.6% patients in TDM de-escalated therapy (reduced dose or stopped)

*Includes: unable to afford co-payment, surgery for adhesive small bowel obstruction, colectomy for flat LGD.
Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab

- Multicenter (BIDMC and UPenn), retrospective, observational study.
- 153 patients with IBD who responded to infliximab and received maintenance therapy and underwent either proactive or reactive TDM, based on the first infliximab concentration / antibodies to infliximab (ATI) measurement (Prometheus Labs)
- Outcomes: Treatment failure, IBD-related surgery, hospitalization, antibodies to infliximab (ATI), and serious infusion reaction (SIR)
Less Treatment Failure with Proactive TDM

LogRank: p<0.001
Breslow: p<0.001

Follow up after start of IFX TDM (years)

At risk: 130 117 78 35 14 1 0
134 52 32 14 3 2 0
Less IBD-Related Surgery, Hospitalization, ATI, and Serious Infusion Reactions with Proactive TDM

Results: Infliximab TC quartiles associated with therapeutic outcomes of interest

- **Treatment failure**: p = 0.001
- **IBD-related surgery**: p = 0.331
- **IBD-related hospitalization**: p = 0.020

ATI and SIR comparisons:

- **Antibodies to infliximab**: p = 0.001
- **Serious infusion reactions**: p = 0.007
Proactive testing algorithm: Dose optimize to infliximab trough > 5 (- 10µg/ml)

Patient in remission on maintenance IFX therapy

ATI Positive

High level ATI
- Change to different anti-TNF
- If failed multiple anti-TNFs change class
- Consider surgery

Low level ATI
- Increase dose +/- Add on IMM

ATI Negative

High IFX concentration*
- Can stop IMM if on combo.
- 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: Decrease interval and consider increase dose (by 2.5mg/kg)
- Low concentration: Decrease interval or increase dose
Standard dosing of infliximab is insufficient in the majority of pediatric CD

Monte Carlo model
REACH & ACCENT I
10 y.o. with CD
Wt., alb, IMM, ATI
Aim = trough > 3ug/ml

Frymoyer et al, JPGN 2016;62:723
What about proactive TDM following reactive testing?

- **Aim:** To evaluate long-term outcomes of proactive infliximab monitoring following reactive testing compared to reactive testing alone in patients with IBD in terms of treatment failure and IBD-related surgery and hospitalization.

- Retrospective multi-center study.
- All consecutive IBD patients on infliximab maintenance therapy who underwent a first reactive testing from September 2006 to January 2015. Patients were followed through December 2015.
  - Group A: patients undergoing proactive infliximab monitoring after reactive testing performed for presumed loss of response or infusion reaction occurred
  - Group B consisted of patients undergoing reactive testing alone.
- Treatment failure was defined as infliximab discontinuation for loss of response or serious adverse event.

- 102 patients
- Median follow up of 2.7 (IQR 1.4-3.8) years
- No baseline differences between groups

Papamichael et al, JCC 2018 (accepted)
<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>Total cohort</th>
<th>Group A</th>
<th>Group B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>102</td>
<td>33</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Male, (%)</td>
<td>54 (53)</td>
<td>16 (48)</td>
<td>38 (55)</td>
<td>0.672</td>
</tr>
<tr>
<td>Age at diagnosis, median (IQR), years</td>
<td>22 (18-31)</td>
<td>22 (18-31)</td>
<td>22 (18-32)</td>
<td>0.758</td>
</tr>
<tr>
<td>Age at infliximab initiation, median (IQR), years</td>
<td>33 (25-43)</td>
<td>37 (31-46)</td>
<td>30 (24-43)</td>
<td>0.072</td>
</tr>
<tr>
<td>IBD type: CD, (%)</td>
<td>70 (69)</td>
<td>24 (73)</td>
<td>46 (67)</td>
<td>0.562</td>
</tr>
<tr>
<td>UC extension: Pancolitis, (%)</td>
<td>16/30 (53)</td>
<td>4/9 (44)</td>
<td>12/21 (57)</td>
<td>0.694</td>
</tr>
<tr>
<td>CD behaviour: B1 / B2 / B3, (%)</td>
<td>36/70 (51) / 14/70 (20) / 20/70 (29)</td>
<td>11/24 (46) / 4/24 (16) / 9/24 (38)</td>
<td>25/46 (54) / 10/46 (22) / 11/46 (24)</td>
<td>0.486</td>
</tr>
<tr>
<td>CD location: L1 / L2 / L3 / L4, (%)</td>
<td>13/70 (19) / 23/70 (33) / 33/70 (47) / 3/70 (1)</td>
<td>5/24 (21) / 6/24 (25) / 12/24 (50) / 1/24 (4)</td>
<td>8/46 (17) / 17/46 (37) / 19/46 (41) / 2/46 (5)</td>
<td>0.787</td>
</tr>
<tr>
<td>Perianal fistulising disease, (%)</td>
<td>30/70 (43)</td>
<td>12/24 (50)</td>
<td>18/46 (39)</td>
<td>0.450</td>
</tr>
<tr>
<td>Smoking ever, (%)</td>
<td>21 (21)</td>
<td>8 (24)</td>
<td>13 (19)</td>
<td>0.603</td>
</tr>
<tr>
<td>Prior ileocolonic resection, (%)</td>
<td>16/70 (23)</td>
<td>7/24 (29)</td>
<td>9/46 (20)</td>
<td>0.383</td>
</tr>
<tr>
<td>IFX dosing other than 5 mg/kg q8w, (%)</td>
<td>46 (45)</td>
<td>14 (42)</td>
<td>32 (46)</td>
<td>0.832</td>
</tr>
<tr>
<td>Anti-TNF naive, (%)</td>
<td>95 (93)</td>
<td>30 (91)</td>
<td>65 (94)</td>
<td>0.679</td>
</tr>
<tr>
<td>Concomitant IMM, (%)</td>
<td>32 (31)</td>
<td>12 (36)</td>
<td>20 (29)</td>
<td>0.498</td>
</tr>
<tr>
<td>IFX concentration, median, (IQR), μg/ml</td>
<td>6.2 (1.5-11)</td>
<td>6.4 (2.4-11.1)</td>
<td>5.4 (1.4-11.1)</td>
<td>0.646</td>
</tr>
<tr>
<td>ATI, (%)</td>
<td>18 (18)</td>
<td>4 (12)</td>
<td>14 (20)</td>
<td>0.410</td>
</tr>
<tr>
<td>Type of assay: HMSA, (%)</td>
<td>48 (47)</td>
<td>12 (36)</td>
<td>36 (52)</td>
<td>0.145</td>
</tr>
</tbody>
</table>

Papamichael et al, JCC 2018 (accepted)
Less treatment failure in group that had proactive TDM following reactive testing as opposed to just reactive testing.

Proactive IFX monitoring after reactive testing, n=33
Reactive testing alone, n=69

LogRank: p=0.001
Breslow: p=0.001

Follow up after start of IFX TDM (years)

At risk: 69 52 32 14 3 2 0 0 0
          33 33 26 21 14 6 4 1 0
Less IBD-related hospitalizations in group that had proactive TDM following reactive testing as opposed to just reactive testing.
Proactive TDM
(Optimized monotherapy with anti-TNF)

• Combination therapy with infliximab and immunomodulator improves outcomes

• Combination therapy with immunomodulator increases anti-TNF concentration and decreases anti-drug antibodies

• Combination therapy has been associated with increased adverse events (opportunistic infection, lymphoma and hepatosplenic T-cell lymphoma)

• Optimized monotherapy with anti-TNF may be an alternative to combination therapy
Best evidence for combination therapy is in biologic and immunosuppressive naïve patients with moderate to severe Crohn’s (SONIC)

**Primary End Point**

![Graph showing proportion of patients (%)]

- AZA + placebo: 30 (51/170)
- IFX + placebo: 44 (75/169)
- IFX + AZA: 57 (96/169)

Patients in the IFX+AZA group contributed a greater number of patients to higher IFX concentration quartiles than IFX monotherapy.

Corticosteroid-Free Remission at Week 34 Depends on Serum Trough IFX Concentration (Week 30) Not Whether Patient is on Combination Therapy

- Within same quartile, comparable efficacy of monotherapy and combination therapy
- More than twice as many patients achieved corticosteroid-free remission at week 34 from higher quartiles of IFX monotherapy compared to those on combination therapy with low IFX concentrations

<table>
<thead>
<tr>
<th>IFX Concentration at Week 30 (μg/mL)</th>
<th>Patients Achieving CSFR34 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: &lt;0.84 μg/mL</td>
<td>48.7 (n=9)</td>
</tr>
<tr>
<td>Q2: 0.84 μg/mL to &lt;2.36 μg/mL</td>
<td>65.5 (n=23)</td>
</tr>
<tr>
<td>Q3: 2.36 μg/mL to &lt;5.02 μg/mL</td>
<td>66.7 (n=21)</td>
</tr>
<tr>
<td>Q4: ≥5.02 μg/mL</td>
<td>78.6 (n=14)</td>
</tr>
</tbody>
</table>

Long term outcomes of “optimized monotherapy” with infliximab

- 31 patients
- All patients eventually titrated to IFX trough concentration > 3 ug/ml
- 83% of patients achieved a trough concentration > 5 ug/ml
- No patient stopped infliximab at end of data collection
- Median follow-up time: 3.4 years

- Continue to monitor trough concentrations

Proactive TDM
(When stopping immunomodulator (in combination with anti-TNF))

- Best data for combination therapy short-term (year)
- Stopping immunomodulator does not appear to affect 1-2-year remission rates
  - Associated with higher crp and lower anti-TNF concentrations
- Want adequate trough anti-TNF concentrations (before and) after stopping immunomodulator
  - Check anti-TNF concentrations before and after discontinuing immunomodulator
Withdrawal of immunomodulator after 6 months of remission in combination with infliximab

- Prospective RCT
  - 40 DIScontinued IMM
  - 40 CONtinued IMM
  - Followed for 2 years

Immunomodulator withdrawal is associated with significantly lower infliximab trough and higher CRP
Infliximab concentrations halved with stopping azathioprine

Tedesco et al, DDW 2016
Number of patients with infliximab trough < 1 went up to 40% with stopping AZA

Tedesco et al, DDW 2016
Proactive TDM (Induction)

- Patients with active disease require more drug
- Early drug concentrations correlate with short-term and long-term outcomes
Moderate-severe UC: ATI develop early and are associated with low infliximab concentrations and worse outcomes

- 19 patients with mod-severe UC treated with infliximab
- 58% endoscopic response (week 8)
- **Infliximab concentrations at week 6 higher in responders**
  - 8.1ug/mL vs. 2.9ug/mL in non-responders (p=0.03)
- **6/8 non-responders had +ATI** (vs. 1/11 responders) (p<0.01)
  - ATI seen as early as day 18
- Patients with high CRP had lower infliximab concentrations (p=0.001)
Early infliximab trough concentrations correlate with short term mucosal healing in UC
Early IFX trough concentrations are associated with persistent remission in pediatric IBD patients

**TABLE 2. Week 14 Infliximab Levels and Outcomes**

<table>
<thead>
<tr>
<th>Week 54 Outcome</th>
<th>IFX14 Median Level, μg/mL</th>
<th>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>4.7 versus 2.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>3.2 versus 2.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Clinical and laboratory remission</td>
<td>4.2 versus 3.0</td>
<td>0.07</td>
</tr>
<tr>
<td>SDR14</td>
<td>5.5 versus 3.1</td>
<td>0.05</td>
</tr>
<tr>
<td>SDR22</td>
<td>5.1 versus 3.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

^P value: Wilcoxon rank sum test. Bold text indicates significant P values.

**Wk 14 IFX > 7 = PPV 100% of Persistent Remission**
Issues with drug concentration monitoring

• Optimal trough concentration window is unclear
• Timing of testing
• Test that is accurate, accessible, and inexpensive

• Prospective data on implementation of TDM
Table 4. Suggested Target Trough Concentrations When Applying Reactive Therapeutic Drug Monitoring in Patients With Active Inflammatory Bowel Disease on Maintenance Therapy With Anti–Tumor Necrosis Factors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested trough concentration, (\mu g/mL)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>(\geq 5)</td>
<td>Six studies (929 patients) provided data on proportion of patients not in remission above predefined infliximab thresholds (1, 3, 5, 7, and 10 (\mu g/mL)). Based on these, proportion of patients not in remission decreased from 25% when using an infliximab threshold of (\geq 1 \mu g/mL), to 15% with an infliximab trough concentration of (\geq 3 \mu g/mL), to approximately 4% with an infliximab trough concentration of (\geq 7 \mu g/mL) or (\geq 10 \mu g/mL)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>(\geq 7.5)</td>
<td>Four studies provided data on proportion of patients not in remission above adalimumab trough concentration (\geq 5.0 \pm 1 \mu g/mL) or (7.5 \pm 1 \mu g/mL). On analysis of different thresholds, proportion of patients not in remission progressively decreased from 17% when using an adalimumab threshold (\geq 5.0 \pm 1 \mu g/mL), to 10% with an adalimumab trough concentration of (\geq 7.5 \pm 1 \mu g/mL). Different studies used different assays, and there are limited data on comparability of trough concentrations identified in different assays for adalimumab. It is unclear what proportion of patients on standard (40 mg every other wk) or escalated adalimumab dosing (40 mg every wk) would be able to achieve these thresholds</td>
</tr>
<tr>
<td>Certolizumab Pegol</td>
<td>(\geq 20)</td>
<td>One study provided data from an exposure response pooled analysis from 9 trials. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 42% when using a certolizumab threshold of (\geq 10 \mu g/mL) to 26% with a certolizumab trough concentration of (\geq 20 \mu g/mL)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Unknown</td>
<td>There is a lack of sufficient evidence available to establish a target trough goal</td>
</tr>
</tbody>
</table>

---

*Studies used to derive different target trough concentrations were cross-sectional studies of patients on maintenance therapy in various stages of remission/response, to identify what proportion of patients were in remission (or not in remission), above and below specific thresholds. They were not specifically designed to evaluate patients who had a secondary loss of response. Details are available in accompanying Technical Review.*
Consensus statement on TDM in IBD by Australian IBD Consensus working group

<table>
<thead>
<tr>
<th>Statement</th>
<th>Acceptance (%)</th>
<th>EL</th>
<th>RG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target drug trough levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. In IBD patients with luminal disease a steady state trough infliximab level between 3 and 8 µg/mL is generally recommended</td>
<td>96</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td>18. In IBD patients with luminal disease a steady state adalimumab trough level between 5 and 12 µg/mL is generally recommended</td>
<td>95</td>
<td>II</td>
<td>C</td>
</tr>
<tr>
<td>19. In certain situations higher or lower trough levels than the above ranges may be appropriate</td>
<td>100</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>
# Optimal drug concentrations (µg/mL)?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conc. (µg/mL)</th>
<th>What I do (remission)</th>
<th>Reactive (AGA)</th>
<th>What I do (reactive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deeper remission</td>
<td>&gt;8</td>
<td>&gt;10</td>
<td>&gt; 5</td>
<td>&gt;10-15</td>
</tr>
<tr>
<td>Week 14</td>
<td>&gt;7</td>
<td>&gt;10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adalimumb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical remission</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deeper remission</td>
<td>&gt;8</td>
<td>&gt;10-12</td>
<td>&gt; 7.5</td>
<td>&gt;10-15</td>
</tr>
<tr>
<td>Week 4</td>
<td>&gt;7</td>
<td>&gt;10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ustekinumab > 4.5 µg/ml
Vedolizumab > 27.5 (week 6)
Certolizumab > 23.3 (week 8)

Battat et al, CGH 2017
Williet et al. 2016
Colombel et al. 2014
Feuerstein et al, 2017
Attitudes and barriers towards therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease

**Primary Aim:**
- Determine the proportion of physicians performing TDM of anti-TNF therapy in patients with IBD
- Determine barriers towards the implementation of TDM

**Methods:**
- Web-based questionnaire distributed to:
  - American College Gastroenterology (ACG) and Crohn’s Colitis Foundation of America (CCFA)

403 respondents

Grossberg et al, IBD 2017
Results: Use of TDM

Q: Do you check anti-TNF drug concentrations and anti-drug antibodies?

90.1% of gastroenterologists surveyed answered YES

Grossberg et al, IBD 2017
Barriers to TDM

<table>
<thead>
<tr>
<th>Top 3 most important barriers to TDM</th>
<th>N, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty about insurance coverage of test</td>
<td>314 (77.9)</td>
</tr>
<tr>
<td>High out-of-pocket cost for the patient</td>
<td>308 (76.4)</td>
</tr>
<tr>
<td>Time lag from serum sample to result of TDM</td>
<td>155 (38.5)</td>
</tr>
<tr>
<td>Lack of good evidence-based medicine of the usefulness of TDM in IBD</td>
<td>144 (35.7)</td>
</tr>
<tr>
<td>Lack of availability of TDM in clinical practice</td>
<td>84 (20.8)</td>
</tr>
<tr>
<td>Lack of knowledge of how to interpret and what to do with the results of TDM</td>
<td>80 (19.9)</td>
</tr>
<tr>
<td>TDM is cumbersome and/or time consuming</td>
<td>52 (12.9)</td>
</tr>
<tr>
<td>Lack of overall knowledge of TDM</td>
<td>39 (9.7)</td>
</tr>
</tbody>
</table>

If all barriers were removed:

Physicians already using TDM would do it more proactively
36% -> 68%

81.6% of gastroenterologists who do not currently use TDM, would use TDM if all barriers were removed.
# Common US Labs for TDM

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Drugs</th>
<th>Assay</th>
<th>Drug Tolerant</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Prometheus       | IFX, ADA, VDZ  | HMSA   | Yes           | • Best studied
• $$$ - can be significant out of pocket costs                              |
| LabCorp/Esoterix | IFX, ADA, VDZ, GOL | ECLIA | Yes           | • Better coverage
• Antibody levels can be quite confusing (ng/ml).                           |
| Mayo             | IFX            | ?      | No            | • Better coverage
• Doesn’t measure antibody with drug present                                |
| Miraca           | IFX, ADA, CTP, VDZ, UST, GOL | ELISA | No            | • Most tests available
• Better coverage
• Can’t measure antibody with drug present                                  |
In practice

- Know your test (and use it)
  - Drug tolerant assay?
  - Cost (to patient)?
- Know what to do with your results
  - BRIDGe; Australian Consensus Statement
- If nothing else, test reactively
- Proactive testing likely best
  - Check after induction
  - Follow during maintenance
What to do with the results?

Anti-TNF optimizer

Found at: www.BRIDGeIBD.com

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

Melmed et al, CGH 2016
TDM conclusions (so far)

• Positive association between trough concentration and clinical outcomes
• Drug concentrations and anti-drug antibodies help guide decisions

• Reactive TDM
  • More cost effective and more appropriately directs therapy than empiric dose escalation
  • Proactive following reactive is better than reactive testing alone

• Proactive TDM (maintenance)
  • Improves outcomes and it is cost-effective
  • When compared with reactive TDM, decreases risk of treatment failure, IBD-related surgery and hospitalization, ATI, and SIR.
  • Optimized monotherapy may be alternative to combination therapy
  • If you stop concomitant immunomodulator, check anti-TNF concentration prior to and after discontinuation

• Proactive TDM (induction)
  • Early drug concentration correlates with longer-term outcomes

• Issues – optimal trough concentration window; timing of testing; test that is accurate, accessible, and inexpensive; prospective data on implementation of TDM
Question

Which has been associated with a decrease in monoclonal antibody drug clearance?

A. High baseline CRP
B. Low albumin
C. Concomitant use of immunomodulator
D. Presence of anti-drug antibodies
Question

• Proactive TDM when compared to reactive TDM was shown to be associated with:
  • A. Fewer IBD-related hospitalizations
  • B. Less antibody to infliximab formation
  • C. Less treatment failure
  • D. All of the above