Therapeutic Drug Monitoring of Biological Agents in IBD

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Biological Agents = Monoclonal Abs

- Synthetically made proteins

- **ALL** have the potential for causing immunogenicity
  - Very low rates in vedolizumab and ustekinumab (<5%)

### Range of rates (%) of ADAbs formation to biologics in patients with IBD

<table>
<thead>
<tr>
<th>Biologic agent</th>
<th>All studies (n)</th>
<th>CD (n)</th>
<th>UC (n)</th>
<th>CD or UC (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.0–65.3 (73)</td>
<td>2.9–60.8 (22)</td>
<td>6.1–41.0 (8)</td>
<td>0.0–65.3 (43)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.3–38.0 (22)</td>
<td>0.3–35.0 (11)</td>
<td>2.9–5.3 (3)</td>
<td>14.0–38.0 (8)</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>3.3–25.3 (4)</td>
<td>3.3–25.3 (4)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>1.0–4.1 (4)</td>
<td>1.0–4.1 (2)</td>
<td>3.7 (1)</td>
<td>4.0 (1)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>0.4–2.9 (2)</td>
<td>–</td>
<td>0.4–2.9 (2)</td>
<td>–</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>0.7 (1)</td>
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<td>–</td>
<td>–</td>
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</tbody>
</table>

<sup>a</sup>Only studies reporting rates of ADAbs were included (eight studies did not report specific proportions of patients developing ADAbs).

<sup>b</sup>Immunogenicity analyses are product- and assay-specific.

<sup>c</sup>One selected study was excluded from analysis as this had a small sample size (n = 28) and a high rate of immunogenicity (79%).

- -, no publications available; ADAbs, anti-drug antibodies; CD, Crohn’s disease; n, number of studies; UC, ulcerative colitis.

Vermeire et al. Therap Adv Gastroenterol. 2018
Biological Agents = Monoclonal Abs

• Synthetically made proteins

• **ALL** have the potential for causing immunogenicity
  • Very low rates in vedolizumab and ustekinumab (<5%)

• Loss of response

• Infusion reactions
  • Immediate-type: shortness of breath, flushing, anaphylaxis
  • Delayed-type hypersensitivity reactions: migratory polyarthritis, jaw pain, 3-7 days after infusion

*Vermeire et al. Therap Adv Gastroenterol. 2018*
Who is at risk for developing Abs?

- Increased clearance of protein-based monoclonal Abs
  - High inflammatory burden (high CRP/high fecal cal)
- Low serum albumin level
- Extensive colitis

- HLA-DQA1*05 haplotype
  - Genetic determinant of immunogenicity to anti-TNF agents
  - This haplotype increases risk of immunogenicity to IFX and ADA by 2-fold

Abreu. DDS Perspective. 2019
Sazonovs et al. bioRxiv. 2018
Avoiding immunogenicity

• In the past – dose of IV glucocorticoids pre-IFX

• Addition of immunomodulator
  • Thiopurine
    • 6-TGN ~125 pmol/8 x 10^8 (compared to 230-450 when used as monotx)
  • Methotrexate
    • 12.5 mg po weekly

• Avoiding ‘low’ serum drug levels

Yarur et al. CGH. 2015
Colman et al. JCC. 2015
Why do we monitor Pts and perform TDM?

• Get it right the first time
  • First biologic is the ‘best’ shot for the patient
  • Earlier we are successful at controlling disease, the better the outcomes

• What are we looking for?
  • Not enough drug
  • Antibodies
  • Wrong drug class

Slide courtesy of Corey Siegel
Therapeutic Drug Monitoring

• TDM can be performed at any point of therapy
  • During induction
  • Anytime during maintenance

• TDM can be performed
  • Proactively while patients are in clinical remission
  AND/OR
  • Reactively in response to suboptimal disease control
Proactive vs Reactive TDM of biologics

• Reactive TDM
  • Generally accepted
  • Wait until loss of response or infusion reaction, then try to fix it

• Proactive
  • Optimize dosing to maximize effect
  • To prevent loss of response
What we know...

• Pts with high inflammatory burden (extensive colitis, deep ulcers, perianal fistulizing disease) need higher circulating drug levels for better remission rates and mucosal healing

  • Pts with fistulizing disease → need higher levels of drug to have a benefit → mean IFX trough for fistula healing was 16 µg/mL (Prometheus)

• What we also know.....
  • Current standard when losing response → Reactive TDM

Yarur et al. APT 2017
Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Clinical Decision Support Tool

Adults with IBD, treated with anti-TNF agents

Active IBD*

Reactive TDM
(check trough and anti-drug antibodies)
(very low quality evidence, weak recommendation)

Anti-TNF TROUGH ADEQUATE? 
(on maintenance therapy, for achieving clinical response/remission)?
(Infliximab ≥5 mg/mL; Adalimumab ≥7.5 mcg/mL; Cetuximab pegol ≥20 mcg/mL)

Yes

Suspect mechanistic failure – consider switching to drug of different class
[Note: optimizing index therapy may be a reasonable alternative, especially if reactive TDM is performed in asymptomatic patients with ongoing endoscopic activity, or in patients with perianal disease where target trough concentrations may be higher; additionally, a small proportion of patients with luminal disease may still achieve clinical response with optimization of index therapy by targeting higher trough concentrations]

No

Check anti-drug antibody (ADA) levels

Low/absent trough, NO detectable ADAs

Absent trough, high-titer ADAs

Consider non-immune-mediated pharmacokinetic failure – optimize index therapy (shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent)

Consider immune-mediated pharmacokinetic failure – switch therapy (switching within class or outside drug class)

Low trough with low- or high-titer ADAs

Higher trough, lower ADA

Approach uncertain

Lower trough, higher ADA

Quiescent IBD
(clinically and endoscopically)

Continue anti-TNF therapy; no recommendation in favor or against routine proactive Therapeutic Drug monitoring (knowledge gap, no recommendation)

Feurestein et al. Gastro 2017

*Active IBD is defined as objective findings of active disease based on biochemical markers, endoscopic or radiologic disease activity, with or without symptoms

For pts losing response to anti-TNF
# TDM at Secondary Loss of Response

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<th>Drug Concentration</th>
<th>Subtherapeutic drug trough concentration</th>
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<td>Undetectable ADAAb</td>
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<td></td>
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<tr>
<td>Detectable ADAAb</td>
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**FIRST**: look at trough concentration

→ if optimal, then ADAbs are probably inconsequential

→ if trough low or undetectable, then examine ADAbs

Maintenance ‘Therapeutic’ Trough Concentrations SUGGESTED by AGA

- Infliximab ≥ 5 µg/mL – higher troughs for perianal dz, etc..
- Adalimumab ≥ 7.5 µg/mL
- Certolizumab Pegol ≥ 20 µg/mL
- Golimumab ≥ 1.4 µg/mL
- Vedolizumab ≥ 5.1-11.0 µg/mL → >15 (Abreu/Siegel)
- Ustekinumab ≥ 1.0-4.5 µg/mL → 8 (Abreu) or > 4.5 if not Prometheus; >2-4 (Siegel)

Abreu. DDS Perspective. 2019
**TDM at Secondary Loss of Response**

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<td>Undetectable ADAb</td>
<td>Nonimmune-mediated pharmacokinetic failure (51%)</td>
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<td></td>
<td><img src="51%25" alt="" /> Dose escalate by either increasing the dose or decreasing the interval between drug administrations</td>
<td><img src="25%25" alt="" /> Switch to drug out of class</td>
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<td>Detectable ADAb</td>
<td>Immune-mediated pharmacokinetic failure (19%)</td>
<td>Mechanistic or pharmacodynamic failure (5%)</td>
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<td><img src="19%25" alt="" /> Switch to drug in class and consider adding an immunomodulator</td>
<td><img src="5%25" alt="" /> Switch to drug out of class and consider adding an immunomodulator</td>
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Before switching the anti-TNF.....

• Important to recognize that target trough levels may be higher for certain pts
  • Would be reasonable to optimize the anti-TNF in certain individuals with perianal disease, extensive colitis, and those with partial improvement (clinical remission/active endoscopic)

• Make sure that patients truly have active inflammation
  • do not solely rely on sxs

• Make sure that the patients do not have a complication such as a stricture which will never respond to medical therapy
Reporting of antibodies varies depending on different assays. Uniform thresholds for clinically relevant antibody titers are lacking.
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<td>Responders to anti-TNF therapy losing response <strong>recommend measuring</strong> serum drug levels to assess reason for loss of response</td>
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<td>AGA Therapeutic Drug Monitoring in IBD</td>
<td>2017</td>
<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.</td>
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<td>ECCO Crohn’s disease</td>
<td>2017</td>
<td>Loss of response: Where available, measurement of serum anti-TNF trough levels and anti-drug anti-bodies could be used to <strong>guide optimization strategy</strong></td>
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<td>2016</td>
<td>Assessment of anti-TNF drug and antibody concentrations was <strong>rated appropriate</strong> at the end of induction therapy in primary non-responders and in secondary non-responders.</td>
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<td>Toronto Consensus UC</td>
<td>2015</td>
<td>Loss of response <strong>TDM for optimization</strong> and before switch and switch out of class for better decision process.</td>
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## Where do the guidelines stand with PROactive monitoring?

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TAXIT
Trough Concentration Adapted Infliximab Treatment

• **Patients:** Infliximab maintenance therapy with stable clinical response

• **ALL** 263 pts underwent IFX dose optimization to trough level of 3-7ug/ml

• After target level was achieved, pts were randomized to:
  • Proactive TDM: Infliximab dosing based on trough concentration
  • Infliximab dosing based on clinical symptoms and CRP

• **Primary outcome:** Clinical and biochemical remission at 1 year

One-time dose escalation in Crohn’s disease pts with subtherapeutic concentration resulted in better disease control

After the initial dose optimization, the proportion of pts achieving remission at 1 year with routine proactive TDM vs NO TDM was not different

TAXIT

• This study indicates that an initial TDM for dose optimization may be beneficial – while further routine repeated TDM does not show benefit

• At 1 year, pts who did not receive proactive TDM
  → Higher rates of anti-drug antibodies and undetectable trough levels
  → This might increase risk of dz flares and tx failure in long term studies

Proactive TDM vs. Standard of Care

• Retrospective observational study
• 126 IBD pts who responded to IFX – on maintenance therapy
  → Proactive TDM vs standard of care (reactive TDM or empiric dose escalation)
• Pts who underwent proactive TDM prior to every IFX infusion
  → Less likely to d/c IFX 2/2 disease flare or infusion reaction

Probability on Infliximab

Weeks
Personalized Anti-TNF Therapy in Crohn’s disease (PANTS)

• Prospective observational UK-wide study

• **Aim**: Identify clinical and pharmacokinetetic factors that predict
  • primary non-response at **week 14** after starting treatment
  • non-remission at **week 54**, and
  • adverse events leading to drug withdrawal

• **Inclusion Criteria:**
  • Anti-TNF-naive pts (≥6 years) with active luminal Crohn's disease (raised CRP >3 and/or raised fecal calpro >50) at the time of first exposure to IFX or ADA
  • Patients were evaluated for 12 months or until drug withdrawal
• Anti-TNF treatment failure is common and is predicted by low drug concentrations, mediated in part by immunogenicity
Maybe careful Monitoring also works

• 122 biologic-naïve adult patients with active CD → IFX/IMM

• At week 14, randomized:
  • dose increases (2 maximum) in steps of 2.5 mg/kg based on clinical symptoms and biomarker analysis and/or serum infliximab concentrations (dose intensification strategy [DIS]1 group)
  • dose increase from 5 to 10 mg/kg based on the same criteria (DIS2 group)
  • dose increase to 10 mg/kg based on clinical symptoms alone (controls)

→ Increasing dose of IFX based on a combination of symptoms, biomarkers, and serum drug concentrations does NOT lead to corticosteroid-free clinical remission in a larger proportion of pts than increasing dose based on symptoms alone

Conclusions

• Reactive drug monitoring helps – but risks waiting until drug has failed
  • More cost effective
  • More appropriately directs therapy than empiric dose escalation

• Data are accumulating to support proactive TDM
  • Cost is improving – but not everywhere.......  
  • Early drug concentration correlates with longer-term outcomes (TAXIT, PANTS)

• What to do....
  • Reactive TDM
  • Consider checking trough after induction – week 14 for IFX; week 8-14 for ADA
  • Aim for goal trough concentration (but be practical)
  • As of now, reserve proactive TDM in quiescent IBD receiving maintenance therapy for:
    • Optimization in monotherapy
    • If plan to de-escalate and stop concomitant immunomodulator