Use of Anti-TNF Antibodies and Other Serologies for Managing IBD

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Personalized Medicine: IBD

• Why does this apply to IBD?
  – IBD involves a heterogeneous group of patients with inherently variable disease courses.

• What is involved?
  – Identifying those at high risk for rapid progression
  – Tailoring treatment strategies to:
    • maximize response
    • minimize loss of response/relapse
    • address risks associated with specific medications in certain patient populations

Personalized Medicine (PM): IBD

• Tools available or in development to meet these goals
  – Therapeutic Drug Monitoring
  – Serology and Biomarkers
  – Genetic testing
  – Microbiota Analysis

PM: Serology and Biomarkers

• Originally used for diagnosis, role now more for predicting phenotype (prognosis).
• Serological expression of immune response may represent this host gene-luminal bacterial interaction.
• Major serologic responses measured in humans:
  – ASCA = Anti-Saccharomyces cerevisiae (baker’s yeast)
  – OmpC = Anti-outer membrane porin C of E coli
  – I2 = CD related protein from Pseudomonas fluorescens
  – pANCA = perinuclear anti-neutrophil cytoplasmic antibody
  – Flagellin Antibodies = CBir1, anti-A4-Fla2, anti-FlaX
PM: Serology and Biomarkers

- Presence of such antibodies have been associated with complicated Crohn’s disease:
  - penetrating and stricturing disease, need for surgery and post-operative recurrence.
- Serology NOT helpful in predicting response to therapy, but newer biomarkers may be helpful.
  - Apolipoprotein A1/E, complement C4B, Beta2 glycoprotein, clusterin
- Not currently standard practice, but knowledge of serology may help guide medication choice.


PM: Genetics

- Over 163 loci have been linked to IBD (30 CD and 23 UC specific), but only represent a limited view of heritability.
- Current/Future Roles
  - Predicting course of disease (e.g. NOD2)
  - Predicting side effects of medications (e.g. IL23R)
- May be most valuable when combined with serologic and clinical disease factors.

Lees CW et al. Gut.2011;60(12):1739
PM: Fecal Microbiota

- Advances in microbial analysis allow sequencing the microbiomes of IBD patients and monitoring for change.
- Depletion of certain *Firmicutes* and *Bacteroides* have been associated with active disease, relapse risk and medication responsiveness.
- Success of fecal microbiota transplantation (FMT) studies has been mixed.
  - Sub analyses suggest greater success with acquisition of the donor microbial signature and acquisition of specific bacterial flora and the compounds they produce.

Moayyedi P; et al. Gastro. 2015;149(1):102

Therapeutic Drug Monitoring (TDM)

- The process of measuring serum levels with dosing titration to achieve a concentration within a prescribed therapeutic range.
- Used commonly in transplant patients (e.g. with tacrolimus, cyclosporine) and with certain antibiotics.
- In IBD:
  - Longer experience with azathioprine/6MP, more recent experience with biologic TNF antagonists.
Thiopurine Drug Metabolism

Each individual's TPMT activity results in differences in metabolism, directly affecting efficacy and risk of toxicity


TDM: Azathioprine

- Measuring thiopurine methyltransferase (TPMT) enzyme levels allows prediction of myelosuppression and hepatotoxicity.
- Metabolites help with efficacy and safety:
  - Therapeutic window for 6-TGN is 230-400, above this myelosuppression risk increases.
  - A 6-MMP >5700 is associated with 3x >hepatotoxicity
- Other applications of TDM:
  - When 6-MMP:6-TGN ratio is 12:1-20:1, consideration of allopurinol 100mg + azathioprine 50 mg may be indicated.
  - For combo therapy, a level of 6-TGN of 125 pmol/8x10⁸ RBCs
  - Benchmark level when TPMT >30.


TDM: Infliximab (IFX) and other biologics

• Rationale:
  – Lack of response and durability of current biological anti-TNF agents.
  – Post hoc analysis of the registry trials for infliximab (ACCENT I) and SONIC showed an association between higher levels and remission.
  – Across a number of studies, there was a significant difference in level among those in clinical remission vs. relapse (RR 2.9) and in those achieving endoscopic remission (RR 3).

Moore C et al. J Crohns colitis 2016; Epub ahead of print

TDM: Definitions

• Pharmacokinetics
  – Definition: the study of absorption, distribution and elimination of a given medication.
  – Varies by drug make up, route of administration, degradation and elimination.
    • IV has high peak and is more predictable than SQ
    • Elimination of mAbs by reticuloendothelial system, but ½ life varies by type (murine 1-2d), chimera (10-14d), humanized (10-20d), mAb+PEG (+2 weeks)
    • Clearance is affected by albumin, BMI, gender, inflammation state, use of immune modulators and anti-drugs antibodies.

Vaughn BP et al. Inflamm Bowel Dis 2015; 21(6):1435
TDM: Concentration testing options

- Enzyme-linked immunosorbent assay (ELISA)
  - Can detect IFX at .002-1.4mcg/ml threshold. Can only detect antibodies (Ab) in absence of IFX drug.
- Radio-immunoassay (RIA)
  - Similar to ELISA, only in Europe
- Fluid phase mobility shift assay (FMSA).
  - Prometheus labs only, can detect both drug and Ab
- ECLIA (electrochemiluminescence immunoassay)
  - Labcorp only, can detect both drug and Ab.

- All the above are available for IFX, all but RIA for adalimumab (ADA) and only ELISA for certolizumab, vedolizumab.

Vaughn BP et al. Inflamm Bowel Dis 2015; 21(6):1435

TDM: Concentration cutoffs

- With biologics, the therapeutic window is not well defined, just the trough.
- The trough levels have been defined by association with remission rates, mucosal healing, CRP levels, histologic healing, fistula response.
- IFX: Study results range from 1.4-12 mcg/mL with most common goal range of 3-7 mcg/mL.
- ADA: 4.85-7.8 mcg/mL, most common is use of 4.9 mcg/mL.

Vaughn BP et al. Inflamm Bowel Dis 2015; 21(6):1435
Anti-TNF trough concentrations correlate with outcome

<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 (Maser CGH 2006)</td>
<td>IFX</td>
<td>Detectable</td>
<td>Clinical remission, CRP, Endoscopic remission</td>
<td>Trough assessed after 1 year (range after 6-37 infusion)</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 (Lamblin JCC 2012)</td>
<td>IFX</td>
<td>&gt;5.6</td>
<td>Reduced CRP</td>
<td></td>
</tr>
<tr>
<td>CD (Drohne Gastro 2011)</td>
<td>IFX</td>
<td>Undetectable</td>
<td>Loss of response</td>
<td></td>
</tr>
<tr>
<td>UC (Arias JCC 2012)</td>
<td>IFX</td>
<td>&gt;7.19</td>
<td>Sustained response</td>
<td></td>
</tr>
<tr>
<td>UC (Seow GUT 2010)</td>
<td>IFX</td>
<td>Detectable</td>
<td>Higher rates of remission, Endoscopic improvement</td>
<td>Undetectable serum IFX associated with colectomy</td>
</tr>
<tr>
<td>CD/UC (Yanai AIG 2011)</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 (Roblin CHG 2014)</td>
<td>ADA</td>
<td>&gt;4.9</td>
<td>Mucosal healing</td>
<td>Higher trough concentrations associated with clinical remission and mucosal healing</td>
</tr>
<tr>
<td>CD/UC (Yanai AIG 2011)</td>
<td>ADA</td>
<td>&gt;4.5</td>
<td>Failed to respond to increase in ADA or change to another anti-TNF</td>
<td>Population was patients with LOR</td>
</tr>
<tr>
<td>CD/UC (Roblin CHG 2014)</td>
<td>ADA</td>
<td>&lt;4.9 ug/mL</td>
<td>Clinical response to ADA dose intensification</td>
<td>Prospective trial with ADA demonstrating benefit of dose optimization for low trough concentration</td>
</tr>
<tr>
<td>UC (Velayos CGH 2013)</td>
<td>ADA</td>
<td>&gt;4.58 ug/mL</td>
<td>Week 12 clinical response</td>
<td>Week 2-4 concentration predicts week 12 response</td>
</tr>
<tr>
<td>CD (Colombel CGH 2014)</td>
<td>CTP</td>
<td>Higher quartile (mean value for highest quartile: 30.1 ug/mL)</td>
<td>Endoscopic and clinical response and remission</td>
<td></td>
</tr>
</tbody>
</table>

Adapted with permission from Vaughn BP

Immunogenicity and anti-drug Ab cutoffs

- **Immunogenicity**
  - Risk Factors: murine component, route of admin (SC>IV), dosing schedule, immunosuppressive use
  - Implications: secondary loss of response, acute or delayed infusion reactions, induction of autoimmunity.
    - Across studies, presence of antidrug Abs is associated with loss of clinical response and lower drug levels.

- **Cut-offs:**
  - High level(>15 mcg/mL) may be more detrimental than low level, but any level may increase clearance and infusion reaction risk.

Vaughn BP et al. Inflamm Bowel Dis 2015; 21(6):1435
How to use drug and antibody levels

• Categories of findings (make a 4 square here).

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic drug, no antibody</td>
<td>Low drug, no antibody</td>
</tr>
<tr>
<td>Low drug, positive antibody</td>
<td>therapeutic drug, detectable antibody</td>
</tr>
<tr>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

• Response by scenario:
  – A- change agent, possibly mechanism
  – B- intensification
  – C- change agent, consider adding IM or intensification
  – D- consider intensification, addition of IM

Patient cases

• **Patient 1:** 25 yo male with history of UC x 7 years, on 5 mg/kg infliximab monotherapy for 5 years now with breakthrough symptoms in week 6-7. IFX level <1, Antibodies (ATI) = 6.4.
  – What would you do next?

• **Patient 2:** 50 yo woman with UC x 2 years after prolonged flare achieved remission on infliximab 5 mg/kg monotherapy with intolerance to MTX and AZA. Dose held 4 weeks due to surgical procedure that lead to flare and empiric increase to 10 mg/kg q6-8 weeks. After 9 months, in remission and tolerating doses every 8 weeks. Trough levels of IFX check with IFX concentration of 22 and ATIs undetectable.
  – What would you do next?
TDM in practice: Reactive Approach

• Empiric dose adjustment is most common.
• Most common use of TDM in practice: testing when patient is symptomatic.
• Potential benefits: identify those who would not benefit from escalation, decrease dose where appropriate.
• Outcomes of empiric dose escalation vs. optimization guided by reactive testing similar in response and remission, but at a greater cost.
• Confirm that IBD is active before testing


Confirm activity and consider other causes of symptoms.

• SIBO
• Bile Salt diarrhea
• Accentuated gastro-colic reflex
• Anorectal sphincter dysfunction
• Food intolerance, lactose intolerance, celiac sprue/NCGS
• Drug/meds (e.g. mesalamine, MMF, non-GI meds)
• Infections- SSCE, C. diff, CMV, Parasites
• Intestinal stricture or obstruction, Intra-abdominal adhesions
• IBS

SSCE = Salmonella, Shigella, Campylobacter, E. coli
How to use drug and antibody levels

• Categories of findings:

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Outcomes based on IFX concentration and Antibody status

• Test results impacted treatment in 73% of pts.

<table>
<thead>
<tr>
<th>TDM results</th>
<th>Action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtherapeutic IFX</td>
<td>Dose escalation</td>
<td>Response* 86%</td>
</tr>
<tr>
<td>Subtherapeutic IFX</td>
<td>Switch anti-TNF</td>
<td>Response 33%</td>
</tr>
<tr>
<td>Therapeutic IFX</td>
<td>No Action</td>
<td>62% in complete remission</td>
</tr>
<tr>
<td>Antibodies detected</td>
<td>Switch anti-TNF</td>
<td>Response 92%</td>
</tr>
<tr>
<td>Antibodies detected</td>
<td>Dose escalation</td>
<td>Response 17%</td>
</tr>
</tbody>
</table>

*complete or partial response

Dose escalation of adalimumab after loss of response

<table>
<thead>
<tr>
<th>Group</th>
<th>ADA level Antibody status</th>
<th>Clinical Remission 6-months (%)</th>
<th>Durability of Response (mo)</th>
<th>Clinical Remission in failures switched to IFX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ADA &gt;4.9 No AAA</td>
<td>29</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>B</td>
<td>ADA &lt;4.9 No AAA</td>
<td>67</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>C</td>
<td>ADA &lt;4.9 AAA &gt;10</td>
<td>12</td>
<td>5</td>
<td>80</td>
</tr>
</tbody>
</table>


confirmed reactive IBD or concern for antibody mediated side effect

ATI Positive

- High level ATI (>15 ug/ml)
  - Change to different anti-TNF
  - If failed multiple anti-TNFs change class
  - Consider surgery

- Low level ATI (<15 ug/ml)
  - Increase dose

ATI Negative

- Therapeutic* or high IFX concentration
  - Unlikely to get benefit from increased IFX or alternate anti-TNF. Change class outside of anti-TNF and/or consider surgery

- Low* IFX concentration
  - Increase IFX dose
  - If level undetectable consider increase dose and next infusion at 6 weeks
  - Consider addition of IMM

Patient case #3

- 33 y.o. female who has secondary loss of response to ADA. Addition of AZA and reload with shorter intervals has recaptured response and remission for 6 months. Now she is flaring once more:
  - How do you approach the next biologic? Combo vs. monotherapy? Early optimization by week 14 with level monitoring?

TDM in practice: Proactive Approach

- Definition:
  - checking a level of drug early on to allow optimization of the drug level into a therapeutic window to minimize loss of response and antibody development.

- Retrospective data of the outcomes of proactive monitoring vs. usual care (empiric dose change and reactive testing) in a single center cohort showed:
  - >durability of infliximab and higher trough [ ] as a surrogate for continued remission.

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 3-7 ug/mL
- Randomized to:
  - Infliximab dosing based on clinical symptoms and CRP
  - Infliximab dosing based on trough concentration (proactive)
- Primary outcome: Clinical remission at 1 year

**TAXIT algorithm**

- **TLI measurement**
  - Undetectable TLI (TLI <0.3 µg/mL)
  - ATI measurement
    - High ATI level (ATI >8 µg/mL)
    - Stop
    - Low ATI level (ATI <8 µg/mL)
      - **TLI <3 µg/mL**
        - 1) interval decrease (by 2 weeks) to min 4 weeks
      - **3 µg/mL ≤ TLI ≤ 7 µg/mL**
        - 2) dose increase (by 5 mg/kg) to max 10 mg/kg
      - **TLI >7 µg/mL**
        - interval increase (by 2 weeks)
        - no dose adaptation

Vande Casteele et al. Gastroenterol. 2015; 148: 1320-9
TAXIT

Infliximab trough levels

- undetectable TLI
- TLI < 3µg/ml
- 3 µg/ml ≤ TLI ≤ 7 µg/ml
- TLI > 7 µg/ml

Figure: infliximab trough level (TLI) at time of screening (n=275)

Vande Casteele et al. Gastroenterol. 2015; 148: 1320-9

TAXIT results

- Dose escalation for Crohn’s disease improved disease control

Before optimization

After optimization

HBI < 5 (clinical remission)

64.3%

88.1%

*p=0.02

Vande Casteele et al. Gastroenterol. 2015; 148: 1320-9
TAXIT results

• Primary endpoint - 1 year after optimization:
  – No difference in remission rates between concentration dosed and clinically dosed groups (p=0.77)

• Secondary endpoint:
  – Concentration-dosed group needed rescue therapy less frequently than clinically dosed group
    • 5.5% vs. 17.3% (p=0.004)
  – Non-significant trend towards fewer acute infusion reactions

• Similar cost between both groups

TAXIT: Recommendations

1. Dose optimize to achieve IFX trough levels within interval 3-7 µg/mL

2. Re-evaluate levels after 6 months
TDM in practice: Proactive Approach

- **Patient in remission on maintenance IFX therapy**
  - **ATI Positive**
    - **High-level ATI (≥150 µg/mL)**
      - Change to different anti-TNF
      - If failed multiple anti-TNFs, change class
      - Consider surgery
    - **Low-level ATI (<150 µg/mL)**
      - Increase dose
  - **High IFX concentration**
    - Reduce dose
    - If at 3mg/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 8 weeks
    - Low level: increase IFX by 50-100mg

Vaughn BP et al. Inflamm Bowel Dis 2015; 21: 1435 - 42

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TDM: Cost-Effectiveness

- **Potential costs:**
  - Cost of the test, cost of the drug increase in someone clinically stable
- **Potential savings:**
  - Prevention of flares, hospitalizations and surgeries.
  - De-escalation of drug dose (15-27% from limited studies)
- **As new tests are developed, cost should fall.**

- **Modeling data:** TDM $31,870 vs $37,266/QALY
- **TAXIT data:** TDM 20,723 Euros vs 21,023/QALY

Vande Casteele et al. Gastroenterol. 2015; 148: 1320-9
TDM in practice: future directions

- Guidance for de-escalation of therapy
- Empiric monotherapy with early dose optimization
- Individualized dosing by disease phenotype (e.g. fistulae), CD, UC and age/pregnancy.
- Further tailoring choice of initial medications to individual patients.

Summary: take home points

- Of serologic tests, therapeutic drug monitoring (TDM) is the most applicable to clinical practice at present.
- Both reactive and proactive TDM have advantages over empiric dosing changes.
- Proactive TDM may help prevent relapse, antibody formation and possibly monotherapy with less risk.