Optimizing anti-TNF Therapy for the Treatment of Inflammatory Bowel Disease

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Relevant Financial Disclosures

- None
Learning Objectives

- Understand the role of combination therapy with anti-TNF in the management of IBD
- Recognize the need to individualize anti-TNF therapy dosing and potential role of accelerated dosing in induction of remission
- Recognize the need to adjust anti-TNF therapy through therapeutic drug monitoring
Case 1

- 48 year old female with a history of ileocolonic Crohn’s disease first diagnosed at the age of 42. The patient was previously underwent an ileocecectomy 3 years after the diagnosis of Crohn’s. Post-operatively, she was maintained on infliximab 5mg/kg every 8 weeks and was doing well until 6 months ago when she had increasing RLQ pain.
She underwent an ileocolonoscopy which showed moderately active inflammatory changes at the anastomotic site (Rutgeert’s i2).

A MR enterography showed moderate 10cm length inflammatory changes in the distal terminal ileum.

Her Infliximab drug level was undetectable with a positive antibody to infliximab of 122ng/ml (normal <22).

Her CRP was 15.
She presents to the clinic to discuss further treatment options.

1. Increase the dosing of infliximab to 10mg/kg
2. Add in 4.8g mesalamine
3. Add in 6-mercaptopurine
4. Change to another anti-TNF agent and add in 6-MP
Can therapy safely alter the natural history of IBD?

- Induce and maintain gastrointestinal healing
- Prevent need for steroids
- Prevent strictures and penetrating complications
- Prevent extra-intestinal complications
- Decrease hospitalization/surgery
- Decrease long-term cost of care

Disease complications

Years

Natural course

*Slide courtesy of Stephen B. Hanauer, MD. Crohn’s and Colitis Foundation of America 2008 Advances in Inflammatory Bowel Disease.*
Week 30 SONIC: Steroid-free Remission

Median IFX Concentration

Steroid-free Clinical Remission at Week 30 by IFX Trough Level

N=97
N=109

P<0.001

1.6
3.5

Steroid-free Clinical Remission

% of Patients

Serum IFX Concentration* (mg/ml)

0
>0-1
>1-3
>3-6
>6

19/32
13/23
43/59
36/49
31/43

Week 30 SONIC: Immunogenicity


![Graph showing percent of patients in different treatment groups.](image-url)
## Combination Therapy

<table>
<thead>
<tr>
<th></th>
<th>SONIC</th>
<th></th>
<th>COMMIT</th>
<th></th>
<th>UC SUCCESS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mono</td>
<td>Combo</td>
<td>Mono</td>
<td>Combo</td>
<td>Mono</td>
<td>Combo</td>
</tr>
<tr>
<td><strong>Corticosteroid-free remission (%)</strong></td>
<td>44</td>
<td>57</td>
<td>78</td>
<td>76</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td><strong>Cortocosteroid-free remission at Week 50 (%)</strong></td>
<td>35</td>
<td>46</td>
<td>57</td>
<td>56</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Mucosal Healing (%)</strong></td>
<td>30</td>
<td>44</td>
<td>N/A</td>
<td>N/A</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td><strong>IFX Concentration</strong></td>
<td>1.6</td>
<td>3.5</td>
<td>3.8</td>
<td>6.4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Dulai et al, Gut, 2015
Combination Therapy with Enteral Nutrition

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favors ED + Infliximab</th>
<th>Favors Infliximab Alone</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirai et al - 2012</td>
<td>31</td>
<td>24</td>
<td>3.04 [1.34, 6.92]</td>
</tr>
<tr>
<td>Matsumoto et al - 2005</td>
<td>15</td>
<td>4</td>
<td>0.88 [0.23, 3.39]</td>
</tr>
<tr>
<td>Sazuka et al - 2012</td>
<td>23</td>
<td>22</td>
<td>4.01 [1.37, 11.71]</td>
</tr>
<tr>
<td>Tanaka et al - 2006</td>
<td>30</td>
<td>22</td>
<td>2.40 [1.11, 5.18]</td>
</tr>
<tr>
<td>Yamamoto et al - 2009</td>
<td>25</td>
<td>16</td>
<td>1.79 [0.54, 5.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>206</td>
<td>197</td>
<td>2.43 [1.58, 3.74]</td>
</tr>
</tbody>
</table>

Total events: 124 / 88
Heterogeneity: Chi² = 3.56, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.03 (P < 0.0001)
Can we revert immunogenicity?

**Patient 1**
- Infliximab
- Anti-infliximab antibodies (ATI)

**Patient 2**
- Infliximab
- Anti-infliximab antibodies (ATI)

**Patient 3**
- Infliximab
- Anti-infliximab antibodies (ATI)

**Patient 4**
- Infliximab
- Anti-infliximab antibodies (ATI)

- Start MTX
- Start 6-MP
- Start AZA
- Start AZA

Weeks 0, 10, 20, 30, 40, 50, 60
Concentration (mcg/ml)

Ben Horin S, Clin Gastroenterol Hepatol 2013
Consecutive cohort of patients (n=128); 105 CD, 23 UC where IFX was restarted after a median drug holiday of 15 months (at least >6 months).

Success at Week 14, 1 year, and end of follow-up (median 4 years); ATI and trough level (TL) assessed

Results

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Short-term</th>
<th>Year 1</th>
<th>End of Follow-Up</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATI (at 2nd infusion) detectable N=31</td>
<td>71%</td>
<td>54.8%</td>
<td>38.7%</td>
<td>0.14 (0.026-0.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P=0.021)</td>
</tr>
<tr>
<td>IMM at restart N=84</td>
<td>91.6%</td>
<td>74.7%</td>
<td>66.6%</td>
<td>6 (1.3-2.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P=0.019)</td>
</tr>
<tr>
<td>Reason for discontinuation (remission &amp;/or pregnancy)</td>
<td>90%</td>
<td>77.5%</td>
<td>66.6%</td>
<td>2.70 (1.09-6.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P=0.033)</td>
</tr>
<tr>
<td>TL (at 2nd infusion) &gt; 2 μg/ml N=43</td>
<td>93%</td>
<td>74%</td>
<td>70%</td>
<td>2.94 (1.18-7.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P=0.021)</td>
</tr>
</tbody>
</table>

Conclusion: Restarting IFX after a drug holiday is safe, with success predicted by absence of early ATI formation, IMM at recommencement, and not having had previous infusion reactions

Take Home Point #1

Among IBD patients on anti-TNF therapy, combination therapy with an immunomodulator should be initiated to reduce immunogenicity, augment effect of anti-TNF therapy, and improve clinical response.
Case 2

- 26 year old male who was diagnosed with pan-ulcerative colitis approximately 8 months ago. Initially, he was placed on a short course of Prednisone and Mesalamine 4.8g/day. He did fair after 4 months on this regimen with a reduction of bowel movements to 5 bowel movements/day and 1 nocturnal bowel movement. However, he has difficulty weaning his Prednisone below 10mg/day due to symptom relapse.
He subsequently ran out of prednisone and had 20+ bowel movements/day. Attempts to increase his dose of prednisone to 60mg daily only resulted in partial symptom improvement to 10 bowel movements/day.
He presents to the Emergency Department and was admitted.

Laboratory testing shows

- Albumin 2.0
- CRP 20
- Hgb 7.6
- pANCA positivity, ASCA negativity
- C diff negative
- Flexible sigmoidoscopy shows deep ulcerations to 45cm. Biopsies pending for CMV.
You are consulted and asked what to do next:

1. Initiate Methylprednisolone 100mg IV every 8 hours
2. Consult Colorectal Surgery for total proctocolectomy
3. Start infliximab 5mg/kg
4. Start infliximab 10mg/kg
# Factors Affecting the Pharmacokinetics of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Impact on Pharmacokinetics</th>
<th>Presence of ADAs</th>
<th>Concomitant use of IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreases serum mAbs</td>
<td>• Decreases serum mAbs</td>
<td>• Reduces formation</td>
</tr>
<tr>
<td>• Threefold-increased clearance</td>
<td>• Threefold-increased clearance</td>
<td>• Increases serum mAbs</td>
</tr>
<tr>
<td>• Worse clinical outcomes</td>
<td>• Worse clinical outcomes</td>
<td>• Decreases mAb clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Better clinical outcomes</td>
</tr>
<tr>
<td>mAB, monoclonal antibody; ADA, antidrug antibody</td>
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</tr>
</tbody>
</table>

Rapid IFX Clearance: Mechanism of Non-Response in UC

Detectable Serum Trough Infliximab Associated with Higher Remission Rate and Endoscopic Improvement in UC

- Cohort study; N=115 patients with moderate to severe UC
- Follow-up: median 13.9 months
- Key Finding: Detectable serum infliximab was associated with:
  - Higher remission rates (69% vs. 15%; \( P<0.001 \))
  - Endoscopic improvement (76% vs. 28%; \( P<0.001 \))
Pharmacokinetics of Infliximab Induction Therapy in Patients With Moderate to Severe UC

- Multicenter, prospective observational study in anti-TNF-naïve patients (N=19) with moderate-to-severe UC (Endoscopic Mayo 2/3)¹

**MAJOR FINDINGS:**
- Median trough level before third infusion (week 6) was 2.5 ug/ml for endoscopic non-responders versus 8.2 ug/ml for responders (P=0.03).
- Patients with CRP>50 µg/mL had lower IFX concentration (P=0.001)
- IFX lost in stool in severe IBD colitis and higher concentrations predicted lower response²

**LESSONS LEARNED:**
- Standard dose of infliximab may not be enough to induce response because infliximab loss via stool in severe colitis
- Patients with CRP>50 or with more clinically significant colitis, may need higher doses of infliximab to get to therapeutic levels

pANCA Positivity and Need for Accelerated Dosing

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>pANCA Negativity</th>
<th>pANCA Positivity</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Esters 2002</td>
<td>194</td>
<td>247</td>
<td>17</td>
</tr>
<tr>
<td>Ferrante 2007</td>
<td>34</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Taylor 2001</td>
<td>25</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>342</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Total events</td>
<td>253</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 1.19, \text{df} = 2 (P = 0.55); I^2 = 0\%

Test for overall effect: \( Z = 2.04 (P = 0.04) \)
Take Home Point #2

- Among patients with IBD colitis, accelerated or higher dosing with anti-TNF therapy may be necessary to induce clinical remission, particularly if the patient is positive for pANCA with more UC-like phenotype.
Case 3

- 38 year old female with a history of ileocolonic Crohn’s disease. She has been doing well since her diagnosis on combination therapy of 6-MP and adalimumab 40mg SQ every 2 weeks. She presents to clinic with complaints that in the last 3 months, she has been having increasing stool output to 4 bowel movements/day (from 1/day). She also complains of increasing dull RLQ pain.
MR enterography showed a 6cm segment of inflammatory changes in the distal terminal ileum

Her C diff PCR was negative
She asks you what is the next treatment recommendation for her?

1. Increase her adalimumab dosing to every week
2. Check the adalimumab level and antibody to adalimumab
3. Switch her to infliximab
4. Treat her with immodium to reduce her bowel movements
Effect of Trough Serum Infliximab Concentrations on Clinical Outcome Beyond 52 Weeks

Trough serum infliximab
- Detectable
- Undetectable

<table>
<thead>
<tr>
<th>Patients in remission (%)</th>
<th>Patients with endoscopic improvement &gt;75% (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Patients with CRP &lt;5 mg/dL (%)</td>
<td>Patients with complete endoscopic remission (%)</td>
</tr>
<tr>
<td>76</td>
<td>47</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Adalimumab Trough Serum Levels and Clinical Response in Patients with Crohn’s Disease


Patients with Sustained Clinical Response (%)

Sustained Clinical Response (weeks)

ADA TR>0.33 µg/mL, n=104
ADA TR<0.33 µg/mL, n=16

P=0.01
Recapturing Response with Dosing Adjustment of Infliximab in HACA Negative Patients

Clinical Outcomes of Patients with Detectable Antibodies to Infliximab or Sub-therapeutic Infliximab Concentrations

<table>
<thead>
<tr>
<th>Response to test</th>
<th>Complete/partial response (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable HACA</td>
<td>Increase infliximab</td>
<td>1/6 (17)</td>
</tr>
<tr>
<td></td>
<td>Change anti-TNF</td>
<td>11/12 (92)</td>
</tr>
<tr>
<td>Subtherapeutic concentration</td>
<td>Increase infliximab</td>
<td>25/29 (86)</td>
</tr>
<tr>
<td></td>
<td>Change anti-TNF</td>
<td>2/6 (33)</td>
</tr>
</tbody>
</table>

HACA, Human anti-chimeric antibodies

Prospective Therapeutic Drug Monitoring to Optimize Infliximab Maintenance Therapy in IBD

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

- Evaluated probability of remaining on IFX, up to 5 years

Likelihood of being on Infliximab

Patients with secondary IFX failure randomized to:
- IFX intensification group: IFX 5mg/kg every 4 weeks OR
- Algorithm group:
  - Low IFX and No ATI: IFX q4
  - ATI positive and low IFX: adalimumab
  - High IFX +/- ATI: stop anti-TNF

Conclusions: Treatment of IFX failure using an algorithm significantly reduces average costs without compromising care

Take Home Point #3

- Routine therapeutic drug monitoring among patients on anti-TNF is necessary to ensure long-term clinical remission.
- Therapeutic drug monitoring is also the most cost-effective strategy compared to empiric dose escalation.