If My IBD Patient Is Well on Combination Therapy What Should I Do? Be Happy or De-Escalate?

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Disclosure Statement

In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Objectives

• Outline rationale for and against de-escalation
• Explore de-escalation options
• Evaluate factors that may help predict success of de-escalation
• Suggest future directions
Why De-Escalate?

• Risk of adverse events
  – Infection
  – Malignancy
• Side effects
• High cost of medications
• Patient and family satisfaction

Common Arguments Against De-Escalation

• Goals reached → Be happy
• Immunogenicity
• Lower response rates after re-initiation of biologic
• Limited additional options
• Complete puberty to promote growth
• Paucity of data, particularly pediatric

De-Escalation Options

– Immunomodulator
– Anti-TNF

– Immunomodulator
– Anti-TNF
– Both
Combination Therapy → Immunomodulator Dose De-Escalation

Immunomodulator Dose De-Escalation

- No interventional studies re: IM dose de-escalation for combination therapy

6-TGN Concentration Correlates with IFX Trough in Combination Therapy

“Therapeutic levels” of 6-TGN were not necessary to achieve higher IFX troughs.
Combination Therapy → Biologic Dose De-Escalation

Trough Concentration Adapted InfliXImab Treatment (TAXIT)

Eligibility
- Maintenance IFX ≥ 14 weeks
- Full or partial responder
- No ATI > 8 µg/ml
- Stable dose immunomodulators

Dose Optimization Phase
72/263 (27.4%) required dose reduction due to high trough

1. Reduce dose to 5 mg/kg (if applicable)
2. Prolong interval by two weeks (up to 12 weeks)
Combination Therapy → Withdrawal of Immunomodulator

**Dual Therapy – Withdrawal of Immunomodulator**

- 80 patients w/ inactive disease on ≥ 6 mo dual therapy, randomized to continue or stop IM
  - Continued IFX at 5 mg/kg q8
- Primary endpoint: Discontinue or escalate IFX
- Discontinuation group: Median 24 mo dual therapy


**Dual Therapy – Withdrawal of Immunomodulator**

- No difference between groups
  - Primary endpoints
  - Mucosal healing
- Laboratory differences between groups

Withdrawal of Immunomodulator Does Not Decrease IFX Trough

- Retrospective review of adult CD patients on maintenance IFX (n=223)
  - 71% also on IM
- 74% (158) on combo therapy withdrew IM
  - Based on durable clinical response (median 13 mo)
  - IFX levels prospectively drawn but not available to clinicians

Withdrawal of Immunomodulator Does Not Decrease IFX Trough

- Median follow-up 29 months
  - 38% flared requiring IFX dose escalation (20% prior)
  - 18% discontinued IFX at mean time 67 months
- Infliximab trough levels remained stable
  - Median: 3.2 µg/mL before withdrawal
  - Median: 3.7 µg/mL after withdrawal
- At time of IM withdrawal
  - IFX trough >5 → No patients lost response (n=27)
  - Undetectable IFX trough → 6/7 lost response

Is 6 Months a Good Target for Dual Therapy?

- Prospective adult CD cohort study of anti-TNF induction responders on dual therapy with AZA x 6 mo
  - 22/132 stopped AZA < 6 mo due to intolerance

![Bar chart showing Anti-TNF dose escalation due to loss of response](image)
Is 6 Months a Good Target for Dual Therapy?

- Pediatric IBD registry
  - 502 pediatric CD patients starting anti-TNF
- IM > 6 mo:
  - Longer duration of anti-TNF
  - Shorter time to anti-TNF dose escalation
- Thiopurine and MTX
- Did not account for therapeutic monitoring

Proposed Algorithm for IM Discontinuation After 6 Mo Durable Response on Combination Therapy

1. Check infliximab trough
   - < 5
     - Consider IFX monotherapy
     - Inflximab trough target > 5
   - 1.5
     - Consider continuing dual-dose infliximab and anti-TNF
   - Undetectable
     - Do not stop IM
     - Check IFX antibody, dose escalation

Combination Therapy → Withdrawal of Anti-TNF
Maintenance of Remission After IFX Stopped

- Prospective study of 115 adult CD patients
  - Steroid free remission x 6 months (CDAI < 150)

- 44% relapse rate in first year (based on CDAI)

- Relapse → restarted IFX
  - 88% clinical remission by 3rd IFX dose
  - No infusion reactions over first 3 doses (w/ steroid pre-treatment)

Stratifying Risk for Relapse After IFX Stopped

<table>
<thead>
<tr>
<th>Risk factors for relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Absence of surgical resection</td>
</tr>
<tr>
<td>WBC &gt; 6.0</td>
</tr>
<tr>
<td>Hb ≤ 14.5</td>
</tr>
<tr>
<td>CRP ≥ 5.0 mg/L</td>
</tr>
<tr>
<td>Calprotectin ≥ 300 µg/g</td>
</tr>
<tr>
<td>CDEIS &gt; 0</td>
</tr>
<tr>
<td>IFX trough ≥ 2 mg/L</td>
</tr>
<tr>
<td>Steroids 6-12 mo before trial</td>
</tr>
</tbody>
</table>

≤2 risk factors → 15% risk of relapse at 1 yr

Anti-TNF Trough and Drug Withdrawal

Retrospective cohort (n=48): Deep remission, discontinued anti-TNF

Deep Remission → Undetectable trough may suggest ability to de-escalate
Risk Factors for Relapse After Anti-TNF Withdrawal

- Higher risk of relapse
- Active endoscopic disease
- Clinically active disease (low Hb, high CRP, WBC, FC)
- Shorter duration of treatment
- Shorter duration of remission
- Longer time from dx to anti-TNF initiation
- Detectable anti-TNF trough
- Younger age (< 25 in adult studies)
- Recent anti-TNF dose intensification or steroids
- Shorter duration of treatment
- Longer time from dx to anti-TNF initiation

Stratifying Risk for Relapse with Treatment De-Escalation

Table 4: Risk factors of relapse in case of treatment de-escalation according to disease and therapeutic factors

- Deep remission: endoscopic remission with complete histological healing
- Clinical response and biomarker normalization
- Short treatment duration
- Previous disease (in case of CD)
- Severe disease
- Clinical parameters
- Severe endoscopic lesions
- Treatment with thiopurines

Anti-TNF Withdrawal with Deep Remission

- Prospective, 52 adult IBD patients
  - Endoscopic remission, calprotectin < 100 µg/g
  - 84% also on IM

- 67% clinical remission at median 13 months
  - 85% were also in endoscopic remission

- No specific risk factors associated with relapse

- Infliximab reinitiation successful & well tolerated
Studies of Anti-TNF Withdrawal for IBD

Table 1: Studies on the discontinuation of anti-tumor necrosis factor – therapy in inflammatory bowel disease

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Anti-TNF – therapy</th>
<th>Median follow up, mo</th>
<th>OR at the end of follow up, %</th>
<th>Clinical benefit after reintroduction of anti-TNF, 36 weeks for remission, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1</td>
<td>38%</td>
<td>29</td>
<td>55</td>
<td>104</td>
</tr>
<tr>
<td>CD2</td>
<td>50%</td>
<td>61</td>
<td>35</td>
<td>125</td>
</tr>
<tr>
<td>CD3</td>
<td>3%</td>
<td>24</td>
<td>66</td>
<td>102</td>
</tr>
<tr>
<td>CD4</td>
<td>5%</td>
<td>28</td>
<td>40</td>
<td>75</td>
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<tr>
<td>CD5</td>
<td>5%</td>
<td>12</td>
<td>57</td>
<td>75</td>
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<tr>
<td>CD6</td>
<td>5%</td>
<td>26</td>
<td>41</td>
<td>75</td>
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<tr>
<td>CD7</td>
<td>5%</td>
<td>12</td>
<td>57</td>
<td>75</td>
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<tr>
<td>CD8</td>
<td>5%</td>
<td>26</td>
<td>41</td>
<td>75</td>
</tr>
<tr>
<td>CD9</td>
<td>5%</td>
<td>12</td>
<td>57</td>
<td>75</td>
</tr>
<tr>
<td>CD10</td>
<td>5%</td>
<td>26</td>
<td>41</td>
<td>75</td>
</tr>
</tbody>
</table>

Successful reintroduction of anti-TNF therapy is possible

Novel Approach – Intermittent Anti-TNF Therapy?

Alternative Options for Maintenance Therapy?
Aminosalicylates

- UC
  - Could be suitable choice for maintenance of remission
  - No data following de-escalation

- Crohn Disease
  - No data

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Maintenance Therapy with Enteral Nutrition for Crohn’s Disease?

- Prospective, 12 mo study of adult CD patients in remission (CDAI<150)

**EN group:** 50% calories from elemental diet via overnight NG & low fat diet during day (n=20)

**Normal diet** (n=20)

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Pharmacologic De-Escalation ➔ Dietary Therapies?

*Clinical and Mucosal Improvement With Specific Carbohydrate Diet in Pediatric Crohn Disease*

*Stanley A. Cohen, Benjamin D. Gold, Susan M. O’Brien, Jeffrey L. Lewis, Angela Stoll-Bauer, Kathy Houk, Laura Ecker, and Jeffrey N. Mazar.*


*Partial Enteral Nutrition with a Crohn’s Disease Exclusion Diet Is Effective for Induction of Remission in Children and Young Adults with Crohn’s Disease*

*Katherine Sigel-Klein MD, Yanis W. Haddad MD, MS, N. Segal MD, M. Zeng, L. Torii, S. A. Cohen, and K. Houk.*

*Pediatr Gastroenterol Nutr 2004;29: 1333–1341*

*Lifestyle-related disease in Crohn’s disease: Relapse prevention by a semi-vegetarian diet*


*Gastroenterol Clin N Am 2006;35: 665–690*
Newer/Future Therapies

• Vedolizumab
• Ustekinumab
• Tofacitinib (oral JAK inhibitor)
• Mongersen (oral SMAD7 antisense)
• AJM300 (oral α4 integrin antagonist)
• Targeted pathway therapy

Future Questions

• Applicable to patients with more complicated disease behavior?
  – Not represented in most of these studies
• Better predictive factors
  – Biomarkers?
  – Changes in microbiome?
• Which medications more desirable long-term?
  – Risk
  – Cost

Pediatric Considerations

• Paucity of pediatric data
  – Adult data possibly not applicable
  – Need pediatric studies
• Do adult risk factors apply?
  – Age < 25 risk factor for relapse
• Should de-escalation wait until growth completed?
If Considering De-Escalation

• Objectively restage disease → Deep remission
  – Labs/calprotectin
  – Endoscopic
  – Imaging (e.g. bowel ultrasound?)

• Frequent monitoring after de-escalation
  – Consider serial calprotectin*
  – Radiographic/endoscopic when appropriate
  – Therapeutic monitoring

• Aggressive response to relapse


Summary

• Goal deep remission before de-escalation
• Evidence supports anti-TNF dose de-escalation
• Combination therapy and durable remission
  – Consider anti-TNF monotherapy
• Data unclear re: de-escalation to IM monotherapy
  – Reinduction possible for relapse
• Pediatric data necessary