Mono or Combination Therapy with Biologics in IBD: Developing an Individualized Approach

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Nomenclature for IBD Management

THEN...
- Step Up
- Top Down
- “Aggressive” therapy
- “Last ditch”
- “Hail Mary”
- “Save for last”
- “Avoid at all cost”

NOW...
- Individualized care
- Deep remission: (clinical remission + mucosal healing)
- Optimization of therapy: therapeutic monitoring and metabolic assessment
- Accelerated step care
Patients in Your Practice

- **Patient #1:** 26 yo female Crohn’s ileocolitis * 3 years
  - Steroids
  - Thiopurine * 2 years
  - Active symptoms more than 25% of the year
- **Patient #2:** 18 yo male Crohn’s colitis and perianal
  - Newly diagnosed, presents with diarrhea, skin tags
- **Patient #3:** 31 yo female Crohn’s ileitis and jejunum
  - Failed step care with 5-ASA, steroids, thiopurine
  - Responded to addition of anti-TNF to thiopurine for the last 6 months
- **Patient #4:** 50 yo male UC failing 5-ASA, steroids

What prevents us from using biologics earlier and maximizing combination therapy?

- Perception that biologics should be “saved” for last
- Perception that biologic therapies are riskier than other therapies
- Fear of complications of combination therapy
- Cost of biologics
- Physician uncertainty about how to use combination therapy: the “step up” mindset
Mono vs. Combo Therapy of TNF-inhibitors in IBD: What are the issues?

Artificial construct

Monotherapy

- Less expensive in short term
- Patients’ preference?
- Easier for healthcare team
- Previous clinical trial data supports this approach
- As effective as combo after failing IMM

Combination Therapy

- More effective in prospective randomized trials
- Reduces rates of antibody formation
- Results in higher blood concentrations of the biologic
- Similar side effect profile to monotherapy

The Rationale Behind Combination Therapy in IBD

- There is much room for improvement in current treatment strategies (>50% failure rate in short and long term)
- Multiple drugs = multiple therapeutic targets
- Biologic therapy + IMM reduces immunogenicity, preserves response over time
- Stable disease control results in disease modification
What’s the Evidence for Combination Therapy? Know the Study Designs!

- **Patients failing IMMs before biologic therapy** may not benefit from combination approach.

- **Patients who failed IMMs before biologic therapy and are stable on combination therapy** may be withdrawn from the IMMs, without loss of response to the biologic for at least two years.

- **Patients who are IMMs-naïve** have efficacy benefit of combination therapy (particularly with endoscopic evidence of disease and elevated CRP).

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**Do Concomitant Immune-modulators Improve Efficacy of Infliximab in CD and UC?**

![Graph showing the efficacy of Infliximab in CD and UC with or without concomitant immune-modulators.](image)

Patients failing IMMs before biologic therapy may not benefit from combination approach.

The Patient not Responding to Thiopurine: Consider Metabolites

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<tr>
<th>6-TGn</th>
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<td>Low (&lt;230)</td>
<td>Low or undetectable</td>
<td>Non-adherent or underdosed</td>
<td>Discuss adherence, increase dose</td>
</tr>
<tr>
<td>Low (&lt;230)</td>
<td>High (&gt;5700)</td>
<td>6-MMP shunter</td>
<td>1. Increase thiopurine, or 2. Consider allopurinol, or 3. Switch agents</td>
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Withdrawal of Concomitant IMM in Crohn’s disease while on Infliximab (failure of IMM before IFX)

No need for early ‘rescue’ IFX: primary endpoint

Median IFX levels, Week 8 to Week 104 combined

Patients who failed IMM before biologic therapy and are stable on combination therapy may be withdrawn from the IMM, without loss of response to the biologic for at least two years (caveat- know your patient)


Azathioprine, Infliximab or Combination Therapy for Crohn’s Disease (SONIC)
Corticosteroid-Free Clinical Remission at Wk 26

• Naive to IMM and anti-TNF
• TPMT “normal”
• Median dz duration 2.4y

Azathioprine, Infliximab or Combination Therapy for Crohn’s Disease (SONIC)

Mucosal Healing at Week 26


Azathioprine, Infliximab or Combination Therapy for Crohn’s Disease (SONIC)

Corticosteroid-Free Clinical Remission at Wk 50

All randomized patients (N=508)*


* Patients who did not enter the Study Extension were treated as non-responders
COMMIT: MTX plus IFX in new onset CD patients

- No difference in ITT analysis, duration of disease <2 years, by CDAI score
- No difference in infectious AEs (58.7% MTX vs 61.9% PBO)


What about Ulcerative Colitis?
Infliximab, Azathioprine, or Infliximab + Azathioprine for Moderate to Severe Ulcerative Colitis (UC SUCCESS)

**Primary Endpoint: Steroid-Free Remission at Week 16**

- **AZA (N=76):** 24% (N=18)
- **IFX (N=77):** 22% (N=17)
- **IFX+AZA (N=78):** 40% (N=31)

P-values:

- P=.017
- P=.813
- P=.032

**Secondary Endpoint: Mucosal Healing at Week 16**

- **AZA (N=76):** 37% (N=28)
- **IFX (N=77):** 55% (N=42)
- **IFX+AZA (N=78):** 63% (N=49)

P-values:

- P=.295
- P=.028
- P=.001

### Immunogenicity of Combination Therapy

**Immunogenicity of TNF Antagonists with and without Concomitant Immune Modulators (IMS)**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Episodic Maintenance</th>
<th>Scheduled Maintenance</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>IMS-</td>
<td>IMS+</td>
</tr>
<tr>
<td>Infliximab(^1) (CD 5 mg/kg) (CD 10 mg/kg)</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Infliximab(^2) (UC 5 mg/kg) (UC 10 mg/kg)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Certolizumab(^3) (PRECISE I)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab(^4) (PRECISE II)</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Adalimumab(^5) (RA, all doses)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Adalimumab(^6) (CLASSIC II)</td>
<td></td>
<td></td>
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### Immunogenicity of TNF Antagonists with and without Concomitant Immune Modulators (IMS)

<table>
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### Safety of Combination Therapy in IBD

**Risks of therapy compared to risks of ineffectively treated disease**
### Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>AZA + placebo (N=161)</th>
<th>IFX + placebo (N=163)</th>
<th>IFX + AZA (N=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with ≥ 1 AE, N (%)</td>
<td>144 (89.4%)</td>
<td>145 (89.0%)</td>
<td>161 (89.9%)</td>
</tr>
<tr>
<td>Pts with ≥ 1 SAE, N (%)</td>
<td>43 (26.7%)</td>
<td>39 (23.9%)</td>
<td>27 (15.1%)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>9 (5.6%)</td>
<td>8 (4.9%)</td>
<td>7 (3.9%)</td>
</tr>
<tr>
<td>&gt;1 Infusion reactions</td>
<td>8 (5.0%)</td>
<td>22 (13.5%)</td>
<td>9 (5.0%)</td>
</tr>
</tbody>
</table>

TB - 1 patient treated with infliximab and azathioprine  
Colon cancer - 2 patients treated with azathioprine monotherapy  
Death - Post colectomy, in a patient treated with azathioprine monotherapy

Azathioprine, Infliximab or Combination Therapy for Crohn’s Disease (SONIC) Immunogenicity Results at Week 30*

* Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis. PK data at Wk 30 was not available for 1 patient treated with AZA + placebo, 3 patients treated with IFX + placebo, and 4 patients treated with AZA + IFX.


Infliximab (IFX) levels in patients taking concomitant immunosuppressives

- Increased IFX blood levels in IMM takers

<table>
<thead>
<tr>
<th>IFX levels (median + IQR)</th>
<th>No immunosuppressives</th>
<th>Immunosuppressives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max IFX</td>
<td>2.42 µg/mL (1–10.8)</td>
<td>6.45 µg/mL† (3–11.6)</td>
</tr>
<tr>
<td></td>
<td>21 µg/mL</td>
<td>33.4 µg/mL</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>6.15 µg/mL (3–11.6)</td>
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</tr>
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<td>33.4 µg/mL</td>
<td>31 µg/mL</td>
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†p=0.065

Vermeire et al. Gut. 2007; 56:1226-31
The Lymphoma Discussion

- NHL risk with thiopurines +/- anti-TNF
- Hepatosplenic T-cell lymphoma drives many decisions. Should it?
- Many unanswered questions
  - Duration
  - Dose
  - Attenuated risk with dose reduction or withdrawal?

Proposed Approach to Mono or Combo Therapy in IBD

1. Failing Thiopurine
   - Reassess disease
   - Reassess adherence
   - Optimize therapy (metabolites?)

2. Add anti-TNF therapy

3. If Response
   - 6 months
   - Withdraw Thiopurine?
   - Dose reduction of Thiopurine?
Proposed Approach to Mono or Combo Therapy in IBD

Imm/anti-TNF naive

What is prognosis?

High Risk

Low Risk

Combo IMM/TNF

Step Care

If achieve deep remission

Male? MTX instead of Thiopurine?

If deep remission

If not deep remission

12 months

Possible withdraw Therapy (which one?)

or

Dose reduction of Thiopurine?

Proposed Approach to Mono or Combo Therapy in IBD

Anti-TNF Monotherapy

Stay the course adherence to maintenance schedule

Losing Response?

Reassess Disease

Assess drug level/antibodies

Add IMM?

Change drug/mechanism
Patients in Your Practice

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- **Patient #4**: Same as #3 but male

- **Patient #5**: 50 yo male UC failing 5-ASA, steroids
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9. Possible withdraw Therapy (which one?)
10. Or
11. Dose reduction of Thiopurine?

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Dose reduction of Thiopurine?

Individualized Approach to IBD Management 2011-2012

- Prioritize:
  - Review goals of therapy
  - Understand prognosis of your patient- is this newly diagnosed?

- Optimize:
  - Use the best treatment available for your patient
  - Choose objective time points and endpoints of your treatments
  - Prevent complications (screen, vaccinate)
  - Educate about adherence and safety

- Maximize:
  - Use the right dose!
  - Minimize immunogenicity (load, combine, maintain)
  - Monitor for relapse

- Strategize:
  - How long before you reassess?
  - How long before you move on to another treatment?
  - Would you adjust dosing or strategy after some time?
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