Combination Therapy in Crohn’s Disease: When and How Long

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Mono or Combo: Why is the pendulum swinging?

- **COMBO**
  - Reduced Immunogenicity and higher troughs
  - Combined clinical trials and cohorts with mAbs

- **MONO**
  - Efficacy
  - Safety

- **SONIC**
  - Lymphomas/Hepatosplenic T-cell lymphomas
Principle #1: Relapse is Anticipated After Biologic Induction Without Maintenance Therapy
Retreatment Benefit With Infliximab

Clinical response defined as a ≥ 70-point decrease in CDAI score from baseline.

*Patients responding to an initial infusion.

CDAI=Crohn’s Disease Activity Index
Principle #2: Even with Maintenance Therapy Loss of Response is Common
**ACCENT I: Infliximab Maintenance in CD**

*Among 335 patients responding at Week 2*

Principle #3: In Pivotal Clinical Trials no Differences in Efficacy for Biologics With/Without Combination Immunomodulators

- Infliximab
- Adalimumab
- Certolizumab Pegol
Patients not randomized to Combination therapy

Trials not powered to evaluate Combination therapy

IMM=immunomodulator
Principle # 4: In Prospective Clinical Trials with Immunomodulator Naïve Patients... Combination Therapy was Superior
Evidence for Combination Therapy in Immunosuppressive-naive Patients SONIC

Corticosteroid-free clinical remission at Week 26

AZA=azathioprine; IFX=infliximab
Principle #5: Factors Associated with Loss of Response

- Serum levels
  - Recovery with increased doses/decreased frequency
- Immunogenicity
  - Immunogenicity is associated with decreased serum levels
- Loss of mechanism
- Duration of disease
- Prior anti-TNF therapy
Principle #6: Factors Associated with Immunogenicity

Low-Dose Induction
Episodic Therapy
No Concomitant Immunosuppressive

All Lead to Low Trough Levels
Sub-threshold **trough** levels associated with:

- Loss of response
- Immunogenicity
Trough Levels of Infliximab Are Predictor of Continued Response

*P < .001

Question #1: Can We Stop Immunomodulator and Continue Biologic?
Effect of Discontinuing Immunomodulator on Long-term Efficacy of Infliximab: IMID Trial

No need for early ‘rescue’ IFX: primary endpoint

Median IFX levels, Week 8 to Week 104 combined

- Continued
- Discontinued

Log Rank (Cox): 0.735; Breslow: 0.906

80 patients randomized to continue (*CON, n=40) or to interrupt (**DIS, n=40) immunomodulators (azathioprine or methotrexate) 6 months after the start of infliximab (5 mg/kg IV)

IFX=infliximab
Infliximab Trough Levels at Time of Withdrawal of Immunosuppressive Predict Time to Loss of Response

Time to Loss of Response after Immunomodulator Withdrawal

- Undetectable
- Detectable ≤5
- >5

Log rank $P < .001$

IMM=immunomodulator
Other Predictors of Loss of Response to Infliximab after Azathioprine Withdrawal in Crohn’s Disease After Combination Therapy (GETAID)

- Less Time on Combination
  - > 811 Days (3 years)

- High CRP
  - Not in Remission

AZA=azathioprine; CRP=C-reactive protein; IFX=infliximab
Question #2:  
Can We Stop Biologic and Continue Immunomodulator?
Discontinuation of Infliximab in Patients in Stable Remission on Combination Therapy (Azathioprine Maintained)

52 relapses in 115 patients
Median (±SE) follow up 21 ± 1 mo

Proportion Without Relapse

# at risk: 115 102 79 63 51 47 39 27 20 12 9

Multivariate analysis of factors predicting time-to-relapse after stopping infliximab

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient± SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous resection</td>
<td>1.44±0.51</td>
<td>.005</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.25±0.36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemoglobin ≤14.5 g/L</td>
<td>1.71±0.52</td>
<td>.001</td>
</tr>
<tr>
<td>Leukocyte &gt;6x10^9/L</td>
<td>0.62±0.32</td>
<td>.05</td>
</tr>
<tr>
<td>hsCRP ≥5 mg/L</td>
<td>0.98±0.35</td>
<td>.005</td>
</tr>
<tr>
<td>Fecal calprotectin ≥300 mcg/L</td>
<td>1.13±0.42</td>
<td>.01</td>
</tr>
</tbody>
</table>

Simplified multivariate model without infliximab trough level and CDEIS

hsCRP=high sensitivity C-reactive protein
Predictive model for the time-to-relapse

Kaplan Meier time-to-relapse curves according to multivariate models and scores generated through Cox model using multiple imputations method.

Complete Model

No. deleterious factors

<4

4

5-6

>6

Months since infliximab withdrawal

Proportion without relapse

hsCRP=high sensitivity C-reactive protein
Principle # 7: Major Risks of Infections are Related to Steroids
Risk Factors for Opportunistic Infections
The Mayo Experience

- Case-control study of all opportunistic infections between 1998-2003
- 2 controls for each case (matched on type IBD, age, gender, residence)
- 100 opportunistic infections identified

<table>
<thead>
<tr>
<th>Medications</th>
<th>OR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medication</td>
<td>2.7 (1.5-4.8)</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>2 medications</td>
<td>9.7 (3.3-28.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3 medications</td>
<td>infinite</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>2.2 (1.1-4.8)</td>
<td>.037</td>
</tr>
<tr>
<td>AZA/6-MP</td>
<td>2.5 (1.2-5.1)</td>
<td>.015</td>
</tr>
<tr>
<td>IFX</td>
<td>11.2 (0.8-153.3)</td>
<td>.07</td>
</tr>
<tr>
<td>6-MP/AZA + steroid</td>
<td>15.7 (4.1-59.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>6-MP + IFX</td>
<td>1.6 (0.1-18.7)</td>
<td>.71</td>
</tr>
<tr>
<td>6-MP/AZA + IFX + steroid</td>
<td>infinite</td>
<td></td>
</tr>
</tbody>
</table>

6-MP=6-mercaptopurine; AZA=azathioprine; IFX=infliximab
Steroids are the biggest risk for infections

<table>
<thead>
<tr>
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<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.01</td>
<td>0.99-1.03</td>
</tr>
<tr>
<td>Female</td>
<td>1.24</td>
<td>0.81-1.90</td>
</tr>
<tr>
<td>Moderate or severe CD</td>
<td>2.11</td>
<td>1.10-4.05*</td>
</tr>
<tr>
<td>Current use of infliximab</td>
<td>1.40</td>
<td>0.95-2.07</td>
</tr>
<tr>
<td>Current use of 6MP/AZA/MTX</td>
<td>0.88</td>
<td>0.61-1.27</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.21</td>
<td>1.46-3.34*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.38</td>
<td>1.56-3.63*</td>
</tr>
</tbody>
</table>

*P<.05

### SONIC Summary of Adverse Events Through Week 50: All Randomized Patients

<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>Patients with ≥1 AE, n (%)</td>
<td>144 (89.4%)</td>
<td>145 (89.0%)</td>
<td>161 (89.9%)</td>
</tr>
<tr>
<td>Patients 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>
</tbody>
</table>

Combination Therapy had Lowest Risk Of Infections

AE=adverse event; AZA=azathioprine; IFX=infliximab; SAE=serious adverse event
Principle #8: Risks of Lymphomas are Related to Thiopurines
Exposure to Thiopurines and Lymphomas in IBD

HR thiopurines = 5 [CI 95%: 2-14]

Increases with Age

Beaugerie L et al., Lancet. 2009;374:1617-1625
Hepatosplenic T-cell lymphomas

• Main features
  – Rapidly fatal lymphoproliferations
  – Young men <35 years
  – Non EBV-related
  – Combination therapy thiopurines/anti-TNF, and less frequently monotherapy with thiopurines
  – Rare within the first two years of treatment

• Rare (<0.1 /1000 PY) – 20 cases with combination therapy and 16 with AZA or 6-MP monotherapy

6-MP=6-mercaptopurine; AZA=azathioprine; EBV=Epstein-Barr Virus; TNF=tumor necrosis factor
Combination Therapy

Positive:

Pharmacokinetics

Higher drug levels

Immunosuppression

Synergistic efficacy

Negative:

Optimizing 2 drugs?

Infections (Steroids)

Malignancy (Thiopurines)
Risk-Benefit of Stopping Combination Therapy

**Benefits**
- Reduced risk of lymphoma (?)

**Risks**
- Disease Flare
- Disease Progression
Principle #9: Biologics can be resumed for patients who relapse if...

Prior Therapy >6-12 months

Combination with Steroids + Immunosuppressives
Long-term efficacy of Infliximab re-treatment (GETAID)

Kaplan Meier loss of response over time in the STORI cohort

52 retreated patients after 6.6 months drug holiday; 6/52 only loss of response over a median follow-up of 24 months

c/o Edouard Louis, MD
Experience with restarting IFX (Leuven)

Discontinuation of IFX after restart

No stop of IFX (%)

0 0.2 0.4 0.6 0.8 1

0 12 24 36 Months after restart

IFX=infliximab
All Patients Treated with IS + Steroids for first few reinfusions

Pragmatic Approach to Combination Therapy

• Combination therapy is most effective, least risky induction therapy
• Immunogenicity usually overcome in long-term treatment (>6-12 months)
• Infection risk driven more by steroids
• Neoplasia risk driven more by thiopurines
• Consider reducing to monotherapy for:
  – Young males
  – Individuals in deep, sustained remissions
    • Can be re-treated with combination therapy