Stopping Biologics: A North American Perspective?

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## Financial Interest Disclosure
(over the past 24 months)

<table>
<thead>
<tr>
<th>Category</th>
<th>Companies</th>
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<tbody>
<tr>
<td><strong>Grant/Research Support</strong></td>
<td>Abbott, ActoGeniX, Bristol-Myers Squibb, Centocor, CombinatoRx, Elan/Biogen, Genentech, Merck, Millenium, Novartis, Protein Design Labs, Tillotts, UCB Pharma, Wyeth,</td>
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Topics Covered

- The value of combination therapy
- Stopping therapy: Pros vs Cons
- Lessons from RA
- Lessons from CD
- STORI
- Safety considerations
- What do I do in clinical practice?
Azathioprine Maintenance Therapy After Corticosteroid-Induction in Crohn's Disease

- Single center double-blind placebo controlled trial, n=63
  - Phase 1: combined effect of prednisolone plus AZA vs placebo over 12 weeks
  - Phase 2: following completion of phase 1, compared AZA vs placebo over 12 months

Candy et al. Gut 1995;37:674
Surgery Rates for CD and the Use of Immunosuppressives over 3 Decades

Azathioprine Monotherapy vs Infliximab Plus Azathioprine in Steroid-Dependent Crohn’s Disease

Remission (CDAI<150) and off steroids (%)

Week 12
- Placebo week 0, 2, 6 + AZA / 6-MP (n=58)
- Infliximab 5 mg/kg week 0, 2, 6 + AZA / 6-MP (n=57)

Week 24
- Placebo week 0, 2, 6 + AZA / 6-MP (n=58)
- Infliximab 5 mg/kg week 0, 2, 6 + AZA / 6-MP (n=57)

Week 52
- Placebo week 0, 2, 6 + AZA / 6-MP (n=58)
- Infliximab 5 mg/kg week 0, 2, 6 + AZA / 6-MP (n=57)

AZA = Azathioprine
6-MP = 6-Mercaptopurine

Lemann et al. Gastroenterology 2006;130:1054
Early Combination Therapy vs Conventional Management of Crohn’s Disease

Patients in remission without steroids or surgical resection (%)

- Early combined (n=65)
- Conventional therapy (n=64)

- 6 months: 60% (Early combined) vs 35.9% (Conventional therapy)
- 12 months: 61.5% (Early combined) vs 42.2% (Conventional therapy)

*p=0.0062
**p=0.0278

Early Combination Therapy vs Conventional Management of Crohn’s Disease: Complete Ulcer Disappearance

**p=0.003

SONIC: Clinical Remission Without Corticosteroids at Week 26

Colombel et al., New England J Med 2010
Topics Covered

• The value of combination therapy
• **Stopping therapy: Pros vs Cons**
• Lessons from RA
• Lessons from CD
• STORI
• Safety considerations
• What do I do in clinical practice?
Stopping Therapy: Pros

- May not be needed for long term efficacy
- Less toxic
- More convenient
- Less costly
Stopping Therapy: Cons

• May be less effective

• Risk of sensitization

• May not necessarily be more safe

• May lose the opportunity to change the natural history of the disease
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The Seductive Fantasy: Long Term Remission without Biologics in Early RA

- 20 early (<12 months) poor-prognosis RA
- Randomized, double-blind controlled trial evaluating multiple regimens: MTX+PLB vs MTX+IFX – the Winner
- At 1 year, better MRI scores with no new erosions
- At 2 yrs: 1 yr after stopping IFX, 70% sustained response

The Reality (I)

- One half of patients who were carefully monitored by a treat-to-target approach required re-introduction of treatment

- Re-introduction was unsuccessful in ~ 25% of patients

- Risk of sensitization – limited number of biologic drugs

- Can I really risk stopping in my worst patients?
The Reality (II)

- Why should the disease go away?

- IBD results from environmental and genetic factors that you have not altered with short term therapy

- T lymphocytes are long-lived and pathogenic clones are not ablated with conventional treatments
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AZA Withdrawal

Lémann M et al. Gastroenterology 2005;128:1812
AZA Withdrawal in Patients Treated With Combination Therapy

- Eighty (80) patients, 6 months treatment IFX 5 mg/kg q8+IS
- Randomised (1:1) to continue or discontinue IS; 2 years follow-up
- Forty-nine (49) underwent a 2 year ileo-colonoscopy

Potential for Loss of Efficacy

After IS withdrawal:
5-15% vs 0% of patients with undetectable trough levels beyond one year

Median CRP level significantly higher (2.8 vs 1.6 mg/l; P<0.005)

Relapse Rate after Infliximab Discontinuation

43.9% relapse at 1 year

52.2% relapse at 2 years

## Predictors of Relapse

<table>
<thead>
<tr>
<th>Clinical history and characteristics</th>
<th>P value</th>
<th>IFX frequency last 6 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.63</td>
<td>Scores and biological variables</td>
<td>P value</td>
</tr>
<tr>
<td>Gender</td>
<td>0.22</td>
<td>CDAI &gt;20</td>
<td>0.045</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.84</td>
<td>CDEIS ≥2</td>
<td>0.002</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.036</td>
<td>CDEIS &gt;0</td>
<td>0.033</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>0.07</td>
<td>Presence of ulcers</td>
<td>0.20</td>
</tr>
<tr>
<td>Disease location</td>
<td>0.73</td>
<td>ANA</td>
<td>0.81</td>
</tr>
<tr>
<td>A-P disease</td>
<td>0.17</td>
<td>ATI</td>
<td>0.39</td>
</tr>
<tr>
<td>Fistula</td>
<td>0.12</td>
<td>Fecal calprotectin ≥250 microg/g</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stricture</td>
<td>0.13</td>
<td>CRP hs ≥5 mg/l</td>
<td>0.0006</td>
</tr>
<tr>
<td>Previous steroid treatment</td>
<td>0.067</td>
<td>IFX trough level ≥2 micro/ml</td>
<td>0.25</td>
</tr>
<tr>
<td>IS naïve</td>
<td>0.96</td>
<td>ESR &gt;16</td>
<td>0.16</td>
</tr>
<tr>
<td>IS type</td>
<td>0.12</td>
<td>Plt count</td>
<td>0.86</td>
</tr>
<tr>
<td>IS duration</td>
<td>0.41</td>
<td>WBC &gt;6000/ml</td>
<td>0.08</td>
</tr>
<tr>
<td>IFX duration</td>
<td>0.44</td>
<td>Hemoglobin ≤14.5 g/dl</td>
<td>0.038</td>
</tr>
<tr>
<td>IFX scheduled from the start</td>
<td>1.00</td>
<td>6TGN</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*Louis E et al. Gastroenterology. 2012 Jan;142(1):63-70*
Predictive Model for the Time-to Relapse: Risk Factors

**Simplified Model**: the same without steroid use, CDEIS and IFX trough levels

![Graph showing the proportion without relapse over months since infliximab withdrawal with different numbers of pejorative factors.](image)
Topics Covered

• The value of combination therapy
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• Lessons from CD
• STORI
• Safety considerations
• What do I do in clinical practice?
The Bottom Line on STORI

“Currently there is no good medical reason to stop IFX in patients in stable remission”

E. Louis  Principal Investigator STORI, BMJ 2012
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Serious Infection in IBD: The Role of Multidrug Therapy

- Causality difficult to establish
- Mayo Clinic case-control study of opportunistic infection:
  - any vs no drug OR 2.6 (1.4–4.7)
  - infliximab OR 4.4 (1.2–17.1)
  - corticosteroid OR 3.4 (1.8–6.2)
  - azathioprine OR 3.1 (1.7–5.5)
  - 2 drugs OR 12.9 (4.5–37)
  - 3 drugs OR - infinite

# Summary of Adverse Events Events Through Week 30

<table>
<thead>
<tr>
<th></th>
<th>AZA + placebo (n=161)</th>
<th>IFX + placebo (n=163)</th>
<th>IFX + AZA (n=179)</th>
<th>Total (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weeks of treatment</td>
<td>21.1</td>
<td>24.1</td>
<td>24.8</td>
<td>23.4</td>
</tr>
<tr>
<td>Subjects with ≥ 1 AE, n (%)</td>
<td>138 (85.7%)</td>
<td>135 (85.3%)</td>
<td>156 (87.2%)</td>
<td>433 (86.1%)</td>
</tr>
<tr>
<td>Subjects who d/c study agent due to an AE, n (%)</td>
<td>37 (23%)</td>
<td>19 (11.7%)</td>
<td>25 (14.0%)</td>
<td>81 (16.1%)</td>
</tr>
<tr>
<td>Subjects with ≥ 1 SAE, n (%)</td>
<td>39 (24.2%)</td>
<td>26 (16.0%)</td>
<td>25 (14.0%)</td>
<td>90 (17.9%)</td>
</tr>
<tr>
<td>Subjects with ≥ 1 infection, n (%)</td>
<td>60 (37.3%)</td>
<td>58 (35.6%)</td>
<td>66 (36.9%)</td>
<td>184 (36.6%)</td>
</tr>
<tr>
<td>Subjects with ≥ 1 serious infection, n (%)</td>
<td>8 (5.0%)</td>
<td>4 (2.5%)</td>
<td>6 (3.4%)</td>
<td>18 (3.6%)</td>
</tr>
<tr>
<td>Subjects with ≥ 1 infusion rxn, n (%)</td>
<td>8 (5.0%)</td>
<td>22 (13.5%)</td>
<td>9 (5.0%)</td>
<td>39 (7.8%)</td>
</tr>
</tbody>
</table>

*Sandborn et al., ACG 2008 annual meeting, abstract #29*
### Safety Data From the TREAT Registry

**Cox proportional hazard regression (multivariate)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use of IFX</td>
<td>1.1</td>
<td>0.6–1.8</td>
</tr>
<tr>
<td>Current use of AZA/6-MP/MTX</td>
<td>0.8</td>
<td>0.5–1.2</td>
</tr>
<tr>
<td>Current use of GCS</td>
<td>2.0</td>
<td>1.3–3.0*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.1</td>
<td>1.3–3.2†</td>
</tr>
<tr>
<td><strong>Serious infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use of IFX</td>
<td>1.4</td>
<td>1.0–2.1</td>
</tr>
<tr>
<td>Current use of AZA/6-MP/MTX</td>
<td>0.9</td>
<td>0.6–1.3</td>
</tr>
<tr>
<td>Current use of GCS</td>
<td>2.0</td>
<td>1.4–2.9**</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.2</td>
<td>1.5–3.1†</td>
</tr>
</tbody>
</table>

*p=0.002; **p<0.001; †p<0.0001

6-MP = 6-mercaptopurine; AZA = azathioprine; CI = confidence interval; GCS = glucocorticoid steroids; IFX = infliximab; MTX = methotrexate

*Lichtenstein et al. Gastroenterology 2006;130:A-71*
*Lichtenstein et al. Gastroenterology 2007;132: A-178*
# A Pooled Analysis: RCTs of Infliximab in IBD

<table>
<thead>
<tr>
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<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
<th>All Inflammatory Bowel Diseases</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Infliximab</td>
<td>Placebo</td>
</tr>
<tr>
<td>No. (%) pts with serious infection</td>
<td>9 (5.6%)</td>
<td>55 (4.5%)</td>
<td>6 (2.4%)</td>
</tr>
<tr>
<td>Incidence per 100 pt-yrs</td>
<td>8.3</td>
<td>7.63</td>
<td>2.87</td>
</tr>
<tr>
<td>95% CI</td>
<td>(3.80,15.76)</td>
<td>(6.10,9.43)</td>
<td>(1.05,6.24)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.547</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Lichtenstein GR. Am J Gastroenterology. 2012;107(7):1051-63*
Lymphoma Risk with Thiopurines: CESAME

n =19486 exposed: 30%+14.5%
23 incident lymphomas
OR= 5.28 (2.01-13.9, p=0.0007)

Conclusions

• Discontinuation of our most effective therapy comes at a cost of relapse

• No high quality RCTs have examined this issue in CD!

• The therapeutic index of stopping is unknown

• What do I do in practice?
"It's nice that you've learned to tie your shoes, but you're really too young to quit while you're ahead."