Practical Approach to Immunomodulator and Biologic Use in Crohn’s Disease

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Azathioprine & 6-MP: Remission Maintenance in Crohn’s Disease

Prefontaine E. Cochrane Database of Systematic Reviews 2009(1). Art No: CD000067
Practical Approach: Metabolite Monitoring

- Check in non-responders to identify reasons for non-response:

<table>
<thead>
<tr>
<th></th>
<th>6-TGN</th>
<th>6-MMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate dose</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Non-adherence</td>
<td>↓↓↓</td>
<td>0</td>
</tr>
<tr>
<td>6-MMP shunting</td>
<td>↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>↑↑↑</td>
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</table>

Case #1: Steroid Dependent Crohn’s

<table>
<thead>
<tr>
<th>6-MP dose</th>
<th>6-TGN</th>
<th>6-MMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>106</td>
<td>5400</td>
</tr>
</tbody>
</table>

6-MP dose increased to 125 mg - still no response

<table>
<thead>
<tr>
<th>6-MP dose</th>
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<tbody>
<tr>
<td>125 mg</td>
<td>112</td>
<td>14,786</td>
</tr>
</tbody>
</table>

*AST- 89; ALT- 105*
CASE #2

- 25 yo F with Crohn’s ileocolitis
- Steroid refractory course- started on 6-MP at 75 mg qd (1.0 mg/kg) with no response
- Metabolite levels:
  - 6-TGN  23
  - 6-MMP Undetectable

Practical Approach: Metabolite Monitoring

- Check in non-responders to identify reasons for non-response:

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MTX (IM) Treatment of CD


TIME TO RELAPSE IN STUDY GROUPS

Intestinal Resection Rate in CD Remained Stable Over 25 Years

No significant change over time


Anti-TNF Engineered Antibodies

Mouse
Human

Chimeric monoclonal antibody
Human recombinant antibody
Humanized Fab fragment

Infliximab
Adalimumab
Certolizumab pegol

PEG = Polyethylene glycol

PEG = Polyethylene glycol
**ACCENT I, CHARM, and PRECiSE 2 Results**

**ACCENT I**
- (infliximab)
- 80 mg (%)
- 64.1

**CHARM**
- (adalimumab)
- 6080

**PRECiSE 2**
- (certolizumab)

*5 mg/kg dose.
**Maintenance trial with 80/40 mg induction dosing. Randomized responders = CR-70 at week 4. Week 26 remission among randomized responders on 40 mg every other week dosing.

**Recent Lessons and Questions**

- Despite degree of “humanness” all anti-TNF agents are immunogenic
- Better response with early treatment
- Switching to second agents for loss of response or intolerance works but there is a diminished effect
- Are concomitant immunomodulators needed?
Treat Early
Switch in cytokine profiles (Th1→Th2) in IL-10−/− mice during the clinical course of colitis

**IL-12**

- **Pre**
- **Early**
- **Late**

**IFN-γ**

- **Pre**
- **Early**
- **Late**

**IL-4**

- **Pre**
- **Early**
- **Late**

**IL-13**

- **Pre**
- **Early**
- **Late**

**PRECiSE 2: Response and Remission to Certolizumab pegol by Disease Duration**

Schreiber S. Am J Gastroenterol 2010;105:1584-82
CHARM: Response by Disease Duration

Wk 26 Remission

- Placebo
- Adalimumab

Schreiber S. J Crohns Colitis 2013;7:213-21

Wk 56 Remission

Switching to 2nd anti-TNF Agent
Adalimumab 4 week Remission: CLASSIC vs GAIN

CLASSIC (TNF naïve) vs GAIN (Prior IFX)

- Placebo
- ADA 160/80 mg

Gastroenterology 2006;130:323-33
Ann Intern Med 2007;146:829-38

WELCOME: Certolizumab after secondary failure to infliximab

PRECISE 2 vs WELCOME

- Wk 26 Remission
- Wk 26 Response

Schreiber S. NEJM 2007;357;239-250
Gastroenterology 2009;136(Suppl1): Abstract 143
Concomitant Immunomodulator

Top Down vs. Step Up Therapy

Early combined immunosuppression

- Infliximab- 5 mg/kg at 0, 2 & 6 weeks AND Azathioprine- 2-2.5 mg/kg (MTX if intolerant)
- If symptoms persisted → Methylprednisolone
- If responded but symptoms recurred:
  - Infliximab first
  - If still symptomatic → Methylprednisolone

D’Haens G. Lancet 2008;371:660-7
Conventional treatment

- Methylpred (32 mg) or budesonide (9 mg) with 10 week taper
- If symptoms persisted → Methylprednisolone at 64 mg qd and azathioprine
- If responded but symptoms recurred:
  - Steroids → Azathioprine → Infliximab

D’Haens G. Lancet 2008;371:660-7

Corticosteroid Use

D’Haens G. Lancet 2008;371:660-7
CDAI < 150 & Off Steroids

![Graph showing the proportion of patients in remission for early combined immunosuppression group and conventional management group.](image1)

Mucosal Healing at 2 years

![_bar_graph showing mucosal healing at 2 years for early immunosuppression and conventional treatment](image2)

D’Haens G. Lancet 2008;371:660-7
SONIC

Azathioprine 2.5 mg/kg + placebo infusions

Infliximab 5 mg/kg + placebo capsules

Infliximab 5 mg/kg + Azathioprine 2.5 mg/kg

Primary Endpoint (Corticosteroid-free Remission at Week 26)

Secondary Endpoint (Week 50)

Visits

Week 0*
Week 2
Week 6
Week 10
Week 14
Week 18
Week 22
Week 26*
Week 30
Week 38
Week 42
Week 46
Week 50
Week 54

* Infusions
* Endoscopy performed at Weeks 0 & 26

Steroid-Free Clinical Remission Wk 26

Primary Endpoint

Proportion of Patients (%)
0 20 40 60 80 100

52/170 75/169 96/169

AZA + placebo IFX + placebo IFX+ AZA

p<0.001 p=0.009 p=0.022

ACG Regional Postgraduate Course - Washington, DC
Copyright 2013 American College of Gastroenterology
Steroid-Free Clinical Remission Wk 26

Patients with CRP $\geq 0.8$ mg/dL & Lesions on Baseline Endoscopy (n=204)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>28.0 (21/75)</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>56.9 (37/65)</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>68.8 (44/64)</td>
</tr>
</tbody>
</table>

But questions remain…

- Who should get aggressive early therapy?
- If start combination therapy:
  - Can one of the medications be stopped and, if yes, when?
  - Safety considerations?
- Do combination treatment results also apply to adalimumab and certolizumab pegol?
Early Predictors of Aggressive Disease Course

- Young age at diagnosis
- Need for steroid therapy at diagnosis
- Perianal disease
- Extensive small bowel disease
- Deep ulcers on endoscopy
- Clinically severe disease

Can one of the agents be withdrawn after achieving remission with dual therapy?
Withdrawal of Infliximab

1-year relapse rate = 44%

Multivariate Model for Relapse

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No surgical resection</td>
<td>4.2</td>
<td>0.005</td>
</tr>
<tr>
<td>hsCRP ≥ 5 mg/L</td>
<td>2.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Hg ≤ 14.5 g/dL</td>
<td>5.5</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC &gt; 6.0</td>
<td>1.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Fecal calprotectin &gt; 300</td>
<td>3.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Immunosuppressive Withdrawal

Van Assche G. Gastroenterology 2008;134:1861-8

Predictors of infliximab failure after azathioprine withdrawal

• Retrospective observational study
• 48 patients who had received IFX + AZA for ≥ 6 months → AZA D/Ced

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of comb tx ≤ 811 days</td>
<td>7.46</td>
<td>0.01</td>
</tr>
<tr>
<td>CRP &gt; 5 mg/L</td>
<td>4.79</td>
<td>0.008</td>
</tr>
<tr>
<td>PLT &gt; 298</td>
<td>4.75</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Oussalah A. Am J Gastroenterol 2010;105:1142-9
### Safety

#### Infection Risks in Observational Studies

<table>
<thead>
<tr>
<th></th>
<th>Steroids</th>
<th>AZA/6-MP</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious</strong></td>
<td>2.2</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>(1.5 – 3.3)</td>
<td>(0.5 – 1.2)</td>
<td>(1.1 – 2.0)</td>
</tr>
<tr>
<td><strong>Opportunistic</strong></td>
<td>3.4</td>
<td>3.1</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>(1.8 – 6.2)</td>
<td>(1.7 – 5.5)</td>
<td>(1.2 – 17.1)</td>
</tr>
<tr>
<td><strong>Post-Op</strong></td>
<td>5.5</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>(1.1-27.3)</td>
<td>(0.4-4.0)</td>
<td>(0.9-2.5)</td>
</tr>
</tbody>
</table>

Blonski W et al. DDW 2010: T1287.
SONIC Adverse Events- Week 54

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts with ≥ 1 AE, n (%)</th>
<th>Pts with ≥ 1 SAE, n (%)</th>
<th>Serious Infections</th>
<th>Infusion Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo (n=161)</td>
<td>144 (89.4%)</td>
<td>43 (26.7%)</td>
<td>9 (5.6%)</td>
<td>9 (5.6%)</td>
</tr>
<tr>
<td>IFX + placebo (n=163)</td>
<td>145 (89.0%)</td>
<td>39 (23.9%)</td>
<td>8 (4.9%)</td>
<td>27 (16.6%)</td>
</tr>
<tr>
<td>IFX + AZA (n=179)</td>
<td>161 (89.9%)</td>
<td>27 (15.1%)*</td>
<td>7 (3.9%)</td>
<td>9 (5.0%)*</td>
</tr>
</tbody>
</table>

* P < 0.05 for IFX + AZA vs IFX only therapy
° Including 1 death from sepsis

Combined Use of Immunosuppressive Drugs
Increased Risk of Opportunistic Infections

<table>
<thead>
<tr>
<th>Number of Immunosuppressant Medications</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Reference</td>
</tr>
<tr>
<td>1</td>
<td>2.9 (1.5-5.3)</td>
</tr>
<tr>
<td>2 or more</td>
<td>14.5 (4.9-43)</td>
</tr>
</tbody>
</table>

## TREAT Registry:
### Predictors of Serious Infections

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/severe disease</td>
<td>2.24 (1.57, 3.19)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.43 (1.11, 1.84)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1.57 (1.12, 2.10)</td>
</tr>
<tr>
<td>Narcotics</td>
<td>1.98 (1.44, 2.73)</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>1.23 (0.97, 1.57)</td>
</tr>
</tbody>
</table>

Lichtenstein GR. Am J Gastroenterol 2012;107:1409-22

## Cancer Risk

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lymphoma</th>
<th>NMSC</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurines</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Combination</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
</tr>
</tbody>
</table>

Mason M. Inflamm Bowel Dis 2013, in press
Jean-Paul Achkar, MD, FACG

Cancer Risk with Anti-TNFs- RA Studies

Lopez-Olivo MA et al. JAMA 2012;308:898-908

36 cases of HSTCL in IBD from 1996 to 5/2010

- **Demographics:**
  - Age 12-58 yo; Median = 22.5
  - 29 males, 2 females; 5 unknown
  - 26 Crohn’s, 9 UC, 1 IC

- **Medical tx:**
  - 20 infliximab + thiopurine- median time to onset = 5.5 years (1–13.5 yrs):
    - 4 also got adalimumab
    - 1 also got adalimumab and natalizumab
  - 16 thiopurine alone- median time to onset = 6 years (3-17 yrs)

Kotlyar DS. Clin Gastro Hep 2011;9:36-41
Practical Approach: Take Home Points

- Tailor therapy in Crohn’s depending on severity of initial disease - objective markers of inflammation
- Use of anti-TNF agents early in disease course is associated with higher response rates
- Top-Down approach associated with better outcomes
- For immunosuppressive naïve patients, combination of infliximab & azathioprine is best for induction of remission & mucosal healing over 1 year
- Risk/Benefit considerations - most risks uncommon