Debate:
Initiation of maintenance treatment in moderate to severe Crohn’s disease: Immunomodulators vs biologic agents

The case for immunomodulators

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Disclosures

• In the past 12 months, I have served as a consultant with the following manufacturers of commercial product(s) discussed in this CME activity:
  – Janssen Pharmaceuticals (consulting fee)
  – UCB (consulting fee)
  – Abbvie (consulting fee)

• I will be discussing an unapproved use of a commercial product in my presentation.

The Biologic Tsunami

Do Thiopurines Maintain Remission?

Pediatrics

Adults


Do Thiopurines Maintain Remission?


Adult Study Population

<table>
<thead>
<tr>
<th>N</th>
<th>27</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>13.0 ± 2.3</td>
<td>13.4 ± 2.5</td>
</tr>
<tr>
<td>% male</td>
<td>55%</td>
<td>64%</td>
</tr>
<tr>
<td>% ileocoeitis</td>
<td>70%</td>
<td>79%</td>
</tr>
<tr>
<td>% current smokers</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Mean PCDAI</td>
<td>46.7 ± 13.9</td>
<td>44.7 ± 16.4</td>
</tr>
<tr>
<td>% PCDAI ≥30</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>% on steroids</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Azathioprine Efficacy in Peds CD: Paris**

- Single pediatric IBD center
- AZA monotherapy ≥ 2 yrs f/u
- Indications for AZA
  - At Dx or 1st relapse
  - PCDAI >30
  - Severe/extensive mucosal lesions
  - Steroid or EN dependent
  - Post-resection (n=10)

Remission rates

- No risk factor predicted response except surgery as remission induction
- Few relapses after 12 months in those in remission at 1 yr

Riels R, et al. IBD 2011;17:2138-43

**HOW ABOUT METHOTREXATE?**

**Methotrexate Use as First Line Immunomodulator is Increasing in CD**

Data from the Pediatric IBD Collaborative Research Group Registry

22/81 (27%) receiving MTX as first IM experienced >1yr sustained steroids, thiopurine, surgery, and anti-TNF free remission

Sunseri W. Inflamm Bowel Dis 2014;20:1341–1345

**Methotrexate in Pediatric CD**

<table>
<thead>
<tr>
<th>Retrospective studies</th>
<th>Location</th>
<th>Steroid Free Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective studies</td>
<td>Location</td>
<td>Steroid Free Remission 6 months</td>
</tr>
<tr>
<td>Wilott S, et al. Inflamm Bowel Dis 2011;17:2521–6</td>
<td>Canada</td>
<td>37%</td>
</tr>
</tbody>
</table>

**ANTI-TNF EFFICACY**

**REACH**

Pediatric Infliximab Trial

<table>
<thead>
<tr>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 10</td>
</tr>
<tr>
<td>Response</td>
</tr>
<tr>
<td>a = 1.95</td>
</tr>
<tr>
<td>88</td>
</tr>
<tr>
<td>64</td>
</tr>
<tr>
<td>33</td>
</tr>
</tbody>
</table>

*Reduction from baseline of ≥ 15 points in PCDAI score and a PCDAI score ≤ 30.
†PCDAI score ≤ 10.

Hyams et al. Gastroenterology 2007;132:863-873
Mucosal Healing with CD Monotherapy

Single-center adult CD trial 2007-2009 N=51
Inclusions:
- Previously identifiable ulcerations on ileocolonoscopy
- Clinical remission for at least 3 months on monotherapy

No difference in histologic inflammation score among the three different therapies


IMagINE 1: Adalimumab in Peds CD

Remission: 26 wks
Remission: 52 wks

Hyams J, et al Gastro 2012;143:365-74

Long-Term Evolution of Disease Behavior in CD

Children: 88% inflammatory at Dx
70% inflammatory at 32 mos.

Paris, France
- 230 adults
  - 42 on 6MP/AZA
- All B1 at inclusion
- At 5 yrs
  - All subj: B1 → B2 = 10%
  - B1 → B3 = 26%
  - 6MP/AZA: B1 → B2 = 10%
  - B1 → B3 = 17%


Olmsted County, MN, USA
- 248 adults
  - 22 on 6MP/AZA
- All B1 at study inception
- 6MP/AZA associated with nonsignificant decrease in risk for B2 or B3
  - OR 0.87 (0.31-2.40), p=0.78

Cousens J, et al. IBD 2002;8:244-50
This KT, et al. Gastroenterol; 2010;139:1147-55

Effect of Thiopurine Rx on Change in CD Behavior

Patients at risk N = 2002 552 229 95 37

Paris, France
- 230 adults
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Cousens J, et al. IBD 2002;8:244-50
This KT, et al. Gastroenterol; 2010;139:1147-55

Do immunomodulators result in mucosal healing?

Do immunomodulators affect the progressive change in CD behavior?
Evolution of Pediatric CD Behavior: PIBDCRG

- Data extracted from a larger study evaluating serologic and genetic predictors of complicated pediatric CD
- All subjects with uncomplicated inflammatory (B1) CD behavior at diagnosis

Mean Age @ Dx (yrs) 11.5 ± 2.6
Gender (% male) 65%
Duration of F/U (yrs) 5.2 ± 1.7

CD Phenotype at last f/u
B1 91
B2 6
B3 8
Perianal penetrating 11

13/14 within 5 yrs of Dx

DO THIOPURINES AFFECT THE RATE OF SURGERY?

Thiopurines Decrease Risk of Surgery in Crohn’s Disease

<table>
<thead>
<tr>
<th>Location</th>
<th>Years of study</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramadas AV, et al.</td>
<td>1986-2003</td>
<td>Thiopurine use in the 1st year of dx: OR 0.47 (0.27-0.79; p=0.005)</td>
</tr>
<tr>
<td>Picco MF, et al. Am J Gastro 2009;104:2754-9</td>
<td>1994-2005</td>
<td>Immunomodulator use (&gt; 6 mos): HR 0.41 (0.21-0.81; p=0.011)</td>
</tr>
<tr>
<td>Lakatos I, et al. Am J Gastro 2012; 107:279-88</td>
<td>1997-2009</td>
<td>Aza started within 1.5 yrs of dx: HR 0.48 (0.18-0.83; p=0.023)</td>
</tr>
<tr>
<td>Vernier-Massouille et al. Gastro 2008;132:1108</td>
<td>1988-2002</td>
<td>Azathioprine use: HR 0.61 (0.33-0.78; p=0.001)</td>
</tr>
</tbody>
</table>

Treatments: Complicated vs Inflammatory CD

<table>
<thead>
<tr>
<th>Treatments (n=68)</th>
<th>Corticosteroids</th>
<th>Immunomodulators</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1*</td>
<td>46/55 (84%)</td>
<td>45/55 (89%)</td>
<td>24/55 (44%)</td>
</tr>
<tr>
<td>B2+B3*</td>
<td>12/13 (93%)</td>
<td>7/13 (54%)</td>
<td>2/13 (15%)</td>
</tr>
</tbody>
</table>

P Value
0.6734
0.0077
0.1100

^ Treatments prescribed at any time during the first 5 years of f/u
* Treatments prescribed prior to the development of B2 or B3

Markowitz J et al, DDW 2011

Immunosuppressive Rx Does Not Decrease the Rate of Intestinal Resection

- Among all 5 cohorts, 190 subjects required resection
- Duration of pre-op immunosuppression
  - N = 80 → none
  - N = 92 → less than 3 months
  - N = 16 (9%) → at least 3 months

Cumulative 5 yr risk of receiving IS ranged from 0.13 – 0.56 (p<0.001)
Cumulative risk of intestinal resection at 5 yrs unchanged (0.34 – 0.36 in each cohort)

- Among all 5 cohorts, 190 subjects required resection
- Duration of pre-op immunosuppression
  - N = 80 → none
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Thiopurines Decrease Risk of Surgery in Crohn’s Disease

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- Duration of pre-op immunosuppression
  - N = 80 → none
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  - N = 16 (9%) → at least 3 months

Surgery in Pediatric CD: Effect of Thiopurines

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<tr>
<th>Location</th>
<th>Years of study</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vernier-Massouille</td>
<td>2008-2010</td>
<td>HR 0.51 (0.33-0.78; p=0.005)</td>
</tr>
<tr>
<td>Gupta N</td>
<td>2006-2010</td>
<td>HR 0.8 (0.4-1.4; p=NS)</td>
</tr>
<tr>
<td>Schaeffer M et al.</td>
<td>2010-2015</td>
<td>HR 0.47 (0.27-0.79; p=0.005)</td>
</tr>
</tbody>
</table>

Gupta N, et al. Gastroenterol 2006;130:3089–3077
THIOPURINES AND GROWTH

Growth is Not Improved after Thiopurine Therapy

North American Registry (PIBDCRG) 2009
- N = 176
- Started 6MP/AZA by:
  - 3 months = 49%
  - 1 year = 60%
  - 2 years = 86%
- Compared to baseline, growth velocity not improved at 1 or 2 years after Dx

Glasgow, Scotland 2012
- N = 116
- Started 6MP/AZA by:
  - "early" = 12%
  - 1 year = 43%
- Slight improvement in height velocity at 2 and 3 years
- Multivariate regression analysis: negative association between height Z-score and azathioprine use

Effect of Immunomodulators on Natural History of CD

Corticosteroid free maintenance +++
Change from B1 → B2 or B3 +
Decrease risk of 1st surgery ++
Improve growth 0

WHAT ABOUT TOXICITY?

Immunomodulator Toxicity

Thiopurines
- Leukopenia (3.8%), severe (1.2%)
- Severe infection (<1%) - sepsis, varicella
- Pancreatitis (<5%)
- Abnormal LFT (7-15%)
- Intolerance (nausea, vomiting, diarrhea)
- Malignancy

Methotrexate
- TERATOGENICITY: Pregnancy Class X
- Pneumonitis/pulmonary fibrosis
- Severe hepatotoxicity
- Intolerance (nausea, vomiting, diarrhea)
- Photosensitivity

Potential Adverse Effects of Infliximab

- Hypersensitivity reactions
  - Acute
  - Delayed/Serum sickness
- Immunogenicity
- Headache
- Rash

- Infections
- Demyelinating disorders
- Autoantibodies
- SLE-like
- Pancytopenia
- Hepatotoxicity
- Heart Failure
- Malignancy
**Systematic Review: Infection and Lymphoma in Pediatric IBD**

<table>
<thead>
<tr>
<th>Infection Risk</th>
<th>Pediatric anti-TNF/10,000 PYF</th>
<th>Thiopurine/10,000 PYF</th>
<th>Corticosteroids/10,000PYF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infection</td>
<td>352</td>
<td>333</td>
<td>730</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphoma Risk</th>
<th>Pediatric anti-TNF/10,000 PYF</th>
<th>SEER/10,000 PYF</th>
<th>Thiopurine/Adult anti-TNF/10,000 PYF</th>
<th>SEER/10,000 PYF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid neoplasia</td>
<td>2.1</td>
<td>0.58</td>
<td>4.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>1.05</td>
<td>0.12</td>
<td>2.25</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>1.05</td>
<td>0.40</td>
<td>2.25</td>
<td>6.1</td>
</tr>
</tbody>
</table>

All comparisons not significant


**Skin Cancer and IBD Therapy**

Skin Cancer and IBD Therapy

Table 2: Impact of medications on skin cancer risk among inflammatory bowel disease patients.

<table>
<thead>
<tr>
<th>Medication</th>
<th>NMSC</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Etanercept</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcium inhibitor</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Biological</td>
<td>(CD)</td>
<td>(CD)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>(CD)</td>
<td>(CD)</td>
</tr>
<tr>
<td>NMSC, non-melanoma skin cancer; CD, Crohn’s disease.</td>
<td>* Trazonid or cyclosporine.</td>
<td>* Inflixim or adalimumab.</td>
</tr>
</tbody>
</table>


**Overall Durability of IFX**

Grossi V, et al. DDW 2014

**Thiopurines and Hepatosplenic T-Cell Lymphoma in IBD: No Anti-TNF Therapy**

<table>
<thead>
<tr>
<th>N</th>
<th>16 (9 CD, 7 UC/IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr: Median (Range)</td>
<td>22.5 (15-35)</td>
</tr>
<tr>
<td>% male</td>
<td>62.5% (31.5% ??)</td>
</tr>
<tr>
<td>Duration TP Rx, yr: Median (Range)</td>
<td>6 (3-17)</td>
</tr>
</tbody>
</table>


Risk Estimates for HSTCL with Thiopurine But No Anti-TNF

- All patients on thiopurine Rx: 1.4/10,000 pt-yrs
- All males <35 yrs on thiopurine: 145,000
- 1.7404

**Increased Effectiveness of Early Therapy With Anti–Tumor Necrosis Factor-α vs an Immunomodulator in Children With Crohn’s Disease**

- Triads matched to clinical characteristics of the children treated with infliximab monotherapy in first 3 months after dx
  - Disease activity by PCDAI
  - Age at dx
  - Linear growth
  - Perianal disease
  - Deep ulceration on initial colonoscopy
  - CD location
  - Laboratory studies
  - Propensity score analysis


**Effect of Concomitant IM Use on IFX Durability**

Grossi V, et al. DDW 2014

Data from the Pediatric IBD Collaborative Research Group Registry
Effect of Thiopurines versus Methotrexate on IFX Durability

- No IM while on IFX/IM + IFX for ≤ 3 mos
- IM at IFX start for ≥ 6 mos

Grossi V, et al. DDW 2014

We need to risk stratify our CD patients

- Children with characteristics of severe disease do best with early infliximab therapy (but not all children have severe CD)
- Immunomodulator efficacy ~40-60% over 18 months with relatively stable long term maintenance benefit after 2 years
- Anti-TNF efficacy 50-85% over 12 months, but with progressive loss of durability over time for monotherapy
- Benefit of combination therapy (IM + biologic) greatest if IM therapy >3-6 months at initiation of anti-TNF
- Start maintenance with an immunomodulator!!
  - ?Gender specific? → MTX: ♂, 6-MP/AZA: ♀