Pros and Cons of Combination Therapy (Anti-TNF + IM) in Treating Children with IBD

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Disclosures

• Janssen: consultant, Advisory Board, research support
• Abbvie: Advisory Board, consultant
• Celgene: consultant
• Takeda: consultant
• Receptos: consultant
• UCB: consultant
• Boehringer-Ingelheim: consultant
• Allergan: consultant
• Lilly: consultant
• Astra Zeneca: consultant
• Genentech: consultant
How best can we now treat pediatric IBD recognizing that to change the natural history we need to intervene early
Timing is Important: Earlier is Better

Colombel et al. Gastroenterology 2017;152:351
How Do We Treat Today

• It is time to STOP using the term “conventional therapy” to mean CS, 5ASA, IM, EEN

• Anti-TNF agents are used in up to 60% of children with Crohn’s disease and 25% of those with ulcerative colitis within 2 years of diagnosis

• Biologic therapy is NOT unconventional
Biologic Therapy: Opportunities and Problems

- Primary non-response in only minority of patients
- Many patients with an initial response to anti-TNF therapy experience secondary LOR requiring dose escalation or a switch to another TNF antagonist
- Loss of clinical benefit can be due to increased clearance of the drug in the presence or absence of antibodies to infliximab (ATI)
- Serum infliximab trough concentrations correlate with clinical response, clinical remission, and mucosal healing in patients with IBD
Non-drug Factors Influencing Anti-TNF Clearance

<table>
<thead>
<tr>
<th>Factor</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>High body mass may increase clearance</td>
</tr>
<tr>
<td>Gender</td>
<td>Increased clearance in men</td>
</tr>
<tr>
<td>High baseline TNFα, CRP</td>
<td>Increased clearance</td>
</tr>
<tr>
<td>Low albumin</td>
<td>Increased clearance</td>
</tr>
<tr>
<td>Age</td>
<td>Older age with slower clearance</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Decreases clearance; may downregulate Fc-γ receptor expression on monocytes; reduce antibody formation</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>Reduce antibody formation</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>May reduce antibody formation</td>
</tr>
</tbody>
</table>

Optimizing Anti-TNF-α Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases

Bella Ungar, Idan Levy, Yarden Yavne, Miri Yavzori, Orit Picard, Ella Fudim, Ronen Loebstein, Yehuda Chowers, Rami Eliakim, Uri Kopylov, Shomron Ben-Horin

Clinical Gastroenterology and Hepatology
2016;14:550-557
Higher levels are required for mucosal healing compared to symptom improvement
What Does That Really Mean?

• You need to do this correctly whether you choose monotherapy or combination therapy and that means ensuring good drug levels
• Choose your drugs wisely
• Mitigate risk no matter what the strategy
MONOTHERAPY VS. COMBINATION THERAPY
Questions

- By what mechanisms might combination therapy be superior to monotherapy?
- How long is combination therapy needed?
- Can an IM be added after starting monotherapy if there is LOR?
- Does it matter if the IM is a thiopurine (TP) or methotrexate (MTX)?
- Can I achieve similar results with TDM with monotherapy?
- What are the safety concerns with combination therapy, and are they different with TP vs. MTX?
Why Might Combination Therapy Be Better?

• If patient both IM and bio naïve then you may have intrinsic anti-inflammatory effects of each therapy

• Or you may have better trough levels and less antibody with combination
Azathioprine, Infliximab or Combination Therapy for Crohn’s Disease (SONIC) in IM and Biologic Naïve Patients
Corticosteroid-Free Clinical Remission at Wk 50

All randomized patients (N=508)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>24.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>34.9</td>
<td>p=0.028</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>46.2</td>
<td>p=0.035</td>
</tr>
</tbody>
</table>

41/170 14% ATI Mean 1.6 ug/ml
59/169 1% ATI Mean 3.5 ug/ml
78/169

* Patients who did not enter the Study Extension were treated as non-responders


Drug levels and ATI at 30 weeks
No difference in ITT analysis, duration of disease <2 years, by CDAI score

No difference in infectious adverse events (58.7% MTX vs 61.9% PBO)

Patients pre-treated with CS before infusions
The COMMIT trial: PK data

- MTX + IFX ATI in 4% vs 20% for IFX monotherapy (p < 0.01)
- IFX level 6.35 ug/ml vs 3.75 in IFX monotherapy (p =0.08)
- 92% of patients with detectable IFX trough were a treatment success.

But what if IM experienced prior to anti-TNF
Do Concomitant Immunomodulators Improve Efficacy of Infliximab in CD and UC?

Withdrawal of Concomitant IMM in Crohn’s disease while on Infliximab (failure of IMM before IFX)

No need for early ‘rescue’ IFX: primary endpoint

Log Rank (Cox): 0735; Breslow: 0.906

Median IFX levels, Week 8 to Week 104 combined

IFX trough levels (μg)

Higher CRP in DIS vs. CON

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>AZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFX levels (median + IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max IFX</td>
<td>6.15 μg/mL (3–11.6)</td>
<td>5.65 μg/mL† (2.87–10.8)</td>
</tr>
<tr>
<td></td>
<td>33.4 μg/mL</td>
<td>31 μg/mL</td>
</tr>
</tbody>
</table>

\[^p=0.065\]
How Long Do You Need to Use the Immunomodulator
Concomitant Use of Immunomodulators Affects the Durability of Infliximab Therapy in Children with Crohn’s Disease

Table 1. Clinical and demographic features of study population (n=502)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients N=502</th>
<th>No IM while on IFX N=135*</th>
<th>IM at IFX start for ≤6 months N=144*</th>
<th>IM at IFX start for &gt;6 months N=194*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male)</td>
<td>278 (59%)</td>
<td>77 (57%)</td>
<td>83 (58%)</td>
<td>118 (61%)</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>11.8 ± 2.7</td>
<td>11.8 ± 2.9</td>
<td>11.9 ± 2.7</td>
<td>11.8 ± 2.4</td>
</tr>
<tr>
<td>Range</td>
<td>1-16</td>
<td>3-16</td>
<td>1-16</td>
<td>4-16</td>
</tr>
<tr>
<td>Disease distribution at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel only</td>
<td>41 (8%)</td>
<td>9 (7%)</td>
<td>14 (10%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>Large bowel only</td>
<td>120 (24%)</td>
<td>31 (23%)</td>
<td>32 (22%)</td>
<td>48 (25%)</td>
</tr>
<tr>
<td>Both small and large bowel</td>
<td>339 (68%)</td>
<td>95 (74%)</td>
<td>98 (68%)</td>
<td>129 (67%)</td>
</tr>
<tr>
<td>Mean age at 1st IFX infusion (years)</td>
<td>13.3 ± 2.8</td>
<td>13.1 ± 3.1</td>
<td>13.4 ± 2.8</td>
<td>13.3 ± 2.6</td>
</tr>
<tr>
<td>Range</td>
<td>1-22</td>
<td>3-21</td>
<td>1-21</td>
<td>5-19</td>
</tr>
<tr>
<td>Median follow-up from 1st IFX infusion (months)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>33</td>
<td>27</td>
<td>27</td>
<td>42</td>
</tr>
<tr>
<td>Time from diagnosis to 1st IFX infusion**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 months</td>
<td>138 (27%)</td>
<td>63 (47%)</td>
<td>31 (22%)</td>
<td>31 (16%)</td>
</tr>
<tr>
<td>3-6 months</td>
<td>60 (12%)</td>
<td>6 (4%)</td>
<td>21 (15%)</td>
<td>29 (15%)</td>
</tr>
<tr>
<td>6-12 months</td>
<td>81 (16%)</td>
<td>10 (7%)</td>
<td>31 (22%)</td>
<td>39 (20%)</td>
</tr>
<tr>
<td>12-24 months</td>
<td>104 (21%)</td>
<td>24 (18%)</td>
<td>26 (18%)</td>
<td>52 (27%)</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>119 (24%)</td>
<td>32 (24%)</td>
<td>35 (24%)</td>
<td>43 (22%)</td>
</tr>
</tbody>
</table>

Concomitant Immunomodulator Improves Durability

Can an Immunomodulator be added after starting monotherapy if there is loss of response?
Addition of an Immunomodulator to Infliximab Therapy Eliminates Antidrug Antibodies in Serum and Restores Clinical Response of Patients With Inflammatory Bowel Disease

Ben-Horin et al.
CGH 2013;11:444
Open circles represent ATI
Closed circle represents IFX

More likely to be successful with lower titer ATI
Thiopurine or Methotrexate

Most IBD data on combination therapy is with thiopurines
Most RA data on combination therapy is with methotrexate
A Multicenter, Randomized, Double-Blind Clinical Trial of Combination Therapy With Adalimumab Plus Methotrexate Versus Methotrexate Alone or Adalimumab Alone in Patients With Early, Aggressive Rheumatoid Arthritis Who Had Not Had Previous Methotrexate Treatment: The PREMIER Study

Breedveld et al. Arthritis & Rheumatism 2006;54:26
Mean change from baseline in total Sharp scores over time, by treatment group. $P < 0.001$ versus adalimumab alone and versus methotrexate (MTX) alone; § $P < 0.001$ versus MTX alone; $P < 0.002$ versus adalimumab alone and $P < 0.001$ versus MTX alone.

Breedveld et al. Arthritis & Rheumatism 2006;54:26
Methotrexate vs. Thiopurines in Pediatric Crohn’s Disease

What if you don’t want to use combination therapy?

- **Standard of care dosing frequently does not result in optimal dosing schedules** (may be why real life experience is superior to clinical trials)
- You need to check drug levels to optimize likelihood of durability
- Dashboard management
PK Dashboard Optimizing Induction of Infliximab

Input: age, gender, weight, albumin, disease activity, previous dosing, levels, etc.

Courtesy of Marla Dubinsky, MD
Key Principles With Anti-TNF Therapy

• **Exposure** – response relationship repeatedly shown in all studies of anti-TNF therapy

• **Adequate levels associated with better response/remission, durability**

• **Inadequate levels associated with poorer response/remission, durability**

• **Recognize these factors in your therapeutic plan**

• **Check levels/ATI when feasible**
Managing Risk
Angst often persists with our therapeutic decisions

Why? We want the best therapy with managed risk. We are very averse to complications.
FEAR!

It is all about cancer.
Risk of Malignancy With Thiopurines

• Azathioprine is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.
• First listed in the Fourth Annual Report on Carcinogens (1985), still there in the 13th
• Listed between asbestos and benzene

http://ntp.niehs.nih.gov/go/roc12
Multiple Mechanisms of Carcinogenesis With Thiopurines

- DNA damage
- Decreased immunosurveillance (TP are cytotoxic for NK and cytotoxic T cells which restrict proliferation of EBV infected and immortalized B cells)
- Emergence of oncogenic viruses (EBV)
- Promotes the incorporation of 6-TG into DNA of dividing stem cells of the skin (keratinocytes) during replication. Incident UVA light penetrates to the stem cell layers and in the presence of molecular oxygen, generates ROS within DNA itself. These ROS can oxidize DNA 6-TG contributing to mutagenic processes. The accelerated accumulation of these photodynamic mutations in skin cells contributes to the development of skin cancer.

Cytogenetic Analysis of case 14. 18 yr old male, azathioprine only. Three cytogenetic analyses were performed. The first analysis showed trisomy 13 in one cell. The second analysis showed a possible deletion of chromosome 17 in three cells. The third (shown) reveals 42-45, X, del Y, isochromosome 7q (10), del(7)(q22), der(9)t(8;9)(q13;p22), add(11)(q23) in 5 of 39 cells (13%).

Kotlyar et al. Am J Gastroenterol 2010;105:2299
Increased Malignancy Risk with Adalimumab Combination Therapy Compared to Monotherapy

Pooled data from ADA RCT 1594 pts/3050 pt years. Compared to SEER

No increased risk vs. SEER for ADA monotherapy for NMSC or any malignancy

ADA + IM 3x increased risk for malignancy other than NMSC
ADA + IM 5X increased risk for NMSC
ADA + IM 8X increased risk compared to SEER for lymphoma

Figure 1. (A) Risk of malignancies excluding NMSC with adalimumab (ADA) monotherapy or combination therapy compared with the general population. (B) Risk of NMSC with ADA monotherapy or combination therapy compared with the general population. IMM, immunomodulator.

Osterman et al. Gastroenterology 2014:146:941
Adjusted Risk of Lymphoma: Hazard Ratio Per Years of Exposure

United States Veteran Affairs Health System: 36,891 pts with UC, 88%>40yr, 93% male, 76% white

Khan et al. Gastroenterology 2013;145:1007
Duration of Thiopurine Exposure In Relation to Development of HSTCL

≥2 yrs of exposure in most but even less possible

Caution:

Not the same

Pediatric patients

Adult patients
What About Methotrexate?

• Little IBD data

• Adult psoriasis: Conflicting
  - 2x risk of SCC in adults with ≥4 yr exposure or total dose ≥3g vs. no mtx\(^1\)
  - 4x risk of lymphoma following high dose mtx\(^2\)
  - No increase risk of SCC or lymphoma\(^3\)

• Adult Rheumatoid arthritis: Conflicting

• Largest experience is with the CORRONA observational registry of adults with RA; 27, 654 subjects; 6806 eligible for propensity scoring to match characteristics; 179 cancers; Compared risk with mtx, biologics, and nbDMARDs. No clear signal

\(^1\) Cancer 1994;73:2759, \(^2\) Arch Dermatol 2006;142:1132, \(^3\) J Invest Dermatol 2000;114:587
Rheumatoid Arthritis

- National Data Bank for Rheumatic Diseases
- Longitudinal study, 1998-2005
- 89,710 patient years of follow-up
- Overall lymphoma rate was 106/100,000 person-years, SIR 1.8 (CI 1.5-2.2) compared to SEER
- OR for lymphoma in anti-TNF exposed vs. unexposed was 1.0 (CI 0.6-1.8)
- OR for those who received anti-TNF + MTX vs. MTX only was 1.1 (CI 0.6 to 2.0)
- No increased risk for lymphoma with infliximab alone
- Virtually identical data from Swedish Cancer Registry

Infliximab not Associated With Increased Risk of Malignancy or Hemophagocytic Lymphohistiocytosis in Pediatric Patients With Inflammatory Bowel Disease


Gastroenterology 2017
A

B

Hyams et al. Gastroenterology 2017
Results: Pooled Unadjusted Incidence Rates Stratified by Thiopurine Exposure

<table>
<thead>
<tr>
<th></th>
<th>Thiopurine exposed ±Biologics</th>
<th>Thiopurine non-exposed ±Biologics</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients, N</td>
<td>3814</td>
<td>1877</td>
<td>5691</td>
</tr>
<tr>
<td>Total PY F/U</td>
<td>16646.4</td>
<td>6990.8</td>
<td>23637.2</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>events/1000 PY, [n]</td>
<td>0.72 [12]</td>
<td>0.29 [2]</td>
<td>0.59 [14]</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.37, 1.26</td>
<td>0.04, 1.03</td>
<td>0.32, 0.99</td>
</tr>
<tr>
<td>HLH</td>
<td>0.20 [5]</td>
<td>0[0]</td>
<td>0.21 [5]</td>
</tr>
<tr>
<td>events/1000 PY [n]</td>
<td>0.09, 0.70</td>
<td>0.00,0.43</td>
<td>0.07, 0.49</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Stratification of entire study population by thiopurine exposure demonstrated an increased but statistically not significant risk of malignancy and HLH in thiopurine-exposed patients compared to thiopurine non-exposed patients

• Similar results when cohorts/study population were stratified by methotrexate exposure

Hyams et al. Gastroenterology 2017
Addendum

• Since submission for publication (June 2016) 2 additional cases of malignancy have occurred in the DEVELOP cohort
• 8 year old male in Germany with a 5 year history of UC whose medication exposures included 5-ASAs, corticosteroids, and azathioprine (3 years). No biologic exposure. Patient died 5 months
• 19 year old male in the USA with a 5 year history of UC whose medication exposures included 5-ASAs, antibiotics, corticosteroids, and 6-mercaptopurine (5 years). No biologic exposure. Patient still alive.
Hemophagocytic Lymphohistiocytosis (HLH) or Macrophage Activation Syndrome

- Rare, deadly and potentially reversible disorder of cellular immunity characterized by phagocytosis of bone marrow elements by inappropriately activated macrophages
- May be primary/congenital defect or associated with immunosuppression (CS, thiopurines, anti-TNF)
- CMV, EBV infections described in IBD patients

1 James et al. IBD 2006;12:573
## Results: HLH Cases (n=5)

<table>
<thead>
<tr>
<th>Age, Gender, IBD dx</th>
<th>Duration of IBD prior to HLH dx (y)</th>
<th>Duration of IBD therapy prior to HLH dx (y)</th>
<th>Infectious Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IFX</td>
<td>ADA</td>
</tr>
<tr>
<td>16 y F CD</td>
<td>1.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16 y M CD</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16 y F CD</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15 y F CD</td>
<td>1.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>19 y M CD</td>
<td>7.0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All patients received corticosteroids and/or 5-ASAs, and were not exposed to any other biologic therapies

*This patient was also diagnosed with B-cell lymphoma

** Unknown if primary infection or reactivation of CMV

Hyams J., et al. Gastroenterology 2017
Mono vs. Combo Therapy of TNF-inhibitors in IBD: Benefit vs. Risk

**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 in naïve patients
- Reduces rates of antibody formation
- Results in higher blood concentrations of the biologic
- Increased risk of malignancy with thiopurines

USE THE RIGHT DOSE OF YOUR ANTI-TNF AGENT AND MONITOR LEVELS AND ANTIBODY FORMATION
And so Dr. Jones,
When you started anti-TNF therapy in this teenage boy who had been on 6MP for 4 years and then continued the 6MP for 2 more years what were you thinking?
Risk of Lymphoma With Combination Therapy with Anti-TNF and Thiopurine

• Is it the combination or is it the thiopurine that is causing the problem?
• Ideal comparison groups are not easily identified
Lymphoma Associated with Combination Therapy

26 studies, 8905 patients, 21,178 pt years
Majority of anti-TNF pts with previous IM exposure

Anti-TNF vs. SEER  SIR 3.23 (95% CI 1.5-6.9)

For ages 20-54, SIR for NHL for males was 5.4 (95% CI 1.3-18.1)
For females SIR was 3.8 (95% CI 0.7-15.9)

HSTCL: The 900 lb gorilla in the room
<table>
<thead>
<tr>
<th>Medication Category</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurines</td>
<td>46</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>8</td>
</tr>
<tr>
<td>Adalimumab + Natalizumab</td>
<td>2</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>1</td>
</tr>
</tbody>
</table>

**Note:** Medication categories are not mutually exclusive