Efficacy and Safety of Treatment for Pediatric IBD

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Objectives

• Review standard therapies for pediatric inflammatory bowel disease

• Discuss rationale for “top-down” treatment algorithm

• Review safety information for current therapies

• Preview anticipated therapies
Treatment of Pediatric IBD

Goals

• Improve growth and nutrition
• Improve quality of life
• Maximize therapeutic response
• Minimize toxicity
• Prevent disease complications
• Mucosal healing
• Promote psychological health
Pediatric IBD “Step-Up” Algorithm

Surgery

Remicade/Humira

Prednisone  6-MP/Imuran
Steroids  Methotrexate
Budesonide  Enteral Nutrition

Antibiotics  Aminosalicylates  Probiotics
Aminosalicylates (5-ASA)

- Locally reduce inflammation in the bowel
- First-line therapy for UC
  - Questionable efficacy for Crohn’s
- Chemoprotective effect?
- Well tolerated
  - Headaches, GI complaints most common
  - 3-5% with allergy to medicine
5-ASA Delivery Systems

- PENTASA
- ASACOL/LIALDA/APRISO
- COLAZAL/AZULFIDINE/DIPENTUM
- ENEMA

Locations:
- JEJUNUM / ILEUM / ASCENDING / DESCENDING / SIGMOID / RECTUM
- SMALL BOWEL
- COLON
- SUPP
Efficacy of 5-ASA’s

Ulcerative Colitis

• Oral therapy effective for induction and maintenance of remission
• Rectal, oral + rectal → More effective than just oral for distal disease

Crohn’s disease

• Efficacy unclear for induction or maintenance of remission
Antibiotics

• Decrease inflammation by changing or eliminating bacteria in GI tract

• Multiple indications for Crohn’s
  – Perianal disease
  – Abscess
  – Prevent post-operative recurrence
  – Treatment of mild or moderate disease

• Not proven effective for UC

Flagyl (metronidazole)

Cipro (ciprofloxacin)
Probiotics

• Live microorganisms → Alter flora of gut

• Promote more favorable bacteria
  – ↓ inflammation

• Many different preparations

• UC → Effective, particularly for pouchitis

• Crohn’s → Not proven effective
Systemic Corticosteroids

- Oral (prednisone), IV (Solumedrol), or rectal
- Suppress active inflammation
- Indication: Acute UC or Crohn’s flare
- Provide immediate symptomatic relief
  - Do not promote healing of GI tract
- **Not** indicated for maintenance therapy
  - Lose efficacy, side effects
Corticosteroids

Common Side Effects

• Growth retardation
• Contribution to ↓ bone mineral density
• Excessive weight gain
• Cosmetic
  – Acne, moon facies, hirsutism
• Psychological
  – Sleep disturbance, mood instability
• Increased risk of infection
**Budesonide**

**UCERIS** *(budesonide)*

UCERIS is not indicated for Crohn’s disease; it is indicated for the induction of remission in patients with active, mild to moderate UC

**TARGET:**
Full length of colon

**MMX® technology:**
Pill dissolves at pH ≥7.0, the approximate pH level near the entry to the colon

**Dosage:** 9-mg tablet QD

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**Entocort® EC** *(budesonide)*

Entocort® EC is not indicated for UC; it is indicated for the treatment of active, mild to moderate Crohn’s disease involving the ileum and/or ascending colon

**TARGET:**
Ileum/ascending colon

**Controlled ileal release:**
Pill dissolves at pH >5.5, the approximate pH level of the duodenum

**Dosage:** 3 mg x 3 capsules QD
Immunomodulators

- Suppress immune response that triggers intestinal damage in IBD
- Good maintenance medications
- Steroid sparing effects
- Require longer period of time for efficacy

No live vaccines

Imuran (azathioprine)

Purinethol (6-MP)

Methotrexate
6-MP/Imuran

• Oral medication administered every night
• Requires 3-4 months for maximal efficacy
• Effective for Crohn’s Disease and UC
  – Maintenance of remission
  – Decrease in steroid requirements
  – Perianal disease
  – Prevention/treatment of post-operative recurrence
Imuran (AZA) and 6-MP Metabolism

AZA → 6-MP → 6-thiouric acid → 6-TGN

TPMT
- 89% have normal activity
- 11% have intermediate activity
- 0.3% have low activity
Methotrexate

• Better studied in Crohn’s disease
  – May improve growth, perianal disease

• Administered once weekly
  – Subcutaneous injection vs. oral

• Laboratory monitoring required

• Requires 6-8 weeks for efficacy
  – Faster onset of action compared to 6-MP
  – Does not require monitoring of metabolites
6-MP/AZA and MTX Adverse Effects

**6-MP/AZA**
- Nausea
- ↓ white blood cell count
- Liver toxicity
- Pancreatitis
- Increased infection risk
- Increased skin cancer risk
- Slightly increased lymphoma risk

**Methotrexate**
- Nausea
- ↓ white blood cell count
- Liver toxicity
- Poor appetite
- Increased infection risk
- Reaction at injection site
- No documented increased cancer risk
- Teratogenic
Enteral Nutritional Therapy

TO BE DISCUSSED LATER!
Biologic Therapies

- Pro-inflammatory cytokines contribute to inflammation in IBD
  - TNFα is elevated in IBD patients

- Biologics block and neutralize cytokines

- Used to treat moderate to severe Crohn’s disease and ulcerative colitis
Humanization of Anti-TNF agents

Adapted from Rutgeerts Gastro 2009;136:1182
Remicade (infliximab)  
Humira (adalimumab)

• Moderate to severe Crohn’s disease
  – Decreases steroid requirement
  – Mucosal healing
  – Healing of perianal disease
  – Improvement of growth
  – Bone health
  – Prevention of post-operative recurrence

• Ulcerative colitis
  – Treatment of moderate to severe disease
  – Prevention of surgery
Improved Growth with Infliximab

Anti-TNF α Therapy

**Remicade (infliximab)**
- Intravenous infusion
- Loading dose
  - 0, 2, 6 weeks
- Maintenance dose
  - Every 8 weeks
- Can escalate if necessary

**Humira (adalimumab)**
- SQ injection
- Loading dose
  - Multiple injections wk 0,2
- Maintenance dose
  - Every 2 weeks
- Can escalate if necessary

Need to pre-screen for tuberculosis
No live vaccines
Does Early Use of Biological Therapy Improve Efficacy? Growth?

- Biologic therapy
- 6-MP/AZA/Methotrexate
- Steroids
- Surgery
Corticosteroid-Free Clinical Remission at Week 50

SONIC Trial

SONIC Trial

Mucosal Healing at Week 26

Early Anti-TNF Therapy in Pediatric Crohn Disease

- Observational cohort of pediatric CD patients (inflammatory)
- Propensity score analysis matched patients on baseline characteristics in 68 triads
  - Early anti-TNF (<3 mo)
  - Early immunomodulator
  - Neither
- Early anti-TNF
  - Higher remission rate
  - Improved height z-score

*Remission: PCDAI≤10, steroid free, no surgery

Walters TD et al. *Gastroenterology* 2014; 146:383-91
Risk of Treating vs. Not Treating

Risk of Treatment

Risk of Disease
Long-Term Evolution of Pediatric Crohn Disease is Structural Damage

What we (parents, patients and physicians) are most concerned about:

Infection

Lymphoma
Pediatric IBD Risk of Serious Infection: A Systematic Review

Serious Infections per 10,000 Patient-Years

- Ped Anti-TNF: 325
- Ped IM: 352
- Adult Anti-TNF: 654
- Ped Steroids: 730

P<0.001
P=0.65

Vaccination

• Ensure that vaccines are up to date at time of diagnosis

• All non-live vaccines should be given
  – Annual flu shot
  – HPV vaccine

• Avoid live vaccines if immunosuppressed
  – MMR, Varicella, intranasal flu, others
  – Try to confirm Varicella immunity prior
  – Consider pneumococcal vaccine
## Risk versus Benefit of Biologics and Immune Suppressants in IBD

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual, pt-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin Lymphoma (baseline)</td>
<td>2/10,000</td>
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<tr>
<td>Non-Hodgkin Lymphoma (on IM)</td>
<td>4/10,000</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (on anti-TNF)</td>
<td>6/10,000</td>
</tr>
<tr>
<td>Hepatosplenic T-cell Lymphoma</td>
<td>Unknown</td>
</tr>
<tr>
<td>Death from sepsis</td>
<td>4/1000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5/10,000</td>
</tr>
</tbody>
</table>

Adapted from Siegel CA. Comprehensive approach to patient risk. Risk versus benefit of biologics and immune suppressants. In: Targan S, Shanahan F, Karp L, eds. Inflammatory Bowel Disease: Translating basic science into clinical practice
Risk of Developing NHL – No immune suppression

<table>
<thead>
<tr>
<th>Patient with Crohn’s disease (without immune suppression)</th>
</tr>
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</table>

- Estimated annual risk = 2 per 10,000 treated patients
Risk of Developing NHL -- Immunomodulator

Estimated annual risk = 4 per 10,000 treated patients
Risk of Developing NHL – Immunomodulator & Anti-TNF

Patient with Crohn’s disease receiving combination anti-TNF + Immunomodulator Therapy

Estimated annual risk = 6 per 10,000 treated patients
Future Therapies
Leukocyte Adhesion

\[ \alpha_4 \beta_1 \text{integrins/VCAM-1} \]
\[ \alpha_4 \beta_7 \text{integrin/MadCAM-1} \]

Adapted from Rutgeerts et al. Gastro 2009;136:1182

201 cases PML after natalizumab became available for prescription in July 2006

Adapted from Rutgeerts et al. Gastro 2009;136:1182
**Vedolizumab for Induction of Remission in Adult UC**

Table 2. Outcome Measures at Week 6 in the Trial of Induction Therapy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N = 149)</th>
<th>Vedolizumab (N = 225)</th>
<th>Percentage-Point Difference (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response†</td>
<td>38 (25.5)</td>
<td>106 (47.1)</td>
<td>21.7 (11.6–31.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical remission‡</td>
<td>8 (5.4)</td>
<td>38 (16.9)</td>
<td>11.5 (4.7–18.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mucosal healing§</td>
<td>37 (24.8)</td>
<td>92 (40.9)</td>
<td>16.1 (6.4–25.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Vedolizumab for Maintenance of Remission in Adult UC

Table 3. Outcome Measures in the Trial of Maintenance Therapy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=126)</th>
<th>Vedolizumab Every 8 Wk (N=122)</th>
<th>Vedolizumab Every 4 Wk (N=125)</th>
<th>Between-Group Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number/total number (percent)</td>
<td>percentage points (95% CI)</td>
<td>P Value</td>
<td>percentage points (95% CI)</td>
</tr>
<tr>
<td>Clinical remission at wk 52</td>
<td>26/126 (15.9)</td>
<td>51/122 (41.8)</td>
<td>56/125 (44.8)</td>
<td>26.1 (14.9–37.2)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>29.1 (17.9–40.4)</td>
</tr>
<tr>
<td>Mucosal healing at wk 52</td>
<td>25/126 (19.8)</td>
<td>63/122 (51.6)</td>
<td>70/125 (56.0)</td>
<td>32.0 (20.3–43.8)</td>
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<td></td>
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<td></td>
<td>36.3 (24.4–48.3)</td>
</tr>
<tr>
<td>Glucocorticoid-free remission at wk 52§</td>
<td>10/72 (13.9)</td>
<td>22/70 (31.4)</td>
<td>33/73 (45.2)</td>
<td>17.6 (3.9–31.3)</td>
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<td></td>
<td>31.4 (16.6–46.2)</td>
</tr>
</tbody>
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Tofacitinib (oral JAK inhibitor)

Modulates signaling for multiple important pro-inflammatory cytokines

• Phase 2 trial in ulcerative colitis\(^1\)
  – Orally dosed twice daily x 8 weeks
  – Better than placebo for clinical response, clinical remission, endoscopic response, endoscopic remission

• Phase 2 trial in Crohn disease\(^2\)
  – Orally dosed twice daily x 4 weeks
  – No better than placebo for clinical response, clinical remission (but high placebo response rate)
  – Improvement in CRP, calprotectin (better than placebo)

Ustekinumab for Active Crohn Disease

Prevents binding of IL-12 and IL-23 to receptors

• Adult CD patients with anti-TNF failure

• **Induction phase** (6 weeks)
  – Better clinical response
  – Not more likely than placebo to induce remission
  – IV administration

• **Maintenance for those with response** (22 weeks)
  – More likely response and remission
  – SQ administration

Fecal Microbiota Transplantation

- Provide donor stool to affected patient in effort to alter microbiome
- Effective and safe treatment for *C. diff*
- Efficacy in IBD **not established yet**
- Side effects common
  - Fever/chills
  - Elevation of CRP
  - Diarrhea
Trichuris suis (whipworm)

• Several small observational studies suggested possible effect in Crohn disease

• Recent phase 2 trial was discontinued after interim analysis
  – Treatment did not outperform placebo
  – No safety concerns
  – High placebo response