Management and Medical Therapies for Crohn disease: strategies to enhance mucosal healing

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New onset Crohn’s Disease

- 10 year old girl presents with background of vague abdominal discomfort, low grade fevers, lack of weight gain (1 year), poor linear growth (<2 cm in 1 year)

- Rapid deterioration! Within 2-3 weeks: anorexia, weight loss (3 kg), fatigue, fevers, transient E. nodosum
Ileocolonic Crohn Disease at first evaluation (Paris: L3 + L4a)

Discontinuous disease

Deep ulcers in transverse colon and ileum (20 cm)

Small round and linear ulcers in stomach (+ve granuloma)
Current medical therapies for pediatric Crohn’s disease to consider for this girl

**Treating active luminal disease**
- anti-TNFα antibodies
- corticosteroids
- enteral nutrition
- sulfasalazine (5-ASA)

**Maintaining remission of luminal disease**
- anti-TNFα antibodies
- azathioprine/MP
- methotrexate

Level one evidence of efficacy based on multi-item measures of disease activity
Outline: “Medical management and strategies to enhance mucosal healing”

- The spectrum of Crohn disease
- What are our current treatment goals...pratically?
- Strategizing to achieve such goals
Outline

- The spectrum of Crohn diseases
- Current treatment goals
- Strategizing to achieve such goals
Inflammatory bowel disease

Clinical Phenotypes

Ulcerative Colitis  Crohn Diseases

A SPECTRUM of related disorders
## Paris Classification of Pediatric IBD

### Crohn Disease

<table>
<thead>
<tr>
<th>Location</th>
<th>Behavior</th>
<th>Modifiers</th>
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</thead>
<tbody>
<tr>
<td>L1 - Terminal Ileum</td>
<td>B1 – Inflammatory</td>
<td>L4a, L4b and L4ab</td>
</tr>
<tr>
<td>L2 – Colon</td>
<td>B2 – Strictureing</td>
<td>P - Perianal</td>
</tr>
<tr>
<td>L3 – Ileocolon</td>
<td>B3 – Penetrating</td>
<td>Growth</td>
</tr>
<tr>
<td></td>
<td>B2B3</td>
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**Severity?**

Not classified for CD

<table>
<thead>
<tr>
<th>Age (years)</th>
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<tbody>
<tr>
<td>A1a</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>A1b</td>
<td>10-&lt;17</td>
</tr>
</tbody>
</table>

Levine, Griffiths et al, Inflamm Bowel Dis 2011; 17 :1314-21
Spectrum of pediatric Crohn’s diseases: classification by macroscopic disease location

Children aged <10 years at diagnosis

Children aged >10 years but < 15 years at diagnosis

Data from Hospital for Sick Children, Toronto: 2000-2004

Sherlock M, DDW 2011
Crohn’s: A progressive disease

Progression of digestive damage and inflammatory activity

Digestive Damage

Inflammatory Activity (CDAI, CDEIS, PCR)

Disease onset  Diagnosis  Early Disease

Pre-clinical  Clinical

Pariente et al. Inflamm Bowel Dis 2011;17:1415-1422
Crohn’s diseases vs ulcerative colitis

- Chronically active inflammation (variations in activity)
- More truly a disease of exacerbations and remissions
Spectrum of disease Crohn Disease severity (with traditional therapies prior to 2000)

Global symptom severity during 5-year follow-up

- **Mild sx only**
- **Moderate exacerbations**
- **Chronically Severe** (Despite immunemodulators and often enteral nutrition)
- **Chronically severe then resection**

Pre-pubertal Children from the Greater Toronto Area

No change comparing 1980-89 (Griffiths, Gut 1993) versus 1990-1996
Outline

- The spectrum of Crohn diseases
- Current treatment goals
- Strategizing to achieve such goals
Goals of treatment in paediatric Crohn’s disease

**TRADITIONAL TREATMENT GOALS**

- Induce and maintain clinical remission (symptom control)
- Facilitate growth (a marker of success of therapy)

**CURRENT TREATMENT GOALS**

- Achieve and maintain mucosal healing
- Deep remission (minimize pan-intestinal damage)
Why have treatment goals have moved “beyond symptoms”?

- Recognition of the discrepancy between symptoms and status of intestine in Crohn’s disease.
- Greater appreciation of the chronic, continuous inflammation present in Crohn’s disease with traditional therapies.
- Greater access to means of re-evaluating healing (MRE; ultrasound; endoscopy; fecal inflammatory biomarkers).
- Availability of therapies able to achieve mucosal healing.
Reassessment ileocolonoscopy in an 8 ½ year old with 5 years disease duration: on azathioprine followed “clinically”
Practical questions in “treating to target” of mucosal healing

● Can we predicted progression or non-progression of disease?

● Can we make use of biomarkers (e.g. fecal calprotectin) or repeated colonoscopic examinations to monitor patients better?

● If we re-evaluate “regularly” via ileocolonoscopy and MR enterography…..should we step-up treatment (i.e. biologics) in presence of macroscopic “disease” irrespective of symptoms?

● Should we use biologics (anti-TNF) more readily and earlier even in very young children?
Outline

- The spectrum of Crohn diseases
- Current treatment goals
- Strategizing to achieve mucosal healing
Index patient: Ileocolonic Crohn Disease at first evaluation (Paris: L3 + L4a)

- Discontinuous disease
- Deep ulcers in transverse colon and ileum (20 cm)
- Small round and linear ulcers in stomach (+ve granuloma)
Managing Crohn’s disease: “top-down” (early anti-TNF) or step-up?

- Exclusive enteral nutrition or corticosteroids followed by immunomodulator for maintenance?

  OR

  Early use of anti-TNF as induction and maintenance?
Pediatric Crohn’s disease Guidelines: induction and maintenance  ECCO/ESPGHAN

Ruemmele F et al, J Crohn Colitis 2014

- Exclusive Enteral Nutrition (EEN) is recommended as first line therapy to induce remission in children with active luminal CD [EL1] 96% agreement

- Oral corticosteroids are recommended for inducing remission in children with moderate to severe active luminal CD if EEN is not an option [EL2 (Pediatrics), EL1 (Adults)] 96% agreement

- Thiopurines or methotrexate are recommended as options for maintenance of steroid-free remission in children at risk for poor disease outcome  [EL2 (pediatrics), EL1 (adults)] 96% agreement
Pediatric Crohn’s disease Guidelines: induction and maintenance ECCO/ESPGHAN

Ruemmele F et al, J Crohn Colitis 2014

- Anti-TNF therapy is recommended for inducing and maintaining remission in children with chronically active luminal CD despite prior optimized immunomodulator therapy [EL2] 100% agreement

- Anti-TNF therapy is recommended for inducing remission in children with active steroid-refractory disease [EL2] 100% agreement

Consider as primary therapy for selected children at high risk for poor outcome

- Anti-TNF therapy is recommended as primary induction and maintenance therapy for children with active perianal fistulizing disease in combination with appropriate surgical intervention [EL2] 84% agreement
In light of our treatment goals, what concepts should influence recommendations?

- Comparative abilities of therapies to heal intestine

- Whether timing matters, if one class of therapy is more effective

- Benefit vs risk considerations
What concepts should influence recommendations?

- Comparative abilities of therapies to heal intestine
- Whether timing matters, if one class of therapy is more effective
- Benefit vs risk considerations
Steroids: Infrequent mucosal healing despite clinical remission

Clinical remission with steroids is not associated with mucosal healing

Endoscopic status in patients with clinical remission after 7 weeks of prednisolone 1 mg/kg daily (n=131; 92% of total population)

Open-label study with EEN: Simplified endoscopic scores before and after

Grover et al, J Gastroenterol 2013
Mucosal healing with thiopurines and with biologics: prospective data

Complete mucosal healing* at week 26

*No remaining visible lesions at week 26 endoscopy

Azathioprine results in mucosal healing: previous observational data

Mucosal healing in 33 patients on azathioprine assessed 24 +/- 14 months into treatment

D'Haens et al, GI Endoscopy 1999
What concepts should influence recommendations?

- **Comparative abilities of therapies to heal intestine**

- **Whether timing matters, if one class of therapy is more effective**

- **Benefit vs risk considerations**
Response and remission with anti-TNF therapy by duration of Crohn’s Disease

Colombel et al, NEJM 2007

PRECISE trial (certolizumab)
Response to infliximab induction in luminal inflammatory pediatric Crohn’s disease

Single-centre experience: 195 patients

Significant covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Time from diagnosis to IFX induction (Years)</td>
<td>0.79 (0.68 - 0.91)</td>
</tr>
<tr>
<td>Early IFX (&lt;18mo from diagnosis)</td>
<td>7.01 (1.56 - 31.56)</td>
</tr>
<tr>
<td>Male</td>
<td>2.24 (1.09 – 4.60)</td>
</tr>
</tbody>
</table>

Church P, et al: Inflamm Bowel Dis 2014
Primary non-response uncommon in inflammatory CD: beware established stenosis

ALTERNATE TREATMENT: surgical resection
Early Biologic Therapy versus conventional Management

Newly diagnosed, antimetabolite, anti-TNF, or steroid-naïve CD patients (n=133)

- Conventional therapy (n=66)
  - Steroids
  - AZA
  - MTX
  - Steroids

- Early aggressive (n=67)
  - IFX (0,2,6 weeks) + AZA
  - IFX
  - Steroids

Proportion of Patients Receiving Infliximab

Numbers for the top down group indicate patients who required episodic IFX

Complete endoscopic remission (absence of ulcers) after 2 years of treatment

Early Biologic Therapy vs Conventional Management of Crohn’s Disease

- Early aggressive (n=26): 73 patients
- Conventional therapy (n=23): 30 patients

**p=0.003

CCFA RISK Stratification Study
New Onset Pediatric Crohn’s Disease

Crohn’s disease: 552 children with complete data and 1 yr f/u

TREATMENT in first 3 months

- Anti-TNFα only, n = 68
- Early IM only, n = 248
- No early immunotherapy, n = 236

Propensity Score Matching

- Anti-TNFα only, n = 68
- IM only, n = 68
- No early immunotherapy, n = 68

Walters TD, Gastroenterology 2014
### Characteristics at Diagnosis of Propensity Score Matched Sample

#### Therapy in the first 3 months

<table>
<thead>
<tr>
<th>Feature</th>
<th>Anti-TNFα only (N=68)</th>
<th>IM only (N=68)</th>
<th>No Early immunotherapy (N=68)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (IQR)</strong></td>
<td>13.8 yrs (11.0-15.4)</td>
<td>11.3 yrs (10.3-13.4)</td>
<td>11.5 (10.7-13.3)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Paris age &lt;10 years</td>
<td>9 (13%)</td>
<td>8 (12%)</td>
<td>7 (10%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>46 (68%)</td>
<td>34 (50%)</td>
<td>44 (65%)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 (n, %)</td>
<td>67 (20%)</td>
<td>37 (23%)</td>
<td>30 (18%)</td>
<td></td>
</tr>
<tr>
<td>L2 (n, %)</td>
<td>85 (26%)</td>
<td>48 (29%)</td>
<td>37 (22%)</td>
<td></td>
</tr>
<tr>
<td>L3 (n, %)</td>
<td>181 (54%)</td>
<td>79 (48%)</td>
<td>102 (60%)</td>
<td>0.21</td>
</tr>
<tr>
<td>PCDAI &gt;30</td>
<td>42 (62%)</td>
<td>42 (62%)</td>
<td>41 (60%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Presence perianal disease</td>
<td>16 (24%)</td>
<td>12 (18%)</td>
<td>12 (18%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Deep ulceration</td>
<td>41 (60%)</td>
<td>41 (60%)</td>
<td>41 (60%)</td>
<td>1.0</td>
</tr>
<tr>
<td>CRP (X ULN)</td>
<td>5.09 (2.0-9.03)</td>
<td>5.85 (1.55-20.1)</td>
<td>6.00 (2.8-20.6)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

ESR, platelet count, albumin, Ht z-score also part of the model, all
# Subsequent therapies

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>Additional Agents added 3 to 6 months</th>
<th>Additional Agents added 6 to 12 months</th>
<th>Total Additional Anti-TNF use 3 to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM but not anti-TNF by 3 months</td>
<td>6 anti-TNF</td>
<td>14 anti-TNF</td>
<td>20 anti-TNF (29%)</td>
</tr>
<tr>
<td>Neither IM nor anti-TNF by 3 months</td>
<td>19 IM</td>
<td>8 IM</td>
<td>(27 IM)</td>
</tr>
<tr>
<td></td>
<td>8 anti-TNF</td>
<td>5 anti-TNF</td>
<td>13 anti-TNF (29%)</td>
</tr>
<tr>
<td></td>
<td>3 IM + anti-TNF</td>
<td>4 IM + anti-TNF</td>
<td></td>
</tr>
</tbody>
</table>

Walters TD, Gastroenterology 2014
12 Month Outcomes for the three early therapy approaches: PCDAI≤10 without resection

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Achieved steroid-free, surgery-free remission by 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-TNF by 3 months</td>
<td>85%</td>
</tr>
<tr>
<td>IM by 3 months</td>
<td>60%</td>
</tr>
<tr>
<td>No immune therapy by 3 months</td>
<td>54%</td>
</tr>
</tbody>
</table>

Chi squ $p = 0.0003$

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF vs IM</td>
<td>25%</td>
<td>4</td>
</tr>
</tbody>
</table>

Walters TD, Gastroenterology 2014
Interpretation

- In clinically similar populations of children with Crohn’s disease, *early* (<3 mon) therapy with anti-TNFα was superior to early IM or no early immunotherapy despite later addition of those agents: PCDAI remission, CRP, growth

- It doesn’t mean that everyone should get anti-TNFα therapy, rather that we need to better define further characteristics of patients that are at risk of progressive disease without such therapy
Concerns about early anti-TNF therapy in children

- Some patients would be overtreated
  - some have mild/non-progressive disease
  - Limited extent of disease?

- Safety concerns

- Secondary loss of response: importance of sustaining response

- Cost and access

- Exit strategy?
Our practice: timing of anti-TNF therapy in pediatric Crohn’s Disease

- Steroid-refractory (but inflammatory) disease (usually colonic CD)

- Accelerated fashion...i.e. after corticosteroids/enteral nutrition help clinically but as a maintenance alternative to immunomodulators

- As initial treatment in select patients, considering disease location and extent
  - Severe perianal fistulizing disease
  - Extensive, severe colonic disease...concomitantly with steroids
  - Delayed recognition of disease, growth impairment

- When immunemodulator fails to achieve steroid-free sustained remission
Positioning of anti-TNF: exposure to immunomodulators prior to infliximab

Single-centre experience: 195 patients

- Azathioprine
- Methotrexate
- None

Church P, Inflamm Bowel Dis 2014
Durability of response

Individualization of regimen (dose escalation or interval shortening) was common especially in first 1-2 years of maintenance therapy (standard of care).

Secondary Loss of Responsiveness

- Complete loss of benefit from IFX after significant benefit had been obtained, despite adjustment of dose and/or dosing interval.

Church P, et al Inflamm Bowel Dis 2014
Height improves significantly when potential remains at time of anti-TNF induction.

Church P, et al. Accepted, Inflamm Bowel Dis.
Anti-TNF-α Antagonists

Chimeric monoclonal antibody

Humanized monoclonal antibody

Infliximab

IV infusion

Adalimumab

Subcutaneous injection
<table>
<thead>
<tr>
<th><strong>ANTI-TNF induction and maintenance therapy of pediatric Crohn disease: infliximab and adalimumab trials</strong></th>
<th><strong>Infliximab (REACH)</strong> N=112 (mean age 13.3 years) (Hyams et al, Gastroenterology 2007)</th>
<th><strong>Adalimumab</strong> N=188 (mean age 13.5 years) (Hyams et al, Gastroenterology 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior anti-TNF treatment</td>
<td>None (all anti-TNF naïve)</td>
<td>Included 83 pts with secondary Loss of response/intolerance to infliximab</td>
</tr>
<tr>
<td>Concomitant IM during study</td>
<td>99% throughout (thiopurines usually)</td>
<td>62% from start to week 26; 46% after week 26</td>
</tr>
<tr>
<td>Response rate (drop in PCDAI ≥ 15) after induction</td>
<td>88% at week 10</td>
<td>87% of anti-TNF naïve patients</td>
</tr>
<tr>
<td>Remission rate at week 26</td>
<td>60% of week 10 responders randomized to 5 mg/kg q 8 weekly maintenance</td>
<td>63% of anti-TNF naïve week 4 responders randomized to high dose for body weight q 2 weeks</td>
</tr>
<tr>
<td>Remission rate at week 52</td>
<td>56% of week 10 responders randomized to 5 mg/kg q 8 weekly maintenance</td>
<td>46% of anti-TNF naïve week 4 responders randomized to high dose for body weight q 2 weeks</td>
</tr>
</tbody>
</table>
“Safety concerns”: neoplasia risk

- Thiopurines alone
- Anti-TNF alone
- Anti-TNF in combination with thiopurines
Hepatosplenic T-cell lymphoma occurrences

Estimated Risks:
Males <35 yrs on Thiopurines: 1/7404
Males <35 yrs on Thiopurines + Anti-TNF: 1/3534


- 37 cases in IBD (35 male)
- 18 on anti TNF therapy + thiopurine (17 male)
- 19 on thiopurine therapy alone
- Age 12-58 (mean 26)
- 1-24 infusions (8 had <3 infusions)

Graph showing the number of cases over time with a peak in Dec 2006 and a decline in Mar 2007, followed by a rise in Sept 2007 and another peak in April 2008.
Efficacy ....... and ........ Safety
Important with either top-down or step-up

- More attention to biomarkers (serologic and fecal) and re-evaluation of intestine (MRE/colonoscopy)
- Need for predictors of such aggressive progression......and of mild disease
STORI trial: Time to “confirmed” relapse

52 patients with “confirmed” relapse
44 relapses during first year

Canadian Children’s IBD Network

The Canadian Children Inflammatory Bowel Disease Network: A Joint Partnership of CIHR and the CH.I.L.D Foundation

10 academic centres, where children at first assessed for suspected IBD