Evaluating Efficacy in Pediatric Inflammatory Bowel Disease Clinical Trials: Current Issues and Defining a Strategy for the Future

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Disclaimer

• The opinions presented here are solely those of the presenters and do not represent those of the Food and Drug Administration
Scope of Problem

• Data on precise numbers of children with IBD are lacking; estimates range from 50,000 to 100,000\(^1\)

• In general children tend to have more extensive and severe disease than adults with greater likelihood of complicated behavior\(^2,3\); high need for corticosteroids and high likelihood of CS dependence\(^4\)

• Growth and development are unique pediatric issues; up to 30% of pediatric Crohn’s disease patients have growth delay\(^5\)

In February 2010 the IBD Working Group of the British Society of Pediatric Gastroenterology published a set of guidelines for Pediatric IBD care\(^1\):

“There is a paucity of paediatric trials of high methodological quality to provide a comprehensive evidence-based document.”

Therapy today is: consensus-based, best available paediatric literature, extrapolated from adult studies, and based on clinical expertise.

\(^1\)Sandhu et al. J Pediatr Gastroenterol Nutr 2010
## Current Therapy for Newly Diagnosed Children with Crohn’s Disease (N=1271)*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>By Q1</th>
<th>By Q2</th>
<th>By Q4</th>
<th>By Q8</th>
<th>By Q12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>927 (76%)</td>
<td>943 (78%)</td>
<td>968 (83%)</td>
<td>1008 (89%)</td>
<td>1022 (93%)</td>
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<tr>
<td>6MP/Aza</td>
<td>634 (53%)</td>
<td>728 (63%)</td>
<td>807 (72%)</td>
<td>854 (81%)</td>
<td>880 (89%)</td>
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<tr>
<td>Methotrexate</td>
<td>71 (6%)</td>
<td>103 (9%)</td>
<td>141 (14%)</td>
<td>199 (24%)</td>
<td>225 (36%)</td>
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<tr>
<td>5-ASA/SASP</td>
<td>783 (64%)</td>
<td>821 (68%)</td>
<td>849 (72%)</td>
<td>870 (79%)</td>
<td>871 (86%)</td>
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<tr>
<td>Infliximab</td>
<td>145 (11%)</td>
<td>202 (16%)</td>
<td>281 (22%)</td>
<td>395 (31%)</td>
<td>449 (35%)</td>
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<tr>
<td>Adalimumab</td>
<td>2 (0.2%)</td>
<td>9 (1%)</td>
<td>18 (2%)</td>
<td>41 (5%)</td>
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<td>Enteral Nutrition</td>
<td>72 (6%)</td>
<td>77 (7%)</td>
<td>83 (8%)</td>
<td>96 (12%)</td>
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<tr>
<td>Antibiotics</td>
<td>388 (33%)</td>
<td>435 (38%)</td>
<td>491 (46%)</td>
<td>559 (58%)</td>
<td>589 (71%)</td>
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*Pediatric IBD Collaborative Research Group Registry, Unpublished data 2012
## Current Therapy for Newly Diagnosed Children with Ulcerative Colitis (N=486)*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>By Q1</th>
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<td>5-ASA/SASP</td>
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<td>426 (89%)</td>
<td>437 (92%)</td>
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<td>1 (0.2%)</td>
<td>4 (1%)</td>
<td>6 (2%)</td>
<td>6 (3%)</td>
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*Pediatric IBD Collaborative Research Group Registry, Unpublished data 2012
# Approved Drugs for IBD

<table>
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<tr>
<th>Agent</th>
<th>Adult Approval</th>
<th>Pediatric Approval</th>
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<tbody>
<tr>
<td>Azulfidine</td>
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<tr>
<td>Pentasa</td>
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<td>No</td>
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<tr>
<td>Asacol</td>
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<tr>
<td>Asacol HD</td>
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<tr>
<td>Lialda</td>
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<tr>
<td>Apriso</td>
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</tr>
<tr>
<td>Canasa</td>
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<tr>
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</tr>
<tr>
<td>Prednisone</td>
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</table>

* Grandfathered in, minimal data

<table>
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<tr>
<th>Agent</th>
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<th>Pediatric Approval</th>
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</thead>
<tbody>
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<tr>
<td>Remicade UC</td>
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<td>Humira</td>
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<td>Cimzia</td>
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<tr>
<td>Tysabri</td>
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<tr>
<td>Azathioprine</td>
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<tr>
<td>6MP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Azulfidine® Label (2009)

- Original approval June 1950
- Small studies have been reported in the literature in children down to the age of 4 years with ulcerative colitis and inflammatory bowel disease. In these populations, relative to adults, the pharmacokinetics of SSZ and SP correlated poorly with either age or dose.
- Initial dosing for children, six years of age and older: 40 to 60 mg/kg body weight in each 24-hour period, divided into 3 to 6 doses. Maintenance: 30 mg/kg body weight in each 24-hour period divided into 4 doses.
- Minimal data to support this. Liquid formulation no longer available
Contemporary History of Pediatric Approved Therapy

- Colazal: Approved 2006, for up to 8 weeks of therapy. 6 years after adult indication. 68 patients studied, 2 dose comparison. No maintenance indication.
- Adult dose is three 750 mg COLAZAL capsules 3 times a day; (6.75 g/day)
- Pediatric dose is EITHER: Three 750 mg COLAZAL capsules 3 times a day (6.75 g/day) or one 750 mg COLAZAL capsule 3 times a day (2.25 g/day)
- There were no statistically significant differences between the two doses in the pediatric study though numerically the improvements were greater across the board with the higher dose. But the sample size was limited and therefore no statistical difference.
Contemporary History of Pediatric Approved Therapy


• Remicade UC: Approved September 2011 for pediatric ulcerative colitis, 6 years after adult approval (Sept 2005). 60 patients studied, 2 dose maintenance comparison.
What Does This Tell Us?

- Clinical trial data are very limited in pediatric IBD.
- Pediatric clinical trials invariably occur many years after adult approval, involve small numbers of patients, usually not powered to show statistically significant endpoints.
- Pediatric clinicians prescribe medications for children with IBD for years without pediatric specific data and prior to regulatory approval.
Lack of Adequate Pediatric IBD Clinical Trials Data Leads to Treatment Uncertainties

• Is pediatric IBD pathogenesis/severity the same in children and adults?

• Can we assume efficacy is similar in children and adults (i.e., extrapolation is reasonable)?
  - Might be better in children with less co-morbidities, shorter duration of disease, lack of smoking, etc.

• Medication dosing
  - Metabolism of drug in children may be very different; data available suggest higher pediatric requirements

• Increased demands for long-term follow-up
  - Greater duration for natural history of disease and for risk of serious complications, e.g., cancer, to be observed

• Evidence based data are largely insufficient at this point
Response to Infliximab in Crohn’s disease: Children vs. Adults

* Primary Endpoint in REACH: Defined as decrease in PCDAI score $\geq$15 points from baseline with total score $\leq$30 points. Clinical Response in ACCENT I defined as a reduction in CDAI score $\geq$25% and $\geq$70 points.

Current Lack of Clarity of Desired Outcomes Hampers Development of Pediatric Clinical Trials

- Desired outcomes of therapy must be:
  - Measurable
  - Clinically meaningful

- Who is best to evaluate outcome?
  - Patient vs. parent vs. physician

- Are subjective parameters adequate or does there need to be objective evidence of improvement?

- When do we evaluate the outcome?
Defining a Global Desired Outcome: Child, Parent, Physician Views

• Child: Feel better, treatment doesn’t hurt, no CS, look like other kids (i.e., normal growth and development), age appropriate activity, safe

• Parent: safe, relief of symptoms, works long-term, no CS, affordable, ease of administration, minimize time lost from work and school

• Physician: absence of symptoms, no CS, ensures growth and development, works long-term, need to maximize adherence or high likelihood of loss of effect, safe
What Are We Measuring to Determine Outcome?

- Signs and symptoms – activity indices (PCDAI, PUCAI, CDAI, Mayo); variably try to blend both subjective and objective parameters
- “P” reported outcomes (PRO) – patient report, parent reported, physician reported
- Quality of life – IMPACT
- Growth and Development – growth curve, Tanner staging, musculoskeletal health
What Are We Measuring To Determine Outcome?

- Inflammation – CRP, fecal calprotectin, mucosal assessment
- Structural damage – MRE, CTE

No single parameter gives the whole picture
Confounders in Assessing Pediatric Outcomes

- Divergent histories from child and parent common; parent usually > child in perception of severity
- Growth delay may be dissociated from activity of GI symptoms but indicates inflammatory activity; a growth stunted asymptomatic child is not a success story
- Symptoms may be unrelated to inflammation – e.g., stricture, functional gastrointestinal disorders
- Perirectal disease may impair quality of life but be dissociated from luminal disease activity
- Lab/endoscopy results often do not correlate with symptoms
Concomitant Functional Gastrointestinal Disorders in Patients with IBD

• Prevalence of Symptoms Meeting Criteria for Irritable Bowel Syndrome in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. Halpin S, Ford A. Am J Gastroenterol (in press)

• 39% of all adult IBD patients met criteria for IBS; common in those in IBD remission

• Data in pediatric IBD insufficient but clinical experience suggests commonality of co-morbid functional symptoms which would complicate patient-only reported outcomes
The Two Extremes of Patient Assessment

- Rely on patient report, physician global assessment alone (largely subjective)
- Rely on doing everything: signs, symptoms, lab results, fecal markers of inflammation, endoscopy, colonoscopy, VCE (largely objective)
- The first is potentially misleading, the second impractical, not cost-effective, and may have untoward consequences
Consequences of Under Treatment vs. Risks of Over Treatment

• Under estimation of disease activity may lead to under-treatment and “smoldering” mucosal inflammation may increase subsequent risk of disease progression, cancer\(^1,2\), disease relapse (CD), surgery

• Over estimating disease activity may lead to the needless exposure to medications with significant toxicity, i.e. need to treat IBS and not escalate Rx for IBD (i.e. anti-TNF\(\alpha\) is not good for IBS)

\(^1\)Rutter et al. Gastroenterology 2004;126:451; \(^2\)Gupta et al. Gastroenterology 2007;133:1009
Defining Disease Severity of Patient Populations for Inclusion in Clinical Trials

- What is mild disease? Moderate disease? Severe disease?
- Is physician global assessment adequate? Unlikely
- Do we have adequate data defining disease severity by standard severity instruments (PCDAI, PUCAI)? Yes, but gold standard has been physician global assessment!
Is Clinical Response Enough, Or is Clinical Remission The Only Acceptable Endpoint?

- Response – improvement in symptoms. Often used as primary outcome in clinical trials, true impact depends upon where you start and end. Is it clinically meaningful?
- Severe to moderate, severe to mild, moderate to mild, etc. There may have been response but the child is still ill. Does it last for 2 weeks, 2 months, 2 years? Response should not be a primary outcome measure of medications that will be used long-term
- Placebo response a concern
Is Clinical Response Enough, Or is Clinical Remission The Only Acceptable Endpoint?

- Remission – the child, parent, and physician’s goal
- Does this mean absence of symptoms or absence of demonstrable inflammation?
- Does it last for 2 weeks, 2 months, 2 years?
- Is it CS-free remission?
When is the Appropriate Time to Determine Outcome?

- Induce/Maintain clinical response – short time frame; mechanism of action and severity of disease important
  - mild symptoms, 5-ASA like medication, tolerance for response at 4-12 weeks acceptable
  - moderate/severe symptoms (e.g., fulminant colitis), time frame shorter

- Induce/Maintain clinical remission – different connotation; longer time frame, and need for durability of remission; should end points be beyond 1 year? Should be CS-free
Is Mucosal Healing Necessary?

• Mucosal response/remission: If these predict long-term outcome then critical to determine but unclear when to evaluate; data suggest mucosal healing is associated with improved future course\textsuperscript{1,2}

• To date there are no prospective data in children which answer the questions of
  1. Is mucosal healing associated with short and long-term clinical outcomes in pediatric IBD?
     - Improved future disease activity, less complications or development of future cancer
  2. What is mucosal healing? Endoscopic vs. histologic?

\textsuperscript{1}Baert et al. Gastroenterology 2010;138:463, \textsuperscript{2}Colombel et al. Gastroenterology 2011;141:1194
Endoscopic status in patients with clinical remission after 7 weeks of prednisolone 1 mg/kg daily (n=131; 92% of total population)

Conclusion: prolonged clinical remission with steroids is not associated with mucosal healing

Illustrative Case

- A 17 year old male was diagnosed with UC 5 years ago.
- He states that he has a normal stool 2x/day, no blood, no cramps
- All labs are normal
- Meds include 5-ASA, 6-MP
- PUCAI = 0
- Routine f/u colonoscopy performed
PRO: inactive disease
PUCAI: inactive disease
Mayo endoscopy score 2: active disease
In the end though...

- A clinical outcome assessment will not always be the same as a disease activity assessment, but it is what the patient is most concerned about (now)

- Improving the natural history of the disease is what the patient is most concerned about in the future
What Are The Challenges?

- Do we need a placebo control arm to assess efficacy? Is it feasible? How long is exposure to placebo?
- Role of endoscopy to assess treatment benefit in children (safety of colonoscopy in children; feasibility; when is/is not indicated)
- Timing of pediatric trials during drug development
Is a control arm feasible or ethical for a pediatric trial?

- Importance/need likely proportional to “softness” of endpoints used (e.g., PGA vs. growth)
- Pediatric disease severity adversely affects ethics of using placebo
- Feasibility would largely depend upon timing: poor acceptance by families when their child is sick and drug is commercially available
Role of endoscopy to assess treatment benefit in children

• Mucosal healing is a “hot” surrogate biomarker
  – Clinically meaningful (?)—does it change outcome?
• Current trial data demonstrate practical issues:
  – Achieved in only 15/62 at 12 weeks in EXTEND¹
  – Low rate of inter-observer concordance in CD (27%)²
  – High rates in placebo arm in UC (up to 47%)³

2. Travis SP et al. Gut 2012;61:535e42
Poor Correlation of Physician Assessment With Endoscopic Activity of Ulcerative Colitis

Sensitivity of clinical assessment determining endoscopic disease was 56%

19% of pts deemed to have active clinical disease had a normal endoscopy

Regueiro et al. IBD. 2011;17:1008
Role of endoscopy to assess treatment benefit in children

• Pediatric specific issues:
  – Endoscopy has become safe/easy to do (for the doctor)
  – Expense (anesthesia)
  – Larger disease extent (where do you look?)
  – Lack of data on effect of long-term outcomes
  – Lack of validated scoring systems
  – Need/desire to correlate to surrogates (CRP, fecal markers, growth velocity, etc.)
Requirements for Assessment of Mucosal Healing

- Ulcerative colitis – flexible sigmoidoscopy may be adequate, though may require sedation or anesthesia in most pediatric patients.
- Crohn’s disease – full colonoscopy would be required, as well as video capsule endoscopy in selected cases. Sedation/anesthesia for all.
- Concepts of structural healing are evolving; limitation of resources for methodologies such as MRE, as well as patient acceptance. CT will not be a viable pediatric option.
Surrogate Markers Will be Required

- Particularly applicable to pediatrics
- Fecal markers of inflammation such as calprotectin, lactoferrin need to be incorporated into clinical trials
- The role of CRP needs better definition
- Need greater evidence base
Timing of pediatric trials during drug development

• Historically has been “me too” after adult trials
• “Purity” of pediatric IBD offers opportunity to better define best phenotypes for response
• Pediatric patients are more severe—”deserve” earlier access vs. more vulnerable —”deserve” protection
• Care is concentrated in academic centers that are bonding together—an accessible clinical trial network (COG-like)
When in the course of drug development is a pediatric trial feasible or ethical?

- Too early, potentially expose children to increased risk
- Too late, unwillingness to go into trial when drug is already available; profile of pediatric patients entering trials very different than adult patients; no such thing as professional clinical trial patient
- If too late then we are extrapolating adult doses to children
How Do we Increase the Number of Pediatric Patients/Families Willing to Go into trials?

- Many recent pediatric trials have had significant recruitment from Eastern Europe because of difficulty in enlisting patients in U.S.

- Current issues and solutions:
  - timing of studies (access to meds)
  - over bearing requirements (visits, blood draws, endoscopy)
  - Realities of pediatric practice: sweat equity (need infrastructure and support of clinical researchers)
Issue: Who decides benefit vs. risk?

- Paternalism vs. responsible practice
- Clinicians educate patients and families daily on clinical options.
- As aggressive disease phenotypes are classified/identified, should clinical trials be offered earlier?
Issue: Third Party Coverage

- Lack of pediatric trials/FDA approval presents major issue for pediatric healthcare workers and patients/families when adult-approved therapy is deemed “experimental” by third party payers for use in children

- Remicade was used “off label” for many years despite great barriers placed by many third party payers. Continues to be an issue for children <6 years of age
Unmet Need for Translational Studies

- Unprecedented opportunity to study prognostic markers in well-defined populations
- Genetic and other translational parameters
- Will this affect recruiting, consenting?
- Who evaluates scientific merit?
- Who pays?
Key Points - Summary

• Children represent a significant, but heretofore under-studied population with IBD

• Children have the most severe disease, and the longest duration of potential disease burden, as well as time for complications of therapy to develop

• Clinical trials on most therapies used in pediatric IBD are lacking

• Treatment goals must include not only improvement/cessation in symptoms (response/remission) but normalization of growth and development; durability of response and remission are critical

• Remission should be CS-free
Key Points - Summary

- No single outcome measure will adequately represent all aspects of illness (symptoms, inflammation, functioning)
- Non-invasive monitoring techniques to assess inflammation need to be developed and validated
- Unless there are pediatric data on efficacy, dosing and safety, pediatric patients will still get therapies newly approved for adults without the benefit of controlled data and dosing experience
- Placebo controlled trials of medications known to be effective in adults will not be acceptable to patients, parents, or clinicians
Key Points - Summary

• Delayed development and start of pediatric clinical trials will continue to hinder recruitment into pediatric studies; earlier integration of physician experts into the development process may improve final product.

• Translational research must be incorporated into clinical trials.

• Long term follow up of large numbers of pediatric patients for safety signals is important; these cannot be the sole responsibility of pharma and need to be co-directed by physicians, regulatory authorities, consumers. There needs to be transparency in the process and monitoring.
Question/Issue List for Panel Discussion

• Is extrapolation from adult trials sufficient for pediatric labeling? Total vs. partial vs. none?

• Do we need to objectively define disease activity in our study populations? Elevated CRP, recent colonoscopic evaluation, surrogate markers?

• Is response enough as the primary endpoint or should we insist on remission? Should we insist on CS free?

• What is a reasonable length of time at which to assess durability?

• Should earlier incorporation of pediatric patients be mandated? At what time in the approval process? Phase II, Phase III adult development?
Question/Issue List for Panel Discussion

- Should any drug that has potential applicability for adult IBD be given FDA approval only after pediatric experience?
- Who should be involved in those decisions?
- What steps can be taken to increase the participation of pediatric patients in trials?
- Should translational science be mandated for clinical trials to better understand response/failure? Are there mechanisms to partner pharma/academia/NIH?
Fundamental Assumptions For Accepting Extrapolation From Adults to Children

- Disease pathogenesis similar
- Disease progression similar
- Response to intervention similar
- Populations have similar exposure-response relationships
Limitations of Extrapolation

- Dose cannot be extrapolated
- Safety cannot be extrapolated
Is it reasonable to assume that children, when compared to adults, have a similar:

(a) disease progression? (b) response to intervention?

- No
- Yes to both

Is it reasonable to assume a similar exposure-response (ER) in children when compared to adults?

- No
- Yes

Is there a PD measurement that can predict efficacy in children?

- No
- Yes

Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentrations based on ER, then safety trials at the correct dose.

“Full Extrapolation”

Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentration based on ER, then safety trials at the correct dose

“Partial Extrapolation”

Conduct PK studies to achieve drug levels similar to adults, then safety trials at the correct dose

“No Extrapolation”

Conduct PK studies to establish dose, then pediatric efficacy and safety trials

“No Extrapolation”