Changing the paradigm: Removing barriers, building bridges

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Disclosures

- Advisory Board: Janssen, Abbvie
- Consultant: Pfizer, Receptos, Allergan, Boehringer-Ingelheim, Lilly

We will all agree that….

- Pediatric IBD is often a severe condition with dramatic impact on quality of life requiring substantive intervention
- With the exception of VEO-IBD (≤2 years old) adult and pediatric disease is similar
- The term “conventional therapy*” needs to be discarded as 25% (UC) to 70% (CD) of affected children are treated with therapies beyond “conventional” ones, largely biologics
- New and emerging therapies may offer considerable advantage over “conventional” therapy
- There remains a large unmet need for additional therapies in children
- To date our efforts to bring new therapies to children quickly have been grossly delayed and inadequate

*corticosteroids, 5-aminosalicylates, thiopurines, methotrexate, antibiotics

History of Pediatric IBD Biologic Drug Development

Drug	Indication	Adult Approval	Pediatric Approval	Delay
Infliximab	CD	1998	2006	8 years
Infliximab	UC	2005	2011	6 years
Adalimumab	CD	2008	2014	6 years
Adalimumab	UC	2012	Not yet	?
Certolizumab	CD	2008	Not yet	?
Golimumab	UC	2013	Not yet	?
Vedolizumab	CD	2014	Not yet	?
Vedolizumab	UC	2014	Not yet	?
Ustekinumab	CD	2016	Not yet	?
Tofacitinib	UC	2018	Not yet	?

3/10, 30%

What Happens During the Period Between Adult and Pediatric Approval

- Third party payers reject use because considered “experimental”, i.e., not in the label
- Third party payers demand failure of conventional therapy before entertaining appeals
- Children denied the use of potentially effective therapy unless used off-label; the current system encourages off-label use.
- Physicians, patients, and families employ extrapolation of efficacy and dose based on adult experience
- Single center retrospective studies become the “standard of care”
- No systematic pK, pD, efficacy data collected during off-label use
- No systematic safety reporting
- We have perfected this system over the past 20 years!

WHY?

What are the barriers?

Barriers: Regulatory Viewpoint

- Uncertainty regarding the similarity of exposure-response (ER) between adults and pediatrics broadly limits degree of extrapolation
- Reluctance of sponsors to conduct robust dose finding in Phase 2 in adults for each disease state; when ER relationship is not well characterized in adults, it is difficult for FDA to agree to study design for pediatrics prior to review of adult phase 3 data.
- Delays in receiving draft pediatric protocols and rapid negotiation surrounding key details
- Challenges in defining endpoint measures that adequately span the full pediatric age range (e.g., PRO in very young children)
- Reluctance from community to require and prioritize obtaining long term (end of study) endoscopy data, which FDA feels is crucial to confirming a real benefit of a new drug in the pediatric population.

Barriers: Industry Viewpoint

- Adequate safety in adults must be established prior to starting pediatric studies
  - Anxiety about any SAE in a child that might jeopardize adult approval and use
- Reluctance to start any pediatric study until certainty that there will be adult approval
- Early pk/pD studies in adolescents or younger children might delay or even jeopardize adult approval with unexpected safety event
- Lack of alignment of FDA and EMA; back and forth disagreements, lack of clarity, late requests to change pediatric plans
- Perceived ambiguity between regulatory agencies and even within different divisions of a single regulatory agency about the required criteria for applying extrapolation of efficacy to pediatric drug development programs
- Pediatric trials are labor intensive, cost more per subject enrolled
- New formulations may need to be developed
- Preference to wait to invest in pediatric studies until later in the life cycle of drugs marketed for adults

Barriers: Investigator Viewpoint

- There is no reason to participate in a clinical trial when the medication can be given off-label
- Will not use a placebo or sham placebo (ineffective dose) when it has already been shown that placebo is inferior, and when there may be other approved drugs (adult) that the patient has not tried
- Will not immunize patients to a biologic by using too low a dose, or placebo during active withdrawal periods
- The washout period from previous therapy is too long; children with moderate/severe disease cannot wait for prolonged screening and delay in enrollment
- Maintaining a high CS dose for up to 12 weeks is unacceptable
- Requirement to be sick enough to get into the study, but not offering a therapy that is quickly effective, precludes study enrollment
- Three colonoscopies is too many

Barriers: Patient/Family Viewpoint

- Why go into a trial when our doctor can give us the drug anyway, or use another drug
- I will not allow my sick child to receive a placebo
- Too many visits
- Too many blood sticks
- Too many procedures
- Unable to dose adjust or add rescue medication; no flexibility like in routine clinical care

Barriers: My Summary

- No regulatory or self-imposed industry mandates to expedite pediatric trials
- Adult approval is the business driven goal ($ ROI)
- Delay in pediatric trials until long after adult approval subverts any chance of speedy enrollment and completion of pediatric trial
- No incentive for clinicians in the U.S., patients, families to participate AFTER drug receives adult approval
- <u>Nothing will change unless WE change it</u>

Overarching Guiding Principles to Building Bridges

- There is no simple solution that will make everyone happy
- We can't continue doing what we are doing
- Our most vulnerable population, with the need for the longest exposure to medical therapy for their chronic disease, is adversely affected every day
- Where can we compromise, find common ground
- Need alignment

Bridge 1: Extrapolation

- ACCEPT extrapolation of efficacy if similarity of exposure to adults with the chosen dose for children can be assured, and exposure-response can be matched
- Every study to date has shown similar if not improved efficacy in children compared to adults with similar drug exposure
- Our focus needs to move to dosing and safety
- Good dose ranging in adults to adequately characterize dose/exposure-response relationship in adults will help facilitate extrapolation to children
- Leverage real world observational/registry data to augment safety profile

Bridge 2: Timing

- It is unconscionable to not have pediatric pK/pD data, and ER data, and at minimum short-term safety data, prior to adult approval and release
- There is no statute, regulation, or advisory that prevents pK/pD studies in children
- These studies must commence no later than mid Phase III in adults and establish ER curve in children and see if similar to adults

Bridge 2: Timing

- Study age 12-17 years first, dose ranging, pk/pD. In reality these will often be treatment resistant patients, but if mode of action and safety profile good then may well get earlier disease course patients
- Roll these patients into long term safety study when appropriate
- Utilize these data to inform smaller efficacy studies to begin after phase 3 completed and during CSR preparation. Utilize ER data from adult studies and preliminary pediatric data to limit size of pediatric study

Bridge 3: Placebo

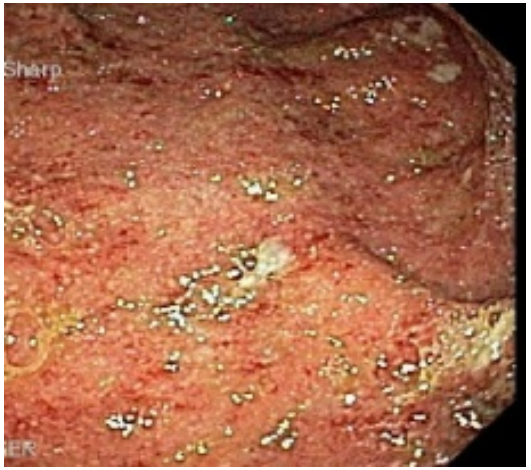
- No investigator or patient/family will accept placebo once it has been shown in adults that the drug is better than placebo, and the drug is available for administration off study
- Controversy remains whether investigators and patients/families will accept placebo if study design minimizes number of patients so exposed, minimizes time to possible rescue and if it is yet unknown whether drug is better than placebo
- Including placebo must teach us something or it is unethical
- Consider placebo use when remission attained, not just response, but not with drugs where withdrawal may engender immunogenicity (e.g., biologics)

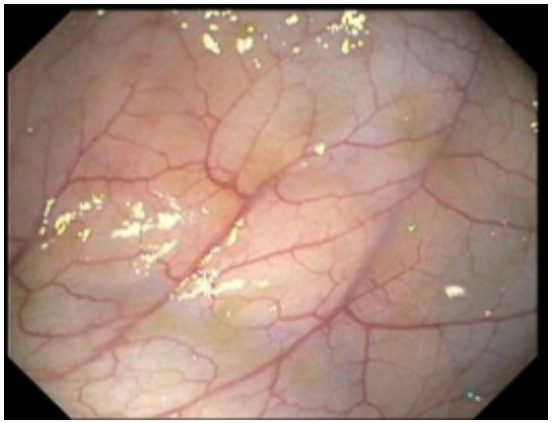
Bridge 4: Study design

- Shorten enrollment process to no more than a few days. Cannot keep sick children sick before offering intervention
- Use TDM to demonstrate sub-therapeutic drug level of previous therapy and thereby shorten washout period
- Reach consensus on CS exposure guidelines, may be different for children than adults
- Accept that endoscopic evaluation is the new gold standard, but time them to garner maximum information. Two is preferable to three. Try to develop surrogate markers for short term efficacy in addition to symptom improvement
- Set realistic enrollment targets; pediatric studies will not be powered for efficacy

Study Design: Endpoints

Need to remember we are treating <u>inflammatory</u> bowel disease





Study Design: Endpoints

- Consider endoscopic response/remission as the primary outcome goal in ulcerative colitis

  Avoids inaccuracy in symptom based reporting
  Centralized endoscopy, histology*

- Reasonable to assume that improvement/cessation in inflammation will result in symptom response/remission
- Transmural nature of Crohn's disease makes it more difficult
- Functional comorbidities like IBS make symptom assessment problematic in some patients

*histology currently exploratory. Gather the data!

Bridge 5: Legislative protection

With all due respect, fear of litigation should not prevent us from knowing the pharmacokinetics and pharmacodynamics of medications that will be used in children

We have Institutional Review Boards, and routinely use unblinded external independent DSMBS in pediatric studies, to protect the interest of patients and ensure that benefit and risk are balanced

Require pharma to obtain pediatric data prior to adult approval, and offer incentives to do so

Bridge 6: Universal agreement

- A process must start to reach international agreement
- It will be painful, and it will take time
- Further delay hurts children
- Effort funded by pharma, regulators, professional societies, foundations
- Start now. No more than a 2 year timeline from start to finish to develop globally accepted guidelines
- Cooperation will be better than confrontation

We have waited too long

#ibdkidscounttoo