Enrolling Adolescents into Adult Phase 3 Trials

Case Study: Inflammatory Bowel Disease

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Background

- Historically pediatric patients are studied *after* adult studies are completed and a new drug is approved for adults.
- Results in delays between an adult approval and a pediatric approval that average 8 to 10 years.
- In that time, there is often widespread off-label use of drugs, which puts pediatric patients at risk due to uncertainties regarding safety, efficacy and appropriate dosing, and results in lost opportunities to collect those data in a controlled and monitored clinical trial setting.

Background

- Efforts to decrease delays in initiation and completion of pediatric studies have not yet resulted in much improvement in these timelines.
- This continues to place a burden on pediatric patients and their families seeking access to newer therapies.
- One potential solution is to include a subset of pediatric patients (adolescents) into adult phase 3 trials pre-approval.

Inflammatory Bowel Disease (IBD)

- IBD includes diagnoses of Crohn's disease (CD) and Ulcerative Colitis (UC)
  - 2 related, but distinct entities
- Both conditions are chronic, lifelong autoimmune disorders affecting the GI tract, characterized by significant morbidity, reduced quality of life, and at times increased mortality, and which require long term treatment for optimal management.
- Pathophysiology is incompletely understood, but includes the interplay between genetic susceptibility (more than 160 genes identified) as well as environmental factors/triggers (such as infection, antibiotic use, Western diet).
- IBD affects an estimated 1.3 million patients in US, the majority of whom are adults

Pediatric IBD

- 25% of IBD cases are diagnosed in childhood, with a peak onset in adolescence
- ~5-10% of all IBD patients in the US are <18 years of age, making this a relatively rare disease in childhood
- The goal of treatment (regardless of age) is to achieve a stable, durable state of disease remission, including minimizing bothersome symptoms, healing the inflamed mucosa, and avoiding surgery and other complications.

Current Approvals in Pediatric IBD

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	?

- 5 drugs each approved for moderate to severe UC and CD, but only 1/5 approved for pediatric UC and 2/5 for pediatric CD

Barriers to Timely Completion of Pediatric Studies

- Several medications approved for adult IBD have become standard of care in pediatric IBD clinical practice, leading to difficulties with study enrollment.
  - Patients and families may be less willing to take on additional burden of trial participation, when the drug is accessible to them off label through their healthcare provider.
  - Clinicians may be less inclined to participate or refer patients to participate in a trial for a therapy that is widely regarded as effective based on accumulating anecdotal experience.
    - This is not only for reasons of patient convenience, but also has been raised as an ethical issue, pertaining to the inclusion of vulnerable subjects in research.

A Potential Solution: Early Enrollment of Adolescents

- Could early enrollment of adolescents (into adult phase 3 studies, pre-approval) be a possible solution to several of these challenges?

What must be present to consider this approach?

- Sufficient similarity in disease progression and anticipated response to therapy between adult and pediatric patients to support extrapolation
- Prospect of direct benefit to pediatric patients
- Adequate preliminary dosing and PK information to support dose selection in adolescents
- Adequate nonclinical and preliminary clinical safety data in adults to support use in pediatric patients

Similarity in IBD

- Sufficient similarity in disease progression and response to treatment between adult and pediatric patients is generally accepted by the IBD community and FDA.
- This is based on similarities between phenotypes and complications, as well as in response to treatment.
  - Though many treatments are used off label, in general, treatments that are useful in adults have been shown to have similar treatment effect in pediatric patients.*
  - To date, reports on the safe and effective use of many of these medications published by the larger pediatric IBD centers, registries and other sources have not identified any examples where a treatment that is efficacious in adults does not benefit pediatric patients.

*often based on clinical experience, published data and expert opinion, as there are a paucity of controlled clinical trials in this population.

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Prospect of Direct Benefit

- As required by 21 CFR 50 Subpart D, an investigational drug which incurs more than minimal risk… must offer the prospect of direct benefit to individual subjects.

- Initially prospect of benefit was interpreted by both the Agency and Industry Sponsors to mean *clearly confirmed* efficacy data in adults, but the standard is changing as basic science advances, in order to meet the evolving needs of pediatric patients and families.
- Examples of acceptable data in support of prospect of direct benefit vary by the disease, severity of disease, and anticipated risk profile of the drug.
  - In IBD, we may be able to accept encouraging phase 2 efficacy and safety data in adults.
  - In some conditions (those that occur only in infants or children, without analogous condition in adults), it may be necessary to accept encouraging animal data to support the prospect of benefit; otherwise, it may never be possible to develop treatments for certain conditions.

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Dose selection is crucial

- Robust data from phase 2 studies in adults supporting that the chosen dose(s) are likely to be efficacious is an absolute requirement for this approach.
- Data across a wide variety of drugs and diseases support the assertion that adolescents can generally be treated with the same dose as adults and expect similar systemic exposure.*
- Within IBD, we have examples of confirmatory data across multiple products that support this assertion.

*Momper JD, Mulugeta Y, Green DJ, Karesh A, Krudys KM, Sachs HC, Yao LP, Burckart GJ. Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. JAMA pediatrics. 2013 Oct 1;167(10):926-32.

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Support of Safety

- Extrapolation concept applies to efficacy, and not safety. However…
- Enrolling adolescents before a final characterization of the risk/benefit profile of a drug (i.e., pre-approval setting) requires careful consideration of the known and anticipated risks to pediatric patients, informed by:
  - knowledge of other drugs in class, nonclinical studies, risks of no treatment and/or unregulated off-label use
- It is important to acknowledge that waiting for "certainty" is not always in the pediatric patients' best interest.
- If the alternative remains off-label use of a drug because there is no other option available to control a serious disease, the option to enroll adolescents into a clinical trial in the pre-approval setting (with careful oversight and close monitoring) may become an more acceptable option.

Operational Considerations

- Site selection
  - Option to have adolescents referred to an adult site for trial participation
  - Open new sites at higher volume pediatric centers to run the same program

- Trial design considerations
  - Placebo control
    - Rescue therapy, option to exit to open label, issue of equipoise / other available therapies
  - Number of blood draws, visits, and assessments
  - Performance characteristics (validity and reliability) of certain patient-reported outcome (PRO) tools developed for use in adults may not be well established, particularly in the younger adolescents
    - Both the concepts captured, as well as the language used, may require some modification

Other considerations

- Timing of implementation
  - A possible approach to address questions about prospect of direct benefit might be to delay initiation until an interim analysis for futility has been conducted, and an interim DSMB review of safety has occurred
- Sample size of sub-population
  - For a given disease and drug, what constitutes an acceptable sample size of the sub-population that would support an approval for that group, *vs* what would only serve to inform additional necessary pediatric trials
  - May be a moving target pending outcomes and safety issues that may not be fully apparent at the outset.

Successes and Challenges

- The approach to including adolescents into adult phase 3 trials is new in IBD, and is not met with clear enthusiasm by all stakeholders due to:
  - Concerns about differences between FDA and other regulatory bodies
  - Reluctance to expose pediatric patients to an “unknown”
  - Uncertainties regarding whether a small number of enrolled pediatric patients will be adequate to support an early approval below age 18
  - Perceived risk to adult program (efficacy or safety related) on part of industry sponsors
- However, this approach has been clearly successful in some disease areas (asthma, anti-infectives, etc.) and, therefore, warrants consideration.
- Remains one of several potential strategies aimed at achieving a shared goal of collecting adequate data in pediatric patients to appropriately label drugs for safe and effective use, in a timely manner.

Thank you