ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

When Should Pediatric Inflammatory Bowel Disease Patients Be Allowed to Take Approved Therapies for Adults?

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G&H If an inflammatory bowel disease therapy works for adults, can it be extrapolated that the therapy may also work for adolescents and children?

MK Extrapolation of effectiveness is reasonable in the majority of cases while also acknowledging the very strong and unmet need for pediatric-specific research. Although the term extrapolation is often used in the context of regulatory decision-making and approval, this question refers to extrapolation for the purpose of clinical care. In general, pediatric inflammatory bowel disease (IBD) and adult IBD are similar enough that I believe extrapolation is reasonable. For starters, many people with adult IBD were diagnosed during childhood, so it is the exact same disease. For other patients, although there may be some differences between pediatric-onset and adult-onset IBD in terms of severity, extent, phenotype, and extraintestinal manifestations, the conditions share similar genetics, pathophysiology, natural history, and response to therapy. Indeed, all of the treatments that are effective in adult IBD have also been effective in pediatric IBD. Therefore, in the absence of pediatric data on effectiveness, extrapolation of adult effectiveness data seems reasonable to me, particularly for older children and adolescents. I have a bit more uncertainty as to how extrapolation relates to younger children, particularly those with very early-onset IBD (VEOIBD, diagnosed in children under 6 years of age) and those with infantile-onset IBD (diagnosed in children aged 2 years or younger). This is because smaller children may have increased drug clearance and/or their disease pathology may be different than for older children, with a higher prevalence of monogenic defects linked to different immune pathways.

G&H Could all biologics, small molecules, and Janus kinase inhibitors approved for adults with IBD therefore theoretically be used safely and effectively in adolescents and children who have IBD?

MK Although extrapolation of effectiveness is generally reasonable, as discussed previously, it does not let us off the hook for conducting rigorous studies in children. There are still many questions related to clinical and comparative effectiveness that need to be answered. What is the magnitude of response that can be expected in children compared with adults? What groups of patients are more likely to respond, respond deeply, and respond durably? How does the effectiveness of each biologic and small molecule compare with one another? How should these patients be dosed to achieve optimal benefit? How should these agents be sequenced, combined, and/or integrated into the therapeutic armamentarium along with nutritional and surgical treatments? More research is also needed on safety. Children are not just little adults. Although the range of possible side effects may be similar in children and adults, the magnitude of the risks, especially when measured in absolute terms, may differ. For example, several advanced therapies, defined as biologics and small molecules, have been associated with increased risks of heart disease, thromboembolism, and/or malignancy based on adult studies. As the prevalence of these conditions increases with age in the general population and the magnitude of these treatment-associated risks increases with age in the adult IBD population, pediatric safety data are urgently needed to inform benefit-to-risk calculations for pediatric IBD. There may also be treatment-associated malignancies that are more common

in children than adults. For example, hepatosplenic T-cell lymphoma, often associated with azathioprine and 6-mercaptopurine in combination with anti–tumor necrosis factor (TNF) treatment, appears to be more common in children and young adults as compared with older individuals. Another safety consideration is the risk of infections. Exposure to infections is greater in the pediatric population because children go to school and generally are more social than adults. Therefore, the rate of infections may be higher and immune suppression may increase the severity of these infections. However, as children are less likely to have comorbidities than adults, the severity of infectious complications of advanced therapy may not be as significant as in adults. These general questions apply to all the newer advanced therapies. With this in mind, I am a strong proponent of conducting clinical, comparative-effectiveness, and safety studies in the context of real-world clinical care so that we can collectively learn from every patient and begin to amass the data needed to address these unanswered questions.

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G&H In current clinical practice, when should adult IBD therapies be considered for pediatric or adolescent IBD patients?

MK In the United States, only infliximab and adalimumab are US Food and Drug Administration (FDA)-approved for pediatric IBD, with ustekinumab gaining recent approval of the European Medicines Agency (EMA) for the treatment of pediatric Crohn's disease. With that in mind, it is very reasonable to consider adult IBD therapies in pediatric patients who did not achieve or sustain adequate response to currently approved agents. If a patient had an initial positive response to anti-TNF therapy followed by a secondary loss of response, perhaps because of immunogenicity, then trying a second anti-TNF agent could make sense. If a patient never responded or lost response for a reason other than immunogenicity, then transitioning out of class to one of the newer advanced therapies would be reasonable. When moving out of class, more comparative-effectiveness research is needed to understand the positioning of available agents and which should come next in the sequence.

Another unanswered question is when to consider surgery relative to subsequent medical treatment. If second-line therapy does not work, third-line therapy is less likely to work, and patients experience diminishing returns of subsequent medical therapies. Although patients, parents, and physicians may prefer to avoid surgery if possible, when children are sick for sustained periods of time while moving from one medicine to the next, they miss out on important aspects of life, growth, and educational, psychological, and social development. Deciding between medical therapy and surgical therapy is very important.

For patients naive to anti-TNF therapy, the positioning of newer advanced therapies is a complex question. There are clinical factors as well as patient and family preferences, for which shared decision-making is going to be very important. Does the patient and/or family prefer an already approved medication that has a 20-year track record of effectiveness and safety data behind it, or does the patient and/or family prefer a medicine that is a little newer and may have a more favorable effectiveness and/or safety profile (although pediatric data are limited)? There are also other aspects to medical decision-making. What is possible in terms of insurance approval and authorization? These decisions are often dictated by payors rather than patients, families, and clinicians. Medical-legal considerations, at least in the United States, may also be significant.

Finally, there are still ongoing questions about what should be done if a patient falls short of the goal of treatment (mucosal healing). These include what to do when a patient is clinically feeling well, has an excellent quality of life, has laboratory tests and biochemical findings suggestive of remission, and whose growth and nutritional status have improved, but the patient has not yet achieved mucosal healing. Should the patient switch therapy, or should clinical but not deep remission be accepted, given that not all treatment switches result in improvement and may result in worsening disease control?

G&H Who should be the drivers of the decision-making process for the use of adult treatments in pediatric patients?

MK The drivers should be a combination of the clinician, the parents, and the child, with the child component titrated to a developmentally appropriate level. Many adolescents are often equal decision-makers with their parents, but even younger children can and should be engaged in

the process. Sometimes this means a single conversation with everyone in the same room, and sometimes this means separate conversations, with clinicians having more nuanced discussion with parents than would be appropriate with a child present. A combination of conversations with different audiences is often typical. It is worth mentioning that all too often payors have been inserting themselves into the decision-making process owing to denials and the requirement for prolonged, time-consuming appeals processes. This needs to change so that children can access the care they need when they need it.

G&H How should children and adolescents be evaluated prior to considering adult IBD treatment?

MK Whether for on-label treatment or off-label treatment, the same general considerations should be evaluated. What is the disease being treated—Crohn's disease or ulcerative colitis? What are the severity and current disease activity? What are the extent and phenotype of the disease? What are the extraintestinal manifestations and/or other immune-mediated comorbidities? It is preferable to select a therapy that will be effective in treating the luminal and extraintestinal manifestations, along with comorbidities, if possible. Are the patient's symptoms being driven by intestinal inflammation, which may respond to IBD medications, or are they secondary to anatomic strictures, disorders of gut-brain interaction, or other etiologies that require a different management approach?

G&H Should children and adolescents using adult drugs receive special monitoring (eg, for growth, development, safety)?

MK Yes to all of the above. Pediatric gastroenterologists are especially attuned to symptom burden and functional status in pediatric patients. Are patients doing everything they want to be doing (and need to be doing)? Are they impacted by fatigue? What, if anything, is holding them back? Mental health is very important and quite intertwined with IBD, so patients also need to be monitored for anxiety and depression. Growth, nutritional status, and pubertal development as well as psychosocial and educational development are also very important to monitor. Another key consideration is monitoring adherence, particularly in adolescent patients.

G&H What are the priorities of research?

MK As alluded to previously, there are still many unanswered questions for which further research is needed. We need to better understand the magnitude of intended effects (ie, clinical effectiveness) in the pediatric population as well as the comparative effectiveness of agent A vs agent B, the sequencing and combining of different agents, and the absolute risk and magnitude of potential side effects. The holy grail is the concept of precision medicine. Can clinicians get to a point where they understand a patient's biology well enough to target the right mechanism for the right patient at the right time of their illness?

Dosing is another area where more research is needed. The older the child and the higher the weight, the more comfortable clinicians are with extrapolation from adult data about dosing. For younger children, particularly those with VEOIBD, more data are needed about pharmacodynamics, pharmacokinetics, and how to use exposure matching approaches to identify dose regimens for younger children. As the clearance of advanced therapies may be more rapid in younger children, more research is needed about customized and precision dosing in this population.

G&H How can approval of adult drugs be accelerated for children?

MK Availability and access to non–anti-TNF advanced therapies remain a challenge, as the absence of regulatory approval hinders insurance approvals. Although many of these medicines have been used in children for more than a decade, they are still not FDA-approved in this population, leading to frustration for many pediatric gastroenterology clinicians as well as pediatric patients and families. Particularly for older children and adolescents, relying on extrapolation for efficacy makes sense for a number of reasons. First, there are more similarities than differences between pediatric and adult disease, as mentioned previously. Also, our collective experience over the past several decades has shown that medications that work well in adult IBD also work well in pediatric

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IBD. Encouraging the enrollment of older adolescents in adult trials will be very important to begin to capture data early in the course of drug development and even before approval. Many pediatric gastroenterologists, including myself, favor enrolling children in an open-label, active treatment group rather than a placebo group of adult studies, therefore allowing a head start on the collection of effectiveness and safety data, even prior to FDA approval of adult drugs. I think that would speed up approval. I also want to emphasize that regulatory approval is just the first step, as postapproval clinical, comparative-effectiveness, and safety research will then be needed to better inform treatment choices in this population.

There are a number of adult trials that are currently enrolling older adolescents, and many advanced therapies are undergoing separate pediatric trials. Ustekinumab data from the recent UNITI Jr and UNIFY Jr trials have recently been published, leading to recent EMA approval. Vedolizumab studies are underway and have completed enrollment; those results are eagerly awaited. Thus, development and progress are underway; they are just going slowly.

Disclosures

Dr Kappelman is a consultant to Takeda and Eli Lilly and a shareholder in Johnson & Johnson.

Suggested Reading

Atia O, Shavit-Brunschwig Z, Lev-Tzion R, et al. Maintenance treatment with vedolizumab in paediatric inflammatory bowel disease (VEDOKIDS): 54-week outcomes of a multicentre, prospective, cohort study. *Lancet Gastroenterol Hepatol.* 2025;10(3):234-247.

Hyams JS, Winter HS, Mulberg AE, Zuckerman E. An open letter to the Food and Drug Administration and pharmaceutical industry concerning drug approval for children with inflammatory bowel disease. *Inflamm Bowel Dis*. 2024;30(12):2523-2525.

Mulberg AE, Conklin LS, Croft NM; I-ACT for Children Pediatric Extrapolation Working Group. Pediatric extrapolation of adult efficacy to children is critical for efficient and successful drug development. *Gastroenterology*. 2022;163(1):77-83.

Steiner SJ, Adler J, Saeed SA, et al; ImproveCareNow Learning Health Network. Effectiveness and safety of ustekinumab in pediatric Crohn's disease: results of the REALITI study [published March 2, 2026]. *J Pediatr Gastroenterol Nutr*. doi:10.1002/jpn3.70372.

Turner D, Assa A, Malham M, et al. Reshaping study design for faster extrapolation-based drug approval in pediatric inflammatory bowel diseases: an ESPGHAN-NASPGHAN position paper. *J Pediatr Gastroenterol Nutr*. 2026;82(3):867-894.

Turner D, Russell RK, Wine E, et al. Response to FDA draft guidance on pediatric IBD drug approval trials: a consensus statement from the IBD Porto Group. *J Pediatr Gastroenterol Nutr*. 2025;80(1):238-241.

US Food and Drug Administration. Pediatric inflammatory bowel disease: developing drugs for treatment guidance for industry: draft guidance. Released July 2024. https://www.fda.gov/media/180126/download.

Wine E, deBruyn J, Crowley E, Griffiths AM; Canadian Children IBD Network. Response from the Canadian Children Inflammatory Bowel Disease Network to the US Food and Drug Administration draft guidance for industry on pediatric inflammatory bowel disease: developing drugs for treatment. *J Can Assoc Gastroenterol*. 2024;7(6):397-398.