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Targeted Dosing as a Precision Health Approach to Pharmacotherapy in Children with Inflammatory Bowel Disease

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Abstract

As clinicians have begun to provide targeted pharmacotherapy for children with inflammatory bowel disease (IBD), several ethical challenges have arisen. In this paper, we review 3 challenges related to applying a precision health approach to pediatric IBD populations: selection of a disease monitoring method, pharmacotherapy optimization, and economic considerations in clinical decision making.

Precision Health Approaches for Pediatric Patients with Inflammatory Bowel Disease

Over the past several years, there has been increased attention directed towards precision health in pediatric medical care.[1] Precision health is particularly relevant when considering how to manage pediatric chronic disease and, specifically, how to personalize medical care that considers children's unique needs. Inflammatory bowel disease (IBD) is an example of a pediatric chronic illness for which precision health is particularly valuable.

IBD, consisting of Crohn's disease and ulcerative colitis, is an autoimmune condition affecting the gastrointestinal tract.[2] This disease process is marked by periods of disease flares (eg, intractable bloody diarrhea, marked weight loss and growth failure, debilitating abdominal pain, fatigue) and remission. The primary treatment for IBD in both children and adults consists of immune suppressive medications, nutritional support, and abdominal or colorectal surgery when necessary.

Patients who are diagnosed with IBD during childhood often have a more severe disease course than patients who are diagnosed during adulthood. Enduring periods of relapsing and remitting disease from a young age can lead to significant functional limitations (eg, not able to go to school or work) and poor quality of life throughout patients' lives.[3,4] When considering precision health in this vulnerable pediatric population with IBD—for example, for differential diagnosis or prognostication[5,6]—the central focus should be a more targeted approach to immune suppressive pharmacotherapy that limits the opportunity loss described above and supports health gains throughout a child's life.

The current Food and Drug Administration (FDA) approach to pharmacotherapy for pediatric IBD is a one-size-fits-all dosing strategy in which drug dosing and guidance are extrapolated from adult trials.[5] This approach is problematic and raises ethical concerns because pharmacokinetic data in children suggest that they have significantly different dosing needs than adults.[7] Yet drug approvals for children remain stagnant, and off-label use is the norm for most medications prescribed to children.[8] Specifically, there is a lack of pediatric clinical trial data from phase 2 and 3 drug trials, resulting in data from adult studies informing best-guess drug dosing of adult-only approved medications in clinical care for children.

Targeted pharmacotherapy is increasingly recognized as a preferable treatment approach as it accounts for differences in children's genes, environment, psychosocial functioning, and lifestyle. However, ethical challenges arise when clinicians apply a precision health approach to pediatric IBD by adopting targeted dosing strategies. This article outlines 3 key ethical challenges: choice of disease monitoring method during targeted pharmacotherapy, optimization of targeted pharmacotherapy, and economic considerations in targeted pharmacotherapy.

First Challenge: Choice of Disease Monitoring Method during Targeted Pharmacotherapy

When applying a precision health approach to pediatric IBD patients undergoing pharmacotherapy that suppresses the immune system, choosing age-appropriate disease monitoring methods is of utmost importance since off-label drug use is often standard of care.[9] In adult IBD care, monitoring disease by endoscopy with mucosal biopsies is the best method to optimize health outcomes. In pediatric IBD care, repeated endoscopy is not feasible given the repeated general anesthesia requirement.[10] Since the gold standard in IBD treatment is to visualize healed mucosa by endoscopy, pediatric IBD specialists need to judiciously recommend endoscopy at strategic points in care (eg, at diagnosis or when changing therapies) and rely on the best approximation of endoscopy (ie, blood tests, stool markers, disease activity scores) to make decisions about targeted pharmacotherapy.

The primary ethical challenge facing pediatric IBD specialists is the equipoise of risk versus benefit of repeated endoscopies in children (and associated complications including adverse neurological effects of repeated general anesthesia during early childhood).[11] The risk versus benefit tradeoff is often patient-specific and cannot be generalized to the entire pediatric IBD population. The clear benefit of endoscopies is precision and accuracy in assessing true disease burden and the associated confidence in treatment decisions. While noninvasive blood and stool monitoring tests are available, they are less precise and pose challenges. For example, consistent adherence to stool collection for fecal calprotectin levels (a potentially accurate surrogate for endoscopy[12]) can be impractical for children.[13]

Another important ethical question relates to reliance on patient-reported outcomes in children for purposes of monitoring treatment effects for targeted pharmacotherapy. While patient-reported outcomes provide valuable information about the patient experience and IBD symptoms,[14] reliance on patient-reported outcomes is inherently subjective and has been shown to be an imprecise measure of mucosal-level inflammation.[15] The challenges associated with patient-reported outcomes can be seen clearly when considering abdominal pain. Complaints of abdominal pain in youth are often indicative of active disease and chronic inflammation. However, more than a quarter of youth experience recurrent abdominal pain during disease remission that is not related to inflammation.[14,16] Thus, patients' reporting of abdominal pain on patient-reported outcomes could reflect an active IBD flare or pain related to non-IBD causes (eg, irritable bowel syndrome, hypersensitivity, functional abdominal pain). Solely relying on patients' reporting of abdominal pain for disease monitoring raises ethical concerns as it can result in increased and unnecessary interventions (eg, endoscopies, ionizing radiographic tests) and pharmacotherapy (eg, opioids or escalating use of steroids and biologics).[17,18] Exposing children to such treatments can result in negative health outcomes such as adverse neurological effects of anesthesia, including developmental and behavioral problems,[19] and increased risk for future opioid misuse.[20,21] Given these challenges and risks, it is important for clinicians to actively listen to and validate patients' experiences and reporting of physical symptoms while not solely relying on patient-reported outcomes to guide IBD treatment decisions when applying a precision health approach.

Second Challenge: Optimization of Targeted Pharmacotherapy

Once a child has been diagnosed with IBD or disease activity progresses, initiating or escalating treatment is warranted. Infliximab (IFX) is the mainstay therapy to achieve remission in pediatric and adult populations with IBD.[22,23] As highlighted above, pediatric dosing is based on adult clinical trials. However, pediatric IFX dosing needs often exceed recommended dosing guidance. For example, reliance on adult dosing in children with Crohn's disease can lead to less than 41% probability of adequate drug exposure.[24] Such significant discrepancies in drug clearance profiles between children and adults can result in early drug failure and worse outcomes for children with IBD.[24]

Choosing the correct pharmacotherapy and targeting pharmacotherapy in an evidence-based way is critical to ensuring appropriate patient care aimed at optimizing future health gains. Early modification of IBD through targeted pharmacotherapy can potentially lead to a milder disease course later in life.[25] Conversely, inadequately treated disease during childhood can potentially lead to more refractory disease during adulthood.[26] The ethical challenge arises when dosing guidance by governing bodies, including the FDA, is based on populations (ie, adults) that are inherently different than the treated population (ie, children), as is the case with IFX. Using guidelines that do not promote best quality care for pediatric IBD populations and that potentially lead to

negative long-term health outcomes poses a significant conundrum for clinicians. There is a significant need for more IBD pharmacotherapy trials (eg, of IFX) with pediatric IBD populations to address ethical concerns—namely, beneficence—that arise when large-scale trials on the safety and efficacy of IBD pharmacotherapies do not include children.

Third Challenge: Economic Considerations in Targeted Pharmacotherapy

In today's era of biologics, IBD therapies have become increasingly effective but costly.[27] Prior to the advent of biologics like IFX, cost-effective IBD care was traditionally focused on containing acute care costs, such as frequent hospitalizations and emergency department visits. Currently, however, the cost of these deliverables is outpaced by the cost of pharamcotherapies.[28] Approximately half of all costs for Crohn's disease are attributed to medications.[28] Since children endure worse disease severity and need early immune-modifying therapies, pediatric patients with IBD are more expensive to treat than adults.[29] The incidence of pediatric-onset IBD has also increased and is higher than previously anticipated.[30] For these reasons, applying targeted pharmacotherapy to pediatric IBD patients can lead to high costs for patients, families, and hospital systems.

Given the increasing demand for biologics and rising health care costs, appropriate IBD treatment has come under scrutiny. Finding the right drug and dose for an individual patient must balance the clinical appropriateness of the medication against the likely cost to the patient and society. While precision in monitoring and dosing is more difficult without consensus-driven outcome measures (ie, repeated endoscopy) and pediatric clinical trial data, overtreating or undertreating pediatric IBD has long-term consequences, often for both the individual and society.

Clinicians sometimes face the ethical challenge of altering pharmacotherapy strategies based on whether a patient has commercial insurance or Medicaid. Health systems are well aware of what commercial payers will reimburse and what Medicaid will not. When expensive therapies that are not covered or not covered fully under Medicaid are started for patients with Medicaid, health systems invariably lose money. Reimbursements from private insurers subsidize the therapy plans of those patients who have inadequate insurance coverage. Some clinicians are aware of the intricate bidirectionality of revenue streams, which may factor into pediatric IBD clinical decision making. Prioritizing hospital revenue and society over the individual (eg, not using biologics on children with Medicaid due to lack of reimbursement) runs the risk of undertreating vulnerable populations of children, leading to inadequate disease management and worse longer-term health outcomes. An important future direction would be to assess the extent to which economic considerations factor into pharmacotherapy decisions among pediatric IBD specialists. This data would support further discussion between clinicians and hospital systems about the ethical challenges related to targeted pharmacotherapy and how to provide the best quality care to pediatric IBD patients while protecting all parties from financial harm.

Resolving Ethical Challenges for Pediatric IBD Patients

In summary, children with chronic diseases such as IBD are vulnerable, and in an effort to provide precision health to them, numerous ethical considerations arise that highlight the opportunity for individual-level and system-level improvement.[31] Children with IBD are not small-sized adults, and clinical endpoints of therapy using age-appropriate, noninvasive methods of disease monitoring are urgently needed.[32,33] Extrapolation of drug dosing guidance from adult IBD data can lead to a suboptimal, one-size-fits all approach for children that can impair pharmacotherapy effectiveness, affect long-term outcomes, and raise safety concerns. Finally, economic considerations are increasingly a part of clinical decision making that will require patient-centered discussions and systematic thought from all stakeholders.

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