Clinical Trials (Clinical Perspective)

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Introduction

Recent epidemiologic studies report that up to 30% of new cases of inflammatory bowel diseases (IBD) are diagnosed in childhood [1]. Pediatric IBD seem to be more extensive and severe than the adult-onset forms, with a frequent need of second-line therapies, including immunomodulators and biologics, and a more complicated disease course [2, 3]. However, excluding the very-early-onset diseases (before 5 years of age), their pathogenesis, histopathological features, and response to treatments seem to be similar to the adult-onset disease [4], and most therapeutic pediatric strategies are simply "extrapolated" from adult trials in an "off-label" use. Indeed, randomized clinical trials (RCTs) in children could be more difficult for several reasons: first of all ethical concerns, due to the natural vulnerability of this population, and then for the relative paucity of eligible patients, because of the lower number of incident and prevalent cases, compared with adults. Moreover, parents, worried about possible therapy adverse events and/or for additional invasive tests and visits, are more hesitant to have their children recruited in intervention trials, compared to adult patients. Often, the same physicians hesitate to enroll small patients to intervention studies involving invasive procedures.

However, children with IBD represent a unique cohort of patients to be explored, including the initial host immune response, the need for early "aggressive" treatment, the genotype-to-phenotype relationship, and the natural disease course which are concerned. Above all, because of the low impact of environmental factors that may influence adult-onset disease (e.g., comorbidities, disease duration, drugs, smoking), the knowledge of the pathogenetic pathways of pediatric IBD can provide insights into the initial mechanisms underlying the disease [5].

A crucial factor when evaluating the efficacy of different treatments in children with IBD is the ability to compare new drugs to known therapies in a meaningful way. Randomized clinical trials lead to gold standard evidence on the efficacy of pharmacologic and nonpharmacologic therapy of IBD. An ideal clinical trial should answer to well-defined primary research endpoints in specific study populations and should provide results that are significant both statistically and clinically. Steps that describe RCTs are clear definition of the primary (and secondary) outcomes, definition of the eligible population, randomized assignment to the treatment regimen, and standardized and well-defined interventions. Moreover, a well-defined study population is based upon clear outlined inclusion and exclusion criteria. Trial design should be sufficiently linear to fulfill the trial's questions; on the other hand, it must not be so weighty that physicians cannot complete the study. Very recently, an evidence-based, expert-driven practical statement paper of the pediatric ECCO committee on the outcome measures for clinical trials in pediatric IBD has been published [6]. Several important outcomes have been highlighted for the future RCTs on pediatric IBD, the first being the recommendation of defining steroid-free mucosal healing (MH) as assessed by endoscopy as the primary endpoint for all preauthorization trials for a new drug authorization. Mucosal healing has emerged as a specific treatment endpoint in adult IBD, both in clinical trials and in clinical practice, as it is associated with a reduced risk of disease exacerbations in the long term, treatment escalations, and colectomy [7, 8]. Sparce prospective studies in children have been performed using MH as a primary outcome so far [9]. In the case of therapies already demonstrated to induce MH in adult trials, ECCO experts recommend to use objective measures of disease activity [weighted Paediatric Crohn's Disease Activity

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Index (wPCDAI) or Paediatric Ulcerative Colitis Activity Index (PUCAI)] as primary endpoints, although MH is always suggested as secondary outcome in subgroups of patients. Specific importance should be given to the timing of assessment of primary and secondary outcomes, being 6–12 weeks of therapy the optimal time window suggested for the induction of remission and 12 months to evaluate the maintenance of steroid-free remission. One of the main barriers to perform a pediatric RCT is the potential need of placebo arm. Indeed, although a randomized, double-blind, parallel group trial is regarded as the ideal study design for assessing the efficacy of a new drug, this can prompt ethical and feasibility problems for pediatric studies [10]. In the same guidelines, ECCO experts stated that placebo-controlled trials are hardly suitable in the design of clinical trials for the vulnerable population of children with IBD. A placebo may be considered for evaluating additional treatments, provided that both study groups (treatment and control) receive effective therapy. A recent joint position paper from ESPGHAN, ECCO, the global PIBDnet, and the Canadian pediatric IBD network further states that placebo should only be accepted in children with IBD when true equipoise exists against the active therapy, whereas it should not be used when previous adult trials have already shown the efficacy of the active treatment, supported by clinical experience in children [11].

Recently, the Food and Drug Administration (FDA) has declared that pediatric studies are not necessarily required for all new treatments; however, "extrapolation" from adult trials should always be taken into account of drug pharmacokinetics, pharmacodynamics, and evaluation of potential and real side effects/toxicities. However, it is still emphasized that the pharmaceutical industry should focus on pediatric pharmacokinetic studies for those medications with a strong potential impact in children; moreover, specific pediatric outcomes, including the impact on growth and bone-related issues, cannot be evaluated based on adult studies. Therefore, an accurate balance between the concerns of conducting a pediatric trial and the advantages of having well-defined data should always be sought for any proposed trial.

Summary

Up to now, only few RCTs in children with IBD have been performed. Although pediatric and adult IBD probably share their pathogenetic mechanisms, histopathological damage, and response to therapies, an accurate balance of the usefulness of the data collected in adult studies and those particularly required for the optimal knowledge of the efficacy and safety of new drugs suggested for pediatric IBD should always be considered. Partial extrapolation of adult data could be reasonable and tolerable, when including data on drug pharmacokinetic and pharmacodynamics, together with its potential or real adverse events; however, pediatric RCT is needed to identify specificities of treatment strategies in children, understand the long-term impact of new treatment strategies on specific outcomes (growth and bone-related issues), and ensure that children with IBD can access to new treatments in an acceptable period of time.

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