Use of Placebo in Pediatric Inflammatory Bowel Diseases: A Position Paper From ESPGHAN, ECCO, PIBDnet, and the Canadian Children IBD Network

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See Commentary on ''The Use of Placebo in Pediatric Inflammatory Bowel Diseases'' by Winter on page 5.

ABSTRACT

Performing well-designed and ethical trials in pediatric inflammatory bowel diseases (IBD) is a priority to support optimal therapy and reduce the unacceptable long lag between adult and pediatric drug approval. Recently, clinical trials in children have been incorporating placebo arms into their protocols under conditions that created controversy. Therefore, 4 organizations (the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; European Crohn's and Colitis Organization; the Canadian Children IBD Network; and the Global Pediatric IBD Network) jointly provide a statement on the role of placebo in pediatric IBD trials. Consensus was achieved by 94 of 100 (94%) voting committees' members that placebo should only be used if there is genuine equipoise between the active treatment and placebo; for example, this may be considered in trials of drugs with new mechanisms of action without existing adult data, especially when proven effective alternatives do not exist outside the trial. Placebo may also be used in situations where it is an ''add-on'' to an effective therapy or to evaluate exit-strategies of maintenance therapy after long-term deep remission. It has been, however, agreed that no child enrolled in a trial should receive a known inferior treatment both within and outside the trial. This also includes withholding therapy in children who show clinical response after a short induction therapy. Given the similarity between pediatric and adult IBD regarding pathophysiology and response to treatments, drugs generally cannot be considered being in genuine equipoise with placebo if it has proven efficacy in adults. Continued collaboration of all stakeholders is needed to facilitate drug development and evaluation in pediatric IBD.

Key Words: clinical trials, European Crohn's and Colitis Organization, European Medicines Agency, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, US Food and Drug Administration, pediatrics, Pediatric Inflammatory Bowel Disease Network (PIBDnet)

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What Is Known

- A placebo arm has been incorporated into the protocols of recent regulatory trials in pediatric inflammatory bowel diseases.
- This new stance has led to controversy among stakeholders regarding the appropriate place of placebo in children with inflammatory bowel diseases.

What Is New

- This position paper from ESPGHAN, ECCO, the global PIBDnet, and the Canadian Pediatric IBD network states that placebo should only be used in pediatric inflammatory bowel diseases when true equipoise exist against the active treatment.
- Placebo should be avoided when the active treatment has been proven to be effective in prior large trials in adults, supported by clinical experience in children.
- No child enrolled in a trial should receive a known inferior treatment than the standard of care.
- This includes withholding maintenance treatment in a child responding to a short induction treatment.
- The group emphasizes that it is important to perform pediatric trials to understand how to use the new drug in children.
- Placebo can be used when it is an add-on treatment to an effective treatment and after a long period of deep remission.

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After approval of new therapies for adults with inflammatory bowel diseases (IBD), there is a long delay before pediatric trials are started, and an even longer delay until such therapies receive pediatric approval (Fig. 1). Although children and adolescents with IBD may have more aggressive and extensive disease than adults, it is generally accepted that the pathophysiology and response to treatment are similar in the 2 groups (excluding very-early-onset IBD). This has led pediatric gastroenterologists to widely apply ''off-label'' use of the therapies approved for adult use.

Recently, regulators united to discuss common approaches toward a much-needed harmonized drug-development process in pediatric IBD (1,2). Among others, they concluded that partial extrapolation of efficacy from informative adult studies may be appropriate, allowing for small pediatric trials that are underpowered to demonstrate efficacy. It was also suggested that a placebo arm should generally be included in pediatric IBD maintenance trials (2). The regulators stated that the risks of placebo are minimal if an early escape strategy is embedded within the protocol. This led to an international controversy among the stakeholders with ongoing constructive discussions with regulators.

This position paper from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), the European Crohn's and Colitis Organization, the Canadian Children IBD Network, and the global Pediatric IBD Network is written after an intensive face-to-face discussions and multiple e-mail exchange within the groups and its governing boards and an open dialogue initiated by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It is supported by 94 (94%) of the 100 pediatric IBD experts who voted, from the relevant governing committees of the 4 supporting organizations (see Appendix for a list of supporting members, http://links.lww.com/MPG/A573). Two Canadian bioethicists were involved in the discussions as well as the ethics committee of ESPGHAN.

WHERE IS THE RIGHT PLACE FOR PLACEBO IN PEDIATRIC IBD TRIALS?

According to the Declaration of Helsinki and the EU GCP Directive (2001/20/EC), no child enrolled in a trial should receive a known inferior treatment available outside the trial (3). Similarly, the 2014 Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans cautions that where there is an established therapy, use of a placebo may deprive participants of needed therapy (http://www.pre.ethics.gc.ca/pdf/eng/tcps2–2014/TCPS_2_FINAL_Web.pdf). Thus, the use of placebo-controlled trials in children is generally considered adequate only if there is clinical equipoise, both against the active comparator within the trial and against standard of care outside the trial. Equipoise is defined ''a genuine uncertainty on the part of the expert community about the therapeutic benefits of each arm.'' This may be the case when a new therapy with a novel mechanism of action without established data in adults is to be evaluated in children, when no other alternatives with proven efficacy exist outside the trial. Placebo may also be used in situations where it is an ''add-on'' to an effective therapy, while the effective therapy is continued. In children with IBD with longstanding deep remission with proven mucosal healing, discontinuation of effective treatment may be clinically reasonable and thus randomization to placebo or a drug treatment may be considered. This, however, has not been the design of phase-3 pediatric trials hitherto performed for regulatory purposes.

CONCERNS ARISING FROM THE DESIGN OF PRESENT TRIALS

Concerns have arisen in view of the study design of a recently launched clinical trial to examine the role of a biologic agent in pediatric ulcerative colitis (UC). In this phase-3 trial, children with moderate-to-severe disease responding to a short open label induction phase are randomized to 3 maintenance groups, including placebo. The apparent justification for including placebo is that it would be unclear whether the biologic drug is effective in children. The drug, however, has proven to be effective in large placebo-controlled trials in adults with IBD and is already approved for use in adults for that indication. This drug has been used extensively ''off-label'' for several years in children, and the clinical experience of many pediatric IBD experts supports the conclusion that the drug is effective also in children. Therefore, the question whether equipoise exists in pediatric trials is markedly influenced by how much the medical community accepts extrapolation of results from prior adult IBD placebo-controlled trials to the pediatric patient. If one accepts sufficient extrapolation, then once a drug has been proven to be effective in adults and is being used ''off label'' in children, study design must take into account the fact that offering a placebo may be inappropriate because it does not meet the requirements of standard of care and noninferior treatment.

Practically, the medical community accepts extrapolation on an everyday practice. Pediatric IBD experts are using therapies approved for adult IBD in their pediatric patients years before pediatric data are available. In fact, there has not been hitherto any single precedent in which an IBD drug proved to be effective in

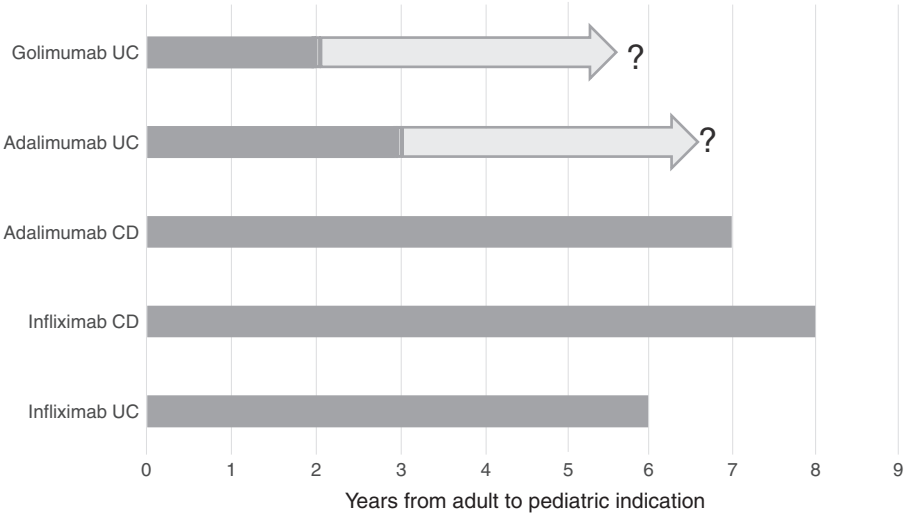

FIGURE 1. Years interval from approval of biologics in adults to approval in children. Top 2 indications have not received pediatric approval yet and pediatric trials are ongoing; the light gray arrows illustrate the anticipated future years to approval.

adults but not in children (eg, steroids, budesonide, 5-ASA, azathioprine, methotrexate, cyclosporin, infliximab, adalimumab, thalidomide, beclomethasone diproprionate, and so on; Fig. 2). Therefore, the adequacy for using placebo after just a few weeks of active therapy in pediatric patients with a severe and treatable disease has been questioned, and many pediatric gastroenterologists resist participating in such a trial that would expose some of their patients to withdrawal of an apparently effective therapy. Members of this group are aware that other studies are presently planned with a similar design using a placebo control for drugs that have been proven effective in prior adult placebo controlled trials.

ESPGHAN, European Crohn's and Colitis Organization, the Canadian Children Inflammatory Bowel Disease (IBD) Network, and the global Pediatric IBD Network take the view that one should not include a placebo arm in pediatric IBD trials if this leads to withholding therapy that can be reasonably assumed to be beneficial, based on the results of trials from adults, strengthened by preceding clinical experience in pediatric patients. It is questionable whether continuing existing treatment, such as thiopurines, can be considered effective treatment because the drug has failed previously, as evident from the inclusion of the child with active disease to a trial.

It should be emphasized, however, that the group recommends extrapolation of drug efficacy only for IBD and each disease must be considered individually. It should also be emphasized that although prior adult IBD data predict effectiveness also in children, it does not exempt the scientific community and pharmaceutical companies to conduct randomized-controlled studies in children to understand dosing, safety, and the best way to use the drug in children. We propose to consider pediatric trial designs in which the

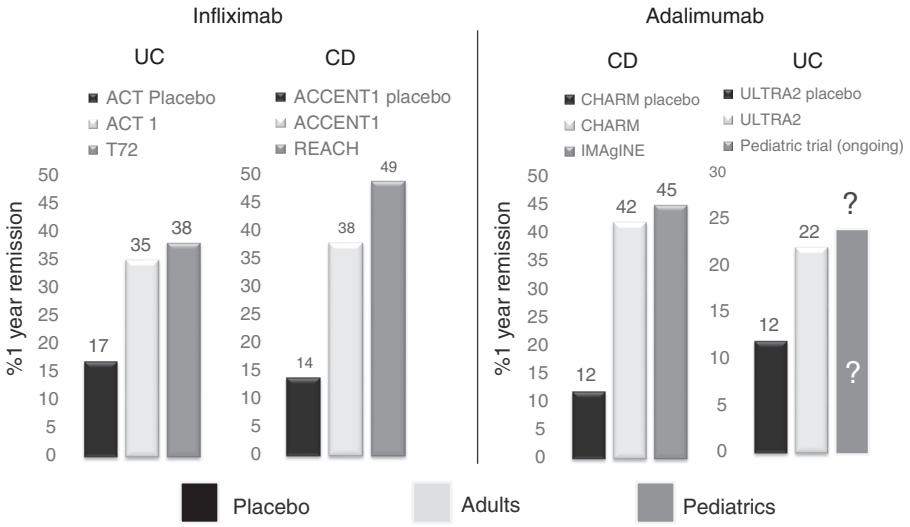

FIGURE 2. Comparison of adult and pediatric biologics trial results. For the sake of fair comparisons between pediatric and adult trials, REACH data reflect complete intention to treat (including primary nonresponders), and the IMAgINE and CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trials include only those who were infliximab naïve.

comparator would be an active arm of an established standard treatment and also perform studies focusing on pharmacokinetics, pharmacodynamics,(PK/PD), and safety. We also propose focusing more attention on young children (2–11 years of age), given the open questions on appropriate drug dosage in this population.

Regarding maintenance therapy, an early trial by Markowitz et al (4) on the effect of thiopurines in an inception cohort of children with Crohn disease (CD), which was performed when maintenance treatment in newly diagnosed children was not considered standard of care, showed clear superiority of maintenance treatment over placebo, after an open-label induction period with steroids. Since then, many studies with different drugs, in various populations and conditions confirmed that exacerbation would occur unless children are kept on maintenance treatment, especially following a moderate-severe exacerbation that is the typical prerequisite inclusion into biologics trials. The more extensive nature of pediatric IBD as compared with adults, the risk of lasting growth impairment, and the fact that children depend on the decision of their caregivers, mandates that children who had moderate-severe IBD are not left without available effective treatment. Caregivers must make all choices for the best interest of their child and cannot consent to participation of their child in a drug trial only for the benefit of future patients, as altruistic adults may elect to do for themselves. Withholding treatment deviates from accepted clinical practice and standard of care, as recommended in the present pediatric guidelines of managing UC and CD (5,6).

It has been proposed that children with IBD randomized to placebo may benefit, because the placebo-induced clinical remission has been reported as high as 20% in UC and CD (7,8). Objective measures of mucosal inflammation, however, are now considered more appropriate as primary outcomes (9). When using complete mucosal healing as the study outcome, placebo remission rate is very low or even zero, as previously reported (10,11).

DRUG WITHDRAWAL AFTER CLINICAL RESPONSE AND LATER REINTRODUCTION

Regulators presently foresee study design in children as an open-label induction phase, followed by drug withdrawal in responders with randomization to active drug and placebo and potential later reintroduction of the active drug, if needed (2). Response, however, does not equal remission and children with moderate-severe disease at trial entry who are considered responders may still have active disease at the time of randomization. Standard clinical practice would not lead to interrupting drug treatment in children with residual active disease. In fact, standard clinical practice mandates continuation of a long-term maintenance active treatment in all children after moderate-severe attack even if they achieve complete remission after a short induction therapy (5,6).

If one would randomize only children who achieved ''complete'' clinical remission, a practical difficulty arises. Assuming a clinical remission rate of ~30% after a short induction phase, as in prior pediatric biologics trials (12–14), one would need to enroll >1000 children into the induction phase to achieve an adequately powered study during the maintenance phase with a placebo and 2 arms with different dosages, which is not really feasible. Enrolling 200 children to the induction phase would yield a power of <25% in the maintenance phase under the same assumptions. Indeed, the regulators concluded about the studies of IBD in children: ''In the setting of partial extrapolation, clinical studies do not need to be fully powered for efficacy'' (2). If trials are not powered to demonstrate efficacy, the need of placebo becomes even more questionable.

A further concern about the presently proposed study designs is the potential disadvantage of the temporary withdrawal of biologics regarding later efficacy and safety. The STORI (infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors) trial studied 115 adults with CD treated with both infliximab and immunomodulator for at least 1 year, who were in steroid-free clinical remission for at least 6 months (15) and in whom infliximab treatment was then stopped. Most patients with signs of mucosal inflammation (as usually evident 6–8 weeks after starting induction treatment) flared shortly after discontinuation of the drug. A total of 12% of those re-treated with infliximab did not respond any more. Similarly, in other studies, the average nonresponse to re-introduction of biologics after a temporary drug withdrawal has been 10% to 15%, and most studies included selected cohorts of patients with long standing remission with concomitant immunomodulators (15–22). Thus, this figure likely represents a conservative nonresponse estimate. A meta-analysis of 7 studies showed that a temporary biologic drug withdrawal is associated with significantly higher rate of serious infusion reactions (23). Therefore, the study designs based on drug withdrawal in patients responding to induction therapy and the possibility of later re-introduction may put participating children at a significant disadvantage, and hence remain highly controversial.

CONCLUSIONS

Performing timely, well-designed, and ethically sound clinical drug trials in pediatric IBD is an important priority since at present too many medications are prescribed as ''off label'' in children. The development and assessment of drugs for pediatric IBD, however, will not be facilitated if trial designs are considered inappropriate or nonenrollable by the medical community and/or patients. Placebo-controlled trials continue to be the criterion standard for drug evaluation, but they can only be used in pediatrics if there is clinical equipoise, that is, a genuine uncertainty shared by the medical community about the therapeutic benefits of each arm. Further discussion and close collaboration of all stakeholders, including medical-scientific societies, patient organizations, regulatory agencies, and the pharmaceutical industry is needed to facilitate optimal care for children and adolescents with IBD.

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