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Use of placebo in pediatric inflammatory bowel diseases: A position paper from ESPGHAN, ECCO, PIBDnet and the Canadian Children IBD Network

Dan Turner[1,2,3,5], Sibylle Koletzko[1,3,6], Anne M. Griffiths[1,3,4,7], Jeffrey Hyams[3,8], Marla Dubinsky[3,9], Lissy de Ridder[1,3,10], Johanna Escher[1,3,10], Paolo Lionetti[1,3,11], Salvatore Cucchiara[1,2,3,12], Michael J. Lentze[1,13], Berthold Koletzko[1,6], Patrick van Rheenen[2,14], Richard K. Russell[1,2,3,15], David Mack[4,16], Gigi Veereman[1,3,17], Séverine Vermeire[2,18], Frank Ruemmele [1,3,19]

[1] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

[2] European Crohn's and Colitis Organization (PECCO)

[3] Global pediatric IBD network (PIBDnet)

[4] Canadian Children IBD Network: a joint partnership of the Canadian Institutes of Health Research and the CH.I.L.D. Foundation

[5] Institute of Pediatric Gastroenterology, Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Israel; [6] Ludwig-Maximilians-University of Munich, Dr. von Hauner Children's Hospital, Univ. of Munich Medical Center – Klinikum der Universität München, München, Germany; [7] The Hospital for Sick Children, University of Toronto, Canada; [8] Connecticut Children's Medical Center, Hartford, Connecticut, USA; [9] Department of Pediatrics, Feinstein IBD Center, Icahn School of Medicine, Mount Sinai, New York, USA; [10] Department of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; [11] Department Neurofarba, University of Florence – Meyer Hospital, Florence, Italy; [12] Sapienza University of Rome, Italy; [13] Dept. Pediatrics, Children's Hospital Medical Center, University Hospitals, Bonn, Germany; [14] University of Groningen, University Medical Centre Groningen, Netherlands; [15] The Royal Hospital for Children, Glasgow, UK; [16] Children Hospital of Eastern Ontario, University of Ottawa, Canada; [17] Children's University Hospital, Brussels, Belgium; [18] University Hospitals Gasthuisberg, Belgium; [19] Hôpital Necker-Enfants Malades, Paris, France;

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Correspondence

Dan Turner MD, PhD

Juliet Keidan Institute of Pediatric Gastroenterology

Shaare Zedek Medical Center

P.O.B 3235

Jerusalem 91031, Israel

Tel +972-2-6666482

Fax +972-2-6555756

Email: turnerd@szmc.org.il

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ABSTRACT

Performing well designed and ethical trials in pediatric inflammatory bowel diseases (IBD) is a priority to support optimal therapy and to 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, four organizations (ESPGHAN, ECCO, the Canadian Children IBD Network and the global pediatric IBD network (PIBDnet)) jointly provide a statement on the role of placebo in pediatric IBD trials. Consensus was achieved by 94/100 (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. However, it has been 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 in regards to 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.

Keywords: pediatrics; study design; placebo; clinical trials; FDA; EMA; ESPGHAN; PIBDnet; ECCO

Introduction

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 (Figure 1). While 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 two groups (excluding very early onset IBD). This has led pediatric gastroenterologists to widely apply “off-label” use of 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 ESPGHAN, ECCO, the Canadian Children IBD Network and the global Pediatric IBD network (PIBDnet) is written following intensive face-to-face discussions and multiple email exchange within the groups and its governing boards and an open dialogue initiated by the United States 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 four 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 Helsinki declaration and the EU GCP Directive (2001/20/EC), no child enrolled in a trial should receive a known inferior treatment (3). Similarly, the 2014 Canadian Tri-Council Policy Statement (TCPS) 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 of the trial. Equipoise is defined as "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, especially 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 IBD children 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. However, this has not been the design of phase-3 pediatric trials performed for regulatory purposes.

Concerns arising from the design of current 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 UC. In this phase-3 trial, children with moderate to severe disease responding to a short open label induction phase are randomized to three maintenance groups, including placebo. The apparent justification for including placebo is that it would be unclear whether the biologic drug is effective in children. However, the drug 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 in account the fact that offering a placebo may be inappropriate as it does not meet the requirements of standard of care and non-inferior 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 (Figure 1), since the evidence supports similarity between pediatric and adult IBD in regards to genetics, pathophysiology, immunology and response to treatments. In fact, there has not been hitherto any single precedent where an IBD drug proved to be

effective in adults but not in children (e.g. steroids, budesonide, 5-ASA, azathioprine, methotrexate, cyclosporin, infliximab, adalimumab, thalidomide, beclomethasone diproprionate etc; Figure 2). Therefore, the adequacy for using placebo following 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 currently planned with a similar design using a placebo control for drugs which have been proven effective in prior adult placebo controlled trials.

ESPGHAN, ECCO, the Canadian Children IBD Network, and the global PIBDnet 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 since 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 how to use the drug in children. We propose considering pediatric trial designs in which the comparator would be an active arm of an

established standard treatment, and to 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) who currently are mostly excluded from drug trials, given the open questions on appropriate drug dosage in this population.

With regards to maintenance therapy, an early trial by Markowitz et al. on the effect of thiopurines in an inception cohort of children with 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 (4). 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 to 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 represents a clear deviation from accepted clinical practice and standard of care, as recommended in current pediatric guidelines of managing UC and CD (5, 6).

It has been proposed that children with IBD randomized to placebo may benefit, since the placebo induced clinical remission has been reported as high as 20% in UC and CD (7, 8). However, objective measures of mucosal inflammation 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 currently 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). However, response does not equal remission and children with moderate-severe disease at trial entry who are considered responders may still have active disease at 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 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 two 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 with respect to 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 with respect to currently proposed study designs is the potential disadvantage of temporary withdrawal of biologics with regards to later efficacy and safety. The STORI trial followed 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. As many as 12% of those re-treated with infliximab did not respond any more. Similarly, in other studies the average non-response to re-introduction of biologics after a temporary drug withdrawal has been 10-15% and most studies included selected cohorts of patients with long standing remission with concomitant immunomodulators. Thus, this figure likely represents a conservative non-response estimate (15-22). 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, 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. However, the development and assessment of drugs for pediatric IBD will not be facilitated if trial designs are considered inappropriate or non-enrollable by the medical community and/or patients. Placebo-controlled trials continue to be the gold standard for drug evaluation, but they can only be used in pediatrics if there is clinical equipoise, i.e. 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.

REFERENCES

1 Sun H, Papadopoulos EJ, Hyams JS, et al. Well-defined and reliable clinical outcome assessments for pediatric Crohn disease: a critical need for drug development. J Pediatr Gastroenterol Nutr 2015;60:729-36.

2 Sun H, Vesely R, Nelson RM, et al. Steps toward harmonization for clinical development of medicines in pediatric ulcerative colitis-a global scientific discussion, part 2: data extrapolation, trial design, and pharmacokinetics. J Pediatr Gastroenterol Nutr 2014;58:684-8.

3 European Union. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. Eur J Health Law 2008;15:223-50.

4 Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology 2000;119:895-902.

5 Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr 2012;55:340-61.

6 Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis 2014;8:1179-207.

7 Garud S, Brown A, Cheifetz A, et al. Meta-analysis of the placebo response in ulcerative colitis. Dig Dis Sci 2008;53:875-91.

8 Su C, Lichtenstein GR, Krok K, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. Gastroenterology 2004;126:1257-69.

9 Ruemmele FM, Hyams JS, Otley A, et al. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. Gut 2015;64:438-46.

10 Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology 2012;142:1102-11 e2.

11 Peyrin-Biroulet L Deep remission in Crohn's disease: is it the end of the placebo effect? Clin Gastroenterol Hepatol 2014;12:347.

12 Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007;132:863-73; quiz 1165-6.

13 Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology 2012;143(2):365-74 e2.

14 Hyams J, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2012;10:391-99 e1.

15 Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012;142:63-70 e5; quiz e31.

16 Reich K, Wozel G, Zheng H, et al. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: results of a randomized, long-term extension trial (RESTORE2). Br J Dermatol 2013;168:1325-34.

17 Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:402-13.

18 Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of Clostridium difficile infection in inflammatory bowel disease. Clin Gastroenterol Hepatol 2007;5:339-44.

19 Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin gastroenterol hepatol 2004;2:542-53.

20 Brandse JF, Peters CP, Gecse KB, et al. Effects of infliximab retreatment after consecutive discontinuation of infliximab and adalimumab in refractory Crohn's disease. Inflamm Bowel Dis 2014;20:251-8.

21 Baert F, Drobne D, Gils A, et al. Early trough levels and antibodies to infliximab predict safety and success of reinitiation of infliximab therapy. Clin Gastroenterol Hepatol 2014;12:1474-81 e2; quiz e91.

22 Laharie D, Chanteloup E, Chabrun E, et al. The tolerance and efficacy of a postponed retreatment with infliximab in Crohn's disease primary responders. Aliment Pharmacol Ther 2009;29:1240-8.

23 Lee LY, Sanderson JD, Irving PM Anti-infliximab antibodies in inflammatory bowel disease: prevalence, infusion reactions, immunosuppression and response, a meta-analysis. Eur J Gastroenterol Hepatol 2012;24:1078-85.

LEGENDS TO FIGURES

Figure 1: Years interval from approval of biologics in adults to approval in children

Footnote: Top two indications have not received pediatric approval yet and pediatric trials are still ongoing; the light gray arrows illustrate the anticipated future years to approval.

Figure 2: Comparison of adult and pediatric biologics trial results

Footnote: For the sake of fair comparisons between pediatric and adult trials, REACH data reflect complete ITT (including primary non responders) and the IMAgINE and CHARM trials include only those who were infliximab naïve

Supplemental Data: Appendix

Figure 1

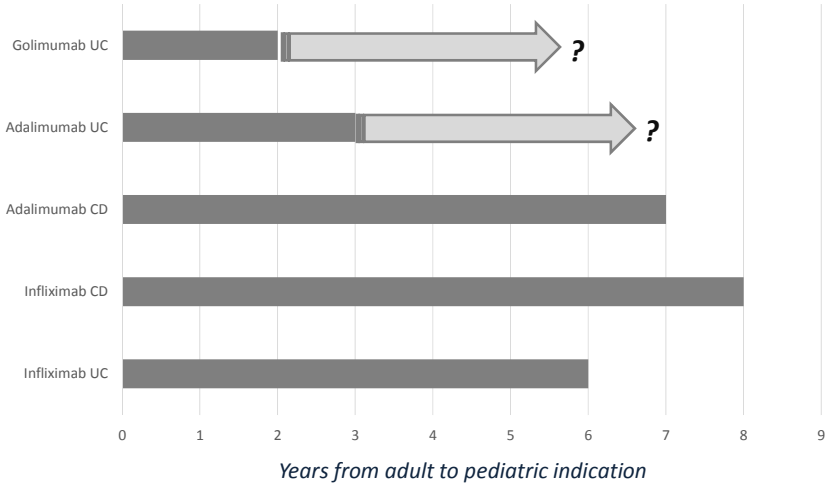

Figure 2