Expediting Drug Development for Pediatric Inflammatory Bowel Disease: A Discussion With Stakeholders

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ABSTRACT

Lack of scientific consensus on efficacy endpoints and outcome assessments presents a hurdle for global drug development in pediatric inflammatory bowel disease (IBD). Multiple stakeholders participated in a meeting November 2015, sponsored by The Pediatric IBD Foundation, which is a 501c3 organization formed by parents of children with IBD whose mission is to improve the lives of children with Crohn disease and ulcerative colitis by supporting innovative research and educational programs (*www.pedsibd.org*). With representatives of the Food and Drug Administration, European Medicines Agency, pediatric gastroenterologists, and representatives of the pharmaceutical industry, this meeting was organized to harmonize present thinking about various aspects of global drug development in pediatric IBD. The meeting was designed to be interactive, allowing participants from the pharmaceutical industry, regulatory agencies, academia, and clinical practice an opportunity to collaborate in a public forum and to identify potential strategies to expedite drug evaluation in children. Before the meeting, a questionnaire focused on the hurdles hindering approval of medications used to treat children with IBD was sent to all participants and other pediatric gastroenterologists in North America and Europe with expertise in IBD. Responses were reviewed by the steering committee and results presented at the meeting. Following the presentation of the survey, participants were divided into small groups composed of representatives from academia, industry, regulatory agencies, and members of the Pediatric IBD Foundation and assigned the task of working together to find solutions to the hurdles that had been identified. Hurdles hindering approval included pediatric trials start later in the development process; lack of enrollment in pediatric trials; lack of monitoring safety registries that might expedite approval; different priorities among stakeholders. This 1-day meeting discussed how to expedite pediatric drug development in IBD therapy. Hurdles for achieving approvals of pediatric indications for treatments of IBD were identified.

Key Words: expedited approval of medications, off-label use of medications, pediatric inflammatory bowel disease

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The Pediatric IBD Foundation convened a meeting on November 9, 2015 with representatives of the Food and Drug Administration (FDA), European Medicines Agency (EMA), pharmaceutical industry, and the Steering Committee of the Pediatric IBD Foundation, composed of pediatric gastroenterologists in academia and clinical practice. The goal of the meeting was to discuss the current obstacles to clinical development of medications used to treat children with inflammatory bowel disease (IBD). Clinical outcome measures, study design, and the use of placebo controls were not addressed as they were discussed at previous meetings including Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics and the EMA workshop on ulcerative colitis (UC) and Crohn disease (CD) (1–3). This meeting was designed to be interactive allowing participants from the pharmaceutical industry, regulatory agencies, academia, and private practice an opportunity to collaborate in a public forum and to identify potential strategies to expedite drug evaluation in children. We now report a summary of this 1-day meeting.

PREPARATION FOR ALL STAKEHOLDERS BEFORE MEETING: SURVEY OF ISSUES

To focus the discussion and facilitate preparation for interactive sessions, a survey assessing the importance of various issues affecting pediatric drug development for IBD was distributed and compiled by the company ScienceTrax before the meeting. The survey was sent to 100 US-based physicians in private or academic practice, pharmaceutical industry employees, and FDA and EMA representatives. The FDA participants chose not to respond to the survey. There was a 47% response rate with 91% having an MD degree. The majority of responders (68%) were employed in a hospital or academic setting; 27% were employed in a pharmaceutical company. The elements of the IBD survey are described in Supplemental Digital Content, Figure 1, http://links.lww.com/MPG/B226.

ORGANIZATION OF MEETING

After the initial presentations, there were breakout sessions with 7 to 10 attendees in each group representing industry, regulatory agencies, and clinicians/clinical trial investigators. (Supplemental Fig. 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/B187*) Topics for discussion also included off-label use in children and denouement of the day's deliberations. Each integrated breakout group, was assigned the task of discussing 4 important ''hurdles'' hindering pediatric IBD drug development and suggesting solutions. The hurdles discussed were the following: why pediatric trials start late in the drug development process; what are the reasons for slow enrollment in pediatric clinical trials; monitoring safety during and after approval of new medicines; and exploring the perception that there is limited harmonization among industry, regulators, and clinicians.

Summary of Perspectives

All stakeholders expressed concern that medications used to treat pediatric conditions, including many gastrointestinal illnesses, are frequently prescribed off-label. On average, it takes nearly 9 years from the time of a product's approval for use in adults until the label is updated to include pediatric data in the United States. This significant gap results in off-label use in the pediatric population during this time period (4). When physicians prescribe a medication that has been approved in adults without relying upon information derived from a pediatric development program, they are inferring dosing and safety data from the adult patient experience. There are many reasons that providers choose to prescribe off-label medications. Some may not be aware that the product has not been approved for pediatric use and prescribe based on published case reports or small case series describing uncontrolled use of the medication. These practices contribute to the lack of evidence to support indications and product labeling in children with IBD; pediatric patients are not enrolled in appropriate pediatric development programs based on the assumption that the efficacious and safe dose in children has already been determined.

Efficient and scientifically sound clinical development programs will lead to drug approval and reduce off-label use of medications for treatment of children with IBD. Many drugs used in pediatrics are used off-label (used based on limited or absent data in the drug label on correct dosing, safety, and efficacy). Pediatric studies conducted under current federal laws (Best Pharmaceuticals for Children Act [BPCA] and the Pediatric Research Equity Act) including studies sponsored by the NIH through BPCA generate much-needed data on the safety and effectiveness of medications used in pediatric patients to reduce off label use both in the US and ex-US regions as discussed now. Similarly in the EU, mandatory pediatric drug development is regulated by the EMA ensuring that medicines used to treat children are subject to ethical research of high quality and are appropriately authorized for use in children, and to improve collection of information on the use of medicines in the various subsets of the pediatric population. Through the mechanism of the BPCA, the National Institute for Child Health and Disease has developed a pediatric drug development program that sponsors clinical trials of off-patent drugs (drugs that no longer have a marketing exclusivity) that need further dosing, safety, or effectiveness information in the pediatric population.

All stakeholders involved in the drug development process including, but not limited to, academia, industry, patient and disease advocacy groups, and regulatory agencies must work collaboratively for these objectives to be met. In an effort to enhance global regulatory harmonization of clinical development of treatments for pediatric UC and CD trials, the FDA took the lead in organizing the international IBD Working Group, which consists of multidisciplinary scientists from the FDA, EMA, Health Canada and the Pharmaceuticals and Medical Devices Agency of Japan. The Working Group's mission is to support drug development in pediatric IBD by advancing scientific knowledge on efficacy endpoints, trial design, extrapolation approaches, and pharmacokinetics. The immediate goal is to harmonize the design of pediatric clinical development programs among jurisdictions, including trial design and efficacy endpoints, extrapolation approaches, and leveraging of pediatric pharmacokinetic data. The update of the EMA Guidelines on IBD is ongoing and one of the relevant issues under discussion is how to apply extrapolation from adults to avoid unnecessary studies in pediatric patients and to expedite development timelines while maintaining regulatory standards of required evidence (5). High-quality post-marketing registries may not only be used to provide further data on the approved drug post authorization, but also to obtain data leading to an improved understanding of the disease. The challenges in pediatric drug development in IBD are real and are generalizable. Compared to adults, IBD in pediatric patients is relatively rare, and drugs for both pediatric CD and UC have received orphan designations in the United States based on the low prevalence of these conditions. In addition facilitating pediatric drug development requires: efficient and effective trial design; validated endpoints; physicians capable of executing trials compliant with regulatory statute; efficient patient recruitment and retention; proper dose selection; appropriate formulation; determination of ability to extrapolate data from adult studies and to apply those data to pediatric drug development; and utilization of new methods for dose selection and pharmacokinetic studies including simulation and modeling. Depending on the anticipated benefit/risk balance of an intervention, sponsors may wish to have adequate data from adult studies to confirm this balance is favorable before initiating studies in pediatric patients. If extrapolation of efficacy is to be considered, a sufficient understanding of the pharmacokinetic/pharmacodynamics relationship and the placebo response requires adult data to be available before finalizing pediatric IBD study designs and protocols.

The limited number of potential patients leads to practical limitations in the ability of sponsors to conduct large adequately powered and robust clinical trials. A limited number of clinical study sites have the relevant patient population and are qualified to perform clinical studies. Participation in a clinical study is more burdensome than receiving treatment in clinical practice, due to the need to document symptoms via a patient diary, need to travel to study sites, and other factors. Study-mandated endoscopic evaluations, particularly the bowel cleaning preparation, may require time away from school or activities. Finally, the inclusion of placebo comparators in studies of a severe disease such as pediatric UC may lead to concern from investigators and parents, especially after efficacy has been demonstrated with the same drug or class of drugs in adult studies.

The integration of these concepts requires a partnership with industry. The clinical trial programs for adalimumab (Humira) in pediatric CD and UC were summarized by Abbvie as an example of the burdens encountered in trial development and execution. The first indication for Humira in IBD was for adult CD, based upon the results of 3 global placebo-controlled pivotal trials in 1478 patients which were conducted from 2002 to 2006 and enrolled at rates ranging from 0.29 to 0.70 patients/site/month, depending on the study. Discussions with regulatory agencies regarding the global clinical trial for adalimumab in pediatric CD began in mid-2006, and the study (IMAgINE-1, N = 192) was initiated in 2007, the same year as the US and EU approvals for Humira for adult patients with CD. IMAgINE-1 had several design similarities to the adult studies (ie, no endoscopic evaluations, entry and primary endpoints

were based upon symptom-driven indices, and the patient population included only patients with intolerance or failure to treatment with conventional therapy and/or anti-tumor necrosis factor therapy); however, IMAgINE-1 did not employ a placebo comparator. IMAgINE-1 enrolled at a slower rate (0.18 patients/site/month) than the adult CD studies. IMAgINE-1 was completed in 2010, and Humira was approved for pediatric CD in 2012 in the EU and 2014 in the United States. Initial pediatric trial design discussions with regulatory agencies began in 2011, before the 2012 US and EU approvals of Humira for adult UC. Protocol agreement for the global pediatric UC trial (ENVISION, N = 225) was achieved in 2013. ENVISION shares several design elements with the adult trials, including similar entry criteria and the use of endoscopy to confirm study eligibility and for the study maintenance (but not induction) endpoint. A key similarity between ENVISION and the adult studies, but a key difference between ENVISION and IMAgINE 1, is the inclusion of a placebo comparator. Because of the rarity of pediatric UC, the complexity of the study design, and the inclusion of endoscopy in ENVISION, the projected enrollment was expected to be lower (0.08 patients/site/month) than IMAgINE-2. Unfortunately, observed enrollment has been lower than projected, with the inclusion of placebo in the study cited by study investigators as the main driver of slow enrollment.

SURVEY RESULTS

Results of the premeeting survey that was conducted to assess the importance of various issues affecting pediatric drug development for IBD among stakeholders are appended in Supplemental Tables 1, 2, and 3 (Supplemental Digital Content 2, *http://links.lww.com/MPG/B188*). There are multiple factors hindering enrollment in clinical trials for drugs that are already approved to treat adults with IBD but are prescribed off-label for children (Table 1). These include the lack of investigators willing to enroll patients in clinical trials for a medication that can be prescribed off label. In comparison, enrollment in clinical trials for drugs that are not already approved to treat adults with IBD would be of greater interest to potential investigators, but support for testing in children needs appropriate study design and safety. There was a discordance between concerns of industry and investigators regarding operational feasibility and identification of appropriate patient population for testing. Some clinicians felt that the clinical trials developed for approval were not feasible.

There was concordance among respondents that safety registries are important for monitoring adverse effects associated with therapies for pediatric IBD. Responders indicated that registries could have an important role in monitoring the adverse effects of treatments of IBD that have been approved for use in adults, but are being used off-label in children with IBD. The individual stakeholder roles in developing these registries are an important area for further discussion.

Finding Solutions: Results of the Working Groups

The recommendations from the working groups that discussed finding solutions to hurdles demonstrated how investigators, industry, and regulators can work together to find ways to expedite drug development. Possible solutions to the specific hurdles addressed in this meeting are specifically delineated below.

Hurdle 1

Pediatric trials start later than adult trials in the development process of a new medication.

The timing of pediatric clinical trials relative to commercial availability of the study drug was identified as an important factor in the decisions of clinicians, family, and patients to participate in a clinical trial. Clinicians and representatives of regulatory agencies concurred that early inclusion of children in the overall clinical drug program, for example, in late phase II or early phase III, once preliminary safety data in adults are available, would facilitate expeditious approval of pediatric indications. A dedicated pediatric trial team could be organized early in the drug development process, with the goal of initiating pediatric testing when recruitment to the adult phase II/III trials begins. Certain stakeholders emphasized the need to include adolescents in the initial adult phase 3 trials. Discussions of alternatives to executing pediatric trials closer to the approval of the adult indication included use of real-world data registries executed in multicenter collaborations (in which the efficacy observed in children treated with the product off-label is captured); however, concerns were raised that such real-world research may inadvertently promote off-label use.

Hurdle 2: Lack of Enrollment in Pediatric Trials

Investigators participated in a discussion about study design as a contributing hurdle to enrollment. Critical discussion elements of improving pediatric clinical trial development centered on the need for proof of mucosal healing and the acceptance of multiple invasive procedures in a pediatric trial. The lack of sufficient data in

TABLE 1. Delays in pediatric inflammatory bowel disease drug development from each stakeholder's perspective

Industry	Regulatory/EMA	Investigators
Lack of clinical study sites with adequate patient population and knowledge of good clinical practice	Lack of clinical study sites with patient population/good clinical practice	Lack of financial incentives for trial enrollment
Burden of clinical trial to patient, including travel, and complexities including sample collection, procedures, and visit windows and concerns over use of placebo; invasive procedures causing time away from school	Deficient harmonization amongst the global academic communities to expedite clinical trials Academics and clinicians can have differing perspectives on endpoint and clinical outcome assessment	Concerns of safety and bias towards enrollment in trials amenable to specific interests
Safety concerns leading to unwillingness to invest before phase 3	Lack of both understanding regulatory policy in academic community and the impact on drug development	Pediatric drug development is a low priority for pharmaceutical companies
Low financial return from pediatrics		No mandate for early pediatric trials

EMA = European Medicines Agency.

understanding natural history in this regard cannot be understated. The potential role of surrogate biomarkers, including fecal lactoferrin or calprotectin could enhance the feasibility and clinical impact on patient care and the design of future trials in lieu of endoscopic evaluation. Clearly the development of a surrogate marker has its own intricacies and requires advance thought in development. The role of placebo in pediatric clinical trial development was not discussed at this meeting.

The timing of pediatric clinical trials relative to commercial availability of the study drug was identified as an important factor in the decision of a family or patient to participate in a clinical trial. When a medication is already commercially available, although off-label for pediatric patients, many families and clinicians prefer to prescribe or receive unapproved medications rather than enroll in a clinical trial. This practice may most likely affect the second or third agent in a class already shown to be effective and, perhaps, would be less the case for an agent that had a novel mechanism of action that was yet to be used in pediatric IBD.

Potential solutions to address trial burden to patient and families included telemedicine and other ''virtual'' means to connect the trial center with local care providers and patients. Such technology could facilitate monitoring visits and allow subjects to continue school and activities with a minimal loss of time. Facilitating and leveraging resources for easier pediatric subject enrollment at centers either by identifying centers willing to be committed to enrollment or by creating a global Pediatric Clinical Trial Network were also identified as a potential solution for facilitating enrollment that would lead to earlier drug approval for children with IBD.

Hurdle 3: Monitoring Safety During Postmarketing Registries

Once a new medication intended to treat adult or pediatric IBD receives regulatory approval, industry sponsors may be required to perform post-marketing surveillance to detect rare adverse events that may not have manifested themselves in the phase II or III clinical trials. Such registries are usually focused on one individual drug, and enroll hundreds or thousands of patients receiving that medication. The panel discussed limitations of such ''single drug registries.'' The panel discussed the feasibility and challenges of a true natural history registry, where patients could be tracked long-term over the life cycle of their illness, irrespective of what medications they were receiving. At this point, there is no incentive for industry sponsors to fund such a registry, or clarity regarding who would have ownership of the data. The Pediatric IBD Foundation has been working to create a public-private safety registry for children with IBD that would allow access to all stakeholders.

Hurdle 4: Impact of Inherent Differences in Individual Goals of Each Stakeholder Group (Patients, Clinicians, Industry, Regulators) on Collaboration to Achieve the Shared Goal of Expedited Development of New Treatments for Inflammatory Bowel Disease

There is an inevitable tension among pharmaceutical companies, the FDA, patients, families, and clinicians. Industry wants to develop and bring to market new medications quickly, efficiently, and profitably. The FDA and EMA recognize the need for new therapies and want to facilitate timely development and approval of new treatments; however, in doing so must assure the treatments are safe and effective. Families want new medications that will provide a cure or at least relief from suffering and a normal life for their children, whereas at the same time protecting their children from the risks of taking an investigational drug and the risks/discomfort of study procedures. Clinicians want to help develop new drugs that improve the care and health of their patients, and protect their patients from unsafe and ineffective medications and the inherent risks of participation in clinical trials of unapproved medications. Potential opportunities to enhance collaborative dialogue among all of the stakeholders begin early in the development of study protocols. Success is built upon finding common ground, developing trusting relationships, and discussions that lead to compromise. Establishing an environment in which all stakeholders can work together may lead to the rapid approval of new, effective, and safe therapies that can improve the health and quality of life of children living with IBD.

SUMMARY

This meeting modeled how groups with differing responsibilities for drug development could work together to find solutions to problems delaying development and approval of medications to treat IBD in children. The feedback was overwhelmingly positive with most individuals expressing a desire to continue the discussions until solutions are implemented. Although there was a consensus that approval for medications used to treat children with IBD was critical, many drugs are already being used off label. To restrict the use of these medications would not benefit children. Perpetuation of the status quo of lengthy delays for pediatric approval after initial adult approvals, while tolerating off label prescribing, raises concerns. Safety registries may provide information on the safety of off-label use during this gap, but establishing efficacy of a particular drug in the pediatric population is unlikely to be accomplished within a registry. The limited number of potential pediatric patients with IBD needs to be balanced with the desire for adequately powered clinical trials. There are a limited number of clinical study sites that have the relevant patient population that can enroll sufficient numbers of subjects into clinical studies. Participation in a clinical study is more burdensome than prescribing off-label treatment in clinical practice, and invasive study–related procedures reduce the acceptability of study participation. The inclusion of placebo comparators in studies of a severe disease such as UC may lead to concern from investigators and parents, more so than in adult studies. Depending on the anticipated benefit/risk balance of an intervention, sponsors may wish to have adequate reassurance from adult studies that this balance is favorable before initiating studies in pediatric patients. If extrapolation of efficacy from adult to pediatric populations is to be considered, a sufficient understanding of the pharmacokinetics and the exposure/response relationship in adults is necessary before finalizing the pediatric IBD study designs and protocols. These are principles well established in recent FDA guidance on pediatric clinical pharmacology (6). Coordinated use of extrapolation and global agreement among regulatory agencies on pediatric development plans will result in development of efficient development programs, favorably affecting the time to achieving pediatric drug approval. Support for this conclusion is supported positively from the recent publications demonstrating a spirit of collaboration from the pediatric literature, specifically focused on pediatric IBD and pediatric drug development (7–13).

Parents were represented by the members of the Pediatric IBD Foundation who convened and sponsored the meeting. Hurdles for achieving approvals of pediatric indications for treatments of IBD were identified. The challenge is to continue the dialogue and work together to identify and implement solutions. This manuscript summarizes what stakeholders thought were hurdles to achieving early approval of medications used to treat children with IBD. We

hope that publishing this manuscript will enlighten all parties to the realization that we all need to work together to overcome the obstacles identified at this meeting.

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