Best Pharmaceuticals for Children Act (BPCA)
Dermatology Therapeutic Area Working Group Conference Call and Webinar
August 23, 2012
10:00 a.m.–11:05 a.m. ET

Participants

Rosemary Addy, M.H.S.
Carl C. Baker, M.D., Ph.D.
Julie Block
Beth Drolet, M.D.
Lawrence F. Eichenfield, M.D.
Roselyn E. Epps, M.D.
Jacqueline N. Francis, M.D., M.P.H.
Adelaide Hebert, M.D.
Thomas Hultsch, M.D., Ph.D.
Alyson Karesh, M.D.
Marie Ann Leyko, Ph.D.
Denise Pica-Branco, Ph.D.
Elaine Siegfried, M.D.
Brian Smith, M.D., M.H.S., M.P.H.
Donna Snyder, M.D.
Perdita Taylor-Zapata, M.D.
Jonathan K. Wilkin, M.D.
Teri Moser Woo, Ph.D.

Purpose

The purpose of the call and webinar was to provide an overview of the Pediatric Trials Network (PTN), presented by Dr. Smith, and to review the member assignments and the charges for the four subcommittees of the Dermatology Working Group.

Subcommittee Membership

Dr. Siegfried noted that the subcommittees' membership is currently unbalanced. It is possible to be on more than one committee. There is sufficient representation on the Atopic Dermatitis and Drug Development Issues subcommittees, but currently only Dr. Lucky is on the genodermatosis committee. Dr. Baker volunteered to be part of that committee. Dr. Hebert volunteered for any subcommittee that is in need of members, and Dr. Siegfried asked her to work on the genodermatosis committee. Dr. Siegfried said that some members of the Pediatric Dermatology Research Alliance (PeDRA) are interested in providing input for the presentation the Dermatology Working Group will present in December and therefore might be interested in participating in the subcommittees. Dr. Taylor-Zapata noted that members of PeDRA could join the Dermatology working group as long as they have been briefed on and understand the goals of the working group.

Invitations will be sent after the call to members who might chair the subcommittees with more than two members. A chairperson acts as the subcommittee's record keeper and will use the template provided by Dr. Taylor-Zapata to develop the summary of the subcommittee's recommendations.

Dr. Siegfried asked for clarification from Dr. Taylor-Zapata as to what the expectations are for the working group. Dr. Taylor-Zapata clarified that the subcommittees will meet over a 4- to 6-week period to develop their own recommendations, and then a general call with the entire Dermatology Working Group will be scheduled. The working group will then prioritize what the members consider to be the most important areas for study. All these recommendations are reviewed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), where those recommendations are prioritized again based on several criteria. After this point, recommendations go to the PTN for further prioritization, if appropriate. All recommendations from all working groups are presented to the U.S. Food and Drug Administration (FDA). Ms. Karesh clarified that the reason that the FDA does not provide formal responses to the recommendations is because the function of the working group is to provide feedback and recommendations to the NICHD, not to receive feedback from the FDA.

Presentation on the PTN

Dr. Smith from the Duke Clinical Research Institute (DCRI) participated in the call for Dr. Daniel Benjamin, principal investigator (PI) and part of the faculty for the DCRI. The PTN is a contract between the DCRI and the NICHD, with the primary objective to create an infrastructure for investigators to conduct trials that improve pediatric labeling for off-patent therapeutics and child health. The PTN is studying product formulation, drug dosing, efficacy, safety, and device evaluation.

The PTN is led by the NICHD, and there is a separate BPCA Data Monitoring Committee that oversees the safety of all the trials conducted. The Program Management and Clinical Operations Core of the PTN is the administrative core at the DCRI, tasked with overseeing the components of the trials, which include network management, site selection, protocol development, and data dissemination. Under the administrative core are several other core groups that are led by investigators outside of Duke:

- Clinical Pharmacology Core and Pharmacometrics Core—heavily involved in developing the trials once molecules for study are chosen
- Safety and Ethics Core—has global oversight of the trials monitoring and safety
- Devices Core—identifies devices to be studied
- Mentorship Core—heavily invested in mentoring junior fellows who can become pediatric trial investigators on their own.

Dr. Smith outlined the process of how the PTN works with the National Institutes of Health (NIH):

- PTN molecules for study come from the BPCA priority list of off-patent therapeutics.

- Investigators submit a concept sheet—a two-page summary of what they would propose for a trial—to the PTN administrative core.
- The PTN administrative core reviews the science and feasibility.
- If approved, the PTN forms a protocol development team, consisting of a protocol chair, thought leaders, pharmacologists, and operations experts.
- The NIH provides small amount of startup funding to the PTN.
- The PTN sends scope of work and budget to the NIH.
- The PTN selects sites from the Rapid Start Network based on site study interest, the site PIs, and previous history of enrollment.
- The PTN executes the trial.

Dr. Wilkins asked for clarification about the objectives for the studies and whether the goal was simply to conduct Phase 1 studies or to fund studies to lead to changes in pediatric labeling. Dr. Smith responded that the purpose would depend on several factors. Individual divisions at the FDA have different approaches to including different types of information on the label, which often depends on the molecule itself. It is easier to change the label for molecules for which extrapolation can occur from adults, once dosing and safety in children has been established. Smaller studies can be undertaken to establish pharmacokinetic (PK) and safety data and then extrapolate efficacy. The budget does not allow for Phase 3 studies for every molecule, so the PTN tries to study several molecules in smaller trials in an effort to spread resources. Dr. Wilkins noted that antimicrobial agents present a good opportunity to conduct small studies that could bring about changes in labeling. Dr. Taylor-Zapata noted that the NIH approach is resource-dependent—requiring both time and money—so that is why the NIH has the current conservative approach to conducting these studies.

In response to a request by Dr. Siegfried, Dr. Taylor-Zapata clarified that the goal for this group is to provide global recommendations to the NICHD; the current goal is not to present concept sheets or more detailed study presentations to submit to the PTN.

Dr. Smith said there are 15 trials in the PTN that are either completed, in site startup, or in protocol development: eight for 2011, five for 2012, and two planned for 2013. Three of the eight 2011 trials have completed enrollment—metronidazole, Phase 1 in infants; acyclovir, Phase 1 in infants; and the tape device study, a larger study. Most of the PTN trials are Phase 1 studies, although some are data-based trials, in which available databases are mined for safety information. Sildenafil is an example of a Phase 1 trial, which then will move forward with a Phase 2 trial in 2013. Approximately 50 percent of the trials involve some pharmacogenomics work for both safety and PK data.

Dr. Smith used the “Safety and PK of Multiple Dose Metronidazole in Premature Infants” trial as an example of how the process works:
- Population: 24 infants <32 weeks gestational age with suspected serious infection
- Duration of enrollment process: original target 18 months; finished in 12 months
- Study participation: participated in the study for up to 15 days, consisting of 2–5 days of study drug followed by 10 days of adverse events monitoring
- Number of sites: 3.

The DCRI has two separate Rapid Start Networks—one for industry-sponsored studies and one for NIH-funded studies. The Rapid Start Network identifies sites that agree to work with the DCRI under a master service agreement that is linked with the institution rather than a therapeutic area, so that it can be used across all study programs. Working within this network system in a given study can reduce the time spent on the site contracting process by as much as 4 weeks. These sites are monitored in terms of data quality and enrollment efficiency. Dr. Siegfried asked how these sites are chosen. Dr. Smith responded that many of the sites were initially identified as a result of two NIH-sponsored studies that took place in 2007. As new molecules were identified, more sites were selected based on input from outside investigator recommendations of those studies, and those sites were subsequently brought into the Rapid Start Network.

Dr. Siegfried asked for clarification about the function of the Safety and Ethics Core of the PTN. Dr. Smith responded that a trial's protocol is reviewed by the BPCA Data Monitoring Committee for final approval. All the trials undergo review at the FDA division where that molecule's approval rests, and there is the normal institutional review board oversight at the site. The protocols are mostly not high-risk, and there is a fair amount of oversight prior to ever actually administering the drugs. In some studies, the patients may already be getting the drugs and the study investigators are simply collecting the data. Feedback from the FDA consists of safety data on the protocol itself; recommendations for regulatory/labeling changes would not occur until after the study.

Discussion

Dr. Hultsch commented that there appears to be a disconnect between the stated objective of labeling changes and the informal Phase 1 studies that the PTN undertakes. He asked if perhaps collaboration with industry would be a means of facilitating the larger, more expensive Phase 3 studies that could result in labeling changes. Dr. Smith responded that there is no incentive for industry to invest in studies for these off-patent therapeutics. Dr. Karesh interjected, from the FDA perspective, that dosing information changes without a finding of safety and efficacy tends to go on labeling only in cases where there are safety concerns. Dr. Taylor-Zapata noted that the NIH has the mandate to impact labeling but the NIH has no control over that labeling, only the FDA does. The NIH must conduct the studies and work with colleagues at the FDA to improve labeling, but the final decision lies with the FDA. She commented that the NIH and FDA have had a good and successful working relationship in the past and that it is an ongoing process, as the legislation changes. In terms of the task of the working group, the NIH is looking for ideas and recommendations. She also clarified that the $25 million BPCA funding includes everything: infrastructure, the PTN, the clinical studies, and so on.

Dr. Wilkins echoed what Dr. Taylor-Zapata said: There are limited resources for lofty objectives. He mentioned that a guidance document produced by the FDA would be useful. There is a guidance document on atopic dermatitis at the FDA Web site. He noted that the Dermatology Working Group could give to the NICHD suggestions for kinds of information to be included in a similar guidance document and encourage that the FDA develop such a document.

Dr. Siegfried said that she will work over the next month with Brandy Weathersby, Circle Solutions, to schedule calls for the subcommittees and identify possible chairs for those subcommittees. Dr. Lucky commented that she thought it would be good to ensure that any invitations to join the subcommittees are not limited to the PeDRA group; Dr. Siegfried will work with Dr. Lucky to identify other possible members.

Dr. Drolet asked whether it would be possible to get the final recommendations from previous working groups to be used as examples of what the working group's task is and what they should produce. These will be sent out to everyone.

Action Items:

- Dr. Siegfried will send out invitations to join the subcommittees and will identify possible chairs.
- Examples of recommendations from previous working groups will be sent to the entire Dermatology Working Group membership.