Best Pharmaceuticals for Children Act (BPCA)
Dermatology Therapeutic Area Working Group Conference Call and Webcast
May 3, 2012
1:30 p.m.ET–2:17 p.m. ET

Participants

Carl C. Baker, M.D., Ph.D.
Kimberley W. Benner, Pharm.D., B.C.P.S., F.A.S.H.P.
Katherine Berezny, M.P.H.
Elizabeth Durmowicz, M.D.
Oluchi Elekwachi, Pharm.D., M.P.H.
Jacqueline N. Francis, M.D., M.P.H.
Norma Gavin, Ph.D.
Maria K. Hordinsky, M.D.
Wendla Kutz, M.S.N, C.N.S, P.N.P.
Marie Ann Leyko, Ph.D.
Hanna Phan, Pharm.D., B.C.P.S.
Alex Silver
Donna Snyder, M.D.
Perdita Taylor-Zapata, M.D.
Kelly Wade, M.D., Ph.D.

Purpose

The purpose of the conference call was to describe the background of the BPCA and to solicit input from the experts as to what pediatric therapeutics are needed in dermatology.

Background

Dr. Taylor-Zapata described the background of the BPCA, which is a legislative mandate to improve the effectiveness and safety of medicines used in children. The BPCA encourages the pharmaceutical industry to perform pediatric studies to improve labeling for drug products used in children in exchange for an additional 6 months of patent exclusivity. The BPCA started with advocacy of the American Academy of Pediatrics (AAP) and the work of the Pediatric Pharmacology Research Units to ensure that if a drug is used in children it would have been studied in children, not just in adults. The 1998 U.S. Food and Drug Administration Modernization Act (FDAMA) established this exclusivity, which was continued in the 2002 BPCA and reinstituted in the 2007 FDA Amendments Act.

A smaller function of the BPCA provides for the National Institutes of Health (NIH) to establish a program that will sponsor needed studies of important drug products—usually off-patent drugs—in cases where the pharmaceutical company would decline to perform the studies. The NIH pediatric drug development program has two main components: (1) to develop and establish a prioritization process that will reach out to experts in the medical community in order to

identify gaps in pediatric therapeutics, including drugs and biologics that need further study, and (2) to conduct clinical trials of primarily off-patent drugs that have been prioritized for further study. The estimated $25 million necessary for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to fund studies that will address and subsequently close knowledge gaps for therapeutics used in children comes from 20 Institutes within the NIH. The prioritization process involves stakeholders including the NIH; the NICHD; the FDA pediatric division; the FDA review division; members of academia, the AAP and other professional societies, industry, and advocacy groups; and parents.

The BPCA 2002 focused on particular drugs and the public health benefit of those drugs and consulted with pediatric experts and the FDA. The NIH was reactive—rather than proactive—to Written Requests. With the BPCA 2007, however, the focus changed to therapeutic areas rather than specific drugs, and the NIH began to be proactive in the process, developing Proposed Pediatric Study Requests (PPSRs).

The activities within the BPCA 2007 for drug development and testing fall into three general categories with the goal of drug label changes:

- Identifying and prioritizing therapeutic needs
- Developing PPSRs to gather additional information—for example, pharmacokinetic, safety, or efficacy information
- Conducting clinical studies.

With the initial phase of the BPCA 2002 implementation, many issues were uncovered and many lessons have been learned:

- There is a pervasive lack of preclinical, phase 1, and phase 2 clinical trial data on dosing, safety, and efficacy in drugs that have been used in pediatrics for years, even decades.
- It is difficult to predict dose-response or concentration-response relationships.
- The unforeseeable nature of some clinical responses in immature individuals leads to the possibility of unanticipated adverse reactions, which are often unique to pediatric patients.
- The threat of effects on growth, development, or health long after the drug's administration highlights the need for innovative designs in safety studies.
- There are many ethical and feasibility issues involved pediatric clinical trials: the use of placebo, sample size, formulations, outcome measures, parental permission, and child's assent.
- Pediatrics lags behind adult medicine in advances in science and technology, including the development and assessment of biomarkers of disease, characterization of adverse drug reactions, pharmacometrics, and pharmacogenomics.

The NIH began with outreach to key experts in the field of pediatric pharmacology through conducting pharmacoepidemiology research, mass outreach to major pediatric organizations (from 2004 to 2009), Requests for Information published in the global NIH Guide for Grants and Contracts, therapeutic working groups on a small scale in 2005 (and on a larger scale later), and BPCA Annual Meetings to which all working groups are invited. Once the prioritized drugs/indications have been vetted by experts in pediatrics, the NIH develops a priority list of needs in pediatric therapeutics. Lessons learned have resulted in changes to make the

prioritization process more objective, including increasing the outreach to include a broader range of stakeholders, such as those in advocacy and industry, earlier in the process; developing therapeutic area-specific working groups; and including outside evaluators in the evaluations.

To this point, the activities in support of the BPCA have yielded

- 16 funded clinical trials
- Key lessons in study design, patient recruitment, data analysis, and need for formulations
- 18 publications and 26 abstracts
- Training programs such as the National Institute for General Medical Sciences-NICHD T32 Clinical and Developmental Pharmacology Training Network
- The Asthma Outcomes Workshop and Prematurity and Respiratory and Outcomes Program, a collaboration with the National Cancer Institute/Children's Oncology Group and the National Heart, Lung, and Blood Institute
- Labeling changes for propylthiouracil and pralidoxime.

Four or five studies have been completed this year and will be submitted for label changes.

In 2008, with the implementation of the new legislation, the NICHD prioritized 16 therapeutic areas. The NIH identifies two to three therapeutic areas of focus each calendar year—either a particular drug or a drug's formulation, dosing, safety, or efficacy—and establishes working groups charged with that area of study. The 2012 working groups will focus on dermatology and rheumatology. A statement of the purpose of the working groups can be found on the BPCA Web site at http://bpca.nichd.nih.gov.

Working groups meet to discuss the therapeutic needs in the identified areas and to make recommendations of drugs (drug classes), biologics, and/or other areas of research that affect therapeutics that need further study in pediatrics. The working groups summarize current knowledge, the current standard of care, and existing data; identify the barriers to and gaps in knowledge; and suggest ways to address these barriers and/or knowledge gaps. Specifically, the NIH is looking for the following information:

- Proposed therapeutic area
- Proposed therapeutic drug class/agent/device
- Background information on drug use, effectiveness, etc.
- Identification of the gaps:
  - Clinical need (brief description): Lack of pediatric dosing, safety, efficacy
  - Research need (brief description)
  - Ethical concerns (brief description)
  - Feasibility concerns (barriers to study)
  - Final recommendations.

Dr. Taylor-Zapata outlined the following procedures for the Dermatology Working Group:

- The group will meet via teleconference three to four times in a calendar year.
- Minutes of all meetings will be posted on the BPCA Web site.
- Recommendations from the group will be presented at the BPCA Annual Meeting.

- Other outcomes may include consideration for future studies, workshops, and/or publications.

Dr. Taylor-Zapata noted that the NICHD is not attempting to duplicate the efforts of other Institutes that have already led and funded studies in particular areas. The NICHD became interested in the needs in the treatment of severe atopic inflammatory disease as a result of the recommendations from the 2010 outreach process.

Discussion

Dr. Taylor-Zapata asked whether severe atopic inflammatory disease is an area that needs more study. Dr. Baker responded that severe atopic dermatitis is an area discussed most frequently and that there is a need for further research in the pathophysiology of the disease and in the link between the disease and genetics. The general agreement is that there are no good drugs available for treatment of severe atopic dermatitis. There is also little evidence supporting that the drugs currently used for children can safely and effectively be used for pediatric conditions. Dr. Baker will provide the link to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Pediatric Dermatology Roundtable Discussion summary to the group.

Dr. Hordinsky noted that the black-box warning for the FDA-approved topical calcineurin inhibitors (TCIs) resulted in the resumption of the primary use of steroids as treatment for severe atopic dermatitis. This highlights that there are not good controlled studies of topical steroid use in children. Additionally, treating children with severe atopic inflammatory diseases—atopic dermatitis, asthma, and allergic rhinitis—is currently a significant challenge, and these diseases would be an important and useful focus to consider. While there are some well-done studies on low-potency FDA-approved inhibitors, there are not enough data on high- or mid-potency steroids to make any informed treatment decisions regarding their use in pediatric patients.

Dr. Taylor-Zapata asked whether there are any additional outcome measures besides hypothalamic-pituitary-adrenal axis suppression. Dr. Baker responded that that is an important measure because parents want to ensure that there is no adrenal cortical suppression with the use of the medications. Dr. Kutz agreed and noted that parents are not always compliant because the data are inconclusive regarding the medications' efficacy and side effects. Other factors that complicate a pediatric patient's response to treatment include the ways different ethnic groups may respond to the steroid as well as cultural differences such as how they bathe, the frequency of bathing, and other culture-specific factors. Children with food allergies can also react differently to medications.

Dr. Taylor-Zapata asked whether there are sufficient data on the long-term safety and efficacy of the TCIs. Dr. Hordinsky responded that companies making those drugs are currently leading studies. A subgroup children with alopecia areata—an immune-mediated disease of the hair follicle that results in the total loss of all body hair—have atopic dermatitis in addition to alopecia areata. These patients are challenging to treat because there are two inflammatory conditions coinciding.

Dr. Baker asked whether the etiology of alopecia areata is associated with phylogram mutations. Dr. Hordinsky said that phylogram mutations have been found in some patients with atopic dermatitis and in some patients with both diseases, but she did not know whether the studies that had been done were primarily on adults.

Other possible areas of study suggested by the call participants include the following:

- Pediatric hemangiomas and other vascular malformations (Dr. Baker)
- Beta blockers to treat hemangiomas (Dr. Wade)
- Other topical agents to reduce microbial flora (Dr. Hordinsky)

Dr. Taylor-Zapata asked whether there is a high rate of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in children with atopic dermatitis. Dr. Baker referred to a recently published article (Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Research*. 2012;22(5):850–9.) While this study found a large amount of *Staphylococcus aureus* during a dermatitis flare-up that changed back into a normal diverse microbiome, it did not find a preponderance of MRSA.

Dr. Taylor-Zapata said she would send the summary of this call to the group and asked for feedback via e-mail on publications that are available that might assist the group. During the next call, the group members will review what they have individually learned and decide on next steps.

Action Items:

- All members of the Dermatology Working Group are invited to the BPCA Annual Meeting in November 2012.
- Dr. Carl Baker will provide the link to the NIAMS Pediatric Dermatology Roundtable Discussion Summary: www.niams.nih.gov/News_and_Events/Meetings_and_Events/Roundtables/2011/ped_derm_roundtable.asp.
- Dr. Taylor-Zapata will ensure that both a roster of the Dermatology Working Group's membership and a summary of this conference call are distributed to the group.
- Circle Solutions, Inc., will be in contact with the Dermatology Working Group's members regarding the next conference call, to be held in 4 to 6 weeks.
- Call participants should send feedback to Dr. Taylor-Zapata via e-mail.