

**Best Pharmaceuticals for Children Act (BPCA)
Dermatology Therapeutic Area Working Group Conference Call and Webinar
June 28, 2012
11:00 a.m.–12:00 p.m. ET**

Participants

Carl C. Baker, M.D., Ph.D.
Kimberley W. Benner, Pharm.D.
Katherine Berezny, M.P.H.
Elizabeth Durmowicz, M.D.
Lawrence F. Eichenfield, M.D.
Roselyn E. Epps, M.D.
Jacqueline N. Francis, M.D., M.P.H.
Adelaide Hebert, M.D.
Maria K. Hordinsky, M.D.
Thomas Hultsch, M.D., Ph.D.
Wendla Kutz, M.S.N.
Anne Lucky, M.D.
Ian M. Paul, M.D., M.Sc.
Hanna Phan, Pharm.D.
Elaine Siegfried, M.D.
Alex Silver
Donna Snyder, M.D.
Perdita Taylor-Zapata, M.D.
Surendra K. Varma, M.D.
Kelly Wade, M.D., Ph.D.
Jonathan K. Wilkin, M.D.
Teri Moser Woo, Ph.D.

Purpose

The purpose of the conference call was to provide background to the Dermatology Therapeutic Area Working Group as to the areas of interest in therapeutic needs in dermatology and to outline the next steps for the working group.

Introductions

Dr. Taylor-Zapata welcomed everyone to the meeting, introduced Dr. Siegfried as the working group leader, and turned the meeting over to Dr. Siegfried. Dr. Siegfried thanked Dr. Taylor-Zapata and the BPCA for the opportunity to address the unmet needs in therapeutics for pediatric dermatology patients.

Dr. Siegfried asked call participants to introduce themselves and give their background and interest in this working group:

- Dr. Siegfried: Pediatric dermatologist, St. Louis University; pediatric patients with eczema account for her greatest time commitment and academic interest.
- Dr. Hebert: Pediatric dermatologist, University of Texas Medical School, Houston, Texas; sees eczema as a huge problem with pediatric patients and would love to see additional therapeutic options for these patients who are so difficult to treat.
- Mr. Silver: founder of the nonprofit Jackson Gabriel Silver Foundation, which is named for his son who was born with recessive dystrophic epidermolysis bullosa (EB) and funds research that is aimed at treating and curing all forms of EB.
- Dr. Lucky: Cincinnati Children's Hospital; pediatrician and pediatric dermatologist; current interest is in EB and improving the quality of life for children with EB via good research and development of new treatments.
- Dr. Durmowicz: Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA).
- Dr. Baker: Keratinocyte Biology and Diseases Program Director, Division of Skin and Rheumatic Diseases, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH).
- Dr. Kutz: Medical Officer (Dermatology), Division of Dermatology and Dental Products, Office of Drug Evaluation III, Office of New Drugs, CDER, FDA.
- Dr. Snyder: Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER, FDA; was trained in and practiced general pediatrics and has also worked with an institutional review board.
- Dr. Paul: Professor of Pediatrics and Public Health Sciences, Penn State College of Medicine; general pediatrician with interest in clinical pharmacology and therapeutics and clinical trial work.
- Dr. Francis: Medical Officer, Office of Device Evaluation, CDER, FDA.
- Ms. Berezny, Program Manager, Pediatric Trials Network, Duke Clinical Research Institute.
- Dr. Wade: Neonatologist, Children's Hospital of Philadelphia; interest in clinical pharmacology, clinical trials, and patient safety.
- Dr. Epps: Pediatrician and dermatologist; was Chief of Dermatology at Children's National Medical Center, now in private practice; has served on FDA safety committees for the past 14 years and consulted to NIH regarding drugs in children.
- Dr. Woo: Pediatric nurse practitioner and member of the National Association of Nurse Practitioners (NAPNAP); works in general pediatrics and teaches pharmacology; has written extensively in nurse practitioner literature on pharmacology; particularly interested in learning how there can be more drug options for use in primary care.
- Dr. Hultsch: Senior Director, Translational Medicine, Genzyme Research and Development Center; longstanding interest in developing drugs in atopic dermatitis (AD).
- Dr. Varma: Pediatric endocrinologist with an interest in clinical pharmacology, Texas Tech University School of Medicine.
- Dr. Hordinsky: Professor and Chair, Dermatology, University of Minnesota.
- Dr. Eichenfield: Chief, Pediatric and Adolescent Dermatology, University of California, San Diego, School of Medicine.

- Dr. Wilkin: Chairman, Medical Advisory Board, National Rosacea Society; Member, American Academy of Dermatology; Ad Hoc Task Force on Academy's Efforts with the FDA; Member, Scientific Advisory Board, Nuvo Research Inc.; Member, Clinical Advisory Board, Anacor Pharmaceuticals, Inc.; sees a major lack of products for AD, a very costly, chronic, and problematic pediatric disorder.
- Dr. Phan: Clinical pharmacist for pediatric pulmonology and immunology, University of Arizona.
- Dr. Benner: Professor of Pharmacy Practice, Samford University McWhorter School of Pharmacy, Birmingham, Alabama; practices in the pediatric intensive care unit ICU; interest in and has authored manuscripts on psoriasis and AD.

Presentation by Dr. Siegfried

Dr. Siegfried gave a presentation discussing the therapeutic needs in pediatric dermatology that was developed with the assistance of the four pediatric dermatologists who are part of this group.

Conditions Needing Further Study. Dr. Siegfried noted that there are not evidence-based guidelines for drugs used to treat pediatric diseases. AD is a common disease and represents a great unmet need. Because of the lack of data, AD is at the top of the list for conditions needing further study. Other conditions needing further study include hemangioma of infancy, which affects 10 percent of children; alopecia areata, which has no FDA-approved treatment; and genodermatoses. Dr. Lucky expanded on the area of genodermatoses; she is most familiar with EB. These diseases affect a small number of patients but have a devastating effect. These diseases are orphaned in terms of treatment, with very little industry support because of the small numbers of patients. Dr. Lucky pointed out that these diseases do not just affect the child but affect the whole family.

Drugs of Interest

- Topical therapies for AD—Although there are a few topical medications with data, there is a need for new formulations, delivery systems, and chemical entities (e.g., selective glucocorticoid receptor agonist (SGRA) and phosphodiesterase inhibitors); Dr. Siegfried stressed that children should be included in early-phase studies.
- Systemic therapy for severe AD: existing and emerging immunosuppressants, cytostatic and biologic agents (e.g., anti IL-4)—Because AD is a disease of childhood, it is very important that children should be included in the early-phase studies for these drugs as well.
- Beta blockers for hemangioma of infancy—Topical and systemic, including selective.
- Hydrocortisone valerate (Westcort; prior FDA request)—The pediatric dermatologists recommend this be taken off the list of drugs of interest, as it is not a priority for study.

Type of Patients

- Infants and children with AD—There are no FDA-approved treatments for infants, making this area of study crucial.
- Children with severe AD—About 1 or 2 percent of children with AD have very severe disease, and about 20 percent of children have AD, which represents a very large number of pediatric patients.

- Children with AD and comorbid conditions—There is emerging recognition of co-morbid conditions with AD; these subsets are important, because AD is most likely a phenotype and the comorbidities may identify specific subsets that need different approaches for treatment.
- Infants with hemangiomas.
- Children with conditions attributable to identified genetic mutations where therapeutic intervention could impact the outcome.

Ages

- < 2 months—This is a largely ignored age group; further study is sorely needed.
- 2–12 months.
- 1–5 years.
- 6–10 years.
- 11–18 years.

Collaborators

- Hemangioma Investigative Group (HIG)—This is a group of pediatric dermatologists who have contributed much regarding the epidemiology of hemangiomas and are now instrumental in developing propranolol.
- Pediatric Dermatology Research Alliance (PeDRA)—This group was formed in order to formalize the collaboration of pediatric dermatologists in both investigator-initiated and pharmaceutical company trials. The development of PeDRA was influenced by the Pediatric Oncology Collaborative model as a way to get beyond individual doctors or groups of doctors coming up with their particular ways of treating diseases. There is a special interest in systemic therapy for diseases such as AD and psoriasis, and in attempting to set up a network that would allow prioritization of the best and most influential research on pediatric disease. PeDRA will have a meeting preceding the Society for Pediatric Dermatology meeting. So far, this is a completely unfunded effort.
- The Epidermolysis Bullosa Clinical Research Consortium (EBCRC) is a group of 10 clinical centers for the care of EB in North America, Canada, and South America. The first project is to create a combined database housed at Stanford University to which all the centers can contribute data. The consortium allows members to have access to larger numbers of patients for approved studies. The EBCRC has been funded generously by groups such as the Jackson Gabriel Silver Foundation, but more help is needed to move forward.
- Industry—Working with industry provides a good opportunity to make progress in developing drugs for the pediatric population.

Brandy Weathersby, Circle Solutions, will add as a future item to have Ms. Berezny give more information regarding the Pediatric Trials Network at the Duke Clinical Research Institute.

Types of Studies Needed

- FDA-mandated pediatric clinical trials for new drugs and biologics—The pediatric dermatologists recommend following the European Medicines Agency model, which mandates clinical trials in children for new drugs.
- Clinical database.
- Randomized controlled trials:

- Age-stratified outcomes—With AD, there may be an opportunity to prevent disease; drugs that may not be efficacious for adults might be so for children.
- Treatment (dosing and safety).
- Prevention—Includes preventing the disease itself, halting disease progression, or changing the natural history of the disease.
- Epidemiology/surveillance.
- Comparative effectiveness—There are no evidence-based data, particularly for the systemic drugs for children with AD, but having comparative efficacy studies is always easier to enroll for children when there are comparative efficacy studies, and these studies give additional useful information.

Dr. Durmowicz gave the group background information on FDA-mandated clinical studies. There are two laws that help support pediatric drug development: the Pediatric Research Equity Act (PREA) and the BPCA. The focus in this working group is on off-patent drugs and those products for which information cannot be obtained from the pharmaceutical companies. The other portion of the BPCA provides incentives for pharmaceutical companies to do pediatric studies in return for 6 months of patent exclusivity. PREA is a mandatory law that has five triggers for study:

- New active ingredient
- New indication
- New dosage form
- New dosing regimen
- New route of administration.

Dr. Durmowicz noted that with the passage of PREA, drug companies in the United States, as in Europe, are required to develop a pediatric plan for study earlier in development.

AD. Dr. Siegfried said that severe AD represents approximately 50 percent of her own practice but accounts for about 80 percent of her time, and effective treatment for pediatric patients is a huge unmet need. Dr. Siegfried pointed out additional issues surrounding AD that make additional study in pediatrics necessary:

- AD has been identified as a top priority by the Society for Investigative Dermatology and the November 2011 NIAMS Pediatric Dermatology Round Table.
- This disease affects 20 percent of school-aged children.
- Eighty percent of children who present with AD experience onset of the disease earlier than age 2.
- AD is a chronic disease that requires treatment in much the same way as any other chronic disease, such as diabetes or asthma.
- AD represents a high economic and quality-of-life burden. Dr. Lucky noted that families are turning to untested methods of treatment, including natural and homeopathic remedies, out of desperation at the lack of treatment options available. This can present not only a high economic burden, but it can also be dangerous.
- AD disproportionately impacts underinsured and black children. This manifests in a large number of unnecessary emergency room visits and hospitalizations for children who have poorly controlled disease.

- Early treatment of AD may limit disease progression.
- There are limited patient-support resources compared to other common chronic pediatric diseases (juvenile rheumatoid arthritis, juvenile diabetes, asthma).
- Few evidence-based treatment options are available for treatment of AD and consist of:
 - Ten FDA-approved topical corticosteroids for use in children, with only three FDA-approved in young children; maximum of 4 weeks of data are available.
 - Two topical calcineurin inhibitors with black-box warnings; insurance constraints and families' fear of the drugs because of the black-box warnings have severely limited use of these drugs for treatment of AD in children.
- The black-box warnings have had a huge negative impact on enrolling children in the phase four registries, because parents are wary of the black-box medications. Dr. Eichenfield added that, historically, the disease has not been given as much attention due to the intermittent nature of the disease's presentation in the first 2 years of life. However, the impact of the disease on the patient and families can be significant. In addition, there is emerging literature on the comorbidity association with AD and Attention Deficit Disorder and other mental health effects from AD. There will also be some additional epidemiological data within the next year that suggests higher rates of lipid abnormalities and hypertension, for example. This information regarding comorbidities may drive further study in AD. Dr. Hordinsky noted that children who present with both extensive alopecia areata and very severe AD are extremely difficult to treat because there are two diseases presenting together, neither of which has a good treatment when extensive and severe.
- There is no FDA-approved systemic treatment for severe AD.
 - Current standard of care: cyclosporine A, azathioprine, methotrexate, and mycophenolate mofetil.
 - AD is a disease of children and there needs to be study in the pediatric population, even in the early planning stages. Dr. Wilkins pointed out that there is an ethical component to the lack of pediatric study, given that adults can accept the risk of a new drug whereas the children cannot understand that risk. Dr. Siegfried asked Dr. Wilkins if perhaps a discussion of the barriers to further pediatric study might be useful in future working group calls. Dr. Wilkins responded that it is a complex issue and having some discussion and perhaps a guidance document for industry and researchers would be helpful. Dr. Siegfried suggested the formation of a subgroup to discuss when to include children in pediatric AD and to produce a guidance document. Dr. Durmowicz clarified that the FDA does consider pediatric patients a vulnerable population, so that the FDA prefers to get preliminary proof of safety and efficacy in adults. However, when there is a primarily pediatric disease, the FDA does want to involve pediatric patients in the process sooner. This is a complex process that will depend on the nonclinical data on toxicity, experience with the product, and the severity of the condition, among other factors. Dr. Hultsch added that the development of the immune system in children makes it particularly difficult to study any new chemical entity or biologic. This is further complicated when studying a population with a compromised immune system, such as those children with AD. There is also a need for guidance on what to measure to assess the development of the immune system in young children and how to monitor the effects of new drugs on a developing immune system. Dr. Siegfried said that this could be another area for a subgroup to discuss. Dr. Kutz echoed Dr. Wilkin's comments regarding pediatric study in

the drug development process and noted that she believes it is necessary for any drug that would treat a disease that occurs primarily in children to be studied in children before it comes to market.

- Lack of indication or lack of age-specific FDA-approved medication impacts access to treatment because of private and state-supported insurance denials and because use of the medication is prohibited even for compassionate use.
- Research needs
 - Consensus use of a single standardized severity assessment
 - Biomarkers to define subtypes and to predict and reflect response to treatment
 - Centralized databases
 - Clinical: patient-entered and clinician-entered
 - Investigational (Global Resource of Eczema Trials [GREAT] database at www.greatdatabase.org.uk)
- Resources
 - PeDRA
 - Harmonising Outcome Measures for Eczema (HOMES) is an international collaborative group that seeks to define a minimum set of core outcomes for future eczema (AD) research. The next meeting will be in San Diego in April 2013. HOMES is exploring whether the FDA and/or the NIH will be interested in participating in this meeting. The goal is to have a rich methodology for exploring outcomes in eczema.

Next Steps:

- A subgroup will be formed to discuss pharmacologic issues for new drug development in children.
- A subgroup will be formed to discuss ethical issues surrounding pediatric trials.
- A subgroup will be formed to determine what kind of information should be included in a national or possibly international database. This closely resembles the work the EBCRC is already doing, so Dr. Lucky will spearhead this subgroup and contact the other members of the EBCRC to see who might be interested in participating.
- Dr. Hultsch suggested a subgroup that would focus on pediatric immunology issues.
- The members will better define the subgroups, call for volunteers/participants, and then plan for the next call.