

**Best Pharmaceuticals for Children Act (BPCA)
Rheumatology Therapeutic Area Working Group Conference Call and Webcast
May 10, 2012
2:00 p.m.ET–3:00 p.m. ET**

Participants

Mara Becker, M.D., M.S.C.E.
Marcia Buck, Pharm.D., F.C.C.P., F.P.P.A.G.
Elizabeth Durmowicz, M.D.
Jamie Gao
Norma Gavin, Ph.D.
George Greeley for Oluchi Elekwachi, Pharm.D., M.P.H.
Gordon Klein, M.D., M.P.H.
Rosemarie Neuner, M.D., M.P.H.
Ronald Portman, M.D.
Michael Reed, Pharm.D.
William Rodriguez, M.D., Ph.D.
Laura Schanberg, M.D.
Douglas Silverstein, M.D.
Janice Sullivan, M.D.
Perdita Taylor-Zapata, M.D.
Pamela Weiss, M.D., M.S.C.E.

Purpose

The purpose of the conference call was to describe the background of the BPCA and to solicit input from the experts about pediatric therapeutics needs in rheumatology.

Background

Dr. Taylor-Zapata emphasized that the focus of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Obstetric and Pediatric Pharmacology Branch is pediatric therapeutics. The BPCA is a legislative mandate to improve the effectiveness and safety of medicines used in children. The advocacy of the American Academy of Pediatrics (AAP) and the work of the Pediatric Pharmacology Research Units led to the BPCA. The 1998 U.S. Food and Drug Administration (FDA) Modernization Act gave pharmaceutical companies the incentive of 6 months of patent exclusivity in exchange for studies in children. This exclusivity was continued in the 2002 BPCA and reinstated in the 2007 FDA Amendments Act.

The FDA implements the main component of BPCA, encouraging industry to perform studies to improve labeling for children in exchange for an additional 6 months of patent exclusivity. The National Institutes of Health (NIH) implements the smaller component of the BPCA— establishing a program to sponsor needed studies of important drug products in cases where the pharmaceutical company declines to perform the studies. The NIH pediatric drug development

program has two main components: (1) developing a prioritization process to identify gaps in pediatric therapeutics, including drugs and biologics that need further study, and (2) conducting clinical trials of primarily off-patent drugs that have been prioritized. Twenty NIH Institutes contribute to BPCA funding.

The BPCA process begins with prioritization, which leads to Written Requests or Proposed Pediatric Study Requests (PPSRs) and clinical studies. Data from the clinical studies are submitted to the FDA for labeling changes.

The 2002 BPCA focused on particular drugs, drawn from an FDA master list. The NIH funded studies based on the public health benefit and consultations with pediatric experts and reacted to Written Requests from the FDA. The 2007 BPCA focuses on therapeutic areas, prioritized based on public health benefit and consultation with experts. The NIH is more proactive, developing PPSRs.

The stakeholders in the prioritization process include the NICHD; the FDA pediatric division and review division; and members of academia, the AAP and other professional societies, industry, and advocacy and parent groups.

The NICHD has learned a number of lessons since the BPCA began. There is a pervasive lack of preclinical and phase I and phase II clinical trial data on dosing, safety, and efficacy in drugs that have been used in pediatrics for years or even decades.

The prioritization process involves outreach to key experts in pediatric pharmacology, pharmacoepidemiology research, and mass outreach through major pediatric organizations and Requests for Information in the NIH Guide for Grants and Contracts. The BPCA program initiated therapeutic area working groups in 2005 and created an annual working group process in 2009. The working group members will receive invitations to the BPCA Annual Meeting.

The BPCA has prioritized a broad range of therapeutic areas. Accomplishments include

- Funding 16 clinical trials
- Producing 18 publications and 26 abstracts
- Developing clinical pharmacology training programs such as the National Institute for General Medical Sciences-NICHD T32 Program
- Collaborating with the National Cancer Institute/Children's Oncology Group; the National Heart, Lung, and Blood Institute; and the Clinical and Translational Science Awards
- Producing labeling changes for propylthiouracil and pralidoxime and completing five additional studies that will be submitted for labeling changes.

Each year, the NIH identifies two or three therapeutic areas and establishes working groups in each area. The 2012 working groups will focus on dermatology and rheumatology. The NIH asks groups to recommend drugs and drug classes, biologics, and other areas of research that affect pediatric therapeutics that require further study. The groups meet via conference call three to four times in a calendar year. Minutes of the calls will be posted on the BPCA Web site. The groups will present their recommendations at the BPCA Annual Meeting in November or

December. In addition to recommendations, the working groups may produce workshops or publications. The group will have another conference call in 4–6 weeks and will receive invitations to the 2012 BPCA Annual Meeting.

The BPCA mandate focuses on therapeutics—the NICHD does not want to duplicate other Institutes' efforts in rheumatology. During the BPCA outreach process in 2010, rheumatology was identified as an area of interest.

Discussion

Dr. Taylor-Zapata asked whether hydroxychloroquine is still used and needs study. Dr. Becker said that other drugs might be more important. Hydroxychloroquine is used in combination with other drugs to treat conditions such as lupus, but it is used more extensively in adult rheumatology. Dr. Schanberg said that hydroxychloroquine is commonly used and has not been studied in children. It is part of the standard of care for pediatric lupus and dermatomyositis patients but does not treat juvenile idiopathic arthritis (JIA) well. The drug should not be removed from the priority list.

Dr. Schanberg said that the length of treatment is a major therapeutic issue for children with rheumatic diseases. Unlike adults with rheumatoid arthritis, children with JIA do not need treatment forever. More knowledge is needed about combination therapies in children, especially combination therapies with methotrexate. Dr. Becker added that formulations are an important issue. Administering drugs is challenging when there are only a few options.

Dr. Klein noted that bone loss accompanies many rheumatic diseases, and the inflammatory process is probably the main cause. Some information indicates that bone resorption, and possibly the liberation of calcium, feed the inflammatory process. Bisphosphonates could be used to reduce or eliminate bone loss. Dr. Schanberg said that pediatric rheumatologists are wary of using bisphosphonates in children. Dr. Klein said that in burn patients, there is a significant and acute inflammatory response. One dose of intravenous bisphosphonate preserves the bone for at least 2 years. The inflammatory process may continue, but the bone is spared. The extent to which the bone is contributing to the intensity of the inflammatory response is not known. A study endpoint could be whether bisphosphonates decrease the length of therapy.

Dr. Rodriguez asked about studies of bisphosphonates in juvenile animals. Dr. Klein was not aware of any animal studies, but he noted that data on children with osteogenesis imperfecta show no toxicity. In the burn population, there are no side effects with one dose. Dr. Rodriguez asked how long exposure would be in patients with chronic conditions. Dr. Klein said the answer was not known. The literature on the use of pamidronate in infants and children with osteogenesis imperfecta does not show toxicity.

Dr. Silverstein said that, based on his experience in the BPCA Renal Working Group, the group should focus on confined studies that can be performed prospectively in a relatively short time. The group should think about studies that are feasible, can recruit enough patients to have a good power analysis, and have a definite endpoint.

Dr. Taylor-Zapata asked whether methotrexate is used across multiple diseases and conditions. Dr. Schanberg said that it is used alone and in combination to treat multiple conditions, including lupus, dermatomyositis, scleroderma, inflammatory uveitis, and JIA. Dr. Becker said that information about optimal formulations and doses is lacking. Methotrexate is an anchor drug for the treatment of many diseases, but the drug is not well understood. Dr. Klein said that the drug is known to cause bone loss, and it may be useful to evaluate bone loss as an endpoint. Dr. Schanberg said she did not think the drug caused bone loss in the doses routinely used. Dr. Klein said this question should be raised.

Dr. Schanberg said that more information is needed about the side effects of methotrexate. Children's families often complain about headaches, school issues, and nausea. Dr. Becker agreed that quality of life issues have not been investigated and can affect adherence. More information is needed about how supplementation with folic acid or folinic acid affects the side effects and efficacy of methotrexate. Dr. Schanberg noted that there is no information about how to dose and administer folate, and practices vary among rheumatologists. Dr. Becker said that there is some evidence that patients with psoriasis and rheumatoid arthritis who are supplemented with folate do not do as well as patients who do not receive folate.

Dr. Rodriguez asked how often methotrexate is used with other drugs. Dr. Schanberg said that it is commonly used with biologics, and there is a little information about this use. Methotrexate is also used with steroids, sulfasalazine, hydroxychloroquine, and non-steroidal anti-inflammatory drugs. It is occasionally used in triple therapies, which are not as common in pediatric as in adult rheumatology. There is almost no information about the safety and benefits of combination therapies. Dr. Becker agreed and noted that there are some data on methotrexate with newer biologics and with leflunomide, but the use of leflunomide is limited in children because there are only two dose options. Dr. Schanberg said that informal information about combination therapy could be collected from the pediatric rheumatology registry.

Dr. Schanberg said that the group should also consider mycophenolate, which is being used in more pediatric rheumatic diseases but does not have a pediatric indication. Dr. Neuner noted that mycophenolate also does not have any adult rheumatoid indications.

Dr. Taylor-Zapata asked whether withdrawal studies have been done in pediatric rheumatology. Dr. Schanberg said some studies have been done at about 3 months, but rheumatologists do not think 3 months is sufficient to control diseases.

Dr. Schanberg noted that Imuran is not well studied in children. This drug was used to treat lupus, but use has fallen off with increased use of mycophenolate.

Dr. Becker suggested that pulse Solu-Medrol should be compared with oral corticosteroids. Dr. Schanberg said that pulse and oral therapies have only been compared in lupus. Pulses are better at extinguishing the interferon signature. Dr. Silverstein said that pulse therapies have been studied in renal diseases. Dr. Schanberg added that the dose and preparations for intraarticular

steroids should be studied. Dr. Klein noted that corticosteroids cause bone loss and the use of bisphosphonates should be considered.

Dr. Rodriguez asked about the use of the tumor necrosis factor (TNF) inhibitor etanercept, and Dr. Schanberg said that it is used often. There is some information about safety, but not enough. Etanercept is effective in treating JIA in patients who have failed methotrexate. Little is known about optimal dose, when to start it, how long to use it, and in which patients it should be used. Dr. Becker noted that the dosing range is small, and little is known about higher doses. Data for other biologics suggest that younger patients may require higher doses. More information is needed about when and how to stop therapy.

Dr. Durmowicz noted that TNF inhibitors are approved for the treatment of JIA. Etanercept is approved for ages 2 years older and adalimumab is approved for weights down to 15 kilograms.

Dr. Weiss said that infliximab is used frequently. Some rheumatologists are using high doses, and there are no data to guide that use. Dr. Neuner said that infliximab failed to show efficacy for JIA and was associated with a high rate of tuberculosis. This information is in the label. Dr. Weiss said that the Children's Hospital of Philadelphia uses the drug to treat uveitis. Dr. Neuner thought there were some phase II proof-of-concept studies for infliximab in adult uveitis, but it failed to show efficacy. Dr. Schanberg said that this was not true in pediatric inflammatory eye disease and that there were many problems with the infliximab study. Infliximab works like other anti-TNF agents in treating arthritis. Rheumatologists know from practice that all of the anti-TNF agents work.

Dr. Becker noted that there is variability in response to all agents. It is important to understand the factors that contribute to this variability. Dr. Schanberg said there are no studies comparing biologics.

Dr. Rodriguez asked about creatine supplementation in pediatric rheumatology; a study on this topic is listed on the ClinicalTrials.gov Web site. Dr. Becker said she was not aware of any studies of creatine supplementation.

Action Items:

- A second conference call will be scheduled in 4 to 6 weeks.