Best Pharmaceuticals for Children Act (BPCA)
Hematology Working Group Conference Call and Webcast
August 18, 2011
1:00 p.m.–2:00 p.m. ET

Participants

Marcia L. Buck, Pharm.D., F.C.C.P., F.P.P.A.G.
Allan Doctor, M.D.
Beth Durmowicz, M.D.
Oluchi Elekwachi, Pharm.D., M.P.H.
Jonathan Goldsmith, M.D.
Alyson Karesh, M.D.
John Kelleher, M.D.
Paul M. Kent, M.D.
Gordon L. Klein, M.D., M.P.H.
Joseph H. Laver, M.D., M.H.A.
J. Steven Leeder, Pharm.D., Ph.D.
Lori Luchtman-Jones, M.D.
Lynne Maxwell, M.D., F.A.A.P.
Kathleen Neville, M.D., M.S.
Victor Santana, M.D.
Kristin Snyder, M.D.
Perdita Taylor-Zapata, M.D.
Courtney Thornburg, M.D., M.S.
Surendra Varma, M.D., F.A.A.P.
Athena F. Zuppa, M.D., M.S.C.E., F.A.A.P., F.C.P.

Purpose

The purpose of the call was to:
- Review discussion points from the working group's first conference call and webcast
- Provide more specific details on recommendations from the working group's first conference call and webcast
- Finalize points and any future assignments.

Introduction

Dr. Taylor-Zapata reviewed the purpose and process of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's (NICHD) BPCA program. For 2011, the three therapeutic areas are pulmonary, hematology, and renal. The groups will meet via teleconference two or three times a year. Minutes of meetings will be posted on the BPCA Web site and distributed to working group members. The working groups' recommendations will be presented at the 2011 annual BPCA prioritization meeting and could lead to future studies, workshops, and publications.

Discussion

A table of discussion points was distributed before the call. Dr. Thornburg led the group's discussion of these points, noting that they focus primarily on anticoagulation therapeutics. Dr. Thornburg proposed that the group start with drug-dosing studies since one of the goals is to identify new pediatric-specific indications for the drugs. Treatment alternatives and novel agents would be included in the drug-dosing studies. Incorporated within the study designs, the group could recommend ancillary studies on things such as biomarkers, safety, formulations, and drug delivery.

Discussion topics were as follows:

- Diseases and conditions of interest are thrombosis and stroke.
- Drugs of interest are heparin and warfarin as standard anticoagulants, with dosing adapted from adults.
- Dr. Buck noted two unique populations for study: infants and obese pediatric patients. Issues for obese pediatric patients involve dosage based on actual, ideal, or adjusted weight. These issues apply to any of the anticoagulant drugs.
- Another population to consider is infants in cardiac intensive care units (ICUs).
- Anticoagulation studies of oncology patients have mostly focused on devices such as central venous catheters and associated coagulation problems. Most of the data are from Canadian studies. Some patients with paraneoplastic syndrome develop thrombosis, but it is very rare.
- Thrombosis has been associated with asparaginase chemotherapy, but it is different than catheter-induced coagulation problems.
- Dr. Doctor said the incidence of functionally significant thrombosis is higher in cardiac pediatric critical care patients, many of whom are infants. Extracorporeal device support is another problem, with dialysis and extracorporeal membrane oxygenation the two principal areas. Thrombosis also occurs with external ventricular assist devices. Anticoagulation plans are currently not based on scientific evidence. Another area lacking evidence is monitoring anticoagulation therapy.
- Heparin and citrate protocols in ICUs are possible areas to be studied.
- A potential study population is patients receiving long-term parenteral nutrition in order to determine approaches to minimize catheter clotting. Tissue plasminogen activator (tPA) sometimes minimizes clotting but not always.
- The working group's primary focus could be treatment strategies, with a secondary focus on prevention strategies (e.g., for long-term catheters and total parenteral nutrition).
- An issue for dosing and efficacy studies is how outcomes will be monitored and what assessment tools will be used.
- In adult safety studies, bleeding is the primary outcome. Longer term outcomes are the prevention of clots and recurrence of clots, for example, in post-thrombotic syndrome.
- Aluminum loading associated with long-term heparin therapy is another possible outcome of interest because of risks of bone and liver complications.
- Networks that could conduct the hematology studies include the Pediatric Heart Network, the NICHD Neonatal Research Network, the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN), and the PALISI (Pediatric Acute Lung Injury and Sepsis

Investigators) Network. The Pediatric Heart Network has about 10 sites, the CPCCRN has 8 sites, and the PALISI Network has about 30 sites. The PALISI Network has a subgroup devoted to transfusion studies.

- Studies of newer anticoagulant agents could be sponsored by industry. However, the focus of BPCA-sponsored studies is off-patent drugs that are not required to be studied by industry.
- The BPCA program has not collaborated with the U.S. Food and Drug Administration (FDA) orphan drug program. The two programs could collaborate if a need is identified.
- Another area of possible dosing studies involves reversal agents such as tranexamic acid, protamine, and vitamin K. These studies could be incorporated into the anticoagulant studies. A call participant noted that the patient population for reversal agents is smaller than the anticoagulant population and the use of reversal agents is not common. Because of this, studies of the anticoagulant population should be a higher priority.
- Many of the adult drugs that are used for heparin-induced thrombocytopenia **(**HIT**)** are off-patent and are good candidates for pediatric studies.
- Although aspirin is used to prevent clotting in nonbiological shunts in children with complex congenital heart disease, there are no assays of efficacy. Possible aspirin studies would be monitoring dose effect and determining biomarkers of response.
- Dr. Klein proposed that the working group consider a broad epidemiologic study of the incidence of clotting under a variety of circumstances, which could be used to structure a dose-response study. An epidemiologic study could, for example, provide information on the incidence of catheter-related thrombosis in ICU populations.
- The working group will consider registries, prospective studies, and dosing studies.
- Dr. Neville reported that the FDA is sponsoring a pharmacogenetics study of warfarin to compare effects in children versus adults.
- Pharmacokinetic (PK) studies are relatively straightforward to design. For clinical outcomes, relevant pharmacodynamic (PD) endpoints will need to be determined for lab assays and will be important for study design.
- Drug-dosing study designs will need to be responsive to the FDA on the value of pharmacogenetic markers.
- PK/PD studies will need to incorporate genetics or include up-front genetic screening.
- Currently, there are no robust functional clotting assays, and there have been no head-to-head comparisons of the utility of existing assays.
- Dr. Maxwell explained that the steps for relabeling are to identify candidate drugs and prioritize them and then have the FDA issue Written Requests (WRs). At this time, the Hematology Working Group should identify drugs that need to be studied in children and the ways to study them (e.g., PK/PD studies and biomarkers).
- Dr. Luchtman-Jones noted that there is a need for an alternative monitoring option (e.g., a finger or toe stick) for unfractionated heparin or partial thromboplastin time or ideally both. A commercial instrument is available, but it has not been widely accepted or validated. Heparin monitoring studies generally draw from heparinized lines.
- Monitoring aspirin therapeutics is an issue. An initial study could look at functional assays to identify endpoints for clinical studies.
- Several adult studies using platelet function to determine dose-response are underway.
- The working group could target specific types of clots and include PK studies and monitoring as part of dose-response comparisons.

- Results of an epidemiologic study could strengthen the case for using specific drugs in specific situations.
- Studies of pediatric oncology patients who get clots might allow comparisons of drug therapies or drug therapy versus no therapy. Treatment versus prevention could also be studied in this patient population. Because of the number of pediatric oncology subgroups, it may be necessary to look at specific treatments for specific conditions.
- With regard to cross-cutting issues, postdialysis patients have a risk of vascular clots and might be considered. If the working group thinks this is a relevant issue, a joint call with the Renal Disease Therapeutic Area Working Group could be set up.
- Other study populations to consider are hemophilia patients and patients with renal failure.

Next Steps:

- Dr. Klein will provide references for the studies of aluminum-loading associated with long-term heparin therapy.
- Drs. Taylor-Zapata and Thornburg will draft a list of areas requiring more information (e.g., WRs that have already been issued, epidemiology data available from networks) and circulate it to the working group.
- Working group members are asked to indicate their areas of interest.
- Drs. Taylor-Zapata and Thornburg will develop a list of assignments for the working group.
- Sara Kistler of Circle Solutions, Inc., will contact the Renal Disease Therapeutic Area Working Group to determine its interest in a joint conference call.
- Ms. Kistler will poll the working group about the time for the next conference call.