

**Best Pharmaceuticals for Children Act (BPCA)
Renal Disease Working Group Conference Call and Webcast
September 8, 2011
11:00 p.m.–12:00 p.m. ET**

Participants

Laurie Conklin, M.D.
Beth Durmowicz, M.D.
Stuart L. Goldstein, M.D.
Frederick Kaskel, M.D., Ph.D.
Kelley Norris, Pharm.D., B.C.P.S.
Uptal Patel, M.D.
Ronald Portman, M.D.
Natella Rakhmanina, M.D., Ph.D., F.A.A.P., A.A.H.I.V.S.
Michael Reed, Pharm.D., F.C.C.P., F.C.P.
Douglas Silverstein, M.D.
Amy Taylor, M.D., M.H.S., F.A.A.P.
Perdita Taylor-Zapata, M.D.
Phil Walson, M.D.
Ann Zajicek, M.D., Pharm.D.

Purpose

The purpose of the call was to provide specific details about recommendations from the first call.

The BPCA Program

Dr. Taylor-Zapata asked the group to discuss specific details, feasibility, and study design for the discussion points distributed before the call. During the next call, the group will prioritize its recommendations.

Dr. Kaskel noted that the group made recommendations about three topics: anemia, osteodystrophy, and chronic kidney disease (CKD). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) held a meeting in July 2011 on CKD and clinical trials. Before that meeting, the American Society of Pediatric Nephrology surveyed its members and identified four priority areas: hypertension, vitamin D and phosphate control in renal osteodystrophy, anemia, and chronic acidosis.

Dr. Goldstein noted that two discussion points listed under CKD were actually related to acute kidney injury (AKI): short-term use of statins for the prevention of AKI and drug metabolism and clearance of continuous renal replacement therapy (CRRT). The table should be corrected. There are some data from Canada on the use of statins after cardiopulmonary bypass to prevent AKI. Statins have not been evaluated in infants.

Anemia. Dr. Kaskel discussed recent U.S. Food and Drug Administration (FDA) black box warnings and Centers for Medicare and Medicaid Services (CMS) concerns about using erythropoiesis-stimulating agents (ESAs) to raise hemoglobin above a certain level. ESAs are associated with cardiovascular adverse outcomes in adults with CKD and end-stage kidney disease (ESKD), but there are no data that show adverse outcomes in children. There are new requirements that lower target hemoglobin levels, and target hemoglobin levels in children have not been studied.

Dr. Goldstein noted that anemia affects exercise tolerance, growth, and neurocognitive development. A logistical concern is that studies will be limited by the CMS quality incentive program (QIP) target hemoglobin levels, which may be too low for children. The need for systematic study of long-term outcomes of ESAs should be communicated to the CMS. Short-term outcomes will be difficult to measure, unless exercise tolerance or cardiac function are used.

Dr. Kaskel said that the CMS would wait for data, and the BPCA provides a mechanism to address this gap. He was involved in a recent National Quality Forum that looked at target hemoglobin levels, and data are lacking for a number of issues. Dr. Goldstein agreed that studies are needed to determine levels that make sense for children. Dr. Silverstein emphasized that the studies should be well designed and should focus on issues that are unique to pediatrics, such as neurocognitive development and linear growth. Studies must begin in the next 12–18 months, before the CMS QIP limits are applied to pediatric patients.

Dr. Kaskel asked whether a biomarker of ESA treatment could be used to study dosing. Dr. Goldstein said that exercise tolerance tests could show improvement without requiring long-term neurocognitive development testing. Dr. Walson suggested including cardiovascular effects such as microvascular flow, blood pressure, and echocardiogram measurements. Dr. Silverstein suggested looking at wall stress. Dr. Walson said previous studies found that echocardiograms could show acute changes in dimensions and wall stress with changes in blood pressure.

Dr. Kaskel asked whether studies would look at CKD patients before dialysis. Dr. Goldstein explained that the dialysis population is seen frequently, and dialysis can be used to control ESA dose and get rapid responses in hemoglobin. Studies can look at myocardial stunning intradialytically. If patients are monitored by a Crit-Line, studies could look at rates of hypoxemia during treatment as a measure of cardiovascular function. Including CKD would increase the number of patients, and an ancillary study could be added to the CKD in Children (CKiD) study. A randomized or prospective trial would be more difficult because follow-up in CKD patients is so variable. Studies should be restricted to CKD stages 3 and 4, in which patients require ESAs. The QIP and the black box warnings address ESKD.

Dr. Walson suggested randomizing patients to high and low levels of hemoglobin. Dr. Silverstein said that there were confounding elements when looking at cardiovascular function in patients with ESKD, but previous studies have dealt with this issue. The study would be easier with the ESKD population than with the CKD population. Patients with ESKD are a captured population, and the research would apply to issues that concern the CMS. Dr. Goldstein expressed concern

with doing only observational studies. The black box warning came from two prospective non-ESKD studies. People may be following the QIP recommendations. The study should be conducted in a format with consent and institutional review board (IRB) approval.

Dr. Kaskel summarized that knowledge gaps could be addressed by a prospective study of ESKD patients involving hemodialysis and peritoneal dialysis. There is some interest in looking at early biomarkers such as cardiovascular markers and exercise physiology. A protocol for a multicenter study should be developed for presentation at the December BPCA Annual Meeting.

Dr. Silverstein asked whether B-type natriuretic peptide (BNP) would be a useful biomarker. Dr. Walson said that various forms of BNP would be easy to measure, and pediatric patients should have stored plasma samples.

Dr. Patel noted that the original goal of anemia treatment was transfusion avoidance, but the goal has shifted to normalization. Although many children stay on dialysis, transplantation is the treatment of choice, and dialysis is often temporary. Finding a point between transfusion avoidance and optimization of function on dialysis may lead to strategies that minimize toxicity.

Osteodystrophy. Dr. Kaskel noted that one of the working groups at the NIDDK CKD meeting discussed adult data showing that fibroblast growth factor 23 (FGF-23) is a marker of cardiovascular risk in the CKD and ESKD populations. Dr. Anthony Portale analyzed CKiD data and found that FGF-23 levels increase as kidney function deteriorates in children as in adults. He also found that a large number of CKiD children had left ventricular dysfunction.

Dr. Goldstein said that a study showed higher FGF-23 in children with cardiovascular calcification. Higher serum phosphorus and malnutrition are confounders in children with calcification. He expressed concerns about confounding and adherence and noted that hypertension, malnutrition, and inflammation will be problems. While osteodystrophy is a major cause of morbidity in children with CKD and ESKD, it is not clear how a trial could demonstrate outcomes unless the study only looks at biomarkers.

Dr. Kaskel said that at the NIDDK CKD meeting, Dr. Myles Wolf presented data in adults showing that FGF-23 elevation starts before serum phosphorus elevation. Dr. Goldstein said that cause and effect are not clear, and it is not known whether FGF-23 acts independently. Dr. Kaskel asked whether this was a gap worth studying.

Dr. Walson asked whether any treatments decrease FGF-23. Dr. Kaskel said that adult studies would look at this issue. Dr. Silverstein said that it would be difficult to design a multicenter study because the endpoint is uncertain. Dr. Goldstein agreed; it is not known whether preventing FGF-23 levels from rising will improve outcomes.

In response to a question about vitamin D, Dr. Goldstein explained that parathyroid hormone is used to judge vitamin D dosing. He did not know whether there was a relationship between parathyroid hormone and FGF-23. A participant asked about sclerostin, and Dr. Kaskel said this

was a new biomarker. Dr. Walson said that vitamin D dosing in renal disease is an unknown. Dr. Goldstein added that this area is important but too complex to address with this group.

CKD and AKI. Dr. Goldstein explained that the pharmacokinetics (PK) of many life-saving medications are not understood in AKI. Dosing guidelines are based on animal data and small studies or are extrapolated from ESKD. The majority of children who develop AKI in the intensive care unit are treated with CRRT. There are minimal data on dosing when patients are on CRRT, and rational dosing guidelines are needed.

Dr. Goldstein works with the Prospective Pediatric CRRT Registry Group (ppCRRT)—a group of 12 U.S. centers that has done some prospective observational studies and FDA work to bring devices to children. The ppCRRT is working with pharmacologists such as Dr. Alexander Vinks to create computer-generated models based on the main factors that affect CRRT and AKI PK, including age, dose of dialysis, residual renal function, percent of fluid overload, and hepatic function. The models will be tested in a group of children in a multicenter network.

Dr. Walson suggested that the ppCRRT collaborate with Dr. Daniel Benjamin's group at Duke University, which is conducting BPCA-funded convenience PK studies. Leftover samples from children receiving drugs could be used to create population PK models. Network coordination would be needed to collect, store, and analyze samples. Dr. Goldstein said that Dr. Benjamin would not have information about the dose of dialysis, when it was delivered, tubing type, and so on. The study will need 45 patients per drug for modeling. The goal is to set up a network that will collect samples and data on children on CRRT. The study would look at both CRRT and AKI before dialysis. The research would be multidisciplinary—only 7 percent of AKI is related to primary kidney disease. Most AKI is related to liver failure, bone marrow transplants, cardiac failure, lung disease, and solid organ transplants.

Dr. Goldstein said that the study would include centers that use different modalities, but the study is not powered to randomize patients to different modalities. He noted that a protocol for the study has already been developed.

Other Issues. Dr. Walson said that, for the BPCA process, devices should be listed as an area that deserves study. Dr. Goldstein agreed and noted that most devices are adapted for children but not developed for children. The CRRT study would be a device study.

Dr. Goldstein asked whether an Investigational Device Exception (IDE) would be needed to enroll young children in the CRRT study. Dr. Silverstein said that one device is not approved for use in children weighing less than 20 kg. If the study would include patients who weigh less than 20 kg, it would make sense to get an IDE. The IDE can be reviewed relatively quickly. Dr. Goldstein noted that the device and drugs would be given for their recommended indications, not as part of the study. The study would only check blood levels, with IRB approval and informed consent. Centers may use a variety of devices; the study would not standardize the devices used. Dr. Silverstein will talk with his superiors about this issue.

Dr. Walson asked about contrast-induced nephropathy (CIN). Dr. Goldstein said that CIN is a major issue for adults. While CIN does occur in children, few children with CKD receive contrast agents. The short-term outcome is AKI, but a study would have to follow children for many years to examine long-term outcomes.

Action Items:

- The table of discussion points will be corrected to show that short-term use of statins for the prevention of AKI and drug metabolism and clearance of CRRT are related to AKI, not CKD.
- Dr. Silverstein will talk with his superiors about whether an IDE would be required for the CRRT study.
- Dr. Taylor-Zapata and Brandy Weathersby of Circle Solutions, Inc., will send out assignments and a conference call summary and will poll for a time for the third conference call.
- The next conference call will be scheduled in early to mid October.