Best Pharmaceuticals for Children Act (BPCA)
Rheumatology Therapeutic Area Working Group Conference Call and Webinar
November 9, 2012
3:30 p.m.–5:00 p.m. ET

Participants

Mara Becker, M.D., M.S.C.E.
Polly Ferguson, M.D.
Alyson Karesh
Gordon Klein, M.D., M.P.H.
J. Steven Leeder, Pharm.D., Ph.D.
Ronald Portman, M.D.
Michael Reed, Pharm.D.
William Rodriguez, M.D., Ph.D.
Douglas Silverstein, M.D.
Janice Sullivan, M.D.
Perdita Taylor-Zapata, M.D.
Mary Toth, M.D.
Carolyn Yancey, M.D.

Purpose

The purpose of the call was to present and discuss the recommendations from the Rheumatology Working Group's subcommittees. A written report with the recommendations from each subcommittee was distributed to working group members prior to the conference call.

Welcome and Introductions

Dr. Becker welcomed participants and asked the subcommittee presenters to introduce themselves.

Presentations from Working Group Subcommittees

Bone Biology Subcommittee

Members: Gordon L. Klein, M.D, Mary Toth, M.D.

Dr. Klein said the Bone Biology Subcommittee recommends a trial of intravenous (IV) bisphosphonates in pediatric patients with rheumatologic or other conditions that require steroids for more than 6 months. Bisphosphonates are approved by the U.S. Food and Drug Administration (FDA) for use in adults to treat or prevent steroid-associated bone loss. Dr. Klein reviewed the mechanisms by which bisphosphonates work, including a secondary mechanism (not described in the subcommittee's written report) involving an antiapoptotic effect on osteoblasts and osteocytes that has been experimentally demonstrated. The adverse effects (AEs) associated with the use of bisphosphonates in adults include osteonecrosis of the jaw in cancer

patients, atypical femoral fractures, and theoretical hypocalcemia. These are theoretical AEs in children but have not been reported in studies of children with osteogenesis imperfect (OI) or when given acutely in children with burn injuries. According to a study on the FDA Web site, children taking steroids who receive zolendronate show an increase in bone mineral density, but there is no correlation with fracture incidence or frequency of bone pain; however, this is a difficult cause-and-effect relationship to establish. In children with OI, the use of IV pamidronate decreases fracture incidence and bone pain.

The Bone Biology Subcommittee recommends a randomized, placebo-controlled double-blind study using bisphosphonate, probably on an acute basis and perhaps only a one-time dose, and following the patients using dual-energy x-ray absorptiometry (DXA) every 3 months for about a year to see whether there is a difference in bone loss. If preliminary analysis of data shows benefit, it might be more ethical to stop the study and give the drug to all patients.

Dr. Rodriguez said this plan sounded exciting and asked whether there are existing registries that follow patients for longer than a year or whether such a registry could be developed. Dr. Becker said Dr. Laura Schanberg is one of the principal investigators with the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Network (CARRAnet) registry, so there is the possibility to work with a registry that is up and running. The challenge would be to incorporate a bisphosphonate component in the registry. Dr. Klein noted that, presumably, patients would take the drug while using steroids. He said there is a question about whether bisphosphonates should be used in cases of pure inflammatory bone loss.

Dr. Becker asked about knowledge of dosing in children and pharmacokinetic (PK) data. Another concern is whether any steroid dose would be worthwhile or whether it would have to be standard steroid doses for 6 months. Dr. Klein said that regarding steroid doses, adults use 7.5 milligrams (mg) per day, so that could be a potential guideline. Regarding bisphosphonate dosing, the Montreal Shriner studies give the bisphosphonate intermittently with a total of about 9 mg per kilogram (kg) per year. Lower doses of the drug are given more frequently to younger children, and doses are increased but given less frequently as the children get older. A study would probably need to start with known doses that do not produce toxicities.

Dr. Yancey said Dr. Rosemarie Neuner could not be on the call but wanted her to share some concerns. The issue of femur fractures in adults who use bisphosphonates and the overall safety of these products are still under review at the FDA. Dr. Klein said the American Society for Bone and Mineral Research is also looking at this issue. Femur fractures affect about 1 percent of adult bisphosphonate users, so there is an issue of risk versus benefit, and the number of adults receiving bisphosphonates is large. Atypical fractures associated with bisphosphonate have not been reported in OI patients, but hard data are needed to determine the risk of fractures in children.

Dr. Toth said the subcommittee's concern is the lack of knowledge about what can safely be used for children on steroids who have fractures. Thus, the subcommittee is proposing that the children will be on steroids for at least 6 months; they will be followed with DXA exams to determine bone densities. The likelihood of atypical fracture is small in this group of patients.

Dr. Silverstein said he thought this would be a worthwhile study to do in children who receive steroids but he wondered what the study would be able to show using only a single dose of bisphosphonate. Dr. Klein replied that in his experience with burn patients who received the drug, there were differences in bone density seen from one dose at 6 weeks post-burn, and these differences persisted for 2 years. He would strongly support use of a registry to get fracture information. It is known that there is some relationship between bone density and fracture risk, especially with steroid use, and vertebral fractures are hard to detect. Because the bisphosphonate makes a difference at least 2 years out with burns, and because zolendronate can have lasting effects for up to 5 years, the subcommittee believes that differences will be seen by randomizing patients to receive the drug.

Dr. Becker said researchers are just beginning to recognize how inflammatory rheumatic conditions affect bone density. The working group may need to consider recommending studies to better understand the inflammatory process to determine a baseline. Dr. Klein said everyone will have the same degree of inflammation. It may be possible to relate the inflammatory response to the steroid dose, for example, by measuring cytokine or other markers. A severe enough inflammatory response will trigger a stress response, so endogenous glucocorticoids can add to this problem.

Dr. Silverstein noted that there have some reports of renal toxicity, so it may be good to check baseline serum creatinine levels and adjust dosage based on glomerular filtration rates. Dr. Klein agreed and said bisphosphonates are not given to those with significant kidney impairment.

Fibromyalgia Subcommittee

Members: Michael D. Reed, Pharm.D. (Chair), Douglas Silverstein, M.D., Janice Sullivan, M.D., Surendra K. Varma, M.D.

Dr. Reed commented that this subcommittee has no specific rheumatology expertise, although some subcommittee members did speak with their rheumatology colleagues. He noted that in pediatrics, there are no medications labeled for use in fibromyalgia and that it is difficult to find studies looking at drug treatment. The subcommittee decided not to look at purely analgesic drugs, such as opiates, or at tramadol. The members defined some specifications they felt were important in constructing recommendations and recommended the study of two drugs that met their criteria: amitriptyline and venlafaxine. Studying these two drugs through the BPCA seems appropriate based on clinical use of the drugs in children and adolescents with fibromyalgia, the drugs' proposed mechanism of action relative to proposed pathophysiology, drug availability, drug cost, coverage by Medicaid and third-party payers, lack of pediatric labeling, and the unlikelihood of any company paying for such a drug development plan. The subcommittee wanted a study that would be feasible to conduct.

Prior to choosing drugs to recommend for study, the subcommittee reviewed newer drugs, including serotonin-norepinephrine reuptake inhibitors (SNRIs) such as milnacipran (Savella) and neuropathic pain drugs such as duloxetine and pregabalin. The neuropathic pain drugs have been studied in children, and these are generally double-blind studies in children ages 13 to 17. PK, pharmacodynamics (PD), and if necessary, pharmacogenetic (PG) studies were done to

define doses for those studies. The sponsor of Savella had similar studies ongoing in the treatment of juvenile fibromyalgia, but the studies are now listed as terminated. Difficulty enrolling patients may be a problem.

The subcommittee concluded that if the BPCA chooses to study fibromyalgia therapeutics, amitriptyline and venlafaxine are probably the two drugs that best meet the criteria the subcommittee outlined. There are no good PK/PD/PG data for either of these agents, and the subcommittee was unable to find any data where anyone had attempted to look at the concentration of the active moiety of the parent plus the active metabolite in any of the pediatric studies. The subcommittee members believe feasibility will be a challenge in being able to identify and find the patients for studies in pediatrics. There are no studies of these drugs in fibromyalgia in children. These two agents are still commonly used; no dose-defining studies would need to be done, so they would fit into a classic drug development design.

Dr. Leeder said he thought that with respect to a compound like venlafaxine, which is such a good CYP2D6 substrate, available data indicate that CYP2D6 pharmacogenetics are more important than ontology with respect to variability in the dose-exposure relationship. Dr. Reed agreed. Dr. Leeder recommended looking into a PG-aided PK study design and doing the PK study on core metabolizers and extensive metabolizers to capture both extremes of the population. This is a more efficient way to determine the anticipated range of the population—by studying as close to the extremes as possible. Dr. Reed agreed.

Dr. Klein said he wonders how broad the spectrum of presentation of fibromyalgia is in children and whether, depending on the variability of symptoms, they should all be treated in the same way. Dr. Reed said that compared with the normal distribution of pain across a population of non-fibromyalgia patients, the variability of pain in fibromyalgia patients is much greater. Although there are poor studies of pharmacologic management of these patients, there are some good, validated outcome measures (even for children, there are age-appropriate outcome measures) that may compensate for the lack of good studies. The outcome measures include quality of life, pain, functional disability, anxiety, and other factors.

Dr. Becker commented that some people prefer to describe the syndrome as amplified musculoskeletal pain instead of fibromyalgia. When she uses amitriptyline, she starts with a low dose, but it is based on nothing. The outcome measures the subcommittee listed are perfect. People are using amitriptyline for chronic abdominal pain, chronic headaches, and all kinds of pain. Studies may be able to answer some questions, even if fibromyalgia is heterogeneous.

Dr. Silverstein said that if the proper patient population is selected and a study is developed using this therapy and outcome measures, it might be possible to get around some of the noise.

Idiopathic Uveitis Subcommittee

Members: Andreas Reiff, M.D., Steven Spalding, M.D., Mary Toth, M.D.

Dr. Toth said the subcommittee decided to use the terminology of noninfectious uveitis because it might be easier to enroll patients into trials. However, there is variation in severity of disease

depending on the location of the uveitis, as well as chronicity and damage already occurring before enrollment in a trial. Most agents that are FDA approved are topical and intravitreal steroid injections. No systemic therapies have been approved, and clinicians use a lot of systemic therapies for children with uveitis either associated with juvenile idiopathic arthritis (JIA) or idiopathic uveitis. Methotrexate is the most common immunosuppressant drug used in chronic and refractory uveitis. There are data on azathioprine, mycophenolate, tacrolimus, and cyclosporine, but methotrexate is the most worthwhile to use for first-line therapy for patients who have failed corticosteroid treatment. Other drugs often used in those who fail methotrexate include anti-tumor necrosis factor (anti-TNF) alpha medications such as adalimumab, and other drugs such as abatacept and tocilizumab.

The subcommittee recommended a two-phase trial using methotrexate as the initial drug to treat noninfectious uveitis in children over the age of 2. This would include uveitis associated with JIA and idiopathic uveitis. If patients do not respond, they would move into the second phase of the study, which would use TNF inhibitors or one of the anti-interleukin (IL)-6 drugs, abatacept, or anti-IL-1 drugs. Outcome measures would include visual acuity, anterior chamber cell density, FLARE, intraocular pressure, ability to discontinue steroids, and control of uveitis.

Dr. Klein asked whether doses of methotrexate for uveitis are the same as for other rheumatic conditions. Dr. Toth said the methotrexate dose is about 10 mg/m^2 and the subcommittee recommends titrating to 15 mg/m^2. The dose can even go to up to 60 mg per week. The drug must be given subcutaneously, not orally, and the safety of higher doses of methotrexate and other drugs would need to be measured. Dr. Klein noted that methotrexate in high doses is known to have bone toxicity, so he suggested getting periodic DXAs on these patients.

Dr. Becker said there may be a trial about to start at the Oregon Health Sciences University looking at tocilizumab for treatment of uveitis. This study may not yet be recruiting.

JIA and Systemic JIA Subcommittee

Members: Polly Ferguson, M.D. (Chair), Marcia Buck, Pharm.D., William Rodriguez, M.D., Ph.D., Carol A. Wallace, M.D., Pamela F. Weiss, M.D.

Dr. Ferguson said this subcommittee wanted to emphasize the importance of a registry to provide a mechanism for pharmacosurveillance for JIA and to answer questions such as how medications for JIA are really used in clinical practice, what the adverse events are, and what the safety signals for potential adverse events are. CARRA CoRe is a consolidated registry that is interested in long-term drug and safety surveillance, especially of biologic medications, to consolidate this information in one spot so that each pharmaceutical company does not do it differently. Dr. Becker said the FDA has said that the CARRA CoRe model can fulfill postmarketing requirements and is negotiating with a number of companies to get this registry off the ground. The CARRAnet registry has 5,000 patients enrolled so it can collect data quickly. Dr. Rodriguez said he would be interested in seeing how the registry collects the data. Dr. Becker said she could get that information for him.

Dr. Ferguson said the subcommittee discussed the IL-1 drug anakinra. Clinical questions related to this drug include the comparative effectiveness of anakinra versus traditional therapy, what the short- and long-term side effects of the drug are, and what phenotype should be targeted with agents such as anakinra for initial therapy. Some children with systemic JIA develop features of a life-threatening complication called macrophage activation syndrome; anakinra is used to treat this complication and to treat those with severe systemic JIA.

The American College of Rheumatology published guidelines on how to treat JIA and systemic JIA. Anakinra became available after the guidelines were published, so the guidelines are under revision. This drug is being used commonly to treat JIA, but it is not FDA approved for treatment of systemic JIA. It is important to understand the role of this drug in the management of systemic JIA and determine its efficacy and adverse effects. The drug is approved for treatment of moderate to severe active rheumatoid arthritis in patients 18 and older who have failed treatment with other agents, but pediatric dosing is not clear. There may be a false sense of safety about this drug due to the lack of safety data in children.

Dr. Becker commented that the drug is supplied in 100 ml vials and with a .67 ml syringe, which makes trying to administer a dose of 1 mg/kg very challenging. Dr. Ferguson said the dose must be measurable for the parents. Dr. Rodriguez suggested that the owner of the drug could provide information about devices to use to reduce the possibility of error. The drug owner might be willing or able to provide a better means of administration. Dr. Ferguson agreed that the drug owner could be asked about this. Another problem is that the drug is very painful when given as an injection, which must be done every day. This may be a pH problem because the drug was designed for IV delivery, and the subcutaneous route is secondary.

Dr. Klein asked about compliance if pain is involved, and Dr. Ferguson said this is an issue. It must be a severe disease for parents to be willing to give a shot to their child every day. People get tired of doing it and stop, and then the symptoms come back. Dr. Klein suggested that it might be possible to develop a different way to administer the drug. Dr. Portman said if it is a safety issue, the FDA can approach the issue. He thought the maker of the drug might be responsive to this issue.

Dr. Ferguson next discussed the use of infliximab and other TNF inhibitors for any type of JIA. Efficacy studies are needed as the drug is being used widely, and insurance companies resist its use. Some children are doing well on one of the FDA-approved TNF inhibitors but over time the drug loses efficacy; a question is whether infliximab can help the patient regain control. Data are needed on short-term and long-term side effects of the drug and in relation to the effects of dose escalation. Dr. Ferguson reviewed other details about infliximab, which are provided in the subcommittee's document.

In response to a question about a study of infliximab in children, Dr. Ferguson described a study in which an IV placebo was used and elicited a strong placebo response. Also, there were not enough patients enrolled in the study initially. In her opinion, to solve this problem, a study would probably need to have more patients on standard doses.

Dr. Becker asked whether upping the outcome measure to perhaps a 50 or 75 percent improvement, rather than 30 percent, would weed out the placebo response. Dr. Ferguson said it would. Also, most children with JIA who respond to biologics experience dramatic improvements. Dr. Becker said one of her colleagues looked at industry data related to that trial and found higher clearance in younger children, perhaps due to a higher resting energy expenditure. She suggested looking at differences in appropriate dosing based on age and at resting energy expenditure. Dr. Becker said part of the struggle for clinicians treating these patients is the need to fight for the medications they are using instead of using the drugs that are "low-hanging fruit." Dr. Ferguson agreed and said the subcommittee thought that children deserve to have something studied that would make a significant impact.

Dr. Klein asked whether duration of improvement was being addressed. Dr. Ferguson said this could be looked at through a registry; otherwise, this issue is not being studied. Dr. Klein suggested looking at the gastrointestinal experience with infliximab; patients develop tolerance fairly quickly, and the drug becomes less effective. Dr. Ferguson said she has not had a lot of children lose efficacy on infliximab, but she has had to escalate the dose somewhat.

Pediatric Systemic Lupus Erythematosus (SLE) Subcommittee

Members: Larry Jung, M.D. (Chair), Ronald Portman, M.D., Marilynn Punaro, M.D., Scott Weir, Pharm.D., Ph.D.

Dr. Becker presented for this subcommittee. Most patients with pediatric lupus develop renal disease and require large amounts of steroids and other medications, which can set up patients for considerable morbidity. One of the clinical needs is to reduce lifetime exposure to cyclophosphamide. A CARRA survey showed that most providers use the National Institutes of Health (NIH) protocol in prescribing IV cyclophosphamide. This is a relatively high dose. The Euro-lupus protocol was developed to use lower doses and reduce toxicity. The subcommittee's report states that it would make sense to attempt to determine the lowest possible effective dose for a drug such as cyclophosphamide, which has dose-dependent toxicity rates.

Other areas of clinical need were to develop evidence for the treatment of refractory or extra-renal lupus and to develop evidence for treatment of neuropsychiatric lupus (NP-SLE). SLE is a challenging disease with a heterogeneous presentation that often occurs in teenagers, and some have neuropsychiatric manifestations that have not been systematically studied. Dr. Becker reviewed the needs assessment portion of the template, noting that adverse effects are numerous.

The subcommittee recommended a study of a lower dose cyclophosphamide regimen (the Euro-lupus protocol adapted for children) compared with the dose in the NIH protocol for induction therapy of pediatric proliferative lupus nephritis. This will provide an opportunity to test the efficacy of a less toxic dose of cyclophosphamide in children with lupus, as well as provide data for both efficacy and safety not currently available for the most commonly used regimen in children.

The subcommittee also recommended a comparison of the safety and efficacy of IV soludmedrol with cyclophosphamide, mycophenolate, and rituximab in pediatric lupus-induced seizures and

cerebral vascular events. This will determine whether other immune-modulatory agents will be effective in the treatment of a subgroup of pediatric NP-SLE patients.

Outcome measures would need to be developed and agreed upon, and pediatric dosing would need to be established for the Euro-lupus protocol. CARRAnet has a consensus treatment plan being piloted for the standard NIH protocol with cyclophosphamide versus mycophenolate with three different steroid regimens in the induction of pediatric proliferative lupus nephritis.

Closing Remarks

Dr. Becker thanked the presenters and other participants for their efforts and said this is an amazing opportunity to help shape priorities to better treat patients.

Brandy Weathersby, Circle Solutions, Inc., reminded the group about the BPCA annual meeting to be held on December 4 in Rockville, MD.

Action Item:

- Dr. Becker will send Dr. Rodriguez information on how the CARRA registry collects data.