Best Pharmaceuticals for Children Act (BPCA)
Rheumatology Therapeutic Area Working Group Conference Call and Webinar
August 9, 2012
3:00 p.m.–4:00 p.m. ET

Participants

Mara Becker, M.D., M.S.C.E.
Polly Ferguson, M.D.
Nadia Hejazi, M.D.
Lawrence Jung, M.D.
Gordon Klein, M.D., M.P.H.
J. Steven Leeder, Pharm.D., Ph.D.
Marie Ann Leyko, Ph.D.
Rosemarie Neuner, M.D., M.P.H.
Denise Pica-Branco, Ph.D.
Michael Reed, Pharm.D.
William Rodriguez, M.D., Ph.D.
Laura Schanberg, M.D.
Douglas Silverstein, M.D.
Steven Spalding, M.D.
Perdita Taylor-Zapata, M.D.
Mary Toth, M.D.
Pamela Weiss, M.D., M.S.C.E.
Carolyn Yancey, M.D.

Purpose

The purpose of the call was to discuss the following:
- Welcome to new members
- Quick identification/introduction of members on the call
- Review of discussion points document
- Discussion on specific BPCA therapeutic area subcommittees tasks
- Hydroxychloroquine discussion
- Therapeutic subcommittee signup
- Action items before the next call.

Discussion

Dr. Becker noted that idiopathic uveitis will now be a condition for study and that juvenile idiopathic arthritis (JIA) and systemic JIA will be combined into one committee. The other subcommittees are on fibromyalgia, pediatric systemic erythematosus (SLE), and bone biology. Formulations will not be a separate committee.

Dr. Becker briefly summarized the discussion on these diseases from the previous conference call:

- **Idiopathic Uveitis.** There is very little information on therapeutics for idiopathic uveitis in children with JIA. It is a common condition, which would provide the opportunity to look at monoclonal antibodies and other disease-modifying antirheumatic drugs such as infliximab, adalimumab, abatacept, mycophenolate, methotrexate, and combination therapy.
- **JIA and Systemic JIA.** It will be important to balance study into the new, promising biologic drugs with study into the common drugs that are used extensively but about which there is little information. There has been discussion about proposing further study on anti-IL-1 agents; they are not currently indicated for systemic JIA treatment.
- **Fibromyalgia.** There is interest in studying Lyrica and amitriptyline. It is difficult to find pediatric patients who are not already taking amitriptyline; the Clinical Audit of Care in Rheumatoid Arthritis (CARA) registry could possibly be a source to find these patients.
- **Pediatric SLE.** Drugs of interest in this area include mycophenolate mofetil, azathioprine, cyclophosphamide rituximab, and hydroxychloroquine.
- **Bone Biology.** Areas of study include use of bisphosphonates in pediatric rheumatology patients and screen frequency/guidelines for bone loss.

Dr. Becker invited Dr. Klein to expand on the bone biology study area. Dr. Klein said that bone biology involves two adaptive responses in rheumatologic conditions: inflammatory response and endogenous stress response. The endogenous glucocorticoids that are produced cause bone loss. Bisphosphonates have been shown to assist in stopping this bone loss, specifically in patients who have osteogenesis imperfecta. There has been no evidence of growth impairment, hypocalcaemia, atypical femoral fractures, or osteonecrosis of the jaw. The processes involved in these diseases are conducive to bone loss, and most of the drugs, most notably steroids, could not only fail to address bone loss but could possibly increase it. Dr. Klein suggested that it would be helpful to study the effect of bisphosphonates in some very specific situations because there is some safety information available for bisphosphonates. This could serve as a substitute analog for conditions where steroids are used to treat chronic inflammatory conditions and could possibly involve co-administration of bisphosphonate with evaluation every 6 months for changes in bone density. Dr. Schanberg? mentioned that the type of study Dr. Klein suggested would be more appropriately a National Institutes of Health (NIH) Research Grant Program study because it is a new concept. The study may need to begin with a more general question, such as long-term safety of bisphosphonates in rheumatic children or differentiating between bone loss from inflammation versus bone loss from drug use.

Hydroxychloroquine. Dr. Rodriquez asked the group how often anyone has used a "combo," such as hydroxychloroquine combined with methotrexate. He referred to a Finnish study that showed certain combinations of a biologic and methotrexate are superior to any other combinations currently in use. Dr. Schanberg responded that in the rheumatology area, this is referred to as triple therapy, which is the combination of methotrexate, hydroxychloroquine, and sulfasalazine. This has been shown to be as effective in adults as other biologics and other types of therapies. However, three medications could be too many for a child to take, and there may be formulation issues. This is not a common therapy for children. Dr. Ferguson commented that she

prescribes the combination of methotrexate and hydroxychloroquine frequently for JIA, especially if the patient's insurance will not cover a biologic; she almost never uses methotrexate monotherapy. There are no child-specific data suggesting that the combination is better than methotrexate alone, but studies on this subject conducted by Dr. James O'Dell from the University of Nebraska Medical Center in adult rheumatoid arthritis do show this. Although sulfasalazine would work well in this combination, it is not a viable option for use in children because it requires twice-daily doses and because allergic reactions are often a problem.

Dr. Schanberg said that looking at a comparison of the efficacy of the combination of methotrexate and hydroxychloroquine versus methotrexate monotherapy would be a useful and worthwhile question to address. There are 7,500 children in the CARA registry, of which 1,200 are currently taking hydroxychloroquine. Dr. Rodriguez pointed out that there is some research into the differences in how this drug works in the pediatric population and that it would be important to find out what adjustments in compounding and dosing have to be made in order for hydroxychloroquine to be safe for children. Currently, dosing for adults is based on avoiding adverse effects, in this case eye disease, as opposed to efficacy to address the actual disease. Dr. Ferguson noted that she is unaware of information on pediatric ocular toxicity of hydroxychloroquine, but Dr. Schanberg said that could possibly be addressed by using the CARA registry.

Another advantage to using a combination of drugs is the lower cost of the combination compared with a biologic. There is a proposal submitted to the National Institute of Arthritis and Musculoskeletal and Skin Diseases for a planning grant to study the use of methotrexate to prevent extended oligoarthritis. It might also be useful to further explore the use of hydroxychloroquine sulfate (Plaquenil). A high percentage of lupus and dermatomyositis patients are on hydroxychloroquine in addition to other therapies. Dr. Ferguson referred to a study that explored flares in people who discontinued use of hydroxychloroquine either as directed by their physician or at their own instigation versus flares in those who continued the medication. The CARA registry could be a resource for this kind of study. Dr. Toth mentioned that there have been data that coronary artery disease and stroke may be prevented in adults with lupus; this may be an area to study in the pediatric population. Dr. Rodriguez pointed out that it will be important to ensure that there is good long-term follow-up on exposure and that the CARA registry appears to be a good mechanism to do that, but there needs to be formal planning upfront to do that. Dr. Ferguson said that the challenge with cardiovascular disease is that the power is limited because cardiovascular events are uncommon in children. One of the goals of the CARA registry is to follow children into adulthood. Dr. Klein asked about the possibility of using Doppler ultrasound to measure vascular dimensions in these children. Dr. Schanberg responded that to do so would be expensive and challenging because of the need for standardization.

Dr. Taylor-Zapata thanked Drs. Becker and Schanberg for chairing the Rheumatology working group and reviewed the two primary tasks for the subcommittees:

- Provide judgment regarding the scientific questions that need to be addressed regarding drugs, biologics, devices, and/or indications in the specific area of expertise.

  - *These considerations must be within the context of the current FDA-approved label (if it exists), not off-label, noting specifically where pediatric information is underdeveloped or lacking.*
- Provide opinion regarding the feasibility and impact of funding and conducting additional studies about the drug, biologic, device, and/or indication of interest.

Dr. Taylor-Zapata outlined the steps in a template that the members can use to assist them in providing this information, which is due by September 21, 2012:

- Develop a paragraph on the scientific gaps in therapeutics in the chosen field.
- Develop a needs assessment list—a list of what is needed to address the gap(s), such as pharmacokinetic or safety data missing from the label or studies that need to be done.
- Develop a brief reference list for the most relevant articles/journals related to scientific advances and evidence-based treatment in the chosen field.
- Draft a blueprint for feasible and reasonable ways to close the gap(s).

Dr. Taylor-Zapata clarified that this information should not be very detailed, perhaps a page long, with specific information about the population for study and a proposed design. She stressed that these are recommendations to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the NIH; there is no funding guarantee for these recommendations. These recommendations will be submitted to the Pediatric Trials Network, which will then prioritize viable options. The subcommittees may have one or two conference calls, after which they would present their recommendations to the Rheumatology Working Group.

Dr. Yancey revisited the question of randomized withdrawal study design. Based on her experience, there has been concern about randomized withdrawal studies in pediatric rheumatology because of clinical flares. Dr. Ferguson responded that almost all children with JIA who are in clinical remission on medications for a period of time are given a trial off medicine. It is standard practice to take children off medication if they have been disease-free for a given period—2 years, for example—and doing so presents an excellent opportunity to collect data. This model is different from the randomized withdrawal studies that have been done on some of the biologics, for example, where children are taken off medications after a specific period of time and flares are measured. Instead, the model Dr. Ferguson was discussing would include children who are in remission and are discontinuing medication regardless of their participation in the study. This could be possibly be accomplished by conducting a pragmatic trial rather than a randomized trial.

Dr. Becker noted that it would be helpful for subcommittees to have a chairperson. Dr. Ferguson will be the chairperson for the JIA/systemic JIA subcommittee, Dr. Spalding will join the idiopathic uveitis subcommittee, Dr. Marilynn Punaro will join the lupus subcommittee, and Dr. Reed will join the fibromyalgia subcommittee. Dr. Toth is willing to be on whichever subcommittee needed. Dr. Leyko will review the subcommittees and respond next week with her preference, and she offered to help with literature searches on the chosen drugs of study. Drs. Becker and Schanberg will provide expertise on rheumatology for those subcommittees that do

not have a rheumatologist among its members. A member can be on more than one subcommittee if desired.

Action Items:

- Brandy Weathersby, Circle Solutions, will resend the e-mail with the subcommittee choices to those who were unable to attend the call with a deadline for members to submit their preference.
- Ms. Weathersby will send an updated member roster once all the members have chosen their subcommittees.