Best Pharmaceuticals for Children Act (BPCA)
Rheumatology Therapeutic Area Working Group Conference Call and Webcast
June 19, 2012
10:00 a.m.–11:00 a.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.
Marie Ann Leyko, Ph.D.
Rosemarie Neuner, M.D., M.P.H.
Denise Pica-Branco
Ronald Portman, M.D.
Marilynn Punaro, M.D.
Michael Reed, Pharm.D.
William Rodriguez, M.D., Ph.D.
Laura Schanberg, M.D.
Steven Spalding, M.D.
Perdita Taylor-Zapata, M.D.
Mary Toth, M.D.
Surendra Varma, M.D., F.A.A.P.
Carol Wallace, 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
- Brief summary of minutes from the May 10 call
- Review of unmet therapeutic needs
- Suggested studies
- Suggested study outcomes
- Prioritization of needs
- Action items before the next call.

Discussion

Drs. Becker and Schanberg are the working group chairs, and they will lead the group's conference calls.

New Members. The following pediatric rheumatologists have been invited join the group: Dr. Polly Ferguson, Dr. Lawrence Jung, Dr. Punaro, Dr. Spalding, Dr. Wallace, and Dr. Scott Weir.

Summary of May 10 Conference Call. Dr. Becker summarized background information about the BPCA, a legislative mandate to improve the effectiveness and safety of medications used in children. The U.S. Food and Drug Administration (FDA) implements the main component of the BPCA program, which encourages industry to perform studies to improve pediatric labeling in exchange for an additional 6 months of patent exclusivity. The National Institutes of Health (NIH) implements a program to sponsor needed studies.

The NIH drug development program has two components: (1) a prioritization process to identify gaps in pediatric therapeutics and (2) clinical trials, primarily of off-patent drugs. Twenty NIH Institutes contribute to BPCA program funding. Prioritization leads to Written Requests or Proposed Pediatric Study Requests and clinical studies. Data from clinical studies are submitted to the FDA for labeling changes.

This year, rheumatology has been identified as a priority area. The group has been asked to identify research that can affect pediatric therapeutics. Conference call minutes will be posted on the BPCA Web site. The group will have three or four calls and will present recommendations at the BPCA Annual Meeting. The meeting will take place in December 2012.

Review of Unmet Therapeutic Needs. A template was circulated to the group listing issues discussed during the first conference call. During that call, the group discussed the following drugs: **hydroxychloroquine, methotrexate, folate, mycophenolate, azathioprine, Solu-Medrol, etanercept, infliximab, adalimumab, and intravenous (IV) immunoglobulin**.

Dr. Wallace suggested adding **anakinra**. Newer anti-interleukin-1 (anti-IL-1) drugs are coming out, but anakinra is rapid acting. She also suggested adding **rituximab**. Dr. Becker asked about other anti-B cell therapies used in adults. Dr. Wallace said that drug companies are studying epratuzumab and Benlysta in children, so these drugs may not be appropriate candidates.

Dr. Rodriguez asked how often ketoprofen is used in pediatrics. Data are available for long-term exposure in adults, but the drug is not labeled for use in pediatric rheumatoid arthritis or juvenile idiopathic arthritis (JIA). Dr. Wallace said that ketoprofen is not used, and nonsteroidal anti-inflammatory drugs (NSAIDs) are used only for a short time. Dr. Schanberg provided an update that the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry shows that **NSAIDS** are used long term for spondyloarthropathy. Dr. Rodriguez said data are being developed on the Biopharmaceutics Classification System characteristics of ketoprofen in pediatrics.

Dr. Reed asked about the value of COX-2-specific NSAIDs in patients on long-term NSAIDs. Dr. Schanberg said that Pfizer had a registry for Celebrex but had a hard time finding patients. COX-2 inhibitors are used less than more standard NSAIDs in pediatrics. Dr. Wallace said that an enhanced drug surveillance system collected information about adverse events in JIA patients from about 40 sites and 120 investigators. Few adverse events were recorded for NSAIDs. Dr. Schanberg expressed interest in **diclofenac**, which is used for spondyloarthropathy. Dr. Becker said that there was not much information about COX-2 inhibitors, and she did not use them

frequently. They should be added to the list, but they may not be prioritized. Dr. Wallace suggested studying NSAIDs that are administered once per day, such as **piroxicam and meloxicam**.

Dr. Toth suggested adding golimumab, which is approved for adults in monthly injections. Dr. Taylor-Zapata said that if industry is studying golimumab in children, it would not be appropriate for this group to prioritize for a BPCA study.

Dr. Becker noted that Dr. Klein suggested looking at **bisphosphonates** in children. She asked whether there was interest in **cyclophosphamide**, which is used in oral and IV forms. It was suggested that a study could compare a standard protocol with a Euro-Lupus protocol to see whether less of the drug could be used.

Dr. Wallace noted that **sulfasalazine** is used to treat spondyloarthropathy, but dosing is not well understood. Dr. Schanberg added that there are questions about whether sulfasalazine is the right formulation. Gastrointestinal doctors use Asacol. Dr. Becker said there were questions about adverse effects, safety, and identifying patients with sensitivity to sulfasalazine.

Dr. Schanberg added that there is not much information about **triple therapy— sulfasalazine, methotrexate, and plaquenil**—in children. Dr. Ferguson sent a comment about the use of **plaquenil and methotrexate** together and whether plaquenil enhances the efficacy of methotrexate.

Areas Needing Further Study. Dr. Becker reviewed the areas already discussed: **appropriate length of treatment, safety and benefits of combination therapies, frequency of safety monitoring in commonly used drugs, optimal dosing, formulations of drugs currently in use, impact of bone loss, treatment of comorbid conditions, and head-to-head efficacy studies in biologics**.

Dr. Wallace said that the **treatment of uveitis** in children with JIA needs further study.

It was suggested that the use of **diclofenac gel** for pain relief be studied. In children without much subcutaneous tissue, there might be more absorption than expected. Diclofenac gel is used in rehabilitation to relieve pain in bursitis and tendinitis.

Dr. Punaro noted that anakinra does not have an indication for systemic arthritis. The company that acquired the drug is small and does not have much funding. Safety data are available, but tocilizumab is the only drug with an indication in systemic arthritis.

Dr. Schanberg said that in the treatment of JIA, the anti-IL-6 agent has an indication, but the anti-IL-1 agent does not, even though it may be more effective and safer. Dr. Punaro noted that rheumatologists use anakinra first because of its safety and effectiveness. The preservative in anakinra causes burning, and changing the formulation would be beneficial, but the company may not have money or time to change the formulation.

The group discussed the possibility that the company could partner with the FDA. Dr. Neuner said there was not a mechanism for this type of partnership. The change would need to be initiated by the sponsor, and a change in formulation is a major undertaking that could change the immunogenicity and efficacy profiles. Dr. Portman added that a formulation change engenders a Pediatric Research Equity Act requirement for another study. Dr. Neuner said that suggesting changes in formulations might not be appropriate. Suggesting a new indication may be feasible.

Dr. Durmowicz said that adequate data would be needed to support the new indication. Dr. Neuner said that the FDA would need to have an internal discussion about whether data from the CARRA registry could be used. Other drugs have been approved through this process, but the process may no longer be considered acceptable. The group did not know whether anakinra was on patent. Dr. Rodriguez said that data requirements are considered on a case-by-case basis. Dr. Becker said the group could discuss adapting the registry to collect data that may be useful. Dr. Schanberg suggested submitting a proposal to the Pediatric Trials Network. Dr. Neuner said that the protocol would need to be vetted internally at the FDA early in the process.

Dr. Yancey said that pharmacokinetics/pharmacodynamics (PK/PD) studies in pediatrics would be needed in addition to a single safety/efficacy study. Adult data can support the pediatric indication. Dr. Rodriguez said that the FDA discourages extrapolation of adult safety and PK/PD data. Dr. Portman added that efficacy could be extrapolated, but pediatric safety and PK/PD studies would be needed.

Patient Populations. Dr. Becker asked whether the group should consider autoinflammatory disorders. There are drugs indicated for autoinflammatory disorders that are not indicated for rheumatology patients. Chronic pain patients are not listed, but the use of diclofenac gel is interesting.

Participants suggested adding **idiopathic uveitis and fibromyalgia**. For fibromyalgia, **Lyrica** is being studied, and a study of lorazepam was recently discontinued. The NIH funded a study of amitriptyline, but that arm of the study was dropped because it was difficult to find pediatric patients who were not already taking amitriptyline. The CARRA registry includes 150-200 patients with fibromyalgia and may have data about the use of **amitriptyline**.

Prioritization of Needs. The group agreed to prioritize therapeutic needs before discussing the types of studies needed. They will seek input from the pediatric rheumatology community and establish subcommittees to work on specific drugs and make presentations to the full group.

The group discussed whether to reach out to pediatric rheumatologists only in the United States or worldwide. Dr. Rodriguez noted that there is a drive toward interaction between the European Medicines Agency (EMA) and the FDA. Dr. Becker suggested using the worldwide rheumatology listserv for outreach. Dr. Schanberg said CARA has regular interaction with an EMA representative; she suggested inviting this representative to join the group. She will contact the representative and send the contact information to Brandy Weathersby and Deborah Stein at Circle Solutions, Inc.

Dr. Becker said that priority areas include drugs used to treat uveitis, mycophenolate, anti-IL-1 agents, methotrexate, and combination therapy. Dr. Schanberg noted that there is a tension between prioritizing more serious conditions with the sickest children and harshest medications and prioritizing conditions that are more common, less morbid, and understudied. It was suggested that the group aim for a middle ground; getting input from the entire field may be helpful. Insurance companies increasingly prevent the use of drugs that do not have indications.

Dr. Spalding said that uveitis is a middle ground—it is a common condition that would provide the opportunity to look at drugs for which there is little information. Dr. Schanberg said that CARRA is planning to work on a project with an inflammatory eye disease network. A complication with studying uveitis is that the condition involves two doctors instead of one. Dr. Spalding said that a study could provide an opportunity to address that issue. Dr. Schanberg said that funding more doctors could be a problem.

Drs. Becker and Schanberg will prepare a list of priorities and send it to the group for comment. After the comments are incorporated, the group will have another opportunity to review the list before it is sent to the pediatric rheumatology community. Dr. Taylor-Zapata said she could help with the logistics of organizing subgroups and preparing documents.

Action Items:

- Dr. Schanberg will contact the EMA representative that has worked with CARRA about joining the group, and she will send the representative's contact information to Ms. Weathersby and Ms. Stein.
- Drs. Becker and Schanberg will prepare a list of priorities and send it to the group for comment.