Pediatric Dermatology Research Alliance

May 17, 2016

TO: U.S. Food and Drug Administration (FDA)

RE: Comments on Patient-Focused Drug Development for Psoriasis

We are writing today on behalf of the Pediatric Dermatology Research Alliance (PeDRA), an organization comprised of 68 institutions and 220 clinicians and researchers who have united to form a research arm of the Society for Pediatric Dermatology. PeDRA provides a platform for large multicenter investigations capable of greater impact and discovery for pediatric patients. PeDRA members are physicians, scientists and patient advocacy groups dedicated to a common goal: advance research, education and clinical care for children suffering from the physical, emotional and psychiatric impacts of skin disease. Psoriasis and alopecia areata are two such diseases. We were delighted to learn about the 2016-17 public forum meetings on Patient-Focused Drug Development convened by the FDA, with two focusing on psoriasis and alopecia areata.

PeDRA was represented at the FDA Forum on psoriasis on March 17th, 2016, by two pediatric dermatologists and a severely impacted psoriasis patient and his parents. On behalf of our organization and the patients we serve, we offer the following statement to provide background, context and support for patient-focused pediatric research related to psoriasis.

Psoriasis in children

Psoriasis is a common inflammatory disorder that affects the skin, nails and joints. Both adults and children of all ages are affected. In fact, onset in childhood occurs in up to one-third of cases.[i] Psoriasis follows a chronic relapsing and remitting course over a lifetime. Psoriasis is more than skin deep. This disease brings a deep burden with it, particularly to children. Physical impacts of the skin lesions include pain and itch. In children who suffer from psoriatic arthritis, reduction in activity is common. The emotional burden of having a disfiguring skin disease during the formative years of life take a toll by way of teasing and bullying which can result in social isolation. The overall rate of comorbid medical conditions in psoriasis patients under the age of 20 is double that of their peers who do not have psoriasis. Pediatric psoriasis patients are at higher risk for components of the metabolic syndrome, especially obesity, as well as dyslipidemia, diabetes, and hypertension. Of equal importance is the potentially detrimental effect of psoriasis on a child's quality of life. Kids with psoriasis may suffer from poor self-esteem, depression and anxiety, which can persist into adulthood leading to poor work performance and other downstream effects.[ii,iii]

Psoriasis in children vs. adults

One of the major discrepancies between pediatric and adult psoriasis is the lack of tested and approved treatments for children. Almost all of our therapies for pediatric psoriasis are based on anecdotal evidence, expert opinion and precedent because there are inadequate data upon which to develop standardized clinical guidelines and treatment protocols such as those that exist in pediatric oncology and in pediatric rheumatology. This creates a challenge in their management, particularly for those with more severe disease, who may need systemic therapy for adequate control but face significant hurdles in ability to access these medications.

Adults with psoriasis have benefited from a vastly improved treatment profile over the last decade, with at least 10 new therapies for moderate to severe disease reaching phase 3 trials and/or approval. The growing pipeline of targeted therapies for adults with psoriasis offers numerous choices for patients who fail to respond to one or more agents. But these breakthroughs very much require extension to the pediatric and adolescent population who have zero approved options for moderate to severe disease.

The vastly improved pool of treatment options for adult psoriasis over the last decade has eclipsed the research needed to develop, test and approve therapies for the pediatric psoriasis population. Psoriasis in children is still very much an understudied, underserved and under recognized disease. From 1979 to 2007 in the United States, fewer than 1% of children with psoriasis were prescribed systemic or biologic medications, whereas in adults, prescriptions for systemic therapies for psoriasis increased by 110% from 1996 to 2005.[iv] There are several possible explanations for this discrepancy. Lack of research, and therefore data, guiding the choice of therapy and lack of FDA approval are foremost among them. Further, research on the effects of chronic inflammation suggests that the effects of untreated disease may be as bad as or worse than those of the medications used to treat it. [v]

As an example, a 16 year-old female patient still had >40% body surface area (BSA) involvement despite treatment with phototherapy, methotrexate and topical steroids for 2.5 years. Neither of the remaining traditional systemic options – cyclosporine or acitretin – was optimal for this patient given a need for chronic therapy and their respective renal and skeletal health risks (and potential for teratogenicity with acitretin). Despite adequate trial and failure of other therapies, biologic treatment with a TNF inhibitor was denied by the insurance plan. This was despite published randomized controlled trials showing efficacy and safety in adolescents (published as early as 2008 in the New England Journal of Medicine) and significant safety data down to age 2 years from approved use to treat pediatric rheumatoid arthritis and Crohn's disease treatment.[vi] The patient ultimately had to wait another 2 years until she turned age 18 years and was deemed eligible to receive etanercept, which decreased her disease to a manageable 4-5% BSA.

Age of onset of psoriasis

The most common age of onset for psoriasis is between 18 and 35 years of age, but adolescents, children, and even infants can develop the disease. Jonathan is an 8 year-old boy who presented with a rare combination of severe atopic dermatitis and plaque psoriasis. His psoriasis involved his trunk, scalp, elbows, knees, palms and soles. He came to the pediatric dermatology office because he had to stop playing baseball due to the pain, cracking and bleeding of his hands and feet. His scalp psoriasis was so severe it would bleed and hurt when he wore a baseball cap. The other kids teased him because he was different. His friends no longer played with him because they were afraid of "catching" his disease. They refused to sit near him in the dugout during baseball games because of his psoriasis. Other parents made rude and invasive remarks to his mom. Jonathan is a smart, motivated boy who wants a treatment that is safe for him, but will allow him "to just be a normal kid like everybody else." His mom tries to hide her tears in the office, and she stays strong for him as we discuss all of the treatments that are FDA-approved for adults with psoriasis, but not kids. She understands that the risks of the medications may be significant in some cases, but the risk of social withdrawal, depression, and even other health concerns such as heart disease known to affect patients with severe psoriasis are possibly much worse than the treatments themselves.

This family represents one of thousands who suffer unnecessarily over the decision to use a drug that is safe and effective in adults but only "experimental and off-label" for children. Jonathan advocated for his goal for safe and effective, well-studied treatments to be available to children by serving as the "master of ceremonies" at the National Psoriasis Foundation Psoriasis Walk in San Francisco last year. His disease still remains uncontrolled, as his insurance has denied systemic therapy based on his age.

The most vulnerable groups are the very young children – those with onset in infancy, and young childhood, and those with onset before age 12, as the long-term consequences of an inflammatory disease can be devastating medically, and that of a disfiguring disease in early adolescence can have a lifelong impact on social, educational and occupational functioning.

Severity in pediatric psoriasis

Psoriasis is usually classified as mild, moderate or severe. A common measurement for moderate-severe psoriasis is when at least 10% of the body is covered in psoriasis. At least one quarter of pediatric psoriasis patients have moderate-severe disease. Even when "mild" psoriasis affects the elbows, knees and scalp, these are all exposed sites that are visible to others and embarrassing for patients. Intervention for these children typically involves the application of topical medicines, including at least moderately potent topical steroids, for months and months. For those with moderate-to-severe disease, these topically applied medications are not appropriate or sufficiently effective.

In these children, only phototherapy and off-label use of systemic medications are options. Phototherapy, while the safest option available, is time-consuming and typically requires access to office-based ultraviolet light a few times weekly, which is logistically impossible for many families. As a result, the majority of moderate-to-severe pediatric patients are advanced to systemic therapy. In a recent retrospective review co-sponsored by PeDRA, 390 psoriatic children from the US and Europe were treated with systemic medications, including 230 children from the US, all off-label.[vii] Most common among these were methotrexate (almost 70 percent) and the TNF inhibitors (almost 30%). We three practitioners have treated hundreds of children with psoriasis with systemic medications. The lack of on-label indication for systemic medications has made initiation more difficult, result in delays and hurdles with payers, especially with the decision to use a biologic, despite growing evidence of safety.[viii]

When young people develop psoriasis, it affects them not only physically but also emotionally. It may influence how they view and interact with the world, the activities they take part in, the people they seek out as friends and the interests they develop. We can tell story after story of children and adolescents whose lives were changed by finally getting the psoriasis in good control with the use of systemic agents. Personalities change from downtrodden and minimally interactive in the clinic setting to upbeat, smiling and chatting – and the change in outlook about school, participating in sports and interactions with other children can be startling. These observable changes in quality of life are critical, as they translate to school productivity and interaction, which result in downstream stability and productivity as adults.[ix]

There are also forms of psoriasis that do not cover as much body surface area, but are considered severe. For example, palmoplantar psoriasis affects "only" the palms of hands and the soles of feet but is so painful and the thickening of skin so unwieldy that it often renders a person unable to function, walk, or live a "normal" life. Despite the localized disease, we routinely have to use systemic medications for therapy. For example, Alan's palmoplantar psoriasis led to his giving up basketball, his favorite activity. As a 10-year-old boy, giving up the sport was devastating to him and changed his access to a critical mode of social engagement. Super-potent topical steroids and phototherapy were insufficient, and Alan eventually responded only to the combination of retinoids and adalimumab. A less common but potent form of psoriasis, erythrodermic psoriasis, may cover 100% of the body and is a generalized redness vs. presenting in thick plaques. Erythrodermic psoriasis often requires hospitalization and is potentially fatal. Control typically is achieved only by the introduction of systemic medications. David is an 11 year-old boy who presented with 90% body surface area erythroderma. His psoriasis had progressed so severely that he had fever, shaking and chills, requiring admission to the hospital. He had missed the last 6 weeks of school with painful red skin, unable to walk. His parents reported that, "our doctor said that he cannot have any medicine until he turns 18. We can only use creams." We started him

on methotrexate and adalimumab- neither approved for children with psoriasis. He responded within a few days, and is now home, back at school, playing in the band and very happy. He, nor any of the other children mentioned in these anecdotes, have had an adverse effect to the therapies.

In our own experiences with psoriatic children ranging in age from infancy through adolescence and requiring systemic medications, side effects are unusual and rarely result in discontinuation. In contrast to European countries and Canada, we in the US have had more challenges in prescribing systemic therapies, especially biologic therapies for pediatric psoriasis. We suggest that having FDA-approved systemic therapies, especially when coupled with guidelines for their use in pediatric patients and careful tracking through a prospective registry of use of any systemic medication, could more easily uncover any potential safety signals.

Recommendations and Conclusion

There are enormous clinical and research gaps between adult and pediatric patients with psoriasis, yet the disease is as severe with more potential negative impacts on overall quality of life and health in children. Managing children with psoriasis is a challenge on many fronts. The disease is complex, often-changing, impacts all domains of quality of life – physical, mental and social— and we have no approved systemic therapies to treat the severely affected. Coupled with psoriasis's association with obesity and data showing that uncontrolled inflammation may lead to serious cardiovascular and cerebrovascular disease later in life, these children are like ticking medical time bombs. Parents are desperate for answers, and children are desperate to "just be normal." We dedicate a large part of our clinical activity to severe inflammatory skin diseases, and pediatric psoriasis is far behind adult psoriasis in terms of research on treatments. This should not continue in a country with such profound medical sophistication. We ask the FDA to reconsider the stance on research testing in children, because the ill effects of undertreated disease may be equal to, or worse, than the potential side effects of the drugs used to treat it. We must rely on adult data to treat children, and pediatric subspecialists understand that kids are not just "little adults". It is time to close the research gap and offer testing for children. Our patients and parents would welcome it, and we cannot deny them any longer.

The cases discussed herein are devastating examples of children and adolescents trying to be normal, but unable to develop socially, physically and psychologically because of their skin disease. The sequela of untreated psoriasis need to be considered in the total context of the patient: giving up sports may be easy for an adult, but devastating to a child whose self-esteem, social adjustment, and physical health depend on it. Because of the paucity of validated, approved treatments for our pediatric psoriasis population, dermatologists are challenged daily to obtain solutions for their young patients. Drug manufacturers, even when interested in bringing therapies to children, have been

previously deterred by the regulatory challenges posed to them in conducting pediatric trials. We need more recognition – at the policy level and in the national "conversation" – that children and adolescents with psoriasis should be included in therapeutic trials. We are thrilled that the FDA is taking steps toward addressing this gap in clinical care and research.

On behalf of the Psoriasis Investigator Group of the Pediatric Dermatology Research Alliance, we sincerely thank you for your time.

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