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**EARLY CAREER
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November 13, 2017

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

RE: Comments on Alopecia Areata Patient-Focused Drug Development

We are writing on behalf of the Pediatric Dermatology Research Alliance (PeDRA), an organization comprised of 230 clinicians and researchers from 68 institutions who have united to form a research arm of the Society of Pediatric Dermatology. This collaborative research network 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. We were enthusiastic about the 2016-17 public forum meetings on Patient-Focused Drug Development convened by the FDA, including the recent one focusing on alopecia areata.

PeDRA was represented at the FDA Forum on alopecia areata on September 11, 2017 by two pediatric dermatologists, Drs. Yasmine Kirkorian and Kalyani Marathe. Two hundred patients living with alopecia areata and their families bravely attended and spoke out to help broaden knowledge about the condition.

Alopecia Areata in Children

Alopecia areata (AA) is a non-scarring form of hair loss occurring in children and adults. It is an autoimmune condition that results in hair follicle inflammation and loss of hairⁱ. The lifetime risk is 1.7% in the general population of the United States (incidence 0.1%-0.2%)ⁱⁱ. The three main categories are: alopecia areata (patchy hair loss), alopecia totalis (loss of all scalp hair) and alopecia universalis (loss of all body, face, and scalp hair). Alopecia areata is a chronic disease; for many, it relapses and remits over a lifetime. Many patients who progress to the most severe forms of the disease do not regrow their hair. As a result of the visibility, chronicity and unpredictability of relapses the disease carries with it a deep psychosocial burden, particularly in children who are just developing their sense of self. Physical impacts of the disease include the loss of hair, changes in nails, irritation of eyes from lack of eyebrows and eyelashes and sometimes dripping nose because of lack of hair in the nose. Patients also complain of sweating of the scalp, making exercise and sports activities more difficult. Additionally patients with alopecia areata are at increased risk of concomitant autoimmune diseases, including Type 1 diabetes, thyroid disease, celiac disease, rheumatoid arthritis, vitiligo, multiple sclerosis, inflammatory bowel disease and psoriasisⁱⁱⁱ. The emotional impact of sudden loss of hair (something that is part of one's identity) often leads to bullying and teasing; children with alopecia areata are often assumed to have cancer and to be undergoing chemotherapy, creating additional stigma. Some children withdraw from school and many experience clinical anxiety and depression. Children with the milder

forms of alopecia are just as likely to experience these psychiatric changes as those with the most severe forms^{iv}. These changes affect the quality of life for the patient and their family and often persist into adulthood, affecting work performance and relationships^v.

Alopecia Areata in children vs. adults

One of the major discrepancies between pediatric and adult alopecia areata is the lack of clinical trials being performed in children^{vi}. None of the varied treatment options for AA prevent or alter the course of the disease and none are approved in children. In general very few therapies have been evaluated in large randomized control trials and all of these studies have been in affected adults. Although current options are not curative or preventative, many patients experience some hair regrowth with current therapies, the most common of which is daily application of potent topical steroids. Particularly in children, these therapies are based on anecdotal evidence and expert opinion: inadequate data exist upon which to develop standardized clinical guidelines and treatment protocols. The management for pediatric patients with the most severe disease is limited by access to trials and systemic medications. Ongoing therapeutic trials with Janus kinase (JAK) inhibitors, based on recent genetic studies and promising improvement in mouse models, are not enrolling children with alopecia areata. As a result, children have limited to no access to these medications. Systemic immunosuppressive therapies, such as the broad immunosuppressant methotrexate, are used in some children but failure rates are high and sustained response is uncommon. For many children, treatment consists of education, assessing risk for other autoimmune disease, managing expectations, providing resourcing for adjustment to the alopecia and supporting the child and family.

In contrast, adults with alopecia are able to tolerate treatments like intralesional steroid injections and benefit from access to trials of systemic medications/biologic medications. Similar to psoriasis prior to biologic therapies, the therapeutic armamentarium for adults with AA has been limited. During the last few years, more than 20 clinical trials with topical and systemic therapies (including alefacept, abatacept, secukinumab, tofacitinib, ruxolitinib, hydroxychloroquine and ezetimibe/simvastatin) have been initiated for adults; there was only a single trial (phototherapy trial) for children with alopecia areata (clinicaltrials.gov). The most promising targeted therapies are the broad acting T cell antagonists (JAK inhibitors, PDE4 inhibitor), Th2 antagonists (tralokinumab), and IL-23/IL-17 antagonist (ustekinumab); these offer choices for adults with AA who fail to respond to intralesional injections or topical therapies (7). With many agents now available for psoriasis and an increasing number in trial for atopic dermatitis, AA is the next inflammatory skin disease to undergo a dramatic alteration in its therapeutic paradigm through introduction of disease-specific drugs with better efficacy and safety profiles^{vii}. These breakthroughs will require extension to the pediatric and adolescent population, in which AA is poorly

understood and for whom our use of therapies is based on a handful of retrospective chart reviews and experience with off-label use of medications, even for moderate to severe disease.

The inherent challenges of trials in pediatric patients (including strict regulations for conduct of trials in pediatric subjects) prevent pharmaceutical companies and academic centers from developing, testing and approving therapies for the pediatric alopecia areata population. Alopecia areata in children is still understudied and under recognized.

Despite lack of approved therapies, patients and families are desperate for treatment. Patients have traveled to the Dead Sea to apply salts to their scalps, used homeopathic medications and made major dietary changes. Families spend thousands of dollars a year on wigs, scarves, hats, tattooing for eyebrows and eyelashes, over-the-counter thickening shampoos and other non-medical therapies. One of our patients was admitted for hypervitamin D because the family was trying to use natural remedies when all other medical treatments failed. She was subsequently started on topical JAK inhibitors and had full regrowth of her hair.

When young people develop alopecia universalis, it not only affects them physically but also emotionally and psychologically. As an example, "Sarah," is a 16-year old female patient who had 100% loss of scalp, body, and facial hair, including her eyelashes and eyebrows. She failed treatment with topical steroids, topical contact sensitizers, systemic methotrexate and plaquenil for 4+ years. She no longer attended school because of anxiety and depression related to her adjustment to this disease. No remaining traditional systemic options remained, but a promising oral JAK inhibitor (tofacitinib) was denied by insurance. This patient had to wait an additional 1-year to obtain the medicine through a pharmaceutical company patient assistance program due to prohibitive costs. During this time she was treated for depression and was home-schooled. Six months after starting the medication, she had regained 80% of her scalp hair, eyebrows and eyelashes. She returned to school and applied for college out of state, a huge accomplishment. This medication changed her life trajectory. Another 14-year old male, "Steve", presented with one patch of alopecia on his eyebrow that quickly progressed to all hair on the head and body. This valedictorian of his 8th grade class and athlete became withdrawn and stopped playing sports for fear that his hat would come off and he would be bullied. After start of a systemic JAK inhibitor he regrew all of his hair and resumed sports. Some adults might say having no hair is "no big deal", but for school-age children and adolescents, this can be devastating. Our younger patients express fear that they are dying because they hear strangers whisper about their assumed cancer. Even siblings of our patients are bullied about their different-looking sibling. Access to therapy has the potential to change the lives of entire families.

Age of onset of alopecia areata

Approximately 66% of alopecia areata patients are diagnosed before the age of 30. Alopecia areata has two peaks of onset – one in childhood and one in adulthood – though it has been reported in all ages. Children as young as 12 months of age can be affected and the first peak of disease is age 4-6 years. Various factors can affect the progression of AA. Beyond the extent of hair loss, one of the most important factors for a poor prognosis is early onset of disease (especially those who present before the age of 3 years)^{viii}. As with other autoimmune conditions, there is likely a genetic predisposition to alopecia areata but the triggers are unknown.

Severity of pediatric alopecia areata

While hair loss most commonly localizes to the scalp, hair anywhere on the body may be affected. Alopecia areata is typically characterized by focal patches of non-scarring hair loss on the scalp. In half of the patients with patchy alopecia areata, individual episodes of hair loss last less than one year and hair spontaneously regrows. These patients may experience recurrent episodes of hair loss that spontaneously regrow or respond quickly to treatments. Even in these patients, the unpredictable course of the disease and inability to cover bald patches can provoke great anxiety. Other patients have a progressive course with more stubborn disease that does not spontaneously remit and is refractory to multiple treatments. About 5-10 % of AA cases will progress to more severe forms involving loss of all scalp hair (alopecia totalis, AT), loss of all hair on the scalp and body (alopecia universalis, AU) or an overlap between the two. Patients with alopecia totalis (AT) or alopecia universalis (AU) usually have a poor prognosis, and treatment failure is seen in most patients regardless of the type of standard therapy. Moreover, the relapse rate is high in patients with these severe forms of alopecia areata (AA). Unfortunately, there are currently no means to predict which patients will have limited and brief involvement and which patients will have extensive hair loss of longer duration. We need more research on markers of active disease and better tests to predict prognosis ^{vii, ix}.

Recommendations and Conclusion

There are enormous clinical and research gaps between adults and children with alopecia areata, yet this disease likely negatively impacts the overall quality of life of children more than adults. Managing children and their families with alopecia areata is a challenge on many fronts. The disease is variable, complex, and unpredictable. It impacts all domains of quality of life: physical, mental and social, yet we have no systemic therapies to adequately treat those severely affected. Parents are desperate for understanding and therapy as they see the effects this disease has on school performance and participation. Children just want to be “typical” again. They don’t want to worry about whether they can swim or play sports, whether their wig might fall off, that someone notices one of their bald spots and assumes they have cancer, or whether they will be bullied

on the bus or in the classroom. Coupled with the association with other autoimmune disorders, these children need therapies that could be potentially disease modifying and reduce risk of secondary autoimmune disease. We dedicate a large part of our clinical activity to the care of children with autoimmune and inflammatory skin diseases. We know that progress in the research and treatment for pediatric alopecia areata is far behind that of adult alopecia areata. The need for these children and their families is urgent. We ask the FDA to reconsider the stance on research testing in children. Lack of treatment and lack of studies leads to lack of standardized protocols for children, putting our most vulnerable at risk. It is time to close the research gap for children and offer options to children and their families.

The cases described here are just some of thousands that we as pediatric providers see every day. The psychological and physical effects are devastating for children who are trying to grow physically, emotionally and psychologically. Going to school, socializing, playing with friends, participating in sports, and developing self-esteem are all needed to become mature, well-adjusted adults. Because we lack validated treatments for our pediatric alopecia population, dermatologists and other pediatric subspecialists are challenged to find solutions for these young patients. Even motivated drug manufacturers have been deterred by the regulatory challenges posed to them in conducting pediatric trials, particularly for our youngest patients. We need to recognize at the national and policy level that children and adolescents with alopecia areata should be included in therapeutic trials. We understand that there are potential risks to any new therapy, but emphasize the devastating effect of alopecia on the health of our affected children, necessitating moving as quickly as possible from adult to pediatric trials. We are once again delighted that the FDA is taking steps to addressing this gap in clinical care and research.

On behalf of the Inflammatory Investigator Group of the Pediatric Dermatology Research Alliance (PeDRA), we thank you for your time.

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