Theme Editorial

Atopic Dermatitis: Aiming for Total Disease Control

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Atopic dermatitis (AD) is a chronic, relapsing, inflammatory condition of the skin, in most cases associated with a prominent immune response dominated by type 2 elements.[1] The disease often starts in the first months of life, carrying a burden for the baby and the family, with lost nights of sleep due to intense pruritus, irritability, difficulties with meals, bath time, and dressing, and a long time spent with topical skin care. Delayed diagnosis and undertreatment (often linked to "steroid phobia") are common features among infants with AD who are referred to specialized care for the disease. In older children, adolescents, and adults, the impact in quality of life is even greater, with decrease in self-esteem, concerns with appearance, impairment of school and work performance, impact on participation in sports, difficulties with social activities, bullying, and sleep disturbance.[1] These limitations and feelings are often shared with family members, amplifying the burden of the disease.

AD in infancy is associated with an increased risk of other atopic manifestations including food allergy and asthma in later life, with the risk increasing with severity and early age of onset of the AD. Reasons for this are incompletely understood, but may include shared genetic or environmental risk factors or an increased risk of sensitization to food and aeroallergens through damaged and inflamed skin. This raises the possibility that prevention of AD, or early aggressive treatment and effective management, may have added benefits in preventing the development of other allergic diseases in later childhood.[2]

In the past few years, there has been tremendous progress in the treatment of AD, with emergence of new therapeutic agents for both topical and systemic use. In particular, treatment of patients with moderate to severe disease who have failed topical therapies and to whom systemic therapy is indicated has moved from traditional immunosuppressors including cyclosporin A and methotrexate, long-term use of oral corticosteroids, and phototherapy, to more targeted therapies with increased effectiveness, faster improvement of symptoms, and a more favorable safety profile (Figure 1). New therapies include the anti−IL-4 receptor alpha antibody dupilumab, which blocks the effects of both IL-4 and IL-13, key cytokines of the type 2 immune response. Dupilumab was the first biological therapy developed for AD, and is currently approved for treatment of children, adolescents, and adults with moderate and severe AD in many countries. Effectiveness of dupilumab and other new therapies expected to be approved for AD in the near future has changed patients' lives dramatically, making it possible for the treating physician to aim for total control of the disease in patients with AD.[3]

In this Theme Issue of the *Journal of Allergy and Clinical Immunology: In Practice*, worldwide experts in AD share their knowledge, expertise, experience, and views in outstanding articles, with the aim of helping clinicians to provide the best care for patients with AD. In their Clinical Management Review, Mancuso et al[4] describe the strategies for management of severe AD in children, including the recently approved topical treatment with the phosphodiesterase-4 inhibitor crisaborole, and treatments in development with the topical Janus kinase inhibitors ruxolitinib and delgocitinib, and with therapies targeted at modifying the skin microbiome of patients with AD. In addition, the authors provide an appraisal of phototherapy and systemic treatments including immunossupressors, biologics, and small molecules in the pediatric population, emphasizing the importance of judicious considerations when deciding to start a systemic therapy for a child with AD. A notable observation is that many pediatric dermatologists now use dupilumab as first-line treatment for moderate to severe AD when topical therapies are not adequate, and phototherapy is not sufficient or unavailable. Finally, insights into early aggressive treatment of AD, the role of food and environmental allergens, and diets are very helpful.[4]

In their Clinical Commentary Review, Maintz et al[5] invite us to take a deep dive into the tools available to assess extent, severity, and control of disease, burden of disease, and quality-of-life impairment in patients with AD, through both the patient/family and physician's perspectives. In particular, the authors describe the value of using validated tools, and the possibilities of using mobile technologies to monitor disease activity and control, especially in the context of the coronavirus disease 2019 pandemic. It is the experience of one of the authors of this editorial (L.K.A.) that the use of Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) and Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (cDLQI)/Infant's Dermatology Life Quality Index (iDLQI) tools facilitated management of patients with AD during times of limited in-person access to health care; however, other validated tools are available for this purpose. Therefore, the clinician is invited to choose from available validated tools, find which ones are feasible to apply even in the busy clinical

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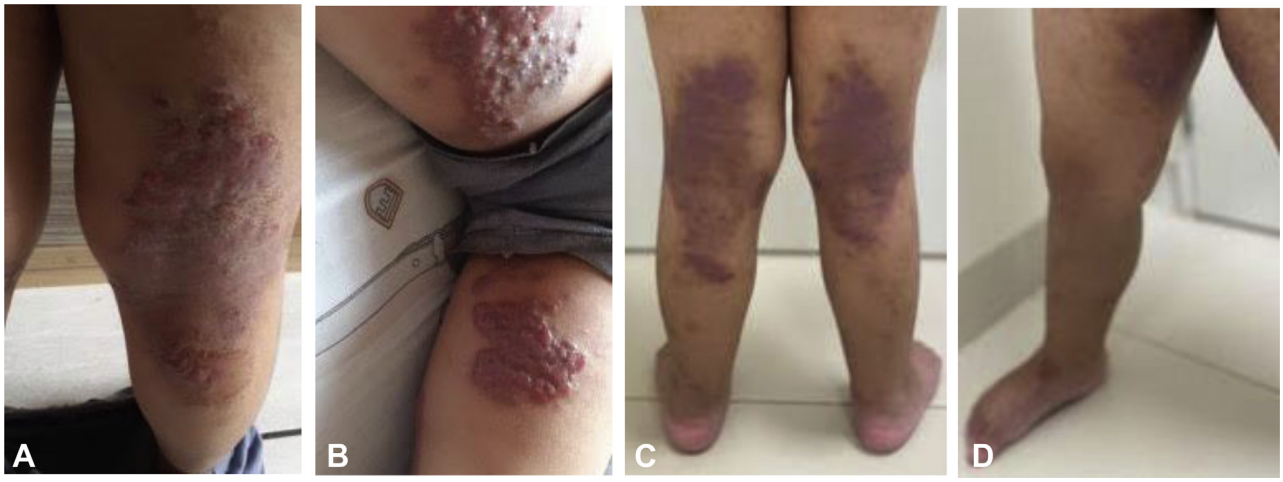

FIGURE 1. Six-year-old boy with severe AD. Two recent hospital admissions to treat severe skin infection with intravenous antibiotics, due to *Staphylococcus aureus* and *Staphylococcus haemolyticus*. Total IgE 2252.8 kU/L; IgE to *Dermatophagoides pteronyssinus* 83.2 kU/L (high level ≥3.5 kU/L). Sensitization to egg, shrimp, hazelnut, peanut, soy, and peach. Normal serum immunoglobulins and blood lymphocytes. **A** and **B,** Infiltrated, papulated, erythematous, intensively pruritic lesions; skin biopsy showed acanthosis, hyperkeratosis, parakeratosis, and lymphocytic perivascular infiltrate and fibrosis in the dermis. **C** and **D,** Marked improvement 2 weeks after the first dose of dupilumab on January 26, 2021, with remaining hyperchromic lesions. SCORAD 73 (10 sleep, 10 pruritus) and 23 (0 sleep, 2 pruritus); EASI 23.2 and 8; IGA 4 (severe disease) and 3 (moderate); cDLQI 14 (very large effect on child's life) and 5 (small effect), before and 2 weeks after the first dose of dupilumab, respectively (starting dose of 600 mg followed by 300 mg every 4 weeks, according to age of 6 years and body weight of 25 kg). *cDLQI*, Children's Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Score; *IGA*, Investigator's Global Assessment; *SCORAD*, SCORing Atopic Dermatitis. Courtesy of Sarah Sella Langer, MD, Clinical Hospital of Ribeirão Preto Medical School, with permission from the patient's parents.

schedule, outside clinical trials, and evaluate whether adding this approach will lead to benefit to patients and better clinical care.[5]

In a Grand Rounds Review, Stadler et al[6] warn us about possible inborn errors of immunity masquerading as AD-like conditions. Important clues would be an onset of eczema before age 2 months, extensive disease, disseminated viral infections including herpes, coxsackie, and molluscum contagiosum, recurrent diarrhea, endocrinopathy, failure to thrive, and severe food allergy. In this scenario, an early diagnosis of an inborn error of immunity is essential to prevent complications.[6]

And finally, in their Clinical Management Review, Ahn et al[7] walk us into emerging new systemic treatments for AD, in both late- and early-stage clinical trials, and provide us with approaches on how to choose the right treatment for our patients. With novel therapies coming soon, the process of shared decision making as highlighted by the authors includes appraisal of effectiveness, possible short- and long-term side effect and risks, administration route, age of licensing of each product, availability, and cost.

We are facing exciting times, as novel therapies for AD are emerging; however, many issues remain unanswered.[8] Research into possible AD prevention strategies continues, with recent studies also exploring the effect of these strategies on related outcomes such as food allergy.[9] Availability of the new therapeutic agents may be limited in many areas of the world due to the high cost of these medications,[10] and biomarkers to predict efficacy and to help decide when to stop the treatment have not been identified. However, the possibility of reaching total control of AD symptoms, leading to fulfillment of life expectations for patients with AD, should be our main target as clinicians.

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