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The Changing Landscape of Atopic Dermatitis - Focusing on JAK Inhibitors

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KEY WORDS

janus kinase inhibitors; atopic dermatitis; molecular targeted therapy; baricitinib; upadacitinib

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Doi

10.23822/EurAnnACI.1764-1489.120

To the editor

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, with a lifetime prevalence of 15-20% in developed countries, with 20% of patients suffering from moderate-to-severe disease (1). According to the 2010 Global Burden of Disease Study, AD carries some of the highest disease burden worldwide, comparable to other chronic conditions like diabetes mellitus and cystic fibrosis (2). Described as the 'itching that erupts', clinically it is characterized by highly pruritic recurrent eczematous lesions with a negative impact in health-related quality of life (1), with a reported increased risk of developing depression and anxiety (1). AD is associated with several atopic and non-atopic comorbid conditions (3). The most common comorbidities are allergic rhinitis and asthma (present in up to one-quarter to one-third of patients) (4-6). Classically AD was regarded as a disease of early childhood (where the prevalence can reach 25%) but recent data shows prevalence in adults reaching 7 to 10% (7). This translates to a significant proportion of patients with persistent or adult-onset disease.

Phenotypically, it is an extremely heterogeneous disease, thought to be triggered by environmental factors in genetically susceptible individuals. It presumably encompasses a variety of subtypes with distinct and overlapping pathophysiological mechanisms with varying degrees of epidermal barrier disruption, activation of different T-cell subsets and dysbiosis of the commensal skin microbiota, which interact and contribute to cause the varying clinical presentations (1).

The molecular basis for AD has been increasingly understood as well as for pruritus. AD is characterized by skin epidermal barrier disruption which leads to chronic inflammation with epidermal hyperplasia and cellular infiltrates, including T-cells, dendritic cells, eosinophils, and type-2 T-helper cell (Th2) (8). Regarding inflammatory pathways, it is linked to increased T-helper (Th) immune response, elevated levels of inflammatory cytokines, including Th2-associated interleukin (IL)-4, -13, -31, Th22-associated IL-22, and Th1-associated interferon (IFN)-gamma, with downstream activation of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway (9). The cellular infiltrate of AD lesions mainly consists of CD4+ T cells, which are considered the key

drivers of inflammation (2). Although IgE has been considered a hallmark of atopic diseases, including AD, IgE itself is not a key mediator of AD pathogenesis (8).

The current management of AD includes a combination of emollients, antibiotics, anti-pruritic, and topical anti-inflammatory therapies. In the cases when this approach is insufficient, mainly the moderate-to-severe AD, the treatment remained challenging and limited. Systemic corticosteroids can only be used in short courses, and so, until recently, cyclosporine was the only systemic option approved in many European countries, unfortunately with limited efficacy and safety concerns with long-term therapy. Off-label options included methotrexate, azathioprine and mycophenolate-mofetil, with similar response rates, and also limited by their safety profile (10,11).

Despite an obvious unmet need regarding systemic treatment options, the cornerstone of AD treatment has remained relatively unchanged for over 15 years. But this is not the case anymore, as the field is currently evolving at a rapid pace. The growing understanding of the mechanism for AD, particularly focused on suppressing the skewed immune activation, is leading to an expanding pipeline of new and targeted topical and systemic therapies, similar to what happened in psoriasis (12).

Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently approved two targeted therapies for AD: crisaborole (a topical PDE4i) and dupilumab (an injectable monoclonal antibody against the IL-4 receptor A) (13,14).

Dupilumab, a human monoclonal antibody that blocks receptor binding of IL-4 and IL-13 (reducing Th2 response), approved for the treatment of adults with moderate-to-severe AD, was a natural approach to a targeted therapy (15). Clinical trials have demonstrated that it significantly improved clinical and patient-reported outcomes in the majority of patients. It also has a favorable safety profile. Frequent adverse events reported were mostly mild-to-moderate and included nasopharyngitis, upper respiratory tract infection, injection site reactions, and conjunctivitis (the only dupilumab-specific side effect). An added benefit is the effect on asthma. Dupilumab has recently received the approval from EMA as an add-on maintenance therapy for severe asthma with type 2 inflammation (16,17).

Despite dupilumab, the need for alternative treatments remains. Only 40% of patients on dupilumab with background topical corticosteroids (TCS) achieved clear or almost clear skin (18). Other biologic drugs currently being studied include pitrakinra (that specifically blocks IL-4), tralokinumab and lebrikizumab (that selectively target IL-13), and nemolizumab (an IL-31 receptor inhibitor, the first biologic specifically targeting IL-31, also known as the 'pruritus cytokine').

Pitrakinra is a recombinant human IL-4 protein that binds to IL-4R α , therefore specifically blocking IL-4. The results from a 25-person phase II clinical trial from 2006 are still awaited (19).

Tralokinumab is an IgG4 humanized monoclonal antibody that acts by competitively blocking IL-13 attachment to its receptor subunits (IL-4R α /IL-13R α 1 and IL-13R α 2 decoy receptor). In the phase IIb clinical trial, that included 204 patients, there was a statistically significant number of patients achieving EASI-75 and EASI-50, as well as an increased number of patients who achieved an IGA of 0 or 1. A phase III clinical trial was initiated in May 2017 and is expected to be completed in June 2020 (19).

Lebrikizumab also targets IL-13. It acts by binding to IL-13 and preventing the epitope needed for IL-4R binding from attaching. Unlike tralokinumab, it does not affect binding to IL-13R α 2. A 12-week phase IIb trial showed that the group in the 125 mg of lebrikizumab once monthly achieved an EASI-50 that was statistically significant, despite all groups including the placebo receiving intensive topical corticosteroid regimens throughout the study.

IL-31, produced by Th2 cells and in lesser quantities by Th1 cells, appears to be involved in acute and chronic phases of AD and it seems to mediate transmission of itch sensation to the central nervous system. It also inhibits eosinophil apoptosis and is involved in disruption of skin barrier via downregulation of profilaggrin and filaggrin (19).

Nemolizumab is a monoclonal antibody that acts on the IL-31 receptor A. In a 12-week phase two clinical trial that enrolled 216 moderate-to-severe AD patients, monthly subcutaneous injections of nemolizumab showed a decrease in EASI, itch, improvement in Dermatology Quality of Life Index (DLQI), and improved sleep quality. Still, it is not clarified yet if nemolizumab controls AD or only AD-associated pruritus (19). But monoclonal antibodies are far from being the only area of excitement regarding new treatment options.

Another important area of focus in AD is the development of new oral agents with minimal side effect profiles, including the category of small molecules. Small molecules are non-biologic drugs that modulate inflammatory cytokines and affect signaling pathways in immune cells. Several oral small molecules with differing mechanisms of action are being investigated for AD, namely JAK inhibitors, phosphodiesterase inhibitors and histamine receptor antagonists (20). In this category, JAK inhibitors are a promising therapeutic class that so far is proving again and again to be a safe bet and maybe even a JAKpot for the treatment of AD.

JAK/STAT pathway is a master regulator of immune function, involved in the downstream signaling of inflammatory cytokines, including interleukins, interferons, and multiple growth factors. The mammalian JAK kinase family is composed by four different members (JAK1, JAK2, JAK3, and tyrosine kinase 2 - TYK2) (21). Many different proinflammatory cytokines (including IL-4, IL-5, IL-13, and IL-31) elicit their pathophysiologic functions through JAK-STAT pathway, inducing Th2

and eosinophil activation, B-cell maturation, up-regulation of epidermal chemokines, and down-regulation of anti-microbial peptides (22). This makes JAK inhibitors broad-acting small molecules for oral or topical administration, with anti-inflammatory and anti-proliferative activity.

Their success in rheumatoid arthritis and other inflammatory diseases made them an important focus of therapeutic research for AD. They inhibit the kinase component of JAKs, preventing them from phosphorylating and stopping the transduction of intracellular signaling. Unlike psoriasis or alopecia areata, in which only one JAK pathway is upregulated, atopic dermatitis is associated with increased signaling through all four JAKs (JAK1, JAK2, JAK3, and TYK2) (23). Due to their good oral bioavailability and lack of immunogenicity, oral JAK inhibitors address some of the limitations of biologics for the treatment of moderate-to-severe AD. Topical formulations are therapeutic options for mild-to-moderate AD (20,21).

The first published randomized clinical trial demonstrating a clinical benefit of a topical JAK inhibitor in atopic dermatitis appeared in September 2016 (24). Within 2 years, 7 different agents entered randomized trials targeting the pathway: oral upadacitinib, oral abrocitinib (PF-04965842), oral baricitinib, oral ASN002, oral tofacitinib, topical tofacitinib, topical ruxolitinib and topical delgocitinib.

Results thus far are encouraging, with the majority of the patients achieving the primary outcome of their trial as well as reporting improvement in pruritus and quality of life. Of note, both selective JAK1 inhibitors upadacitinib and abrocitinib (PF-04965842) received breakthrough therapy designation from the FDA for treatment of patients with moderate-to-severe atopic dermatitis. Based in preliminary phase II data, upadacitinib (a selective JAK1 inhibitor) seems to achieve even better outcomes than dupilumab (21). Also relevant is an improvement in pruritus as soon as week 1 and skin improvement as soon as week 2, positioning it as an excellent option for induction of remission (21). If the short time to response is a class feature is yet to be determined. Baricitinib (a non-selective JAK inhibitor) also reported improvement in pruritus as soon as week 1 (25).

The most extensive safety data for JAK inhibitors has come from tofacitinib, ruxolitinib and baricitinib for their use in

rheumatoid arthritis and myelofibrosis. Overall, JAK inhibitors are well tolerated and have good safety profiles. There is a slight increased risk herpes zoster, but the most frequent adverse effects are nasopharyngitis and upper respiratory tract infections (26,27). There is a slight increase in CPK (asymptomatic) as well as slight changes in hemogram, the latter being dose dependent and transient. Importantly, there does not seem to be an increased risk of malignancy (20). Of note, EMA has recently issued restrictions in the use of tofacitinib, while it reviews the risk of pulmonary embolism in patients under 10 mg twice daily dose (the drug is approved for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis; it is not being pursued for atopic dermatitis treatment) (28).

Finally, burden of atopic dermatitis in the pediatric population will certainly not be overseen. In the coming years, the pediatric patients will certainly become an important investigational focus and the gap between the number of adult trials and pediatric trials in atopic dermatitis is expected to decrease, as there are already some ongoing trials enrolling pediatric patients.

Without a doubt, these are exciting times in AD. In the near future the physicians' ability to help improving the patients' lives will increase. However, despite overall confidence it will be important to be aware of unexpected risks. Although the side effect profile of these new drugs appears safe, long-term effects are still unclear. Going forward, it will be important to better define the different subtypes of AD, and to be able to early identify the patients who are in need of a maximum treatment. These new directed therapies will soon change current algorithms of care and its careful use will allow practitioners to provide optimal therapy while minimizing adverse impacts on safety and cost.

Conflict of interests

Maria Alexandra Rodrigues has no research contracts or conflicts of interest to declare.

Tiago Torres declares the following research contracts and conflicts of interest:

AbbVie, Celgene, Janssen-Cilag, Leo-Pharma, Eli-Lilly, Pfizer and Sanofi-Genzyme.

References

- Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Prim* 2018; 4(1):1.
- Hay RJ, Johns NE, Williams HC, et al. The Global Burden of Skin Disease in 2010: An Analysis of the Prevalence and Impact of Skin Conditions. *J Invest Dermatol* 2014; 134(6):1527-1534.
- Oliveira C, Torres T. More than skin deep: the systemic nature of atopic dermatitis. *Eur J Dermatol* 2019. [Epub ahead of print].
- Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: A US population-based study. *J Allergy Clin Immunol* 2013; 132(5):1132-1138.
- van der Hulst AE, Klip H, Brand PLP. Risk of developing asthma in young children with atopic eczema: A systematic review. *J Allergy Clin Immunol* 2007; 120(3):565-569.
- Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. *J Am Acad Dermatol* 2008; 58(1):68-73.

7. Abuabara K, Yu AM, Okhovat J-P, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. *Allergy* 2018; 73(3):696-704.
8. Malik K, Heitmilller KD, Czarnowicki T. An Update on the Pathophysiology of Atopic Dermatitis. *Dermatol Clin* 2017; 35(3):317-326.
9. Bao L, Zhang H, Chan LS. The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. *JAK-STAT* 2013; 2(3):e24137.
10. Politiek K, van der Schaft J, Coenraads PJ, de Bruin-Weller MS, Schuttelaar MLA. Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis. *Br J Dermatol* 2016; 174(1):201-203.
11. van der Schaft J, Politiek K, van den Reek JMPA, et al. Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol* 2015; 172(6):1621-1627.
12. Torres T. Atopic Dermatitis: The New Therapeutic Revolution in Dermatology. *Acta Med Port* 2017; 30(10):669.
13. Eichenfield L, Stein Gold L. Addressing the Immunopathogenesis of Atopic Dermatitis: Advances in Topical and Systemic Treatment. *Semin Cutan Med Surg* 2017; 36(2S):S45-S48.
14. Boozalis E, Semenov YR, Kwatra SG. Food and drug administration approval process for dermatology drugs in the United States. *J Dermatolog Treat* 2018; 29(6):536-538.
15. Ferreira S, Torres T. Dupilumab for the Treatment of Atopic Dermatitis. *Actas Dermosifiliogr* 2018. Epub 2018 Feb 13.
16. Rodrigues MA, Nogueira M, Torres T. Dupilumab for atopic dermatitis. Evidence to date. *G Ital Dermatol Venereol* 2019. [Epub ahead of print].
17. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017; 389(10086):2287-2303.
18. Kalamaha K, Reis E, Newton S, et al. Atopic dermatitis: a review of evolving targeted therapies. *Expert Rev Clin Immunol* December 2018;1744666X.2019.1560267.
19. He H, Guttman E. JAK Inhibitors for Atopic Dermatitis: An Update. *Am J Clin Dermatol* 2018. Epub 2018 Feb 13.
20. Regeneron. Dupixent (dupilumab) approved for severe asthma by European Commission [Internet] 2019; Available from: <https://newsroom.regeneron.com/news-releases/news-release-details/dupixent-dupilumab-approved-severe-asthma-european-commission/>
21. Rodrigues M, Torres T. JAK/STAT inhibitors for the treatment of atopic dermatitis. *J Dermatolog Treat* 2019. Epub 2019 Jan 31.
22. Brunner PM, Guttman-Yassky E, Leung DYM. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017; 139(4):S65-S76.
23. Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yannopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov* 2016; 15(1):35-50.
24. Bissonnette R, Papp KA, Poulin Y, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol* 2016; 175(5):902-911.
25. Guttman-Yassky E, Silverberg JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol*. February 2018.
26. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis* 2017; 76(7):1253-1262.
27. Keystone EC, Genovese MC, Schlichting DE, et al. Safety and Efficacy of Baricitinib Through 128 Weeks in an Open-label, Longterm Extension Study in Patients with Rheumatoid Arthritis. *J Rheumatol* 2018; 45(1):14-21.
28. European Medicines Agency. Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs [Internet] 2019. Available from: <https://www.ema.europa.eu/en/news/restrictions-use-xeljanz-while-ema-reviews-risk-blood-clots-lungs>.