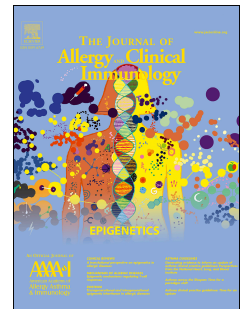


Journal Pre-proof

Leveraging the nice face of Janus kinase inhibition - Ruxolitinib cream in atopic dermatitis

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Editorial

Leveraging the nice face of Janus kinase inhibition -

Ruxolitinib cream in atopic dermatitis

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Journal Pre-proof

We are currently experiencing a fascinating time with regards to the impressive number of new drug development programs ultimately leading to a hopefully substantial increase of the therapeutic options in the management of atopic dermatitis (AD)^{1, 2}. This pipeline includes a number of new biologics such as tralokinumab and lebrikizumab as well as small molecules such as the Janus Kinase inhibitors (JAKi) which are currently also developed in dermatology to further extend, besides Dupilumab, the options for the systemic therapy of moderate to severe AD³ and other inflammatory skin disorders. JAKi are more or less specific inhibitors of the so-called Janus Kinases which are characterized by two near-identical phosphate-transferring domains, ie. have two faces. Due to their relative low molecular weight, the JAKi are expected to penetrate the epidermal barrier and to pharmacologically act directly on the inflammatory site. Thus, topical JAKi may represent a new alternative to the current anti-inflammatory compounds used to treat AD.

In this issue of the *Journal of Allergy and Clinical Immunology*, Kim et al. report on a controlled phase 2b (dose finding) study comparing different concentrations (0.15%, 0.5% and 1.5%) and regimens (QD and BID) of the JAKi Ruxolitinib in a cream formulation with placebo and Triamcinolone acetonid (TCA) 0.1% cream, a well accepted standard topical steroid in the management of AD⁴. The target population in this study was patients suffering from mild to moderate forms of AD. The key findings of this study can be summarized as follows: (i) compared to placebo and TCA, topical Ruxolitinib induces a rapid improvement of pruritus; (ii) Ruxolitinib displays a positive benefit/risk ratio; (iii) 1.5% Ruxolitinib cream is clearly more efficacious than placebo and seems to be superior to TCA cream in overall efficacy; (iv) the kinetics of the response in the Ruxolitinib arms suggest that the therapeutic effect seems to further improve after the 4 weeks time point of the primary endpoint.

There are currently more than 90 patented JAKi which all have the potential to be the subject of a clinical development program and particularly in dermatology⁵. Similar to their targets, the JAKi can be considered to have two faces: a useful “nice face” due to their wanted therapeutical activity and a rather “nasty face” resulting from the potential safety issues linked to their activity on cytokine receptors needed for eg. physiological hematopoietic functions. Classically, JAKi are classified into either (i) pan-JAKi (such as Delgocitinib/JTE-052, Peficitinib or Tofacitinib); (ii) bispecific JAKi such as Ruxolitinib or Baricitinib (JAK1/JAK2); these are also called first generation

JAKi and (iii) monospecific JAKi such as Upadacitinib, Abrocitinib, Filgotinib, Itacitinib (all JAK1), PF-06651600 (JAK3), BMS-986165 (TYK2) also called second generation JAKi ⁶. Most of these compounds are currently in clinical development programs for systemic application. Due to their low molecular weight of approximately 300 Da and thereby being smaller than the theoretically epidermal penetration cut-off of 500 Da, they can also be integrated in an appropriate galenic formulation for a topical therapy. Delgocitinib/JTE-052 ointment has been submitted in 2019 to the Japanese pharmaceuticals and medical devices agency (PMDA) for the treatment of AD and will potentially be the first approved topical JAKi in dermatology.

Specific JAKi applied systemically typically exhibit a rather narrow therapeutic window and thereby may display safety issues when, intentionally or unintentionally, applied in higher doses or in patients at risk to develop side effects related to the unwanted immunopharmacological impact (the “nasty face”). In contrast, most of the topical JAKi currently in development (including Ruxolitinib and Delgocitinib) have a broadened spectrum of inhibition which has potentially a number of advantages related to the blockage of numerous cytokines receptors involved in the generation of different types of inflammation without having systemic effects. Thus, topical application of JAKi favours the therapeutic aspect (the “nice face”) while reducing the risk for safety issues. In this study, the systemic exposure was low but the body surface area (BSA) treated was limited to 20%. However, when applied to large body surface areas, their adsorption can potentially lead to significant blood concentration which may in turn exhibit systemic effects. This may potentially hamper their use in severe forms of AD where the epidermal barrier dysfunction and the BSA usually reaches more than 50%.

The lack of systematic analysis of the JAK expression on epidermal and dermal cells hampers our understanding of the exact mode of action of JAKi applied either topically or systemically. Nevertheless, the broad spectrum of JAKi such as Ruxolitinib also offers the option to use Ruxolitinib in chronic inflammatory skin disorders dominated by another immune response than a T2-type immune response such as Psoriasis or Lupus. It is expected that future studies will explore such indications other than AD.

Another interesting characteristic of JAK inhibition is the fast mode of action with regards to the pruritus. This is likely due to the rapid blockage of IL-31, IL-4 and IL-13 cytokine receptors expressed on the nerve endings responsible for the itching

sensation in AD⁷. This phenomenon is clearly a significant advantage of JAKi in the management of an eminently itching chronic condition such as AD. Nemolizumab and Dupilumab most probably exert their anti-pruritic activity^{8, 9} via a similar but clearly more delayed mechanism inherent of the class of biologics. On the other hand, despite the rapid relief of pruritus, the report of Kim et al. also suggests that topical Ruxolitinib may also exhibit a delayed control of inflammation since they observed a gradual and continuous improvement until the 8th week of application. Thus, Ruxolitinib and other topical JAKi bear the potential to represent alternatives to available anti-inflammatory compounds such as topical steroids, calcineurin-inhibitors or Crisaborole in the management of mild to moderate AD.

Most remarkably, in contrast to many other phase 2 studies, this trial included 0.1% TCA cream as a comparator allowing the head to head comparison of Ruxolitinib to a standard therapy. The results obtained at the primary end point at 4 weeks suggests a clear superiority of 1.5% Ruxolitinib over 0.1% TCA. In combination with the rapid relief of itching, this finding is of significant importance from a market access point of view, particularly when considering the reimbursement aspect of Ruxolitinib in countries where health technology assessment agencies (HTA) often determine the fate of new therapeutic developments.

Taken together, topical Ruxolitinib exhibits a number of interesting characteristics implying that it represents a promising new and safe alternative for the management of mid to moderate AD. This is further supported by the reported superiority compared to a classical topical steroid such as 0.1% TCA. Moreover, Ruxolitinib has the potential to be used in other chronic skin disorders which, as for AD, may need a long term control of the underlying inflammatory reaction.

References

1. Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: End of the drought? *J Allergy Clin Immunol* 2017; 140:633-43.
2. Bieber T. Novel therapies based on the pathophysiology of atopic dermatitis. *Journal Deutsche Dermatologische Gesellschaft* 2020; (in press).
3. Cotter DG, Schairer D, Eichenfield L. Emerging therapies for atopic dermatitis: JAK inhibitors. *J Am Acad Dermatol* 2018; 78:S53-S62.
4. Kim B, Howell M, Sun K, Papp K, Nasir A, Kuligowski M. Treatment of atopic dermatitis with Ruxolitinib cream (JAK1/JAK2 Inhibitor) or Triamcinolone cream. *Journal of Allergy and Clinical Immunology* 2019.
5. Gadina M, Le MT, Schwartz DM, Silvennoinen O, Nakayamada S, Yamaoka K, et al. Janus kinases to jakinibs: from basic insights to clinical practice. *Rheumatology (Oxford)* 2019; 58:i4-i16.
6. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov* 2017; 16:843-62.
7. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. *Cell* 2017; 171:217-28 e13.
8. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, et al. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. *N Engl J Med* 2017; 376:826-35.
9. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med* 2016; 375:2335-48.

The nice face

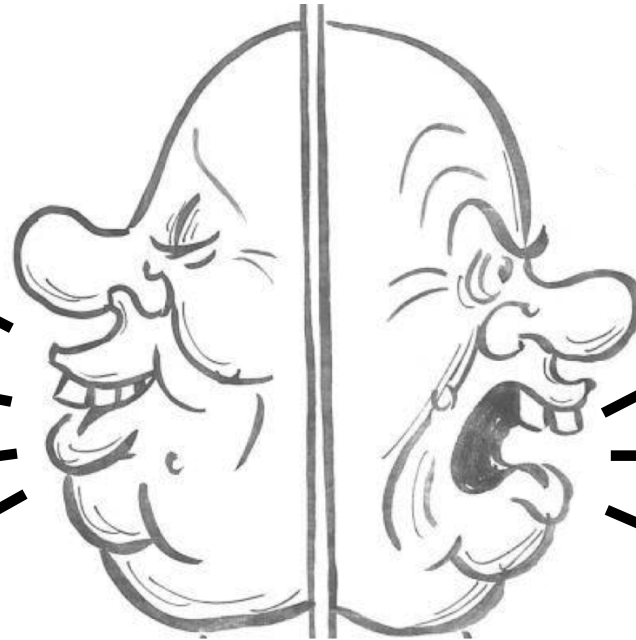
The nasty face

Control of
pro-inflammatory
cytokines

Itch control

Barrier
improvement

Control of T cell
proliferation/
effector function



Impairment of
anti-viral defence

Thromboembolic
events

Impairment of
haematopoiesis

Legend to Figure 1: **The two faces of Janus Kinase inhibition in atopic dermatitis.**

As for the dual functionality of the Janus Kinases and depending on the cytokine receptor they are associated as well as the doses used, their inhibition may lead to beneficial (nice face) or potentially harmful (nasty face) effects. In contrast to systemic application, the topical application of JAK inhibitors on a individually yet-to-be-defined maximal body surface area may leverage the local beneficial effects while the very limited systemic exposure may significantly improve the safety profile.