SHORT COMMUNICATION

Acneiform Lesions but not Acne after Treatment with Janus Kinase Inhibitors: Diagnosis and Management of Janus Kinase-acne

Fabienne BALLANGER[1], Nicole AUFFRET[2], Marie-Thérèse LECCIA[3], Jean Paul CLAUDEL[4] and Brigitte DRÉNO[5*]
*[1]Private practice, Talence, [2]Private practice, Paris, [3]Department of Dermatology, Allergology and Photobiology, CHU A Michallon, Grenoble, [4]Private practice, Tours and [5]Nantes University, INSERM, CNRS, Immunology and New Concepts in ImmunoTherapy, INCIT, UMR 1302/EMR6001, FR-44000 Nantes, France. *E-mail: brigitte.dreno@atlanmed.fr*
Accepted May 10, 2023; Published Jun 22, 2023
Acta Derm Venereol 2023; 103: adv11657. DOI: 10.2340/actadv.v103.11657

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway has been linked to the pathogenesis of many inflammatory skin diseases. The Janus kinase (JAK) family comprises JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). JAK inhibitors (JAKi) target various kinases, leading to suppression of the JAK-signal transducers and activators of the transcription pathway, which plays a major role in the pathogenesis of multiple immune-mediated conditions, such as rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and atopic dermatitis (AD) (1).

MATERIALS AND METHODS

Our group of experts in acne performed a literature search on JAKi prescribed in subjects with AD which reported cases of acne, using the following key word combinations: JAK inhibitors + atopic dermatitis + acne, JAK inhibitors + atopic dermatitis + side effects, JAK inhibitors + atopic dermatitis + acneiform eruptions, JAK inhibitors + atopic dermatitis + folliculitis.

A short overview of current knowledge on this subject is presented here, together with hints about how to manage this type of lesion.

RESULTS

Several articles report that JAKi trigger acne vulgaris (acne) in patients with AD (1–6). Correia et al. reported that, in AD, 13% of patients had acneiform lesions when treated with upadacitinib at 15 mg, and 17% had these types of lesion when treated at doses of 30 mg. In 68% of all cases, mild inflammatory lesions with papules and pustules, mainly on the face, were reported (7). Lesions on the trunk were present in 32% of patients; the authors recommended conventional topical acne treatment approaches. Moreover, upadacitinib was reported to induce inflammatory lesions in patients with AD more frequently than in those with rheumatoid arthritis. However, the younger age of patients with AD and the skin examination performed by the dermatologist may explain the difference between these 2 conditions. Similar dose-dependent results were reported for abrocitinib (100 mg: 12%, 200 mg: 6%); conversely, baricitinib caused only mild inflammatory lesions in 2.9% of patients. Acneiform lesions were described in 2 phase 3 trials with baricitinib (5.7% and 4.7% with 4 mg), 5.5% and 5.8% with 2 mg, and 0.5% and 1.9% with the placebo (8).

Guo et al. (9) performed a meta-analysis of the safety of JAKi based on 7 studies including 3 clinical trials and 4 observational studies. In the clinical trial group, acneiform lesions were observed in 13.2% of subjects.

To date, the role of JAKi in the pathogenesis of acne remains to be elucidated. It was only recently that JAK1 and JAK3 proteins (but not JAK2) were reported to be overexpressed in acne lesions, with no significant correlation between the severity of acne, patients' age, sex, family history or duration of acne (10). Thus, activation of the JAK pathway may play a role in the development of inflammation and, consequently, JAK1 and JAK3 may potentially be considered as new acne therapy targets.

Acneiform lesions appear quickly after initiating JAKi. The profile of this inflammatory acne seems to belong to a spectrum of 4 distinct profiles: (*i*) lesions appear in patients with no previous history of acne; (*ii*) exacerbation of pre-existing acne, which may sometimes be associated with nodules; (*iii*) transient acneiform eruptions: lesions develop after the start of JAKi treatment, disappear after having been appropriately treated (mostly local treatment) and do not relapse, even after treatment has been stopped although JAKi treatment continued; and (*iv*) chronic acneiform eruption: in certain patients with no history of chronic acne, lesions may develop after the initiation of JAKi treatment, thereby requiring continued treatment over a prolonged period.

Drug-induced acneiform lesions have been observed previously with epidermal growth factor or methyl ethyl ketone inhibitors (11, 12). Thus, we suggest naming the drug-induced acneiform lesions in patients treated with JAKi, "JAK-acne".

When starting JAKi treatment, it is important to discuss with the patient the risk of JAK-acne as a potential side-effect. In patients with clinically significant acne at JAKi initiation, concomitant acne treatment should be adapted. In these patients, the risk of acne exacerbation is present. Another important point is to explain to the patient that JAKi discontinuation due to JAK-acne remains exceptional, that JAK-acne is mainly mild, that it can be controlled well using suitable treatments, and that it disappears after JAKi treatment has been stopped at the end of treatment for AD or other skin condition.

In patients treated with JAKi and developing acneiform lesions, contrariwise to acne, inflammatory lesions occur first and are predominant over retentional lesions.

Moreover, no hormonal influence has been described and no information is available concerning hyperseborrhoea or atrophic and hypertrophic scars, which may be explained by the fact that sebaceous glands are not the main target of drug-induced acneiform lesions.

While there is no major difference in treatment between "teenage acne" and JAK-acne, in drug-induced acneiform lesions, the question of stopping or maintaining the liable treatment has to be discussed. Obviously, with lesions being mainly inflammatory, benzoyl peroxide and/or fixed combinations, associated with cyclins or not, are the most frequently indicated treatment. In the context of *Staphylococcus aureus* being predominant in AD, topical antibiotics, especially macrolides, should be avoided, as they can cause bacterial resistance as soon as after 3 weeks of use. Inflamed lesions in JAK-acne are, at least partially, related to cutaneous JAKi-induced dysbiosis. Thus, it is important to prescribe adequate adjuvant skin care, using cosmetics that help to restore the natural skin barrier, and to respect the pH of the skin with cleansers with a pH of approximately 5 and non-comedogenic moisturizers.

DISCUSSION

Acne is a chronic inflammatory skin disease of the sebaceous follicle. The hormonal factor, innate immunity and the microbiome play a crucial role in the onset of acne lesions. Dysbiosis with an unbalanced presence of *Cutibacterium acnes* (*C. acnes*), characterized by a loss of *C. acnes* phylotype diversity and *C. acnes* biofilm production, is another proof for acne (13–15).

To date, the physiopathology of inflammatory acneiform lesions or JAK-acne, induced by JAKi remains unknown. No relationship with hyperseborrhoea or loss of diversity of *Cutibacterium acnes* or proliferation of phylotype 1AI, or proliferation or disappearance of *S. epidermidis* has been demonstrated in JAK-acne.

Dermatologists should take care to correctly differentiate acne from acneiform lesions, triggered by drugs. Studies to understand the mechanisms of JAK-acne better are necessary to allow for suitable care and prevention, while patient information remains an important element in medical care.

ACKNOWLEDGEMENTS

The authors acknowledge the writing support of Karl Patrick Göritz, SMWS, France

This expert group is organized and funded by Galderma International.

Conflicts of interest: The authors receive honoraria from Galderma International to participate in an expert board on acne.

REFERENCES

1. Nezamololama N, Fieldhouse K, Metzger K, Gooderham M. Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: a review of abrocitinib, baricitinib, and upadacitinib. Drugs Context 2020; 9: 2020-8-5.
2. Nakashima C, Yanagihara S, Otsuka A. Innovation in the treatment of atopic dermatitis: Emerging topical and oral Janus kinase inhibitors. Allergol Int 2022; 71: 40–46.
3. Wood H, Chandler A, Nezamololama N, Papp K, Gooderham MJ. Safety of Janus kinase (JAK) inhibitors in the short-term treatment of atopic dermatitis. Int J Dermatol 2022; 61: 746–754.
4. Nogueira M, Torres T. Janus kinase inhibitors for the treatment of atopic dermatitis: focus on abrocitinib, baricitinib, and upadacitinib. Dermatol Pract Concept 2021; 11: e2021145.
5. Silverberg JI, Thyssen JP, Fahrbach K, Mickle K, Cappelleri JC, Romero W, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. J Eur Acad Dermatol Venereol 2021; 35: 1797–1810.
6. Wan H, Jia H, Xia T, Zhang D. Comparative efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe atopic dermatitis: a network meta-analysis. Dermatol Ther 2022; 35: e15636.
7. Correia C, Antunes J, Filipe P. Management of acne induced by JAK inhibitors. Dermatol Ther 2022; 35: e15688.
8. King B, Ohyama M, Kwon O, Zlotogorski A, Ko J, Mesinkovska NA, et al. Two phase 3 trials of baricitinib for alopecia areata. N Engl J Med 2022; 386: 1687–1699.
9. Guo L, Feng S, Sun B, Jiang X, Liu Y. Benefit and risk profile of tofacitinib for the treatment of alopecia areata: a systemic review and meta-analysis. J Eur Acad Dermatol Venereol 2020; 34: 192–201.
10. Awad SM, Tawfik YM, El-Mokhtar MA, El-Gazzar AF, Abdel Motaleb AA. Activation of Janus kinase signaling pathway in acne lesions. Dermatol Ther 2021; 34: e14563.
11. Anforth R, Liu M, Nguyen B, Uribe P, Kefford R, Clements A, et al. Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. Australas J Dermatol 2014; 55: 250–254.
12. Aydingoz IE, Tukenmez Demirci G, Agirbasli D, Oz-Arslan D, Yenmis G. The investigation of the amounts and expressions of epidermal growth factor, epidermal growth factor receptor, and epidermal growth factor receptor gene polymorphisms in acne vulgaris. J Cosm Dermatol 2021; 20: 346–351.
13. Dréno B, Dagnelie MA, Khammari A, Corvec S. The skin microbiome: a new actor in inflammatory acne. Am J Clin Dermatol 2020; 21: 18–24.
14. Mias C, Mengeaud V, Bessou-Touya S, Duplan H. Recent advances in understanding inflammatory acne: deciphering the relationship between cutibacterium acnes and Th17 inflammatory pathway. J Eur Acad Dermatol Venereol 2023; 37: 3–11.
15. Dagnelie MA, Montassier E, Khammari A, Mounier C, Corvec S, Dréno B. Inflammatory skin is associated with changes in the skin microbiota composition on the back of severe acne patients. Exp Dermatol 2019; 28: 961–967.