A case series of acne following Janus kinase inhibitors in patients with atopic dermatitis

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Key words: acne; adverse event; atopic dermatitis; baricitinib; JAK inhibitor; pathogenesis of acne; upadactinib.

INTRODUCTION

The Janus kinase (JAK) family is a group of tyrosine kinases that is coupled to the cytoplasmic signal transducer of transcription (STAT) factors and mediates cytokine signaling. Four different JAKs, namely JAK1, JAK2, JAK3, and tyrosine kinase, harbor different cytokine receptors relevant to the pathophysiology of many inflammatory skin diseases, including atopic dermatitis (AD), psoriasis, and alopecia areata. Therefore, several JAK inhibitors have reached the market or are still in clinical development as a novel therapeutic option for inflammatory diseases.

However, some experts pose concerns about the potential of unexpected adverse effects (AEs) that result from the involvement of unintended pathways along with the target ones. JAK inhibitors have undergone many in-practice studies and clinical trials related to safety concerns. Although the severity, frequencies, and characteristics of AEs are slightly different for each JAK inhibitor, there are common AEs that are frequently observed, like upper respiratory tract infection, headache, herpes simplex infection, and acne.[1]

The occurrence of acne has been associated with oral JAK inhibitors, especially in the population with AD, compared with other indications. However, a recent study in Denmark, showed similar 12-month prevalence and incidence rates per 1000 person-years of acne in AD and the general population, although the risk of acne with AD compared with healthy individuals increases in 30- to 40-year-old women.[2]

The current paper discusses the possible impact of baricitinib and upadacitinib on the development of acne in 8 patients with AD, and it characterizes the time course, morphologic features, distribution, severity, and management.

Abbreviations used:

AD:	atopic dermatitis
AE:	adverse events
JAK:	Janus kinase
mTORC1:	mammalian target of rapamycin complex 1
RA:	rheumatoid arthritis
STAT:	signal transducer and activator of transcription

CASE SERIES

We retrospectively reviewed the medical records and photographs of 92 patients who visited the department of dermatology at the Kyunghee University hospital between June 2021, and May 2022 and were prescribed systemic JAK inhibitors. Forty-nine and 11 patients were prescribed baricitinib 4 mg and upadacitinib 15 mg, respectively for AD treatment. Of these, 8 (13.3%), including 6 treated with baricitinib (12.3%) and 2 with upadacitinib (18.2%), showed acne occurrence or exacerbation. Extracted data included patient demographics, acne characteristics, significant risk factors, and previous and concomitant medications. The mean age of patients with acne was 29.6 years old (range: 21-37 years, SD: 5.3 years), whereas the mean age of total patients with AD was 36.3 years old. The sex ratio of the 8 patients with acne was 1.6 women to 1 man, in contrast to the 60 patients with AD showing 0.54 women to 1 man. Seven patients (87.5%) were overweight or obese based on the World Health Organization body mass index classifications for the

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Funding sources: None.

IRB approval status: Approved (IRB number : 2022-08-079).

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JAAD Case Reports 2022;30:11-6.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.09.029

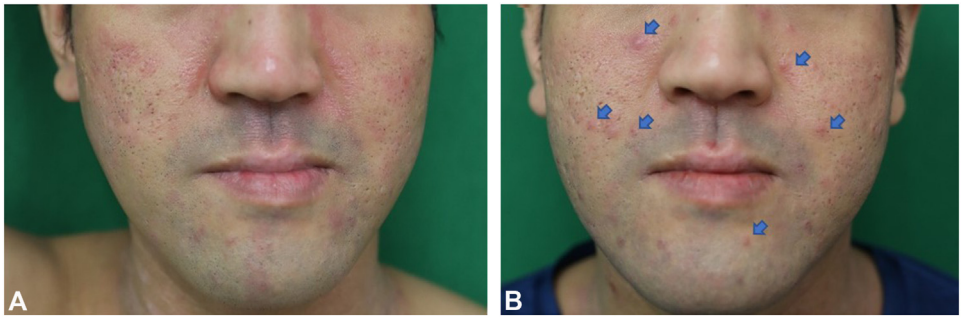

Fig 1. Acne exacerbation of a patient 1 following Janus kinase inhibitors; (**A**) before, (**B**) after.

Table I. Demographic information of patients

No.	Used JAK inhibitor (dose)	Sex/ Age (yrs)	Body mass index (kg/m^2)	Previous acne history	Time to onset of acne (wks)	History of topical agents on face
1	Baricitinib (4 mg)	M/33	Obesity (28.39)	Adult onset*	6	TCI
2	Baricitinib (4 mg)	M/23	Overweight (23.99)	*De novo*†	4	TCS, TCI
3	Baricitinib (4 mg)	F/30	Overweight (23.99)	*De novo*	8	-
4	Baricitinib (4 mg)	M/21	Overweight (23.43)	Adolescent onset	6	TCI
5	Baricitinib (4 mg)	F/37	Overweight (24.98)	*De novo*	3	TCS, TCI
6	Baricitinib (4 mg)	F/30	Normal (22.31)	*De novo*	4	TCS
7	Upadacitinib (15 mg)	F/30	Overweight (24.74)	Adolescent onset	8	TCS
8	Upadacitinib (15 mg)	F/33	Overweight (23.28)	*De novo*	16	-

AD, Atopic dermatitis; *F*, female; *JAK*, Janus kinus; *M*, male; *RA*, rheumatoid arthritis; *TCI*, topical calcineurin inhibitor; *TCS*, topical corticosteroid.

*The age standard for distinguishing adult-onset acne from adolescent onset one is 25 years old; concerning the study by Kaur et al 2016.[4]

†*De novo* means the case that a patient has never had acne before the initiation of the JAK inhibitor.

Asian population.[3] Patient 6 also showed a body mass index very near the overweight threshold. Five patients had not had acne before the treatment; however, the others had had acne with adolescent-onset or adult-onset, both of which were aggravated by JAK inhibitors (Fig 1). The mean time to the onset of the first occurrence of acne following JAK inhibitor therapy was 6.9 weeks (range: 3-16 weeks, SD: 4.1 weeks). The demographic information of the patients is summarized in Table I.[4]

The severity of the acne was assessed using the Global Acne Grading System.[5] The severity of acne is divided into 4 grades consisting of mild, moderate, severe, and very severe. All cases of acne were mild or moderate. No one discontinued the treatment with the JAK inhibitor. Eight showed the dominance of inflammatory lesions, including papules, pustules, and nodules, whereas only 1 presented predominance of comedonal lesions with just a few papules. Inflammatory cysts and acne scars did not occur. As far as the distribution is concerned, 6 patients had acne on the face primarily focusing on the marginal section, including the forehead, cheeks, and chin; on the other hand, the other 2 showed the widely-distributed acne on the entire face, extending into the perinasal and perioral areas (Fig 1). There was no trunk and back involvement. In addition, reflectance confocal microscopy, a noninvasive imaging technique, was used to check for *Demodex folliculorum*. Two patients showed *Demodex,* which was found on the forehead and cheek (Fig 2). Morphologic features and the severity grading of the 8 patients are shown in Table II

One patient experienced spontaneous resolution without any treatment modality. Of those who needed action for acne, most patients required topical agents alone or in combination with dose reduction of JAK inhibitors. Five patients were prescribed nadifloxacin 1% cream, but most showed a moderate-to-poor response. Patients 1 and 4 improved after switching from baricitinib to dupilumab and upadacitinib. Three patients who were treated with adapalene 0.1%/benzoyl peroxide 2.5% gel showed a good response. However, patient 8 reported that the acne on the forehead continued to occur until the last follow-up. Patient 3 responded moderately to adapalene 0.1%/benzoyl peroxide 2.5% gel, but after switching to metronidazole 0.75% gel after identifying demodicosis by reflectance confocal microscopy,

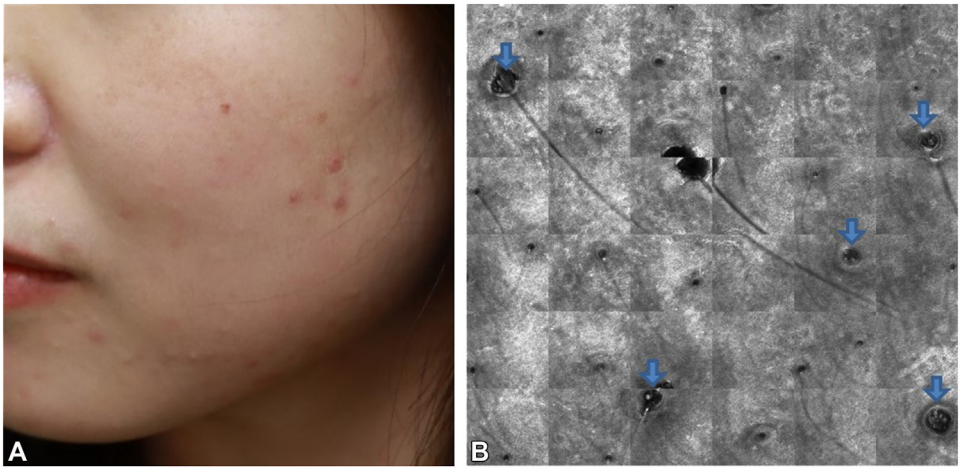

Fig 2. A, Several inflammatory papules on the left cheek of patient 3 and (**B**) reflectance confocal microscopy imaging showing *Demodex folliculorum* infested in follicular openings.

showed a more rapid and greater response. Three of the 6 patients who were treated with baricitinib required a dose reduction to 2 mg/day and showed rapid clinical improvement.

DISCUSSION

There are different kinds of JAK inhibitors depending on the interrupted pathways. For example, baricitinib is a selective JAK1/JAK2 inhibitor indicated in AD and rheumatoid arthritis (RA) with Food and Drug Administration approval. On the other hand, upadacitinib is a selective JAK1 inhibitor with comparably narrower coverage but more selectivity for cytokine inhibition, which is indicated in RA, ulcerative colitis, and spondyloarthritis, as well as AD and psoriatic arthritis. There are several AEs involving the use of JAK inhibitors. Among them, acne is noticeable because it has been reported in the population with AD whereas rarely seen in other populations, such as RA, psoriatic arthritis, spondyloarthritis, and inflammatory bowel disease.

In this study, 60 patients were prescribed baricitinib and upadacitinib for moderate-to-severe AD, and 8 experienced acne with an incidence of 13.3%. Several trials investigating JAK inhibitors for AD have reported acne as one of the main AEs. Acne occurred during the 16-week double-blind placebo-controlled period in 10% of patients with upadacitinib 15 mg and 14% with upadacitinib 30 mg, compared with 2% with placebo.[1] In addition, daily use of 100 mg and 200 mg abrocitinib resulted in 1.3% and 5.8% incidence rates of acne (vs 0% in patients receiving a placebo), respectively, suggesting a dose-dependent relationship similar to that noted with the use of upadacitinib.[6]

One of the reasons acne occurs more in the population with AD than in others is assumed to be related to the age of the patients. The mean age of patients with acne occurrence following JAK inhibitors was 29.6 years, with 37 being the oldest, which means that acne occurred within the age range of adult acne. This is in keeping with the results of Thyssen et al[2] who showed that the incidence of acne decreases with age, with the highest incidence rate per 1000 person-years in 18- to 29-year-olds; 11.2% and 9.2% in both the general population and population with AD, respectively. By contrast, the patients who participated in studies for RA and psoriatic arthritis, were aged >50 years.[7,8] Another point is that patients with AD tend to be treated with systemic immunosuppressants or topical steroid/calcineurin inhibitors that may lead to acne and use comedogenic emollients and ointments more than other populations.

Our study showed that acne occurred in a female-dominant way with a sex ratio of 1.6 women to 1 man. This coincides with the general view that adult acne is found more among women and is sometimes called adult female acne. Moreover, it is intriguing that the body mass index of most of the patients is > 23 kg/m^2, meaning a tendency to be obese. According to a large-size population-based study, there is a mild positive correlation between AD and being overweight or obese.[9] On the other hand, another study presents evidence that in young adults, being overweight and obese is inversely associated with acne.[10] Snast et al argues that the activated adipose tissue might play a protective role in acne. This is directly in contrast to our cases, in which patients with acne were mostly obese. With respect to the pathogenesis of JAK inhibitor-induced

Table II. Summary for morphologic features and severity grading using the Global Acne Grading System

No.	Sex/ Age (yrs)	Subtypes according to the involved area	Subtypes according to inflammation*	Demodex or not (If any, detected area)	GAGS (Mild, moderate, severe, or very severe)	Lesion counts
1	M/33	Whole†	Inflammatory	-	Moderate	Comedone: 0 Papule: 31 Pustule: 3 Nodule: 6 Cyst: 0
2	M/23	Marginal (Forehead, cheek)	Mixed	+ (forehead)	Mild	Comedone: 12 Papule: 9 Pustule: 0 Nodule: 0 Cyst: 0
3	F/30	Marginal (Forehead, cheek, perioral, chin)	Inflammatory	+ (left cheek)	Mild	Comedone: 35 Papule: 16 Pustule: 0 Nodule: 0 Cyst: 0
4	M/21	Whole	Inflammatory	-	Moderate	Comedone: 11 Papule: 19 Pustule: 8 Nodule: 3 Cyst: 0
5	F/37	Marginal (Forehead, cheek)	Inflammatory	-	Mild	Comedone: 5 Papule: 15 Pustule: 3 Nodule: 0 Cyst: 0
6	F/30	Marginal (Cheek, posterior neck)	Inflammatory	-	Mild	Comedone: 0 Papule: 0 Pustule: 3 Nodule: 0 Cyst: 0
7	F/30	Marginal (Forehead, cheek, chin)	Inflammatory	-	Moderate	Comedone: 42 Papule: 13 Pustule: 5 Nodule: 3 Cyst: 0
8	F/33	Marginal (Forehead, cheek)	Noninflammatory	-	Mild	Comedone: 23 Papule: 3 Pustule: 0 Nodule: 0 Cyst: 0

F, Female; *GAGS*, Global Acne Grading System; *M*, male.

*Because there is no specific standard about the dominance of inflammatory or noninflammatory acne when both exist mixed, we assume that if the number of inflammatory lesions is > 11, the patient is categorized into an inflammatory type. If the number is not exceeding 10 and shows similar dominance with the number of noninflammatory lesions, then the patient is categorized into mixed type. Lastly, the rest of them are classified into noninflammatory types.

†Whole involvement includes the forehead, cheek, perinasal, perioral, and chin.

acne in patients with obesity, we consider that the mammalian target of rapamycin complex 1(mTORC1) signaling is activated in adipose tissue and participates in the increased lipid deposition.[11] JAK inhibitors may help in accelerating the activation of mTORC1 in adipose tissue by suppressing the STAT pathway.[12] Acne is one of the mTORC1-driven disease demonstrated in the nutritional signaling of the high-glycemic load.[13]

The detailed mechanism of JAK inhibitor-related acne remains unclear. Acne is usually caused by abnormal follicular keratinization induced by the increased proliferation of keratinocytes, which is partly regulated by the epidermal growth factor.

Theoretically, JAK inhibitors may lead to hyperkeratinization of follicles because JAK-STAT signaling involves the downstream signal transduction of the epidermal growth factor receptors.[14] Another possibility is that an immune slant toward T helper 1 and 17 after T helper 2 signaling inhibition may induce inflammatory lesions, and immune inhibition by JAK-1 inhibitors may play a pivotal role in the change of microbial colonization of the skin, including the colonization of *Demodex folliculorum*.[2] In contrast, there is a study showing the upregulation of JAK1 and JAK3 in acne skin lesions, which indicates that activation of the JAK signaling pathway is potentially related to acne pathophysiology, hinting at the possibility of therapeutic application of JAK inhibitors.[15] There is still marked heterogeneity in the interaction between the JAK pathway and acne eruption.

Acne was mild or moderate in all cases in this study. There was no treatment discontinuation, and the 3 patients taking baricitinib 4 mg improved after a dose reduction to half of the dose. Two of them escalated their dose again because of insufficient efficacy toward the AD lesions and experienced the aggravation of acne again. This suggests that the occurrence of acne might be dose-dependent. Therefore, to address both acne and AD lesions simultaneously, it is important to determine the appropriate dosing for each individual during the course of the disease. In the case of upadacitinib, the starting dose for both patients was 15 mg, the minimum dose for sales approval; hence, a lower dose option was unavailable. Instead, topical antibiotics, benzoyl peroxide, and retinoids were used.

Nadifloxacin cream 1% seemed ineffective in treating acne caused by JAK inhibitors, but adapalene 0.1%/benzoyl peroxide 2.5% gel was relatively encouraging. The existence of *Demodex folliculorum* may be related to the occurrence of acne because demodicosis was found to be significantly higher in the acne vulgaris groups than in the healthy groups. Patient 3 who had *Demodex* mite infestation responded well to not only adapalene 0.1%/benzoyl peroxide 2.5% gel but also metronidazole 0.75% gel, which is highly effective for papules and pustules of rosacea. Although no study has directly compared the efficacy of the 2 agents in patients with acne, 1 study shows that metronidazole gel 2% is an effective and well-tolerated medication for acne vulgaris.[16]

This study has some limitations, including the small number of cases and the gap in the number of cases between baricitinib and upadacitinib that prevents direct comparison. Moreover, we could not assess patient-related factors and the features of acne at different starting doses.

In conclusion, we presented 8 cases of acne occurrence or aggravation following baricitinib and upadactinib use. All cases were mild or moderate and clinically controllable with temporary dose reduction or topical therapies. Considering continuing reports related to acne, it seems definite that JAK inhibitors tend to induce acne, especially in the AD population compared with other populations. Further research to elucidate the mechanism behind JAK inhibitor-associated acne might be needed.

Conflicts of interest

None disclosed.

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