SKIN

BRIEF ARTICLE

Use of Upadacitinib to Treat Atopic Dermatitis Refractory to Dupilumab in Elderly Patients

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ABSTRACT

Atopic dermatitis (AD) is a relapsing and remitting inflammatory skin disease that can significantly impair an individual's quality of life. Elderly-onset AD is increasing in prevalence in developed countries, likely due to aging populations. When AD is refractory to both topical steroids and dupilumab (a systemic IL-4Rα inhibitor), there remains a lack of guidelines for treatment in elderly populations. Herein, we describe the treatment of dupilumab-refractory AD in five elderly patients (≥ 65-years-old) with upadacitinib, a novel JAK inhibitor rarely used in elderly patients due to an elevated risk of systemic side effects. In this report, we found upadacitinib successfully improved these elderly patients' atopic dermatitis, with minimal adverse events. Presently, all five patients continue with this treatment.

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin disease that most commonly presents in childhood with itch, eczematous lesions, and a relapsing and remitting course.[1] Elderly-onset AD is a subgroup of adult-onset AD, with increasing prevalence in industrialized countries, likely due to aging populations.[2]

Topical corticosteroids and moisturizers are first-line treatments of AD.[3] If non-responsive to topical medications, dupilumab, a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 via blockage of IL-4 receptor subunit α (IL-4Rα), may be required.[4,5] For AD refractory to dupilumab, combining dupilumab with methotrexate, azathioprine, or cyclosporine can be an option.[6] However, the elderly population presents as a difficult cohort to treat, as they often have comorbidities preventing use these adjunctive medications.[7] Upadacitinib is a selective Janus kinase 1 inhibitor (JAK1 inhibitor), approved for treatment of moderate-to-severe AD in adults.[8] The efficacy and safety of JAK inhibitors in the elderly patient population have yet to be fully elucidated due to strict inclusion criteria of clinical trials.[9] Herein, we describe the use of upadacitinib in five elderly patients (≥ 65-years-old) with AD refractory to dupilumab.

CASE SERIES

Case 1

A 77-year-old female presented with a one-year history of worsening pruritis, treated with topicals, hydroxyzine, nortriptyline, and gabapentin. A diagnosis of AD was made, dupilumab was initiated. At 6-month follow-

up, body surface area (BSA) affected by eczematous patches was 30% (an increase from pre-dupilumab baseline of 10%). After 1.5 years of dupilumab therapy, improvement was reported, however, full remission was not achieved due to an eczematous patch on her scalp. After two years of treatment with dupilumab, the patient was switched to upadacitinib 15 mg, QD due to eczematous flares on neck, upper extremities, back, and buttocks. Presently, the patient continues treatment with upadacitinib, with improvement. No adverse events (AEs) were reported.

Case 2

A 65-year-old female with no significant past medical history, presented to the clinic with eczematous facial patches. Dupilumab was initiated for a diagnosis of AD. After two years of dupilumab use, the patient experienced a severe flare, with eczematous patches on upper and lower extremities, face, and neck. Despite topicals, flaring continued, so a prednisone taper was initiated, which controlled symptoms. One year later, symptoms flared again. As such, the patient was switched to upadacitinib 15 mg, QD, and one month later her eczema had improved. After 6 months, the patient self-discontinued treatment. Within one-month, severe flare occurred and upadacitinib 15 mg, QD was restarted. Three months after upadacitinib was restarted, skin was clear of eczema. Presently, the patient continues this regimen. No AEs were reported.

Case 3

A 66-year-old male, presented with severe itching, painful skin, and erythematous, scaly, lichenified plaques on the back and extremities for which the patient had failed topicals, intralesional triamcinolone injections, prednisone, and tralokinumab. Dupilumab was prescribed. Four months later, the patient continued to have flares, so dupilumab was discontinued and upadacitinib 15 mg, QD was prescribed. Five weeks later, there was a significant improvement in eczematous symptoms. However, at patient's two-month follow-up visit after upadacitinib initiation, a down trending white blood cell count (2.8 x 10^3/uL), was noted on CBC, so upadacitinib was paused. Two months later, WBC count trended upwards to 3.1 x 10^3/uL, and treatment was resumed. After one year of treatment with upadacitinib, patient reported 95% improvement of symptoms, with no further complications, and continues treatment today.

Case 4

A 69-year-old male with a past medical history of AD and psoriasis, presented to clinic with severe pruritus and a 17-year history of eczema, previously treated with triamcinolone, antihistamines, mycophenolate mofetil, cyclosporine, and dupilumab. At this time, upadacitinib 15 mg, QD was started, with the patient reporting an immediate improvement in eczematous symptoms. However, within the first two months of treatment, the patient ran out of medication, resulting in severe pruritis. Once restarted on upadacitinib, he experienced immediate relief. At six-month follow-up visit, there were no eczematous lesions on exam. No AEs were reported, and presently, the patient continues this medication.

Case 5

An 85-year-old female presented to our clinic with erythematous, scaly papules and plaques affecting over 80% BSA (Eczema Area and Severity Index (EASI) 115), previously having failed treatment with multiple topicals, prednisone, and narrow-

band ultraviolet B (NBUVB) therapy. Dupilumab was prescribed due to severe itching, irritation, and extensive BSA affected. One month later, EASI 50 was documented, however, frequent eczematous flares continued. Two months later, eczematous patches with superficial excoriations on upper extremities, lower extremities, and trunk were prevalent (EASI 45), only slightly improved from prior visit. Dupilumab was discontinued and upadacitinib 15 mg, QD was prescribed. At the three-month follow-up visit, a slight improvement was noted (EASI 40) and the patient reported less pruritus overall. To see if there would be an incremental benefit at a higher dose, upadacitinib was increased to 30 mg QD. Currently, the patient awaits follow-up to assess the benefit of increased upadacitinib, however, no AEs have been reported.

DISCUSSION

This case-series lends evidence to the idea that upadacitinib can be safely considered in elderly patients. Dupilumab and upadacitinib have two distinct mechanisms of action. Dupilumab is a human monoclonal antibody that inhibits IL-4Rα and upadacitinib is a JAK1 inhibitor that prevents the transduction of signals via the JAK/STAT pathway.[6,10] Due to their differing pathways of action, AD refractory to dupilumab may be responsive to upadacitinib. Regarding other systemic treatments, upadacitinib may be preferred, with a comparison study noting an equal or higher incidence of malignancy and major adverse cardiac events per 100 patient-years among patients prescribed methotrexate and cyclosporine, as compared to upadacitinib.[11]

The data here summarizes the treatment of five elderly patients with AD refractory to dupilumab, successfully treated with the JAK inhibitor, Upadacitinib (**Table 1**). Although the information detailed in this study is promising for treatment of AD in this population, it is a small sample size. Additionally, the patients analyzed were relatively healthy, with limited comorbidities, which may be unusual for the elderly population. Future studies with larger cohorts of elderly patients are necessary to determine the safety and efficacy of this treatment among elderly adults.

IRB Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board Mount Sinai School of Medicine (STUDY-23-01086 on 9/22/2023).

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References:

1. Guttman-Yassky E, Irvine AD, Brunner PM, et al. The Role of Janus Kinase Signaling in the Pathology of Atopic Dermatitis [published online ahead of print, 2023 Aug 1]. J Allergy Clin Immunol. 2023;S0091-6749(23)00970-3. doi:10.1016/j.jaci.2023.07.010
2. Tanei R. Clinical Characteristics, Treatments, and Prognosis of Atopic Eczema in the Elderly. J Clin Med. 2015;4(5):979-997. Published 2015 May 18. doi:10.3390/jcm4050979
3. Kanwar AJ. Adult-onset Atopic Dermatitis. Indian J Dermatol. 2016;61(6):662-663. doi:10.4103/0019-5154.193679
4. Megna M, Napolitano M, Patruno C, et al. Systemic Treatment of Adult Atopic Dermatitis: A Review. Dermatol Ther (Heidelb). 2017;7(1):1-23. doi:10.1007/s13555-016-0170-1
5. Gade A, Ghani H, Rubenstein R. Dupilumab. In: StatPearls. Treasure Island (FL): StatPearls Publishing; January 2, 2023.
6. Narla S, Silverberg JI, Simpson EL. Management of inadequate response and adverse effects to dupilumab in atopic dermatitis. J Am Acad Dermatol. 2022;86(3):628-636. doi:10.1016/j.jaad.2021.06.017
7. Tanei R. Atopic Dermatitis in Older Adults: A Review of Treatment Options. Drugs Aging.

2020;37(3):149-160. doi:10.1007/s40266-020-00750-5
8. Navarro-Triviño F, Alcantara-Luna S, Domínguez-Cruz J, et al. Upadacitinib for moderate to severe atopic dermatitis. Immunotherapy. 2023;15(11):799-808. doi:10.2217/imt-2023-0037
9. Piscazzi F, Gargiulo L, Ibba L, et al. Upadacitinib for the treatment of atopic dermatitis in the elderly: an Italian case series of seven patients. J Dermatolog Treat. 2023;34(1):2245510. doi:10.1080/09546634.2023.2245510
10. Padda IS, Bhatt R, Parmar M. Upadacitinib. In: StatPearls. Treasure Island (FL): StatPearls Publishing; June 3, 2023.
11. Daniele S, Bunick C. JAK Inhibitor Safety Compared to Traditional Systemic Immunosuppressive Therapies. J Drugs Dermatol. 2022;21(12):1298-1303. doi:10.36849/JDD.7187

Table 1. Case-series of five elderly patients prescribed upadacitinib for dupilumab-refractory AD

#	Age[1]	Total days on dupilumab	Reason for Switch	JAK-inhibitor prescribed	Days on JAKi[2]	Status	Adverse Events
1	79	531	Recurrent flares	Upadacitinib 15 mg, QD	374	Improved	No
2	68	1132	Recurrent flares	Upadacitinib 15 mg, QD	952	Improved	No
3	66	117	Recurrent flares	Upadacitinib 15 mg, QD	499	Improved	Down trending WBC[4]
4	69	n/a[3]	Recurrent flares	Upadacitinib 15 mg, QD	269	Improved	No
5	85	113	Recurrent flares	Upadacitinib 30 mg, QD	209	Improved	No

Table I: This table displays the demographics of each patient in this case series who failed dupilumab and was started on upadacitinib for treatment of atopic dermatitis.
1 – Age at start of upadacitinib treatment.
2 – Total days on JAK inhibitor was calculated from start date of JAK inhibitor to date of last documented follow-up.
3 – Days on Dupilumab is unknown as this patient was prescribed dupilumab by an outside dermatologist.
4 – This patient required upadacitinib to be briefly paused due to down trending WBCs. After a subsequent increase in WBC count, the patient was restarted on upadacitinib and currently continuing with treatment with no further adverse events.
Abbreviations: *JAKi*, Janus kinase inhibitor; *QD*, daily; *WBC*, white blood cells.