Patient Preference and Adherence Dovepress

Open Access Full Text Article

CASE REPORT

Amenorrhea in an Adolescent Female as a Rare Adverse Event of Upadacitinib Treatment for Atopic Dermatitis

Yan Teng, Yi Tang, Yibin Fan, Xiaohua Tao*, Yang Ding*

Center for Plastic & Reconstructive Surgery, Department of Dermatology, Zhejiang Provincial People's Hospital, Affiliated People's Hospital of Hangzhou Medical College, Hangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yang Ding; Xiaohua Tao, Center for Plastic & Reconstructive Surgery, Department of Dermatology, Zhejiang Provincial People's Hospital, Affiliated People's Hospital of Hangzhou Medical College, Hangzhou, 310014, People's Republic of China, Email dingyang@hmc.edu.cn; taoxiaohua@hmc.edu.cn

Abstract: Atopic dermatitis (AD) is a common chronic inflammatory cutaneous disease. Upadacitinib, a selective JAK-1 inhibitor, has been approved as a systemic medication for moderate-to-severe AD in patients aged ≥12 years. Although previous studies have examined the safety profile of upadacitinib, this is the first report to describe a potential association between amenorrhea and upadacitinib or other JAK inhibitors. Herein, we report a rare adverse event of amenorrhea in an adolescent female patient who was treated with upadacitinib for AD. This case report expands the range of adverse events potentially associated with upadacitinib therapy.

Keywords: amenorrhea, upadacitinib, atopic dermatitis, JAK inhibitors, adverse event

Introduction

Atopic dermatitis (AD) is a common chronically relapsing inflammatory skin disorder resulting from the dysregulation of the type 2 immune response. The clinical manifestations of AD vary according to the onset age and disease severity. Conventional treatment often exhibits poor efficacy and leads to a high recurrence. Oral Janus kinase (JAK) inhibitors are a new and emerging treatment option for AD. Among them, upadacitinib is an oral JAK inhibitor with greater inhibitory potency against JAK-1 than JAK-2, JAK-3, and tyrosine kinase 2. Upadacitinib has been approved to treat moderate-to-severe AD in adult and adolescent (≥12 years of age) patients. The most frequently reported treatment-emergent adverse events in patients with AD include acne, upper respiratory tract infection, nasopharyngitis, and headache.[1,2] However, drug-related amenorrhea has rarely been observed in this patient population. Herein, we report a case of a Chinese adolescent female patient with AD who experienced amenorrhea due to the administration of oral upadacitinib and subsequently discontinued the medication.

Case Presentation

A 15-year-old female presented with erythematous patches on the facial and periareolar regions for over 10 years. In August 2023, the patient visited our dermatology clinic with symmetrically generalized lichen-like red patches on the face and the flexion surfaces of the limbs. Additionally, the patient complained of intense pruritus that severely hampered her quality of life and even caused sleeping disturbances. The patient had a history of seasonal allergic dermatitis and a family history of allergic rhinoconjunctivitis in her mother. Furthermore, generalized xerosis of the patient's skin was observed. Based on the typical clinical presentation and severity assessment, the patient was diagnosed with severe AD (Eczema Area and Severity Index (EASI): 30.9; Peak Pruritus Numeric Rating Scale score (PP-NRS: 9). Conventional systemic therapeutic agents, including systemic corticosteroid therapy and immunosuppressive agents, were refused owing to concerns about the side effects of long-

Received: 27 June 2024
Accepted: 8 November 2024
Published: 14 November 2024

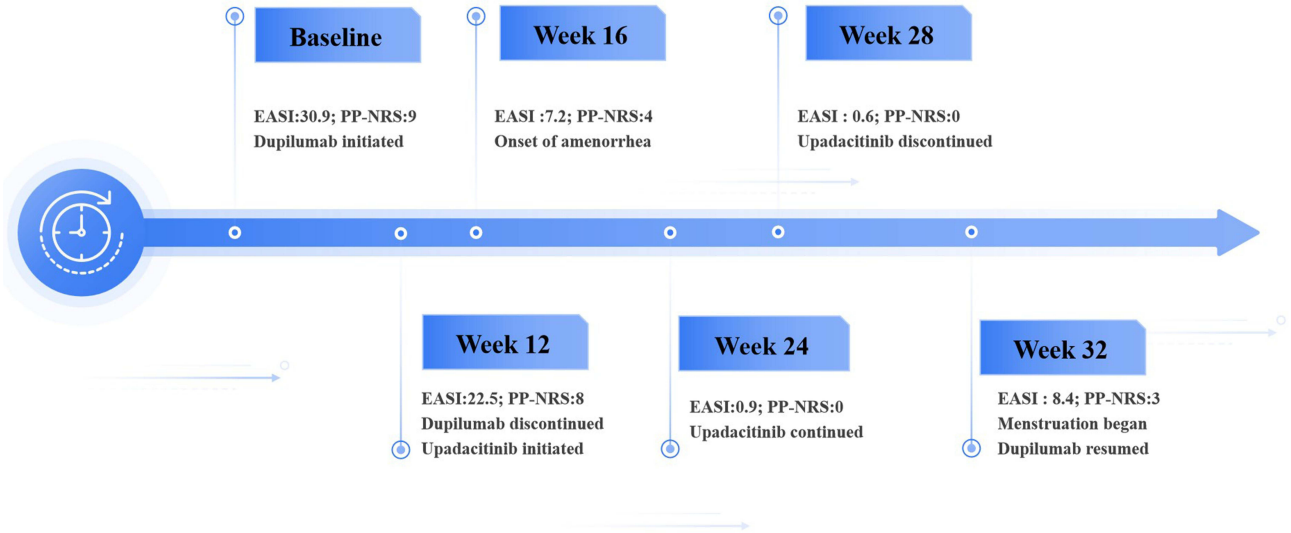

Figure 1 Clinical course of the patient with atopic dermatitis (EASI: Eczema Area and Severity Index; PP-NRS: Peak Pruritus Numeric Rating Scale).

term use. Therefore, treatment with dupilumab, a biologic agent, was initiated in the patient. However, the treatment effect was found unsatisfactory following a 12-week treatment cycle. The patient still complained of intense pruritus, and the facial rash continued to expand (EASI: 22.5; PP-NRS score: 8). Given the disease progression and the urgent need for treatment, treatment with oral upadacitinib (a selective JAK-1 inhibitor) was initiated at 15 mg/day after blood routine examination, biochemistry analysis, coagulation function test, and chest high resolution CT to rule out severe infections, coagulation dysfunction, hepatic failure, renal disorder, and tuberculosis. After 12 weeks of upadacitinib treatment, the patient's skin lesions and pruritus were notably relieved (EASI: 0.9; PP-NRS score: 0). However, 4 weeks after commencing upadacitinib therapy (EASI: 7.2; PP-NRS score: 4), the patient became amenorrheic. The patient had menarche at 13 years of age and experienced regular menses at intervals of 28–35 days. Considering that the patient had no prior episodes of menstrual disorders and reported regular menses, an association with upadacitinib therapy was highly suspected. The patient remained amenorrheic after 16 weeks of continuous upadacitinib therapy (EASI: 0.6; PP-NRS score: 0). Thus, the patient decided to discontinue the medication. At 4 weeks after medication discontinuation (EASI: 8.4; PP-NRS score: 3), the patient's menstruation resumed and a regular menses cycle was restored. However, dupilumab therapy was restarted because of AD recurrence, and the patient is being followed up. A summary of the clinical course of the patient is illustrated in Figure 1.

Discussion

AD is a chronic, recurrent, inflammatory skin disease. This disorder is considered a systemic condition because patients with AD are often complicated with allergic rhinitis, asthma, and other atopic diseases. AD can be classified into four stages based on age: infantile (0–2 years), childhood (>2–12 years), adolescent and adult (>12–60 years), and older adult (>60 years) AD.[3,4] Adolescent AD has a high prevalence worldwide, with nearly one-third of adolescents experiencing moderate-to-severe AD.[5,6] This cutaneous disease severely affects the quality of life of affected adolescents, leading to a considerable psychological burden.[7,8] Due to the insufficient safety and effectiveness provided by traditional systemic therapies (such as systemic corticosteroid therapy and immunosuppressive agents), moderate-to-severe AD in adolescents is often ineffectively controlled. Although dupilumab is used as a first-line systemic medication for treating moderate-to-severe AD in adolescents, its slow onset, limited clinical efficacy, and limitations in injection methods have restricted its clinical application in certain situations.[9] In our case, the patient did not respond well to dupilumab; therefore, therapy was initiated with upadacitinib, the only selective JAK-1 inhibitor currently approved in China for moderate-to-severe AD in adolescents.

Upadacitinib was approved by the US Food and Drug Administration in 2022 to treat moderate-to-severe AD. This oral drug is a highly selective JAK-1 inhibitor that modulates varied key cytokine signaling pathways involved in AD, such as the IL-4, IL-13, and IL-31 pathways. Upadacitinib has elevated inhibitory activity and selectivity for JAK-1 and extremely low inhibitory activity against JAK-2-/JAK-3-mediated cytokines. This unique pharmacological feature effectively avoids adverse reactions associated

with JAK-2/JAK-3 inhibitory activity, thus providing patients with a safer treatment option. Prior studies have examined the safety profile of upadacitinib at doses of 15 mg and 30 mg for treating moderate-to-severe AD in adolescents and adults, and the results have demonstrated that the two doses are well tolerated. Moreover, acne, upper respiratory tract infection, and nasopharyngitis are the most prevalent drug-related adverse events, along with heightened creatine phosphokinase levels and herpes zoster infections also being reported as common adverse events associated with upadacitinib treatment.[10–12] However, most adverse events were mild and manageable, with only a few patients failing to achieve successful treatment termination. In the case of amenorrhea, our patient had no prior history of menstrual disorders. However, menstruation ceased after initiating upadacitinib administration and resumed upon its discontinuation. Therefore, an association between upadacitinib treatment and amenorrhea was strongly suggested.

Drug-induced or therapeutic amenorrhea is a type of secondary amenorrhea, often resulting from drugs in the uterus or mental, neurological, sex hormone, and other neuroendocrine functions that can affect the hypothalamic–pituitary–ovarian (HPO) axis. Drugs can directly or indirectly interfere with the normal neuroendocrine function of the HPO axis via neurotransmitters and receptors, causing diminished gonadotropin secretion and elevated prolactin levels and consequently leading to amenorrhea. Common drugs associated with amenorrhea incidence include antipsychotic drugs, anti-anxiety medications, sedative sleep aids, anti-epileptic and anticonvulsant drugs, sex hormone drugs (such as oral contraceptives or contraceptive devices using progesterone implants), histamine and histamine H1- and H2-receptor antagonists, chemotherapy drugs, selective progesterone receptor modulators (eg, mifepristone), weight loss drugs, antihypertensive drugs, and immunosuppressants.[13] Drug-induced amenorrhea is usually reversible, with menstruation typically being restored naturally after medication discontinuation.[14] To our knowledge, no case reports have described amenorrhea associated with upadacitinib or other JAK inhibitors like tofacitinib or baricitinib,[15,16] making this a rare drug-related adverse event. The underlying mechanisms remain under investigation. It is hypothesized that the JAK-STAT pathway may be involved in the physiologic signaling action at the ovarian follicle level, leading to this idiopathic reaction.

Upadacitinib treatment-induced amenorrhea is a potential but rare drug-related adverse event. However, several limitations of this case should be highlighted. Firstly, this was a single case so the findings are not generalizable. The relationship between Upadacitinib treatment and amenorrhea is not clearly established and could be coincidental. Furthermore, the case does not appear to include a thorough endocrinological work-up (eg, hormonal levels such as FSH, LH, or prolactin) to fully investigate other possible causes of amenorrhea, that limits the understanding of the exact mechanism. The endocrinological studies investigating the exact mechanisms are required in the future. Additionally, long-term follow-up is planned, which is necessary to address how this case impacts future treatment strategies for this patient and others.

Conclusion

This case report presents an adolescent female patient with AD who developed amenorrhea, which may be induced by the Upadacitinib, thereby broadening the spectrum of potential adverse events associated with therapies using JAK inhibitors. Unfortunately, the mechanism underlying the occurrence of amenorrhea has not been clarified endocrinologically. Therefore, endocrinological studies are needed in the future.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Statement

The publication of images was included in the patient's consent for publication of the case. The Hospital Ethics Committees of the Affiliated People's Hospital of Hangzhou Medical College approved publishing the case details.

Consent Statement

The patient and her parents in this manuscript has given written informed consent to the publication of his case details.

Acknowledgments

We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

Funding

The present study was supported by Natural Science Foundation of China (82073453), Zhejiang Medicine and Health Research Fund Project (2024KY750), Zhejiang Medicine and Health Research Fund Project (2024KY650), Zhejiang Medical and Health Science and Technology Project Youth Creative Talents Support Program (2022RC097).

Disclosure

The authors declare that they have no conflicts of interest and no payment for expert testimony for this work.

References

1. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled Phase 3 trials. *Lancet*. 2021;397(10290):2151–2168. doi:10.1016/S0140-6736(21)00588-2
2. 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
3. Tanei R, Katsuoka K. Clinical analyses of atopic dermatitis in the aged. *J Dermatol*. 2008;35(9):562–569. doi:10.1111/j.1346-8138.2008.00524.x
4. Teng Y, Zhong H, Yang X, et al. Current and emerging therapies for atopic dermatitis in the elderly. *Clin Interv Aging*. 2023;18:1641–1652. doi:10.2147/CIA.S426044
5. Kowalska-Olędzka E, Czarnecka M, Baran A. Epidemiology of atopic dermatitis in Europe. *J Drug Assess*. 2019;8(1):126–128. doi:10.1080/21556660.2019.1619570
6. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156(1):44–56. doi:10.1001/jamadermatol.2019.3336
7. Möhrenschlager M, Demolli P, Schmidt V. How does atopic dermatitis in childhood and adolescence affect educational success? *J Eur Acad Dermatol Venereol*. 2021;35(9):1746. doi:10.1111/jdv.17518
8. Pálsson K, Slagor RM, Flachs EM, et al. Childhood atopic dermatitis is associated with a decreased chance of completing education later in life: a register-based cohort study. *J Eur Acad Dermatol Venereol*. 2021;35(9):1849–1858. doi:10.1111/jdv.17346
9. Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2021;157(9):1047–1055. doi:10.1001/jamadermatol.2021.3023
10. Simpson EL, Papp KA, Blauvelt A, et al. Efficacy and safety of upadacitinib in patients with moderate to severe atopic dermatitis: analysis of follow-up data from the measure up 1 and measure up 2 randomized clinical trials. *JAMA Dermatol*. 2022;158(4):404–413. doi:10.1001/jamadermatol.2022.0029
11. Hagino T, Yoshida M, Hamada R, et al. Effectiveness of switching from baricitinib 4 mg to upadacitinib 30 mg in patients with moderate-to-severe atopic dermatitis: a real-world clinical practice in Japan. *J DermatolTreat*. 2023;34(1):2276043. doi:10.1080/09546634.2023.2276043
12. Hagino T, Saeki H, Fujimoto E, et al. Long-term effectiveness and safety of upadacitinib for Japanese patients with moderate-to-severe atopic dermatitis: a real-world clinical study. *J DermatolTreat*. 2024;35(1):2344591. doi:10.1080/09546634.2024.2344591
13. Fanouriakis A, Pamfil C, Sidiropoulos P, et al. Cyclophosphamide in combination with glucocorticoids for severe neuropsychiatric systemic lupus erythematosus: a retrospective, observational two-centre study. *Lupus*. 2016;25(6):627–636. doi:10.1177/0961203315622821
14. Lania A, Gianotti L, Gagliardi I, et al. Functional hypothalamic and drug-induced amenorrhea: an overview. *J Endocrinol Invest*. 2019;42(9):1001–1010. doi:10.1007/s40618-019-01013-w
15. Brunner HI, Akikusa JD, Al-Abadi E, et al. Safety and efficacy of tofacitinib for the treatment of patients with juvenile idiopathic arthritis: preliminary results of an open-label, long-term extension study. *Ann Rheum Dis*. 2024;83(11):1561–1571. doi:10.1136/ard-2023-225094
16. Bieber T, Katoh N, Simpson EL, et al. Safety of baricitinib for the treatment of atopic dermatitis over a median of 1.6 years and up to 3.9 years of treatment: an updated integrated analysis of eight clinical trials. *J DermatolTreat*. 2023;34(1):2161812. doi:10.1080/09546634.2022.2161812