Sudden improvement of alopecia universalis and psoriatic arthritis while receiving upadacitinib: a case-based review

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Summary

Alopecia universalis (AU), an advanced form of alopecia areata (AA), is a condition characterized by the complete loss of hair over the entire skin surface. Recent progress has significantly enhanced our understanding of the pathogenesis of AU. In particular, interferon-γ (IFN-γ) and interleukin (IL)-15 seem to play a pivotal role in the pathogenesis of the disease. Nonetheless, a variety of medications has been used to treat the disease with frequently inconsistent results. Given the broad modulation of the immune system and inhibition of key molecules, including IFN-γ and IL-15, oral janus kinase (JAK) inhibitors represent a treatment option for moderate to severe cases of AA, as demonstrated in case reports supporting their efficacy and tolerability. We present the case of a patient suffering from psoriatic arthritis and AU who experienced a sudden improvement in peripheral arthritis and AU while receiving JAK1 selective treatment with upadacitinib. So far, there are very limited case reports of successful upadacitinib treatment for patients with AA, mostly in patients also suffering from atopic dermatitis. Thus, we provide evidence for the efficacy of upadacitinib in managing AU in adults, as well as in the context of inflammatory arthritis such as psoriatic arthritis.

Introduction

Alopecia universalis (AU) is a condition characterized by the complete loss of hair over the entire skin surface. It is an advanced form of alopecia areata (AA), a chronic, immune-mediated disorder that targets anagen hair follicles and causes nonscarring hair loss, with a significant impact on quality of life (1-4). AA has a prevalence of 1 in 1000 and a lifetime incidence of 2% worldwide.

Until now, a variety of medications has been used to treat this disease that may represent a significant psychological and social burden for affected patients. Limited and patchy cases of AA are typically treated with topical and intralesional corticosteroids, as well as contact immunotherapy. However, when dealing with more severe forms of AA, like AU, the treatment approach involves the use of systemic steroids and other immunosuppressant medications, often with inconsistent results (5, 6).

Recent advancements have significantly enhanced our understanding of the pathogenesis of AA. AA is postulated to be due to loss of immune privilege of the hair follicle, autoimmune destruction, and up-regulation of inflammatory pathways. T-lymphocyte infiltration can be found around the hair follicle, while several key pro-inflammatory molecules, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-15, and interferon (IFN)-γ seem to play pivotal roles. A deeper comprehension of AU has led to the development of targeted therapies such as janus kinase (JAK) inhibitors, developed to specifically target key downstream molecules of pro-inflammatory cytokines, including IFN-γ and IL-15. Indeed, numerous studies and case series have provided compelling evidence supporting the efficacy and tolerability of oral JAK inhibitors as treatment options for moderate to severe cases of AA (7-9). In recognition of these promising findings, baricitinib has recently obtained approval from the U.S. Food and Drug Administration (FDA) for the treatment of severe AA in adults. This approval further validates the potential of JAK inhibitors as a breakthrough therapy for individuals with this challenging condition. Nonetheless, response to baricitinib may be incomplete or lacking in some patients, probably due to the complex immunopathology of AA. Herein, we present a patient with AU and psoriatic arthritis (PsA) who failed baricitinib and was successfully treated with upadacitinib. A literature review was performed to investigate other cases of alopecia treated with this drug.

Methods

Following our case presentation, we conducted a literature search in MEDLINE/PubMed using the terms #upadacitinib and #alopecia. Articles were included in the review if they met the following criteria: i) described adult patients with a diagnosis of alopecia treated with upadacitinib; ii) available patient data; iii) written in English. The flowchart for the elimination of articles is depicted in Figure 1. The combined MEDLINE/PubMed search resulted in 25 records. After the removal of 8 reviews, we screened the remaining 17 records and excluded 3 records based on their titles and abstracts because their topics were not related to cases of alopecia treated with upadacitinib. Subsequently, an additional 3 records were removed as they involved pediatric patients. Ultimately, 11 articles were included in the review.

Case Report

We present the case of a patient with PsA and AU who experienced a sudden improvement in peripheral arthritis and AU while receiving upadacitinib.

A 36-year-old female patient was referred to the Rheumatology Department of Medicine and Surgery at the University of Perugia in September 2022. She had a clinical history of inflammatory arthritis that developed in 2015, primarily affecting large joints and metacarpophalangeal joints.

At the time of diagnosis, the patient tested negative for anti-citrullinated protein antibodies and rheumatoid factor, but her antinuclear antibodies were positive at a titer of 1:160 with a homogeneous pattern. Anti-extractable nuclear antigens were negative. She was initially diagnosed with seronegative rheumatoid arthritis and started on methotrexate at a dosage of up to 15 mg/week. However, due to gastrointestinal intolerance, methotrexate was discontinued. Subsequently, in 2016, she began taking leflunomide at a dosage of 20 mg/day. Noteworthy, she experienced the development of AA, and for this reason, this drug was also discontinued after 6 months, with partial improvement. Over the following years, the patient received treatment with sulfasalazine, which was discontinued due to hypertension, followed by abatacept (125 mg/week), golimumab (50 mg/month), and baricitinib (4 mg/day), all of which were administered for at least 3 months but discontinued due to lack of efficacy. Noteworthy, while receiving baricitinib, the patient was still suffering from AA, and this condition did not improve.

In 2018, she received treatment with infliximab (5 mg/kg) in combination with low-dose methylprednisolone and hydroxychloroquine (200 mg/day), which provided partial benefit for her joint manifestations. Thus, to achieve remission, low-dose methotrexate (7.5 mg/week) was reintroduced in January 2020 and later discontinued after 6 months due to a new worsening of AA. Moreover, despite stopping methotrexate therapy, her skin condition progressively worsened, leading to the development of AU. In October 2020, infliximab treatment was discontinued due to suspicion of drug-induced alopecia associated with anti-TNF therapy. The patient underwent systemic and topical steroid therapies, as well as cyclosporine A at a dosage of 3 mg/kg, but no improvement in her dermatological condition was observed. In January 2021, rituximab therapy was initiated during a flare of arthritis; however, the patient did not receive a second cycle due to flushing after infusion and lack of efficacy. In June 2021, a skin biopsy confirmed the presence of "several hair follicles surrounded by an inflammatory infiltrate composed of CD4+ and CD8+ T lymphocytes". At the time of presentation in our outpatient clinic in September 2022, further questioning revealed a family history of psoriasis, specifically in her maternal uncles. Following the reassessment of the patient's medical history, with the evidence of arthritis involving primarily large joints (knees and elbows), the patient was diagnosed with PsA meeting the CASPAR classification criteria. Considering the presence of active inflammatory joint disease with elevated C-reactive protein (CRP), infliximab therapy was reintroduced due to the previously observed partial benefit on arthritis. However, the treatment was subsequently suspended due to inefficacy. Indeed, the patient demonstrated persistent arthritis at the hands, knees, and elbows based on clinical and ultrasound examination findings, along with consistently elevated CRP levels (1.2 mg/dL). In March 2023, a decision was made to start treatment with upadacitinib at a daily dosage of 15 mg. Remarkably, we witnessed a sudden resurgence of hair growth accompanied by a substantial improvement of arthritis after 3 months of therapy (Figures 2 and 3). The treatment is still ongoing and, after 4 months, no adverse reactions have occurred.

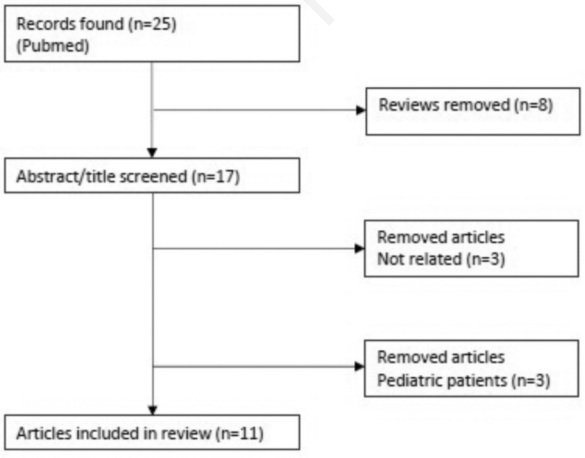

Figure 1. Flowchart showing the elimination process of articles selected for the review.

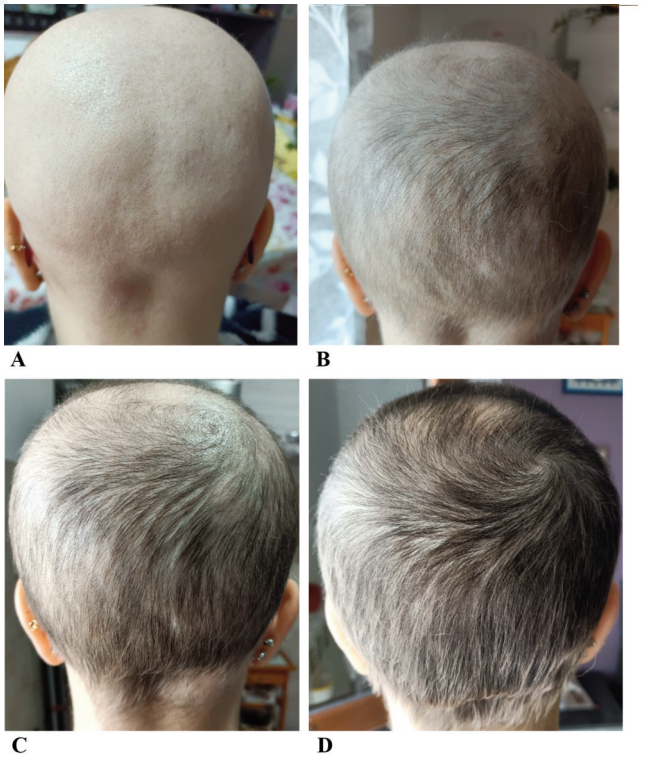

Figure 2. A) Hair at baseline; **B**) hair growth after 6 weeks of treatment with upadacitinib; **C**) hair growth after 2 months; **D**) hair growth after 3 months.

Discussion

The development of AA involves a complex pathway influenced by the interplay of cytokines and their receptors, which are regulated through JAK-signal transducer and activator of transcription (STAT) signaling (10). In AA, the normal immune privilege of the anagen hair follicle is disrupted and key pro-inflammatory molecules including tumor necrosis factor-α, IL-1, IL-15, and IFN-γ seem to play pivotal roles. Studies have demonstrated that the expression of IFN-γ is notably elevated in the lesional skin of AA patients. This cytokine is believed to contribute to the breakdown of immune privilege by upregulating the expression of major histocompatibility complex class I and II molecules in the hair follicles (11-14). The IL-15 pathway is also found to be upregulated in AA (15). Notably, IFN-γ and IL-15 signals are largely mediated by JAK1, specifically, IFN-γ signals through JAK1/2 while IL-15 signals *via* JAK1/3. Both of these pathways can be targeted by JAK inhibitors.

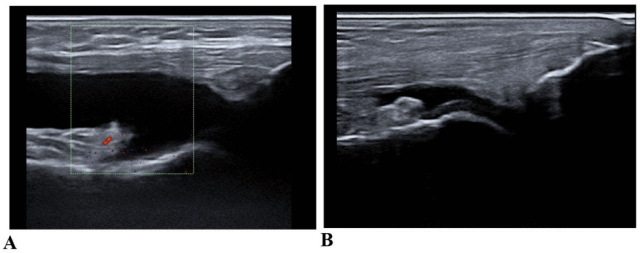

Figure 3. A) Ultrasound evaluation of knee synovitis with severe joint effusion, moderate synovial hypertrophy and positive power-Doppler observed at baseline; B) substantial improvement of synovitis 3 months after starting upadacitinib.

Baricitinib, an oral JAK1/JAK2 inhibitor, recently received approval from the U.S. FDA for the treatment of adults with severe AA based on the positive results from two studies, BRAVE-AA1 and BRAVE-AA2 (7, 16). Our patient had previously attempted a short course of treatment with baricitinib, which, however, demonstrated limited effectiveness in managing her joint disease and in improving alopecia. Upon receiving the diagnosis of PsA, treatment with upadacitinib was started in our patient, achieving a rapid improvement of both arthritis symptoms and alopecia.

The reason for baricitinib failure while experiencing a response to upadacitinib could be explained by the different patterns of selectivity of these JAK inhibitors and by the degrees of pharmacodynamic inhibition of specific molecules (17, 18). Upadacitinib is an approved drug for the treatment of PsA, a setting of patients in which baricinitib was never tested. Baricitinib showed preliminary promising results in a phase 2b trial on patients with psoriasis (19); however, its efficacy was lower compared to other approved drugs such as tofacitinib while data on its efficacy in PsA are lacking (20). Considering the *in vitro* inhibition of cytokine responses in whole blood and the clinical pharmacokinetics of baricitinib and upadacitinib, these agents appear to have a similar effect on IFNγ/pSTAT1 pathways (17, 18). However, baricitinib appears to inhibit JAK1/3 signaling to a lesser extent than upadacitinib with higher levels of IC_{50} in CD4+ T cells and NK cells (18). An increased time above IC_{50} for upadacitinib, compared with baricitinib was also observed, resulting in a greater overall inhibition of STAT signaling during the 24-hour dosing interval for JAK1/3-dependent cytokines (17, 18). This may translate into a greater inhibition of detrimental IL-15-mediated pathways observed in AU. Thus, it is likely that selective targeting of JAK1 may be most beneficial for patients with AA.

To date, data on the efficacy and safety of upadacitinib in adults with AU is based on three case reports (21-23). All patients showed a complete clinical response, and one of them also showed improvement in Crohn's disease.

Table 1. Previous studies about patients with alopecia treated with upadacitinib.

	n. of patients	Skin disease	Concomitant diseases	Previous systemic medication	Outcome	Timing
Johnston *et al.* (21)	1	AU	Crohn's disease	sGC, MTX, adalimumab, ustekinumab	Solved	7 months
Gori *et al.* (22)	1	AU		sGC, MTX, CsA	Solved	4 months
Youssef *et al.* (23)	1	AU	Hypertension, hyperlipidemia, CAD		Solved	4 months
Asfour *et al.* (24)	1	AA	AD	Baricitinib	Improved	1 month
Cantelli *et al.* (25)	1	AA	AD	sGC, CsA, dupilumab	Improved	3 months
Gambardella *et al.* (26)	2	AA	1. AD 2. AD, asthma	1. CsA, dupilumab 2. CsA, AZA, dupilumab	1. Improved 2. Solved	4 months
Novielli *et al.* (27)	1	AA	AD, Crohn's disease	CsA, AZA, dupilumab, infliximab, adalimumab, ustekinumab	Solved	9 months
Walls *et al.* (28)	1	AA	AD	sGC, MTX, CsA, dupilumab	Solved	4 months
Johnston *et al.* (29)	3	AA	1. - 2. AD 3. AD and liver cirrhosis	1. sGC, MTX 2. - 3. sGC	Solved	3-8 months
Flora *et al.* (30)	25	AA	AD (n=4)		Solved (n=25) (median SALT score reduction of 45)	6 months
Chiricozzi *et al.* (31)	19	AA	AD (n=19)	CsA (n=12), sGC (n=4), AZA (n=1), dupilumab (n=8)	52.9% of patients improved (median SALT score reduction of 62.5±40.9)	4-10 months

AU, alopecia universalis; AA, alopecia areata; AD, atopic dermatitis; CAD, coronary artery disease; sGC, systemic glucocorticoids; MTX, methotrexate; CsA, cyclosporine A; AZA, azathioprine; SALT, severity of alopecia tool.

Six case reports involving nine patients with AA have also demonstrated the efficacy of treatment with upadacitinib (24-29). Among these patients, seven had concurrent AA and atopic dermatitis (AD), which also showed good response to treatment. An additional case featured the co-occurrence of AA, AD, and Crohn's disease, the latter of which also significantly improved. Similar to our clinical case, most of these patients were unresponsive or intolerant to conventional treatments such as topical or oral glucocorticoids, methotrexate, cyclosporine A, or dupilumab.

Flora *et al*. conducted a retrospective cohort study of 25 individuals with AA treated with upadacitinib monotherapy (30). All patients experienced rapid regrowth of hair and upadacitinib exhibited a good safety profile throughout the course of treatment.

Furthermore, a recent multicenter retrospective study suggested a favorable effect of upadacitinib on AA presenting in the course of AD (31). Most of the 19 patients evaluated experienced a beneficial effect of this drug on their skin condition, with an overall response rate of 52.9%. The articles incorporated in this review have been summarized in Table 1.

Conclusions

In conclusion, we described the first case of a PsA patient with difficult-to-treat AU who experienced remarkable hair regrowth with upadacitinib therapy. This may constitute a promising therapeutic option in inflammatory arthritis with alopecia, especially in those patients in whom standard treatments are ineffective. Besides providing further evidence supporting the use of upadacitinib in managing AU and AA in adults, the efficacy and safety of this drug for the treatment of alopecia should be further defined by randomized controlled trials.

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