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CASE REPORT

Alopecia Universalis in an Adolescent Successfully Treated with Upadacitinib—A Case Report and Review of the Literature on the Use of JAK Inhibitors in Pediatric Alopecia Areata

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ABSTRACT

Alopecia areata (AA) is a cell-mediated autoimmune disease in which a cytotoxic T-cell response against hair follicles occurs. AA has been demonstrated to frequently co-exist with atopic dermatitis (AD), and the coincidence of atopy predisposes to a more severe course of the disease. To date, therapeutic options in AA, especially in the pediatric population, are mainly limited to corticosteroids, irritants, sensitizers, and immunosuppressive agents. Recently, innovative therapies have emerged, among which Janus kinase (JAK) inhibitors, effective in both AD and AA, appear to be the most promising. Here, a 14-year-old girl with alopecia universalis (AU) and mild AD is demonstrated, who was successfully treated with a selective JAK1 inhibitor, upadacitinib, which has been approved for the treatment of AD in adults and children aged 12 years and older. Resolution of eczema and complete hair regrowth was achieved after 3 months of therapy. Apart from transient mild leukopenia at weeks 4 and 8, no adverse events were noted. Data in the literature on the efficacy and safety of JAK inhibitors in the treatment of AA in the pediatric population is based on single case reports and case series. So far, topical tofacitinib and ruxolitinib, as well as systemic tofacitinib, ruxolitinib, and baricitinib have been used off-label in this indication in children. Upadacitinib is another effective treatment option with a good benefit–risk ratio for patients with AA, including cases coexisting with AD.

Keywords: Upadacitinib; Alopecia areata; Atopic dermatitis; JAK inhibitors; JAK-STAT

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Key Summary Points

The JAK/STAT signaling pathway plays an important role in promoting the inflammatory response around hair follicles and represents a potential therapeutic target in patients affected with alopecia areata (AA)

We present a 14-year-old girl with alopecia universalis (AU) coexisting with mild atopic dermatitis (AD), who showed good response to upadacitinib, a selective JAK1 inhibitor that has been approved for the treatment of AD in patients aged 12 years or older

The literature search revealed several case reports and case series of the successful off-label use of systemic (tofacitinib, baricitinib, and ruxolitinib) and topical (tofacitinib and ruxolitinib) JAK inhibitors in pediatric patients with AA

Upadacitinib seems to be another effective treatment option for patients with AA, including cases coexisting with AD

INTRODUCTION

Alopecia areata (AA) is a cell-mediated autoimmune disease in which a cytotoxic T-cell response against hair follicles occurs. This process results in the shortening of the anagen phase of the hair growth cycle, acceleration of the resting phase, and subsequently, loss of hair [1].

It is estimated that the lifetime expectancy of developing AA in the general population is approximately 2% [2]. Although the disease can develop in patients of any age, it usually starts in those under 40 years. In the pediatric population, AA is classified as the third most common reason for specialist consultation [3]. AA has been demonstrated to frequently co-exist with atopic dermatitis (AD), and the coincidence of atopy predisposes to a more severe course of the disease. AA and AD share several similarities in the pathogenetic pathways, including overexpression of T helper 2 cytokines (Th2), interleukin (IL)-4 and IL-13, altered expression or loss-of-function mutation of atopy-related genes (such as filaggrin), and finally, elevated serum levels of immunoglobulin E (IgE) [4–6]. Although AA is not a life-threatening disease, it carries a significant psychosocial burden. The disease is associated with significantly reduced quality of life and increased risk of depression, particularly among adolescents [7].

To date, therapeutic options of AA, especially in the pediatric population, have been mainly limited to corticosteroids, irritants, sensitizers, and immunosuppressive agents. Recently, innovative therapies have emerged, among which Janus kinase (JAK) inhibitors, effective in both AD and AA, appear to be the most promising. Here, a case of the 14-year-old girl with alopecia universalis (AU) and mild AD is presented, who was successfully treated with a selective JAK1 inhibitor, upadacitinib.

The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the patient and her parents for participation in the study and publication of the article, including publication of clinical photographs.

CASE REPORT

A 14-year-old Caucasian girl was referred to the Department of Dermatology in Rzeszów (Poland) with AU. The first episode of hair loss occurred 16 months before admission to the hospital. At that time, there was a single focus of alopecia in the right retroauricular region. The patient was initially treated with topical 5% minoxidil and mometasone furoate. No improvement was observed, and the disease started to progress. One year prior to referral, the girl experienced a complete loss of scalp hair and partial loss of eyebrows and eyelashes. For 11 months she was treated with immunotherapy with diphenylcyclopropenone (DCP) in increasing concentrations. In addition, narrow

band ultraviolet B (NB UVB) phototherapy was introduced for 3 months, which resulted in partial hair regrowth in several foci. Unfortunately, after severe stress, the patients experienced another episode of complete hair loss. NB UVB phototherapy was restarted, in combination with immunotherapy with DCP; however, this time mediocre hair regrowth was observed. Apart from AU, the patient suffered from mild-to-moderate AD since early childhood. In her previous therapy for AD, she used topical corticosteroids and calcineurin inhibitors. She was otherwise healthy and did not take any medications.

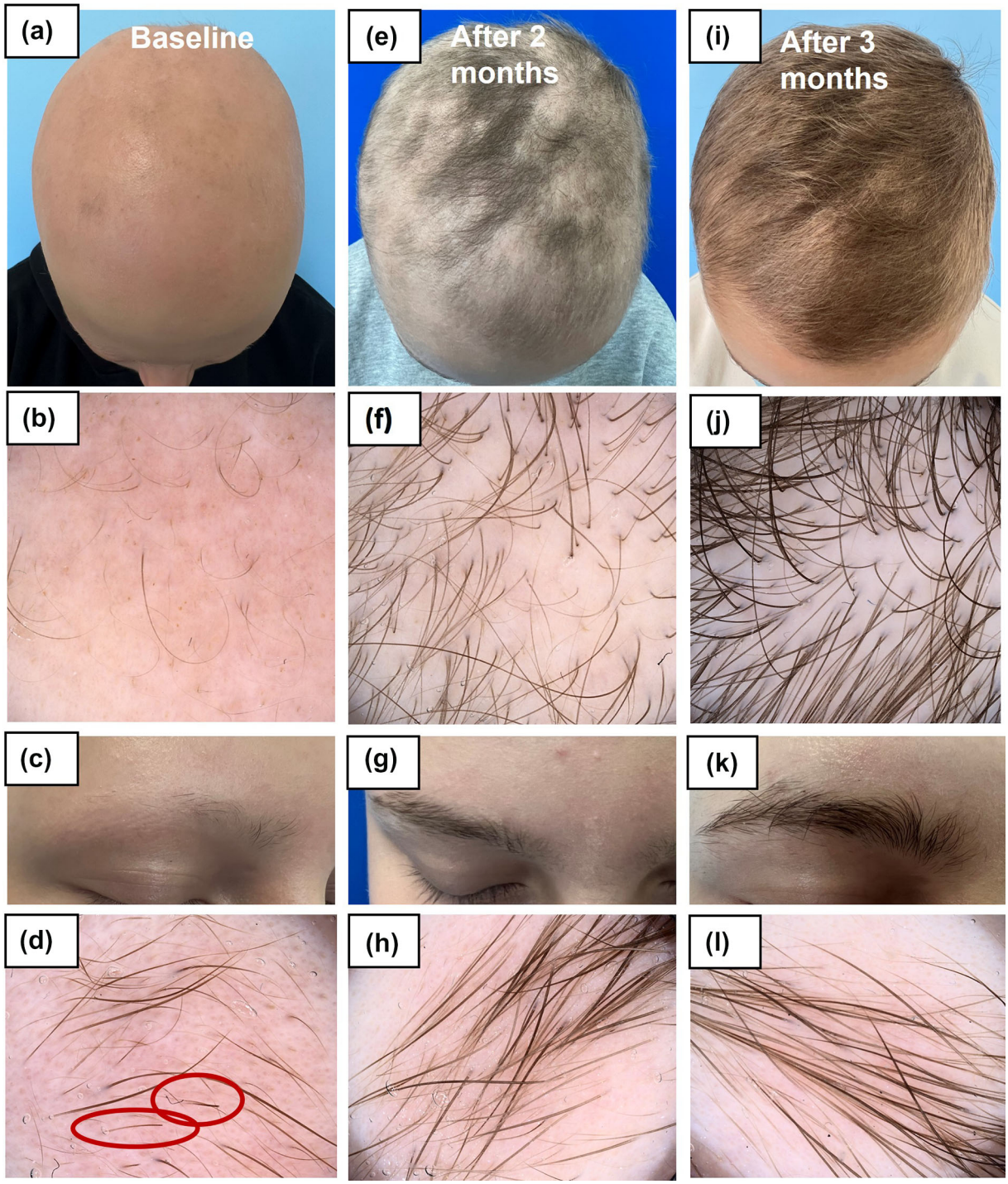
On admission, the patient presented with complete hair loss on the scalp [Severity of Alopecia Tool (SALT) score of 100] [7]. There was also significant loss of the eyebrows and eyelashes. Trichoscopic examination of the scalp showed numerous yellow dots, single upright regrowing hair, single black dots, and exclamation mark hairs (Fig. 1). In addition, eczematous lesions and lichenification were observed on the flexural aspects of the elbows and knees, and generalized skin dryness was noticeable. No nail abnormalities were present.

Baricitinib, a JAK1/2 inhibitor, has been recently approved for the treatment of AA in the adult population [38]. This was the premise to try using a JAK inhibitor in the presented adolescent. During a literature search, we came across recent case reports in adults of AD coexisting with AA successfully treated with a selective JAK1 inhibitor, upadacitinib. Taking into consideration, that upadacitinib (Rinvoq) has proven to be an effective treatment option with a good benefit–risk ratio in adolescents and adults with AD and it has recently been approved for the treatment of moderate-to-severe AD in 12-year-old patients or older, we decided to introduce this medication in the presented patient [8]. Laboratory tests, including full blood cell count, liver and kidney function tests, viral hepatitis markers, and tuberculosis screening (Quantiferon TB Gold) were performed prior to treatment initiation. As no abnormalities were found, upadacitinib at the dose of 15 mg/day orally was started. After 1 month of treatment, we noted complete resolution of eczematous lesions and improvement of AU with significant hair regrowth on the scalp, eyebrows, and eyelashes. Further improvement was observed at subsequent follow-up visits after 2 and 3 months of therapy. At week 12, trichoscopy of the scalp and eyebrows showed presence of normal terminal hair, and no black dots, broken hairs, or exclamation mark hairs were observed (Fig. 1). At last evaluation, SALT score was 0, corresponding to complete hair regrowth on the scalp. Full regrowth of the eyebrows and eyelashes was also noted. Laboratory tests, including complete blood cell count, and liver and kidney function tests, were performed once a month. Transient mild leukopenia was observed—white blood cell (WBC) count was $3.54 \times 10^3/\mu L$ after 4 weeks of therapy and $3.93 \times 10^3/\mu L$ after 8 weeks. At week 12, WBC count returned to normal. No other laboratory abnormalities were noted nor were any other adverse effects of the therapy reported within the treatment period. The patient continues treatment with upadacitinib at the dose of 15 mg/day.

DISCUSSION

Children represent approximately 25% of all AA cases [9]. Therapy of AA consists predominantly of corticosteroids and immunosuppressive agents, irritants (e.g., anthralin), vasodilatators (e.g., minoxidil), or sensitizers [e.g., diphenylocyclopropenone (DCP)] [10, 11]. Over the past few years, the involvement of the JAK and signal transducer and activator of transcription (STAT) pathway in the pathogenesis of many dermatoses has received considerable attention. This has resulted in an increasing number of studies evaluating the efficacy of medications inhibiting the pathway in numerous conditions, including AD and AA.

JAKs are intracellular enzymes that transmit signals for cytokines and growth factors involved in a wide range of cellular processes, including inflammatory responses, hematopoiesis, and immune surveillance [12]. Tofacitinib (JAK1 and JAK3 inhibitor, with little impact on JAK2), ruxolitinib (JAK1/2 inhibitor), and baricitinib (JAK1/2 inhibitor) belong to the first-


(a)
Baseline
(e)
After 2 months
(i)
After 3 months
(b)
(f)
(j)
(c)
(g)
(k)
(d)
(h)
(l)

◀**Fig. 1** Clinical and trichoscopic presentation at **a**–**d** baseline; **e**–**h** after 2 months of therapy with upadacitinib; **i**–**l** after 3 months of therapy with upadacitinib. **a** Nearly complete hair loss on the scalp; **b** trichoscopy showing yellow dots, single black dots, and several regrowing hair; **c** over 50% hair loss of the eyebrows; **d** trichoscopy showing broken hairs and exclamation mark hairs (red circles); **e** significant regrowth of hair on the scalp after 2 months of therapy; **f** trichoscopy showing numerous terminal hair and thin regrowing hair. Single yellow dots were present; **g** complete regrowth of the eyebrows after 2 months of therapy; **h** trichoscopy of the eyebrows showing terminal hair, no broken hairs or exclamation mark hairs were present; **i** complete hair regrowth on the scalp after 3 months of therapy; **j** trichoscopy showing normal terminal hair; **k** complete regrowth of the eyebrows after 3 months of therapy; **h** trichoscopy of the eyebrows showing normal terminal hair

generation of JAK inhibitors. All three drugs are nonselective and target multiple JAKs. Upadacitinib, a selective JAK1 inhibitor, is a representative of the next generation of JAK inhibitors. The JAK-STAT pathway has been shown to play a pivotal role in the dysregulation of immune responses in AD, including enhancement of Th2 lymphocyte responses, activation of eosinophils, maturation of B lymphocytes, suppression of regulatory T cells, and upregulation of proinflammatory cytokines and proangiogenic factors [12]. Recent studies have revealed that interferon (IFN)-γ and IL-15 are crucial in the pathogenesis of AA [13]. The expression of IFN-γ is dependent on JAK1, while IL-15 is dependent on JAK1 and JAK3. Selective targeting of these kinases may be most beneficial for patients with AA [14].

Randomized clinical trials evaluating the efficacy and safety of JAK inhibitors in the treatment of AA in adults are available in the English-language literature [15–18]. However, data on the use of these drugs in this indication in the pediatric population is predominantly based on case reports or case series [9, 14, 19–35]. A summary of these reports is provided in Table 1. So far, tofacitinib 2% in a liposomal base and ruxolitinib 1–2% in a liposomal base have been used in the topical treatment of AA in children and adolescents. Therapy with topical JAK inhibitors was associated with few adverse events, including application-site irritation (n = 1) and mild laboratory abnormalities (n = 2). However, not all patients responded to the treatment. In a case series of eleven children with AA, aged 4–16 years, cosmetically acceptable regrowth was achieved only in three patients [19].

Regarding the systemic use of JAK inhibitors in pediatric AA, most data is on tofacitinib (Table 1) [24–35]. The medication was predominantly used at the dose of 5 mg twice daily, except for younger children aged 4–-5 years, in whom the dose was reduced to 2.5 mg twice daily. In the majority of patients, complete or nearly complete hair regrowth was obtained, the therapy was continued for a period of over 1 year, and few side effects, including mild headaches, upper respiratory tract infections, mild increase in liver enzymes, and diarrhea, were noted. The issue of how long the treatment with tofacitinib should be continued and the maintenance therapy is increasingly often discussed. McKenzie et al. [35] also noted that in patients treated long term with oral tofacitinib, alopecia flares may occur. The authors observed such exacerbations in 8 out 21 children and young adults (age range 6–-20 years) while on tofacitinib. Various strategies to control the exacerbation were used by the authors, including increasing the dose of tofacitinib to 15 mg/day, adding treatment with intralesional triamcinolone or introducing a combination therapy with systemic and intralesional corticosteroids.

There is one report in the literature on the successful treatment of AA in an adolescent with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome with oral baricitinib [20]. CANDLE syndrome, described in 2010, is characterized by a prominent IFN signature. Small molecule JAK inhibitors, which inhibit type I and type II IFN receptor pathways, pose a promising therapeutic option in this entity. Recently, Wang et al. [21], reported a case series of 11 patients with AA, including two participants under the age of 18 years, treated with baricitinib for 20 weeks. Complete remission was achieved in two patients, while three

Table 1 Summary of the case reports and case series on the use of topical and/or systemic JAK inhibitors in AA in the pediatric population

Author, year	Systemic/topical	JAK inhibitor	Dose	Number of participants	Age (years)	Response	Adverse events	Duration of treatment (months)	Comments
Bayart et al., 2017 [14]	Topical	Tofacitinib	2% formulation in liposomal base BID	4	3–15	95% regrowth (n = 1), 20–30% regrowth (n = 2); no response (n = 1)	Mild laboratory abnormalities (50%)	3–12	
	Topical	Ruxolitinib	1–2% formulation in liposomal base	2	4–17	75% regrowth (n = 1); no response (n = 1)	None	3–18	In one patient treatment followed by tofacitinib 1% BID
Putterman et al., 2018 [19]	Topical	Tofacitinib	2% formulation in liposomal base BID	11	4–16	Improvement in SALT score (73%); cosmetically acceptable regrowth (27%)	Application-site irritation (9%)	2–19	
Jabbari et al., 2015 [20]	Systemic	Baricitinib	7 mg QD, increased to 7 mg + 4 mg	1	17	Complete hair regrowth	NA	Ongoing	CANDLE syndrome
Wang et al., 2022 [21]	Systemic	Baricitinib	2 mg BID	2 < 18 years (11 patients total)	15–17	Partial regrowth	NA	5	Topical minoxidil as adjuvant therapy
Liu et al., 2019 [22]	Systemic	Ruxolitinib	10 mg BID	1 < 18 years (eight patients total)	14	91% regrowth	Mild: upper respiratory infections, weight gain, acne, easy bruising fatigue	10	Prior unsuccessful treatment with tofacitinib

Table 1 continued

Author, year	Systemic/topical	JAK inhibitor	Dose	Number of participants	Age (years)	Response	Adverse events	Duration of treatment (months)	Comments
Peterson et al., 2020 [23]	Systemic	Ruxolitinib	20 mg BID (25 mg/m^2), gradually tapered to 10 mg every other day	1	9	Complete hair regrowth	None	Ongoing	
Craiglow et al., 2017 [24]	Systemic	Tofacitinib	5 mg BID	13	12–17	Hair regrowth (69%)	Mild headaches (23%), upper respiratory infections (31%), mild increase in liver enzymes (31%)	2–16	
Castelo-Soccio, 2017 [25]	Systemic	Tofacitinib	5 mg BID	6 < 18 years (eight patients total)	12–19	> 50% hair regrowth (100%)	None	5–18	
Brown et al., 2018 [26]	Systemic	Tofacitinib	5 mg BID	1	8	Complete hair regrowth	Mild headache	6	
Patel et al., 2018 [27]	Systemic	Tofacitinib	5 mg BID	1	17	85% regrowth	Increased appetite, minor weight gain	> 5 (ongoing)	
Ferreira et al., 2019 [9]	Systemic	Tofacitinib	5 mg BID	1	13	Complete hair regrowth	None	19	
Rachubinski et al., 2019 [28]	Systemic	Tofacitinib	5 mg BID	1	15	Complete hair regrowth	None	NA	Down syndrome

Table 1 continued

Author, year	Systemic/topical	JAK inhibitor	Dose	Number of participants	Age (years)	Response	Adverse events	Duration of treatment (months)	Comments
Craiglow et al., 2019 [29]	Systemic	Tofacitinib	5 mg BID (n = 3); 5 mg QD, increased to 5 mg BID after 3 months (n = 1)	4	8–10	Complete hair regrowth (50%), partial hair regrowth (25%)	None	Ongoing	
Dai et al., 2019 [30]	Systemic	Tofacitinib	2.5 mg QD	3	4–5	Nearly complete hair regrowth (33%), > 50% hair regrowth (67%)	Diarrhea (67%), upper respiratory tract infection (33%)	Ongoing	
Jerjen et al., 2021 [31]	Systemic	Tofacitinib	Maximum 4–15 mg/day	14	7–11	Complete hair regrowth (n = 3); > 50% regrowth (n = 7); no response (n = 1)	Mild and transient laboratory abnormalities; self-limiting unilateral lower leg pain (n = 1); mild upper respiratory infections (n = 3)	1.5–38 (ongoing in seven patients)	
Husein-ElAhmed et al., 2022 [32]	Systemic	Tofacitinib	NA	11	7–17	NA	NA	NA	Adult and pediatric patients included in the study

Table 1 continued

Author, year	Systemic/topical	JAK inhibitor	Dose	Number of participants	Age (years)	Response	Adverse events	Duration of treatment (months)	Comments
Kibbie et al., 2022 [33]	Systemic	Tofacitinib	5–10 mg BID	11	8–18	Hair regrowth (73%), minimal or no regrowth (27%)	Headache and dizziness (9%); transient decreased lymphocyte count (9%), transient mild increase in liver enzymes (9%), transient mild increase in triglicerydes (9%)	5–39	
Sardana et al., 2022 [34]	Systemic	Tofacitinib	5 mg BID; tapered to 5 mg every other day	1	7	Complete hair regrowth	None	30	Long maintenance therapy with tofacitinib 5 mg every other day
McKenzie et al., 2022 [35]	Systemic	Tofacitinib	5 mg BID; dose increased to 14 mg/day in two patients with alopecia flare	21	6–20	Significant hair regrowth	NA	12–58	Both children and young adults included; study focused on alopecia flare patterns while on systemic tofacitinib
Current case	Systemic	Upadacitinib	15 mg QD	1	14	Complete hair regrowth	Transient leukopenia	3 months (ongoing)	

CR case report, *CS* case series, *BID* twice a day, *QD* once a day, *CANDLE syndrome* chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature

Table 2 Summary of case reports of alopecia areata (AA) treated with upadacitinib

Author, year	Sex, age (years)	Duration of AA (years)	Previous treatments of AA	AD	Reason for switching to upadacitinib	Dosing of upadacitinib	Duration of treatment (months)	Outcome	Adverse events
Gambardela et al., 2021 [38]	M, 30	5	CsA; dupilumab	Yes	CsA-partial response dupilumab—side effects (severe flare of AD)	30 mg/day, oral	4 months	Remission of AA and AD	None
	F, 42	NA	NB UVB 311 nm; CsA; azathioprine; dupilumab	Yes	No response	30 mg/day, oral	4 months	Remission of AA and AD	None
Gori et al., 2022 [39]	M, 25	4	Topical diphencyprone; triamcinolone i.m., CsA, MTX	No	No response	30 mg/day, oral	3 months	Remission of AA	None
Asfour et al., 2022 [40]	F, 59	35 (relapsing-remitting course)	Baricitinib	Yes	Side effects: severe acne, migraines, recurrent orolabial herpes, lethargy	NA	2 months	Remission of AA and AD	None
Cantelli et al., 2022 [41]	M, 24	10	tGCS, sGCS, CsA, dupilumab	Yes	No response; dupilumab—side effects (paradoxical "red face")	30 mg/day, oral	3 months	Remission of AA and AD	None
Current case	F, 14	1	Topical minoxidil, tGCS, topical diphencyprone; NB UVB 311 nm	Yes	No response	15 mg/day, oral	3 months (ongoing)	Remission of AA and AD	Transient leukopenia

M male, *F* female, *AD* atopic dermatitis, *tGCS* topical glucocorticosteroids, *sGCS* systemic glucocorticosteroids, *CsA* cyclosporin A, *NB UVB* narrow band ultraviolet B

patients, including one of the adolescents, did not respond to therapy at all.

Peterson et al. [23] described a preadolescent patient with alopecia totalis successfully treated with ruxolitinib, a JAK1/2 inhibitor. The efficacy was also maintained with prolonged treatment with a tapered dose of 10 mg every other day. Liu et al. [22] reported a case series of eight patients with AA, including one 14-year-old participant, who were treated with ruxolitinib monotherapy. Six of the eight patients had been treated with tofacitinib prior to initiating therapy with ruxolitinib. In the adolescent patient, no improvement in the SALT score was observed with tofacitinib, while a 91% hair regrowth was noted after 10 months of therapy with ruxolitinib at the dose of 10 mg twice daily.

Upadacitinib is a selective and reversible JAK inhibitor, that preferentially inhibits JAK1 or JAK1/3-mediated signal transduction. Results of phase III randomized clinical trials point at high safety profile and clinical efficacy in the treatment of AD in the pediatric population, both in monotherapy and in combination with topical corticosteroids [36, 37]. As a result, upadacitinib has been recently approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) for the treatment of AD in adults and adolescents aged 12 years or older eligible for systemic therapies [8]. After an extensive literature search, we came across five cases of successful treatment of AA with upadacitinib [38–41]. Concomitant AD was present in four out of five cases. However, the youngest patient was 24 years of age, and none of the reported cases was a pediatric patient. A summary of the aforementioned reports is provided in Table 2. Interestingly, upadacitinib proved to be effective and well-tolerated in patients who experienced side effects [38, 41] or lack of efficacy [38] of therapy with dupilumab for AD. In addition, upadacitinib showed superiority over another JAK inhibitor, baricitinib, in terms of tolerance and hair regrowth in AA [38]. Asfour et al. [40] reported a patient with a 35-year history of relapsing–remitting AA and moderate-to-severe AD, who showed partial hair regrowth and remission of AD with baricitinib; however, the therapy had to be stopped after 6 weeks due to side effects (severe acne, migraines, recurrent herpes). After initiating treatment with upadacitinib, clearance of eczema was observed, as well as hair regrowth in areas that did not respond to previous therapy with baricitinib. The treatment was also well-tolerated, and no side effects were reported.

As the efficacy and safety of upadacitinib in the treatment of AD has already been demonstrated in randomized clinical trials, including in patients under 18 years of age, and there are new reports on the effectiveness of this medication in AA, therapy with upadacitinib should be particularly considered in patients with not uncommon coexistence of these two diseases.

CONCLUSION

Currently, there is a lack of treatment guidelines for pediatric AA, especially coexisting with AD. The role of JAK/STAT signaling in promoting the inflammatory response around hair follicles has been demonstrated in clinical studies. Thus, the JAK/STAT signaling pathway represents a potential therapeutic target in patients affected with AA. To the best of our knowledge, this is the first pediatric case of AA universalis successfully treated with upadacitinib. The medication is also a valuable therapeutic option in patients with the coexistence of two conditions—AA and AD.

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Compliance with Ethics Guidelines. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the patient and her parents for participation in the study and publication of the article, including publication of clinical photographs. We would like to thank the patient for her involvement.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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