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Baricitinib for the Treatment of Moderate-to-Severe Alopecia Areata

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Alopecia areata (AA) is an autoimmune, relapsing, non-scarring condition that causes hair loss, resulting in bald patches on the scalp, beard, eyebrows, eyelashes, and, in some cases, the entire body. AA is one of the most common dermatological disorders, affecting up to 2% of the general population.[1] The pathology is yet unknown, but a common theory is the collapse of the immune privilege of the anagen hair follicles caused by genetic factors, environmental events, and psychological stress.[2] Current treatments for limited AA include topical corticosteroids, minoxidil, and topical immunotherapy. For severe cases-such as alopecia totalis, alopecia universalis, rapid hair loss, or disease duration exceeding 10 years-systemic treatments are recommended.[3] New targeted therapies of AA, including JAK inhibitors, have been developed in recent years. The janus kinase signal transducer and activator of transcription (JAK-STAT) pathway is an intracellular signaling pathway that is dependent on several cytokines associated with AA, including interleukin-2 (IL-2), IL-7, IL-15, IL-21, and interferon-gamma.[4] Baricitinib, a first-generation oral selective inhibitor of JAK1 and JAK2, was Food and Drug Administration (FDA)-approved in 2018 for moderate-to-severe rheumatoid arthritis in adults. Subsequently, baricitinib was approved in Europe (2020) for adults with moderate-to-severe atopic dermatitis.[5] Two recently reported phase 3 trials demonstrated that oral baricitinib was more effective than placebo in treating severe AA.[6] These large-scale studies led to the first FDA-approved treatment for AA in June 2022.[7]

Here, we report a case series of 14 patients with severe, refractory AA treated with oral baricitinib. The baseline characteristics of all patients were assessed, includingage, sex, disease duration, age at AA onset, clinical type of alopecia, the Severity of Alopecia Tool (SALT) scores of each patient, and previous treatments (Table 1). At each visit, we assessed clinical improvements, adverse events, and laboratory tests. All patients had previously received at least one of the following treatments; topical, intralesional corticosteroids, systemic corticosteroids, topical minoxidil, topical immunotherapy (diphencyprone or squaric acid dibutylester), cyclosporine, methotrexate, or oral tofacitinib. The severity of alopecia was assessed using the SALT score. The percentage change in the SALT score from baseline was used to evaluate the treatment response. SALT50, SALT75, and SALT90 were defined as 50%, 75%, and 90% regrowth, respectively. Patients with less than a 5% change in the SALT score were classified as "no-response." There were no findings related to the patients' nails. All patients received baricitinib 4 mg daily as a monotherapy, with treatment durations ranging from 3 to 12 months. They continued with the same dose of 4 mg per day, and their doses remained unchanged. All adverse effects were recorded at each visit.

We treated 14 patients from 18 to 38 years, with a median age of 25 years. The duration of the disease ranged from 12 to 192 months, with a median of 56 months. Table 1 provides a summary of the patient characteristics. Among the 14 patients, four had alopecia universalis, four had alopecia totalis, four had multifocal AA, and two had alopecia ophiasis. The median SALT scores at the beginning of treatment and after treatment were 75% and 25% (range, 25-100%), respectively. Changes in SALT scores are shown in Table 1. Our results showed that three patients (21%) achieved SALT 100 after at least 6 months of baricitinib treatment. Four patients (28%) and one patient (7%) achieved SALT50 and SALT75, respectively. Additionally, one patient (7%) achieved a SALT25 response after six months of baricitinib treatment, while another patient (7%) experienced an incomplete response with a SALT10 after 1 year of baricitinib treatment. One patient (7%) with alopecia ophiasis and one patient (7%) with multifocal AA showed no regrowth after three and five months of baricitinib treatment, respectively. The patient had previously not responded to one year of tofacitinib treatment. In four patients with alopecia universalis, the growth of eyebrows and eyelashes regrowth occurred simultaneously with scalp hair regrowth. Initially, vellus hairs were observed, which later thickened, leading to cosmetic improvement. Three patients achieved SALT50, SALT75, and SALT100 responses at the third, eleventh, and seventh months of the therapy, respectively, with representative images shown in Figure 1 (patients 10, 8, and 2). Three patients (patients 9, 10, and 11) had autoimmune comorbidities, including vitiligo and autoimmune thyroiditis. The antinuclear antibody test was positive

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TABLE 1. Baseline characteristics of all patients

Patient	Age/ sex	Age at onset of AA (years)	Duration of the disease (months)	Subtype	Duration of therapy (months)	SALT score before treatment	SALT score after treatment	Change in the SALT scores (%)	Autoimmune comorbidities	Previous medications
1	33/M	26	80	MAA	7	60	25	58	N	SC and cyclosporine
2	25/M	17	92	AT	7	100	0	100	N	SC cyclosporine, ILC, and minoxidil
3	37/M	35	20	AU	12	100	90	10	N	Cyclosporine, ILC, and TC
4	24/F	14	115	AU	6	100	75	25	N	SC, TC, cyclosporine, minoxidil, and tofacitinib
5	23/F	22	17	AU	12	60	0	100	N	SC, TC, DPCP, MTX, and ILC
6	34/M	32	19	MAA	12	25	0	100	N	TC
7	28/F	12	190	Ophiasis	3	25	25	0	N	Cyclosporine, ILC, and tofacitinib
8	25/F	22	33	AU	11	100	25	75	N	TC
9	23/M	21	22	MAA	9	60	25	58	Vitiligo	Tofacitinib
10	18/M	16	24	AT	3	100	50	50	Autoimmune thyroiditis	SC, DPCP, and minoxidil
11	19/F	7	144	AT	3	100	90	10	Autoimmune thyroiditis	TC and ILC
12	19/M	3	192	AT	4	90	40	55	ANA 1/160+	TC, ILC, and SADBE
13	27/F	13	120	Ophiasis	4	25	20	20	N	TC, ILC, and SADBE
14	38/M	37	12	MAA	5	50	50	0	N	SC and cyclosporine

AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; ANA, antinuclear antibody; DPCP, diphencyprone; F, female; ILC, intralesional corticosteroid; M, male; MAA, multiple alopecia areata; MTX, methotrexate; SADBE, squaric acid dibutylester; SALT, Severity of Alopecia Tool; SC, systemic corticosteroids; TC, topical corticosteroids, MAA: multiple alopecia areata

in one patient (patient 12), with a titer of at least 1/160. The adverse events were mild and included acne (1/14), urinary tract infections (2/14), mild hypercholesterolemia (1/14), and mild increases in creatine kinase (CK) level (3/14). All adverse effects, except for acne, were observed during the 3rd-month visit. The patient with acne was noted during the 9th month. One of the patients with elevated CK was active in sports, and the CK elevation was minimal. Other patients with elevated CK were observed during the 3rd-month visit and returned to normal levels in subsequent visits. During treatment, other laboratory parameters returned to normal levels. One patient experienced nausea and transient tachycardia in the second month of treatment, but no treatment was required. No serious adverse events were observed.

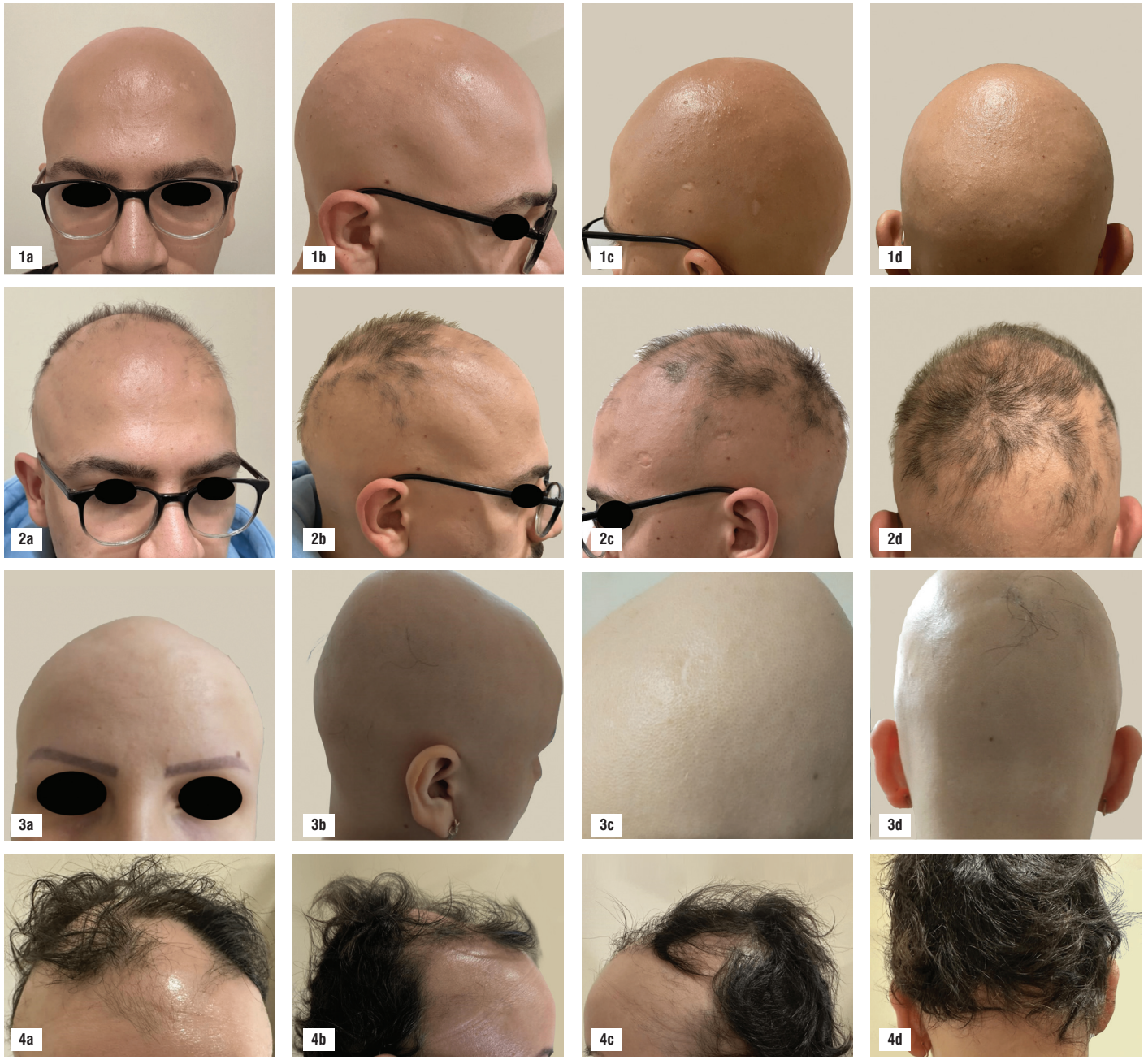
To the best of our knowledge, the pathogenesis of AA involves hair follicles being attacked by autoreactive T-cells activated through *JAK-STAT* signaling pathway. The *JAK-STAT* pathway promotes the production of cytokines, such as interferon gamma and IL-15, which trigger a T-cell-mediated inflammatory response around the hair follicles. These findings on the pathogenesis of AA have led to the development of new targeted therapies involving small molecule JAK inhibitors, resulting in hair regrowth among AA patients.[8] Reported case studies and clinical trials of JAK inhibitors for AA are increasingly providing insights into their efficacy and associated adverse events. Three JAK inhibitors-tofacitinib, ruxolitinib, and baricitinib-have been reported for the treatment of AA. In two current phase 3 trials evaluating efficacy and safety in patients with severe AA (BRAVE-AA1 and BRAVE-AA2), oral baricitinib 4 mg was found to be superior to placebo in promoting hair regrowth at 36 weeks, with sustained improvements observed at 52 weeks of treatment.[6,8,9] In our study, we found that eight of 14 patients (57%) achieved at least a SALT50 response after 3-12 months. Four patients (28%) achieved a SALT50 response, one (7%) achieved a SALT75 response, and three (21%) achieved a SALT100 response.

In a case series of 11 patients, seven patients (64%) similarly achieved a SALT25 response.[10] One patient (7%) with alopecia ophiasis showed no regrowth after 3 months of baricitinib treatment. In a retrospective study evaluating the electronic records of 77 patients with AA treated with oral baricitinib and oral tofacitinib, it was demonstrated that AA patients who failed to regrow any hair with one JAK inhibitor were less likely to respond to a second JAK inhibitor. In our study, we found that the patient who did not respond to baricitinib

treatment had previously been treated with tofacitinib for one year without any response. This patient received only three months of baricitinib treatment, so a longer duration of treatment is necessary to accurately assess the response. Additionally, AA with an ophiasis pattern is known to be resistant to treatment. Another patient in our study with alopecia ophiasis did not achieve a SALT25 response after four months.

Adverse events observed in our study were consistent with those reported in other clinical trials and case series. We identified mild adverse events, including acne, nausea, urinary tract infections, mild hypercholesterolemia, and slight increases in CK levels among our patients. One patient experienced transient tachycardia, which did not require treatment. All laboratory parameters returned to normal levels during the treatment period.

In conclusion, we found that baricitinib is an effective and well-tolerated medication for the treatment of refractory AA. However, this study is limited by its small sample size; therefore, long-term treatment and larger trials are needed to determine the efficacy and safety of baricitinib for AA.



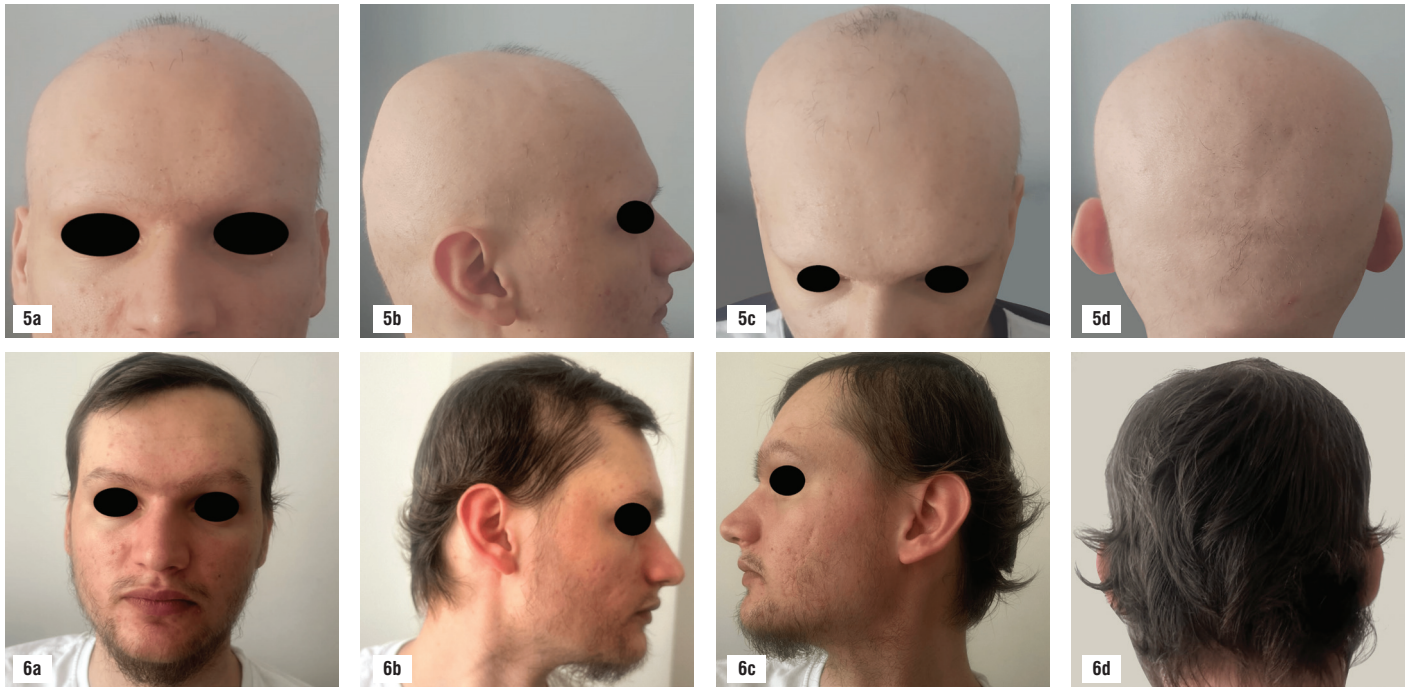


FIG. 1. Clinical presentation of patient 10 with alopecia universalis before treatment (1a-d) and SALT50 response at the 3rd month of the therapy (2a-d); patient 8 with alopecia universalis before treatment (3a-d) and SALT75 response at the 7th month of the therapy (4a-d); and patient 2 with alopecia universalis before treatment (5a-d) and SALT100 response at the 11th month of the therapy (6a-d). [(a) anterior view, (b) right side, (c) left side, (d) posterior view].

SALT, Severity of Alopecia Tool.

Informed Consent: Consent was obtained from the patients for the use of their photographs.

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