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CASE SERIES

# Efficacy and Tolerability of Brevilin-A, a Natural JAK Inhibitor, in Pediatric Alopecia Areata: A Case Series

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**Abstract:** Alopecia areata represents an autoimmune disease that specifically damages growing hair follicles on the scalp and/or around the body. Janus kinase inhibitors have been identified as an effective therapy in adult patients and topical formulations, such as Brevilin-A, might represent a well-tolerated treatment for mild-moderate disease in children and adolescents. The mechanism of action of Brevilin-A, a sesquiterpene lactone isolated from Centipeda minima, could consist in blocking STAT3 and STAT1 signaling as well as the JAKs activity by inhibiting the JAKs tyrosine kinase domain JH1. We report our cases of successful application of Brevilin-A in pediatric patients, suggesting this treatment as a safe and effective therapeutic option also for recalcitrant alopecia areata in pediatric population.

**Keywords:** alopecia areata, brevelin A, pediatric, topical JAK inhibitors

## Introduction

Alopecia areata (AA) represents a frequent autoimmune CD8+T-cell condition which affects the hair follicles on the scalp and body and manifests as round or oval, smooth bald patches of hair loss without signs of cutaneous inflammation or scarring hair loss.[1] In 75% of patients, AA is limited to the scalp, even though it can affect every part of the body where hair follicles are present; typical lesions usually appear as single or multiple patches, but specific clinical patterns can be found, such as ophiasis (linear hair loss localized in temporo-occipital region), sisaipho (linear hair loss in the central area of the scalp), total scalp hair loss, alopecia totalis (AT), or total body hair loss, alopecia universalis (AU).[2] AA occurs in 2% of the global population, but it has been estimated that its prevalence in the pediatric and adolescent population is increasing.[3] Moreover, the onset of AA during childhood has been reported to be associated with more severe disease, poorer prognosis and a detrimental effect on Quality of Life (QoL) of young patients and their family members.[4,5] Interestingly, an inverse relationship was noted between QoL and Severity of Alopecia Tool (SALT) scores, with worse QoL scores in adolescents with lower SALT (25–49%) compared to those with higher SALT scores.[5]

As reported, AA has a multifactorial pathogenesis, in which the combination of genetic factors and triggering factors, such as emotional or psychological distress, causes an hyperactivation of the immune system.[6] This immunological imbalance is mostly mediated by the overexpression of IFN-γ and interleukin 15.[1,2]

Traditional treatments for moderate to severe forms of AA include methotrexate or cyclosporine, but several novel therapeutic options are currently being investigated, such as Janus kinase (JAK) inhibitors. On June 2022, the US Food



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and Drug Administration (FDA) approved baricitinib, an oral, selective and reversible JAK1/JAK2 inhibitor, to treat adult patients with severe forms of AA, defined as 50% or greater scalp hair loss. Long-term results of BRAVE-AA1 and BRAVE-AA2 Phase 3 trials demonstrated the efficacy of the drug over 52 weeks of therapy. The same drug has been currently used in a population of 29 adolescents aged between 12 and 18 years, suffering from moderate-severe AA, showing promising results, even if further studies are mandatory to understand efficacy and safety in this population. More recently, the ALLEGRO phase 2b–3 trial showed the efficacy and safety of ritlecitinib, a new oral, selective dual JAK3/TEC family kinase inhibitor, in patients aged 12 years and older with severe AA treated over 48 weeks.[7] Traditional treatments for mild AA include topical or intralesional steroids, administered as monotherapy or as combination, or systemic steroids.[8] Currently, the topical formulation of JAK inhibitors provide a new therapeutic approach especially in children and adolescents, to reduce systemic exposure and thereby achieving an improved safety profile. Three recent reports about the use of topical tofacitinib and ruxolitinib in 18 pediatric patients (ages 4–17) documented high tolerability in all patients and efficacy in most of them. Side effects included cutaneous local irritation and laboratory abnormalities (leukopenia).

Brevilin-A, is a sesquiterpene lactone isolated from a medicinal plant (Centipeda minima) and represents a topical JAK inhibitor. It seems to block the T lymphocyte activation while stimulating the anagen hair phase, through the inhibition of STAT3 and STAT1 signaling as well as the JAKs activity by blocking the JAKs tyrosine kinase domain JH1.[9,10] Recently, Muscianese et al showed its efficacy and safety in a small adult population affected by patchy AA.[10] Here, we report our experience of topical application of Brevilin-A in pediatric and adolescent age group affected by mild-moderate AA.

## Methods

Fifteen pediatric patients (mean age: 14.7 years; 8 F and 7 M) affected by mild-moderate AA were enrolled in an observational, prospective, open-label study at the Tor Vergata University Hospital of Rome. A stable disease was observed in our cohort study, with no signs of relapse of AA for at least 6 months. The onset of the disease was between 1 and 5 years and all patients had already experienced previous treatments, as high-potency topical corticosteroids, topical tacrolimus, systemic corticosteroids and cyclosporine. None of the patients suffered from other autoimmune diseases, atopic dermatitis or other comorbidities. In 3 cases, the disease had an exacerbation following hormonal or immunological dysfunctions, such as amenorrhea or COVID vaccination. This study was performed in line with the principles of the Declaration of Helsinki.

Two patients had a positive family history of AA. Clinical subtypes were represented by patchy multifocal AA and/or ophiasis, with a mean SALT of 31. Pull test has been performed at baseline and resulted positive in 12 out of 15 patients. Trichoscopic evaluation of the patches at baseline was similar in all patients, showing a typical follicular pattern in the central part of the lesions, and dermoscopic signs of active disease (ie broken hairs or exclamation mark hairs) in the peripheral area.[11]

The main index used to calculate the severity of AA is SALT, a score from 0 to 100 that assesses the extent of the hairless area. To calculate SALT score, scalp was divided into 4 areas: the vertex – 40% of scalp surface area, right profile of scalp 18%, left profile of scalp 18%, posterior aspect of scalp 24%. Percentage of hair loss in each area was calculated as following: percentage of hair loss in vertex = nv; percentage of hair loss in right scalp = nr; percentage of hair loss in left scalp =nl; percentage of hair loss in posterior scalp =np. SALT score = $(nv \times 0.4) = (nr \times 0.18) + (nl \times 0.18) + (np \times 0.24)$.[12]

The impairment of QoL was assessed using the Children's Dermatology Life Quality Index (CDLQI), a 4-points scale (0-never, 1-sometimes, 2-often, 3-almost always) calculated by summing all the points in 10 questions (0–30), used to evaluate items such as symptoms, personal relationships, school work-holiday time, leisure and daily activities and sleep disorders.[13]

Patients were instructed to apply a lotion containing Brevilin-A 0.1% twice a day for 3 months and then once a day for other 3 months as maintenance therapy. Trichoscopic and clinical evaluation, based on SALT score and CDLQI, were performed at baseline (T0) and after 3 (T3) and 6 (T6) months. A complete blood chemistry panel, including blood count, renal and hepatic function and thyroid tests were performed at baseline and 6 months thereafter.

All data were analyzed from an internal database. All results are expressed as the arithmetic mean±SE or percentages. SALT and CDLQI median values analyzed by analysis of variance (ANOVA), followed by Bonferroni's post-hoc test for

quantitative variables. Differences of $p<0.05$ are considered statistically significant. All statistical analyzes were performed using the SPSS 20.0 statistical package (SPSS Incorporated, Chicago).[14]

## Results

At T0, areas where the hair loss was complete (Figure 1A) trichoscopic evaluation showed a follicular pattern, with black and yellow dots in the central part of the patches (Figure 1B), and presence of broken and exclamation mark hairs in the peripheral area, which indicated the active phase of the disease (mSALT: 31). Significant hair regrowth and clearance of the patches at T3 was observed (mSALT: 11.2) and trichoscopic evaluation after the first 3 months showed a regrowing pattern, with vellus hairs and upright regrowing hairs, which can be considered as positive signs of treatment response (Figure 1C and D). At T6, 20% of patients (3) showed a complete resolution of the lesions, with a trichoscopic and clinical pattern of full

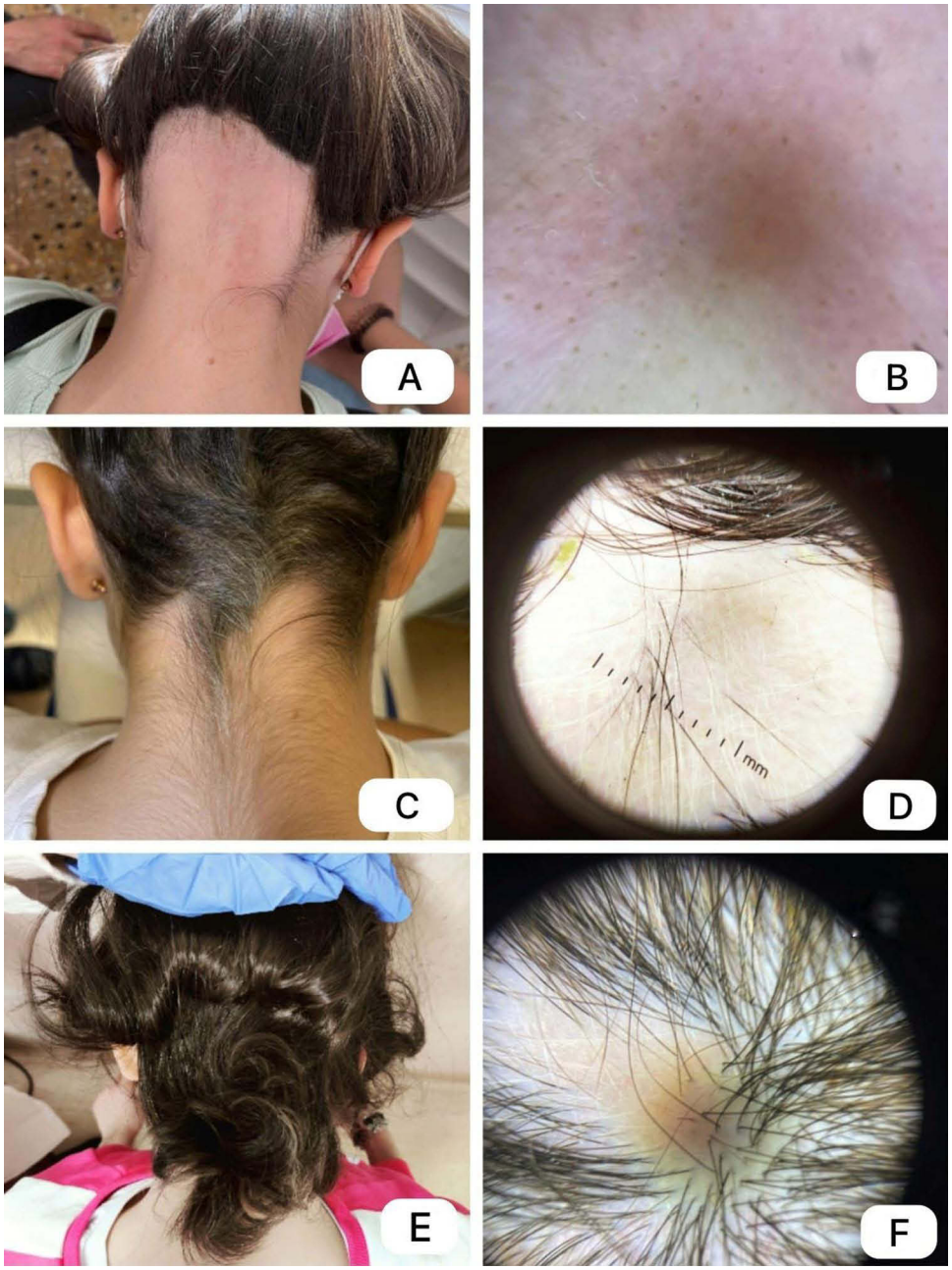


**Figure 1** (**A–C-E**) Clinical findings at T0-T3-T6. (**B-D–F**) Trichoscopic findings at T0-T3-T6.

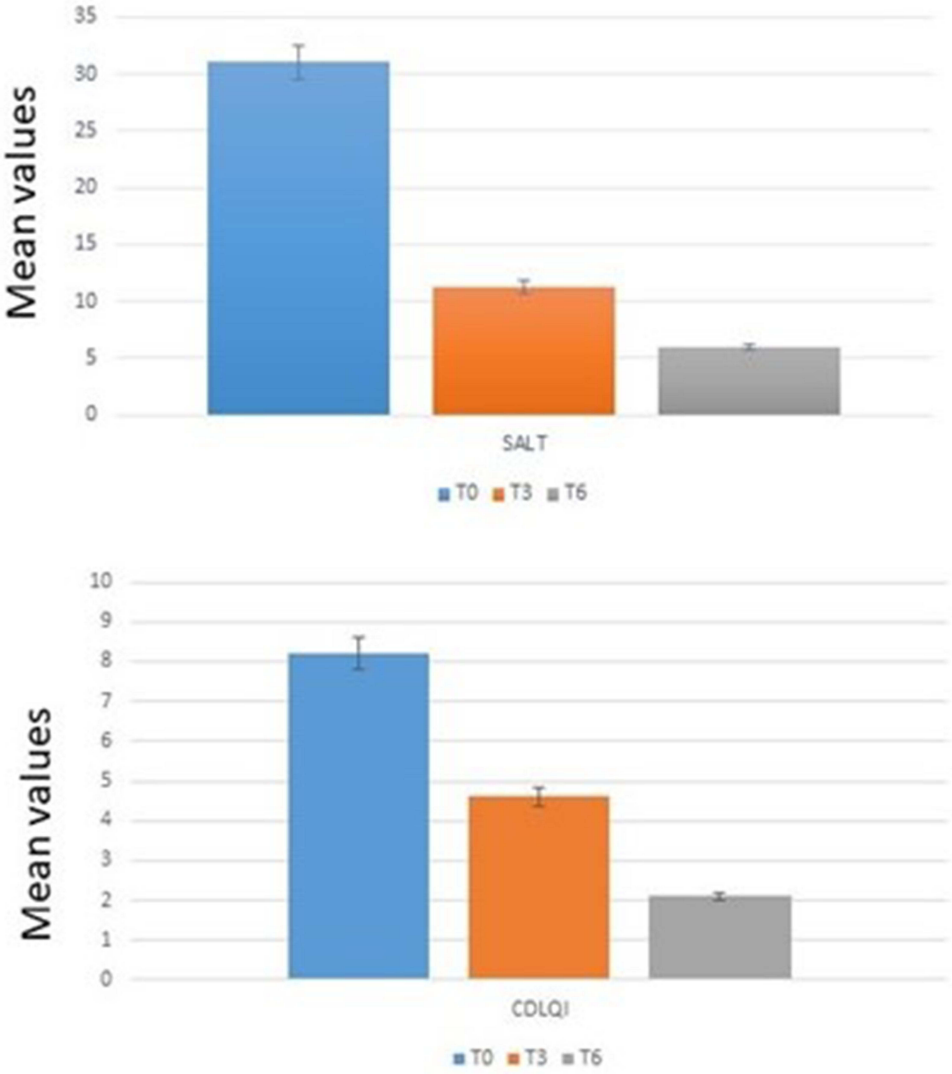


**Figure 2** Bar Graphs showed statistically significant reduction of SALT and CDLQI after treatment (T0 vs T3 and T6). ANOVA test p<0.001.

regrowth, but new patches appeared in different regions of the scalp, where the trichoscopy showed follicular pattern and broken hair; 33.3% of patients (5) presented a partial improvement, with typical regrowing signs at the dermoscopic evaluation. About 46.7% of patients (7) showed a complete clinical and trichoscopic resolution (Figure 1E and F). SALT and CDLQI scores were in our cases higher at baseline (mean values; Figure 2), but after Brevilin-A treatment we showed a statistically significant reduction at T3 and T6 timepoint (ANOVA test; P<0.001). In our series, following the interruption of therapy at T6, only two patients, with a severe form of disease and family history of AA, presented a mild recurrence, making it necessary to continue maintenance therapy.

No patient discontinued treatment due to local or systemic adverse events.

## Discussion

Topical corticosteroids are considered as first-line treatment for pediatric AA, due to minimal side effects and ease of application. Clobetasol propionate 0.05%, applied for a total of 24 weeks (2 cycles of 6 weeks on, 6 weeks off) has shown greater efficacy in the treatment of pediatric patients than other corticosteroids of lower potency.[15] In our study population, all patients had already experienced previous treatments, as high-potency topical corticosteroids, topical tacrolimus, systemic corticosteroids and cyclosporine, with poor results due to lack of response to treatment or interruption of therapy due to the onset of side effects.

Our results demonstrated the efficacy of Brevilin-A as treatment for mild-moderate recalcitrant AA in pediatric population, where the possibility of spontaneous hair regrowth was very unlikely due to the long-standing course of disease: the whole group showed a good response to the therapy, with 46.7% of the patients showing a complete remission of the disease after the treatment with Brevilin-A. A 20% of patients showed a total remission of the treated lesions, but new patches appeared in different regions of the scalp. In 33.3% of patients we observed a partial response, but with a significant improvement of remaining patches, as assessed by both clinical and trichoscopic findings. Moreover, in parallel with the clinical improvement, represented by the reduction in SALT, we observed, as reported by Choi et al, a statistically significant reduction in CDLQI, as a consequence of the improvement in QoL[13]

Although the topical application of Brevilin-A cannot guarantee complete resolution of the pathology, given its chronic-relapsing nature, it nevertheless represents a valid alternative in the management of clinical manifestations. In contrast to the experience of Muscianese et al, where an improvement was observed mainly in multifocal forms of adult patients, our clinical data about younger patients have produced more encouraging results. This data must be analyzed in light of the fact that our population was made up of young patients with a shorter disease history and with a lower mean SALT at baseline compared to the experience reported in literature on the adult population.[10]

Consistent with literature data, our analysis does not indicate significant adverse events of Brevilin-A in pediatric population, nor a lesser effectiveness compared to other topical treatments for recalcitrant AA and can therefore be used for longer periods of time than topical corticosteroids, since there is no risk of skin atrophy.

The pediatric and adolescent periods constitute a critical phase of fundamental importance for the mental development of a future adult individual, consequently the psychological weight of AA in this category of patients requires a better and more in-depth overview. In addition to the clinical assessment of pathology through the SALT, the estimate of the emotional impact, for example through the CDLQI of a patient in this age group, should guide the clinical and therapeutic decision-making process. For this reason, there is a need to implement the therapeutic armamentarium, while waiting for topical therapies with guaranteed efficacy and safety.

The limitations of our study are represented by the small sample size and the lack of a control group which, given the possibility of spontaneous regression of AA, does not allow us to attribute the outcome specifically to the intervention being examined.

However, our data suggested that treatment with Brevilin-A may be considered a promising therapeutic option for recalcitrant AA in pediatric population, especially in cases of mild and moderate severity.

## Abbreviations

AA, Alopecia areata; AT, Alopecia totalis; AU, Alopecia universalis; QoL, Quality of Life; SALT, Severity of Alopecia Tool; IFN, Interferon; JAK, Janus kinase; FDA, Food and Drug Administration; CDLQI, Children's Dermatology Life Quality Index.

## Data Sharing Statement

The data used to support this study are included within the article.

## Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Policlinico Roma Tor Vergata. Informed consent was obtained from all subjects involved in the study.

A parent or legal guardian of the patients provided informed consent for every patient.

## Consent for Publication

Consent to publish has been obtained from all involved patients.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study, design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

## References

1. Barton VR, Toussi A, Awasthi S, Kiuru M. Treatment of pediatric alopecia areata: a systematic review. *J Am Acad Dermatol*. 2022;86(6):1318–1334. doi:10.1016/j.jaad.2021.04.077
2. Hamilton CE, Craiglow BG. JAK inhibitors for the treatment of pediatric alopecia areata. *J Investig Dermatol Symp Proc*. 2020;20(1):S31–36. doi:10.1016/j.jisp.2020.04.005
3. Lee HH, Gwillim E, Patel KR, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2020;82(3):675–682. doi:10.1016/j.jaad.2019.08.032
4. Lyakhovitsky A, Aronovich A, Gilboa S, Baum S, Barzilai A. Alopecia areata: a long-term follow-up study of 104 patients. *J Eur Acad Dermatol Venereol*. 2019;33(8):1602–1609. doi:10.1111/jdv.15582
5. Prendke M, Kanti-Schmidt V, Wilborn D, et al. Quality of life in children and adolescents with alopecia areata-A systematic review. *J Eur Acad Dermatol Venereol*. 2023;37:1521–1534. doi:10.1111/jdv.18848
6. Wang EHC, Sallee BN, Tejeda CI, Christiano AM. JAK inhibitors for treatment of alopecia Areata. *J Invest Dermatol*. 2018;9:1911–1916.
7. King B, Zhang X, Harcha WG, et al. Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata: a randomised, double-blind, multicentre, phase 2b-3 trial. *Lancet*. 2023;401:1518–1529. doi:10.1016/S0140-6736(23)00222-2
8. Bayart CB, DeNiro KL, Brichta L, Craiglow BG, Sidbury R. Topical Janus kinase inhibitors for the treatment of pediatric alopecia areata. *J Am Acad Dermatol*. 2017;77(1):167–170. doi:10.1016/j.jaad.2017.03.024
9. Kim BH, Lee WY, Trinh TA, et al. Hair growth effect of emulsion extracted brevilin-A, a JAK3 inhibitor, from centipeda minima. *Processes*. 2020;8:767. doi:10.3390/pr8070767
10. Muscianese M, Magri F, Leoncini P, Fortuna MC, Caro G, Rossi A. Alopecia areata treated with topical and systemic Brevilin-A: a case series. *Dermatol Ther*. 2021;34(2):14778. doi:10.1111/dth.14778
11. Diluvio L, Matteini E, Lambiase S, et al. Effect of baricitinib in patients with alopecia areata: usefulness of trichoscopic evaluation. *JEADV*. 2024;38:e478–e480. doi:10.1111/jdv.19663
12. Dias SE, Panicker VV, Thomas J, Jagadeesan S, Anjaneyan G, Lekshmi S. Trichoscopic features in diagnosis of alopecia areata and its relation to severity of alopecia tool (SALT) score. *J Pakistan Assoc Dermatolog*. 2018;28(2):152–156152.
13. Choi JW, Kim YH, Kwak H, et al. Impact of pediatric alopecia areata on quality of life of patients and their family members: a nationwide multicenter questionnaire study. *Ann Dermatol*. 2022;34(4):237–244. doi:10.5021/ad.21.202
14. Doldo E, Costanza G, Ferlosio A, et al. High expression of cellular retinol binding protein-1 in lung adenocarcinoma is associated with poor prognosis. *Genes Cancer*. 2015;6(11–12):490–502. doi:10.18632/genesandcancer.89
15. Lenane P, Macarthur C, Parkin PC, et al. Clobetasol propionate, 0.05%, vs hydrocortisone, 1%, for alopecia areata in children: a randomized clinical trial. *JAMA Dermatol*. 2014;150(1):47–50. doi:10.1001/jamadermatol.2013.5764