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Successful Treatment of Alopecia Totalis with Topical Calcipotriol: Serial Case Report and Review of the Literature

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ABSTRACT

Background: Alopecia totalis (AT) often responds poorly to standard therapies. This disease is chronic and relapsing, no effective cure treatment has been established. Calcipotriol is a vitamin D analog and acts as a potent immunomodulatory agent can be used in the treatment of alopecia areata (AA) with promising results. The active form of vitamin D mediates its action by binding to specific vitamin D receptors (VDR) located in the nuclei of target cells. Expression of VDR in keratinocytes is necessary for maintenance of the normal hair cycle.

Objective: Our study aims to show the effectiveness of topical calcipotriol in the treatment of Alopecia Totalis patient.

Methods: Three patients diagnosed with AT, duration of disease 6 – 12 months, refractory to other treatments were selected and were started on topical calcipotriol and were followed up every 4 weeks for 12 weeks. The efficacy was measured by hair regrowth using photographic assessment, Severity of Alopecia Tool score (SALT), Hair Pull Test and physical examination. Patients will be followed up for 6 months after stopping treatment for assessing disease relapse.

Results: The patients showed excellent response with complete

regrowth of scalp hair after a single 12-week treatment course of topical calcipotriol and no hair loss relapse was observed over the next 6 months.

Conclusion: In our patients, a novel treatment option topical calcipotriol was successfully used in the management of AT, in the absence of significant adverse side effects. We recommend that further controlled studies be required to establish safety, confirm efficacy, and disease remission protocol. To our knowledge, this is the first published case series of successful treatment for AT with single topical calcipotriol although the sample size was small.

Keyword: Alopecia Areata, Alopecia Totalis, Topical Calcipotriol, Vitamin D receptor

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INTRODUCTION

Alopecia areata (AA) is a chronic and relapsing hair follicle specific autoimmune disease that leads to non scarring hair loss.¹⁻³ The deterioration in the quality of life caused by the disease and the temporal and financial burden of treatment are the major issues among patients with AA.² The preferred treatments for AA include therapeutic agents, such as topical or intralesional corticosteroid, and contact immunotherapy.¹⁻³ Other treatments, including systemic corticosteroids, anthralin, excimer laser, and novel therapeutics, such as Janus kinase inhibitors, have also been used. Despite the numerous treatment options, the overall prognosis of AA is not favorable, involving relapse and recalcitrant progression. Specifically, patients with severe subtypes, such as alopecia totalis (AT) and alopecia universalis (AU), which involve complete scalp hair loss, have a lower likelihood of hair regrowth than those with patchy alopecia (PA).³ Management of AT and AU can be challenging, and although multiple treatment modalities have been explored, no therapy is currently FDA-approved. Although certain treatments showed significant hair regrowth, no treatment was completely effective. A novel therapeutic option with the use of topical vitamin D analog (calcipotriol) in treatment of AA is emerging. The

effectiveness of calcipotriol in the treatment of AA is controversial, but its limited adverse effects need to be considered.⁴⁻¹⁰ Vitamin D (Vit.D) plays an important role in calcium homeostasis, immune regulation, and cell growth and differentiation.⁶⁻¹⁰ The active form of Vit.D mediates its action by binding to specific Vit.D receptors (VDR) located in the nuclei of target cells.¹⁰⁻¹² The mechanism by which the topical calcipotriol induces hair regrowth in AA lesions is by regulating the differentiation of B cells, T cells, dendritic cells, and the expression of Toll-like receptors.^{5,11-13}

MATERIAL AND METHODS

Three cases, treated topical calcipotriol cream 50 µg/g twice daily for 12 weeks and followed up regularly at 4 weeks intervals. After the end of the 12 weeks, all patient were followed up for 6 months. The efficacy was measured by SALT, hair regrowth using photographic assessment, Hair Pull Test and physical examination. All patients without associated skin diseases like atopic dermatitis, psoriasis, autoimmune diseases (lupus erythematosus, rheumatoid arthritis, scleroderma, and thyroid disorder), patients taking oral corticosteroids in previous 2 weeks, patients applying topical corticosteroid or patients who have received regular Vit.D supplementation in previous 6 months.

Table 1: Patient Details and Treatment Response of Topical Calcipotriol

Serial Number	Age and duration of disease	Sex, of	Previous Treatment	Treatment response, measured by Dermoscopic finding, Physical examination, Hair Pull Test			Follow up
				4weeks	8weeks	12 weeks	
Case 1	30 years old, male, 12 month		Oral methylprednisolone, topical clobetasole and injection steroid Stopped due to noncompliance, and many adverse effects.	Development of new hair follicles and vellus hair growth over scalp	Significant regrowth of hair over scalp, hair pull test negative	Excellent improvement in hair regrowth over scalp, hair pull test negative	Complete hair regrowth at 12 weeks No relapse at 6 months
Case 2	35 years old, male, 8 month		Topical clobetasole and intralesion injection steroids but there is no improvement and the disease remains progressive, atrophy. Decided to discontinue due to his frustration.	Vellus hair formation was seen	Significant regrowth of hair over scalp, hair pull test negative	Good Improvement in hair regrowth over scalp, hair pull test negative	The drug was stopped after 12 weeks of treatment and the patient was followed for 6 months, no recurrence, no side effects
Case 3	17 years old, female, 6 month		Oral methylprednisolone and topical clobetasole, could not be continued due to on going disease progression and many side effect that arise	Significant hair regrowth over the scalp patches	Significant regrowth of hair over scalp, hair pull test negative	Complete hair regrowth, hair pull test negative -	Drug was stopped after 12 weeks of treatment and no recurrence

¹² Table 2: Severity of Alopecia Tool Score (SALT) Before and After Treatment

SALT	case 1	case 2	case 3
Before treatment	100%	95%	95%
After treatment	0%	5%	5%

RESULTS

The clinical profile of patients and dramatic response is summarized in table 1, and SALT score of disease in table 2. The efficacy was measured by hair regrowth using photographic assessment in figure 1.





Figure 1

- A. Clinical photograph at baseline
- B. 4 weeks post treatment
- C. 8 weeks post treatment
- D. 12 weeks post treatment
- E. Clinical photograph at 6 months post treatment were stopped

DISCUSSION

Alopecia areata (AA) is an autoimmune disease directed at the hair follicle. Although usually limited to patchy hair loss over the scalp (focalis), AA can present as total loss of scalp hair (AT) or total loss of both scalp and body hair (AU).¹³⁻¹⁵ Although the exact pathogenesis of AA still unknown up to now, there is a widely accepted hypothesis that AA is related with autoreactivity of cytotoxic T cell. Therefore, intralesion corticosteroid is frequently used for AA to suppression immune block.^{9,13,15} In case 1 and 2 of this study showed no response with intralesion corticosteroid. The other hypothesis is associated with VDR. The keratinocytes lining the outer layer of the hair follicle possess VDR. This VDR plays important role in hair cycle, especially anagen initiation.^{2,3,5-9}

Although a novel therapeutic option with the use of topical vitamin D analog (calcipotriol) in treatment of AA is emerging. The effectiveness of topical calcipotriol in the treatment of AA is controversial, but its limited adverse effects need to be considered.⁴⁻⁹ AA associated with reduced VDR expression reported a complete. A clinical remission after topical calcipotriol ointment 50 µg/mL applied once daily for 3 months.⁶ AA patients using topical 0.005% calcipotriol cream twice daily for 12 weeks had greater than 50% hair regrowth in 65% of patients, greater than 75% hair regrowth in 62.5% of patients and complete regrowth in 27.1%.⁷ Twice daily topical 0.005% calcipotriol in 22 patients with patchy AA resulted in 59.1% of patients demonstrating hair growth within 4.21 ± 2.13 weeks.⁸ Berth *et al*, reported they failed to support its benefit in AT/AU.¹⁴ Studies using topical Vit.D in alopecia areata are inconsistent and limited by small sample size or lack of appropriate controls.⁶⁻⁹ Molinelli *et al*, found evidence to support the efficacy of the topical Vit.D analogue formulation for the treatment of limited AA, with a lower incidence of adverse events compared with the topical clobetasol.¹¹

In our case 3, Oral corticosteroid and topical clobetasol could not be continued due to ongoing disease progression. The most promising therapies with the highest quality data

include diphenylcyclopropenone, squaric acid dibutylester, photodynamic therapy, steroids, and cyclosporine in combination with methylprednisolone. High-quality randomized-controlled trials with large sample sizes are lacking. Unified outcome guidelines are encouraged to facilitate comparison of future studies.^{14,15} Orecchia *et al*, reported topical use of calcipotriol does not potentiate squaric acid dibutylester effectiveness in the treatment of alopecia areata but suggests that calcipotriol has an inhibiting action on cell multiplication.¹⁶

Therefore none of the treatments mentioned above has been ratified by the US FDA, indicating that a new and more effective therapeutic intervention aiming at new targets is needed.¹⁰ Preliminary results suggest a potential therapeutic benefit for topical Vit.D with minor side effects.^{1,3,6,8,9} It has been demonstrated that VDR is strongly expressed in the keratinocytes of human and murine hair follicles and that the lack of expression of VDR is associated with reduced hair follicle growth and epidermal differentiation. Studies of the scalps of AA patients have also shown reduced VDR expression in the hair follicles of affected area. Results from recent studies suggest that topical application of topical calcipotriol has a beneficial effect on patchy AA of the scalp.¹⁰⁻¹² These explain why topical analog of Vit.D can be used to treat AA. In this study, serial case with AT in their scalp fully recovered after application of calcipotriol and we have evaluated the efficacy and safety profile of the topical calcipotriol. All our patients showed a response starting at 4 weeks, 8 weeks and 12 weeks, there was no recurrence after 6 months of therapy was stopped

CONCLUSION

In conclusion, although there are astounding therapeutic effects described in this report, further investigation about the role of the topical analog vit.D in AT through large and well-designed clinical trials is needed to support the clinical application of single topical calcipotriol as a treatment option for this refractory disease.

Table 3: Summary of Clinical Investigations on Single Topical Calcipotriol in Treatments for Alopecia

Study	Patient Number	Intervention	Study Design	Results
Orecchia et al, 1995	28 AA	sensitized with a 2% DBE solution and a 0.001% SADBE solution was applied to the whole scalp. An ointment containing 4 µg/g calcipotriol was applied to the left side of the scalp	Double Blind	topical use of calcipotriol does not potentiate squaric acid dibutylester effectiveness in the treatment alopecia areata but suggests that calcipotriol has an inhibiting action on cell multiplication
Berth et al.2009	20 AT/AU	calcipotriol ointment 50 µg/g applied b.i.d. for 6 months	Double-blind	No response
Kim et al. 2012	1 Patchy AA	calcipotriol topical solution 50 µg/mL applied daily for 3 months	Case report	Complete hair regrowth at 3 months No relapse at 9 months
Suswardana et al. 2014	1 Patchy AA	topical calcipotriol Cream 50 µg/g b.i.d. for 16 weeks	Case report	Complete hair regrowth at 3 months No relapse at 8 months
Cerman et al. 2015	48 AA	topical calcipotriol 0.005% b.i.d. for 12 weeks	Cohort study	Significantly lower SALT score at 12 weeks compared to baseline Hair regrowth greater than >50% seen in 75% of patients, hair regrowth of >75% seen in 62.5%, and complete regrowth in 27.1%
Narang et al. 2017	22 AA	topical calcipotriol 0.005% b.i.d. for 12 weeks	Cohort study	59.1% of patients had hair regrowth, with onset at 4.21 ± 2.13 weeks 9 patients with 0% change, 4 patients with 25% change, 3 patients with 26–50% change, 6 patients with >50% change

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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