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## Treatment of alopecia totalis/universalis/focalis with vitamin D and analogs: Three case reports and a literature review

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Papadimitriou DT was the patient's treating pediatric endocrinologist and contributed to the drafting and editing of the manuscript; Bothou C reviewed the literature and contributed to drafting the manuscript; Dermitzaki E performed the clinical follow-up; Alexopoulos A performed the dermatological evaluations; Mastorakos G reviewed and supervised the manuscript drafting and interpreted the clinical implications; All authors issued final approval for the version to be submitted.

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## Abstract

### BACKGROUND

Alopecia areata (AA) is an inflammatory disease with autoimmune, environmental, and inherited components directed at the hair follicle, either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or total loss of both scalp and body hair (Universalis, AU). Despite multiple treatment modalities, no therapy exists. Vitamin D deficiency in patients with AA/AT/AF influences disease severity and duration, inversely correlating with inflammation histologically.

### CASE SUMMARY

Three girls presented with AT (P1), AU (P2), and AF (P3) at the ages of 1, 5, and 5 years, respectively. For P1-P2, all available treatments implemented for 2 years had failed. We started an initial 6-mo repletion with oral cholecalciferol 2000/4000 IU/d, with no apparent effect. Then we attempted immunomodulation using oral calcitriol and its analog paricalcitol. On calcitriol, 0.5 mcg/d P1 regrew hair within 6 mo. After 4 years, a relapse with loss of eyebrow hair was resolved after doubling the calcitriol dose to 0.5 mcg × 2/d; the results have been maintained for 6 years to date. On calcitriol, 0.25 mcg × 3/d P2 led to the development of asymptomatic hypercalcemia-hypercalciuria, which was immediately resolved by

Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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switching to paricalcitol 2 mcg × 3/d; mild tolerable hypercalciuria was maintained. Hair regrowth was observed at 6 mo, stabilizing only as fur at 12 mo. AF in P3 was resolved completely within 3 mo on a daily high dose (8000 IU) of cholecalciferol.

#### CONCLUSION

Vitamin D may have immunomodulating therapeutic impact on AT/AU/AF, which needs to be explored with further pilot clinical trials.

**Key Words:** Alopecia totalis; Alopecia universalis; Alopecia focalis; Calcitriol; Paricalcitol; Vitamin D; Case report

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**Core Tip:** Alopecia areata (AA) is an inflammatory disease with autoimmune, environmental, and inherited components directed at the hair follicle, either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or total loss of both scalp and body hair (Universalis, AU). Despite multiple treatment modalities, there is no current therapy. Three girls aged 3, 7, and 5 years with AT, AU, and AF were treated with oral calcitriol, paricalcitol, and cholecalciferol, showing hair regrowth at 6, 6, and 3 mo, respectively but only as fur for P2 with AU. Vitamin D may have an immunomodulating therapeutic impact on AT/AU/AF, which needs to be explored with further pilot clinical trials testing the effectiveness and establishing the optimal form and dosage of vitamin D.

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#### INTRODUCTION

Alopecia areata (AA) is a non-scarring T-cell mediated autoimmune disease directed at the hair follicle (HF), either limited to patchy hair loss over the scalp (Focalis, AF), total loss of scalp hair (Totalis, AT), or loss of both scalp and body hair (Universalis, AU). Its prevalence among the young and adult population is 0.7%-3.8%, significantly affecting patients' lives and having psychosocial implications. Management of the disease can be challenging, and despite multiple treatment modalities, no successful treatment is available. Pediatric age and more extensive disease with resistance to initial therapies with corticosteroids may sometimes benefit from a cocktail of established therapies. The likelihood of complete spontaneous regrowth in AA is estimated to be less than 10%, but even then, relapses are common and frustrating[1].

HF is a micro-organ with its own immune and hormonal microenvironment. During the anagen segment of the hair cycle, HF epithelium generates and maintains an area of immune privilege, which is mainly characterized by the low expression of major histocompatibility complex class Ia antigens and local production of immunosuppressive agents. This HF immune privilege (HFIP) is important for the protection of anagen- and melanogenesis-associated antigens from immune recognition by autoreactive CD8+ T cells. The collapse of mechanisms that maintain the HFIP renders the HF susceptible to inflammatory assault, contributing to the development of AA, while growing evidence implicates interferon gamma in triggering HFIP collapse[2].

The role of vitamin D in the proliferation and differentiation of keratinocytes has been extensively studied and well established in the literature. Vitamin D is synthesized in the epidermal keratinocytes from 7-Dehydrocholesterol by ultraviolet B light (290-315 nm) or is acquired through the diet and dietary supplements[3,4]. Further hydroxylation in the liver leads to 25-hydroxyvitamin-D3 (25OHD3) and subsequently in the kidney to the active hormone 1-25-dihydroxyvitamin-D3 (1-25(OH)2D3, calcitriol). The role of the vitamin D receptor (VDR) in the hair cycle was

first suggested by the observation of alopecia in patients with type II vitamin D dependent rickets (VDDR IIA), an autosomal recessive disorder that, due to a defect in the VDR, is characterized by hypokalemia, hypophosphatemia, hyperparathyroidism, rickets, osteomalacia, dental caries, and alopecia universalis[5]. Patients with VDDR IIA have normal hair at birth, possibly because they have normal HF morphogenesis, but they lose their hair between 1 and 3 mo of age. Histological results of VDDR IIA alopecia include a normal infundibular portion of the HF but the lower two-thirds of the HF, below the level of the sebaceous gland, is replaced by irregular epithelial structures and dermal cysts.

Recent studies in mice and *in vitro* support the pivotal role of VDR in the postnatal maintenance of the HF. In the late anagen and catagen phases, there is an increase in VDR expression, which is associated with the decreased proliferation and increased differentiation of keratinocytes, making the presence of VDR a prerequisite for maintenance of the normal hair cycle[6]. However, the roles of vitamin D and the VDR in the hair cycle have not been completely elucidated, and clinical therapies for hair disorders have not been established. However, vitamin D is an important immunomodulator, and vitamin D deficiency has been reported in many autoimmune diseases [7]. Recent retrospective studies among AA patients compared to controls reveal significantly reduced vitamin D levels among patients[8,9].

We present three cases with AT/AU/AF that emphasize the pivotal role of treatment with cholecalciferol, the active hormone calcitriol, and its analogue paricalcitol.

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## CASE PRESENTATION

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### **Chief complaints**

Sudden and total hair loss in the scalp, both the scalp and body, and in multiple focalized areas of the scalp in three girls aged 1, 5, and 5 years, respectively.

### **History of present illness**

Two girls diagnosed with AT and AU based on clinical examination[10], who experienced sudden (within 3 mo) and total hair loss at the age of 1 and 5 years, presented to our pediatric endocrine unit at the ages of 3 (patient #1, P1) and 7 years (patient #2, P2), respectively. For 2 years, all available local and systemic treatments including oral methotrexate had been tried by pediatric and adult dermatology clinics with no results.

A third girl aged 5 years (patient #3, P3) presented with sudden (within the last month) hair loss compatible with AF.

### **History of past illness**

None of the patients were suffering from other chronic dermatological diseases (vitiligo and psoriasis) or other systemic diseases such as diabetes mellitus, anemia, hypothyroidism or hyperthyroidism, systemic lupus, rheumatoid arthritis, chronic renal or liver disease, also autoimmune polyendocrinopathy type 1 was also excluded with the necessary laboratory testing. In P3, although there was normal thyroid function with negative anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies, signs of Hashimoto's thyroiditis were shown in thyroid ultrasonography (U/S) performed by a pediatric radiologist. All three girls were vitamin D-deficient with vitamin D levels (25OHD3) of 60 nmol/L (24 ng/mL) in P1, 50 nmol/L (20 ng/mL) in P2, and 42.5 nmol/L (17 ng/mL) in P3, and normal calcium metabolism and parathyroid hormone (PTH) (PTH < 45 ng/mL)[11]. Zinc, B12, vitamin A, vitamin E, and ferritin levels were within normal range in all patients, also with negative celiac serology.

### **Personal and family history**

None of the patients nor any first-degree family members were suffering from other chronic dermatological diseases (vitiligo and psoriasis).

### **Physical examination**

In P1, there was complete absence of scalp hair and eyebrows. In P2, there was complete absence of body hair. In P3, five localized areas had complete hair loss at the scalp, with a diameter of 3-5 cm, along with a palpable goiter (Figure 1). An experienced pediatric dermatologist found no apparent focal or systemic dermatological



**Figure 1** Hair regrowth in the alopecia totalis case (P1, top) and the alopecia universalis case (P2, middle); and presentation of the alopecia focalis case (P3, bottom).

cause in any of the girls, with absence of signs of skin or nail candidiasis, to exclude the possibility of autoimmune polyglandular syndrome.

### **Laboratory examinations**

All three girls were vitamin D-deficient with vitamin D levels (25OHD<sub>3</sub>) found 60 nmol/L (24 ng/mL) in P1, 50 nmol/L (20 ng/mL) in P2 and 42.5 nmol/L (17 ng/mL) in P3, with the rest of the calcium metabolism and PTH being normal (PTH < 45 ng/mL)[11]. Zinc, vitamin B12, vitamin A, vitamin E, and ferritin levels were within normal range in all patients, also having a negative serology negative for celiac disease.

### **Imaging examinations**

A thyroid ultrasound was performed by a pediatric radiologist. In P3, although there was normal thyroid function with negative anti-TPO and anti-Tg abs, signs of Hashimoto's thyroiditis were found.

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## **FINAL DIAGNOSIS**

P1 had AT, P2 AU and P3 AF.

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## **TREATMENT**

As P1 and P2 were vitamin D-deficient, we started an initial 6-mo repletion with oral cholecalciferol 2000/4000 IU/d at the upper tolerable daily dose, according to the Endocrine Society Clinical Practice Expert Guideline Committee, *i.e.* infants < 1-year 2000 IU daily and children 1-18 years 4000 IU daily[12] ([https://www.endocrine.org/clinical-practice-guidelines/vitamin d deficiency](https://www.endocrine.org/clinical-practice-guidelines/vitamin-d-deficiency)), with no apparent effect on hair growth. Then, based on the previous experience of our group we attempted to induce immunomodulation by oral calcitriol[13-15] in P1 and P2, while both girls were continuously supplemented with cholecalciferol 2000 and 4000 IU p.o., respectively.

Active forms of vitamin D, such as calcitriol (1,25(OH)<sub>2</sub> D, the biologically active form of vitamin D), and its up to 10 times less calcemic analog paricalcitol[16], are used to treat secondary hyperparathyroidism occurring in patients with kidney disease, leading to bone disease. Since they have different effects on calcium metabolism, experience in their use as well as special precautions are required (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c3d5546b-ccd4-4988-9d86-9f0b29e12128>; <https://www.mayoclinic.org/drugs-supplements/paricalcitol-oral-route/precautions/drg-20073059?p=1>).

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## **OUTCOME AND FOLLOW-UP**

Treatment with 0.5 mcg/d P1 grew hair within the first 6 mo of treatment (except a small region at the rear of the scalp; **Figure 1**). After 4 years, there was a relapse with loss of eyebrow hair, which was resolved within 3 mo after raising calcitriol dose at 0.5

× 2 mcg/d. The result has been maintained for 7 years now since treatment initiation with normal calcium metabolism: calcium (Ca) 10.1 mg/dL (normal range: 8.5-10.5 mg/dL), phosphorus (P) 5.1 mg/dL (normal range: 3.5-5.5 mg/dL), alkaline phosphatase (ALP) 318 IU/L (normal range: 199-440 U/L), parathyroid hormone (PTH) 26 pg/mL (normal < 45 pg/mL), 25OHD3 41 ng/mL (normal range: 30-150 ng/mL), 1-25 (OH)2D3 30 ng/mL (normal range: 18-80 pg/mL) and normal 0.08 Ca/Cr ratio in a 2 h morning urine sample (normal range: < 0.22).

Treatment with 0.25 mcg × 3/d p.o. P2 developed asymptomatic hypercalcemia – hypercalciuria (Ca 14 mg/dL, Urine Ca/Cr 1.37 in a 2-h morning sample) within 1 mo and was immediately switched to an even higher corresponding dose of paricalcitol [17] at 2 mcg × 3/d p.o. Then calcium metabolism normalized: Ca 9.8 mg/dL, P 3.8 mg/dL, ALP 146 IU/L, PTH 22.4 pg/mL, 25(OH)D 152.5 nmol/L (61 ng/mL), 1-25 (OH)2 D3 38 ng/mL, apart from mild hypercalciuria (Ca/Cr 0.5 in a 2-h morning urine sample), closely monitored and with normal kidney U/S every 6 mo. Hair regrowth including scalp hair, eyebrows and eyelashes was noted by 6 mo but maintained at 12 mo only as fur (Figure 1). With no further improvement, paricalcitol treatment was discontinued at 12 mo with a complete subsequent relapse of AU.

In P3, treatment with high dose cholecalciferol p.o. (8000 IU/d) completely resolved all focalized alopecia areas within 3 mo with normal hair regrowth at all sites and 25(OH)D levels restored at 155 nmol/L (62 ng/mL). At 6 mo dermatological examination of the scalp was completely normal. Cholecalciferol substitution was continued with a maintenance dose of 4000 IU/d, which does not require medical supervision according to the Endocrine Society Expert Committee guidelines, in order to maintain 25(OH)D levels 100-150 nmol/L[12]. Subsequent follow-ups for 2 years were uneventful.

## DISCUSSION

We present three cases of AT/AU/AF treated with oral calcitriol, its analogue paricalcitol, and high-dose cholecalciferol. Almost complete hair regrowth including scalp hair and eyebrows was accomplished in the girl with AT on calcitriol treatment. A relapse was avoided by raising the calcitriol dose and the patient can be considered cured, with the result being maintained for 7 years now, having a beneficial effect on the girl's well-being. Treatment with calcitriol is being continued though, as calcium metabolism is completely normal, and the family wishes to maintain it being afraid of a possible relapse. In the AU case, calcitriol caused hypercalcemia – hypercalciuria and was switched to paricalcitol, a less calcemic analog. While hair regrowth was noted by 6 mo of treatment with even eyelashes being temporarily restored, at 12 mo scalp hair was still as fur, leading to treatment discontinuation and subsequent complete AU relapse. In the AF case, early onset high dose daily cholecalciferol treatment was successful, restoring completely alopecia areas with no further relapses. Undoubtedly, just three cases do not suffice to suggest generalized use of the presented approach. Nevertheless, the possible implications of vitamin D in the clinical care of patients with AT/AU/AF, as in autoimmune disorders in general, are being examined and discussed. Using high dose cholecalciferol, calcitriol and paricalcitol, we aimed to exert immunomodulatory effects on T-cells while upregulating the expression of VDR on HF and epidermal keratinocytes. For the safety of the off-label use of calcitriol and paricalcitol we based our approach on the previous experience of our group[13,14] and also on published experience of pediatric patients with chronic kidney disease and hyperparathyroidism[18,19], closely monitoring our patients.

It is well established that vitamin D reduces the function and differentiation of T-helper 17 cells, down-regulates the T-helper 1 cells and increases the action of T-regs, resulting in immunomodulation[7,20]. AT/AU, as an inflammatory disease with autoimmune, environmental, and inherited components, is characterized by imbalance of the above-mentioned parts of the immune system. Previous work of our group has shown the negativation of Type 1 associated autoantibodies after treatment with oral calcitriol[13] but also practically the cure of severe atopic dermatitis, also an autoimmune disease, with calcitriol and its analogue paricalcitol[21] a synthetic analogue with 3 times less binding affinity to the VDR but 10-times less effect on calcium metabolism per se[16].

Regarding the role of vitamin D and its receptor (VDR) in hair, it is well established that VDR is expressed in the outer root sheath (ORS), HF bulb, and the sebaceous gland in the HF and participates in differentiation of HFs[6]. VDR knock out mice (VDR KO) have been proved to suffer from alopecia areata[22]. VDR expression is

decreased in HF and epidermal keratinocytes in AA leading to suppression of Wnt/ beta catenin signals and cell differentiation[23]. This downregulation of VDR could be explained either due to the local inflammation that leads to loss of the VDR expression or due to the vitamin D deficiency. This is supported by the hypothesis that vitamin D deficiency is a stimulus for the local inflammation and vice versa, which could lead to a vicious cycle in the chronic status of the disease. Re-appearance of the VDR on HF was detected after topical calcipotriol treatment, a synthetic derivative of calcitriol, used in the treatment of psoriasis[24]. Similarly with other studies presenting small series of patients, using local treatments containing calcipotriol, over 50% experienced improvement of the alopecia manifestations[9,25].

On the other hand, vitamin D deficiency among AA patients is a common finding. Many studies reveal significantly reduced 25(OH)D concentrations among this population[26,27]. Another recent prospective study comparing 30 patients with AA with 30 controls showed that vitamin D deficiency in AA influences disease severity and duration[28]. Simultaneously, VDR expression was reduced in AA and as hypothesized, was inversely correlated with inflammation histologically. These findings suggest, not only the possible relation of vitamin D deficiency with the pathogenesis of the disease but also the potential use of vitamin D as a therapeutic approach. The fact that patients with vitamin D deficiency run a longer course of disease and it takes longer for autoimmunity to regress despite multiple immunosuppressive therapies enhance the hypothesis of a vitamin D role in pathogenesis of AA. Patients with AA have a higher prevalence of vitamin D deficiency and lower 25(OH)D levels than the control groups[29], although further research is needed to elucidate the underlying mechanisms and assess the efficacy of vitamin D in treating AA, as vitamin D may suppress autoimmunity and VDR down regulation.

The study from Daroach *et al*[28] was – to the best of our knowledge – the first effort of systematic supplementation of the vitamin D deficient AA. They used oral cholecalciferol 60.000 IU once weekly for 12 wk and detected clinical improvement and VDR upregulation, even though statistically significant results were not acquired[28]. The reason for this might be that, according to many studies, serum 25(OH)D above a certain cut-off may be required for its immunomodulatory actions but also a minimum duration of treatment for the upregulation of the VDR expression is required[7]. The dosage that has been used in this study would assure normal (30-150 ng/mL) 25(OH)D concentrations, above or around 40-60 ng/mL, as in our AF patient. Though, as in our cases, a pharmacological therapeutic intervention, as the individualized schemes with the active hormone calcitriol and its analog paricalcitol we used, may be required to obtain positive therapeutic results. This is because cholecalciferol is subjected to internal transformation to the active hormone calcitriol to exert most of its immunomodulatory actions and this counterbalance has its limitations[30].

Even if not finally successful in resolving AU in our case, the active hormone calcitriol and its analog paricalcitol had some undeniable and visible effect on scalp and body hair – even as fur -, on eyebrows', and eyelashes' regrowth, indicating that vitamin D possesses an immunomodulating capability that interferes with the mechanism of disease in AA, opening the perspective of more powerful, less calcemic, and potentially more specific calcitriol analogs in the future. Thus, in addition to the cumulative evidence of vitamin D deficiency among alopecia patients, new therapeutic horizons in the complex management of this disease may be envisioned, especially now that newer more potent calcitriol analogues are being tested as anti-cancer and anti-metastatic agents. MART-10 for instance, has 3 times more VDR-binding affinity and much more resistance to CYP24A degradation compared to calcitriol, sparing the side effect of hypercalcemia[31].

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## CONCLUSION

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Treatment with vitamin D in the form of cholecalciferol, as well the active hormone calcitriol and its analogs, such as the already marketed paricalcitol, may be envisioned for patients with AA/AT/AF, however with close monitoring of Ca metabolism parameters. Pilot clinical trials and RCTs are required to prove the effectiveness and safety of this therapeutic approach, as to establish the optimal form and dosage of vitamin D administration, alone or in combination with other treatments.

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