Combined Topical Vitamin D3 Analogues with Steroid in Treatment of Alopecia Areata

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1. Topical Vit D3 analogues:

Vitamin D has been associated with various autoimmune diseases. Recently, vitamin D deficiency has been reported in AA **[1].** Moreover, topical calcipotriol has been reported to be used successfully in treating AA **[2].**

1.1. Vitamin D sources, metabolism and functions

In the human body there are two major forms of vitamin D. More than 90% is vitamin D_3 (cholecalciferol), which is converted from 7-dehydrocholesterol by ultraviolet light B (UVB) exposure in the skin. About 10% is vitamin D2 (ergocalciferol), which comes from dietary sources. Both are biologically inactive **[3].** In the liver, vitamin D is metabolically converted into 25-hydroxyvitamin D (25(OH)D) which is biologically inactive at physiological concentration. 25(OH)D has been considered as one of the most reliable indicator of Vitamin D levels in humans **[4]**. In the kidney, 25(OH)D is further converted to the biologically active metabolites 1, $25(OH)_2D_3$ (calcitriol) by 25(OH) 1α-hydroxy-D. The 1α-hydroxy enzyme is also widely expressed in non-kidney cells including immune cells and is able to convert the inactive 25(OH)D into the active 1, $25(OH)_2D$ in either an autocrine or paracrine manner **[5].**

Vitamin D functions by binding to the vitamin D receptor (VDR), a member of nuclear hormone receptors which is widely expressed in the kidney, immune cells, osteocytes and other types of cells. VDR activated by vitamin D forms a heterodimeric complex with retinoid X receptor. This complex is recruited to the vitamin D response elements in the target genes and interacts with additional co-regulators, influencing the expression of many genes. As such, vitamin D possesses multiple functions and target organs**[6].**

1.2. Vitamin D status in AA

A number of studies demonstrated significantly lower levels of vitamin D in the patients with AA than the control group **[7].** Several studies showed significantly higher prevalence of vitamin D insufficiency in patients with AA than the control group **[8].**

But there were two reports of inconsistent results. A Turkish study found that AA patients had a deficiency of 25(OH)D, but there was no statistically significant difference in the serum vitamin D levels between AA patients and healthy controls. The authors said that this might be due to the universal tendency toward lower values of 25(OH)D in their geographical area, and they noted that the blood samples were collected only once during the late fall and winter months **[9].**

In a study involving 55,929 women in the Nurses' Health Study, 133 cases of AA were identified over a follow-up of 12 years. The association between estimated vitamin D status and self-reported incident AA was prospectively evaluated. No significant association between a predictive score of serum 25(OH)D levels and risk of incident AA was found [10].

Importantly, two systemic reviews and meta-analyses published in 2018 did demonstrate that, patients with AA have a higher prevalence of vitamin D deficiency and lower vitamin D levels than the control group[1,11]. Moreover, several studies revealed that serum vitamin D levels significantly and inversely correlate with the severity of AA [12].

Studies also showed that serum[13] and tissue [8] VDR levels were lower in AA. One study found a negative correlation of tissue VDR and extent of AA.

Taken together, the above data show a substantial link between the levels of vitamin D and AA, suggesting an important role of vitamin D in the pathogenesis of the disease. However, the mechanism underlying this relationship still has to be deciphered [13 ,8].

1.3. Possible role of vitamin D in pathogenesis of AA

Hair loss in AA is caused by the destruction of HF cycle. However, the role of vitamin D in in HF cycling is not clear. Although a study showed in mice that in calbindin-D_{9k} knockout pups, a maternal vitamin D-deficient/low-calcium diet leads to transient noncicatricial alopecia, suggesting a role for calcium and possibly vitamin D in postnatal HF cycling [14],

VDR may function as a selective suppressor/de-repressor of gene expression in the absence of 1, $25(OH)_2D_3$[15].Wnt/β-catenin signaling is a key player in inducing the onset of anagen and maintaining the cycling transition during the initiation and regeneration of HFs[16]. Reduction of VDR expression in AA may be related to decreased hair cycle-related signals-Wnt/β-catenin signals. The decreased expression of VDR in AA is believed to be involved in the disruption of HF cycling in AA [17].

1.4. Vitamin D for treatment of AA

Since vitamin D plays a role in the pathogenesis of AA, it may be considered as a treatment for the disease. The beneficial effects of 1, $25(OH)_2D_3$ supplementation have been observed in experimental autoimmune models, but the systemic use of vitamin D in the treatment of human autoimmune diseases is still under investigation[18].

In the experimental autoimmune models, animals are mostly supplemented with a high dose of 1, $25(OH)_2D_3$, but in humans, this strategy may lead to hypercalcemia[18].

In clinical application of active vitamin D, the supraphysiological doses needed to modulate immune responses may elicit concomitant calcemic side effects. To overcome this limitation, hypocalcemic analogs of active vitamin D with similar immunoregulatory activity are being exploited. Calcipotriol, a vitamin D_3 analogue, which is at least 100 times less calcemic than calcitriol, has been topically used in treating psoriasis with beneficial effects[19].

Early in 1991, **Berth-Jones and Hutchinson**[20] reported a group of 20 patients with alopecia totalis or universalis studied by placebo-controlled double-blind design. Each subject applied ointment containing 50 pg/g calcipotriol to one side of the scalp and matching vehicle to the

other. There was no evidence of a response to calcipotriol in this group of subjects with very severe alopecia. However, new studies reported encouraging results [20].

2. Topical Corticosteroids

2.1. Indications

Topical corticosteroids play a major role in the treatment of many dermatologic conditions. They are FDA-approved and indicated for the use of inflammatory and pruritic presentations of dermatologic conditions. The well-known indications are for diseases such as psoriasis, limited areas of vitiligo, eczema, atopic dermatitis, phimosis, acute radiation dermatitis, lichen planus, lichen simplex chronicus, discoid lupus erythematosus, and lichen sclerosis.They are effective for conditions involving hyper-proliferation, immunological, and inflammatory properties[21].

2.2. Mechanism of Action

The mechanism of action of topical corticosteroids is vast, consisting of anti-inflammatory, anti-mitotic, and immunosuppressive effects[22].The anti-inflammatory effect of topical corticosteroids consists of vasoconstriction, inhibition of the release of phospholipase A2, and a direct inhibitory effect on DNA and inflammatory transcription factors[23]. Vasoconstriction of the blood vessels within the upper dermis decreases the number of inflammatory mediators being delivered to the region applied [22]. The anti-inflammatory effect also occurs from the synthesis of lipocortin which inhibits phospholipase A2, ultimately decreasing the production of prostaglandins and leukotrienes. Topical corticosteroids also act directly at the DNA level to increase the expression of anti-inflammatory genes and indirectly inhibit inflammatory transcription factors, such as NFkb, to decrease the expression of pro-inflammatory genes [22].

The anti-mitotic effect of topical corticosteroids plays a great role in the treatment of psoriasis; it is proposed that this decrease in epidermal mitosis is secondary to an increase in lipocortin, an endogenous glucocorticoid-regulated protein. An anti-mitotic effect is also present in the dermis which inhibits cell proliferation and collagen synthesis[24].

The immunosuppressive effects of topical corticosteroids involve the inhibition of humoral factors involved in the inflammatory response as well as suppression of the maturation, differentiation, and proliferation of all immune cells [25].

2.3. Administration

Topical corticosteroids are administered topically; however, successful administration depends upon obtaining an accurate diagnosis, choosing the correct drug, selecting the appropriate vehicle and potency, and the frequency of application[22].

The vehicle is the carrier of the drug. The vehicle selection depends on the region affected and the type of lesion present. It also functions to hydrate the skin and increase absorption. The vehicle options include the following [21]:

Ointments - administered for thick hyper-keratotic lesions; the most potent vehicle since they are the most occlusive and should not be administered on hair-bearing regions because it may result in folliculitis[21].

Creams - less potent than ointment but cosmetically more appealing since they leave no residue; the drying, non-occlusive nature leads to their administration for acute exudative inflammation and dermatitis within the intertriginous areas [26].

Lotions - less occlusive and greasy; work well in hair-bearing regions

Gels - like lotions, less occlusive and greasy; work well in hair-bearing regions; more beneficial for the scalp as they do not cause matting of thleast occlusive and greasye hair

Foams - highly effective for steroid delivery to the scalp but are costly[27].

The potency of topical corticosteroids is the amount of drug needed to produce a desired therapeutic effect. The gold standard for determining potency is the vasoconstrictor assay which measures the vasoconstrictive properties based upon cutaneous vasoconstriction. The United States classification consists of seven classes, with class I superpotent and class VII least potent[26].

3. **Topical corticosteroids in treatment of alopecia areata**

Several topical corticosteroids with varying levels of efficacy have been used to treat alopecia areata. These include fluocinolone acetonide cream, fluocinolone scalp gel, betamethasone valerate lotion, clobetasol propionate ointment, dexamethasone in a penetration-enhancing vehicle and halcinonide cream[28]. They are a good option in children because of their painless application and wide safety margin. Topical corticosteroids are ineffective in alopecia totalis/universalis Folliculitis is a common side effect of corticosteroid treatment, appearing after a few weeks of treatment. Telangiectasia and local atrophy have also been reported. Treatment must be continued for a minimum of 3 months before regrowth can be expected and maintenance therapy often is sometimes necessary[28].

Lenane, et al., (2014)[29]compared the efficacy and safety of a high- vs low-potency topical corticosteroid in pediatric patients.Finding that topical clobetasol propionate, 0.05%, cream is efficacious and safe as a first-line agent for limited patchy childhood alopecia areata[29].

Lalosevic et al., (2015)[30]in study of combined oral pulse and topical corticosteroid therapy for severe alopecia areata in children. Finding that Combined topical and oral pulse corticosteroid therapy of AA in children shows long-lasting results, without serious side effects[30].

Efficacy and Safety of Topical Calcipotriol 0.005% Versus Topical Clobetasol 0.05%

Molinelli, et al., (2020) [28]finding that Patches treated with calcipotriol ointment showed greater and faster response rates than did those treated with topical clobetasol, although the differences were not statistically significant[28].

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