CHAPTER 38

VITAMIN D TREATMENT IN DERMATOLOGY

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INTRODUCTION

The most important functions of vitamin D which is discovered in 1922 are bone mineralization, absorbtion of calcium from intestine and prevention of rickets. It is known as vitamin D3 of animal origin and it is synthesized from 7-dehydrocholesterol by the action of UVB on the skin and then it is converted to active vitamin D3 (1alpha, 25-dihydroxyvitamin D3) by hydroxylation in liver and kidney, respectively. Active vitamin D3 binds to serum proteins and reaches the target tissue. Target tissues include vitamin D receptor protein (VDR). There exist three analogues of vitamin D3 as topical form which are called calcipotriol, maxacalcitol and tacalcitol.[1,2] It is found that Vitamin D analogs are effective in psoriasis since it inhibits the proliferation and regulates the differentiation of keratinocytes.[3] Many skin diseases also have a similar pathogenesis to pathogenesis of psoriasis.[4] This study is performed to demonstrate the off-label use of vitamin D in skin diseases other than psoriasis.

MATERIAL AND METHOD

Screening about the use of vitamin D in skin diseases was performed by using the PubMed database. The keywords 'vitamin D skin, vitamin D3 skin, maxacalcitol,tacalcitol, calcipotriol' were used. Most of papers were eliminated because of being associated with psoriasis or not being a skin disease. Sixty of them are included in the study. Thirty of them are case reports, eleven of them are comperative studies, ten of them are rendomized-controlled studies (RKS) and eight of them are uncontrolled studies. Papers are categorized by disease; vitiligo (Table 1), keratinization disorders (Table 2), tumoral disorders (Table 3) sclerodermoid disorders (Table 4) and others. (Table 5)

RESULTS

1. Vitiligo

Four RKS were determined. In two studies only PUVA treatment and PUVA-calcipotriol combined therapy were compared.In this studies calcipotriol (0,05 mg/g) was applied to only one side of the body of vitiligo patients who were treated with PUVA.In one of the studies, combined therapy applied side of the body was significantly healed than the other side (%63-%15). At the end of the other study also combined therapy applied side was improved completely in most of the patients (%70).[5,6] In another RKS calcipotriol,betamethasone dipropionate and combined theraphy were compared in forty-nine vitiligo patients. At the end of three months, proportion of healed patients were %6,7, %13,3 and %26,7.[7] Tacalcitol and tacalcitol-NBUVB combined therapy were compared in another RKS. At the end of the study, combine therapy applied side showed significantly ($p<0,0005$) higher repigmentation than the other side.[8] Four comperative studies were determined which compare only NBUVB treatment and NBUVB-calcipotriol combined therapy.In two of these studies combined therapy was more effective than the other treatment.[9,10] In the other two studies there was no

Table 1. Vitiligo

STUDY	CONTENTS	RESULTS	REFERENCES
Comperative	NB-UVB vs Calcipotriol+NB-UVB[4]	2 Effective,2 Noneffective	9,10,11,12
	PUVA vs Calcipotriol+PUVA[2]	1 Effective,1 Noneffective	14,15
	Calcipotriol vs Clobetasol Propionate[1]	Noneffective	16
	Calcipotriol vs Untreated[1]	Noneffective	17
	PUVA vs Calcipotriol+PUVA[2]	2 Effective	5,6
Randomized Controlled	Calcipotriol vs Betamethasone Dipropionate vs Combined Theraphy[1]	Only calcipotriol is noneffective, combined therapy more effective than betamethasone	7
	Nb-UVB vs Tacalcitol+NB-UVB[1]	Effective	8
Uncontrolled	Calcipotriene+Betamethasone Dipropionate[1]	Effective	13

Vitamin D can be applied in other skin diseas with different mechanisms of action.In patients with xerotic skin,mechanism of action is increasing fillagrin expression[44] in hailey hailey disease it is inhibiting acantholysis by transactivates integrin gene.[53] It can also be used in sclerodermoid disease such as morphea by inhibitation of fibroblasts proliferation and regulation of collagen and fibronectin synthesis.[40]

In tumoral disorders vitamin d can be a part of the treatment.In two case reports topical vitamin d was applied to regulate keratinocytes.[34,35] Expecially in old patients who cannot tolerate surgery it can be safe.In an in vitro study it was shown that vitamin d could be effective in premalign lesions due to its regulation of MMP9 and MMP13 expression.[65] Associatively, in a case report maxacalcitol was given to patients with bowen disease and after eight weeks, lesion regressed.[38]

Vitamin d may be successful in hair disorders.In a case report topical patient with alopesi areata was treated with calcipotriol successfully.[62] Hair follicles contain two different cells;epidermal keratinocytes and mesodermal dermal papilla.Both of them have VDR which is necessary for growth of hair.[66,67]

In some of skin diseases such as granuloma annulare and atopic dermatitis.[48,60] vitamin D can be used as systemic therapy. Also, in some studies it was detected that vitamin D is not effective in some diseases such as seborrhoeic dermatitis and hypertrophic scar.[63,64]There is an in vitro study about use of vitamin d in acne vulgaris patients. Propionibacterium acnes is very important for pathogenesis of acne since they induce Th17 differentiation.Vitamin d modulates Th17.[68] In the future, topical vitamin d analogues will may be used for acne.

As a result, vitamin d can be useful in a lot of skin diseases other than psoriyasis due to various mechanisms of action as topical or systemic but it is stil required further and comprehensive studies about use of vitamin d in various skin diseases.

REFERENCES

1. Kira M, Kobayashi T. ,Yoshikawa K. Vitamin D and the Skin. The Journal of Dermatology 2003;30: 429–437,
2. Kragballe K. Calcipotriol: A New Drug for Topical Psoriasis Treatment. Pharmacology & Toxicology 1995, 77: 241-246.
3. Lamba S. , Lebwohl M. Combination therapy with vitamin D analogues. British Journal of Dermatology 2001; 144: 27-32.
4. Holm E, Jemec GBE. The therapeutic potential of calcipotriol in disease other than psoriasis. International Journal of Dermatology 2002, 41, 38-43.
5. Ermis O. , Alpsoy E. , Cetin L. et al. Is the efficacy of psoralen plus ultraviolet A therapy for vitiligo enhanced by concurrent topical calcipotriol? A plasebo-controlled double-blind study. British Journal of Dermatology 2001; 145: 472-475.
6. Parsad D. , Saini R. , Verma N. Combination of PUVA-sol and topical calcipotriol in vitiligo. Dermatology. 1998;197(2):167-70.
7. Kumaran MS. , Kaur I. , Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. JEADV 2006, 20, 269-273.
8. Leone G, Pacifico A. , Iacovelli P. et al. Tacalcitol and narrow-band phototherapy in patients with vitiligo. Clinical and Experimental Dermatology 2006; 31: 200-205.
9. Goktas EO. , Aydın F. , Senturk N. et al. Combination of narrow band UVB and topical calcipotriol for the treatment of vitiligo. JEADV 2006, 20, 553-557.
10. Kullavanijaya P. , Lim HW. Topical calcipotriene and narrowband ultraviolet B in the treatment of vitiligo. Photodermatol Photoimmunol Photomed 2004; 20: 248-251.
11. Khullar G, Kanwar A.J. , Singh S. et al. Comparison of efficacy and safety profile of topical calcipotriol ointment in combination with NB-UVB vs. NB-UVB alone in the treatment of vitiligo: a 24-week prospective right-left comparative clinical trial. JEADV 2015;29(5):925-32
12. Gamil H. , Attwa E. , Ghonemy S. Narrowband ultraviolet B as monotherapy and in combination with topical calcipotriol in the treatment of generalized vitiligo. Clinical and Experimental Dermatology. 2010; 35: 919-921
13. Newman M.D. , Silverberg N.B. Once-Daily Application of Calcipotriene 0.005%-Betamethasone Dipropionate 0.064% Ointment for Repigmentation of Facial Vitiligo. Cutis. 2011;88: 256-259.
14. Cherif F. , Azaiz MI. , Ben Hamida A. , et al. Calcipotriol and PUVA as treatment for vitiligo. Dermatology Online Journal 2003; 9 (5): 4.
15. Baysal V. , Yıldırım M, Erel A. , et al. Is the combination of calcipotriol and PUVA effective in vitiligo? JEADV 2003; 17: 229-302.
16. Köse O. , Gür A.R. , Kurumlu Z. et al. Calcipotriol ointment versus clobetasol ointment in localized vitiligo: an open, comparative clinical trial. International Journal of Dermatology 2002; 41: 612-621.
17. Chiaverini C. , Passeron T. , Ortonne JP. Treatment of vitiligo by topical calcipotriol. JEADV 2002; 16: 137-138.
18. Gulec A.T. , Seckin D. Confluent and reticulated papillomatosis: treatment with topical calcipotriol. British Journal of Dermatology, 141, 1136-1153.
19. Carrozzo M.A. , Gatti S. , Ferranti G. et al. Calcipotriol treatment of confluent and reticulated papillomatosis (Gougerot-Carteaud syndrome). JEADV 2000; 14: 131-133.
20. Koh MJA, Lee JSS, Chong WS. Systematized Epidermal Nevus with Epidermolytic Hyperkeratosis Improving with Topical Calcipotriol/Betametasone Dipropionate Combination Ointment. Pediatric Dermatology. 2013;30: 370-373.
21. Bilgin I. , Bozdag K.E. , Uysal S. et al. Progressive symmetrical erythrokeratoderma – response to topical calcipotriol. J Dermatol Case Rep 2011; 3: 50-52.
22. Kragballe K. , Steijlen PM. , Ibsen HH. et al. Efficacy, tolerability and safety of calcipotriol ointment in disorders of keratinization. Results of a randomized, double-blind, vehicle-controlled, right/left comparative study. Arch Dermatol. 1995;131(5):556-60.

23. Contreras M.E. , Gottfried L.C. , Bang R.H. et al. Axillary intertriginous granular parakeratosis responsive to topical calcipotriene and ammonium lactate. Inteenational Journal of Dermatology 2003: 42: 382-383.
24. Bakardzhiev I. , Kavaklieva S. Successful treatment of disseminated superficial actinic porokeratosis with calcipotriol. International Journal of Dermatology 2012; 51: 1131-1144.
25. Bohm M, Luger T.A. , Bonsmann G. Disseminated superficial actinic porokeratosis: Treatment with topical tacalcitol. J Am Acad Dermatol. 1999;40(3):479-80.
26. Vozmediano JFM, Hita CA, Cabrerizo AG. Sjogren-Larrson Sydrome: Treatment with topical calcipotriol. Pediatric Dermatology 2003;20(2):179-80
27. Umekoji A, Fukai K, Ishii M. A case of mosaic-type bullous congenital ichthyosiform erythroderma successfully treated with topical maxacalcitol, a vitamin D3 analogue. Clinical and Experimental Dermatology, 2008;33(4):501-2.
28. Teraki Y, Sato Y, Izaki S. Successful treatment of stucco keratosis with maxacalcitol. British Journal of Dermatology 2006; 154: 1074-1108.
29. Masatoshi ABE, Yasuda M, Yokoyama Y. et al. Successful treatment of combination therapy with tacalcitol lotion associated with sunscreen for localized Darier's disease. Journal of Dermatology 2010; 37: 718-721.
30. Sadahira C. , Yoneda K. , Moriue T. , et al. Successful treatment of keratosis follicularis squamosa with topical tacalcitol. British Journal of Dermatology 2006 154, pp998-1023.
31. Hayashi H. Treatment of Grover's disease with tacalcitol. Clinical and Experimental Dermatology 2002;27: 160-165.
32. Kim S.H. , Kang J.H. , Seo J.K et al. Successful treatment of lichen spinulosus with topical tacalcitol cream. Pediatric Dermatology 2010;27(5):546-7
33. Femiano F, Gombos F, Scully C. et al. Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. Int. J. Oral Maxillofac. Surg. 2001; 30: 2-406.
34. Batalla A, Carpintero ML, De La Torre C. Disseminated epidermolytic acanthoma with partial response to calcipotriol ointment. The Journal of Dermatology 2013;40(2):144-5.
35. Scanni G, Pellacani G. Topical calcipotriol as a new therapeutic option for the treatment of clear cell acanthoma. An Bras Dermatol. 2014;89(5):803-5.
36. Wakahara M, Kiyohara T, Kumakiri M. et al. Bilateral Nevus Comedonicus: Efficacy of Topical Tacalcitol Ointment. Acta Derm Venereol. 2003;83(1):51.
37. Hayashi J, Matsui C, Mitsuishi T. et al. Treatment of localized epidermodysplasia verruciformis with tacalcitol ointment. International Journal of Dermatology 2002; 41: 817-820.
38. Karashima T, Hashikawa K, Ono F. et al. Successful Treatment of Bowen's Disease with Topical Maxacalcitol. Acta Derm Venereol 2012; 92: 585-663.
39. Caca-Biljanovska NG. , Vlckova-Laskoska MT. , Dervendi DV. et al. Treatment of generalized morphea with oral 1,25-dihydroxyvitamin D3. Adv Exp Med Biol. 1999;455:299-304.
40. Kreuter A, Gambichler T, Avermaete A. et al. Combined Treatment with Calcipotriol Ointment and Low-Dose Ultraviolet A1 Phototherapy in Childhood Morphea. Pediatric Dermatology 2001;18: 241-245,
41. Cunningham BB, Landells IDR, Langman C. et al. Topical calcipotriene for morphea/linear scleroderma. J Am Acad Dermatol 1998;39: 211-5.
42. Ascari-Raccagni A, Dondas A, Dubini A. et al. Biopsy proven morphea treated with tacalcitol ointment: case report. Acta Dermatovenerol Croat. 2010;18(4):248-51.
43. Dytoc MT, Kossintseva I, Ting PT. First case series on the use of calcipotriol-betamethasone dipropionate for morphoea. British Journal of Dermatology 2007; 157: 609-635.
44. Russell M. Assessing the Relationship between Vitamin D3 and Stratum Corneum Hydration for the Treatment of Xerotic Skin. Nutrients 2012; 4: 1213-1218.
45. Wong S.S. , Goh C.L. Double-blind, Right/Left Comparison of Calcipotriol Ointment and Betamethasone Ointment in the Treatment of Prurigo Nodularis. Arch Dermatol 2000;136(6):807-8
46. Katayama I, Miyazaki Y, Nishioka K. Topical vitamin D3 (tacalcitol) for steroid-resistant prurigo. British Journal of Dermatology 1996; 135: 237-240.
47. Gruber-Wackernagel A. , Bambach I. , Legat F.J. et al. Randomized double-blinded placebo-controlled intrainvidual trial on topical treatment with a 1,25-dihydroxyvitamin D3 analogue in polymorphic light eruption. British Association of Dermatologists 2011; 165: 152-163.
48. Camargo CA, Ganmaa D, Sidbury R. et al. Randomized trial of vitamin D supplementation for winter-related atopic-dermatitis in children. J Allergy Clin Immunol. 2014;134(4):831-835.
49. Gniadecki R. Calcipotriol for erythema annulare centrifugum. British Journal of Dermatology 2002; 146: 317-319.
50. Inaba H, Suzuki T, Adachi A. et al. Successful treatment of warts with a combination of maxacalcitol ointment and salicylic acid sticking plaster. Journal of Dermatology 2006; 33: 383-385.
51. Imagawa I , Suzuki H. Successful treatment of refractory warts with topical vitamin D3 derivative in 17 patients. Journal of Dermatology 2007; 34: 264-266.
52. Labandeira J, Vasquez-Blanco M, Paredes C. et al. Efficacy of topical calcipotriol in the treatment of a giant viral wart. Pediatr Dermatol. 2005; 22(4): 375-6.
53. Jeon SY, Ha SM, Ko DY. et al. Hailey-Hailey Disease Treated with Topical Tacalcitol. Ann Dermatol. 2013; 25(3): 389-390.
54. Aoki T, Hashimoto H. , Koseki S. et al. Tacalcitol is effective against Hailey-Hailey disease both in vivo and in vitro. British Journal of Dermatology 1998; 139: 897-901.
55. Escribano-Stable JC, Domenech C, Matarredona J. et al. Tacalcitol in the Treatment of Acquired Perforating Collagenosis. Case Rep. Dermatol 2014; 6: 69-73.
56. Yoshiya H. Effectiveness of topical maxacalcitol for acquired perforating disorder. J Am Acad Dermatol. 2013; 68(6):181-2.
57. Wongkietkachorn K. , Intarasupht J. , Srisuttiyakorn C. et al. Linear Atrophoderma of Moulin: A Case Report and Review of the Literature. Case Rep Dermatol 2013; 5: 11-14.

58. Bohm I, Bieber T, Bauer R. Successful therapy of an IL-VEN in a 7-year old girl with calcipotriol. Hautarzt. 1999; 50(11):812-4.

59. Kim DH, Lee JW, Kim IS. et al. Successful Treatment of Alopecia Areata with Topical Calcipotriol. Ann Dermatol. 2012; 24: 341-344.

60. Boyd AS. Granuloma annulare responsive to oral calcitriol. International Journal of Dermatology 2012; 51: 115-124.

61. Kim WJ, Song M, Ko HC. et al. Topical tacalcitol ointment can be a good therapeutic choice in erythromelanosis follicularis faciei et colli. J Eur Acad Dermatol Venereol 2007; 21: 956-63.

62. Khoo B.P. , Tay Y.K. , Goh C.L. Calcipotriol ointment vs.betamethasone 17-valerate ointment in the treatment of lichen amyloidosis. International Journal of Dermatology 1999; 38: 539-541.

63. Van der Veer WM. , Jacobs XE. , Waardenburg IE. et al. Topical Calcipotriol for Preventive Treatment of Hypertrophic Scars. Arch Dermatol. 2009;145(11):1269-75.

64. Basak PY, Ergin S. Comparative effects of calcipotriol and betamethasone 17-valerate solution in the treatment of seborrhoeic dermatitis of the scalp. J Eur Acad Dermatol Venereol. 2001;15(1):86-8.

65. Meephansan J, Komine M, Tsuda H. et al. Suppressive effect of calcipotriol on the induction of matrix metalloproteinase (MMP)-9 and MMP-13 in a human squamous cell carcinoma cell line. Clinical and Experimental Dermatology 2012;37(8):889-96

66. Demay MB, MacDonald PN, Skorija K. et al. Role of the vitamin D receptor in hair follicle biology. J Steroid Biochem Mol Biol. 2007; 103(3-5): 344-346.

67. Malloy PJ, Feldman D. The Role of Vitamin D Receptor Mutations in the Development of Alopecia. Mol Cell Endocrinol 2011; 347: 90-96.

68. Agak GW, Qin M, Nobe J. et al. Propionibacterium acnes induces an interleukin-17 response in acne vulgaris that is regulated by vitamin A and vitamin D. J Invest Dermatol. 2014; 134(2): 366-373.