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LETTER TO THE EDITOR

Vitamin D and HPV infection: Clinical pearls

Dear Editor,

Treating warts is a great challenge for dermatologists since no single efficacious treatment modality, with ideal efficacy and cure rates, has been introduced up to the present time.[1] Immunotherapy is a novel and emerging therapeutic modality which functions by increasing the cell-mediated immunity. Vitamin D is one of the agents that has been tried as immune therapeutic purposes in warts. This affordable, safe and efficient therapeutic modality can have promising results in the management of warts. Many trials have justified the beneficial effects of intralesional and topical vitamin D in the management of resistant warts.[2]

Vitamin D receptor (VDR), which is present in every part of the skin, including keratinocytes, melanocytes, and fibroblasts is the key component of therapeutic function of vitamin D.[3] As a matter of fact, vitamin D plays an important role in regulating epidermal cell proliferation and differentiation. Moreover, it can induce apoptosis and modulate cytokine production (decrease pro inflammatory ones, such as IL-17 and IL-21 and increase anti-inflammatory ones such as IL-10) and thereby, prevent inflammation. Therefore, keratinocytes proliferation is inhibited which is a therapeutic aim in the management of warts. Interestingly, vitamin D, at low concentrations, can stimulate keratinocyte proliferation and differentiation, while its higher concentrations can inhibit the same.[4]

On the other hand, vitamin D has multiple effects on the human immune system. It inhibits B cells differentiation, thereby preventing immunoglobulins secretion. Moreover, it inhibits T-cells proliferation and stimulates the native immunity by inducing antimicrobial peptide. Hence, its shortage can predispose to bacterial and viral infections, including HPV infection.[3,5] Intralesional injection of vitamin D at the location of cutaneous warts can also stimulate a delayed hypersensitivity response, thereby eradicating local and distant lesions.[6] Moreover, the trauma imposed by the injection per se can result in the resolution of warts in previously sensitized patients.[7]

Studies have shown decreased serum levels of 25-hydroxy vitamin D in patients with genital warts.[8] Moreover, a relationship has been demonstrated between serum vitamin D levels and cutaneous warts.[9] However, it does not seem that its levels reflect the severity of warts or their resistance to treatment.[10]

Vitamin D analogs have been administered to patients with various forms of warts in different formulations and routes; topical vitamin D derivatives, in the form of calcipotriene or maxacalcitol ointment or calcitriol solution, have been successful in treating warts, including anogenital lesions which are among the most difficult-to-treat warts.[11] This formulation has also been effective in managing recalcitrant warts in immunocompromised patients.[12] Furthermore, using topical vitamin D3 with occlusive dressing technique has also been quite effective in warts regression.[12]

Intralesional injection of vitamin D also had been especially beneficial in the regression warts.

A recent study on total of 204 cutaneous warts examined the efficacy of intralesional vitamin D3 solution (0.2 mL of 600 000 IU, per patient, every 2 weeks for a total of four times) and found a 82% complete clearance rate after 4 sessions. The only side effects were mild swelling and itching at the injection site.[13] Aktas et al. reported a similar response rate of 80% after 2 therapeutic sessions conducted every month on 20 patients with plantar wart.[14]

The results of some recent studies on efficacy of intralesional vitamin D were summarized in Table 1.

Tawfik et al. evaluated the effect of injection of vitamin D (7.5 mg/mL) into the base of genital warts on 20 patients, conducted every 2 weeks for 2 months. They found a complete clearance rate of only 11% and concluded that the efficacy of intralesional vitamin D injection for anogenital warts may not be as much as its benefits in treating extragenital ones.[21]

It is interesting that intralesional injection of vitamin D might lead to simultaneous clearance of warts at distant areas following immunotherapy. This phenomenon is known as "field effect" and can be especially beneficial in patients with multiple and inaccessible warts.[22] Oral calcitriol had been used in the treatment of psoriasis and seborrheic keratosis; however, no trials have been performed on its benefits in managing warts.[23]

In general, different studies have shown different and sometimes, conflicting results about the efficacy and cure rates of vitamin D treatment on various warts. This could be explained by the specific subtypes of HPV involved as the etiology of the wart. For example, stronger body T-cell responses induced against HPV genotype 6 could be the reason why genital warts due to this genotype have milder presentations and respond more favorably to immunologic

TABLE 1 Some recent studies regarding clinical efficacy of intra lesional vitamin D on wart treatment.

Study	Intervention	Number of patients	Therapeutic sessions	Complete clearance rate
Al-Sabak et al.[13]	IL vitamin D	40	Every 2 weeks 4 sessions	82%
Aktas et al.[14]	IL vitamin D	20	Every month 2 sessions	80%
Naresh et al.[15]	IL vitamin D	60	Every 3 weeks	80%
Kaviya et al.[4]	IL vitamin D	42	Every 2 weeks	78%
El-Sayed et al.[16]	IL vitamin D	35	Every 2 weeks	63%
	IL 2% zinc sulfate	35	4 sessions	71%
EEM et al.[17]	IL vitamin D	31	Every 2 weeks	35%
	IL PPD	31	4 sessions	69%
Shaldon et al.[18]	IL vitamin D	30	Every 3 weeks	67%
	IL MMR	30	Up to 6 sessions	80%
Raveendra et al.[19]	IL vitamin D	50	Every 2 weeks	84%
	IL PPD	50	4 sessions	76%
Yousaf et al.[20]	IL vitamin D	30	Every 2 weeks	63%
	cryotherapy	30	Up to 6 sessions	43%

treatment, compared to those developed due to HPV genotype 11.[24] On the other hand, higher dose of vitamin D with longer duration and more frequent sessions has been associated with higher cure rates in different studies.[7] Moreover, healing rates have been lower in studies in which dermoscopy had been utilized to confirm complete clearance of warts, as many of the apparently healed lesions might still have wart remnants in dermoscopic examination.[25] Some situations can also affect the therapeutic response of warts to vitamin D; for example, older age, female sex, and cigarette smoking can decrease cure rates of intralesional vitamin D in the management of warts.[26]

Combination of vitamin D immunotherapy with mechanical and destructive therapies such as cryotherapy has also been tried in different studies, with favorable cure rates. However, further studies are needed to confirm it.[27]

Various types of warts in different locations might need different doses of intralesional vitamin D. The maximum dose of vitamin D in each session has been up to 7.5 mg in different studies. The interval between intralesional injection sessions has been 4 weeks, and the total duration or number of sessions has been upon the time of complete clearance.[28,29] It is recommended to use dermoscopy for assessing treatment response and confirming clearance, since naked eye might falsely announce disappearance of some warts, which have not been totally cleared on dermoscopy. This could prevent premature cessation of treatment, thereby diminishing the risk of recurrences.[25]

In conclusion, difficult-to-treat warts are significant challenges for both dermatologists and infectionists. Immunotherapeutic interventions, including intralesional and topical vitamin D, has gained interests in the management of these lesion due to its simple application, good compliance, few side effects, high cure rates and low risk of recurrence. On the other hand, since vitamin D deficiency is a very common problem in many populations and because this micronutrient plays an important role in boosting the immune response, measuring serum levels of vitamin D and prescribing vitamin D supplementation in case of vitamin D deficiency is a reasonable strategy.

Further studies with large sample size are needed to shed more lights on this issues.

AUTHOR CONTRIBUTIONS

P.H., A.G., Z.M., and Z.A. performed the research. P.H. and K.B. designed the research study. K.B. and Z.A. supervised the findings of this work. All authors discussed the results. A.G. wrote the initial draft. Z.A. and Z.M. wrote the revised version.

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All the authors declare that there is no conflict of interest.

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Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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