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Commentary

Cutaneous viral warts – can retinoids change routine management?

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Key Message: Retinoids are effective in treating recalcitrant warts; further studies are required to determine the exact regimen.

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Cutaneous viral warts (CVW) are a common condition encountered by many physicians of different disciplines. CVW can be self-limiting, especially in the pediatric population, although spontaneous regression could be prolonged and last months to years. However, treatment is sought by many who are unwilling to wait for spontaneous clearance, by those who do not experience such resolution and for reasons of preventing infections of other individuals. Aesthetic and functional discomfort caused by CVW and the possible risk of malignancy further favors treating these lesions. As it is impossible to determine which CVW resolve independently and which as a result of treatment, evaluation of treatment efficacy is seriously hampered. Furthermore, the wide range of therapeutic modalities, administered singly or in combination, is an indicator that none were found to be curative, and each has its benefits and disadvantages [1].

Treating CVW should be individualized, i.e., tailored according to the number, site, type, and persistence of the warts; the patients' immune status, compliance and preferences; and the healthcare provider's experience. The therapeutic armamentarium is wide, and consists of destructive agents (keratolytics, cryotherapy, curettage and cautery, laser, photodynamic therapy), antimitotic agents (podophyllin, bleomycin, retinoids), immune stimulants (topical sensitizers, cimetidine), and topical virucidal agents (formaldehyde, glutaraldehyde) [2].

Topical salicylic acid (SA) and cryotherapy are amongst the most common first-line therapies for CVW [3], yet a meta-analysis found that SA has only a moderate therapeutic effect on CVW, and cryotherapy compared with placebo was not found to be therapeutically superior. On the other hand, two trials supported that their combination is more effective than SA alone. Data regarding treatment with 5-fluorouracil (intra-lesional or topical) or 5% imiquimod cream could not be integrated, further demonstrating the lack of consistency in the different regimens treating CVW, and the need for large randomized controlled trials including a comparison to placebo [4].

In a recently published meta-analysis, topical and systemic retinoids were found to be safe and effective for the treatment of mostly persistent CVW in immunocompetent patients. Topical retinoids were not inferior to systemic retinoids, and even demonstrated a lower relapse rate. This could be partially attributed to selection bias, as systemic therapy is preferred over topical therapy in severe cases with prolonged disease course, or when higher numbers of warts or thicker lesions are treated, as topical agents might be impractical. Topical adapalene 0.1% gel with occlusion was the most effective agent for the treatment of plantar warts, with a 97% complete response (CR) rate, and no related irritant contact dermatitis. Oral etretinate 1 mg/kg/day was found to be the most effective amongst systemic retinoids, with a CR rate of 75% and no cases of relapse during a follow-up period of nearly 2 years, yet it was evaluated in only one prospective cohort study. The most studied derivative, isotretinoin, was found to be the second most effective, usually administered at a dosage of 0.5 mg/kg/day (a relatively low dose), leading to a 71% CR rate. Side effects of systemic retinoids treatments were the prevalent mucocutaneous adverse events known to be related to the various vitamin A derivatives [5]. Interestingly, retinoids were also found to have a high CR rate,

low recurrence rate, and good safety profile in treating genital warts, and might serve as appropriate second-line therapy for recalcitrant genital warts that failed to respond to prior treatment modalities [6].

Recently, studies evaluating the efficacy of isotretinoin as an adjuvant therapy in treating CVW were published. Nofal et al. compared the efficacy of treating multiple plane warts with either isotretinoin alone, candida antigen alone, or a combination of both. Isotretinoin alone, given at a dose of 0.3 mg/kg/day for 3 months, led to a 44.4% CR, while candida antigen alone demonstrated a 55.6% CR rate. The combination of both (at the same dosage of isotretinoin) showed a lower CR rate of 38.8% [7]. In contrast, Dave and Abdelmaksoud demonstrated a 100% CR rate with no relapse in a 1-year follow up period, in 12 immunocompetent patients with recalcitrant CVW (11 patients with common warts and one with plane ones, located on the face). Interestingly, isotretinoin was given at a low dose regimen of 0.1–0.2 mg/kg/day every other day for 3 months, with no significant adverse effects [8]. The striking difference in the clearance rate, despite the significantly lower dosage and frequency and the persistent nature of warts, was discussed recently by Nofal and Fawzy, suggesting that it may be partially due to differences in the study population and sample size, further emphasizing that isotretinoin efficacy as an adjuvant therapy and the recommended regimen requires further interventional therapeutic trials [9].

Systemic retinoids were shown to be of benefit in widespread and/or recalcitrant CVW, as often observed in immunocompromised patients, and may harbor an additional chemoprophylactic value for the prevention of non-melanoma skin cancers. The latter is mainly observed with acitretin, which is of high importance in this prone population [10]. Immunocompromised patients exhibited multiple hypertrophic treatment resistant CVW, with a greater risk of malignancy, mostly squamous cell carcinoma, thus treatment with systemic retinoids might be a favorable therapeutic option. Retinoids could be administered as a sole treatment [11,12] or in combination with other modalities such as pulsed dye laser [13], intralesional candida antigen [14], and others.

According to the available data, retinoids appear to be a worthy therapeutic option in immunocompetent patients with recalcitrant warts who fail to respond to first-line accessible modalities, such as SA or cryotherapy, necessitating an alternative or an adjuvant therapy. This may alter the management of CVW, and even prioritize topical retinoids such as adapalene gel, as effective topical agents. Systemic retinoids are suitable in cases of multiple long-standing warts, with the promising equivalent low-dose isotretinoin given as an adjuvant, and thus may be exempt from laboratory monitoring. Further double-blind placebo-controlled studies are warranted in order to establish and validate the most suitable regimen for each patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

M.O.S and A.L. were responsible for gathering data and wrote the first draft of the manuscript. All coauthors contributed to writing of the manuscript. All coauthors have provided important intellectual input and approved the final version of the manuscript.

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