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Commentary: A Novel Topical 2% Povidone-Iodine Solution for the Treatment of Common Warts: A Randomized, Double-Blind, Vehicle-Controlled Trial

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In "A Novel Topical 2% Povidone-Iodine Solution for the Treatment of Common Warts: A Randomized, Double-Blind, Vehicle-Controlled Trial," twenty-one patients aged 8 years and older were enrolled in Phase II clinical trial to assess the efficacy, safety, and tolerability of twice-daily application of a novel 2% topical povidone–iodine solution in a dimethyl sulfoxide vehicle for 12 weeks duration[1]. Patients were blocked randomized into two groups consisting of 14 patients in the active arm and 7 patients in the vehicle only arm. All patients were evaluated at baseline, week 4, 8 and 12 and the results were compared for overall Global Aesthetic Improvement Scale (GAIS) improvement. GAIS is a 5-point scale rating global esthetic improvement in appearance, compared to pretreatment, as judged by the investigator. GAIS scoring for individual warts at each visit was as follows: very much improved (+3), much improved (+2), improved (+1), no change (0) and worse (-1).

For patients randomized into the active arm of treatment, [1]0/13 (77%) demonstrated sustained improvement in the GAIS scale score, defined as an overall positive score derived from the summation of individual assessments at the week 4, 8 and 12 visits. A sustained improvement was defined as wart showing decreased diameter and thickness from baseline. In the 3/13 (23%) patients in the active arm that did not show sustained improvement, the patients' warts remained stable in size, and there were no additional warts at the sites observed. Each of the patients was followed through week 12, and there were no recurrences of warts that cleared before the 12-week time period. There were no serious safety or tolerability issues reported.

Povidone-iodine (PVP-I) is a broad-spectrum anti-microbial that has the ability to eradicate microorganisms including bacteria, viruses, yeasts, molds, fungi, and protozoa. It is well known in the medical community as a pre-operative scrub, however, it is scarcely used outside of this indication despite a strong body of literature supporting its use in a variety of infectious settings[2-7]. PVP-I is non-specific in its mechanism of action and therefore lacks the development of resistance that limits the utility of so many conventional antibiotics and antivirals. It inhibits electron transport and cellular respiration, destabilizes membranes, inhibits protein synthesis and denatures nucleic acids[8].

This study, modeled on similar verruca trials that were listed in the NIH database of clinical trials employed the GAIS score as the primary endpoint, which only measured a decrease in diameter and thickness, not complete resolution of individual lesions. GAIS is not an ideal endpoint for verruca studies, and subsequent investigations would benefit from the use of an absolute number count where efficacy could be demonstrated by resolution and documentation of the change in a number of lesions for each individual patient. This would be a more precise and clinically meaningful endpoint. It is the endpoint we are currently pursuing in our expanded ongoing Phase II trials in molluscum contagiosum. The lack of a standardized grading scale for verruca vulgaris explains the discrepancy in how data is reported in these studies and limits comparison across trials. A collaborative consensus on grading criteria for verruca vulgaris would be beneficial.

When first working with PVP-I in our novel DMSO preparations, we concentrated on nail indications (onychomycosis and paronychia) because there were no universally effective, safe therapies for these very common diseases. The treatment course of these typically lasts up to a year and resistance to the anti-fungals remains a limiting factor of treatment. A topical solution was developed that was able to be easily applied to and under the nail apparatus[5,6,9]. After seeing strong positive results in nail disease, we shifted our focus to poorly treated viral skin diseases. PVP-I's lack of resistance lent itself very well to verruca vulgaris as well, and it was then selected as the follow-up indication. We employed the same PVP-I solution in the small Phase II study which is the subject of this commentary. We learned that a solution was not ideal for treatment of warts for several reasons. The architecture of verruca with its abundant papillomatosis does not provide sufficient surface area for adherence and of the solution, as it tends to run off of the surface of the lesion onto the surrounding skin. The thick layer of hyperkeratotic stratum corneum overlying the virus also provides a barrier to absorption when using a solution. Also, a large portion of the population that suffers from verruca are in the pediatric age range, and they are often less patient in allowing the solution to absorb and dry. Semi-solid vehicles were thus tested, developed and then prescribed to address these shortcomings, and a gel vehicle was found to be most efficacious.

The recent study also was not sufficiently powered to show statistical significance though we did observe a clear trend that warrants further investigation. Unpublished data also demonstrated that the majority of patients cleared with the continuous use of the topical solution, as longer treatment lengths were required given the poor penetration of the liquid. The use of a gel circumvents this issue as it is much more adherent to lesions, hence a 12-week study would presumably be sufficient. A longer study with more subjects has been designed and is currently in pre-enrollment. Additionally, we have begun a global, multi-site investigation of a gel formulation in molluscum contagiosum.

This study raises the fundamental question of how best to eradicate human papilloma virus from mucosal and cutaneous surfaces. There is a lack of consensus guidelines for treatment, no FDA-approved take-home therapies, and no clearly superior therapy. The literature divides itself between immunomodulation, physical means of destruction, targeted anti-viral treatments and idiosyncratic combinations thereof.

Immunomodulators are in theory the most elegant. They represent a promising treatment modality that could lead to resolution without physically manipulating the skin or scarring, and in additional would augment the host response against the causative agent, thereby leading to complete resolution and decreased recurrences[10]. Immunomodulators can be administered systemically, intralesionally, intradermally, or topically with the goal of upregulating the Th1 arm of the immune system. H2 receptor antagonists have long been part of the vernacular however a systematic review concluded that there is incomplete evidence for the efficacy of cimetidine or ranitidine in verruca[11]. Candida antigen and imiquimod studies show equivocal efficacy and both treatments are not without risk of significant side effects[12-17]. Zinc 10mg/kd/day was initially reported to have 76.9-87% total clearance rates at 2 months[18,19], however, subsequent studies revealed a high incidence of side effects and similar clearance rates to placebo (28% vs. 24%)[20,21].

Newer immunomodulatory agents have become available such as Echinacea, green tea catechins, and the quadrivalent human papillomavirus vaccine but few studies have been carried out, and a definite role has yet to be defined due to lack of larger, randomized, placebo-controlled trials[10]. . Photodynamic therapy has also been studied with some success in eradicating lesions, however tolerance of procedure in the pediatric population due to pain in children and true efficacy has yet to be studied[22]. Upregulating the immune system to treat the lesions would be ideal, however, it has yet to be fully elucidated in clinical practice.

Clearance with the anti-viral cidofovir has been reported both topically and intralesionally, but the interpretation of the efficacy is limited by lack of randomized, controlled, double-blinded studies[23,24]. An effective topical anti-viral that could penetrate the keratinized skin, such as dilute PVP-I in a penetration-enhancing gel vehicle, could revolutionize the approach to this disease.

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Conflict of interest statement

K. Capriotti is a co-founder and owns in equity in Veloce BioPharma, LLC

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