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REVIEW ARTICLE

Wart Immunotherapies: A Short Review

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Abstract:

Objective:

To review the efficacy and costs of various contact immunotherapies, contact allergens, intralesional immunotherapies, and intralesional cytotoxic agents for the treatment of recalcitrant warts.

Background:

Cutaneous warts are common viral skin lesions caused by human papillomavirus that can be challenging to treat and frustrating for physicians and patients. Although several treatment options exist, there is no single treatment that can ensure a complete response with lack of lesion recurrence. Immunotherapies for recalcitrant warts present as a cost-effective, efficient therapy option for patients. Intralesional approaches have the added benefit of affecting warts at locations distant to the target location by inducing a systemic T-cell mediated response in the body.

Results:

Various contact immunotherapies, contact allergens, intralesional immunotherapies, and intralesional cytotoxic agents have shown to be effective in treating warts. The costs of each treatment varies drastically from around $10 US to over $1000 US to achieve a complete response. Several antigens were found to be both efficacious and cost effective.

Conclusion:

Although efficacy of several antigens has been confirmed by randomized studies, more randomized comparative studies will need to be performed in order to determine the best antigen and correct standardized doses for the treatment of warts in individual patients. It is important to note that individual response to antigen type and dose may vary among patients. Therefore, further studies may play an important role in the use of immunotherapies in a clinical setting.

Keywords: Warts, Immunotherapy, Immunodermatology, Cutaneous lesions, Intralesional, HPV.

1. INTRODUCTION

Cutaneous warts are common viral skin lesions caused by the infection of the human papillomavirus (HPV). Recalcitrant or recurrent warts may be disfiguring and a source of embarrassment and frustration for patients [1]. Children and immunocompromised persons tend to be most commonly affected by difficult to treat recalcitrant warts [2 - 4] Some lesions may spontaneously disappear but others may persist or even increase in number and size [2, 4, 5]. Although several potential treatment options exist for warts, there is no single treatment that ensures a complete response and lack of recurrence. Treatments may initially be effective but recurrences after treatments are common [4, 5]. Current treatment options include: topical treatments (commonly salicylic acid), cryotherapy, LASER therapy,

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photodynamic therapy, surgical excision, immunotherapies, and home remedies such as duct tape or tea tree oil [6 - 8]. Many of these options are scarring due to their destructive nature while other less invasive options may result in a lack of complete response or an increased chance of recurrence. Some may be painful or cause discomfort for the patient. Additionally, local treatments may be ineffective at treating patients with large lesions or multiple lesions. Furthermore, many of these options have unknown mechanisms of action and varying results among individuals. For this reason, treatment of warts may be challenging and frustrating for both the physician and patient [1]. Unlike the other various options, immunotherapies target specific lesions and upregulate the immune system to recognize and destroy the lesions at the target site and distant locations. This more systemic approach has shown to be an inexpensive, effective method for treatment of individuals with multiple recalcitrant warts in the literature [9]. Although the mechanism has not been completely understood, immunotherapies are believed to work by inducing a systemic T-cell mediated response at the location of contact or injection. It is also suggested that the injection itself may play a role in inducing the immune response [10]. The immunotherapies, thereby, help the body recognize the lesions and destroy them. Several specific antigens have been used for contact (topical) and intralesional immunotherapy treatments for cutaneous warts. Some contact immunotherapy antigens and contact allergens include: diphenylcyclopropenone (DPCP), Imiquimod 5% Cream, Bacillus Calmette-Guerin (BCG), dinitrochlorobenzene (DNCB), tuberculin jelly, and squaric acid dibutylester (SADBE). The most commonly studied intralesional immunotherapy antigens include: Candida albicans, measles-mumps-rubella (MMR) vaccine, tuberculin PPD, killed Myobacterium w, recombinant alpha-2 interferon, and Trichophyton. Bleomycin, an intralesional cytotoxic agent, is also commonly studied. Both intralesional immunotherapy approaches and contact immunotherapy approaches have been shown to be effective in the treatment of warts.

1.1. Efficacy of Contact Immunotherapies and Contact Allergens

Each contact immunotherapy antigen has shown to have varying, but promising, efficacies in the treatment of recalcitrant warts. Suh *et al.* performed an uncontrolled, open-label study which showed DPCP to have a clearance rate as high as 82.9% [11]. Imiquimod was shown to have a success rate of 44%, ranging from 27% to 89% in an evidence-based review performed by Ahn and Huang [12]. In a study on children performed by Salem *et al.*, BCG was shown to have a complete response on 65% of children with common warts and 45% of children with plantar warts [13]. One study exploring the efficacy and safety of SADBE for the treatment of recalcitrant warts in children found that 83% of patients experienced complete clearance. However, only 60% reported no adverse side effects [14]. SADBE is limited because it can cause irritation when treating warts in the genital region [15]. There are some reports of contact dermatitis and blistering as well, especially when treated with higher concentrations [15, 16]. DNCB, although shown to be effective in the treatment of warts, is a known mutagenic and relatively expensive in comparison to other antigens. For this reason, DNCB although effective, is not often chosen because of the vast other antigens available for use immunotherapy. It has since been largely replaced by DPCP and SADBE, which are considered much safer options [17]. Tuberculin Jelly, no longer largely studied as a potential wart therapy, had shown variable efficacy in the literature. Tuberculin PPD intralesional immunotherapy appears to have replaced tuberculin jelly because of its shorter treatment response and strength [17, 18]. Contact immunotherapies present as an effective treatment for recalcitrant therapy for the treatment of recalcitrant warts. Of the contact immunotherapies, DPCP and SADBE are two of the most commonly used therapies because of their high success rates in achieving a complete response to treatment.

1.1.1. Efficacy of Intralesional Immunotherapies and Intralesional Cytotoxic Agents

Intralesional immunotherapies have been the focus of several studies found in the literature. The interest in intralesional approaches may be the result of shorter treatment times, strength, and lesser adverse side effects with promising results. Additionally, intralesional immunotherapies elicit a response of warts at locations distant to the injection site. The injection itself may also help to induce an immune response at the target site. Several antigens have presented as effective options for use in intralesional immunotherapy approaches to treat warts. In a two year study at Mayo Clinic, 80% of patients had a response to Candida antigen with 39% having a complete response to treatment. It was also found that 7 of 8 immuno-compromised patients showed a partial or complete response to the antigen [19]. Another study, which used higher doses of Candida antigen, reported complete response rates as high as 82% [20]. MMR vaccine has shown complete response rates as high as 75% in one study and 81% in another study. Both studies showed low recurrence among patients, but some patients (<30%) experienced flu-like symptoms during treatment [21 - 29]. In a study performed by Saoji *et al.*, tuberculin PPD showed a complete response rate of 76% in four treatments with very minimal adverse reactions to the antigen [22]. Myobacterium w vaccine showed complete response rates as

high as 89% in a study performed by Gupta *et al.* and 93% in a study performed by Garg and Baveja [23, 30]. Another antigen, Alpha 2- interferon, has shown 50-70% complete response rates in genital warts, specifically. One major downside to interferon is that it has a much higher costs than other potential antigens for intralesional immunotherapies [24]. As a result, other antigens are preferred over interferon. Bleomycin, a relatively costly cytotoxic agent, has shown complete response rates ranging from 14-99% in the literature [25]. Studies using Trichophyton alone were not readily found, but Trichophyton was found to increase response rates when combined with other antigens in several studies. Trichophyton combined with other antigens MMR and Candida showed a complete response rate of 71% in a study performed Johnson and Horn [26]. As shown above, various antigens for intralesional immunotherapies have shown extremely high response rates in the literature and may provide a reliable, effective option for patients in the treatment of difficult warts in the clinical setting.

1.1.2. Comparison of Costs of Immunotherapy and Other Therapies

The low costs of many of the antigens used for contact and intralesional immunotherapies present another benefit to their use. Clemens *et al.* performed a comparative study looking at the various costs of treatment options for warts. In the study, cryotherapy, a very commonly used treatment method, costs $562, while Candida antigen only costs $190. Other treatments, such as home remedies and CO_2 laser therapy, also had very low costs at $10-30 and $157, respectively. Pulse-dyed laser therapy was found to costs $360 for complete resolution in a recent study. Bleomycin and Squaric acid costs $495 and $706, respectively. In contrast, alpha-2 interferon is very expensive and typically requires several treatments resulting in an average cost of $1227. These prices represent total costs charged to patient with physician fees included.[27] DPCP costs approximately $30/session and Imiquimod costs as much as $100/session. SADBE has varying costs but is more unstable and costly than DPCP [28]. DPCP, Imiquimod, and SADBE all may require multiple sessions for a complete response. Much like candida, the MMR antigen is also relatively inexpensive at about $26 [29]. Tuberculin agents, such as PPD and BCG, are found for less than $10 [30, 31]. Killed Myobacterium w was found to be another cost-effective option at 450 rupees or approximately $7 in a study performed in India by Garg and Baveja [31]. As seen above, several of the intralesional immunotherapy antigens present as very cost-effective options in comparison to other options the patient may have for treatments. Along with being inexpensive, these immunotherapies are more beneficial because of their potential to treat warts distant to the treatment site. This phenomenon furthers the potential cost-effectiveness of the more affordable intralesional immunotherapy treatment options.

DISCUSSION

Although the mechanism of action of many of the antigens is unknown, immunotherapies provide a safe and cost-effective approach for the treatment of warts. Other more traditionally used therapies such as cryotherapy and salicylic acid, although usually effective in the treatment of warts at the target location, have a tendency to cause irritation of the skin and are not effective in treating patients with multiple warts or those with warts in several locations. Additionally, immunotherapies may even serve as a cheaper option for patients than more traditionally used options depending on the antigen. Intralesional immunotherapy is preferable because of its capability to induce a systemic response in the patient and affect warts at locations distant to the injection site. If proved effective and adopted in clinical setting, intralesional immunotherapy may lessen the frustration experienced by patients and physicians when dealing with recalcitrant warts. The appropriate dosing and location based response rates will need to be explored in future studies to determine the best practices for using intralesional approaches. Presensitization to specific antigens may serve as a means of determining the best antigen for the individual patient as well as inoculating the patient with the antigen. Initial inoculation is beneficial because it can cause the host to elicit a stronger response upon presentation of the antigen through intralesional immunotherapy injection. In addition, intralesional immunotherapies can be combined with other treatment options such as cryotherapy, laser therapy, or salicylic acid to increase the chance of a complete response. Multiple antigens can also be combined to elicit a stronger response to treatment. Finding the correct doses and combinations may be difficult to determine because responses may be different among individual patients. Therefore, future randomized studies will be important for developing a standardized protocol for treating difficult to treat warts in the clinical setting.

CONCLUSION

Immunotherapies for recalcitrant, difficult to treat cutaneous warts present as a cost-effective, efficient therapy option for patients. Intralesional approaches have the added benefit of affecting warts at locations distant to the target

location by inducing a systemic T-cell mediated response in the body. Although efficacy has been confirmed by randomized studies, more randomized comparative studies will need to be performed in order to determine the best antigen and correct standardized doses for the treatment of warts in individual patients. It is important to note that individual response to antigens may vary among patients and this may further complicate the development of standardized doses. Given that patient wishes may vary and no treatment is totally curable nor painless, one should discuss the various options and choose the best option for each patient on an individual basis. Likewise, there are currently too many variables at this point to have definitive treatment plan outlined. Therefore, further studies may play an important role in the use of immunotherapies in a clinical setting.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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