Report

Treatment of recalcitrant warts with intralesional measles, mumps, and rubella vaccine: a promising approach

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Abstract

Background Recalcitrant warts represent a frustrating challenge for both patients and physicians. Although many destructive and immunotherapeutic modalities are available for the treatment of warts, an ideal, universally effective approach has not been explored to date. Recently, intralesional antigen immunotherapy has shown promising efficacy in the treatment of warts. The aim of the study was to evaluate the efficacy and safety of intralesional measles, mumps, and rubella (MMR) vaccine in the treatment of recalcitrant warts.

Methods The study included 70 adult patients with multiple recalcitrant extragenital warts of different sizes and durations, with or without distant warts. They were directly injected, without a pre-sensitization skin test, with 0.3 intralesional MMR vaccine into the largest wart at 2-week intervals until complete clearance or for a maximum of five treatments. Follow-up was made every month for six months to detect any recurrence.

Results Sixty-five patients, 35 men and 30 women, completed the study, and five patients discontinued for various reasons. Complete clearance of the lesions was observed in 41 patients (63%), partial response in 15 patients (23%), and no response in nine patients (14%). Complete response was demonstrated in 74.5% of those presenting with distant warts. Side effects were mild and insignificant in the form of pain during injection, itching, erythema, and edema at the site of injection and flu-like symptoms. Recurrence was detected in two patients only.

Conclusions Intralesional immunotherapy by MMR vaccine is a promising, effective, and safe treatment modality for recalcitrant warts.

Introduction

Recalcitrant warts represent a frustrating challenge for both patients and physicians. Many warts are cosmetically unacceptable and may be painful as in the case of palmoplantar warts or destructive as in the case of periungual warts. In addition, recalcitrant warts continue to multiply and enlarge, making treatment more difficult and spreading of infection to the patient and his contacts more liable.1–3

Although spontaneous resolution of warts has been reported to occur in a significant portion (60–65%) of patients within 1–2 years, about one-third or more do not resolve and become highly recalcitrant to treatment by different modalities, including the most aggressive therapies.4,5

Standard therapeutic modalities for warts, including the recalcitrant ones, are usually of the destructive type that produces nonspecific physical destruction of the visible lesions, rather than eradication of the virus itself. Destructive therapies include medical agents (e.g., podophyllotoxin, trichloroacetic acid in high concentrations, cantharidin, 5-flourouracil, and bleomycin) and surgical methods (e.g., electrocautery, aggressive cryosurgery, curettage, surgical excision, laser ablation, and photodynamic therapy). These approaches are usually uncomfortable, typically require multiple sessions and individual treatment of each wart, and are often associated with variable efficacy, high recurrence, and significant adverse effects such as scarring.6,7

On the other hand, immunotherapeutic agents include: contact sensitizers such as squaric acid dibutylester and diphenycyprone; proinflammatory cytokines such as interferons; immunomodulatory agents such as imiquimod; and immune enhancers such as oral levamisole and zinc sulfate. Other modalities include antiviral drugs such as intravenous cidofovir, systemic retinoids, hypnotherapy, acupuncture, local hyperthermia, therapeutic vaccination, and combinations of the previous agents.8–11

The mounting evidence that cell-mediated immunity (CMI) plays a major role in wart resolution highlights the need for immune protection against human papillomavirus
(HPV) infections and has directed the attention towards stimulation of the patient’s immune system, particularly CMI, to eradicate the virus. Therefore, treatment modalities utilizing immunotherapeutic approaches have been the subjects of many recent trials to overcome the challenging problems in wart therapy.1,9–10

Intralesional immunotherapy by different antigens is one of the immunotherapeutic approaches that has recently received increasing attention and has been proven effective and safe for the treatment of warts, including recalcitrant variants.12–25

We have previously conducted a controlled study on the use of MMR vaccine for the treatment of common warts with different presentations and characteristics.22–23 Herein we evaluate the efficacy and safety of MMR in the treatment of a highly challenging subtype of warts, namely multiple recalcitrant warts.

Patients and Methods

Seventy adult patients with multiple recalcitrant extragenital warts of different sizes and durations, with or without distant warts, were enrolled into this study. Recalcitrant warts were defined as warts persistent for more than two years despite treatment with at least two different modalities. Distant warts were defined as warts at different anatomic sites away from the treated wart. Exclusion criteria consisted of previous allergic response to MMR vaccine, patients with acute febrile illness, previous wart therapy in the last month before enrollment, history of asthma or allergic skin disorders, pregnancy, lactation, and iatrogenic or primary immunosuppression. The diagnosis of warts was made by clinical examination, and patients were advised not to use any other wart therapy during the study period.

After obtaining a written informed consent from all patients, baseline characteristics of the warts, including number, site, size, duration, and presence or absence of distant warts, were evaluated at the start of the study and at each follow-up visit. Without pre-sensitization skin tests, all patients were directly injected with 0.3 ml of MMR vaccine (Trimovax Merieux-Aventis, 0.5 ml, costs the equivalent of $9 in Egypt) into the largest wart using an insulin syringe, which is held parallel with the skin surface with the bevel facing upward. Injections were done at 2-week intervals until complete clearance was achieved or for a maximum of five treatment sessions. Response to treatment was evaluated by the decrease in size of warts and photographic comparison. The response was considered complete if there was complete disappearance of the warts and return of normal skin markings, partial if the warts had regressed in size by 50–99%, and no response if there was 0–49% decrease in wart size. Immediate and late adverse effects of the MMR vaccine were evaluated after each treatment session. Follow-up was done every month for six months to detect any recurrence.

Results

Sixty-five patients, 35 men and 30 women, completed the study, and five patients discontinued for various reasons, including failure to follow up (three patients) and side effects of the procedure such as flu-like symptoms (two patients). Their ages ranged from 18 to 55 years with a mean of 38.9 years. All patients received at least two therapies; one of them was standard classic therapy such as salicylic acid and cryotherapy. Other treatments include medical agents such as retinoic acid, trichloroacetic acid, and zinc therapy, and destructive modalities such as electrocautery, curettage, laser therapy, and surgical excision. All warts were nongenital, with common warts as the most frequent type (40 of 65). All patients had multiple recalcitrant warts, while distant warts were observed in 51 of the 65 studied patients. The duration of the lesions ranged from 2 to 15 years, with a median of 4.7 years.

The results revealed complete response (Fig. 1) in 41 patients (63%), partial response in 15 patients (23%), and no response in nine patients (14%) (Table 1). The average number of treatments to achieve complete response was 3.25. Complete clearance was observed in 74.5% (38 of 51) of those presenting with distant warts.

Side effects were mild and insignificant. Tolerable immediate pain during injection occurred in all patients (100%) and was the most common adverse effect. Other local reactions such as itching (6.1%), erythema (4.6%), and edema (1.5%) at the site of injection were infrequently observed and were mild and transient. Flu-like symptoms that occurred within 12 hours of injection and resolved rapidly within 24 hours by nonsteroidal anti-inflammatory drugs were observed in eight (12.3%) patients. No wounding, scarring, or pigmentary changes were reported in any of the studied patients. Recurrence was observed in two of the completely cured patients (4.8%) after the 6-month follow-up period.

Discussion

Recalcitrant warts represent a troublesome therapeutic issue because the results of the available therapeutic modalities are usually disappointing in terms of efficacy, adverse effects, and high recurrence rates.7 Although several modalities have been recently added to the wide armamentarium of wart therapy, a universally effective approach has not been explored to date.9–15

Based on the advantage of the vaccination schedule in our country, including MMR vaccine, we decided not to use a pre-sensitization skin test because all patients were expected to be immune and this was the case in our previous work on MMR.22–23 In addition, the presence of three
different antigens in MMR makes the probability of sensitivity to the injected antigen very high and the likelihood of anergy to the three antigens extremely low; an observation that has also been reported by other authors.\textsuperscript{16}

The results of the present study (63\% complete response) were higher than those reported by Kus \textit{et al.} (29.4\%)\textsuperscript{18} and Clifton \textit{et al.} (47\%),\textsuperscript{15} who have used intralesional antigen immunotherapy (tuberculin and mumps or \textit{Candida}, respectively) for the treatment of recalcitrant nongenital warts in open-label trials, as was the case in this study (Table 2). The relatively higher response in our study may be attributed to the presence of three viral antigens in MMR vaccine, which potentiate each other and could be associated with higher stimulation of the immune system. Moreover, viable vaccines such as MMR have been proposed to be more immunogenic than skin test antigens such as mumps, \textit{Candida}, and tuberculin.\textsuperscript{20}

On the other hand, the complete response achieved in the present treatment experience was less than that reported in our previous work on MMR (81.4\%).\textsuperscript{22} This might be related to differences in the selected population (resistant warts versus resistant or nonresistant warts), number of warts (multiple versus single or multiple), duration (2 years or more vs. variable duration), and finally, difficult sites were more common in this study as compared to the previous one.

The mode of action of intralesional antigen immunotherapy, including MMR vaccine, is still obscure. It has been postulated that a functional host immune system,
particularly CMI, is a necessary prerequisite for successful intralesional antigen immunotherapy. This may be achieved through the direct effect of the trauma itself, a strong nonspecific inflammatory response against the HPV-infected cells, and through an interaction of stimulated macrophages, T-helper cells, neutrophils, and natural killer cells. It has also been reported that intralesional immunotherapy is associated with release of different immunoregulatory cytokines such as interleukins 2 and 12, interferon-γ, and tumor necrosis factor-α that stimulate a strong immune response against HPV. Moreover, Horn et al. have observed that the antigen injection is associated with proliferation of peripheral blood mononuclear cells that promotes T-helper 1 cytokine responses to eradicate HPV-infected cells.

The design of our study was an open label, nonrandomized, uncontrolled trial. This represents a limitation to the significance of the reported results. However, because most of the enrolled patients were referred to our clinic specifically for immunotherapy by MMR after failure of traditional modalities and the highly recalcitrant nature of the warts that necessitated treatment by an active ingredient rather than placebo, addition of a control group was impractical.

Our patients had warts of longer duration than two years, and not all have responded to at least two therapeutic modalities, including second- or even third-line treatments, so it seems unlikely that the complete resolution in our patients after intralesional MMR immunotherapy was spontaneous.

Recurrence of warts was observed in two of our patients (4.8%) after the 6-month follow-up period. A similar finding of reduction or prevention of recurrences has also been reported by several related studies; an observation that represents an important advantage of intralesional immunotherapy over traditional treatments. This may be attributed to the acquisition of a long-term immunity to HPV through induction of CMI that enables the body to recognize HPV, stimulates the production of memory T cells against the virus, and potentiates the effector response mechanism.

Complete clearance was observed in 74.5% (38 of 51) of the patients presenting with distant warts. Similar findings, in different rates, have also been reported by related studies utilizing intralesional immunotherapy. The clearance of untreated warts, particularly the distant ones, has been explained by the development of a widespread CMI against HPV as a response to antigen injection.

Intralesional antigen immunotherapy is usually associated with mild insignificant side effects, and this was the case in our study. Tolerable pain during injection that did not extend beyond the time of injection was almost steady in every patient. Other local reactions such as erythema, edema, and itching at the site of injection were occasional and transient as reported by similar studies. More aggressive adverse effects of destructive therapies such as scarring and pigmentary changes were not observed in our study as well as other related studies; an advantage that adds weight to this new approach.

On the other hand, flu-like symptoms were the only observed systemic adverse effects. They have been attributed to elaboration of inflammatory cytokines in response to leak of some antigen into the circulation.

**Conclusion**

Measles, mumps, rubella seems to be a highly promising effective and safe treatment modality for warts, including the recalcitrant variants. Because of its low cost, high level of tolerability, widespread effect involving both the treated and untreated warts, and low recurrence rate, we
propose that MMR may be considered a first-line therapy for multiple warts and a second-line therapy for warts recalcitrant to standard therapies.

References

25 Chandrashekar L. Intralesional immunotherapy for the management of warts. *Indian J Dermatol Venereol Leprol* 2011; 77: 261–263.