Intralesional Injection of the Measles–Mumps–Rubella Vaccine into Resistant Palmoplantar Warts: A Randomized Controlled Trial

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Abstract

Background: Common resistant-to-therapy warts pose a challenge to both clinicians and patients. Among many destructive and immunotherapeutic options, no single, fully effective treatment has been suggested yet. Many investigations, including those using intralesional antigen administrations, have demonstrated that cellular immunity plays a major role in the clearance of human papilloma virus (HPV) infection. The aim of the present study was to evaluate the effects of the intralesional injection of the measles–mumps–rubella (MMR) vaccine into resistant-to-treatment palmoplantar warts and its complications.

Methods: In this single-blind, randomized, controlled clinical trial, 60 cases with resistant-to-therapy palmoplantar warts referring to the Dermatology Clinic of Bou-Ali Sina Hospital of Sari between June 2015 and 2016 were randomly assigned to 2 equal groups: the MMR Group received intralesional MMR and the Placebo Group was given saline injection. The injections were administered at 2-week intervals until complete clearance was achieved or for a maximum of 5 injections (<5 injections at 2-week intervals). The study protocol was registered in the Iranian Registry of Randomised Clinical Trials (ID: IRCT2016101027636N3), and the statistical analyses were performed using SPSS, version 17.0. The χ2 test and the F-test were used as appropriate, and a P value less than 0.05 was considered statistically significant.

Results: Complete clearance was observed in 65.2% (14/23) of the patients presenting with resistant-to-therapy palmoplantar warts in the MMR Group and 23.85% (5/21) in the Placebo Group (P=0.021). Recurrence was not observed in any of the completely cured patients at 6 months’ follow-up.

Conclusion: Intralesional immunotherapy with the MMR vaccine may result in a desirable therapeutic response and can be used as an effective and safe treatment option for palmoplantar warts, particularly persistent ones.

Trial Registration Number: IRCT2016101027636N3

What’s Known

• Many destructive and immunotherapeutic treatment options are in use for warts, but no specific treatment has yet been fully effective.
• Intralesional immunotherapy with the measles–mumps–rubella (MMR) vaccine may confer a desirable therapeutic response and can be used as an effective and safe treatment option for palmoplantar warts, particularly persistent ones.

What’s New

• This is the first study to characterize warts as resistant to therapy in intralesional immunotherapy with the MMR vaccine.
• We defined resistant-to-therapy warts as those that persisted for more than 2 years despite the application of at least 2 therapeutic options.

Introduction

Human papilloma viruses (HPVs) are a large family of small,
nonenveloped, double-stranded DNA viruses that are the cause of benign epithelial proliferations or warts. The most common clinical manifestations of these viruses are warts (verrucae), more than 180 individual types of HPVs have been sequenced and all infect epithelial cells, usually with a preference for either cutaneous or mucosal surfaces.

The most common warts on hands and feet are caused by HPV types 1, 2, 4, 27, and 57. Warts have various forms including common (verruca vulgaris), plane or flat, myrmecia, plantar, coalesced mosaic, filiform, periungual, anogenital (venereal or condyloma acuminata), oral, and respiratory papillomas. Palmar and plantar warts are lesions described as rough papules on the palms, soles, and lateral sides of the hands and feet with slight central depression. Warts are self-limited in nature and can disappear after a few months. They can, however, stay for years and even recur.

For all the destructive and immunotherapeutic treatment options that have been proposed for common warts, no specific treatment has yet been fully effective. Many factors such as side effects, costs, pain related to treatment, patients’ age, compliance, and immunity status, and wart location, size, form, and response to previous treatments can affect the choice of treatment.

Local immunotherapy consists of contact sensitizers such as diphencyprone, squaric acid dibutyl ester, intralesional injection of interferon, 5-fluorouracil, imiquimod, Bacillus Calmette–Guerin therapy, and intralesional injection of mumps, Candida, or Trichophyton antigen.

Progression of HPV infection in patients with compromised cellular immunity has been shown in some studies, whereas there has been no indication of increased prevalence of warts in patients with impaired humoral immunity, which displays the main role of cell-mediated immune reactions in HPV-infected tissues.

In a competent body immune system, T Helper 1 cells (CD4+) secrete many different types of cytokines, the most important of which are interferon gamma, interleukin-2 (IL-2), and IL-12. IL-2 stimulates the maturation of the killer T cell and enhances the cytotoxicity of natural killer cells. The critical function of the killer T cell is cytotoxicity, which means recognizing and destroying cells infected with viruses, but they also defend against intracellular bacteria and certain types of cancers.

Some observations have demonstrated that a CD4-dominant immune reaction in an HPV-infected tissue is associated with a high chance of clearing the HPV infection.

One of the strategies involved in the immunotherapy of warts is inducing delayed (cellular) hypersensitivity reactions at the wart tissue. Previous studies have reported that intralesional injection of Candida, Trichophyton, and/or mump skin test antigens causes a great elimination rate in patients receiving intralesional antigens, as compared to the placebo group, because these injected antigens can induce a delayed-type hypersensitivity reaction amazingly to both antigen and HPV-infected cells. This reaction increases the probability of recognizing and clearing the wart virus.

Given that immunotherapy seems to be a rather safe way of wart treatment and, in addition, former studies have shown high rates of wart regression, we conducted the present study to evaluate the efficacy of the MMR vaccine injection in the treatment of resistant-to-therapy palmoplantar warts. To our knowledge, this is the first study to characterize warts as resistant to therapy in intralesional immunotherapy with the MMR vaccine. The aim of the present study was to evaluate the effects of the intralesional injection of the measles–mumps–rubella (MMR) vaccine into resistant-to- treatment palmoplantar warts and its complications.

Materials and Methods

Study Design and Populations

In this single-blind, randomized, controlled clinical trial, 60 cases with resistant-to-therapy palmoplantar warts referring to the Dermatology Clinic of Bou-Ali Sina Hospital of Sari, Iran, between June 2015 and June 2016, were enrolled. Resistant-to-therapy warts were defined as warts persisting more than 2 years despite the application of at least 2 therapeutic options. A written informed consent was obtained from all the patients. The study population’s baseline characteristics including age and gender; wart number, site, size, and duration of presence; and previous wart therapies were evaluated at the outset of the study and at each follow-up visit.

We defined resistant-to-therapy warts as those persisting for more than two years despite the application of at least two therapeutic options. The inclusion criterion was the presence of resistant-to-therapy palmoplantar warts, defined as warts persisting more than two years despite the application of at least two therapeutic methods or warts unresponsive to treatment, which were diagnosed by the expert dermatologist through history taking and physical examination. The exclusion criteria were comprised of acute febrile illness,
Results

At the beginning of the study, 30 patients were enrolled in each group. Seven patients in the MMR Group and nine patients in the Placebo Group did not complete the treatment course for different reasons such as failure to follow up or side effects (mostly pain related to treatment) (figure 1). Finally, 23 patients in the MMR Group and 21 patients in the Placebo Group were evaluated. The MMR Group consisted of 12 (40%) men and 18 (60%) women, whereas there were 11 (36.7%) males and 19 (63.3%) females in the control group, indicating no significant difference between the 2 groups (P=0.11). The mean age of the patients in both groups showed no statistically significant difference (P=0.35). Moreover, there were no significant differences between the groups regarding the demographic data (table 1).

The therapeutic response rates in the two groups according to the time elapsed after treatment are shown in table 2. A comparison of these rates showed a statistically non-significant difference between the two groups after the third intralosional MMR injection (P=0.512). Complete clearance was observed in 60.86% (14/23) (figures 2 and 3) of the patients presenting with resistant-to-therapy palmpoplantar warts in contrast to the Placebo Group (23.85%; 5/21). The results revealed that the MMR Group had 4.6 times more response to treatment than the Placebo Group (regression test analysis). Recurrence was observed in none of the completely cured patients after the 6-month follow-up period. The incidence of side effects during and after injection consisted of mild immediate pain during injection, which occurred in all the patients (100%) and was the most common adverse effect. Other local reactions such as itching (3.4%), erythema (4%), and edema (1.5%) at the site of injection were observed, which were mild and transient.
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**Table 1: Demographic characteristics of the study population**

| Demographic Feature          | MMR Group       | Placebo Group    | P   |
|------------------------------|-----------------|------------------|-----|
| Age                          | 27.2±8.73       | 25.37±9.23       | 0.35|
| Sex                          |                 |                  |     |
| Male                         | 12 (40%)        | 11 (36.7%)       | 0.11|
| Female                       | 18 (60%)        | 19 (63.3%)       |     |
| Number of warts              | 6.5±2           | 6.1±2.5          | 0.22|
| Location of warts            |                 |                  |     |
| Palmar                       | 14 (46.7%)      | 20 (66.7%)       | 0.12|
| Plantar                      | 14 (46.7%)      | 10 (33.3%)       |     |
| Both                         | 2 (6.7%)        | 0 (0.0%)         |     |
| Size of warts (diameter)     | 2.3 cm          | 2.1 cm           | 0.26|
| Duration of the presence of warts (y) | 2.26 | 2.3 | 0.81 |

**Table 2: Clinical results of the intralesional MMR vaccine for the resistant-to-treatment palmoplantar warts**

| Injection Turn | MMR Group | Placebo Group | P   |
|----------------|-----------|---------------|-----|
|                | No response | Partial response | Complete response | No response | Partial response | Complete response |
| First injection | 30 (100%) | 0 (0%) | 0 (0%) | 30 (100%) | 0 (0%) | 0 (0%) | 0.112 |
| Second injection | 26 (89.7%) | 3 (10.3%) | 0 (0%) | 27 (100%) | 0 (0%) | 0 (0%) | 0.312 |
| Third injection | 11 (45.8%) | 11 (45.8%) | 2 (8.3%) | 16 (6.7%) | 8 (33.3%) | 0 (0%) | 0.512 |
| Fourth injection | 5 (21.7%) | 8 (34.8%) | 10 (43.5%) | 10 (47.6%) | 9 (42.9%) | 2 (9.5%) | 0.012 |
| Fifth injection  | 5 (21.7%) | 4 (13.0%) | 14 (65.2%) | 10 (47.6%) | 6 (28.6%) | 5 (23.8%) | 0.021 |

MMR: Measles–mumps–rubella
Flu-like symptoms, which occurred within 12 hours of injection and resolved within 24 hours spontaneously, were observed in 13% of the patients.

Discussion

Common warts are a challenge to both patients and clinicians. They can cause embarrassment to patients by persistence or recurrence and affect patients’ lives by making them feel uncomfortable in their social and leisure activities. We, therefore, sought to study new, safe, and efficient wart therapies.

Evidence showing that cellular immune responses play a critical role in wart clearance has inspired the development of topical and intralesional immunotherapy regimens for patients with multiple and/or persistent warts. The intralesional injection of Candida, Trichophyton, and/or mumps skin test antigens is another approach to immunotherapy for warts. This treatment modality showed a significantly higher clearance rate than a placebo for treated as well as untreated distant warts in a randomized, controlled, clinical trial on patients receiving intralesional antigens. The results of our study, which seems to be the first study on the intralesional injection of the MMR vaccine into resistant-to-therapy palmoplantar warts, demonstrated a highly significant difference between the therapeutic response of common warts to the MMR vaccine and saline. Similar findings were reported by other studies that applied the intralesional MMR vaccine into nongenital warts.

The response rate in the present study (65.2% complete response) was higher than that reported by Kus et al. (29.4%) and Clifton and others (47%), who used intralesional antigen immunotherapy (tuberculin and mumps or Candida, respectively) for the treatment of recalcitrant nongenital warts in open-label trials. The higher response rate in our study may have been caused by different antigens in MMR, which makes the probability of sensitivity to the injected antigen very high. In addition, live vaccines such as MMR are more immunogenic than skin test antigens such as mumps, Candida, and tuberculin. The response rate achieved in the present study was higher than that reported by Nofal and co-workers (63%...
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...which was significantly higher than the mean age of our patients. Furthermore, we had significantly fewer males and significantly more females in our study than did Nofal et al. in their investigation.

One of the previous studies that was very close to our study in terms of design was that of Zamanian et al., who used the intralesional MMR vaccine injection for common warts. In their double-blind, randomized, controlled clinical trial, the mean ages of the male and female patients in the MMR and normal saline groups were significantly higher and lower than those in our study, respectively. The complete response rate reported in our study was higher. This difference may be due to the fact that our 5 times injection of the MMR vaccine might have led to higher stimulation of the immune system than the 3 times injection in the investigation by Zamaninan and colleagues. On the other hand, the complete response rate achieved in the present study (65.2%) was less than that reported in the study by Nofal et al. (81.4%). This might be related to differences in the population selected, number of the warts studied, number of the warts (multiple vs. single or multiple), and duration of their presence (≥2 y).

Intralesional immunotherapy was shown to be associated with the release of important cytokines such as IL-2, IL-12, IFN-a, and TNF-a, which can potenti...
Conflict of Interest: None declared.

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