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Safety, humoral and cell-mediated immune responses to herpes zoster vaccine in subjects with diabetes mellitus

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Summary *Objective:* To evaluate varicella zoster virus-specific cell-mediated immunity and humoral immunogenicity against the herpes zoster vaccine, which is licensed as the Live Varicella Vaccine (Oka Strain) in Japan, in elderly people with or without diabetes mellitus.
Methods: A pilot study was conducted between May 2010 and November 2010 at Kitano Hospital, a general hospital in the city of Osaka in Japan. A varicella skin test, interferon-gamma enzyme-linked immunospot assay and immunoadherence hemagglutination tests were performed 0, 3, and 6 months after vaccination. Vaccine safety was also assessed using questionnaires for 42 days and development of zoster during the one-year observational period. We enrolled 10 healthy volunteers and 10 patients with diabetes mellitus aged 60—70 years.
Results: The live herpes zoster vaccine boosted virus-specific, cell-mediated and humoral immunity between elderly people, with or without diabetes. Moreover, no systemic adverse reaction was found. None of the study participants developed herpes zoster.

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Conclusion: The live herpes zoster vaccine was used safely. It effectively enhanced specific immunity to varicella zoster virus in older people with or without diabetes mellitus.

Introduction

Varicella zoster virus (VZV) causes both varicella and herpes zoster (HZ). Subsequent HZ probably develops with reactivation of VZV as the host cell-mediated immunity (CMI) to VZV decreases below an undefined critical level.[1] Herpes zoster is most common in people older than 60 years who have age-related weakening of the immune system. In fact, HZ is 5—10 times more likely to occur after 60 years of age than in childhood.[2]

The original Oka strain live attenuated varicella vaccine (Oka varicella vaccine®), was first supplied in 1976 under license from the Biken Institute in Japan. Oka varicella vaccine was first used in leukemic children for prevention of chicken pox in the 1970s.[3] Safety and immunogenicity of Oka varicella vaccine were confirmed. Children were vaccinated voluntarily in Japan. This vaccine is also effective to enhance immunity, particularly CMI to VZV for elderly people.[4]

Live, attenuated Oka/Merck VZV vaccine (zoster vaccine, Zostavax®) prevents HZ and its sequelae in immunocompetent adults.[5] The Centers for Disease Control and Prevention (CDC) recommend zoster vaccine for use by people 60 years or older to prevent shingles.[6] However, the original Oka varicella vaccine (the herpes zoster vaccine) is not available for prevention of HZ in Japan. Furthermore, development or improvement of the vaccine is desired for preventing HZ safely in immunocompromised patients, who are more vulnerable to developing HZ than immunocompetent patients are.

The well-known risk factor for HZ is altered CMI.[7] In an earlier study, we reported that patients with several underlying diseases including diabetes are at increased risk for HZ.[8] We also reported that diabetic patients have decreased VZV-specific CMI relative to individuals without diabetes.[9] To evaluate the possible use of the herpes zoster vaccine for the prevention of HZ, we compared diabetic patients to healthy volunteers in CMI and immunogenicity to VZV before and after immunization.

Materials and methods

Objective

To evaluate immunity against the Live Oka strain Varicella Vaccine (herpes zoster vaccine) licensed in Japan in elderly people and people with diabetes of approximately equal age. Vaccine safety was also assessed using a questionnaire.

Design, setting, and participants

A before—after interventional study was conducted between May 2010 and November 2010 at Kitano Hospital, which plays a central role in community health care as a general hospital in the city of Osaka in Japan. The study evaluated 10 healthy volunteers (HV) and 10 outpatients with diabetes mellitus (DM) aged 60—70 years with 6—9.5% glycosylated hemoglobin (HbA1c) levels. Subjects received one subcutaneous injection of 0.5 ml of the live, attenuated varicella vaccines (Oka varicella vaccine®), produced by the Research Foundation for Microbial Diseases of Osaka University (BIKEN). The estimated potency was approximately 50,000 plaque-forming-units (PFU) per dose. HV and DM were first-time vaccinated subcutaneously with one 0.5 ml dose of herpes zoster vaccine. This study was approved by the Kitano Hospital and the Tazuke Kofukai Medical Research Institute Ethics Committee and National Institute of Biomedical Innovation and Kobe University Ethics Committee.

Blood samples were obtained before, as well as 3 months and 6 months after vaccination. Safety and immunogenicity of one dose (for a mean titer of 50,000 PFU of the vaccine) were evaluated. All participants gave their written informed consent after the study had been explained to them. They were requested to report any symptom after vaccination. HV shares no symptoms with DM. This study excluded smokers and HZ patients, in addition to any potential participant with malignant disease, autoimmune disease, renal failure, use of steroids, immunosuppressive drugs or antiplatelet drugs, and those with dermatological disorders which might impede judgment of a skin-test reaction. This trial was registered with the Ministry of Education, Culture, Sports, Science and Technology, Japan (UMIN000003639).

Main outcome measures

A varicella skin test and interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISPOT) assay were both performed to assess CMI to VZV.

VZV skin test

Skin-test reactions with Varicella virus antigen were performed 0, 3, and 6 months after vaccination. Varicella Skin-Test Antigen "Biken", which was licensed in 1990 in Japan, was prepared as described previously.[10] Briefly, 0.1 ml of the VZV skin-test antigen (BIKEN) was injected intradermally. Then erythematous change was measured 24 h after the injection. The long diameter was used as the diameter value. Criteria of reactions were defined as follows: negative (score 0), $<$5 mm; weakly positive (score 1), 5—9 mm; moderately positive (score 2) 10—14 mm; and strongly positive (score 3), $\geq$10 mm with double redness or induration reaction.[4] Skin-test scores and changes in the skin-test reaction were presented as mean $\pm$ standard error (SE). Ratios of conversion from negative to positive and enhancement from a lower to higher score by vaccination were compared between DM and HV groups.