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Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults

Roman Chlibek[a], Karlis Pauksens[b], Lars Rombo[c,d], Gini van Rijckevorsel[e], Jan H. Richardus[f], Georg Plassmann[g], Tino F. Schwarz[h], Grégory Catteau[i], Himal Lal[j,*], Thomas C. Heineman[j]

[a] Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic
[b] Department of Medical Science, Section of Infectious Diseases Uppsala University, Akademiska Sjukhuset, Uppsala, Sweden
[c] Clinical Research Center, Sormland County Council, Uppsala University, Eskilstuna, Sweden
[d] Department of Medicine, Karolinska University Hospital, Stockholm, Sweden
[e] Public Health Service Amsterdam, Department of Infectious Diseases, Amsterdam, The Netherlands
[f] Municipal Public Health Service Rotterdam-Rijnmond, Rotterdam, The Netherlands
[g] Unterfrintroper Hausarztzentrum, Essen, Germany
[h] Central Laboratory and Vaccination Centre, Stiftung Juliusspital, Würzburg, Germany
[i] GSK Vaccines, Wavre, Belgium
[j] GSK Vaccines, King of Prussia, PA, USA

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ABSTRACT

Background: An investigational subunit vaccine containing the varicella-zoster virus (VZV) glycoprotein E (gE) and the $AS01_B$ adjuvant system is being evaluated for the prevention of herpes zoster (HZ) in older adults. A phase II trial evaluating different formulations of this vaccine (containing 25 μg, 50 μg, or 100 μg gE) was conducted in adults ≥60 years of age and showed that all formulations elicited robust cellular and humoral immune responses for up to 3 years after vaccination. In this follow-up study in subjects who received two doses of the 50 μg gE/$AS01_B$ formulation (HZ/su), we assessed the persistence of the immune responses for up to 6 years after vaccination.
Methods: This phase II, open-label, multicenter, single-group trial conducted in the Czech Republic, Germany, Sweden, and the Netherlands followed 129 subjects who had received two doses (2 months apart) of HZ/su during the initial trial. Vaccine-induced immune responses (frequencies of gE-specific $CD4^+$ T cells expressing ≥2 activation markers and serum anti-gE antibody concentrations) were evaluated at 48, 60, and 72 months after the first HZ/su dose.
Results: Six years after vaccination with HZ/su, gE-specific cell-mediated immune responses and anti-gE antibody concentrations had decreased by 20–25% from month 36, but remained higher than the prevaccination values. At month 72, the gE-specific cell-mediated immune response was 3.8 times higher than the prevaccination value (477.3 vs. 119.4 activated gE-specific $CD4^+$ T cells per 10^6 cells), and the anti-gE antibody concentration was 7.3 times higher than the prevaccination value (8159.0 vs. 1121.3 mIU/mL). No vaccine-related serious adverse events were reported between months 36 and 72.
Conclusions: gE-specific cellular and humoral immune responses persisted for 6 years after two-dose vaccination with HZ/su in healthy older adults. No safety concerns were identified.

1. Introduction

Herpes zoster (HZ), or shingles, results from the reactivation of latent varicella-zoster virus (VZV), usually many years after primary VZV infection (chickenpox) that typically occurs during childhood [1]. HZ is characterized by a painful unilateral dermatomal vesicular rash. The most frequent complication is postherpetic neuralgia (persistent pain after resolution of the rash), which can last for months or years [1,2]. The incidence of HZ increases with age, and HZ is most frequent in adults aged ≥50 years [1,2]. Similarly, the incidence of postherpetic neuralgia increases with age [3]. HZ is also more frequent in persons with immunocompromising conditions [2]. Reactivation of latent VZV is believed to occur when VZV-specific cell-mediated immunity (CMI) falls below

* Corresponding author. Tel.: +1 610 787 3481; fax: +1 610 787 7055.
E-mail address: himal.x.lal@gsk.com (H. Lal).

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a critical threshold, either because of aging or immunosuppression [1,2,4,5].

A live attenuated vaccine against HZ (*Zostavax*®, Merck & Co, Inc.), containing a high concentration of the live Oka VZV vaccine strain, is licensed for adults aged ≥50 years [1,6]. However, it is contraindicated for immunocompromised persons and its efficacy against HZ decreases with age [3,7]. Efficacy was 63.9% in adults aged 60–69 years but decreased to 37.6% in adults aged ≥70 years [3]. Moreover, efficacy of *Zostavax*® against HZ decreases gradually after vaccination, from 62.0% at year 1 to 43.1% at year 5 in adults ≥60 years of age [8], and remained statistically significant only through year 8 after vaccination [9].

Recombinant subunit vaccines are alternatives to live attenuated vaccines, notably because of their high immunogenicity when administered with an adjuvant [10]. VZV glycoprotein E (gE) is an attractive candidate antigen because it is a prominent target of VZV-specific $CD4^+$ T-cell responses [11–13]. An investigational recombinant subunit vaccine containing VZV gE and the $AS01_B$ adjuvant system (GSK Vaccines) is currently being evaluated for the prevention of HZ in older adults and in patients with immunocompromising conditions. A phase II clinical trial was conducted in adults ≥60 years of age to evaluate different formulations of this candidate vaccine (containing 25 μg, 50 μg, or 100 μg gE combined with $AS01_B$ or saline) using different schedules (one or two doses). This trial showed that two doses of all the adjuvanted vaccine formulations in older adults had clinically acceptable safety profiles and elicited robust cellular and humoral immune responses that persisted for up to 3 years after vaccination [14]. Furthermore, immunogenicity changed little with increasing age [14,15]. Based on the results of this and other clinical trials [14,15], the 50 μg gE/$AS01_B$ formulation (herein referred to as HZ/su) was selected for further clinical development. Recently, a randomized, observer-blind, placebo-controlled phase III study demonstrated that HZ/su efficacy against herpes zoster was 97.2% (95% confidence interval, 93.7–99.0) in adults ≥50 years of age after a mean follow-up of 3.2 years, and that vaccine efficacy did not decrease with increasing age [16].

To investigate the potential of this candidate vaccine to provide long-term protection against HZ, we assessed the persistence of vaccine-induced immune responses between years 4 and 6 after vaccination in subjects who received two doses of HZ/su.

2. Patients and methods

2.1. Study design and subjects

This follow-up study was a phase II, open-label, multicenter, single group trial conducted in the Czech Republic, Germany, Sweden, and the Netherlands (ClinicalTrials.gov, NCT01295320) between February 28, 2011 and June 20, 2013. This trial followed subjects who had received two doses of HZ/su 2 months apart during a single-blind, randomized, controlled trial that was completed in July 2010 (ClinicalTrials.gov, NCT00434577) [14]. The study protocol was approved by the national independent ethics committees of the participating countries and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all subjects before study entry.

All the subjects who had received two doses of HZ/su 2 months apart (i.e., the 50 μg gE/$AS01_B$ group) in the initial trial were eligible for inclusion in the follow-up trial. Subjects were excluded if they had participated (or planned to participate) in another trial in which they were exposed to an investigational or non-investigational product (pharmaceutical product or device) after the end of the initial study; had received immunoglobulins or any blood products within the 3 months preceding the first blood draw; had received a vaccine containing 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL) or *Quillaja saponaria* Molina, fraction 21 (QS21; Antigenics Inc., a wholly owned subsidiary of Agenus Inc., Lexington, MA) after the end of the initial study.

2.2. Study vaccine

No vaccine was administered in this study. In the initial trial, the subjects were vaccinated with two doses of HZ/su (GSK Vaccines) at months 0 and 2 [14]. HZ/su contains 50 μg of VZV gE and the liposome-based adjuvant system $AS01_B$, which contains the immunoenhancers MPL and QS21 (50 μg each). The vaccine was administered intramuscularly (0.5 mL) in the deltoid region.

2.3. Assessment of immunogenicity

The cellular and humoral immune responses induced by the vaccine were evaluated in blood samples collected 48, 60, and 72 months after the first dose of HZ/su. The frequencies of antigen-specific $CD4^+$ T cells expressing at least two activation markers among interferon-γ, interleukin-2, tumor necrosis factor-α, and CD40 ligand (herein referred to as CD4[2+] T cells) per 10^6 cells were measured by intracellular cytokine staining after in vitro stimulation with gE or with VZV and detection by flow cytometry as previously described [14]. Serum anti-gE antibody concentration (mIU/mL) was measured by a GSK in-house enzyme-linked immunosorbent assay (ELISA) with an assay cut-off of 18 mIU/mL.

2.4. Assessment of safety

Fatal serious adverse events (SAEs), SAEs related to study participation or study vaccine, potential immune-mediated inflammatory diseases, and suspected HZ episodes were recorded between months 36 and 72. Subjects were asked to contact the investigator immediately if they manifested any signs or symptoms that they believed to be serious or if a suspected HZ rash occurred. In addition, the investigator asked about the occurrence of AEs at each visit or contact during the whole study period.

2.5. Statistical analysis

The primary objective of the study was to evaluate cell-mediated and humoral immune responses to HZ/su in healthy older adults overall and for each age cohort (60–69 years and ≥70 years of age) at 48, 60, and 72 months after the first dose of HZ/su. The secondary objectives were to evaluate the safety of HZ/su in healthy older adults (60–69 years and ≥70 years of age) at months 48, 60, and 72 and to collect clinical data on suspected HZ cases. Only descriptive analyses were performed. Unless otherwise specified, data are presented as medians with the first and the third quartiles (Q_1–Q_3).

Immunogenicity was analyzed on the according-to-protocol (ATP) cohort for immunogenicity, which included all evaluable subjects excluding those who reported an HZ episode during the study. The frequency of gE-specific CD4[2+] T cells was calculated as the frequency of CD4[2+] T cells upon in vitro stimulation with gE minus the frequency of CD4[2+] T cells upon stimulation with medium alone (background). Safety was analyzed on the total cohort for persistence, which included all subjects.

3. Results

3.1. Subjects

Among the 714 subjects enrolled in the initial trial, 166 subjects were vaccinated with HZ/su (i.e., the 50 μg gE/$AS01_B$ vaccine group) and 147 completed the study to month 36 [14]. Of the 146 subjects

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