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Short communication

Complications of herpes zoster in immunocompetent older adults: Incidence in vaccine and placebo groups in two large phase 3 trials

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ABSTRACT

Background: An adjuvanted herpes zoster (HZ) subunit vaccine, HZ/su, demonstrated high efficacy against HZ and postherpetic neuralgia (PHN) in two randomized, observer-blind, placebo-controlled trials in adults aged ≥50 and ≥70 years (ZOE-50 and ZOE-70, respectively).

Methods: Data from ZOE-50 and ZOE-70 trials were analyzed to evaluate the efficacy of HZ/su against mortality, hospitalizations, and non-PHN complications of HZ including HZ-associated vasculitis, stroke, and disseminated, ophthalmic, neurologic, and visceral diseases.

Results: In the pooled ZOE-50/ZOE-70 analysis, 1 of 32 HZ/su recipients (3.1%) and 16 of 477 placebo recipients (3.4%) with a confirmed HZ episode had complications other than PHN. Efficacy against HZ-related complications was 93.7% (95% confidence interval, 59.5–99.9%) in adults aged ≥50 years and 91.6% (43.3–99.8%) in adults ≥70 years. Five HZ-related hospitalizations, all in placebo recipients, and no HZ-related deaths were reported.

Conclusions: HZ/su reduces the risk of HZ-associated complications in older adults (NCT01165177; NCT01165229).

1. Introduction

Herpes zoster (HZ) results from the reactivation of latent varicella-zoster virus (VZV) in sensory ganglia, typically years after primary infection [1,2]. The most common complication of HZ, postherpetic neuralgia (PHN), is a chronic neuropathic pain that persists after resolution of the HZ rash [2,3]. In adults aged ≥50 years, the risk of developing PHN can be >30% [4]. Other HZ complications include disseminated HZ, and neurological, visceral, or vascular diseases, including stroke [1,4–6]. HZ ophthalmicus occurs when VZV reactivation affects the ophthalmic branch of the fifth cranial nerve and can involve eye structures (hereafter referred to as ophthalmic disease) [7]. The risk of HZ ophthalmicus among HZ patients ranges between 10% and 15%, with ophthalmic disease in approximately 30–80% of these cases [4,8]. The incidence, severity, and duration of PHN and other HZ complications generally increase with age [4].

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In two phase 3 clinical trials, a HZ subunit vaccine (HZ/su), containing recombinant VZV glycoprotein E and the AS01$_B$ Adjuvant System, was highly efficacious in preventing HZ and PHN in older adults [9,10]. Here, we report the efficacy of HZ/su in preventing HZ-associated complications, hospitalizations, and deaths.

2. Methods

2.1. Study design and participants

ZOE-50 (Clinicaltrials.gov, NCT01165177) and ZOE-70 (NCT01165229) were randomized, observer-blind, placebo-controlled, phase 3 studies conducted concurrently in 18 countries in Europe, North America, Latin America, and Asia-Australia [9,10]. Adults aged ≥50 years (ZOE-50) or ≥70 years (ZOE-70) received two doses of HZ/su (Shingrix, GSK) or placebo intramuscularly at months 0 and 2. The design and results of both studies have been previously published [9,10].

2.2. Study objectives

The primary objectives were to assess HZ/su efficacy against HZ (ZOE-50 and ZOE-70) and PHN (ZOE-70) [9,10]. The secondary and exploratory objectives of each study described here included HZ/su efficacy in reducing HZ-associated complications and efficacy in reducing HZ-related mortality and hospitalizations.

2.3. Assessment of HZ and PHN cases

Subject-reported suspected HZ cases were confirmed by polymerase chain reaction or by an ascertainment committee, as previously described [9,10]. PHN was defined as a 'worst pain' score ≥3 persisting or developing more than 90 days after the onset of HZ rash, based on item #3 of the Zoster Brief Pain Inventory questionnaire [10,11].

2.4. Herpes zoster complications

The following complications of suspected HZ cases were recorded by the investigators as adverse events or serious adverse events, as appropriate: HZ vasculitis; disseminated HZ; ophthalmic, neurologic, or visceral disease; and stroke (definitions in Table 1). In the analysis, these events were considered complications of HZ only if they were associated with a confirmed HZ case.

2.5. Statistical analysis

All analyses were performed in the modified vaccinated cohort [9,10], which excluded participants who did not receive the second dose or who had a confirmed HZ episode within 30 days after the second dose.

In both studies, the incidence of HZ-associated complications in participants with confirmed HZ (overall and by age group) was compared between HZ/su and placebo recipients using the asymptotic standardized unconditional binomial test [12]. The analysis was stratified by age group and weighted according to the proportion of participants in each age group. Efficacy against HZ-related mortality and hospitalizations considered the exact inference on the relative risk stratified for age groups and regions, conditionally to the total number of confirmed HZ cases observed and time at risk. This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the HZ/su versus placebo group) and takes into account the follow-up duration of the subjects within each group. Vaccine efficacy was defined as 1 minus the rate ratio. HZ/su efficacy against HZ-associated complications or against mortality and hospitalizations was demonstrated if the lower limit of the two-sided 95% CI was greater than 0%.

The low number of confirmed HZ cases in the HZ/su group in each study limited the power of the analyses. Therefore, a post-hoc analysis was performed to assess efficacy in reducing the incidence of HZ-associated complications (exclusive and inclusive of PHN) in the combined ZOE-50/ZOE-70 study population, both for participants aged ≥50 years and ≥70 years.

All significance tests were two-tailed. P-values of ≤0.05 were considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute) and StatXact 9.0 (Cytel) procedure for SAS.

3. Results

3.1. Study population

ZOE-50 and ZOE-70 enrolled 15,411 and 13,900 evaluable participants, respectively [9,10]. Since publication of the primary results of ZOE-50 (which was ongoing at the time of publication [9]), 47 additional participants had HZ episodes: 3 in the HZ/su group and 44 in the placebo group. Therefore, during the entire ZOE-50 study period (mean follow-up, 3.9 ± 0.7 years), 263 subjects had a confirmed HZ episode: 9 in the HZ/su group and 254 in the placebo group. In ZOE-70 (mean follow-up, 3.7 ± 0.8 years),

Table 1
Definition of herpes zoster complications.

HZ complication	Definition
Disseminated disease	Defined as ≥6 HZ lesions outside the primary dermatome as per the investigator's judgment
Ophthalmic disease	Defined as HZ affecting any eye structure as per investigator's judgment
Neurologic disease	Defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis, stroke, etc. that was temporally associated with an episode of HZ and, in the opinion of the investigator, directly caused by VZV infection arising from the HZ episode
Visceral disease	Defined as an abnormality of one or more internal organs (e.g., hepatitis, pneumonitis, gastroenteritis) temporally associated with an episode of HZ and, in the opinion of the investigator, directly caused by VZV infection arising from the HZ episode
HZ vasculitis	Vasculopathy or vasculitis (based on clinical, laboratory, or radiologic findings) that was temporally associated with an episode of HZ and, in the opinion of the investigator, directly caused by VZV infection arising from the HZ episode
Stroke	A diagnosis of stroke required that criteria 1, 2, and 3 or criteria 1 and 4 were fulfilled, and in the opinion of the investigator was temporally associated with an episode of HZ Criterion 1: Rapid onset of localizing neurological deficit and/or change in level of consciousness Criterion 2: Localizing neurological deficit or change in level of consciousness that lasted greater than 24 h Criterion 3: No other cerebral process, peripheral lesion, or other disorder is the cause of the localizing neurological deficit or change in level of consciousness Criterion 4: CT or MRI scan evidence of an acute thrombotic or hemorrhagic lesion

CT, computed tomography; HZ, herpes zoster; MRI, magnetic resonance imaging; VZV, varicella-zoster virus.

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