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Herpes zoster subunit vaccine for the prevention of herpes zoster

Abstract

Purpose Published literature on the efficacy and safety of the herpes zoster (HZ) subunit vaccine (HZ/su vaccine) in reducing the risks of HZ and postherpetic neuralgia (PHN) in adults 50 years of age and older, as well as the vaccine's properties and efficacy relative to live attenuated vaccine, is reviewed.

Summary HZ/su vaccine (Shingrix, GlaxoSmithKline) is a recently Food and Drug Administration (FDA)-approved vaccine indicated for the prevention of HZ in adults 50 years of age and older. Based on several Phase III trials, the Advisory Committee on Immunization Practices has preferentially recommended HZ/su vaccine over a live attenuated vaccine previously approved by FDA. Reported overall HZ/su vaccine efficacy in preventing HZ in Phase III trials ranged from 89.8% to 97.2%. Compared with placebo use, HZ/su vaccine in those trials was associated with higher rates of transient local and systemic adverse events (AEs) but similar rates of serious vaccine-related AEs. Other clinical trials of HZ/su vaccine have yielded favorable results in various populations, including adults with a history of HZ, older adults who previously received live attenuated zoster vaccine, adults with human immunodeficiency virus infection, and stem cell transplant recipients.

Conclusion HZ/su vaccine is a recently approved, preferred option to reduce the risks of HZ and PHN in adults 50 years of age or older. Pain at the injection site is the most common AE associated with use of the vaccine.

Disciplines

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Comments

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Herpes zoster subunit vaccine for the prevention of herpes zoster

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Abstract

Purpose. Review and evaluate the efficacy and safety of the herpes zoster subunit (HZ/su) vaccine in reducing the risk of herpes zoster (HZ) and postherpetic neuralgia (PHN) in adults 50 years of age and older, as well as, compare the vaccine properties and efficacy of HZ/su to the currently available zoster vaccine live.

Summary. HZ/su (Shingrix™) is a newly Food and Drug Administration (FDA)-approved vaccine indicated to prevent HZ in adults 50 years of age and older. Based on several phase III trials, the Advisory Committee on Immunization Practices (ACIP) has preferentially recommended HZ/su over the previously available zoster vaccine live (Zostavax®). Overall vaccine efficacy for preventing HZ reported in phase III trials ranged from 89.8 to 97.2%. When studied against placebo, HZ/su was associated with a higher incidence of transient local and systemic adverse events (AE) but a similar amount of serious vaccine-related AE.

Conclusion. A review of published literature demonstrates that the HZ/su vaccine is thought to be an improved alternative to zoster vaccine live in reducing the risk of HZ in adults 50 of years of age and older.

Key points

- HZ/su is a novel vaccine that has proven efficacy in reducing the incidence of herpes zoster infection in patients 50 years of age and older in phase III clinical trials.
- Unlike zoster vaccine live, HZ/su is a non-live recombinant vaccine administered intramuscularly in a two-dose series to be completed two to six months apart.
- HZ/su safety data from phase III trials indicate similar rates of serious vaccine-related adverse events or death when compared to placebo.

Keywords: Herpes zoster subunit vaccine (Shingrix™), HZ/su, zoster vaccine live (Zostavax®), herpes zoster, postherpetic neuralgia, and shingles

Introduction

The herpes zoster virus (HZV), commonly known as shingles, is a debilitating condition caused by reactivation of the varicella zoster virus (VZV). The initial infection presents as chickenpox, which typically occurs during childhood, and is characterized by viremia with diffuse rash and seeding of multiple sensory ganglia where the virus establishes lifelong latency.¹ Although HZ can occur at any age, it is generally more prevalent and severe in older adults with higher rates of morbidity than seen in children and younger adults.^{1,2} There are more than one million cases of HZ each year in the United States.³ According to claims data from a retrospective, observational, cohort study conducted in 2011, the annual incidence rate of HZ in immunocompetent adult patients was 4.47 per 1000 person-years (95% confidence interval [CI]: 4.44–4.50) across all ages. The rate for those 50 years and older was 8.46 (95% CI: 8.39-8.52), for those 60 years and older was 10.46 (95% CI: 10.35-10.56), and for those 80 years and older was 12.78 (95 % CI: 12.49–13.07).⁴ These findings are consistent with other literature supporting that the rate of HZ increases with age.⁵ VZV reactivation increases with age due to a decline in immune response and a weakening of cell-mediated varicella virus specific T-cell activity over time.⁶ Postherpetic neuralgia (PHN) is one of the most common and painful outcomes associated with HZ, and occurs in 10-50% of patients with age increasing risk.^{1,7} Antiviral therapy has been shown to reduce some of the symptoms associated with HZ including rash, but it has not been shown to reduce the incidence of PHN, further complications, or disease burden in older adults.⁷ Vaccination against HZ has become standard care to reduce disease burden and its complications in older adults. The purpose of this literature review is to investigate the effectiveness of HZ/su in

reducing the risk of HZ and PHN in older adults.

Methods

A literature search was conducted through November 2017 using PubMed and Google Scholar to locate clinical trials and other relevant peer reviewed publications which evaluated HZ/su and zoster vaccine live. Search terms utilized were *herpes zoster subunit vaccine*, *HZ/su*, *HIV and herpes zoster subunit*, *herpes zoster subunit and immunocompromised*, *zoster vaccine live*, and *Zostavax*[®]. Additionally, clinicaltrials.gov, zoster vaccine recombinant adjuvanted prescribing information, and zoster vaccine live prescribing information as well as the websites for the Center for Disease Control and Prevention and GlaxoSmithKline (GSK) were utilized to obtain further information. Finally, references from identified articles were also reviewed for inclusion. Outcomes of select phase III clinical trials regarding HZ/su are summarized below. All trials reviewed were conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. While no published randomized, controlled phase III studies have directly compared HZ/su to zoster vaccine live up to this point, the properties and vaccine efficacy of both are reviewed.

Zoster vaccine live and HZ/su background information

Zoster vaccine live, an attenuated vaccine containing the Oka VZV strain, was the first FDA-approved method for HZ prevention in adults 50 years of age and older.^{8,9} It is administered as a one-time subcutaneous injection and must be given within 30 minutes of reconstitution. The mechanism of action of this vaccine is to boost the T-cell

mediated immunity to VZV and thereby provide protection against HZ and PHN. It was first approved in May 2006 for use in patients 60 years of age and older.¹⁰ In March 2011, the FDA extended its indication for use to individuals 50 to 59 years of age; however, the Advisory Committee on Immunization Practices (ACIP) denied to recommend the vaccine for this patient population based on limited data demonstrating protection beyond five years.⁹ ACIP continues to recommend this vaccine for adults aged 60 years and older.

Several clinical trials of zoster vaccine live have previously been conducted.^{9,11-15} Results of the largest randomized, double-blind, placebo-controlled phase III trials, the Shingles Prevention Study (SPS) and the Zostavax Efficacy and Safety Trial (ZEST) can be found in Table 1.^{9,11} Since zoster vaccine live has been shown to be less effective in older age groups, and the efficacy of the vaccine wanes over time, a new HZ vaccine with improved protection against HZ in older adults that provides longer post-vaccination efficacy is needed.

HZ/su is a non-live herpes zoster subunit vaccine that incorporates VZV glycoprotein E (gE) and the AS01_B adjuvant system.¹⁸ VZV gE antigen was selected because it is the most abundant glycoprotein on both VZV virions and cells infected with VZV. In addition, it plays a crucial role in virus replication and cell-to-cell spread while demonstrating a greater immune response when compared to other glycoprotein antigens.¹⁹ This antigen was combined with the AS01_B adjuvant system because AS01_B has been shown to enhance CD4⁺ T-cell and humoral immune response toward the

recombinant protein complex, particularly in older adults.¹⁶

HZ/su must be used within six hours of reconstitution. The dose (0.5 mL) should be administered intramuscularly into the deltoid muscle. HZ/su is a two-dose series, the second dose should be given two to six months following the first dose.²⁰ Each dose of HZ/su contains 50 µg of recombinant VZV gE and liposome-based AS01_B adjuvant system containing 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and 50 µg of Quillaja saponaria Moilina, fraction 21.¹⁶ HZ/su does not contain preservatives.²⁰

Clinical efficacy trials for HZ/su

Zoster Efficacy Studies (ZOE)

The efficacy and safety of HZ/su in preventing HZ has been investigated in two large randomized, triple-blinded, placebo-controlled, multicenter phase III clinical trials: Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50) and Zoster Efficacy Study in Adults 70 Years of Age or Older (ZOE-70).^{16,17} Study sites for both studies were in 18 different countries in Europe, North America, Latin America, Asia, and Australia.

ZOE-50 studied adults age 50 and older.¹⁶ Participants were randomized 1:1 to receive HZ/su or placebo and stratified according to the following age groups: 50 to 59 years, 60 to 69 years, and 70 years and older. Each received two intramuscular doses of HZ/su, or placebo, two months apart. Notable exclusion criteria were history of HZ, prior vaccination against VZV or HZ, immunosuppression, receipt of immunoglobulin or blood product within the previous 90 days, receipt or planned administration of any other

immunization prior to or during the study period, and pregnancy or lactation. The primary outcome was vaccine efficacy in reducing the risk of HZ in the modified vaccinated cohort. The modified vaccinated cohort included all participants who received two doses of vaccine and did not have a diagnosis of HZ within one month of the second dose; whereas, the total vaccinated cohort included all participants who had at least one dose of study vaccine administered. Secondary outcomes were vaccine efficacy in reducing the incidence of HZ in each stratified age group and HZ/su safety and reactogenicity profiles. Safety and reactogenicity were evaluated via diary cards in a subgroup of participants that included all those 70 years of age and older and randomly selected participants from the other two age groups. Serious AE were recorded in all subjects for 12 months following the second dose of HZ/su. Participants were followed for at least 30 months through monthly contacts and annual visits.¹⁶

Total enrollment, demographic characteristics, and main efficacy and safety findings are available in Table 1. Overall, HZ/su was found to reduce the risk of HZ by 97.2% (95% CI, 93.7-99.0) compared to placebo in the modified vaccinated cohort. Similarly, vaccine efficacy in the total vaccinated cohort overall was 96.2% (95% CI, 92.7-98.3) for HZ/su compared to placebo. No significant variations in vaccine efficacy between the age-stratified groups in the modified vaccinated cohort were found.¹⁶

Solicited safety and reactogenicity data reported for the subgroup are available in Table 2; grade 3 reactions are provided below. Grade 3 solicited injection site reactions were reported in 417 out of 4,382 subjects (9.5%) in the HZ/su subgroup participants

compared to 16 out of 4,377 subjects (0.4%) in placebo subgroup participants, and grade 3 solicited systemic reactions were reported in 498 out of 4,375 (11.4%) of the HZ/su subgroup participants compared to 106 out of 4,378 (2.4%) in the placebo subgroup participants. Serious AE throughout the study period occurred in a similar percentage of vaccine and placebo recipients at 9.0% (689 out of 7,698) and 8.9% (686 out of 7,713) respectively. Immune-mediated diseases were observed in 1.0% (n = 78) in the vaccine group and in 1.3% (n = 97) in the placebo group. Moreover, death occurred in 2.2% (n = 167) of the vaccine group and 2.3% (n = 174) of the placebo group during the study. Final results at 60 months were reported in a pooled analysis with ZOE-70 participants and are discussed below. The authors concluded that HZ/su significantly reduced the risk of HZ in adults 50 years of age compared to placebo, with similar efficacy among the three age groups. No safety concerns were identified but solicited injection site reaction did occur more frequently in the HZ/su group.¹⁶

ZOE-70 was a separate parallel study conducted over the same time period as ZOE-50.¹⁷ Even though 24% of subjects enrolled in ZOE-50 were 70 years of age and older, the trial was not specifically powered to assess the efficacy of HZ/su in that oldest age group. Therefore, ZOE-70 was designed to evaluate vaccine efficacy in reducing the risk of HZ in adults 70 years of age and older. Participants were randomized in a 1:1 ratio to receive HZ/su or placebo and stratified according to continent and age (70 to 79 and ≥ 80 years). Each received two intramuscular doses of HZ/su or placebo two months apart. Study population as well as exclusion criteria were identical to that for ZOE-50 except for age. The primary outcome was vaccine efficacy in reducing the risk

of HZ in patients 70 years of age and older via analysis of the modified vaccinated cohort. A pooled analysis including participants from ZOE-50 and ZOE-70 was conducted with the primary outcome of vaccine efficacy in reducing the risk of HZ and PHN in the overall population 70 years of age and older. The secondary outcomes for the pooled analysis were vaccine efficacy against PHN for patients age 50 and above and vaccine safety and reactogenicity. Safety and reactogenicity were evaluated in a subgroup via the same manner as in ZOE-50. Follow up for at least 30 months after the second vaccine dose via monthly contact in addition to annual clinic visits occurred.¹⁷

Twenty-two percent (3,066 out of 13,900) of patients enrolled in ZOE-70 were ≥ 80 years of age; 0.5% (n = 76) were ≥ 90 years of years. Overall vaccine efficacy was 89.8% (95% CI, 84.2-93.7) for HZ/su as compared to placebo. There was no significant difference in vaccine efficacy between the two age groups, 90.0% (95% CI, 83.5-94.4) among adults 70 to 79 years of age (n = 5,114) and 89.1% (95% CI, 74.6-96.2) among adults 80 years of age and older (n = 1,427). In the pooled analysis of 8,250 subjects, vaccine efficacy was 91.3% (95% CI, 86.8-94.5%) in reducing the risk of HZ with no significant difference among adults 70 to 79 years of age (n = 6,468) and 80 years of age and older (n = 1,782) (91.3% [95% CI, 86.0-94.9] and 91.4% [95% CI, 80.2-97.0] respectively). Vaccine efficacy in the pooled cohort for each year through year four was determined at 97.6% (95% CI, 90.9-99.8) during year one (n = 8,250), 92.0% (95% CI, 82.8-96.9%) during year two (n = 8,039), 84.7% (95% CI, 69.0-93.4%) during year three (n = 7,736), and 87.9% (95% CI, 73.3-95.4%) during year four (n = 7,426). Vaccine efficacy against PHN for the pooled modified vaccinated cohort of patients 50 years of

age and older (n = 13,881) was 91.2% (95% CI, 75.9-97.7%). PHN did not develop in any participants younger than 70 years of age in the HZ/su group. Vaccine efficacy against PHN for ≥ 70 years was 88.8% (95% CI, 68.7-97.1). The incidence of PHN in recipients of HZ/su that experienced breakthrough HZ did not differ significantly from the placebo recipients [12.5% (n = 4) vs. 9.6% (n = 36), P= 0.54].¹⁴

Solicited safety and reactogenicity data reported for the subgroup can be found in Table 2. Grade 3 solicited injection site reactions were reported in 43 out of 505 (8.5%) in the HZ/su subgroup participants compared to 1 out of 505 (0.2%) in placebo subgroup participants, and grade 3 solicited systemic reactions were reported in 30 out of 504 (6.0%) in the HZ/su subgroup participants compared to 10 out of 505 (2.0%) in the placebo subgroup participants. Grade 3 reactions were transient, lasting less than 48 hours. Serious AE throughout the study period occurred in a similar percentage of vaccine and placebo recipients at 16.6% (n = 1,153 out of 6,950) and 17.5% (n = 1,214 out of 6,950) respectively. Immune-mediated diseases were observed in 1.3% (n = 92) in the vaccine group and in 1.4% (n = 97) in the placebo group. Death occurred in 6.1% (n = 426) and 6.6% (n = 459) in the HZ/su and placebo groups respectively. One participant death in the HZ/su group was determined by the investigators to be related to study intervention. A 90-year-old with pre-existing thrombocytopenia was diagnosed with acute myeloid leukemia 75 days after receipt the first HZ/su dose and died at 97 days after that dose due to neutropenic sepsis. The authors concluded that HZ/su reduced the risk of HZ and PHN in adults 70 years of age and older with no substantial concerns for safety. Results of ZOE-70 are consistent with results from ZOE-50.

Authors caution that deductions regarding a potential lack of decline in efficacy of HZ/su over time cannot be made until additional follow up over a longer period becomes available.¹⁴

While ZOE-50 and ZOE-70 were large, multicenter trials with a randomized, placebo-controlled design, there are a few limitations to note. First, the number of participants that developed PHN was very low, none under 70 years of age, so there was limited power to evaluate the efficacy of HZ/su in reducing the risk of PHN overall. The reported decline in PHN cannot be directly supported by the study data but seems to be a result of the notable efficacy of HZ/su in preventing HZ reactivation. Second, mean follow up time was 3.2 and 3.7 years respectively; evidence that vaccine efficacy persists over a longer duration is needed. Finally, the studies excluded those with a history of HZ, previous varicella or zoster vaccination, immunosuppression, and pregnancy. These patient populations may benefit from an adjuvanted vaccine since zoster vaccine live is contraindicated in these situations.

The studies summarized below all utilized increases in HZV-specific anti-gE antibodies as endpoints. VZV gE is the most abundant glycoprotein in VZV viral particles and cells infected with VZV. VZV gE plays a central role in virus infectivity, cell-to-cell spread, and progression of the infection.²¹ Therefore anti-gE antibodies are thought to be predictors of disease. The threshold at which anti-gE antibody response correlates to disease prevention is unclear so the use of this surrogate marker predicts immune response to HZ/su but has not been quantitatively correlated to disease prevention.

Use in patients with a history of HZ

An open-label, nonrandomized, multicenter phase III study evaluated the immunogenicity and safety of HZ/su in adults aged 50 years or older with a documented history of HZ.²² Exclusion criteria were active HZ infection, prior vaccination for VZV or HZ, and any confirmed or suspected immunosuppressive condition. HZ/su was administered in two doses, given two months apart. The primary endpoint for immunogenicity was vaccine response rate, defined as increasing anti-gE antibodies four times above baseline, with an objective to meet the lower limit of the 95% CI at three months at or above 60%. Participants were followed for 12 months after vaccine administration. Total enrollment was 96 participants. Most (67.7%) reported having HZ within the previous four years. Median age was 64 (range 50-89) years. Vaccine response rate at three months was 90.2%, which met the prespecified immunogenicity endpoint. Local solicited AE occurred in 77.9% of participants whereas 71.6% of participants experienced general solicited AE. Although there was no comparator group, authors concluded that HZ/su was immunogenic with no safety concerns in this study population of adults at least 50 years of age and a history of physician-documented HZ.²²

Use in patients who were previously vaccinated with zoster vaccine live

An open-label, multicenter phase III study of adults aged 65 years and older compared the use of HZ/su in subjects previously vaccinated with zoster vaccine live (at least 5 years prior) to matched subjects unvaccinated against HZ.²³ Groups were matched on

age, gender, race, and medical conditions. Major exclusion criteria were a history of HZ and immunosuppression. The co-primary objectives were non-inferiority of humoral immune response, measured by anti-gE antibody geometric mean concentration (GMC), and safety and reactogenicity at one month following dose two. There were 430 participants enrolled, all received two doses of HZ/su two months apart. Mean age was 70.9 (SD 4.6) years and 51.2% were female. Humoral immune response to HZ/su was non-inferior in those that previously received zoster vaccine live and those that were not previously vaccinated against HZ (adjusted anti-gE antibody GMC ratio of 1.04, 95% CI 0.92-1.17). Reactogenicity and safety were similar between groups. Solicited AE were transient with a median duration of three days or less. Local reaction occurred in 193 of 215 (89.8%) participants who previously received zoster vaccine live and 187 of 214 (87.4%) participants without previous vaccination. Authors concluded that HZ/su induced strong immune response and was well tolerated regardless of prior vaccination against HZ with zoster vaccine live. Therefore HZ/su may be an attractive option to use for re-vaccination of those who previously received zoster vaccine live.

Use in patients with HIV

The safety and immunogenicity of HZ/su in HIV-infected adults was evaluated in a randomized, observer-blinded, placebo-controlled multicenter phase 1/2a study.²⁴ Eligible subjects had a diagnosis of HIV for at least a year. Those with an episode of VZV or HZ or receipt of vaccination against either virus within the prior 12 months; ongoing treatment with HIV fusion inhibitors, CCR5 inhibitors, or interleukin 2/interleukin 7/interferon gamma; or an opportunistic infection other than oral thrush within the

previous year were excluded. It was unknown whether the standard two-dose regimen would elicit a favorable immune response in HIV-infected individuals, therefore three doses were administered and immunogenicity was evaluated after doses two and three. The co-primary objectives were to evaluate gE-specific humoral and cellular immune responses one month following the third vaccination in the HZ/su group compared to the placebo group, and safety and reactogenicity. Serious AE, new onset of immune-mediated inflammatory diseases, worsening HIV, and HZ were reported throughout the study. Subjects were randomized in a 3:2 ratio to receive HZ/su or placebo at months zero, two, and six.²⁴

Three cohorts of HIV-infected adults were enrolled: 94 with a CD4⁺ count of ≥ 200 cells/mm³ and receiving antiretroviral therapy (ART), 14 with a CD4⁺ count of 50-199 cells/mm³ on ART, and 15 ART-naive adults with a CD4⁺ count of ≥ 500 cells/mm³. Mean age was 46.0 (SD 10.93) years (n = 123), 94.3% (n = 116) of patients were male, and 87.8% (n = 108) were White. Due to widespread use of ART, enrollment for the ART-naive and ART/low CD4⁺ count cohorts was lower than anticipated and had low statistical power. Therefore, efficacy analyses were reported for the pooled ART/high CD4⁺ count and ART-naive cohorts. One month after the third vaccination, CD4⁺ cell markers of cell-mediated immunity and gE-specific humoral immune response were higher in the HZ/su group than in the placebo group ($p < 0.0001$ for both). Both cell-mediated and humoral immune responses persisted through 18 months when the study was completed.²⁴

Local and systemic reactions were common among HZ/su recipients. Pain at injection site was reported in 72 of 73 patients (98.6%) in the HZ/su group and in 6 of 48 patients (12.5%) of the placebo group. Most local and systemic reactions were transient (median duration one to three days) in the HZ/su group. No vaccine-related serious AE, or new onset immune-related inflammatory diseases were reported. Through month seven, 12.2% (9 out of 74) in the HZ/su group and 10.2% (5 out of 49) in the placebo group met protocol-defined criteria for a possible worsening of HIV disease. One subject in the HZ/su group reported HZ 83 days after the first dose. Authors concluded that HZ/su elicited a strong gE-specific cellular and humoral response with a clinically acceptable safety profile in HIV-infected individuals after two doses. The third dose did not add much, if any, immunological advantage.²⁴

Use in patients following stem cell transplant

The safety and immunogenicity of HZ/su was investigated in a randomized, observer-blinded, placebo-controlled phase 1/2a study conducted in adults who underwent autologous HCT.²⁵ Subjects with a history of multiple myeloma, non-Hodgkin lymphoma (B- or T-cell), Hodgkin lymphoma, or acute myeloid leukemia with an autologous HCT in the previous 50-70 days were eligible. Major exclusion criteria were previous receipt of VZV or HZ vaccine, history of HZ within 12 months prior to enrollment, known exposure to VZV post-transplant, receipt of vaccinations (other than inactivated influenza vaccine) or immunoglobulins since transplantation, and woman of childbearing potential. The study compared four groups, one placebo group and three separate active treatment groups. In the first active arm subjects received three doses of 50 µg gE + AS01_B, in the

second subjects received three doses of 50 µg gE + AS01_E, and in the third subjects received one dose of saline followed by two doses of 50 µg VZV gE + AS01_B. Study vaccine was administered at months zero, one, and three. The co-primary objectives were to examine the safety and immunogenicity of the two adjuvanted gE subunit vaccine formulations (AS01_B and AS01_E) in the autologous HCT population and to compare gE-specific immune responses one month following final vaccination between the four groups. Recurrence of underlying malignancy and new onset autoimmune disease or immune-mediated inflammatory disorders were recorded for the duration of the study. Participants were randomized 1:1:1:1.²⁵

A total of 121 participants were enrolled. Median participant age was 59.0 years (range 20-70), 65% were male, and 83.3% were White. One month after receipt of the final dose, cellular and humoral immune responses were higher in all three gE/AS01 groups compared to placebo ($p < 0.0001$ for all comparisons). Although there were no statistical differences in immunity between the AS01_B and AS01_E groups, AS01_B tended to be more immunogenic. Immune responses persisted up to one year post-vaccination.²⁵

Most subjects in the HZ/su groups experienced solicited local and general reactions. Pain at the injection site was the most commonly reported local reaction (75.9-90.0% in the three groups which received HZ/su compared to 13.3-23.3% in placebo recipients) while myalgia (62.1-78.6% in the HZ/su recipients compared to 26.7-30% in placebo recipients) was the most commonly reported general reaction. One serious AE was potentially related to the vaccination according to the study investigator. It was

pneumonia which occurred 105 days after the second dose in the gE/AS01_B two-dose group. Malignancy recurred in 32 subjects. No new onset autoimmune diseases or immune-mediated inflammatory diseases were reported. Although there were nine deaths during the study period none were considered to be related to vaccination. Throughout the study, four cases of HZ were confirmed, two in the gE/AS01_E group and two in the placebo group. Five subjects withdrew from the study due to serious AE. Authors' conclusions were that both adjuvanted vaccine formulations and both AS01_B schedules were immunogenic and well tolerated soon after HCT in this immunocompromised patient population. The vaccine may be a suitable candidate to reduce HZ burden in autologous HCT recipients.²⁵

Current regulatory status

On October 24, 2016, GSK Vaccines Division announced regulatory submission of a Biologics License Application for the candidate vaccine HZ/su (Shingrix™).¹⁰ GSK also filed a marketing authorization application in the European Union and Canada in 2016 and in Japan in April 2017.²⁶⁻²⁷ In early October 2017, HZ/su was approved in Canada for the prevention of HZ in adults 50 years of age and older.²⁸ On October 20, 2017, the FDA approved HZ/su for the prevention of HZ in adults aged 50 years and older.²⁹ The CDC's ACIP subsequently voted to recommend HZ/su to prevent HZ and related complications in immunocompetent adults aged 50 years and older, including those who were previously vaccinated with zoster vaccine live. Furthermore, the group voted to prefer HZ/su over zoster vaccine live moving forward.³⁰

Discussion

Studies summarized above have shown that HZ/su effectively decreases the risk of HZ (overall vaccine efficacy in reported phase III trials ranged from 89.8-97.2%) in older patients, including those > 80.^{16,17,22} Available evidence has not shown a substantial decline in immune response to HZ/su in older age over time (97.6% in year one to 87.9% in year four following administration) but longer-term evaluation is needed.¹⁷

PHN is considered to be a large burden associated with HZ, especially in older patients. All patients that developed PHN in pooled data from ZOE-50 and ZOE-70 were over the age of 70, but the incidence was low.¹⁷ The overall risk of PHN was reduced in patients who received HZ/su, but the protective effect against PHN may have been driven by the lower overall incidence of HZ due to high vaccine efficacy. There is no evidence for additional efficacy for the vaccine against PHN among HZ/su recipients who had breakthrough HZ, but the overall risk of developing PHN among older adults was substantially reduced.

While no direct head-to-head trials evaluating vaccine efficacy of HZ/su compared to zoster vaccine live have been published to date, in separate phase III trials, HZ/su seems to have better efficacy in those older than 70 years of age, higher efficacy for the prevention of PHN, and potentially longer persistence of immunogenicity. However, direct comparison of efficacy results of HZ/su and zoster vaccine live in phase III clinical trials is difficult as the primary endpoints were different for the trials. A head-to-head trial

comparing HZ/su to zoster vaccine live in individuals 50-59 and 70-85 years of age is ongoing (NCT02114333).³¹

The results will provide greater insight in determining differences in efficacy between HZ/su and zoster vaccine live.

When compared to placebo, reactogenicity of HZ/su was greater in all studies. Although pain at the injection site was the most common solicited AE reported in the HZ/su treatment groups, most reactions were transient and considered to be mild to moderate in nature.^{16,17,22} Safety data demonstrated no significant differences in rates of vaccine-related serious AE or death between HZ/su and placebo.

Place in therapy

Newly approved by the FDA, HZ/su is expected to have an expanded role in therapy compared to zoster vaccine live and is being endorsed by the ACIP as the preferred vaccination against HZ. Because HZ/su is a two dose series, completion of the second dose will need to be reinforced.

The efficacy and safety of HZ/su in immunocompromised patients has been demonstrated in two small studies with limited patient populations but additional trials are ongoing. A placebo-controlled, phase III trial examining the efficacy and safety of a two-dose schedule of HZ/su in adults following HCT has completed enrollment and is awaiting results (NCT01610414).³² Another placebo-controlled, phase III trial is evaluating the use of HZ/su in adult renal transplant patients (NCT02058589).³³ The

results of these studies may lead to approval of HZ/su for immunocompromised populations where a gap in protection currently exists.

Conclusion

The risk and severity of HZ increase with age and immunosuppression. Zoster vaccine live has been available for over a decade. However, it has limitations including lower efficacy in patients older than 60 years, a decline in efficacy over time, and a contraindication in immunocompromised patients. HZ/su is a new and preferred option to reduce the risk of HZ and PHN in patients 50 years of age and older. It has advantages over zoster vaccine live and in the future may be appropriate for immunosuppressed patients.

Table 1. Summary of major phase III clinical trials for zoster vaccine live and HZ/su^a

	SPS ¹¹	ZEST ⁹	ZOE-50 ¹⁶	ZOE-70 ¹⁷
Vaccine complex studied	Live attenuated (Oka/Merk strain)	Live attenuated (Oka/Merk strain)	Non-live recombinant subunit (HZ/su)	Non-live recombinant subunit (HZ/su)
Study population	Adults 60 years of age or older with a history of VZV but no history of HZ or vaccination against VZV	Adults 50-59 years of age with a history of VZV but no history of HZ or vaccination against VZV	Adults 50 years of age or older with no history of HZ or vaccination against VZV or HZ	Adults 70 years of age or older with no history of HZ or vaccination against VZV or HZ
Study follow up for efficacy (mean number of years)	3.12 (median)	1.3	3.2	3.7

Total number of patients (n)	38,546	22,439	15,411	13,900
Treatment group, for population evaluated in primary objective (n)	19,270	11,211	7,698	6,950
Placebo group (n)	19,276	11,228	7,713	6,950
Mean age \pm SD (years)	69 (median)	54.9 \pm 2.8	62.3 \pm 9.0	75.6 \pm 4.7
Male (%)	59 [n = 22, 760]	38 [n = 8,554]	38.8 [n = 5,987]	45.1 [n = 6,275]
White race (%)	95.4 [n = 36,774]	94.4 [n = 21,189]	71.8 [11,067]	76.9 [n = 10,695]

Vaccine efficacy in reducing risk of HZ (%)	Overall study population = 51.3, subjects aged 60-69 = 63.9%, and subjects aged ≥ 70 = 37.6% (p<0.001 for all)	69.8 (95% CI, 54.1-80.6)	Overall modified vaccinated cohort analysis = 97.2 (95% CI 93.7-99.0), subjects aged 50-59 = 96.6 (95% CI 89.6-99.3), subjects 60-69 = 97.4 (95% CI 90.1-99.7), subjects aged ≥ 70 = 97.9 (95% CI, 87.9-100.0)	89.8 (95% CI, 84.2-93.7%)
Vaccine efficacy in reducing risk of PHN (%)	66.5 (95% CI, 47.5-79.2%)	Not evaluated	Pooled analysis evaluated in ZOE-70, see next column	Pooled analysis from ZOE-50 and ZOE-70, subjects ≥ 70 = 88.8 (95%, 68.7-97.1%)

Vaccine-related serious adverse events reported in vaccine group (%)	< 0.1 [n = 2]	0 [n = 1]	0 [n = 1]	0.2 [n = 12]
Vaccine-related serious adverse events reported in placebo group (%)	< 0.1 [n = 3]	0 [n = 0]	0 [n = 3]	0.1 [n = 8]

^aHZ/su = herpes zoster subunit, SPS = Shingles Prevention Study, ZEST = Zostavax Efficacy and Safety Trial, ZOE-50 = Zoster Efficacy Study in Adults 50 Years of Age and Older, ZOE-70 = Zoster Efficacy Study in Adults 70 Years of Age and Older, VZV = varicella zoster virus, HZ = herpes zoster, US = United States, PHN = postherpetic neuralgia

Table 2. Safety and reactogenicity results within seven days of vaccination from the reactogenicity subgroups in key Phase III trials evaluating HZ/su^a

	ZOE-50 ¹⁶		ZOE-70 ¹⁷	
	HZ/su [n = 4382] (%)	Placebo [n = 4377] (%)	HZ/su [n = 505] (%)	Placebo [n = 505] (%)
Injection site reaction	81.5 (n = 3571)	11.9 (n = 522)	74.1 (n = 374)	9.9 (n = 50)
Pain	79.1 (n = 3464)	11.2 (n = 490)	68.7 (n = 347)	8.5 (n = 43)
Redness	38.0 (n = 1664)	1.3 (n = 59)	39.2 (n = 198)	1.0 (n = 5)
Swelling	26.3 (n = 1153)	1.1 (n = 46)	22.6 (n = 114)	0.4 (n = 2)
Systemic reaction	66.1 (n = 2894)	29.5 (n = 1293)	53.0 (n = 267)	25.1 (n = 127)
Fatigue	45.9 (n = 2008)	16.6 (n = 728)	32.9 (n = 166)	15.2 (n = 77)
Myalgia	46.3 (n = 2025)	12.1 (n = 530)	31.2 (n = 157)	8.1 (n = 41)
Headache	39.2 (n = 1716)	16.0 (n = 700)	24.6 (n = 124)	10.9 (n = 55)
Shivering	28.2 (n = 1232)	5.9 (n = 259)	14.9 (n = 75)	4.4 (n = 22)
Fever	21.5 (n = 939)	3.0 (n = 132)	12.3 (n = 62)	2.6 (n = 13)
GI symptoms	18.0 (n = 788)	8.8 (n = 106)	10.9 (n = 55)	7.9 (n = 40)

^aHZ/su = herpes zoster subunit, ZOE-50 = Zoster Efficacy Study in Adults 50 Years of Age or Older, ZOE-70 = Zoster Efficacy Study in Adults 70 Years of Age or Older, GI = gastrointestinal

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