Shingrix: A New Herpes Zoster Vaccine

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INTRODUCTION

Herpes zoster, commonly known as shingles, is caused by varicella zoster virus (VZV), which is the same virus that causes chickenpox.[1] After a person recovers from chickenpox, the virus remains dormant in the body. When VZV reactivates, which may be years later, it causes herpes zoster. Not everyone who had varicella zoster virus will develop shingles, but as immunity to the virus declines with age, the risk for developing herpes zoster rises sharply in people over the age of 50.[1]

There are approximately one million cases of herpes zoster in the U.S. annually, and it is estimated that one in three people will develop shingles in their lifetime.[2] In adults over the age of 85, this ratio increases to one in two.[3] Approximately 1% to 4% of adults who develop shingles may be hospitalized for complications, and the majority of these patients tend to be immunocompromised (i.e., with HIV or cancer, or from immunosuppressant medications).[2] Shingles usually affects only one side of the body; it is a painful rash that turns into fluid-filled blisters that break open and subsequently scab in seven to ten days. The entire rash usually clears up within two to four weeks. Between one and five days before the rash develops, patients may complain of pain, itching, numbness, or tingling in the area where the rash eventually presents itself. As the rash typically travels along dermatomes—an area of skin supplied by a single spinal nerve—any pain traveling along that nerve will be felt in that area. There are identical nerves on the right and left sides of the body and they do not cross the body's midline. Consequently, shingles presents as a single-strip rash across one side of the torso, shoulder, or face.

Other symptoms can include fever, headache, chills, upset stomach, and fatigue.[1,2] One of the most serious complication of shingles is postherpetic neuralgia (PHN). Patients with PHN continue to have long-lasting pain in the areas where the rash appeared, even after it clears up. For some patients, PHN may resolve in a few weeks or a month but for others, it can take years. Approximately 10% to 50% of patients who develop herpes zoster will experience PHN.[1]

Other rare but possible complications from shingles include blindness, skin infections, pneumonia, hearing problems, encephalitis, and death.[1,2] Shingles is not contagious; however, if someone comes into direct contact with fluid from the blisters, VZV can be transmitted if he or she is not immune. Prior to the blisters appearing and after the rash has crusted, the person is not contagious.

Patients who develop shingles should always keep their rash covered, avoid scratching, wash their hands regularly, and avoid contact with high-risk individuals (i.e., pregnant women, infants, immunocompromised patients) during the blistering stage.[1,2] Recurrence of herpes zoster is rare, but patients who are immunosuppressed are at increased risk for redeveloping shingles. Herpes zoster is usually treated with antiviral medications, which are most effective when administered within 72 hours after the rash appears.[1] Pain medications may also be prescribed for those with severe pain.

Vaccinating against shingles is the best way to prevent this infection and its complications.[1,2] The original herpes zoster vaccine, Zostavax® or Zoster Vaccine Live (ZVL), was approved in 2006.[4] However, the efficacy of ZVL in preventing herpes zoster was found to be variable, at about a 70% rate of effectiveness in patients aged 50 to 59 and only 38% in patients over the age of 70.[5] Furthermore, in 2016, only an estimated 33.4% of Americans aged 60 years or older had received ZVL.[3]

After more than a decade, a new shingles vaccine, Shingrix® (GlaxoSmith Kline) has been added to the market. Herpes zoster subunit vaccine (HZ/su) was approved by the Food and Drug Administration (FDA) in October 2017 for the prevention of herpes zoster in adults aged 50 and older.[6] It is now recommended as the preferred herpes zoster vaccine in immunocompetent adults in this age range by the Advisory Committee on Immunization Practices (ACIP).[5] This article focuses on the efficacy and safety of HZ/su and its recommended use.

PHARMACOLOGY

An age-related decline in immunity appears to be one reason why adults aged 50 and older are at greater risk for herpes zoster. In general, aging causes a proinflammatory state, a reduced response to vaccines, and reduced immunity to infections, which results in an increased susceptibility to diseases.[3] With shingles specifically, there appears to be a decline in VZV T cell-specific immunity with increasing age.[1,3] Thus, vaccination to prevent shingles is critical in this age group. Unlike ZVL, which is a live vaccine, HZ/su is an inactivated vaccine comprised of VZV glycoprotein E (gE) and an adjuvant suspension called $AS01_B$. Glycoprotein E is found in large numbers on the surface of cells that are infected with zoster virus, and it is required for viral replication.[7] An adjuvant found in several other vaccines is another ingredient of HZ/su; it helps to promote a stronger immune response.[8] The adjuvant in HZ/su is a new formulation known as $AS01_B$, whose role is to stimulate and induce a higher gE-specific cell-mediated immune response.[8] This becomes important especially because of the age-related decline in immune response that is observed in patients who develop shingles.

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PHASE 3 CLINICAL TRIALS

ZOE-50 and ZOE-70 were two phase 3 trials that led to the approval of the HZ/su vaccine.[9,10]

ZOE-50

Phase 3 ZOE-50 was a multinational, randomized, placebo-controlled trial to evaluate the efficacy and safety of two doses of HZ/su in adults aged 50 and older.[9] Patients were excluded if they had a history of herpes zoster, had received previous vaccination against varicella or herpes zoster, or if they were immunosuppressed. Participants were stratified into three age groups of 50–59, 60–69, and > 70 years, and were randomized to receive either two intramuscular (IM) injections of HZ/su vaccine or placebo, with an interval of two months between each injection.

The primary efficacy analysis included the modified vaccinated cohort of 14,759 patients who received two doses of HZ/su (n = 7,344) or placebo (n = 7,415). Participants were similar in both groups, and were mainly comprised of white (72%) females (61%) from Europe (51%) with a mean age of 62 years. Herpes zoster was confirmed in 216 patients in the modified vaccinated cohort, with six patients in the HZ/su group and 210 patients in the placebo group after 3.2 years of follow-up. The incidence of herpes zoster compared with placebo is summarized in Table 1. In the modified vaccinated cohort, the overall incidence of herpes zoster per 1,000 person-years was 0.3 in the HZ/su group and 9.1 in the placebo group, with an overall vaccine efficacy of 97.2% (95% confidence interval [CI], 93.7–99.0; $P < 0.001$). There was no significant difference in vaccine efficacy among the stratified age groups. This study showed that HZ/su significantly reduced the risk of herpes zoster in adults aged 50 and older.[9]

Table 1 ZOE-50: Efficacy of HZ/su on Incidence of Herpes Zoster (HZ) Versus Placebo in Modified Vaccinated Cohort[9]

	HZ/su			Placebo			
Age Group (Years)	N	n	Incidence of HZ per 1,000 Person-Years	N	n	Incidence of HZ Per 1,000 Person-Years	% Efficacy (95% CI)
Overall (≥ 50)	7,344	6	0.3	7,415	210	9.1	97.2 (93.7, 99.0)
50–59	3,492	3	0.3	3,525	87	7.8	96.6 (89.6, 99.3)
60–69	2,141	2	0.3	2,166	75	10.8	97.4 (90.1, 99.7)
≥ 70	1,711	1	0.2	1,724	48	9.4	97.9 (87.9, 100.0)

CI = confidence interval; HZ = herpes zoster; HZ/su = herpes zoster subunit vaccine; N/n = number

ZOE-70

ZOE-70 was also a multinational, randomized, placebo-controlled phase 3 clinical trial whose purpose was to evaluate the efficacy and safety of two doses of HZ/su in adults aged 70 and older.[10] Apart from age, the exclusion criteria were the same as those of the ZOE-50 trial.[9] Patients were first randomized to participate in either ZOE-50 or ZOE-70, then randomly assigned to the HZ/su group or placebo group.[9,10] Participants were stratified in a 3:1 ratio into two age groups: 70–79 years and > 80 years.

The primary efficacy analysis included the modified vaccination cohort of 13,163 participants who received two IM doses of HZ/su (n = 6,541) or placebo (n = 6,622). Participants were similar in both groups and were primarily white (77%), female (55%), and from Europe (54%). The participants' mean age was 76 years. Herpes zoster was confirmed in 246 patients in the modified vaccinated cohort, with 23 in the HZ/su group and 223 in the placebo group after 3.7 years of follow-up. The incidence of herpes zoster compared with placebo is summarized in Table 2. In the modified vaccination cohort, the incidence of herpes zoster per 1,000 person-years was 0.9 in the HZ/su group and 9.2 in the placebo group, with an overall vaccine efficacy of 89.8% (95% CI, 84.2–93.7; $P < 0.001$). The efficacy of the vaccine was not significantly different between the two age groups. In a pooled analysis of participants from ZOE-70 and ZOE-50, including 16,596 in the modified vaccinated cohort, 309 cases of herpes zoster were confirmed, with 25 in the HZ/su group and 284 in the placebo group. The overall vaccine efficacy in the pooled analysis was 91.3% (95% CI, 86.8–94.5%).

The vaccine efficacy against PHN was reported in the pooled vaccinated cohort, including all patients 50 years and older

Table 2 ZOE-70: Efficacy of HZ/su on Incidence of Herpes Zoster Versus Placebo in Modified Vaccinated Cohort[10]

	HZ/su			Placebo			
Age Group (Years)	N	n	HZ Incidence per 1,000 Person-Years	N	n	HZ Incidence per 1,000 Person-Years	% Efficacy (95% CI)
Overall (≥ 70)	6,541	23	0.9	6,622	223	9.2	89.8 (84.3, 93.7)
70–79	5,114	17	0.9	5,189	169	8.8	90.0 (83.5, 94.3)
≥ 80	1,427	6	1.2	1,433	54	11.0	89.1 (74.7, 96.2)

CI = confidence interval; HZ = herpes zoster; HZ/su = herpes zoster subunit vaccine; N/n = number

from both studies. Postherpetic neuralgia occurred in 4 of 32 patients receiving HZ/su and in 46 of 477 patients receiving placebo over a mean follow-up period of 3.8 years. The incidence of PHN per 1,000 person-years was 0.1 in the HZ/su group and 0.9 in the placebo group, showing a vaccine efficacy of 91.2% in adults aged 50 and older (95% CI, 75.9–97.7%; $P < 0.001$). Pooled data in patients aged 70 and older identified a total of 40 PHN cases, with four in the HZ/su group and 36 in the placebo group. The overall incidence of PHN per 1,000 person-years was 0.1 in the HZ/su group and 1.2 in the placebo group, demonstrating a vaccine efficacy of 88.8% (95% CI, 68.7–97.1; $P < 0.001$). PHN did not occur in any patients below the age of 70 who received HZ/su. The incidence of PHN in patients who received HZ/su with breakthrough herpes zoster was not significantly different from patients who received placebo (12.5% and 9.6%, respectively; $P = 0.54$). This study showed that HZ/su reduced the risk of both herpes zoster and PHN in adults 70 years and older.[10]

Prior Vaccination With Zoster Vaccine Live (ZVL)

Grupping et al. performed a phase 3, open-label, group-matched, noninferiority, multicenter study in adults aged 65 or older, previously vaccinated with ZVL within five years or more (HZ-PreVac) and matched to adults who were ZVL-naïve (HZ-NonVac).[11] Participants received two IM doses of HZ/su two months apart. Patients were excluded if they had received a live vaccine within 30 days or any investigational drug or vaccine within 30 days, were on any immunosuppressants or immune-modifying drugs within a specific timeframe, or had a history of herpes zoster. The primary study objectives were to compare the noninferiority of humoral immune responses one month after the second HZ/su dose between the HZ-PreVac and HZ-NonVac groups, and to evaluate the safety and reactogenicity up to one month after the second dose of HZ/su in both groups. Noninferiority of the humoral immune response was determined if the upper limit of the 95% CI of the adjusted anti-gE geometric mean concentration (GMC) ratio of HZ-NonVac over HZ-PreVac was < 1.5.[11]

In 430 participants, the humoral immune response to HZ/su was noninferior in the HZ-PreVac group compared with the HZ-NonVac group (adjusted GMC ratio, 1.04; 95% CI, 0.92–1.17). There were also no differences seen in $CD4^+$ T cells between the groups. The study showed that HZ/su elicits a strong immune response regardless of prior ZVL vaccination.[11]

Coadministration With Influenza Vaccine

Schwarz et al. conducted a phase 3, randomized, open-label, multicenter trial in adults aged 50 and older to determine the immunogenicity and safety of the HZ/su vaccine when coadministered with quadrivalent seasonal inactivated influenza vaccine (IIV4).[12] Patients were stratified by age group and randomized 1:1 to receive either HZ/su and IIV4 at Day 0, followed by a second HZ/su dose at Month 2 (coadministration group), or IIV4 at Month 0 and HZ/su at Months 2 and 4 (control group). Patients were excluded if they had received any investigational drug or vaccine from 30 days prior to the study through 30 days after the second HZ/su dose; influenza vaccine; or long-term treatment with immunosuppressant or immune-modifying drugs within six months before the study. Patients were also excluded if they had previously received varicella zoster vaccine or herpes zoster vaccine, or had a history of herpes zoster. The primary objectives were to evaluate the vaccine response rate (VRR) one month after the second HZ/su dose in the coadministration group, and to determine noninferiority of anti-gE GMCs after the second HZ/su dose, comparing both groups. VRR was demonstrated if the lower limit of the two-sided 95% CI of VRR in the coadminstration group was ≥ 60% . Noninferiority was met if the upper limit of the two-sided 95% CI of adjusted anti-gE GMC ratio of the control group over the coadministration group was < 1.5. A secondary objective was assessing the noninferiority of IIV4 immuno-

Table 3 Percentage of Participants With Solicited Local and Systemic Adverse Events Within Seven Days of Vaccination From ZOE-50 and ZOE-70 Trials[9,10]

	ZOE-50		ZOE-70	
Adverse Event	**HZ/su %**	**Placebo %**	**HZ/su %**	**Placebo %**
Injection-site reaction	81.5	11.9	74.1	9.9
Pain	79.1	11.2	68.7	8.5
Redness	38.0	1.3	39.2	1.0
Swelling	26.3	1.1	22.6	0.4
Grade 3 injection-site reaction*	9.5	0.4	8.5	0.2
Systemic reaction	66.1	29.5	53.0	25.1
Myalgia	46.3	12.1	32.9	15.2
Fatigue	45.9	16.6	31.2	8.1
Headache	39.2	16.0	24.6	10.9
Shivering	28.2	5.9	14.9	4.4
Fever	21.5	3.0	12.3	2.6
Gastrointestinal symptoms	18.0	8.8	10.9	7.9
Grade 3 systemic reaction*	11.4	2.4	6.0	2.0

* Diameter of injection-site redness and swelling reactions, scores: 0 for < 20 mm; 1 for 20–50 mm; 2 for > 50–100 mm; and 3 for > 100 mm. Temperature scores: 0 for < 37.5° C; 1 for 37.5–38.0° C; and 3 for > 39.0° C. All other symptoms scores: 0 for absent, 1 for easily tolerated; 2 for interferes with normal activity; and 3 for prevents normal activity. HZ/su = herpes zoster subunit vaccine

Table 4 Herpes Zoster Vaccine Comparison[4,6,13]

	Shingrix (HZ/su)	Zostavax (ZVL)
Vaccine type	Inactivated, adjuvanted, subunit vaccine	Live-attenuated vaccine
Storage	Refrigerator	Freezer
Dose	0.5 mL, 2-dose series spaced 2–6 months apart	0.65 mL/dose, single dose
Administration	Intramuscular (IM)	Subcutaneous (SC)
Age recommendation (ACIP)	≥ 50 years old	≥ 60 years old
Contraindications	Hypersensitivity to vaccine	Hypersensitivity to vaccine, gelatin, neomycin; immunosuppression or immunodeficiency; pregnancy
Cost* (AWP)	$346 for two doses	$268 for one dose

ACIP = Advisory Committee on Immunization Practices; AWP = average wholesale price; *Red Book Online

genicity in the coadministration group compared with that in the control group.[12]

A total of 828 patients were included in the study, 413 in the co-administration group and 415 in the control group. Among coadministration patients, VRR was 95.8% (95% CI, 93.3–97.6%), and anti-gE GMC ratio was 1.08 (95% CI, 0.97–1.20). Immunogenicity to the IIV4 vaccine was also noninferior between the groups. This study demonstrated that immune responses to both HZ/su and IIV4 were not affected by coadministration.[12]

ADVERSE EVENTS

In ZOE-50 and ZOE-70, data on solicited local and systemic adverse events were collected from participants within seven days of each vaccination (see Table 3).[9,10] In both studies combined, participants aged 50 and older reported the following solicited local and systemic adverse reactions after administration of both doses of HZ/su: pain (78%), redness (38.1%), swelling (25.9%); and myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%), respectively.[6] The incidence of adverse events was greater in participants aged 50 to 69 than in those aged 70 and older. Most adverse reactions lasted for a median of two to three days, and grade 3 solicited systemic reactions were more frequent after the second dose than the first dose.[6] In ZOE-50, 231 serious adverse events were reported within the first 30 days after vaccination, with 103 events in the HZ/su group (1.1%) and 128 events in the placebo group (1.1%) of the total vaccinated cohort. Among those who had serious adverse events, four participants (one from the HZ/su group and three from the placebo group) experienced events that investigators considered to be related to vaccination, including hypotension with syncope, mononeuritis, neurosensory deafness, and musculoskeletal chest pain.[9] In ZOE-70, one death was considered to be related to vaccination with HZ/su.[10] After a mean follow-up of 3.5 years in ZOE-50 and 4 years in ZOE-70, the number and types of serious adverse events were shown to be similar in both HZ/su and placebo groups.[9,10]

DOSING AND ADMINISTRATION

HZ/su is a suspension supplied as two vials—the lyophilized gE antigen component and the $AS01_B$ adjuvant suspension.[6] The gE component is a sterile white powder and the adjuvant is a colorless to pale brown liquid. Prior to reconstitution, HZ/su should be stored in the refrigerator between 2°C and 8°C.[6] Once reconstituted, the final product should be colorless to pale brown and requires inspection for any discoloration or particles before administration. If the vaccine cannot be administered immediately after reconstitution, it can be stored in the refrigerator for use within six hours.[6] The vaccine should be discarded if frozen or if not used within six hours after reconstitution.[6] HZ/su should be reconstituted only with the diluent supplied by the manufacturer. This vaccine is approved for intramuscular administration only[6] and is given as two doses (0.5 mL each): the first at month 0 and the second anytime between two and six months later.[6] HZ/su is contraindicated in patients who had an anaphylactic reaction to any component of the vaccine or who have had a previous dose.[6] Although not contraindicated, HZ/su is not recommended for use during pregnancy, in women who are nursing, or in severely immunocompromised patients, as data are lacking in these populations.[5,6] Table 4 shows a comparison between HZ/su and ZVL.

COST AND FORMULARY CONSIDERATIONS

Herpes zoster is associated with significant economic and public health costs in the U.S.[14] A 2016 cost analysis estimated the annual direct and indirect costs related to herpes zoster as $782 million.[15] In addition, the projected cost of herpes zoster in people 65 years and older will be $4.74 billion by 2030.[14] Table 4 includes a cost comparison between HZ/su and ZVL. The average wholesale price (AWP) of each Hz/su dose is $173, with a total cost of $346.[13] Unlike influenza and pneumococcal vaccines, which are covered by Medicare Part B, herpes zoster vaccines are covered under Medicare Part D, which may present an economic challenge for many Medicare recipients.[14]

CDC RECOMMENDATIONS

In January 2018, ACIP recommended changes to the shingles vaccination based on a summary of available data.[5] As HZ/su provides higher rates of efficacy against herpes zoster and PHN than ZVL, ACIP now recommends HZ/su as the preferred vaccine over ZVL in adults aged 50 and older, regardless of herpes zoster history or previous vaccination with ZVL.[5] However, ACIP advises against the administration of HZ/su less than two months after receiving ZVL.[5] ACIP also recommends HZ/su as the preferred vaccine over ZVL to prevent herpes zoster in adults aged 60 and older.[5] In addition, they advise using HZ/su in patients who have only mild immunosuppression-related medical conditions, who are taking low-dose immunosup-

continued on page 433

continued from page 409

pressive therapy (i.e., inhaled or topical steroids or oral prednisone < 20 mg/day or its equivalent), or who have significant chronic disease (i.e., rheumatoid arthritis, diabetes, kidney disease, or pulmonary disease), except HIV infection.[5] Should a patient have an active outbreak of herpes zoster, vaccination must be delayed until the active stage of infection is over. HZ/su can be coadministered along with other adult vaccines, including IIV4 and pneumococcal vaccines. However, the coadminstration of HZ/su and adjuvanted influenza vaccine has not been studied.[5]

CONCLUSION

In two phase 3 trials, Hz/su significantly reduced the development of herpes zoster in adults aged 50 and older, and of herpes zoster and PHN in adults aged 70 and older.[9,10] Because of its superior efficacy over ZVL, HZ/su is now recommended by ACIP as the preferred vaccine for adults aged 50 and older for the prevention of herpes zoster and PHN.[5] An additional phase 3 trial showed that Hz/su elicited a strong immune response in patients who were previously vaccinated with ZVL.[11] Therefore, ACIP recommends that all adults 50 and older should receive HZ/su regardless of previous ZVL vaccination.[5] It is important to note that HZ/su is a two-dose vaccine, with injections given two to six months apart. Because of the great economic and public health burden caused by herpes zoster and PHN, all immunocompetent adults aged 50 and older should be made aware of the importance of receiving HZ/su and completing the vaccine series.

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