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Shingrix®: A New Herpes Zoster Subunit Vaccine

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There are approximately one million shingles cases in the U.S. each year with approximately 4% of all shingles cases severe enough to result in hospital admission. Up to 30% of patients diagnosed with shingles have weakened immune systems.[1] Herpes Zoster, commonly termed shingles or zoster, is caused when the varicella-zoster virus (VZV), which initially causes varicella, has its primary infection resolve and the virus becomes dormant in the dorsal root ganglia. Shingles manifests once the VZV becomes reactivated, which typically occurs later in life, and causes a painful, itchy rash featuring sensitive blisters. There are 4 cases per 1,000 people in the U.S. each year, with that number jumping to 10 out of 1,000 for people over 60 years of age.[1] The VZV is a linear double stranded DNA molecule made up of 2 segments that are covalently joined with a nucleocapsid that surrounds the genetic material. The virus attaches to heparin sulfate proteoglycan on the cell surface and replication occurs within 4-10 hours. Unlike other herpes viruses, VZV is transmissible through respiratory routes and it is highly contagious. The virus can be transmitted 24 to 48 hours prior to symptom expression. The incubation period of the virus is anywhere from 10-21 days, most frequently 14-16 days.[2]

Zostavax® has been FDA approved for prevention of shingles in people age 60 and older since 2006. Shingrix® was approved in October 2017 and has the Advisory Committee on Immunization Practices (ACIP) preference over Zostavax®.[3] Shingrix® has been approved to prevent shingles in adults aged 50 years and older.[4] Prior to the introduction of Zostavax®, the annual incidence of shingles in patients over the age of 65 had increased steadily from 0.5% to 1.1% from 1994 to 2005. Since 2006, after Zostavax® was introduced, the incidence has remained steady at 1%. The purpose of this article is to review clinical trials discussing Zostavax® and Shingrix® and the future potential of the newer vaccine.

Zostavax® Review

Vaccination with the live VZV vaccine (Zostavax®) produces a detectable IgG antibody humoral immune response in most healthy individuals. The live vaccination also elicits a cell mediated immune response, consisting of expression of varicella zoster specific activation of both CD4+ T helper and CD8+ T lymphocytes. The Zostavax® vaccine is recommended by the CDC for patients age 60 and older. Patients over 60 years of age are most likely to develop shingles, and the vaccine efficacy wanes within the first 5 years after vaccination, giving reason to the suggested age for Zostavax® administration.[1] Zostavax® is a live attenuated virus and should not be used in patients with weakened immune systems due to AIDS, steroid treatments, treatment with biologics, cancer treatments, or bone or lymphatic cancers. Additionally, pregnant women should not receive the Zostavax® vaccine and should wait at least 4 weeks after vaccination before becoming pregnant.[5] Due to administration limitations of Zostavax® there is a need for a vaccination that can be administered to these populations.

Zostavax® does not guarantee prevention of shingles but does help reduce its severity if it occurs. Oxman et al. compared the reduction of shingles occurrence with Zostavax® to placebo in patients 60 years of age or older with either a history of varicella or time spent in the U.S. of 30 years.[5] A total of 38,546 patients were included in the study. The primary endpoint was a severity-by-duration measure of the total pain and discomfort associated with herpes zoster.[5] This was defined as an area under the curve of pain plotted against time in the 182-days since onset of rash. Pain was calculated as a severity-of-illness score using answers to the "worst pain" question in the Zoster Brief Pain Inventory. Follow-up was done with patients over the phone each month for 3-5 years to determine if they had symptoms of shingles. Primary outcome results were 5.42 per 1000 person-years for Zostavax® treated patients, total 481 cases, compared to 11.12 per 1000 person-years for placebo, total 827 cases, ($P<.001$). Of note, trial subgroup analysis revealed that the vaccination may be more efficacious in younger patients. Vaccine efficacy for herpes-zoster in the form of a relative reduction in incidence rate compared between vaccine and placebo patients was 63.9% for patients aged 60-69. Contrarily, in patients aged ≥70 years the relative reduction in incidence rate was only 37.6%.[5] Among all subjects, 1.6% of vaccinated subjects had shingles compared to 3.3% of placebo patients, giving an absolute reduction of 1.6%. In patients who had shingles, those who had the vaccine also had lessened severity

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of symptoms. A severity-of-illness score was recorded as the area under the curve of herpes-zoster-related pain plotted against time after symptom onset. Duration of pain (21 days Zostavax® vs 24 days placebo, P=.03) and mean herpes-zoster severity-of-illness score (141.2 Zostavax® vs 180.5 placebo, P=.008) were lower in the Zostavax® group.[5] This early research indicated Zostavax® was effective at reducing shingles symptoms and reducing the risk of developing shingles patients aged 60 or older.

Later research indicated Zostavax® could be given to patients <60 years with positive results. In 2012 a randomized, double-blind study Zostavax® was compared to placebo in 22,439 patients aged 50-59. The primary outcome was the incidence of shingles in Zostavax® and placebo groups in people aged 50-59. Patients were followed for shingles occurrence for an average of 1.3 years; the study followed patients until 96 shingles cases occurred. Results provided a vaccine efficacy for herpes-zoster (VEHZ) in the form of a relative reduction in incidence rate compared between the groups.[6] The end results were a VEHZ of 69.8% (95% CI, 54.1%-80.6%). Shingles occurred in 0.3% of vaccinated patients compared to 0.9% of placebo patients, giving an absolute reduction of 0.6% in patients who had shingles, the relative reduction in pain, based on a 0 to 10 scale using the Zoster Brief Pain Inventory, was 73.0% (95% CI, 52.7%-84.6%).[6] The study showed patients aged 50-59 could be given Zostavax® and benefit from the vaccination.

Despite the Zostavax® trial results, the current recommendation is to not receive Zostavax® until ≥60 years as shingles is more likely in this population and Zostavax® becomes less effective 5 years after vaccination.[7] There are also some contraindications for Zostavax® including those with severe allergies to components of the vaccine, neomycin, or gelatin should not have Zostavax®. Additionally, as previously mentioned, Zostavax® should not be administered to specific patient populations who have compromised immune systems or pregnant women.

Shingrix® Review

Unlike the live Zostavax® vaccine, Shingrix® is a non-live subunit vaccination – made of a varicella zoster virus glycoprotein and an adjuvant suspension component – for HSV (herpes simplex virus). The risk of VZV increases with age and it is thought to be related to a reduction in VZV specific immunity. Shingrix® has been shown to boost VZV specific immune response, which is thought to be the primary mechanism for its efficacy.

Clinical Trials

Lal, et al. conducted a study in 2015 which proved to be key in the approval of Shingrix®. The primary endpoint was to evaluate overall vaccine efficacy in reducing the risk of herpes zoster, as compared with placebo, in adults who were 50 years of age or older.[10] The trial encompassed 18 countries with 15,411 subjects included. Patients were excluded if they had a history of shingles, previous vaccination against varicella or herpes zoster, an immunosuppressive condition, or other illnesses and conditions deemed possible for interference with results.[10] Secondary endpoints were not all reached by the time of the study research article, as the study was still ongoing at the time.[10]

Subjects were randomly assigned in a 1:1 ratio to receive the HZ/su (Shingrix®) vaccine 0.5 mL IM or a placebo vaccine. Both were given in 2 doses 2 months apart. Patients were contacted monthly for at least 30 months and up to 60 months. If they developed any symptoms of shingles they recorded them and contacted their study location, which worked with them to diagnose their condition. If they had a "unilateral rash with pain" with no other diagnosis it was considered to be shingles.[10] The number cases of shingles confirmed during the follow-up period were 9 in the HZ/su group and 235 in the placebo group. A subgroup of these 244 patients with confirmed shingles was created by excluding the 28 who did not receive the second vaccination or had shingles within 1 month after the second vaccination, leaving a subgroup of 216 patients. In this subgroup (216 patients), only 6 cases were from the HZ/su dosing group. Analysis of the subgroup revealed an incidence of shingles as 0.3 per 1000 person-years in the Shingrix® subgroup and 9.1 per 1000 person-years in the placebo subgroup. Shingrix® efficacy at reducing shingles occurrence was calculated at 97.2% (95% CI, 93.7 to 99.0; P<.001) when compared to placebo.[10]

Along with the primary outcome, the study also reviewed the reactogenicity of the HZ/us vaccine administration. The authors recorded systemic and local side effects and rated reactions on a scale ranging from absent, or 0, to "preventing normal everyday activities", or 3.[10] Results indicated symptoms within 7 days after vaccination occurred in 84.4% (95% CI, 83.3% to 85.5%) of the HZ/su reactogenicity group and 37.8% (95% CI, 36.4% to 39.3%) of the placebo group. However, symptoms "preventing normal everyday activities" happened at a rate of 17% (95% CI, 15.9% to 18.2%) of the HZ/su patients and 3.2% (95% CI, 2.7% to 3.8%) of placebo patients.[10] Injection-site reaction rates in the HZ/su treated patients included pain (79.1%), redness (38.0%), and swelling (26.3%). In placebo patients the occurrences were 11.2% for pain, 1.3% for redness, and 1.1% for swelling. Also reported were systemic reactions including the most prevalent as myalgia, fatigue, headache and others included shivering, fever, and gastrointestinal symptoms. HZ/su patients had occurrences of these symptoms as 46.3% for myalgia, 45.9% for fatigue, and 39.2% for headache. Placebo patients had lower rates: 12.1% for myalgia, 16.6% for fatigue, and 16.0% for headache. Patients should be warned of the risk of side effects with Shingrix®.

A second trial for Shingrix® conducted by Cunningham, et al. focused on patients ≥70 years.[11] The primary objective was to compare HZ/su with placebo to determine the risk reduction of herpes zoster in patients ≥70 years. Data from this study was combined with data from the previous study (Lal, et al.) to also assess risk reduction of shingles and postherpetic neuralgia in patients ≥70 years. Exclusion criteria were history of shingles, vaccination for chickenpox or shingles, or an immunosuppressive condition. A total of 13,900 patients were randomly assigned in a 1:1 ratio to HZ/su or placebo vaccinations with a mean age of 75.6 years.[11]

The study resulted in 270 cases of shingles, with 246 of these being in a modified vaccinated cohort (excluded 24 patients missing second dose of HZ/su or placebo, or having shingles within 1 month after second dose). Of these 246 patients, 23 received HZ/su and 223 received a placebo. Shingrix® efficacy was 89.8% (95% CI, 84.2%-93.7%, P<.001) compared to placebo. The incidence rates were 0.4% in the vaccine group and 3.4% in the placebo group. Incidence rates per 1000 person-years were 0.9 for vaccine and 9.2 for placebo. Combined with data from the trial completed by Lal, et al., a composite efficacy was calculated at 91.3% in the 70 and older age group (95% CI, 86.8%-94.5%).[11] Data was also combined from these two studies to determine effectiveness against postherpetic neuralgia. Once patients were suspected of having herpes zoster, the Zoster Brief Pain Inventory question-

Table 1 | Summary of clinical trials for Zostavax® and Shingrix®

Trial	Population	Treatments	Primary Endpoint	Results
Oxman et al.[5]	Age ≥60 years	Zostavax® vs placebo 0.5 mL IM	HZ BOI score relative risk reduction after a 182-day period after rash onset[a]	HZ BOI score: 2.21 vs 5.68; Relative Risk Reduction: 61.1% (95% CI, 51.1 to 69.1)
Scmader et al.[6]	Age 50 to 59 years	Zostavax® vs placebo 0.65 mL IM	Vaccine efficacy[b] 2 years post-vaccination	HZ incidence[c]: 1.99 vs 6.60; Vaccine efficacy[b]: 69.8% (95% CI, 54.1 to 80.6)
Lal et al.[10]	Age ≥50 years	Shingrix® vs placebo 0.5 mL IM	Vaccine efficacy[d] 30 months post-vaccination	HZ incidence[c]: 0.3 vs 9.1; Vaccine efficacy[d]: 97.2% (95% CI, 93.7% to 99.0%)
Cunningham et al.[11]	Age ≥70 years	Shingrix® vs placebo 0.5 mL IM	Vaccine efficacy[d] with mean follow up 4 years post-vaccination	HZ incidence[c]: 0.9 vs 9.2; Vaccine efficacy[d]: 89.8% (95% CI, 84.2% to 93.7%)

95% CI = 95% confidence interval, **BOI** = burden of illness, **HZ** = herpes zoster, **IM** = intramuscular, **mL** = milliliter
a. The "herpes-zoster burden-of-illness score" represented the average severity of illness among all subjects in the vaccine or placebo groups; it was calculated as the sum of the herpes-zoster severity-of-illness scores of all members of a group divided by the total number of subjects in the group. The herpes-zoster severity-of-illness was defined as product of the Zoster Brief Pain Inventory (a HZ specific pain scale utilizing a 0 to 10 numeric scale, where 0 is no pain and 10 is worst pain) and duration of pain and discomfort in all patients in the study.
b. Vaccine efficacy defined as the relative risk reduction in incidence of HZ 2 years post-vaccination
c. Incidence calculated per 1000 person-years
d. Vaccine efficacy, as a percentage, was defined as 1 minus the ratio of the incidence of herpes zoster in the HZ/su group to the incidence in the placebo group, multiplied by 100

naire was completed daily for 28 days and each week afterwards. Pain evaluation continued until patients were pain-free for 4 weeks or for at least 90 days after the onset of the rash.[11] If the patients scored a 3 or higher (0 to 10 scale with 10 being the worst) on the worst pain in the last day they were considered to have postherpetic neuralgia. For patients aged 50 years and older the efficacy at preventing postherpetic neuralgia was 91.2% (95% CI, 75.9%-97.7%, P<.001) with only 4 of 32 HZ/su patients presenting with neuralgia. This is a great reduction when compared to placebo group with 46 of 477 patients presented with symptoms of postherpetic neuralgia. All patients found to have neuralgia were ≥70 years; the Shingrix® efficacy in this age group was 88.8% (95% CI, 68.7%-97.1%, P<.001).[11]

As with the previous trial, reactogenicity was again investigated, with similar results. Subjects recorded local and system reactions on diary cards for the week after each injection. The same 0 to 3 scale of interference with daily activity as was used in the previous trial was used. Symptoms within 7 days of vaccination occurred in 79.0% (95% CI, 75.2-82.5) of HZ/su patients and 29.5% (95% CI, 25.6-33.7) of placebo patients. A larger amount of patients, 74.1% (95% CI, 70.0-77.8) of HZ/su patients in a reactogenicity group, had vaccination-site related reactions compared to 9.9% (95% CI, 7.4-12.8) of placebo patients. Severe reactions occurred in 8.5% of HZ/su patients and 0.2% of placebo patients.[11] These included symptoms such as pain, redness, and swelling over 100 mm at the injection site, fatigue, and myalgia. In HZ/su vs placebo patients, the rates of symptom occurrence were 68.7% vs 8.5% for pain, 39.2% vs 1.0% for redness, 22.6% vs 0.4% for swelling, 32.9% vs 15.2% for fatigue, and 31.2% vs 8.1% for myalgia. The overall results from this trial indicate Shingrix® is effective still in patients aged 70 and older, but it does maintain a potentially high reaction rate. The effectiveness at preventing shingles and postherpetic neuralgia appears to outweigh the likelihood and severity of reactions, though.

Discussion of Evidence

Not accounting for heterogeneity of the studies, the efficacy rate for Shingrix® was much higher than Zostavax® had obtained in its trials, which are summarized in **Table 1**. Another consideration is the efficacy of Shingrix® in older patients as Zostavax® has reduced efficacy in patients ≥60 years. Subgroup analysis of the primary outcome in the Lal, et al. study evaluated the difference in HZ/su effectiveness among age groups (50-59, 60-69, ≥70) and was determined to be non-inferior between groups (range, 96.6%-97.9%).[10] These results indicate HZ/su could work well across age groups, and could be much more effective in preventing shingles than Zostavax®. Direct head to head studies of Zostavax® vs Shingrix® would need to be conducted to validate the superiority of Shingrix® in preventing herpes zoster.

Herpes Zoster Recommendation Summary

ACIP decided in October 2017 to recommend Shingrix® over Zostavax® for people age 50 and older or to those adults who already received Zostavax®, in an 8 to 7 vote.[3] There are currently no recommendations from the ACIP on how long to wait between Zostavax® and Shingrix® administration. There are also no recommendations on administering the vaccines together, as there are no trials evaluating patients receiving both. Part of the reason for the close vote is panel members are in favor of gathering safety data on Shingrix® for a year or 2 and waiting to see whether supplies proved adequate before endorsing it over Zostavax®.[3] Other things to consider are the fact it takes 2 doses of Shingrix® to Zostavax®'s 1 dose. Those in favor look at the effectiveness of both drugs, where Shingrix® wins out. It is 97% effective at reducing the risk of shingles in people ages 60 to 69, compared to Zostavax®'s rate of 64%. For people aged 70 to 79 the rates at reducing shingles risk are 91% (Zostavax®) vs 41% (Shingrix®), and for those older than 80, the rates are 91%

(Zostavax®) vs 18% (Shingrix®).[3]

Dosing and Administration

Shingrix® is indicated for prevention of shingles in adults ≥50 years but it is not indicated for preventing chickenpox. It is prepared by reconstituting the lyophilized varicella zoster virus glycoprotein E (gE) antigen component with the accompanying AS01B adjuvant suspension component.[4] Once reconstitution is complete, Shingrix® has to be administered immediately or within 6 hours if stored between 36 °F and 46 °F. Two 0.5 mL doses are given intramuscularly, one at month 0 and the second between months 2 and 6.[4] The most common local adverse reactions to Shingrix® are pain (78%), redness (38.1%), and swelling (25.9%) at the injection site. Some more systemic reactions include myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%).

Cost

GlaxoSmithKline, the Shingrix® manufacturer, states Shingrix® will cost $280 for both injections. Zostravax, a Merck product, costs $223.12 This makes Shingrix® 1.26 times more expensive than Zostravax however both vaccinations are costly. With only a $57 difference between the two immunizations, it is likely not to effect the use of Shingrix®.

Conclusion

Herpes zoster vaccines are critical in preventing shingles, especially in older patients who are more likely to develop shingles. Zostavax® has been around for over a decade and while more effective than placebo, it is known to lose its efficacy in older patients or 5 years after the vaccination dose. Shingrix®, on the other hand, has shown to have high shingles risk reduction rates in patients at wide age ranges. Despite the higher cost and side effects, Shingrix® could have improved shingles risk reduction over Zostavax® and its use over Zostavax® will likely increase as post-market safety data results.

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Personalized Medicine Corner

Pharmacogenetics and Tamoxifen in the Treatment of Breast Cancer

Breast cancer is the most common malignancy in women in the United States, with an estimated 266,120 new cases diagnosed in 2018.[1] Tamoxifen, a nonsteroidal antiestrogen, is a critical treatment option that works by competing with estrogen for estrogen receptor-positive breast cancer cells present in 65% - 75% of breast cancer patients. Tamoxifen is a prodrug that is metabolized by CYP2D6 to its active metabolite, endoxifen, which has nearly 100-fold greater antiestrogenic activity than tamoxifen. Endoxifen concentrations can vary from 34% to 54% as a result of variability in the CYP2D6 genotype.[2]

The CYP2D6 gene is highly polymorphic with over 100 known allelic variants including gene deletions and duplications or multiplications. Unlike other cytochrome P450 genes, the CYP2D6 phenotype is determined by adding together the "activity score" of each gene allele. Typically, patients with a CYP2D6 activity score of 0 or 0.5 are classified as poor or intermediate metabolizers, respectively, and have reduced or no CYP2D6 enzyme activity. Individuals with a CYP2D6 activity score of between 1 and 2 are considered normal metabolizers, while those with an activity score >2 are categorized as ultrarapid metabolizers.

In January 2018, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published a guideline for incorporating CYP2D6 phenotype information into prescribing decisions for tamoxifen. Unlike previous CPIC guidelines, patients with a CYP2D6 activity score of 1 can also be classified as intermediate metabolizers. Clinical recommendations are based on evidence that patients with no or reduced CYP2D6 activity (activity score of 0 to 1) may have a higher risk of breast cancer recurrence and worse event-free survival due to reduced conversion of tamoxifen to endoxifen.[2] Specific guideline recommendations are provided below:

- CYP2D6 activity score ≥1.5: Use standard 20 mg/day dose of tamoxifen (patients are expected to achieve therapeutic endoxifen concentrations at standard doses);

- CYP2D6 activity score 0 to 1: Consider hormonal therapy such as aromatase inhibitors instead of tamoxifen because Individuals may not attain therapeutic endoxifen concentration with usual tamoxifen doses. If aromatase inhibitors are contraindicated, a higher tamoxifen dose of 40 mg/day should be used.

CYP2D6 inhibitors, such as bupropion, fluoxetine, paroxetine, duloxetine, and fluvoxamine, can also reduce metabolism of tamoxifen to endoxifen and should be avoided.

The CPIC guideline does not address whether genotyping should be done, but rather provides guidance for use of genotype information when available.

For questions about this guideline contact the UF Health Personalized Medicine Program. Please send an email to PMP-HELP@ctsi.ufl.edu.

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