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Shingrix®: An Overview for Pharmacists

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Abstract

Shingrix® is a recombinant zoster vaccine (RZV) that contains a varicella zoster virus glycoprotein E antigen and the AS01B adjuvant system. This subunit vaccine is approved for the prevention of herpes zoster also known as shingles. A quarter of the population is at risk of developing herpes zoster during their lifetime and two thirds of people with the disease are aged 50 years or older.[1] With the rise in adults aged 50 years or older in the United States due to the aging "baby boomer" generation, it is important that health care providers are properly educated and armed with the information that is needed to understand, educate and administer the Shingrix® vaccination for their patients. It is important that healthcare professionals are comfortable navigating the challenges that result from the novelty of a new herpes zoster vaccine in order to ensure that their patients are effectively covered.

Primary varicella infection is typically seen in children as chickenpox, a disease that's characterized by a rash that progresses to lesions and is commonly accompanied by a fever.[2] Herpes zoster also known as shingles is primarily a disease of sensory nerve ganglia caused by the reactivation of the varicella zoster virus. The virus can remain in a latent state in the nerve ganglia for many years, and with waning immunity the reactivation of the virus results in herpes zoster.[2]

Herpes zoster presents as a painful vesicular rash which is usually distributed in a unilateral and dermatomal pattern along the dorsal root ganglia.[3] Pain is typically the first symptom followed by a rash within two to three days.[3] The site of the rash is usually hyperesthetic and accompanied by severe pain and lesions may continue to form for about three to five days.[3] Postherpetic neuralgia or persistent or recurrent pain, which can last indefinitely, may occur particularly in older patients as a result of a herpes zoster outbreak.[3]

Acute treatment for herpes zoster consists primarily of antiviral therapy and symptomatic treatment. Preventative treatment, however, is often effective and strongly recommended, particularly in older adults who may have been exposed to the primary varicella infection as a child.[3]

Since 2006, Zostavax®, a live attenuated vaccine, has been used as a preventative treatment for herpes zoster.[3] In 2017, a recombinant subunit vaccine, Shingrix®, was approved by the FDA and is now recommended by the Advisory Committee on Immunization Practices as the preferred vaccine for the prevention of shingles.[3]

Shingrix® is a non-live, recombinant subunit vaccine and a combination of an antigen (glycoprotein E), and an adjuvant system (AS01B).[4] That generates a long-term immune response.[5] The AS01B adjuvant induces a local and transient activation of the innate immune system by two immune enhancers: MPL, which signals through Toll-like Receptor 4; and QS-21, which acts through unknown receptors.[5] These two agonists activate antigen presenting cells that enable the recruitment of naive CD4+ T cells.[5]

Drug properties

The Varicella Zoster Vaccine, Shingrix®, is clinically indicated for the prevention of herpes zoster in patients 50 years of age or older.[6] The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of immunocompetent patients 50 years of age or older including those previously vaccinated with Zostavax® who report a previous episode of zoster and patients with chronic medical conditions.[6]

Shingrix® requires reconstitution before administration, and should be administered intramuscularly, preferably in the deltoid muscle of the upper arm.[6] An injection of 0.5 mLs is recommended to be administered as a 2 dose series, with the second dose administered 2 to 6 months after

the first dose.[6] There are no renal or hepatic adjustments required with administration of the vaccine.[6] The unopened vials of vaccine and adjuvant should be stored in the refrigerator, and after reconstitution can be stored under refrigeration for up to 6 hours.[6] If the vaccine has been frozen, or if reconstituted and not used within 6 hours, it should not be used and should be discarded.[6] The suspension of the reconstituted vaccine should be an opalescent, colorless to pale brownish liquid.[6]

The use of Shingrix® is contraindicated if a patient has had a severe hypersensitivity reaction to recombinant zoster vaccine or any component of the formulation.[6] The most frequently reported side effects include: pain, redness and swelling at the injection site, myalgia, loss of strength and energy, headache, shivering, nausea, vomiting, diarrhea, and abdominal pain.[6] Drug interactions include acetaminophen (category risk D: consider therapy modification), fingolimod (category risk D: consider therapy modification), immunosuppressants (category risk D: consider therapy modification), siponimod (category risk D: consider therapy modification), and venetoclax (category risk C: monitor therapy).[6] There is currently no generic available and pricing is about $173.04 per dose of vaccine.[6]

Review of Clinical Recommendations

The ACIP of the Centers for Disease Control (CDC) is the body responsible for making recommendations on vaccinations for the general public.[7] Currently ACIP recommends two licensed products for the prevention of herpes zoster. These products are Zostavax® and Shingrix®, with Shingrix® being the generally preferred agent of the two options.[7] It is recommended that patients 50 years of age or older that do not have a compromised immune system receive 2 doses of 0.5mL of Shingrix®, the first dose at the first visit and then another dose separated by 2 to 6 months.[7] If there is more than 6 months between doses the second dose should still be administered and the series does not need to be restarted.[7] However, if the second dose is given earlier than 4 weeks after the first dose, the second dose must be given again at the correct time interval.[7]

It is important to note that Shingrix® can be administered to a patient that has a minor acute illness, such as a cold.[7] Patients who have a severe anaphylaxis reaction to the vaccine or any of the components as well as patients that are currently infected with herpes zoster, should not receive the vaccine.[7] Shingrix® has not yet been studied in the pregnant or breastfeeding population and should be avoided at this time.[7]

If a patient is allergic to Shingrix®, prefers Zostavax®, or if the patient demands to be immunized and Shringrix® is unavailable, the ACIP recommends to vaccinate with Zostavax®.[7] If the patient does receive Zostavax® and later wants Shingrix®, there must be at least an 8 week interval before Shingrix® can be administered to that patient.[7]

In patients that are immunocompromised, it is important to note that ACIP has not yet made a recommendation for vaccination of this population, as these subjects were not included in clinical trials.[7] These patients also should not receive Zostavax® since, as a live vaccine, it is contraindicated in persons who are immunodeficient or immunocompromised due to disease or therapy. Further trials also need to be established to evaluate Shingrix® in this patient population.[7]

Comparison to Zostavax®

Zostavax® was marketed in 2006 and was the only vaccine available for herpes zoster until Shingrix® was released.[7] Currently, the CDC recommends Shingrix® as the preferred vaccine in the prevention of herpes zoster.[7] While there are no direct head-to-head trials comparing the efficacy between Shingrix® over Zostavax®, there are data in the clinical literature that present efficacy data for each of the two vaccines.

When comparing the efficacy of Zostavax® and Shingrix®, the CDC evaluated clinical trials for both vaccines in the United States. Zostavax® was shown to reduce the incidence of herpes zoster by approximately 51%. It was also shown, however, that the older the subject was, the less effective the vaccine was at preventing herpes zoster. It was estimated that efficacy was approximately 70% for ages 50-59 and declined to around 38% once a patient reached 70 years or older in age. Along with the decline in efficacy based on a patient's age, there was also a decline in the protection a patient had after vaccination.[7,8] After approximately 6 years, protection by the vaccine declined to 35% of the time.[7]

In comparison, in two large clinical trials, ZOE-50 and ZOE-70, it was shown that Shringrix® reduced the risk of herpes zoster in 97% of subjects 50-59 years old, and 91% in subjects aged 70 years or older; within those 70 years of age or older, protection was approximately 85% after 4 years from vaccination.[7,8]

The findings of these clinical trials have been influential in the recommendation of Shingrix® in clinical practice. Currently, more clinical trials are underway to evaluate the efficacy of this vaccine in populations not yet established.

Managing the Shortage

Many providers and pharmacies have had difficulty obtaining Shingrix® vaccine due to drug shortage. Because of its recent FDA approval and its CDC recommendation of use over Zostavax® (zoster live vaccine), the demand has outpaced the supply. In September of 2018, GlaxoSmithKline issued a statement indicating "the accelerated adoption of Shingrix® has led to an unprecedented level of demand," and that they were working on manufacturing more doses of the vaccine.[12] The shortage has led to issues including pharmacists and providers not starting the vaccine series in patients who are indicated because they are concerned a second dose won't be available or because

they are reserving their supply for those who need their second dose.[12]

The CDC acknowledged the shortage and has provided some guidance to providers to help them manage the issue.[12] One important point that they highlighted was educating patients on completing the two-dose series.[12] The CDC acknowledges that patients may remain at risk for herpes zoster if the interval between doses one and two remains longer than the 6 month period.[12] They recommend that if more than 6 months after the first dose has passed, the second dose should still be administered as soon as possible and that the series does not need to be restarted.[12] The second dose of Shingrix® should not be substituted with Zostavax®.[12] Other tips include using www.vaccinefinder.org to find providers who have the vaccine in stock or implementing an e-mail, phone, or text messaging system to alert a patient when a preferred pharmacy or physician office has the vaccine in stock.[12] To keep patients in the loop, the CDC recommends having a waiting list and advising patients to periodically check on vaccine availability.[12]

Cost-effectiveness

Shingrix® has been shown to be effective but one question that remains is, "How cost effective is it?". Randomized control trials show that Shingrix® reduces incidence of herpes zoster by 97% among those 50 years or older and is highly effective even after the age of 70.[9] In a study conducted by Le et al, a cost-effectiveness analysis was conducted comparing Shingrix® to Zostavax® to determine which is more cost-effective.[9]

A Markov model was simulated based on studies conducted from July 1st to July 31st, 2017 comparing no vaccination, vaccination with Zostavax® (1 dose) or vaccination with Shingrix® (2 doses, 2 months apart).[9] Analyses were conducted for persons 60, 70 and 80 year of age.[9] Follow up was 1 year and the primary efficacy endpoint was either experiencing shingles or attendant complications.[9] Incremental cost effectiveness ratios (ICERs) were conducted for costs divided by quality adjusted life years (QALYs), and willingness-to-pay (WTP) thresholds were chosen as $50,000 per QALY by the authors since there is no standard willingness-to-pay threshold in the United States.[9] Costs included direct medical costs and productivity losses.[9] Costs were adjusted for inflation using the Consumer Price Index for Medical Care and expressed in 2016 US dollars.[9] Costs for Zostavax® were based on the Centers for Disease Control and Prevention, and Shingrix® was assumed to be $280 for a 2 dose regimen because at the time of the study it was not yet licensed.[9] Other costs included administration costs based on Medicare's national reimbursement rate, travel and productivity losses for the second dose and productivity losses based on local reactions and hospitalizations.[9] Sensitivity analyses were conducted varying the cost of WTP values, costs for the Shingrix® vaccination, varying adherence and efficacy rates, and varying and excluding different costs.[9]

Based on conducted ICERs for vaccinations at the ages of 60, 70 and 80 years, Shingrix® was shown consistently to be more effective and less expensive than Zostavax® and thus dominated the live vaccine.[9] Sensitivity analyses showed that, at the current price of Zostavax®, Shingrix® would be less costly than Zostavax® up to a price of $350 per series and cost-effective up to a cost of $359 per series.[9] This is important because the current price of the Shingrix® series does fall below both of these prices.[9] Overall, regarding efficacy, duration, vaccine price, and probability of having herpes zoster with-in 12 months or longer after the vaccination, Shingrix® was never shown to be more expensive than Zostavax® and was more effective and less expensive.[9] The findings were insensitive to most model inputs, as long as the adherence to the second dose exceeded 50%.[9] The authors do mention that the updated ACIP recommendation stating a preference for Shingrix® over Zostavax® could affect the results of the study.[9]

Patient and Provider Education

As previously stated Shingrix® is indicated for immunocompetent adults aged 50 years and older. Shingles affects approximately 1 in 3 individuals during their lifetime and affects half of all individuals who live to the age of 85 years or older.[10] The CDC recommends that most adults 50 years and older receive the new shingles vaccine regardless of whether the patient has had chickenpox, shingles in the past, or has been vaccinated with Zostavax®.[10] In adults 50 to 69 years old who received two doses, Shingrix® was 97% effective in preventing shingles; among adults 70 years and older, Shingrix® was 91% effective.[10] In adults 50 to 69 years old who received two doses, Shingrix® was 91% effective in preventing postherpetic neuralgia, and was 89% effective in preventing PHN; among adults 70 years and older.[10]

Pharmacists play an integral role in ensuring that patients receive the vaccinations that they require. Therefore, it is incredibly important for pharmacists to increase their knowledge and awareness regarding vaccination with Shingrix®. Pharmacists should be aware that the vaccine is indicated for adults aged 50 years or older and should engage those individuals in a discussion about being eligible for vaccination with Shingrix®.[11] Pharmacists should understand the importance of adhering to the vaccination schedule for the vaccine. To help ensure series completion pharmacists should schedule their patient's for the second dose of Shingrix® anytime between 2 and 6 months after the first dose.[11] Pharmacists will need to manage the timing of the vaccinations in conjunction with the high demand for Shingrix® and the low supply. Patients should be referred to another provider in the community if they are due for their second dose and their original provider does not have a sufficient supply of Shingrix®.[7] Pharmacists should be sure that their patient's vaccination information is current with the state's immunization information system. This will help other providers access the patient's immunization

record, and it may help facilitate patient reminders to complete the Shingrix® series of doses. Pharmacists will also have to navigate questions concerning common adverse reactions to the vaccination such as pain, redness, and swelling at the injection site and understand the potential risks for various patient populations.

Conclusion

Shingrix® is a recombinant zoster vaccine (RZV) that was approved in 2017 for the prevention of herpes zoster, also known as shingles, in patients 50 years and older. Shingrix® appears to have greater efficacy and cost effectiveness against herpes zoster based on individual trials with either Shingrix® or the live zoster vaccine, Zostavax®. The CDC is a comprehensive resource that can provide pharmacists with education and help during challenging situations, such as a medication shortage. It is important that healthcare professionals, especially pharmacists, are well informed and up-to-date on their vaccination education in order to provide the best care for each individual patient.

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