

Herpes Zoster Effects and Vaccinations

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Introduction

Varicella-zoster virus, VZV, causes both varicella, chicken pox, and herpes zoster, commonly called shingles. Varicella is the primary infection of VZV, which is extremely contagious and commonly seen in younger children. A painful, itchy rash develops around the face, trunk, and extremities of an individual with varicella. Once infected, VZV permanently resides and has a latent period in the cells of the dorsal root ganglia (Arvin 1996). Herpes zoster, HZ, occurs whenever VZV is reactivated in these neurons and causes a painful rash to form on the skin approximate to the neurons affected, usually the thoracic and lumbar areas. Also, HZ is usually seen in the elderly and can cause postherpetic neuralgia when activated. This association was a novel discovery in the 1960s paper written by Dr. Crombie. He showed that age and HZ are inversely related (Crombie 1964). It is estimated one in three people, or about 33%, will develop herpes zoster in the United States (Sampathkumar 2009). Herpes zoster vaccines are extremely important in stopping reactivation of VZV seen in elderly subjects. Stopping VZV reactivation can lead to preventing HZ in immunocompromised individuals, which would be a huge step in preventive medicine. Scientists explore possible immune targets and vaccinations to strengthen defense against VZV reactivation. Many studies are conducted to measure various immune responses to VZV reactivation, to link varicella vaccination with VZV reactivation, and to determine vaccination efficacy and safety in the elderly in an effort to better treat patients with herpes zoster. These topics involving HZ vaccination will be reviewed below.

Zoster Immune Response Studies

A strong immune response is critical in protecting and aiding in recovery from VZV infections. Several studies agree that cell-mediated immunity, CMI, is extremely important in the development of HZ, while other studies sought to determine a relationship between VZV

humoral immunity and VZV reactivation. Humoral immunity refers to B cell and antibody-mediated immunity that helps prevent recurrent infections in the body. CMI includes T-cells, macrophages, and cytokines that destroy virally infected cells. The ELISPOT, gpELISA, and Responder Cell Frequency assays are three common techniques used to isolate immune cells. VZV RCF quantitatively measures for cell-mediated immunity, while gpELISA measures for VZV B cells and antibodies. ELISPOT measures both CMI and humoral immunity by quantitatively and qualitatively measuring desired cytokines produced by specific leukocytes. A study by Levin et al. (2003) researched the immunologic responses to a booster dose of a live, attenuated HZ vaccine in people aged 70-80. Both the VZV-specific ELISPOT and RCF assays revealed increases in CMI after the booster vaccination, and these responses were comparable (Levin et al. 2003). The researchers could rely on these two assays to show that the live, attenuated HZ vaccine could be tolerated and effective for a boost of immunity 5 or more years after the initial vaccine. Another study conducted in 2003 showed similar results to a booster vaccine given to subjects 60 or older. Smith et al. (2003) showed 31-42% of subjects that received a HZ vaccine 8-10 years prior developed a 2X greater rise in ELISPOT response after booster compared to subjects with 2 prior vaccine doses. These studies help establish ELISPOT assays in determining CMI immune responses to HZ.

Levin et al. (2008), under the Shingles Prevention Study, SPS, sought to correlate certain immune responses with the occurrence of HZ. The SPS included a total of 38,546 individuals, and it is a randomized, double blind, and placebo-controlled study of subjects 60 years and older. Levin et al. (2008) measured immunity before and after vaccination and found that there is a decline of VZV-CMI with an increase in age that begins in early adulthood. Both CMI and humoral immune responses significantly increased 6 weeks after vaccination compared to

placebo subjects. They concluded humoral immune responses were not protective against HZ, but that the magnitude of CMI is inversely correlated with developing HZ (Levin et al. 2008). Levin et al. (2006) conducted another study assessing VZV immunity with age and with VZV vaccinated HIV subjects. They found that VZV RCF peaked at age 34 in healthy individuals, but this response declined in subjects aged 61-90 years with the zoster vaccine (Levin et al. 2006). Another study to confirm these findings was done by Weinburg et al. (2010). They, too, found that RCF peaked at the age of 34, and that CMI declines in subjects 61-90 years old. Also, HIV children and adults had lower VZV RCF values in both of these studies (Levin et al. 2006; Weinburg et al. 2010). Moreover, a more desired immune response, like that found in healthy children, can be induced in HIV infected subjects by a varicella vaccine with CD4+ levels greater than 20% (Levin et al. 2006). Therefore, both the varicella and zoster vaccines have immune responses desired by different immunocompromised populations.

A study by Asada et al. (2012) confirms that VZV-CMI is inversely correlated with the severity of HZ and the pain of skin lesions with a VZV skin test. Also, they confirm there is no relationship between VZV-specific antibodies to the severity of skin lesions and pain. Weinberg et al. also associate CMI and humoral immunity to HZ. They found that higher RCF values after one week of HZ rash onset correlates with a lower HZ severity of illness score, and ELISPOT assays after one week of rash onset were significantly higher in subjects with a lower HZ severity score (Weinburg et al. 2009). They did not find any correlation with VZV antibody responses during the first week with protection or reduction of HZ (Weinburg et al. 2009). Tyring et al. (2012) showed that CMI immune responses to HZ were at their peak responses between 1 and 3 weeks after HZ rash onset, as did the Weinburg et al. study (Weinburg et al. 2009). Tyring et al. (2012) also showed that CMI responses are significantly increased at HZ

onset and are at a maximum until 6 weeks after rash onset. These studies have consistently shown the substantial CMI activity induced by HZ. Also, they help determine that VZV humoral responses do not protect against HZ episodes. However, some evidence shows humoral immunity exists as a preventative measure in second episodes of VZV (Asada et al. 2012; Levin et al. 2006; Schmader et al. 2012a; Smith-Norowitz et al. 2009; Weinburg et al. 2009).

One study conducted by Smith-Norowitz et al. (2009) found anti-VZV antibodies circulating in both children and adults that experienced varicella. Specifically, IgG and IgE serum containing anti-VZV antibodies were found in subjects with wild type (81%) and the varicella vaccine (Smith-Norowitz et al. 2009). However, there were no IgE anti-VZV antibodies detected with the very small sample size (n=2) of the vaccinated group. Varicella wild type refers to the virus infection without vaccination. Furthermore, Levin et al. (2006) found that VZV antibody responses remain relatively constant, regardless of age. Schmader et al. (2012a) also found similar results suggesting that age has no effect on circulating VZV specific antibodies. Studies previously discussed report increased humoral responses immediately after vaccination or HZ onset to further confirm humoral immunity has some preventative measure in VZV reactivation (Weingburg et al. 2009; Asada et al. 2012).

Varicella Vaccine Studies Linked to Herpes Zoster

The varicella vaccine is possibly one reason HZ is becoming more prevalent across the world. The CDC recognizes the herpes zoster vaccine, Zostavax®, is at least 14 times as potent as the varicella vaccine, Varivax® (Zostavax 2013). Clearly, neither should be substituted for the other. The varicella vaccine was implemented in the US in 1995, and it is given to children between 12 and 15 months of age. Decided upon in 2006, it is now recommended to give 4-6 year old children a second dose (Marin et al. 2007). Currently, most children are given the

vaccine. However, this raises possible risks for future herpes zoster attacks due to a decrease of the wild type herpes zoster and a decline in CMI over time. The vaccine is a weaker, or attenuated, form of the wild type of VZV. Naturally, we would expect to find a decrease in CMI over time due to the mass immunization with the attenuated version of the vaccine. Exposing oneself to a herpes zoster infected person allows the immune system to boost its specific immune response. The wild type, or non-vaccine form of VZV, would decrease over time. “Effectiveness Over Time of Varicella Vaccine” explores the effect of the vaccine in children. The vaccine shows 97% effectiveness in the first year, but it significantly decreases after the first year of vaccination; specifically, there was only 84% effectiveness from year 2 through 8 after vaccination (Vazquez et al. 2004). Another study found that there was no increase in HZ incidence with a decrease in varicella disease due to varicella vaccination from 1992-2002 (Jumaan et al. 2005). However, a conflicting study by Poletti et al. (2013) shows that Italy, Finland, and the UK’s varicella vaccinations have an increased incidence of HZ that depends upon the presence of boosting factors, such as protective effects of boosting against HZ for unvaccinated individuals. These factors may be declining due to the mass immunization of varicella. Also, Yih et al. (2005) determined that herpes zoster incidence significantly increased from 2.77 to 5.25 per 1,000 people vaccinated with the varicella vaccine in Massachusetts from 1999-2003. Therefore, there are predictions about an increased HZ prevalence due to the decline of protection in the varicella vaccine. However, conflicting studies show that the answer is unclear and more studies need to be conducted.

Immunocompromised children are targets for varicella vaccination studies due to their depressed immune functions. Armenian et al. (2006) administered varicella vaccine to HIV-infected children and assessed immune functions. They found that the vaccine was well tolerated,

and the CMI response in all subjects was significantly higher by week 4 and in 9 patients after 1 year of vaccination (Armenian et al. 2006). Another study by Levin et al. (2006) also showed the vaccine was well tolerated in HIV-infected children, and 79% of the subjects had significant immune responses after 2 doses of vaccine after 2 months and 83% after 1 year. Children with leukemia that were administered a varicella vaccine were found to have a 67% lower risk of HZ compared to children with the wild type varicella (Hardy et al. 1991).

Studies also research whether a catch-up varicella vaccine is necessary in protective effects of VZV reactivations and/or outbreaks. Marin et al. (2005) found that students in Maine had an increased chance for varicella attack rate in higher grades, especially if unvaccinated. However, 22% of the affected were vaccinated (Marin et al. 2005). This could be due to the lack of a catch-up vaccination and a decrease in VZV-specific immune responses in the older children. Marin et al. (2005) conclude that the previously vaccinated children had the natural varicella because of the lack of administering a catch-up dose of the varicella vaccine. Another study found that administration of a second dose of varicella vaccine is significantly more successful compared to just one dose against varicella outbreaks and incidence (Lopez et al. 2006). Therefore, the implementation of a second varicella vaccination may be necessary to sustain desired VZV immune responses, and thus, prevent VZV outbreaks and reactivations.

Zoster Vaccine Studies in the Elderly

Many studies are conducted to evaluate the effectiveness and safety of HZ vaccination in the elderly population (Dendouga et al. 2012; Leroux-Roels et al. 2012; Oxman et al. 2005; Schmader et al. 2012a; Schmader et al. 2012b; Simberkoff et al. 2010; Tseng et al. 2011; Vermeulen et al. 2012). Most studies focus on Zostavax, the current approved live, attenuated HZ vaccine for older adults. Others research adjuvant vaccinations and their effects in the elderly.

For example, a zoster glycoprotein E subunit vaccine was studied and found to have no severe side effects and a higher immunogenic effect compared to a live, attenuated virus in subjects 50-70 years old (Leroux-Roels et al. 2012). This was done with 2 doses of the subunit vaccine, and they recorded subjects up to 30 months post-vaccination. Another study in mice compared different types of the HZ vaccine, containing VZV-specific glycoprotein E subunit non-adjuvant and adjuvant versions (Dendouga et al. 2012). Dendouga et al. (2012) found that the adjuvant vaccine stimulated immunity, but the non-adjuvant version did not. A study of the live, attenuated zoster vaccine was done to assess the safety and efficacy in 50-59 year olds (Schmader et al. 2012a). Schmader et al. (2012a) found that the 1 dose vaccine reduced the efficacy of HZ by 69.8% and was also well tolerated. Therefore, both of these vaccines have protective effects against HZ.

Safety and effectiveness of the live, attenuated zoster vaccine against HZ in the elderly is studied in depth (Oxman et al. 2005; Schmader et al. 2012b; Simberkoff et al. 2010; Tseng et al. 2011; Vermeulen et al. 2012). Oxman et al. (2005) conducted a study with the vaccine in subjects 60 years and older, and they found the vaccine reduced burden of illness of HZ by 61.1%, the incidence of postherpetic neuralgia by 66.5%, and HZ incidence by 51.3%. Another study focusing on adults 60 years or older determined that adding a second dose of the vaccine 6 weeks after the initial vaccine did boost VZV-specific ELISPOT responses, but the duration of the immune boost was not determined (Vermeulen et al. 2012). The vaccine was studied by Tseng et al. (2011) in general practice settings, and they found that administering the vaccine to subjects 60 and older lessened HZ incidence from 13.0 to 6.4 per 1000 people. Simberkoff et al. (2010) studied the safety of a single dose of HZ vaccine in the subjects of the Shingles Prevention Study. They found 1.4% vaccine recipients and 1.4% placebo recipients reported

serious adverse events (Simberkoff et al. 2010). Another study conducted under the SPS was a substudy to evaluate the effectiveness of the HZ vaccine in vaccinated subjects later in their lives. Schmader et al. (2012b) found that the vaccine efficacy for HZ burden of illness decreased from 61.1% to 50.1% and vaccine efficacy for the incidence of HZ decreased from 51.3% to 39.6%, although the differences were not statistically significant. Therefore, the HZ vaccine is safe for older immunocompetent adults. However, the efficacy for Zostavax is shown to diminish over time, specifically beyond 5 years post-vaccination.

After the Shingles Prevention Study, Morrison et al. (2013) gave placebo recipients a free herpes zoster vaccination to determine the safety of HZ vaccine after documented HZ. They found that the vaccine was well tolerated in the elderly with recent episodes of HZ and serious side effects only occurred in 1.37% of the subjects, regardless of past history with HZ (Morrison et al. 2013). Tseng et al. (2012) also studied subjects that had recent episodes of HZ. They found that the incidence of recurrent HZ was 0.99 and 2.20 cases per 1000 people for vaccinated and unvaccinated subjects, respectively (Tseng et al. 2012). Recent episodes of HZ boost the immune system and show that a follow up vaccination after HZ may not be necessary. Therefore, these studies together show that the vaccine is safe to give to all individuals even if they recently experienced HZ (Morrison et al. 2013; Tseng et al. 2012).

Demographics of the elderly were studied to determine if certain predispositions made HZ more likely to occur. Langan et al. (2013) measured the general population's HZ vaccine efficacy in subjects 65 and older. They found that vaccine uptake was especially low in African-Americans (0.3%) and people with low income (0.6%), but that it still reduced HZ episodes for all people vaccinated (Langan et al. 2013). The previously discussed study by Tseng et al. (2011) found the reduced risk of HZ with vaccination was found in all age strata and a majority of

subjects were Caucasian females with more outpatient visits and few chronic diseases. Therefore, older adults with the means to get the HZ vaccine will be better protected from VZV reactivation compared to unvaccinated older adults.

Future Directions

Some questions arise from the findings of these articles: When should a second dose of the HZ vaccine be administered in the elderly? Will the potency of such a vaccine need to be increased to account for the decrease in VZV immunity in the elderly? What are the differences in the approved HZ vaccines, and under what circumstances should one be preferred over another? Current on-going studies are investigating these issues. Currently, HZ vaccination is recommended for adults over the age of 60 to boost immunologic responses in hopes of preventing VZV reactivation. More studies are being conducted to help prevent, treat, and lessen HZ incidence.

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