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EDITORIAL COMMENTARY

Clinical Usage of the Adjuvanted Herpes Zoster Subunit Vaccine (HZ/su): Revaccination of Recipients of Live Attenuated Zoster Vaccine and Coadministration With a Seasonal Influenza Vaccine

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Herpes zoster (HZ; also known as shingles) is a localized disease of the sensory ganglion, nerve, and skin caused by reactivation and replication of endogenous varicella zoster virus (VZV) that established latency in sensory and autonomic neurons during varicella or an inapparent primary VZV infection [1]. The most frequent debilitating complication of HZ is persistent neuropathic pain known as postherpetic neuralgia (PHN) reflecting damage to the sensory ganglion in which the latent virus reactivated and to adjacent neural structures [2]. Early treatment with antiviral drugs reduces the severity and duration of HZ but does not prevent the development of PHN, which may persist for months or years and is frequently refractory to treatment [3–5].

The incidence and severity of HZ and PHN increase with increasing age in association with an age-related decline in VZV-specific cell-mediated immunity (CMI) and are markedly increased in persons with immunocompromise due to disease or immunosuppressive therapies. More than a million new cases of HZ occur each year in the United States [6, 7], and this number is increasing with aging of the population and the increased use of immunosuppressive therapies. In addition, for reasons that are unclear, the age-specific incidence of HZ has been increasing over the past 60 years [8]. These considerations emphasize the need for a vaccine to prevent HZ and PHN.

The Shingles Prevention Study (SPS) [6] demonstrated that the live attenuated zoster vaccine (ZVL) currently licensed in the United States reduced the HZ burden of illness by 61.1% (65.5% in subjects aged 60–69 years; 55.4% in subjects aged ≥70 years), the incidence of clinically significant PHN by 66.5% (65.7% in subjects aged 60–69 years; 66.8% in subjects aged ≥70 years), and the incidence of HZ by 51.3% (63.9% in subjects aged 60–69 years, but only 37.6% in subjects aged ≥70 years). In persons aged 50–59 years, ZVL reduced the incidence of HZ by 69.8% [9]. The efficacy of ZVL in reducing the decrement in quality of life and in the capacity to carry out activities of daily living caused by HZ was similar to ZVL's efficacy for the HZ burden of illness [10, 11]. Rates of serious adverse events (AEs), systemic AEs, hospitalizations, and deaths were low among ZVL recipients and comparable to those among placebo recipients. Local reactions at the injection site were more common in ZVL recipients but were generally mild and transient [6, 12]. ZVL was licensed by the US Food and Drug Administration (FDA) to prevent HZ in healthy adults aged ≥50 years and recommended by the Advisory Committee on Immunization Practices in 2006 for prevention of HZ and its complications, principally PHN, in healthy adults aged ≥60 years [7].

Assessment of immune responses to VZV in the SPS indicated that CMI, but not VZV-specific antibody levels, correlates with clinical efficacy [13, 14]. In a subset of the 50- to 59-year-old ZVL recipients [9] the fold-rise in anti-VZV immunoglobulin G (IgG) correlated with vaccine efficacy [15]. The authors pointed out, however, that fold-rise in anti-VZV IgG is not a mechanistic correlate of efficacy. The ZVL-induced increases in VZV CMI persisted during the 3 years of follow-up, although their magnitude decreased over time [13].

The SPS demonstrated persistence of ZVL efficacy through 4 years postvaccination [6]. Two follow-up studies of the SPS that assessed ZVL efficacy through 11 years postvaccination [16, 17] showed that vaccine efficacy for all 3 outcome measures decreased over time. Statistically significant vaccine efficacy persisted into year 10 postvaccination for HZ burden of illness and through year 8 for incidence of HZ [17]. A large retrospective study of Kaiser Permanente

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electronic medical records confirmed these SPS efficacy data, indicating that effectiveness for incidence of HZ declined from 68.7% in the first year to 4.2% in year 8 postvaccination [18]. Thus, the millions of older adults vaccinated with ZVL during the past decade will need revaccination to maintain their protection against HZ and PHN in later years when the risk of HZ and its complications is markedly increased.

A recombinant VZV glycoprotein E (gE) subunit vaccine in a liposome-based $AS01_B$ adjuvant system (HZ/su; GlaxoSmithKline Biologicals) induces much higher VZV-specific $CD4^+$ T-cell and humoral immune responses in older adults than ZVL [19]. VZV gE is the most abundant glycoprotein in VZV virions and VZV-infected cells and is a prominent target of VZV-specific $CD4^+$ T-cell responses [20, 21]. Immune responses of VZV-seropositive 50- to 70-year-old adults to 2 doses of ZVL alone, HZ/su alone, and HZ/su plus ZVL administered 2 months apart showed that 2 doses of HZ/su induced substantially higher humoral and $CD4^+$ T-cell responses than a single dose. In contrast, the second dose of ZVL failed to boost either $CD4^+$ T-cell or humoral responses beyond those elicited by the first dose. However, solicited general and local reactions were more common in subjects vaccinated with HZ/su alone or with HZ/su plus ZVL than with ZVL alone.

Two large randomized, blinded, placebo-controlled phase 3 studies were conducted concurrently to determine the efficacy and safety of HZ/su in reducing the incidence of HZ and PHN in adults aged ≥50 years (ZOE-50 [22]) and in adults aged ≥70 years (ZOE-70 [23]), stratified by age group (50–59, 60–69, and ≥70 years of age, and 70–79 and ≥80 years of age, respectively). In ZOE-50, vaccine efficacy was 97.2% during a mean follow-up of 3.2 years, with no significant differences in vaccine efficacy in the 3 age strata [22]. In ZOE-70, vaccine efficacy was 89.8% during a mean follow-up of 3.7 years, with little difference between those aged 70–79 years (90.0%) and those ≥80 years of age (89.1%). Pooled data for all subjects aged ≥70 years from ZOE-50 and ZOE-70 showed a HZ/su vaccine efficacy against incidence of HZ of 91.3%. In contrast, ZVL vaccine efficacy for incidence of HZ was markedly reduced in subjects ≥70 years of age (37.6%) compared with subjects aged 60–69 years (63.9%) in the SPS [6]. In the pooled ZOE-50 and ZOE-70 study populations, HZ/su efficacy against PHN was 91.2%, with no cases of PHN among HZ/su recipients <70 years of age.

The article by Grupping et al in this issue of *The Journal of Infectious Diseases* addresses the clinically important issue of safety and immunogenicity of HZ/su in recipients of ZVL. The humoral immune response 1 month after the second of 2 doses of HZ/su administered 2 months apart was noninferior in older adults previously vaccinated with ZVL compared to ZVL-naive adults. Two hundred fifteen adults ≥65 years of age vaccinated with ZVL ≥5 years earlier (group 1: HZ-PreVac) were matched according to age (65–69, 70–79, ≥80 years), sex, race/ethnicity, and comorbidities with 215 adults not previously vaccinated (group 2: HZ-NonVac). Co-primary objectives were to compare humoral immune responses and to evaluate safety and reactogenicity 1 month after HZ/su dose 2 in the 2 groups. Secondary objectives were to compare CMI and humoral responses to HZ/su at baseline and 1 month after the first and second doses of HZ/su in the 2 groups. Anti-gE antibody concentrations were measured by enzyme-linked immunosorbent assay. CMI responses were measured by intracellular cytokine staining and flow cytometry (a multianalyte method with wide dynamic range) [19, 20], using 4 markers weighted toward T-helper 1 immune responses: CD40L, interferon-γ, tumor necrosis factor–α, and interleukin 2. $CD4^+$ T cells expressing at least 2 markers ($CD4^{2+}$ T cells) were considered positive, and the overall metric was the number of $CD4^{2+}$ T cells per million cells. The choice of antibody rather than T-cell responses as the primary endpoint was likely a statistical consideration, as a larger study would have been required for CMI endpoints.

Prior to the first vaccination, all subjects in the HZ-PreVac group and 98% of the subjects in the HZ-NonVac group were seropositive for anti-gE antibodies. Anti-gE antibody geometric mean concentrations (GMCs) were similar in both study groups and increased markedly after both HZ/su doses. Anti-gE antibody GMCs after HZ/su dose 2 were comparable in the 2 study groups, with an adjusted GMC ratio of 1.04. The primary immunologic study objective was met, as the upper limit of the adjusted GMC ratio of the HZ-NonVac group over the HZ-Pre Vac group was below the prespecified 1.5 cutoff. At baseline, the median $CD4^{2+}$ T cell frequency appeared similar in both groups. After HZ/su dose 1, median frequencies of $CD4^{2+}$ T cells increased in both groups, and a greater increase was seen after HZ/su dose 2, with no difference in $CD4^{2+}$ T-cell frequency between study groups. Subjects reporting all-grade AEs and solicited grade 3 AEs were comparable between groups, and there was no evidence of clinically relevant differences in reported unsolicited AEs between study groups. From study start until 30 days after the second HZ/su vaccination, there were 5 serious adverse events (SAEs) in 4 HZ-PreVac subjects and 4 SAEs in 4 HZ-NonVac subjects. None were considered related to vaccination by study investigators. There were no deaths and no HZ cases or potential immune-mediated diseases reported during the active phase of the study. The results of this study showed that prior vaccination with ZVL did not adversely affect the safety, immunogenicity, or reactogenicity of HZ/su. Moreover, robust humoral and cell-mediated immune responses to HZ/su were observed in both prior ZVL recipients and ZVL-naive subjects. Such strong immune responses to HZ/su have now been shown to persist for at least 6 years postvaccination [24]. Safety and immunogenicity of a booster dose of ZVL administered to persons ≥70 years of age who had been immunized with ZVL ≥10 years earlier

has also been demonstrated, but the magnitude and longevity of the humoral and CMI responses were markedly lower than those induced by HZ/su in previous recipients of ZVL [25].

HZ/su may, thus, be an attractive option to revaccinate older adults who were vaccinated with ZVL >5 years earlier. However, the requirement for 2 doses of HZ/su and its increased reactogenicity compared to ZVL may be problematic. Furthermore, while the absence of recognized autoimmune diseases in HZ/su recipients to date is encouraging, it does not eliminate the hypothetical concern that the $AS01_B$ adjuvant system might induce or aggravate autoimmune diseases, especially since the interval between their induction and clinical recognition may be many years. An example is narcolepsy linked to the 2009 H1N1 influenza vaccine, for which HLA linkage and autoantibodies were detected that are characteristic of an autoimmune disorder [26]. Thus, well-designed long-term phase IV studies to establish the safety of vaccines employing powerful adjuvants, such as $AS01_B$, are essential. [27].

In another report in this issue of *The Journal of Infectious Diseases,* Schwartz et al present the results of a phase 3 open-label trial in adults aged ≥50 years demonstrating the comparable safety and humoral immunogenicity of HZ/su and tetravalent inactivated influenza vaccine (IIV4) when the 2 are administered concomitantly at different sites on day zero followed by a second dose of HZ/su at month 2 (Co-ad group, 413 persons), and serially with administration of IIV4 on day zero and HZ/su at months 2 and 4 (control group, 415 persons). Co-primary objectives were to determine the vaccine response rate to HZ/su in the Co-ad group and to demonstrate noninferiority of antibody responses to both vaccines in the Co-ad compared to the control group. The VZV-specific humoral response assay was the same as that used by Grupping et al in their study. A standard hemagglutination inhibition (HI) assay was used to assess the HI titer for each of the 4 strains in IIV4. The secondary objective was to determine IIV4 seroconversion rates for each of the 4 influenza strains.

Noninferiority of concomitant vs sequential administration of ZVL and influenza vaccine in adults ≥50 years of age has previously been demonstrated for IIV3 [28] and IIV4 [29]. In both studies, ZVL and influenza vaccine given concomitantly were well tolerated and antibody responses were comparable in concomitantly and sequentially vaccinated persons. Regulatory and advisory bodies in the United States and other countries have long advocated simultaneous administration of 2 vaccines at different sites (either 1 live attenuated and 1 inactivated vaccine or 2 inactivated vaccines) [30]. Concomitant administration is necessary if we hope to achieve adequate uptake of the many vaccines now recommended for older adults [31].

The report by Schwartz et al is important in providing evidence supporting concomitant administration of IIV4 and the promising HZ/su zoster vaccine.

Although the results are encouraging, caution is required before concluding that the 2 schedules compared in this study are equivalent. The efficacy of IIV is variable and the immune correlates of protection are poorly understood; for example, similar HI titers do not automatically equate to similar efficacy. Complexity is added by the large variety of licensed IIV products. For example, vigilance will be required to determine if the MF59-adjuvanted IIV product causes any increase in AEs if given simultaneously with HZ/su. Immunogenicity is also complex, and while the adjuvants would likely act in separate draining lymph nodes, pyrexia and fatigue can occur after either HZ/su or MF59-adjuvanted IIV, indicating a systemic innate response that could act distally. For now, co-administration of HZ/su with IIV products with similar key characteristics to those studied by Schwartz et al is suggested.

The proliferation of new vaccines and vaccine combinations makes it impossible to base all judgments regarding vaccine usage on results from large, controlled clinical trials. Instead, these decisions will have to be based on results of smaller clinical trials with laboratory measures of clinically relevant correlates of protection as endpoints. For the many vaccines under development that target diseases caused by persistent viral infections, such as herpes zoster, for which elements of CMI are the host defenses of primary importance, it will be important to utilize common protocols and validated laboratory measures of CMI to facilitate comparisons. Intracellular cytokine staining plus flow cytometry is a technology for measurement of virus-specific CMI that can be validated and used in trials of candidate vaccines. Agencies such as the FDA that license vaccines should take the lead in encouraging the development and validation of such technologies and of common protocols that use them to evaluate candidate vaccines. HZ/su (Shingrix®) has been approved in the US and Canada for prevention of HZ in immunocompetent persons 50 years of age and older and, on October 25, 2017, the Advisory Committee on Immunization Practices recommended Shingrix for prevention of HZ and its complications in immunocompetent adults age 50 years and older, including immunocompetent adults who have previously received ZVL.

Notes

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