Unsettled Issues of Zostavax Vaccine

TO THE EDITOR—The article by Schmader et al [1] summarizing a Zostavax trial in 50- to 59-year-old participants raises new concerns and rekindles others [2]. Zostavax vaccine introduces a new virus which, like chickenpox, becomes latent in cranial nerves and autonomic and dorsal root ganglia [3]. These 2 versions of the same virus will permanently populate similar anatomic sites. Moreover, clinical reactivations of both vaccine varicella zoster virus (VZV) and wild-type VZV continue to occur [4, 5]. It is unknown to what extent these reactivations reflect waning immunity or the appearance of novel viral subtypes unrecognizable by existing immunologic defenses [6]. Shingles in young, otherwise healthy individuals cannot be explained on the basis of immunosenescence. More importantly, it is unknown how these 2 distinct viruses interact over time, particularly in hosts who later become immunocompromised. Zostavax is contraindicated in most patients with immunologic impairment and in persons who previously received Varivax. Nonimmune persons should receive Varivax, not Zostavax, but lack of immunity was not an exclusionary criterion in this trial [1].

The levels of circulating anti-VZV antibodies and their prevalence are already high in this population, and the incidence of herpes zoster (HZ) is lower than in older age groups. Periodic fluctuations in anti-VZV antibody levels due to subclinical reactivations of latent VZV may stimulate immunologic memory [7] in the absence of exogenous reexposure. Following natural infections, antibodies to VZV persist for long periods, with a half-life of around 50 years [7]. Yet, the durability of cell-mediated immunity is perhaps more crucial [8]. Although HZ may be severe, it is usually a self-limited, readily recognized, nonfatal clinical entity that responds to treatment with available antiviral agents even in seriously immunocompromised hosts.

Unfortunately, the influence of Zostavax on other serious complications of latent VZV such as meningitis, encephalitis, myelitis, angiopathy, and ophthalmologic infections [9] has not been adequately evaluated. Headache was the most frequent serious adverse event but no information is provided regarding its etiology [1]. Because this study focused on shingles, other virus-induced complications like zoster sine herpete may have been missed, which is comparable to HZ and postherpetic neuralgia for establishing vaccine efficacy. The confirmation of HZ cases centered on detection of VZV DNA by polymerase chain reaction (PCR) in specimens from skin lesions. On the basis of this test, less than half (129 of 277) of atypical cases of suspected HZ were actually confirmed as HZ. One is left wondering what caused the other 148 cases of suspected HZ. Herpes simplex DNA by PCR was also performed but no positive results were reported. Patients with clinical VZV disease may have false-negative tests for VZV DNA by PCR [10], which would result in an underestimation of HZ cases.

In addition, average follow-up in this study was only 1.3 years. No Hispanics were included, and white women, all from developed nations, were overrepresented. Long-term follow-up of Zostavax recipients is prudent and necessary. Further attenuation of the Oka strain of VZV to render it incapable of establishing latency could result in a safer vaccine, particularly for immunocompromised patients. However, in the greater scheme of public health and cost-effectiveness [11], Zostavax should remain a low priority.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References

Reply to Arroyo

TO THE EDITOR—We would like to take the opportunity to clarify some points raised by Dr Arroyo [1] regarding use of zoster vaccine (ZV) and the ZV Efficacy and Safety Trial (ZEST; clinical trials registration: NCT00534248). ZV is not contraindicated in persons previously vaccinated with Varivax [2]. Consistent with the Shingles Prevention Study (SPS), subjects enrolled in ZEST were required to have a history of varicella or residence in a varicella zoster virus (VZV)–endemic area for ≥30 years; VZV antibody titers were not measured prior to randomization [3]. Due to space limitations, ZEST subject ethnicity was not previously reported; 724 (3.2%) Hispanic subjects were randomized. Similar to SPS, headache was the most frequently reported systemic adverse event (AE) in ZEST, not serious adverse event (SAE). There were 2 SAEs of migraine reported in the ZV group (no SAEs with the specific term of headache) and 2 SAEs of headache in the placebo group; none were deemed vaccine-related by the investigators.

For SPS and ZEST, a suspected herpes zoster (HZ) case was a macular, papular, pustular, or vesicular rash in a dermatomal distribution. Given the rarity of zoster sine herpete, it would not be possible to adequately power a study on this endpoint. As the goal was not to miss potential HZ cases (ie, underreporting of events), investigators were instructed to submit any case that could possibly be HZ. The 129 confirmed cases of HZ in ZEST were based on both polymerase chain reaction (PCR) and adjudication by an independent Clinical Evaluation Committee (CEC), using a prespecified algorithm, similar to SPS. Among the VZV PCR-negative cases, 36 were herpes simplex virus–positive (21 in ZV group, 15 in placebo group). The CEC evaluated all cases deemed clinically to be HZ for complications including opthalmic HZ or neurological impairment and determined that these complications did not occur in the study. Additionally, the investigators did not report any HZ events of myelitis, aseptic meningitis, or meningoencephalitis (all unusual complications in immunocompetent individuals). Vaccine efficacy was stable over the average of 1.3 years of follow-up accrued in the study. The duration of vaccine efficacy in persons aged 50–59 years is expected to be at least as long as that observed in the SPS because the booster response should be more robust in younger people [4]. A long-term observational effectiveness study is being conducted to better characterize the duration of protection against HZ [5].

HZ incidence rises dramatically with age, with a large increase observed in those aged ≥50 years. Although postherpetic neuralgia incidence is lower among those aged 50–59 years compared with those aged ≥60 years, the rash, subsequent scarring, and pain from HZ represent a substantial burden for the 50–59-year-old population. Vaccinating individuals aged 50–59 years could potentially eliminate a large fraction of the pain and suffering due to HZ and could also spare a significant number of individuals in this age group from the negative impact of HZ on daily activities, including work loss.

Notes

Author contributions. All authors: data analysis/interpretation, manuscript preparation, and approval of the final version of the manuscript.

Disclaimer. Although the sponsor (Merck) formally reviewed a penultimate draft, the opinions expressed are those of the authors and may not necessarily reflect those of the sponsor.

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