EDITORIALS

A New Vaccine to Prevent Herpes Zoster

Jeffrey I. Cohen, M.D.

Among persons who live until the age of 85 years, herpes zoster will develop in approximately half, with an incidence that seems to be increasing. Although the disease may be mild in healthy young adults, persons over the age of 50 years and those who are immunocompromised are more likely to have complications that include herpes zoster ophthalmicus and postherpetic neuralgia.

The live attenuated herpes zoster vaccine that is licensed in the United States reduces the incidence of herpes zoster by 70% among persons between the ages of 50 and 59 years, by 64% among those between the ages of 60 and 69 years, and by 38% among those 70 years of age or older.[1,2] The vaccine also reduces the incidence of postherpetic neuralgia by 66% among persons between the ages of 60 and 69 years and by 67% among those 70 years of age or older. The only frequent side effects have been injection-site reactions.

Lal et al.[3] now report in the *Journal* the results of a phase 3 trial of a herpes zoster subunit vaccine consisting of a single varicella–zoster virus (VZV) glycoprotein in an $AS01_B$ adjuvant system (called HZ/su vaccine). This vaccine, which was tested in study participants who were not immunocompromised and were 50 years of age or older, had a remarkable 97.2% efficacy in preventing herpes zoster. Unlike the live attenuated vaccine, the HZ/su vaccine had an efficacy that did not diminish with increasing age. The efficacy was 96.6% among participants between the ages of 50 and 59 years, 97.4% among those between the ages of 60 and 69 years, and 97.9% among those 70 years of age or older. The HZ/su vaccine is administered in two doses, whereas the live attenuated vaccine is given in a single dose.

The HZ/su vaccine was adjuvanted with $AS01_B$, which is currently not a licensed adjuvant. This adjuvant consists of monophosphoryl lipid A and QS21, a saponin compound, formulated with liposomes. The adjuvant activates antigen-specific CD4+ T cells and antibody.[4] Cell-mediated immunity, especially production of CD4+ T cells that target VZV, is associated with protection from herpes zoster,[5] whereas antibody protects against varicella.[6] $AS01_B$ has been used in trials of vaccines against malaria, hepatitis B, human immunodeficiency virus (HIV), and tuberculosis.[4]

In the current study, the rate of solicited systemic adverse reactions was 2.2 times as high in the vaccine group as in the placebo group (66% vs. 30%),[3] whereas in a study of the live attenuated vaccine, the rates of systemic adverse events were similar (25% in vaccine recipients vs. 24% in controls).[1] A total of 17.0% of the recipients of the HZ/su vaccine reported grade 3 symptoms that prevented normal activities, as compared with 3.2% in the placebo group. Although many of these symptoms were related to injection-site reactions, grade 3 systemic reactions occurred in 11.4% of the vaccine recipients and 2.4% of the placebo recipients and lasted a median of 1 day. However, the rates of serious adverse reactions and potential immune-mediated diseases (a theoretical concern associated with the use of adjuvants) were similar in the two groups. Since autoimmune diseases are more common among the elderly, it will be important to follow patients receiving this adjuvanted vaccine.

Aside from the apparent increase in efficacy over the live attenuated vaccine, what might be the advantages of the HZ/su vaccine? A trial is under way to compare these two vaccines for efficacy and safety (ClinicalTrials.gov number, NCT02114333). The current live attenuated vaccine is contraindicated in persons with impaired

cellular immunity, which includes persons who are at highest risk for herpes zoster, such as patients undergoing hematopoietic-cell transplantation, those with HIV who have a CD4+ cell count of 200 per cubic millimeter or less, and those receiving high doses of immunosuppressive medications. Since the HZ/su vaccine contains only a single virus protein and therefore cannot replicate, it will probably be safer in such patients, although it is unclear whether the vaccine will elicit a sufficiently protective immune response. A phase 1–2 trial of the HZ/su vaccine involving patients who had undergone autologous hematopoietic-cell transplantation showed that it induced VZV-specific CD4+ T cells that persisted for up to 1 year.[7] A heat-inactivated live attenuated vaccine reduced the incidence of herpes zoster in adults who had undergone autologous hematopoietic-cell transplantation.[8]

A major reason for using a herpes zoster vaccine is to reduce complications associated with the disease, and the elderly have the highest burden of postherpetic neuralgia and hospitalizations for herpes zoster.[9] A study of the HZ/su vaccine in persons who were 70 years of age or older (NCT01165229) was initiated at the same time as the study by Lal et al. and should help to determine whether the vaccine prevents postherpetic neuralgia and other complications of herpes zoster in the elderly, in whom the vaccine is needed most.

The duration of the effectiveness of the vaccine will determine the need for booster doses. A safety and immunogenicity study evaluating a booster dose of the live attenuated zoster vaccine administered 10 or more years after the initial dose has been completed (ClinicalTrials.gov number, NCT01245751). The ability of the HZ/su vaccine to boost immune responses in recipients of the live attenuated vaccine has not been tested. The live attenuated vaccine significantly reduces the burden of illness caused by herpes zoster for 10 years after vaccination but significantly reduces the incidence of herpes zoster for only 8 years.[10] Since the mean follow-up in the study of the HZ/su vaccine was 3.2 years, it will be important to determine the duration of its effect. The results for this vaccine are promising and may provide an important addition to vaccinations for an aging population.

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From the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.

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Nudging Smokers

Cass R. Sunstein, J.D.

In the past 40 years, we have seen a revolution in thinking about thinking.[1,2] The central idea is that human beings depart, in systematic ways, from standard economic approaches to rationality. Because the departures are systematic and predictable, they can be taken into account by researchers, clinicians, and others who want to improve health and reduce premature mortality.

Behavioral scientists have shown, for example, that people are "loss averse"; they tend to dislike losses more than they like corresponding gains. A 5-cent tax on the use of a grocery