

EDITORIAL

Vaccination to prevent zoster in the elderly

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Not long ago, while at a party where the guests were very old friends who had not seen each other for many years, I was chatting with a woman whom I had not seen since my schooldays. I asked about her husband, and she replied that he had recently passed away; she explained, 'He fell.' I gave her my condolences and somewhat later she asked about my occupation. I replied that I was a physician and that I worked on varicella and zoster, including vaccines to prevent those diseases. She then told me the real story of her husband. He developed zoster about the age of 65, which was followed by post-herpetic neuralgia (PHN) that lasted an agonizing 3 years. One day when he was alone in their apartment, he jumped, not fell, off their balcony to his death. This time my condolences were even greater, and I asked her if she minded if I repeated the story to others as I was interested in mentioning the experience as a way to encourage older people to be immunized against zoster. My friend was in complete agreement, if this information could be useful to others and help prevent their suffering.

Amazingly, zoster has only been recognized as a serious problem in fairly recent times, perhaps concomitant with its increase due to longer life expectancies and survival after cancer and transplantation. Zoster is rarely fatal, but it causes a great deal of morbidity, especially in older and immunosuppressed persons. The lifetime chance of developing zoster is estimated at 25%. The pathogenesis of zoster was unclear until the modern age, when it was shown, using molecular techniques, that exactly the same virus that caused the primary varicella-zoster virus

(VZV) infection (either natural or from vaccine) causes zoster [1]. The only explanation can be that zoster is due to reactivation of latent virus acquired during the primary infection. It is not caused by reinfection with VZV. Zoster develops in the setting of a decrease in the cell-mediated immune (CMI) response to VZV [2]. The exact mechanism whereby CMI response prevents zoster is unknown. It may be that CMI response prevents VZV from reactivating in neurons, but it may also be that CMI response in the skin defends the host from the reactivating virus and prevents symptoms. Viral reactivation and development of symptoms may be two separate events.

Although not every person with low CMI response to VZV develops zoster, the realization that a strong association exists between low CMI response to VZV and zoster, particularly in elderly and immunocompromised patients, fuelled interest in developing a vaccine to prevent zoster [1]. By then, in the late 1980s, a live attenuated vaccine against varicella, the Oka strain, had already been developed and was known to be safe, even for immunocompromised children [1, 3]. It has proven to be highly successful in preventing or modifying varicella in healthy children; in June 2006, a second routine dose of vaccine was recommended for all vaccinees in the United States in the hopes of providing better protection against chickenpox [1].

Using the Oka vaccine, therefore, dose ranging studies were performed to examine the amount of virus needed to reinvigorate the CMI response to VZV in healthy individuals over age 60 with a past history of varicella [4]. Studies of safety and immunogenicity in these open-label trials indicated that although a much stronger formulation of the vaccine was required to stimulate the CMI response in older

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individuals than in children, CMI response could be boosted with a lasting response. Open label studies suggested but could not prove prevention of zoster by the Oka vaccine.

These open-label studies, however, led directly to a randomized, double-blind, placebo controlled study, The Shingles Prevention Study, conducted in healthy individuals who were over 60 years of age, in the United States [5]. A total of 38 546 individuals participated; they ranged from 60 to ≥ 80 years of age, with a median of 69 years. The dose of vaccine given ranged from 18 700 to 60 000 plaque-forming units (p.f.u.) of VZV. (In contrast, the varicella vaccine contains 1350 p.f.u.) Study subjects were followed for 3–5 years. The vaccine proved very safe, adverse events were uncommon and were similar in persons who received the vaccine and those who received the placebo. The most common non-serious adverse event was transient pain at the injection site in vaccine recipients (48%), compared to 17% who received the placebo.

After an average follow-up of 3 years, there were 959 cases of confirmed zoster, 315 in vaccine and 642 in placebo recipients. Two analyses were made, one that appears in the original publication about the study [5], and the other, in conjunction with the Food and Drug Association (FDA), which appears in the package insert. Both analyses demonstrated protection against zoster and PHN.

In the original analysis, there was a 61% reduction in pain and/or discomfort in vaccinees compared to placebo recipients [5]. The end-point for the study was not prevention of zoster but rather amelioration of symptoms caused by zoster. Study participants were asked to report skin lesions that might be zoster and were examined, if possible, to obtain laboratory confirmation of the infection. More importantly, subjects were asked to report on pain and interference with daily activities on a scale of 0–10, as specified in the Zoster Brief Pain Inventory, to their physicians. Significant pain was considered as ≥ 3 , and the interval for pain assessment was 90 days after onset of rash. Thus the major end-point of the study was pain, not presence of rash, although in order to report pain, a zosteriform rash had to be present. The scale of pain intensity was used to calculate a score of the ‘burden of illness’ (BOI). In those who received vaccine, there was a 61% reduction of BOI, and a 66% reduction of PHN. In summary, this analysis indicated, as its primary end-point, not that the vaccine prevented zoster but that it prevented the discomfort caused by zoster.

A subsequent analysis, reported in the package insert (see Zostavax[®] website: http://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi.pdf), indicated that the incidence of zoster (not originally a primary end-point) was significantly lower in those who received vaccine compared to those who received placebo. The analysis of whether PHN was prevented was made only in subjects who developed zoster. In the vaccinated group, the incidence of zoster was significantly lower, 5.4 cases/1000 person-years of observation (PYO), compared to 11.12/1000 PYO in the placebo group, giving a vaccine efficacy of 52%. When the data were further analysed by age, the vaccine was 64% effective against zoster in persons aged 60–69, 41% effective in those aged 70–79, and 18% in those aged ≥ 80 years. The younger the vaccinee, the better the vaccine protected against zoster.

In this same analysis, the efficacy of prevention of PHN in subjects *who developed zoster* was 39% overall (8.6/1000 PYO in vaccinees and 12.5/1000 PYO in placebo recipients). Analysed by age, 5% were protected from PHN in vaccinees aged 60–69 years (6.6/1000 PYO for vaccinees and 6.9/1000 PYO for placebo recipients); however, individuals of this age were less likely to develop PHN than older individuals. The vaccine was 55% effective against PHN in those aged 70–79 years (7.7/1000 PYO for vaccinees and 17/1000 PYO for placebo recipients); PHN in this age group is twice the problem than it is in the younger cohort and thus the vaccine was very useful in persons in their seventh decade. Finally the vaccine was 26% effective in protecting individuals vaccinated when aged > 80 years (18.9/1000 PYO for vaccinees and 25.5/1000 PYO for placebo recipients).

In summary, the vaccine provided better protection (64%) against zoster in the youngest cohort of vaccinees, aged 60–69 years. Although vaccinees aged 70–79 years experienced only 41% protection against zoster, however, they had the best protection against PHN (55%).

Why vaccinate?

Zoster is a common disease and PHN occurs in about 25% of persons who develop it, especially in older age groups. The Shingles Prevention Study, which provided highly accurate data on the incidence of zoster using active surveillance, indicated that about 1 million Americans are affected annually. The incidence of PHN after zoster is well known to increase significantly from age 60 with each decade of life. Although

zoster itself can successfully be treated with antiviral drugs, their effect on PHN is minimal [1]. While there is no question that there is significant amelioration of the acute pain of zoster by antivirals, the incidence of PHN remains unchanged, whether antiviral treatment is given or not. Unfortunately, the treatment of PHN itself remains problematic. This is made apparent by the great number of recommended therapeutic approaches, including opioids and similar painkilling drugs, antidepressants at low dosage, anticonvulsives, acupuncture, and a bevy of surgical approaches [6]. Often several approaches are applied at one time, further indicating that no treatment is entirely helpful. Patients may complain of pain for months to years. In the Shingles Prevention Study, 51% of PHN cases lasted longer than 6 months. Hope-Simpson reported that in 20% of PHN cases, pain lasted for more than 1 year [7, 8]. Therefore prevention, not treatment, of PHN is crucial. The only effective current means of prevention is vaccination.

The VZV vaccines are extremely safe. While initial use of a live herpesvirus vaccine was considered controversial because long-term effects were unknown, fears about the vaccine have proven to be unfounded [1]. Over 40 million healthy children and adults have been immunized safely since the vaccine was developed in 1974. Fears about possible theoretical adverse effects such as oncogenicity and neurological dangers have proven unfounded. A handful of severely immunocompromised children inadvertently vaccinated against chickenpox have developed complications such as pneumonia and extensive skin rash, but no fatalities from the Oka strain have been reported [1]. For prevention of zoster in older age groups, the vaccinees have previously had varicella and retain immunity to development of chickenpox. They tolerated the necessary large dose of vaccine virus extremely well, and the incidence of side-effects, as noted above, was minimal. Using polymerase chain reaction (PCR), a highly accurate and sensitive diagnostic technique, in no instance was the Oka strain identified in skin lesions in vaccinees [9]. In contrast, the wild-type virus was usually found by this method in patients reporting a zoster rash [5].

Based on these data, in October 2006 the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended vaccination of healthy individuals in the United States, who were aged >60 years, with one dose of the zoster vaccine (see CDC website: <http://www.cdc.gov/>).

Why not vaccinate?

Because vaccination against zoster has been shown to be safe and effective, the main hesitation about using it widely is expense. A major analysis of cost effectiveness, using computer modelling of existing data on incidence, severity, vaccine effectiveness, and cost of vaccine, concluded that there was a modest increase in quality-adjusted life-year (QALY), 0.6 day, from vaccination. This analysis assumed the vaccine would cost less than \$200, be given to people before age 70, and last 30 years [10]. This analysis was one of the first, and surely not the last, on the cost-benefit of the zoster vaccine. However, estimating the vaccine to last for 30 years may be somewhat misleading. According to life insurance mortality tables, more than 50% of persons immunized at age 60 years will no longer be alive by age 90 years. It has been pointed out that the ultimate decision on whether to use this vaccine routinely and more importantly, how to pay for it, must also take the disease burden, vaccine safety and efficacy, and consumer need into account [11]. The cost of the vaccine alone in the US is \$150 per dose, which is similar to the cost of hepatitis vaccines for adults [10]. For most adult vaccinations (in contrast to most paediatric immunizations), it is necessary to immunize many more individuals than will be expected to develop the disease. This is the situation for immunization against hepatitis B, for example, and it applies to immunization against zoster as well. Widespread immunization of patients in their sixth decade will prevent about 5% from developing PHN. It must be kept in mind, however, that PHN is often disabling and there is no good treatment.

Other obvious considerations include the fact that society's initial expenditure may be greatest in first few years of vaccine use, when vaccination is likely to include individuals aged 60–80 years. Following that, mostly 60-year-olds will be immunized. The increasing numbers of Americans reaching their 60th birthday, as the population ages, will counterbalance this, however.

What do we still need to know about VZV infection in order to better prevent zoster?

Exactly how the vaccine works remains unknown. Stimulation of the CMI response to VZV is obviously important, but the question is whether the important immune response is in the circulating blood cells or in the skin itself, or both. It is also not known if the CMI

response to VZV keeps the virus from reactivating or keeps it from causing disease. Tied to these questions is whether subclinical reactivation of VZV, which can boost immunity to zoster, occurs. In addition, we do not know whether zoster will increase in persons who are now middle aged and have had natural varicella in the past, due to the decrease of circulation of wild-type VZV as a result of widespread vaccine use. Thus far the question remains unresolved [1]. This possibility would provide an additional use for the vaccine.

We also need additional information about the vaccine itself. Can a screening test be developed which identifies those at highest risk, to limit the numbers of people who need to be immunized? The Shingles Prevention Study indicated that the vaccine lasts at least 3 years. We need to know if booster doses of vaccine will be necessary and if so, how often. It is not yet clear whether elderly persons who have never had varicella before, such as adults from locations within tropical climates where the virus does not spread extensively in children, can be safely vaccinated. In the Shingles Prevention Study, a past history of varicella was required for inclusion in the trial. There were no serious adverse events in these individuals. Whether varicella susceptibles might be at greater risk is not yet known.

There are myriad of unknowns regarding the future of immunization against chickenpox. We do not know what percent of varicella-susceptible individuals who are immunized against chickenpox will develop latent infection with the Oka strain. As these individuals age, there may be less zoster in vaccinated populations if they do not have latent infection. If, on the other hand, subclinical reactivation of VZV is important in maintaining long-term immunity against chickenpox, booster doses of vaccine to prevent chickenpox in adulthood may be required. Exactly how immunity to chickenpox and zoster develops needs further study; the mechanisms are probably quite different, because it appears that humoral immunity is a correlate of protection against primary infection but that the CMI response is a correlate of protection against zoster. Undoubtedly, however, this is a simplistic scenario, with considerable redundancy in immune protection against both diseases.

Elucidation of immune correlates of protection against varicella and zoster are both major goals in understanding how vaccines work against VZV.

Finally one would hope for the development of a vaccine that can be used safely in immunocompromised individuals, potentially to prevent chickenpox and zoster.

DECLARATION OF INTEREST

The author has given lectures and acted as a consultant on varicella and zoster vaccines for Merck and GSK.

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