CLINICAL VIGNETTE

Varicella-Zoster Vaccine and Herpes Simplex Virus: Is There Cross Immunity?

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A 61-year-old woman with history of recurrent oral-labial herpes presents to establish care. She reported receiving the shingles vaccine 2 years prior at the age of 59, having never had an outbreak of shingles, but having had chicken pox as a child at the age of 6 or 7. She reports it was "severe with whole body pocks," though no hospitalization, pneumonia, seizures, or encephalitis.

Prior to having received the shingles vaccine, she had 3 to 4 outbreaks of herpes simplex virus (HSV) per year (maximum of 7 under extremes of sun exposure or stress) since the age of 17. She has never had a genital herpes outbreak. She had not taken prophylactic antiviral medications, although she has used acyclovir for individual outbreaks, both pills and ointment. After receiving the singles vaccine in 2013, she had "zero outbreaks." Her sister-in-law had the same effect after her shingles vaccine and asks if there is a connection between the shingles vaccine and her reduction in HSV outbreaks.

The herpes virus family is a large family of over 130 double stranded DNA virusus, 8 of which infect humans – Herpes simplex 1 and 2 (HSV-1 and HSV-2), Varicella-zoster (VZV), Epstein-Barr, Human Cytomegalovirus, human herpes virus 6, human herpes virus 7, and Kaposi's sarcoma-associated herpes virus. HSV-1, HSV-2, and VZV are all part of the alpha subfamily and share many of the same genes and envelope proteins.

A literature search reveals that the pursuit of a vaccine for herpes simplex virus type 1 and 2 has been largely unsuccessful in the typical sense[1-3]. The nearest vaccine we have is for varicela-zoster, also known as chicken pox. The vaccine comes in two formulation: a low-dose vaccine, known as Varivax, that is given to children older than 12 months (available since 1995 from Merck), and a higher dose vaccine, known as Zostavax, that can be given to adults 50 and older (available since 2006, also from Merck). Varivax confers protection from varicella to approximately 96-100% efficacy.[4] The risk of developing shingles from this vaccine is low with only eight cases of herpes zoster reported during 42,556 person-years of follow-up in clinical trials. Zostavax, by comparison, is roughly 60% effective in preventing herpes zoster and post-herpetic neuralgia in those over 60 years of age,[5,6] and 70% effective if given between 50-59 years of age.[7]

There is some evidence that the varicella-zoster vaccine can help to reduce the severity of outbreaks, though less evidence it is effective at complete prevention. HSV-2 vaccine research in a Guinea pig model did reduce the severity of HSV-2 outbreaks and increase antibody levels to HSV-2 when the varicella zoster vaccine was combined with a portion of the HSV-2 virus genome.[8] Many other studies in animals and humans have come to similar conclusions (i.e., a partial response to the vaccine leading to some reduced severity or frequency of outbreak) but no outright success in the same vein as the Varivax vaccine.[3]

More recently, a paper published in 2012 by the Department of Tropical Diseases in the University of Paris by Jacqueline Le Goaster, shows a completely different result.[9] In her prospective study, she recruited 24 patients who were given Varivax from 2005 to 2011 who had oral or genital HSV-1 or HSV-2 and 6-8 recurrences per year. She compared them to 26 non-vaccinated controls who also had recurrent HSV-1 or HSV-2 disease and did not receive an immunization but continued with standard oral therapy with valacylovir or acyclovir. Antibody levels against HSV-1, HSV-2, and VZV were drawn before and after vaccination or placebo, and these were significant for increased immunity to VZV, as would be expected in immunized individuals. The patients were contacted at one, two, and five years after starting the study and self-reported the number of outbreaks they had experienced. The vaccinated group all reported zero recurrences, while the non-immunized group reported outbreaks similar in frequency to what they experienced prior to enrolling in the study.

The original study that led to FDA approval was not as favorable for preventing HSV-1 or HSV-2. Of the 38,546 adults who were sixty years and older, there were 1,308 who developed a rash, suspected to be herpes zoster.[5] Of these rashes, 317 were determined not to be herpes zoster but another type of rash. Of these 317, 49 rashes were determined by PCR to be from HSV: 24 were in the vaccine group and 25 were in the placebo group. This suggested there is no difference in protection towards HSV-1 or HSV-2 lesions afforded by the vaccine.

Possible explanation of the Le Goaster trial (results) is the inclusion of participants less than 50, or the lack of immunity to VZV prior to infection with HSV. It is well-known that the immune system loses efficacy with age, and this principle was specifically demonstrated through prior trials.[5,7] The efficacy of the zoster vaccine in those 50 and older was 70%, while in those 60 and older was 60%. During my personal communications with Dr. LeGoaster, she has not conducted further research into this area and did not offer a plausible

explanation for the difference between her research and the NEJM Oxman trial.

Given the available evidence, it seems far-fetched that the zoster vaccine is as effective in preventing recurrent HSV as Le Goaster's trail has suggested. Although there was objective improvement in the antibody response for VZV, there was no change in HSV antibody, nor objective proof of a lack of recurrence, only subjective reports.

Based on this reasoning and the available literature, there appears to be a lack of support for the efficacy for the shingles vaccine to prevent recurrent HSV. The best treatment for those uncomplicated patients without HIV or chronic kidney disease who wish to suppress recurrence is daily prophylactic treatment with valacyclovir, acyclovir, or famicyclovir.[10,11] As an alternative, these medications can be started 1-2 weeks prior to important events to prevent an untimely outbreak. Complicated patients who suffer from HIV or have chronic kidney disease are likely to benefit from a consult with our infectious disease or nephrology.

Consideration of provocative factors is also important. Lack of sleep, stress, alcohol use, and sunlight exposure are frequently cited, as are certain foods. For unclear reasons, foods rich in lysine and poor in arginine have, in some smaller studies, shown to be protective for outbreaks. Foods with a high ratio of lysine to arginine could be supplemented (yogurt, milk, cheese), while the converse avoided in large quantities (nuts, fruit juices, berries).[12,13] Lysine supplements can also be considered in those without chronic liver or kidney disease (1,000 mg three times a day). And although there was one case reported of Fanconi syndrome in a patient with lysine supplementation,[14] this has not been widely reported. Given the lack of harm in these naturally occurring amino acids, these supplements may be safely mentioned in treatment plans for most patients.

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