Published in final edited form as:
J Infect Dis. 2008 March 1; 197(Suppl 2): S237–S241. doi:10.1086/522129.

Strategies for Zoster Vaccination in Immunocompromised Patients

Jeffrey I. Cohen
Medical Virology Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland

Abstract

A vaccine to prevent zoster in adults 60 years of age or older with healthy immune systems was recently approved by the Food and Drug Administration. This vaccine is contraindicated in persons with certain immunodeficiency states or who are receiving immunosuppressive therapy. Based on studies of the varicella vaccine in healthy and immunosuppressed children, and on studies of zoster vaccines in healthy adults prior to its licensure, a series of strategies are proposed for evaluating the live zoster vaccine in immunosuppressed persons. In addition, the use of other vaccines including heat-inactivated or replication-defective VZV to prevent zoster in immunocompromised persons is also discussed.

Immunocompromised persons such as those with hematologic malignancies, advanced HIV infection or transplant recipients have impaired T cell immunity and rates of zoster that are several times higher than healthy persons (1); those with leukemia have rates that are 50 to 100 times higher. These patients are more likely to develop disseminated zoster or multi-dermatomal disease. Dissemination to various organs including the lung, liver, brain, and spinal cord can occur. Patients with advanced HIV infection may develop recurrent or relapsing zoster, as well as verrucous lesions that persist for months (2).

Prevention of varicella and zoster in immunocompromised patients would reduce the morbidity of these diseases. Varicella immune globulin and acyclovir are available for postexposure prophylaxis to prevent varicella in immunocompromised persons exposed to persons with varicella. A safe and effective vaccine for immunocompromised persons could prevent much of the morbidity associated with zoster.

Comparison of vaccination for varicella and zoster in healthy persons versus immunocompromised patients

Vaccination with the live attenuated Oka virus is used to prevent disease in healthy persons who are exposed to varicella. Varicella vaccine has also been safely given to selected children with leukemia (3), HIV infection (4,5), or liver or intestinal transplant recipients (6). Current recommendations (7) state that persons with impaired humoral immunity can be vaccinated, and vaccination should be considered for asymptomatic or mildly symptomatic HIV-infected children with CD4 T cells≥25%. Varicella vaccine is available for compassionate use in children with acute lymphoblastic leukemia off chemotherapy and in remission for one year

Reprints or correspondence to: Dr. Jeffrey I. Cohen, Medical Virology Section, Laboratory of Clinical Investigation, Bldg. 10, Rm. 11N234, 10 Center Drive, MSC 1888, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, 20892 (E-mail: jcohen@niaid.nih.gov).

Potential conflicts of interest: none reported

(8). Varicella vaccine is contraindicated in patients with malignancy of the bone marrow or lymphatic system, primary or acquired immunodeficiency, and those receiving≥2 mg/kg (or total of >20 mg/day) of prednisone.

The Shingles Prevention Study (SPS) (9) showed that vaccination of older healthy adults with a high potency live varicella vaccine reduced the burden of illness due to zoster, the incidence of postherpetic neuralgia, and the incidence of zoster. Although the vaccine was less effective in reducing the incidence of zoster in persons aged 70 or older than in those aged 60–69, the vaccine was more effective in reducing the severity of illness in the older subjects. The dose of vaccine used was approximately 14-times that of the varicella vaccine used in the United States; a larger dose of vaccine has been associated with a longer duration of immunity in VZV-immune elderly persons (10). Persons who received the vaccine had more reactions at the injection site including erythema, pain, swelling, or pruritus than those who received placebo, but no there was no increase in the rate of serious adverse events with the vaccine. While rashes did occur in persons who were vaccinated, all of those that were analyzed were due to wild-type, not vaccine, virus.

A number of differences between the varicella and zoster vaccines are important to note when considering vaccination of immunocompromised persons to prevent zoster (Table 1). The higher dose of the zoster vaccine might be associated with a higher likelihood of side effects in mild or moderately immunocompromised persons. On the other hand, since virtually all persons receiving vaccine to prevent zoster would already have been infected with VZV and should have some memory T cells, these persons might have fewer rashes compared with those who were never infected with the virus. Studies of leukemic children receiving two doses of varicella vaccine showed that rashes, some of which contained vaccine virus, were almost always observed after the first dose of vaccine (12). Studies of healthy adolescents and adults receiving two doses of the varicella vaccine also showed a much lower rate of rash after the second dose of vaccine (11). The presence of preexisting memory T cells to VZV might be more likely to induce immunity with VZV vaccination than in persons receiving the vaccine for the first time. Finally, while varicella vaccine has been used in immunocopromised persons (see above), there are no published studies of the zoster vaccine in immunocompromised persons.

Strategies for Vaccination of Immunocompromised Persons with Zoster Vaccine

Live varicella vaccine

The Shingles Prevention Study (9) excluded patients who were immunosuppressed due to malignancy, HIV infection, immunosuppressive or cytotoxic chemotherapy (e.g. cancer chemotherapy or treatment for organ transplant recipients), or corticosteroid therapy (≥800 ug per day of beclomethasone dipropionate or its equivalent). Such patients with impaired T cell immunity are felt to be at greater risk for side effects from the vaccine, and less likely to respond to vaccine. Patients with skin cancer or other neoplasms that were stable in the absence of chemotherapy were not excluded.

Optimally, the vaccine could be given to patients who are not yet immunocompromised, but who will be given immunosuppressive therapy in the next several weeks to months. Such patients might be undergoing organ transplantation or have a recent diagnosis of a connective tissue disorder and would receive immunosuppressive therapy in the near future.

The live Oka vaccine virus might be tested in selected patients who have impaired cellular immunity and were not included in the Shingles Prevention Study. The varicella vaccine is considered for asymptomatic or mildly symptomatic HIV-infected children with CD4 T cells

of≥25% (7). In addition, a recent study showed that the varicella vaccine was well tolerated and often induced VZV-specific immune responses in HIV-infected children with CD4 T cells≥15% and a CD4 T cell count of≥200 cells/ul (14). Therefore, asymptomatic or mildly symptomatic adults with HIV infection at risk for zoster with CD4 T cell counts of≥15% and a CD4 T cell count of≥200 cells/ul might be vaccinated with the zoster vaccine in controlled studies. Since the vaccine was not evaluated in persons receiving moderate doses of corticosteroids, or other moderately immunosuppressive therapy, such patients might also be evaluated in future studies. However, since the dose of vaccine given is about 14-times the dose of the varicella vaccine, there might be a higher rate of side effects than that seen with the varicella vaccine.

The use of a live attenuated varicella vaccine to prevent zoster would be contraindicated in persons who have moderately to severely impaired cellular immunity who might develop symptomatic, progressive infection with vaccine virus. Vaccination of moderately or severely immunocompromised patients with live vaccine should be performed in carefully monitored clinical trials in which both the safety and immunogenicity of the vaccine are observed (Table 2). These studies should include analysis of VZV-specific cellular immunity before, during, and after vaccination, as well as close attention to side effects especially the development of rashes after vaccination. Suspicious rashes should be tested by PCR for detection of vaccine virus, and patients whose rashes contain VZV should be treated with antiviral therapy and followed closely.

Vaccination with the live virus vaccine might be less hazardous in immunocompromised persons with detectable cell mediated immunity to VZV. A number of studies have examined VZV-specific immune responses to live VZV vaccination in healthy older subjects (18,19). Several of these studies showed a boost of virus-specific cellular immune responses with live virus vaccine. Responder cell frequencies, which measure proliferation of serially diluted peripheral blood mononuclear cells in response to VZV antigen, have been useful for assaying the cellular immune response to the virus. Persons with detectable levels of responder cells prior to vaccination were 4 to 6 times as likely to respond to the vaccine at 3 months compared to those without detectable responder cell frequencies before vaccination (15). Other tests of cellular immunity, such as lymphocyte proliferation assays, production of cytokines by peripheral blood mononuclear cells, or skin tests in response to VZV antigens have also be used (18).

Inactivated varicella vaccine

Safer vaccines would involve the use of a heat-killed virus vaccine or subunit vaccines. These nonreplicating vaccines might be less effective since they are less likely to present antigens in the context of MHC class I, and therefore might stimulate lower levels of virus-specific CD8 T cell responses than live vaccines.

An early study showed that healthy seropositive adults who received live or heat-inactivated VZV vaccine developed similar titers of virus-specific antibody responses at 6 weeks (20). Another study compared vaccination of 80 healthy persons over 55 years old with a single dose of 4,000 PFU of live VZV vaccine versus a similar dose of heat-killed vaccine (21). Both viruses induced similar levels of VZV antibodies, virus-specific T cells, and production of interferon-gamma by peripheral blood mononuclear cells stimulated with VZV antigen at both 3 months and 1 year after vaccination. Persons who had greater responder cell frequencies to VZV prior to vaccine had the highest responder cell frequencies after vaccination. The live VZV vaccine induced higher levels of MHC class I cytotoxic T cells, but similar levels of NK cell-dependent lysis, when compared to the killed virus vaccine at 3 months after vaccination (22).

A follow-up study using the same dose of live and heat-killed vaccine in 167 healthy older adults (mean age 66) showed that both vaccines boosted VZV antibodies and VZV responder cell frequencies at 3 months, but the level of VZV antibodies and interferon-gamma production by peripheral blood mononuclear cells returned to baseline at 1 year, while the responder cell frequency was still elevated in both groups at 1 year (15). The half life of the boost in virus-specific responder cells was 17.5 months after vaccination with live virus and 21.3 months with inactivated virus, but the difference was not significant.

Redman et al (16) randomized autologous or allogeneic bone marrow transplant patients to receive a heat-inactivated varicella vaccine or placebo. Fourteen patients received 1 dose of heat-inactivated vaccine 1 month after bone marrow transplantation and 14 received placebo. Peripheral blood mononuclear cells were stimulated with VZV antigen and tritiated thymidine uptake was measured to determine the stimulation index. While the stimulation index was higher in patients who received the inactivated vaccine compared with those who received placebo (12.2 vs 4.8) at 3 months after transplant, there was no effect on the incidence of zoster in vaccine recipients compared to controls (38% vs. 36%). In a subsequent study, 24 patients received three doses of heat-inactivated vaccine at 1, 2, and 3 months after transplant and were compared with 23 patients who received placebo. The stimulation index in the vaccinated group was higher than in those who received placebo (8.6 vs. 5.3) at 5 months and the severity of zoster was reduced in the vaccinated subjects compared to the control group at 1 year. However, the incidence of zoster was not reduced in vaccine recipients compared to controls (23% vs. 22%).

A second randomized control trial of heat-inactivated varicella vaccine was undertaken in 119 patients scheduled to undergo autologous hematopoietic cell transplantation for Hodgkin's or non-Hodgkin's lymphoma (17). Unlike the prior study of Redman et al., vaccine or placebo was given within 30 days before transplant as well as at 30, 60, and 90 days after transplant. At 1 year after transplant there was a significantly lower rate of zoster in patients receiving the vaccine (13%) than in those given placebo (33%). The VZV-specific stimulation index in the vaccinated group was significantly higher (42.8) than that in the placebo group (21.3) at 1 year after transplant. The mean percentage of CD4 cells that expressed intracellular interferon-gamma or TNF-alpha in response to inactivated VZV at 6 months after transplantation was higher in those who received the vaccine than in those who did not. Side effects of the vaccine were generally mild and included pain, induration, and erythema at the injection site. The authors postulated that vaccination before transplant induced the production of VZV-specific memory T cells, some of which may have survived the preconditioning regimen, and were restimulated by vaccination after transplant. This study indicates that multiple doses of a heat-inactivated VZV vaccine can reduce the rate of zoster and enhance cellular immunity to the virus in an immunocompromised population.

Other Vaccines

Other approaches to vaccinating immunocompromised patients against zoster might also be tried. A sequential regimen of inactivated vaccine, followed by live virus vaccine, might be considered in an effort to prime the immune system before live virus is administered. A similar sequential approach was used for poliovirus vaccination during the transition from an all live to an all inactivated poliovirus vaccine program for healthy children in the United States.

A subunit vaccine consisting of a viral protein (or proteins) might be used for vaccination instead of killed virus. Such a vaccine might cause less injection site reactions, since the amount of cellular proteins (which are present in live or heat-inactivated VZV vaccines) would likely be reduced. A number of VZV gene products including the immediate-early 4, 62 and 63 proteins and glycoproteins C, E, and I are known to be targets for cytotoxic T cells (13). Unfortunately, it is unknown which of these, or other viral proteins are necessary for protection

against zoster. The addition of adjuvants or other delivery systems, such as presentation of VZV antigens by dendritic cells, would likely improve the cellular immune response to subunit or inactivated virus vaccine. A dendritic cell vaccine would be difficult to administer since it would likely require isolating dendritic cells from the vaccinee, pulsing the cells with VZV antigens, and injecting them back into the vaccinee.

An alternative approach would be to use replication-defective VZV. A number of VZV mutant viruses have been constructed from the Oka vaccine virus that knock-out essential viral gene products that are required for virus replication (23–25). These viruses should be able to infect cells, present nearly all of the viral proteins to the immune system, but not replicate and cause disease. Unlike a killed virus vaccine, such mutants might induce higher levels of MHC class I restricted CD8 T cell responses, which should enhance cellular immunity to the virus. Replication-defective vaccines have the potential to recombine with wild-type virus, and therefore are considered less safe than inactivated vaccines.

Acknowledgements

I thank the Intramural Research Program of the National Institute of Allergy and Infectious Diseases for their support and Dr. Philip Brunell for his comments on the manuscript. The opinions expressed here are those of the author and do not necessarily reflect those of the National Institute of Allergy and Infectious Diseases.

Financial support: Division of Intramural Research, National Institute of Allergy and Infectious Diseases

References

1. Kost RG, Straus SE. Postherpetic neuralgia- pathogenesis, treatment, and prevention. N Engl J Med 1996;335:32–42. [PubMed: 8637540]
2. Oxman, MN. Clinical manifestations of herpes zoster. In: Arvin, AM.; Gershon, AA., editors. Varicella-zoster virus. Cambridge: Cambridge University Press; 2000. p. 246-275.
3. LaRussa P, Steinberg S, Gershon AA. Varicella vaccine for immunocompromised children: Results of collaborative studies in the United States and Canada. J Infect Dis 1996;174 (Suppl 3):S320–3. [PubMed: 8896539]
4. Levin MJ, Gershon AA, Weinberg A, et al. Immunization of HIV-infected children with varicella vaccine. J Pediatr 2001;139:305–310. [PubMed: 11487761]
5. Armenian SH, Han JY, Dunaway TM, Church JA. Safety and immunogenicity of live varicella virus vaccine in children with human immunodeficiency virus type 1. Ped Infect Dis J 2006;25:368–370.
6. Weinberg A, Horslen SP, Kaufman SS, et al. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestinal transplant recipients. Am J Transplant 2006;6:565–568. [PubMed: 16468967]
7. Centers for Disease Control. Prevention of varicella: Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(RR6):1–5.
8. Centers for Disease Control. Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(RR11):1–36.
9. Oxman M, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia. N Engl J Med 2005;352:2271–2284. [PubMed: 15930418]
10. Levin MJ, Murray M, Zerbe GO, White CJ, Hayward AR. Immune response of elderly persons 4 years after receiving a live attenuated varicella vaccine. J Infect Dis 1994;170:522–6. [PubMed: 8077709]
11. Kuter BJ, Ngai A, Patterson CM, et al. Safety, tolerability, and immunogenicity of two regimens of Oka/Merck varicella vaccine (Varivax) in healthy adolescents and adults. Vaccine 1995;13:967–972. [PubMed: 8525689]
12. Gershon AA, Steinberg SP. the Varicella Vaccine Collaborative Study Group of the National Institute of Allergy and Infectious Diseases. Persistence of Immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. N Engl J Med 1989;320:982–7.

13. Arvin, AM. Varicella zoster virus. In: Knipe, DM.; Howley, PM., et al., editors. Fields Virology. Philadelphia: Lipincott-Williams & Wilkins; 2001. p. 2731-2767.

14. Levin MJ, Gershon AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4+ T cells. J Infect Dis 2006;194:247–255. [PubMed: 16779732]

15. Levin MJ, Ellison MC, Zerbe GO, Barber D, Chan C, Stinson D, Jones M, Hayward AR. Comparison of a live attenuated and an inactivated varicella vaccine to boost the varicella-specific immune response in seropositive people 55 years of age and older. Vaccine 2000;18:2915–2920. [PubMed: 10812235]

16. Redman RL, Nader S, Zerboni L, Liu C, Wong RM, Brown BW, Arvin AM. Early reconstitution of immunity and decreased severity of herpes zoster in bone marrow transplant recipients immunized with inactivated varicella vaccine. J Infect Dis 1997;176:578–585. [PubMed: 9291302]

17. Hata A, Asanuma H, Rinki M, Sharp M, Wong RM, Blume K, Arvin AM. Use of an inactivated varicella vaccine in recipient of hematopoietic-cell transplants. N Engl J Med 2002;347:26–34. [PubMed: 12097537]

18. Levin MJ. Use of varicella-zoster virus vaccines to prevent herpes zoster in older individuals. Arch Virol 2001;17(Suppl):151–160.

19. Takahashi M, Kamiya H, Asano Y, Shiraki K, Baba K, Otsuka T, Hirota T, Yamanishi K. Immunization of the elderly to boost immunity against varicella-zoster virus (VZV) as assessed by VZV skin test reaction. Arch Virol 2001;17(Suppl):161–172.

20. Sperber SJ, Smith BV, Hayden FG. Serologic response and reactogenicity to booseter immunization of healthy seropositive adults with live or inactivated varicella vaccine. Antiviral Res 1992;17:213–222. [PubMed: 1314536]

21. Hayward AR, Buda K, Levin MJ. Immune response to secondary immunization with live or inactivated VZV vaccine in elderly adults. Viral Immunol 1994;7:31–6. [PubMed: 7986334]

22. Hayward AR, Buda K, Jones M, et al. VZV specific cytotoxicity following secondary immunization with live or killed vaccine. Viral Immunol 1996;9:241–5. [PubMed: 8978020]

23. Mo C, Suen J, Sommer M, Arvin A. Characterization of varicella-zoster virus glycoprotein K (open reading frame 5) and its role in virus growth. J Virol 1999;73:4197–4207. [PubMed: 10196316]

24. Cohen JI, Krogmann T, Ross JP, Pesnicak LP, Prikhod'ko EA. The varicella-zoster virus ORF4 latency associated protein is important for establishment of latency. J Virol 2005;79:6969–6975. [PubMed: 15890936]

25. Xia D, Srinivas S, Sato H, Pesnicak L, Straus SE, Cohen JI. Varicella-zoster virus ORF21, which is expressed during latency, is essential for virus replication but dispensable for establishment of latency. J Virol 2003;77:1211–1218. [PubMed: 12502838]

Table 1

Comparisons between immunization of immunocompromised persons with the live zoster and live varicella vaccine.

1	The virus titer in the zoster vaccine is ~14-fold higher than the titer in the varicella vaccine (9); therefore vaccination with the zoster vaccine could result in more side effects than with the varicella vaccine.
2	Since rashes are less common after the second dose of vaccine compared with the first dose in both healthy adults (11) and immunocompromised children (12), a prior history of varicella with preexisting memory T cells to the virus suggests that immunization of immunocompromised persons to prevent zoster might be safer than immunization to prevent varicella.
3	Since prior exposure to varicella results in development of memory T cells to the virus (13), vaccination of immunocompromised VZV-seropositive persons to prevent zoster might elicit better immunity than vaccination of seronegative persons to prevent varicella.
4	While the varicella vaccine can be given to certain patients with mild immunodeficiency (7,8), there is no experience in immunizing immunocompromised patients with the live zoster vaccine.

Table 2

Strategies for vaccinating immunocompromised persons with zoster vaccine:

1	Vaccination of VZV seropositive persons who have mildly impaired cellular immunity should be safer than those with more severe immune defects.
2	Vaccination of persons with moderately or severely impaired cellular immunity should be performed in pilot studies with careful monitoring of safety and cellular immune response to vaccination.
3	Vaccination with inactivated vaccine, subunit vaccine, or replication-defective virus should be safer, although may be less effective, than live virus vaccine.
4	Multiple doses of inactivated or subunit vaccine will likely be needed for highly immunocompromised persons (16,17).
5	A sequential regimen of inactivated or subunit vaccine followed by live vaccine might be considered for immunocompromised persons.
6	Vaccination of transplant recipients both before and after transplantation is likely to be more effective and safer than vaccination after transplant alone (16,17).