Prevention of shingles: safety and efficacy of live zoster vaccine

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Abstract: Primary infection with varicella zoster virus (VZV) causes chickenpox (varicella) after which virus becomes latent in cranial nerve, dorsal root and autonomic ganglia along the entire neuraxis. Virus may later reactivate, causing shingles (zoster), characterized by pain and rash restricted to 1–3 dermatomes. More than 40% of zoster patients over age 60 develop postherpetic neuralgia (PHN), pain that persists for months to years. The socioeconomic impact of primary varicella infection has been lessened by introduction of VZV vaccine for children. However, the effect of childhood vaccination on the incidence of zoster is unknown. Virus reactivation correlates with waning cell-mediated immunity (CMI) to VZV with normal aging. Adults exposed to children with varicella may have a boost in CMI to VZV. For at least several more decades, the incidence of zoster may increase as the elderly population grows. The anticipated increase in zoster burden of illness in future decades was a major impetus for the Shingles Prevention Study, a prospective, double-blind, placebo-controlled trial of attenuated VZV vaccine to prevent zoster in older adults. This review discusses clinical and virological aspects of zoster and its complications, current treatment options, and VZV vaccine development along with its future role in disease prevention.

Keywords: shingles; zoster; zoster vaccine

Introduction

Varicella zoster virus (VZV) is a neurotropic herpesvirus that infects nearly all humans. Primary infection causes chickenpox (varicella) after which virus becomes latent in cranial nerve, dorsal root and autonomic ganglia along the entire neuraxis. Decades later, a declining VZV-specific cell-mediated immunity (CMI) allows virus to reactivate, resulting in shingles (zoster), characterized by pain and rash restricted to 1–3 dermatomes. The increasingly widespread use of an attenuated varicella vaccine has nearly eradicated chickenpox in areas of the world where vaccination is employed. The success of a varicella vaccine combined with data showing a boost in CMI to VZV in vaccinated VZV-seropositive adults led to the Shingles Prevention Study (SPS), which revealed that vaccination of VZV-seropositive men and women over the age of 60 reduced the incidence of zoster and postherpetic neuralgia (PHN). This review discusses the epidemiology and pathogenesis of zoster, with a focus on the potential of a VZV vaccine to prevent zoster and reduce the burden of illness on the patient and on society.

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Epidemiology and pathogenesis

Zoster affects approximately 1 million people per year in the United States alone (Oxman et al 2005), with millions more worldwide. No genetic predisposition has been identified (Blackwelder et al 1982). The frequency of zoster is proportionally related to the incidence of chickenpox which is independent of socioeconomic status, population density, gender or ethnic origin (Nagasako et al 2003). Exposure of adults

to infected children is thought to provide repeated boosts in immunity to VZV (Thomas et al 2002). Thus, it is possible that chickenpox vaccination, which has reduced the incidence of childhood varicella, will increase the incidence of zoster in adults (Brisson et al 2000, 2002; Goldman 2005). At the same time, childhood vaccination may result in a lower virus burden in latently infected ganglia, reducing the overall incidence of zoster in adults who were vaccinated in childhood (Arvin and Greenberg 2006). Only time will tell which effect or combination of effects will be important. However, the answer may never be known if recipients of zoster vaccine (now approved by the FDA) results in a decreased incidence of zoster.

Zoster is the result of reactivation of latent VZV and transport to basal epidermis of skin where infected cells produce conditions favoring virus spread, such as the downregulation of interferon-alpha and lymphocyte adhesion molecules (Ku et al 2004). As infected cells die, interferon-alpha is induced in the neighboring cells which slows the spread of VZV and enhances T-cell clearance of the infection (Chen et al 2004; Nikkels et al 2004). An association between zoster and the immune system has been recognized for decades (Miller and Brunell 1970). Zoster occurs most commonly in elderly and immunocompromised individuals, reflecting a decreased number of circulating VZV-responsive $CD4^+$ T cells (Hayward and Herberger 1987; Hayward et al 1991). Unless adults are vaccinated, the incidence of zoster is likely to increase in the growing elderly population, who experience a natural decline in CMI to VZV (Miller 1980; Berger et al 1981) and will have fewer immune boosts from exposure to sick children (Brisson et al 2000; Brisson et al 2002; Goldman 2005). Further, the number of patients treated with immunosuppressive drugs and radiotherapy is increasing, as well as the number of immunosuppressed organ transplant recipients. Finally, the number of AIDS patients increases every year, and they have the highest incidence of zoster, including recurrent and more protracted zoster (Gilden et al 1994). Overall, zoster may be viewed in the context of a continuum in immunodeficient individuals, ranging from a natural decline in VZV-specific CMI with age, to more serious immune deficits seen in cancer patients and transplant recipients, and ultimately in patients with AIDS (Gilden et al 2003).

Burden of illness (BOI)

The zoster BOI is felt by both the patient and society. Although pain and rash usually occur within a few days of each other, the rash of zoster may be preceded by pain for as long as 100 days (Gilden et al 1991; Fristad et al 2002). The pain of acute zoster typically lasts 4–6 weeks and adversely affects activity, mood, interpersonal relationships, sleep and general quality of life (Oster et al 2005; Scott et al 2006). More than 40% of zoster patients over age 60 years experience pain for months or years after resolution of rash (PHN) (Bowsher 1994). The cause of PHN is unknown. Correlative clinical, pathological and virological studies support the hypothesis that PHN may result from persistent virus infection in ganglia (reviewed in Gilden et al 2005).

The zoster BOI to society is reflected in the cost of lost productivity and added cost of providing clinical care. Current estimates of zoster in the United States are from 600,000 to 1,000,000 new cases per year (Goldman 2005, Insinga et al 2005). The estimated mean healthcare provider cost alone, excluding the additional burden of PHN, is $280 per zoster case (Goldman 2005).

Varicella vaccine

Attenuated Oka varicella vaccine was developed by passaging VZV isolated from a 3-year-old boy 11 times in human embryonic lung (HEL) cells, 6–7 times in guinea pig embryo (GPE) cells and 2–6 times in human diploid WI-38 cells (Takahashi et al 1974). Vaccine virus effectively induced an immune response without clinical disease in 23 normal susceptible children; the minimum dose required was 200 plaque-forming units (PFUs) (Asano et al 1975; Takahashi et al 1975). Merck laboratories passaged the virus further though different cell lines including HEL, GPE, WI-38, and MRC-5 human diploid fibroblasts to produce the commercial varicella vaccine (Varivax) which contains 1350 PFUs in 0.5 ml of sterile water (Ellis 1995). After 15 years of testing in the US, Japan, Canada and Europe, varicella vaccine was approved for children at high risk for developing severe and even fatal varicella (Gershon 1987). The protective efficacy of the vaccine virus in normal healthy children during the varicella season was determined to be 100% (491 children) in the first year and 96% (163 children) in the second year by a double-blind placebo-controlled study (Kuter et al 1991). In 1995, live attenuated varicella vaccine was licensed by the FDA for use in individuals at least 12 months of age who have not had varicella. Like wild-type virus, Oka/Merck vaccine virus becomes latent in ganglia and can reactivate to produce zoster (Gelb et al 1987; Brunell and Argaw 2000). To date, the rate of zoster in vaccinated children is comparable to that in healthy children after natural varicella (http://www.varivax.com).

Characteristics of Oka vaccine

Compared to wild-type VZV, Oka vaccine virus produces smaller plaques in HEL cells at 39 °C and grows better at 34 °C (Breuer 2001). In tissue culture, Oka vaccine virus is less efficient than wild-type VZV in spreading from infected T-cells in tissue culture to melanoma cells (Soong et al 2000). While the DNA sequence of parental Oka and vaccine strains of VZV is predominantly similar, 63 mutations in the latter have been detected (LaRussa et al 1992; Hawrami and Breuer 1997; Gomi et al 2002; Cohrs et al 2006). DNA sequence analysis of virus recovered from zoster patients who had been vaccinated earlier showed that nucleotide changes in Oka vaccine virus remained stable after passage through humans (Argaw et al 2000).

Cell-mediated immunity (CMI) and humoral immunity to varicella vaccine

Vaccination of adults with the Oka/Merck vaccine virus produces both antibody and CMI responses within 3 months (Hayward et al 1992). Significantly, CMI to VZV is more important than humoral immunity and correlates with protection from virus reactivation (Zoulek 1985). In adults, two doses of vaccine are required to produce the same magnitude of CMI response produced with one dose of vaccine in children, likely reflecting the natural decline with age in the ability of T-cells to recognize VZV antigens (Arvin and Gershon 1996). In adults, periodic exposure to varicella probably boosts both CMI as well as the humoral response to VZV. The maintenance of high antibody values in vaccinees is explained by endogenous reactivation of the Oka vaccine virus (Krause and Klinman 2000).

Efficacy (short- and moderate-term), safety and tolerability

A randomized single-blind study using different doses (280–28,000 pfu) of live vaccine in 95 healthy VZV-seropositive adults, showed that virus was well-tolerated over a wide range of viral dosage. At 72 hours after vaccination, localized reactions at the site of inoculation were found with doses >2800 PFU (Sperber et al 1992). In 419 children and adolescents who were given a booster dose (3300 pfu) of vaccine 6 years after primary immunization, no serious adverse events were encountered; 180/298 (60%) of the vaccinees developed a 4-fold rise in VZV antibody titers, and CMI to VZV increased (Watson et al 1995). A 12-year follow-up of vaccinated adults who had previously been seronegative or had lost detectable antibody over a 3-month period showed protection from chickenpox (Ampofo et al 2002). Grose (2005) has suggested that genetic variability among wild-type VZV strains may account for differences in the effectiveness of Oka vaccine in Japanese and American children, but these differences have not yet been examined among adults receiving the zoster vaccine.

Zoster vaccine

The VZV vaccine studies and scope of the zoster problem set the stage for the large-scale double-blind, placebo-controlled, multi-center Shingles Prevention Study (SPS) to determine the effect of VZV vaccination in preventing zoster (Oxman et al 2005). Otherwise healthy adults age 60 or older (median age 69 years) were vaccinated with placebo or an attenuated Oka/Merck-VZV vaccine containing 18,700 to 60,000 PFUs of virus, considerably greater than the approximately 1350 PFUs in the Oka/Merck-VZV vaccine administered to American children since 1995. More than 38,000 recipients of the "zoster vaccine" were followed closely for 3 years. The incidence of zoster in the placebo group was 11.1 per 1000-person years. This figure approximates the results of an epidemiological survey performed a decade ago, which revealed zoster exceeding 10 cases per 1000-person years among individuals older than 75 years (Donahue et al 1995). The effect of zoster vaccine was impressive. Compared to placebo, vaccination reduced the incidence of shingles by 51%, the incidence of PHN by 66% and the BOI by 61%.

Like the live childhood varicella vaccine, live zoster vaccine appears to be safe and effective clinically. Overall, serious adverse effects (SAEs) and deaths occurred in 1.4% of both vaccine and placebo recipients. In a subset of more than 6000 subjects who kept daily diaries of minor adverse effects for 42 days, injection site erythema, pain or tenderness, swelling and pruritis were reported in 48% of vaccine recipients compared to 16% of placebo recipients. In the same subset, SAEs were significantly more frequent ($p = 0.03$) in 1.9% of vaccine recipients compared to 1.3% of placebo recipients, although no specific SAE emerged in vaccine recipients. The relative impact of these side effects on the elderly (age ≥ 70) compared to younger patients was not examined but might be important in future analyses, since the at-risk population over age 70 is projected to increase substantially in the coming decades. Although the Oka/Merck VZV vaccine on rare occasions unmasks a childhood immunodeficiency disorder, no cases of disseminated zoster were reported which might have been attributed to zoster vaccine in a person with undiagnosed lymphoma, leukemia or the like.

Quality of life

Various approaches, many of which take into account pain severity as measured on the 0 to 10 Likert scale (0 = no pain, 10 = severe pain), have been taken to measure quality of life in patients with zoster and PHN. The Zoster Brief Pain Inventory (ZBPI) is an assessment containing zoster-specific modifications to the more general Brief Pain Inventory, a widely used questionnaire to evaluate pain. The ZBPI is designed to capture zoster pain severity and interference with functional status in seven spheres of daily life: general activity, mood, walking, work, relations with others, sleep and enjoyment of life. Subjects rate their pain severity on a 0–10 scale when it is at its worst, least, average, and at the time of questionnaire completion. Functional status in all seven spheres is assessed using the same 0–10 scale. The ZBPI worst pain score correlates well with results from the McGill Pain Questionnaire and SF-12, two other commonly used surveys for pain, quality of life and daily living activities (Coplan et al 2004).

When the ZBPI worst pain score is plotted against duration of pain, the area under the curve provides a severity-duration measurement that reflects zoster BOI and is sensitive to changes in incidence, severity and duration (Coplan et al 2004). The resulting BOI measurement correlates favorably with data collected from other commonly used questionnaires, including pain measures from the McGill Pain Inventory, activity of daily living measures from the Zoster Impact Questionnaire and ZBPI, and quality of life measures from the EuroQoL and mental and physical health summaries of the SF-12. The ZBPI and BOI score were the measurement tools chosen to evaluate the effect of zoster vaccine in older individuals (Oxman et al 2005).

Management options

Treatment of herpes zoster with antiviral medication (acyclovir, famcyclovir or valacyclovir) within 72 hours of the onset of rash results in faster healing and a reduced period of pain (Tyring et al 1995, 2000; Wood et al 1996). Of the three drugs, only acyclovir is available generically, but its lower cost must be weighed against its cumbersome five times per day dosing, which may result in reduced patient compliance. Famciclovir and valacyclovir are more expensive, but are preferred by many physicians because of their more convenient three times per day dosing. The effect of antiviral treatment started more than 72 hours after the onset of rash has not been studied.

The use of corticosteroids for herpes zoster is controversial. One study showed that a 3-week course of oral treatment may reduce pain after 2 weeks but with no significant difference from placebo after 3 weeks (Wood et al 1994). In another study, quality of life at 30 days was better with corticosteroid treatment (Whitley et al 1996); however, only adults without significant medical problems such as diabetes or high blood pressure were enrolled, resulting in a disproportionately healthy study population. Thus, those results may not be widely applicable, especially for elderly patients with chronic diseases that may predispose them to zoster. Corticosteroids have no effect on the incidence or severity of PHN. The decision to treat must be balanced against the known risks of corticosteroid therapy.

Early gabapentin treatment during a zoster attack results in less acute pain and may reduce the incidence and severity of PHN (Berry and Petersen 2005). Amitriptyline may have a similar effect (Bowsher 1997). Both medications are postulated to reduce "central sensitization" of pain pathways, resulting in stabilization of the firing threshold of spinal cord neurons in response to afferent sensory stimuli. More clinical studies are needed to evaluate the role of early gabapentin and amitriptyline in zoster to prevent PHN.

Despite antiviral treatment, many shingles patients develop PHN, the most common complication of zoster. Treatment options include opioid analgesics, tricyclic antidepressants, anticonvulsants, topical medications and more invasive therapies such as intrathecal corticosteroids or ganglionic blockade. Based on evidence from Class I or Class II clinical studies, the American Academy of Neurology currently recommends the following medications as moderately or highly effective in the treatment of PHN: gabapentin, pregabalin, tricyclic antidepressants, controlled-release oxycodone or morphine sulfate, and lidocaine patch (Dubinsky et al 2004). These medications were considered to have low levels of side effects. Treatments such as aspirin-based creams or ointments, topical capsaicin, and intrathecal methylpredisolone also have clinical trial data supporting their use, but their efficacy is lower than the first-line agents or their side effects are more limiting. Other treatments such as dorsal root entry zone or stellate ganglion blocks, laser irradiation, and acupuncture are not effective compared to placebo or have only Class IV data supporting their use.

In clinical practice, many PHN sufferers are refractory to available therapy. Patient satisfaction, especially among older individuals, is further compromised by intolerable side effects such as confusion, dizziness, sedation, nausea or other gastrointestinal disturbances. The difficulty of managing PHN indicates the need for a greater understanding of the disease so that treatment can be targeted at the underlying

mechanism(s) of pain. While correlative clinical, virological and pathological data suggest that persistent low-grade VZV activity contributes to PHN pain (reviewed in Gilden et al 2005), and preliminary clinical data on the effect of treatment with intravenous acyclovir followed by oral valacyclovir in patients with PHN suggest that pain can be reduced with antiviral therapy, corroboration of these findings awaits larger double-blind, randomized, placebo-controlled studies.

Conclusion

Zoster vaccine is currently recommended for healthy adults over age 60. One unanswered question is the future risk of zoster in middle-aged adults who were vaccinated in childhood with attenuated VZV compared to the current risk for middle-aged adults, most of whom have had wild-type VZV infection. By 2047, most middle-aged Americans will have received VZV vaccine in childhood. Like wild-type VZV, Oka-VZV vaccine virus becomes latent in ganglia (Gelb et al 1987). If the virus burden is less in ganglia of adults who were vaccinated in infancy, then the incidence of zoster may be reduced compared to those who had naturally occurring chickenpox. On the other hand, CMI to VZV in vaccine recipients may wane over time due to fewer exposures to children with varicella. The desirability of mass childhood varicella vaccination is beyond the scope of this review; however, the impact of this practice on adults may be problematic, at least in the first 50–70 years of a vaccination program (Thomas et al 2002; Brisson et al 2003; Gidding et al 2005; Volpi 2005). The loss of normal boosts to immune responsiveness through exposure to sick children would support the need to vaccinate middle-aged adults. Zoster vaccine would certainly increase CMI to VZV in such individuals, and the boost would likely last for decades.

An earlier discussion of the cost-effectiveness of vaccination (Gilden 2005) emphasized that the SPS used a disease-specific measure, the zoster BOI (Coplan et al 2004) to assess severity of illness among study participants. Herpes zoster BOI scores correlated with Quality Adjusted Life Years (QALYs), the standard denominator of cost-effectiveness (Weinstein et al 1996). The cost-effectiveness of vaccine will depend on its price. For consumers who pay for childhood varicella vaccine (Varivax™), the price is $50–$100 (the sum of the cost of vaccine plus the visit fee). Since the zoster vaccine contains more virus, it might cost more. The durability of zoster vaccine effectiveness and need for booster shots will require further examination (Levin et al 1998). One model suggests that two doses of vaccine at ages 50 and 70 may most effectively reduce the number of cases of shingles (Chapman et al 2003).

Nevertheless, in the SPS, a single dose of zoster vaccine was probably highly cost-effective (in the range of $2,000/QALYs gained, even assuming a vaccine cost of $500). This admittedly rough estimate does not include the cost of complications related to vaccination or provider time required to administer it. However, $2000/QALY is still likely to underestimate cost-effectiveness, since gains in quality of life experienced by vaccine recipients are likely to persist beyond the 3 years of the study. Even if two vaccinations were administered per person, the vaccine should still fall well below the traditional cutoff of $50,000/QALY used to evaluate new therapies, and would appear to be at least as cost-effective as other currently used vaccines (Prosser et al 2004). Zoster vaccine could eventually even be cost-saving, though the complex interaction between varicella vaccination and the incidence of herpes zoster may erode these savings in the near-term (Gidding et al 2005).

The high incidence of zoster found in the SPS placebo group points to an urgent need for effective therapy. While oral antiviral medication shortens the duration of zoster and analgesic medications provide some relief of pain, "an ounce of prevention is worth a pound of cure." Once rash does occur, the effect of rapid and aggressive antiviral or analgesic therapy within the first 72 hours may reduce or even prevent PHN. Comparisons of the cost effectiveness of vaccination and early aggressive treatment of rash will be invaluable in formulating public health recommendations (Volpi 2005). The long-term public health effect of zoster vaccination will need further study, those over age 85 whose CMI response to VZV is likely to be less robust than in people 20–25 years younger. This is important because the Census Bureau projects that by the year 2050, there will be more than 21 million Americans 85 years of age or older (http://www.census.gov/ipc/www/usinterimproj/natprojtab02a.pdf). Vaccination would allow not only a further determination of possible risk to recipients, but also an estimation of vaccine effectiveness in the oldest old. Hopefully, "zoster vaccine" will reduce or eradicate zoster and its related complications, just as measles vaccine has eradicated not only measles, but also measles post-infectious encephalomyelitis and subacute sclerosing panencephalitis in geographical regions where vaccination is used.

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