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REVIEW ARTICLE

Preventing Varicella-Zoster: Advances With the Recombinant Zoster Vaccine

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Prevention strategies against varicella zoster infection include chemoprophylaxis with acyclovir and live attenuated zoster vaccine. However, resistance to acyclovir has been problematic, and safety concerns have limited the use of the live attenuated vaccine in immunosuppressed patients. Recombinant zoster vaccine, made available in 2017 for the immunocompetent host, has been evaluated for safety, immunogenicity, and efficacy in several immunocompromised settings as well. The present review compares the live attenuated vaccine and the recombinant zoster vaccine and highlights data on the use of recombinant zoster vaccine in different immunocompromised states. Robust data are available for the safety, immunogenicity, and efficacy of the recombinant vaccine in the autologous stem cell population, particularly among patients with multiple myeloma. The vaccine appears safe and immunogenic in populations including those with cancer (solid tumors and hematologic malignancies), HIV-infected patients, and renal transplant recipients. Efficacy and safety data in other populations are awaited before use of the recombinant vaccine can be more widespread. It is anticipated that an increased use of the recombinant zoster vaccine, particularly in immunosuppressed patients, would lead to a decreased use of acyclovir prophylaxis.

Keywords. vaccines; varicella-zoster; immune compromised; recombinant DNA vaccine; live attenuated vaccine.

Herpes zoster, a cutaneous or visceral viral infection, is a common clinical problem among older adults and immunocompromised populations such as those with cancer and those undergoing solid organ or stem cell transplantation. For prevention of this serious infection associated with complications, a vaccine has been available for several years. Its use, however, has been limited, as the vaccine contains live attenuated virus that may be hazardous in the setting of immunodeficient states. In 2017, a new recombinant zoster vaccine (RZV) was Food and Drug Administration (FDA) approved for use in immunocompetent patients aged 50 years or older. Because it is a nonlive vaccine containing recombinant glycoprotein E subunit along with an adjuvant system, it poses no apparent threat for the immunocompromised population. The present review will focus on the available data on the live and recombinant vaccines and, importantly, review the data on the new vaccine's efficacy, safety, and immunogenicity in various immunocompromised populations.

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ZOSTER AND DILEMMAS WITH PROPHYLAXIS

Varicella zoster virus (VZV) is a DNA virus of the alpha *Herpesviridae* family. Primary infection with VZV results in varicella or chickenpox, which manifests as an exanthem that begins as macules and progresses to papules and vesicles. After primary infection, the virus establishes permanent latency in the cranial nerves and dorsal root ganglia [1]. Reactivation of VZV occurs later in life, leading to herpes zoster (HZ) infection, commonly manifesting as a painful, unilateral, vesicular, dermatomal rash that typically heals in a few weeks. A common complication of HZ is post-herpetic neuralgia (PHN), which manifests as a chronic pain disorder with increased incidence in the elderly [2], significantly impacting quality of life in those afflicted. The pain is believed to be caused by damaged nerve fibers in the affected nerve root due to necrosis and scarring from the viral infection. VZV-specific cell-mediated immunity (CMI) prevents reactivation and multiplication of latent virus. Progressive decline in CMI is typically seen in the elderly or immunocompromised [3]. About 1 million cases of HZ, predominantly in the elderly, occur in the United States each year.

The incidence of HZ is higher in older adults (age >50 years) and in immunocompromised states such as hematologic malignancies, solid organ and hematopoietic stem cell transplantation, HIV infection, and autoimmune diseases. HZ infection in the immunosuppressed can be more severe, manifesting as disseminated zoster with multiple dermatomal and/or visceral involvement [4]. VZV reactivation has been reported to occur with a frequency of 16%–50%

in patients after allogeneic bone marrow transplantation [5–9], up to 25% in autologous bone marrow transplant recipients [10], 13%–15% in patients with systemic lupus erythematosus on immunosuppression [11, 12], and 30%–40% in HIV-positive patients [13, 14]. Antizoster prophylaxis is included in most institutional guidelines for patients with hematological malignancies such as multiple myeloma and leukemia and for stem cell recipients. Current standard of care for prophylaxis against HZ reactivation in adults following allogeneic and autologous stem cell transplantation is oral acyclovir daily for as long as 1 year after transplant [15]. Duration of prophylaxis may be prolonged even further if the risk of reactivation is deemed high.

Prolonged treatment with acyclovir can be problematic owing to the development of resistance. Acyclovir resistance in herpes has been reported in immune-competent as well as immunocompromised hosts, with higher rates reported in the latter, particularly in the setting of acyclovir prophylaxis [16]. Rates of acyclovir resistance vary among different groups of immunocompromised hosts, with a rate of resistance of 4%–6% in HSV observed among HIV patients [17–19], 11% in HSV patients [19], and 17% in VZV in patients with hematologic malignancies and those undergoing stem cell transplantation [20]. This can create significant challenges in the treatment of HSV or VZV infection. With a similar mechanism of action as acyclovir, ganciclovir and valganciclovir are not active against acyclovir-resistant herpes virus. Alternative drugs to treat resistant cases are foscarnet and cidofovir. Use of foscarnet and cidofovir is limited, as they are only available as intravenous formulations and have a narrow therapeutic index. The 2 agents have significant toxicity potential including myelotoxicity and nephrotoxicity [21]. Pritelivir, a helicase primase inhibitor, a new class of antiviral drug, has been shown to have promise in the treatment of acyclovir-resistant herpes simplex infection [22] and is currently under clinical investigation; however, it has not been found to have activity against VZV. Amenamevir is another potent helicase-primase inhibitor, has activity against HSV (1 and 2) as well as VZV [23], and is approved for the use of herpes zoster in Japan, following completion of a successful clinical trial [24]. Effective antiherpes drugs, in addition to acyclovir, are urgently needed.

AVAILABLE ANTI-VZV VACCINES

The alternative to drugs for prophylaxis is vaccines. Live-attenuated HZ vaccine (Zostavax, manufactured by Merck & Co, Inc., Kenilworth, NJ, USA) was approved by the Food and Drug Administration for use in immunocompetent individuals aged 50 and older [25] and is administered as a single dose. It must be noted that the Centers for Disease Control and Prevention (CDC) does not have a recommendation for routine use of the vaccine in those 50–59 years of age.

The Shingles Prevention Study (SPS), a randomized, double-blind, placebo-controlled study, showed that the incidence of HZ and PHN was significantly reduced with the use of the live attenuated HZ vaccine [26]. However, the efficacy of the vaccine against HZ occurrence decreased with increased age of recipient, with a reported efficacy of 38% in persons aged ≥70 [27]. Studies conducted after the SPS observed that there is waning immunity postvaccination [28–30]. The Short-Term Persistence Substudy [29] demonstrated a decrease in vaccine efficacy for the incidence of HZ from 50% to 40% through 7 years after vaccination, although this was not found to be statistically significant. The Long-Term Persistence Substudy (LTPS) followed vaccine recipients for up to 11 years after vaccination and found that the estimated vaccine efficacy decreased from 51% to 21% [30].

The more recent recombinant subunit vaccine (Shingrix) consists of VZV glycoprotein E (gE) and the AS01B adjuvant system and has been found to be highly immunogenic, with >90% efficacy in adults age >50 years [31]. It was approved by the FDA in 2017 for the prevention of HZ in immunocompetent individuals aged 50 and above [32] and is administered as a 2-dose series. The safety profile of the vaccine is favorable, with few serious adverse events reported. Postlicensure safety data are available [33], and the safety profile of the recombinant vaccine is consistent with that observed in prelicensure trials. Adverse effects (reactogenicity) after receipt of the recombinant vaccine were common and included fever (24%), generalized pain (20%), pain (23%), erythema (21%), and swelling (14%) at the injection site.

There is no trial directly comparing the efficacy and safety of the live attenuated and recombinant zoster vaccines. Table 1 shows the comparative efficacy rates of the 2 vaccines in preventing zoster and post-herpetic neuralgia in the older age groups. RZV had higher efficacy among adults aged >50, with gradual waning of protection over 4 years following vaccination, and thus appears superior to ZVL in reducing the burden of HZ disease [31, 34]. Robust gE-specific antibody and CD4+ T-cell responses are seen with RZV. A strong immune response to the recombinant vaccine (VZV-specific CD4+ T-cell immunity) persisted for 9 years, well beyond the 3–4 years after ZVL. The adjuvant combination is critical for the efficacy and

Table 1. Preventive Efficacies of VZV Vaccines in the Immunocompetent Host

Preventive Efficacy (Age, y)	Live Attenuated Vaccine, %	Recombinant Zoster Vaccine, %
Herpes zoster (50–59)	70	96.6
Herpes zoster (60–69)	64	97.4
Herpes zoster (>70)	38	97.9
Post-herpetic neuralgia (>50)	65.7	91.2
Post-herpetic neuralgia (>70)	66.8	88.8

Abbreviation: VZV, varicella zoster virus.

durability of immune response. AS01 B (adjuvant) was combined with glycoprotein E because of its ability to stimulate both strong CD4+ T-cell and antibody responses in animal models [35]. Potent immunogenicity secondary to the adjuvant system has been demonstrated in immune-competent and immunocompromised hosts [36].

Administration of the recombinant vaccine in patients who had previously received the ZVL has been shown to be immunogenic with a favorable safety profile [37, 38]. In this setting, RZV is recommended to be administered at least 2 months after receipt of ZVL [32]. The recombinant vaccine has also been shown to reduce the impact of zoster on the quality of life of patients who developed breakthrough disease. Curran et al. reported shorter duration and reduced intensity of pain and decreased disruption of daily activities in those who developed breakthrough disease [39]. Vaccination with RZV has also been shown to be more cost-effective than with vaccination with ZVL. In a study conducted by Prosser et al., the cost-effectiveness of the recombinant vaccine was evaluated in comparison to vaccination with ZVL or no vaccination. The primary outcome measure was the incremental cost-effectiveness ratio (ICER), and vaccination with RZV yielded lower cost-effectiveness ratios than vaccination with ZVL. Vaccination with RZV yielded lower total costs than vaccination with ZVL across all age groups due to higher averted disease costs [40].

Another vaccine, inactivated varicella zoster vaccine, licensed by Merck and Co., Inc. (Kenilworth, NJ, USA), has been studied for use in immunocompromised patients in a phase 3 randomized, double-blind, placebo-controlled trial including patients undergoing autologous hematopoietic stem cell transplantation (HSCT) [41]. The investigational vaccine in this trial contained VZV that was inactivated by gamma irradiation. Patients included in the study were those above the age of 18 who were scheduled to receive auto-HSCT within 60 days of enrollment. The regimen required 4 doses; the first dose was given about 30 days before transplantation, and 3 additional monthly doses were administered after transplantation. Study results demonstrated both safety and efficacy of the vaccine over placebo. Patients were followed for a median time of 2.3 years, and the demonstrated vaccine efficacy was 63.8%. However, the development of this vaccine has been discontinued and is no longer pursued.

ROLE OF THE VACCINES IN IMMUNOCOMPROMISED STATES

Currently the CDC recommends the use of both live and recombinant vaccines in persons on low-dose immunosuppression (defined as <20 mg/d of prednisone or equivalent or using inhaled/topical corticosteroids) [25, 32]. Among HIV-infected individuals, both vaccines are contraindicated if CD4 <200 cells/mm^3, while there is no recommendation for those with CD4 >200 cells/mm^3. Either vaccine (live attenuated or the recombinant subunit) is recommended, if age appropriate for the following situations/persons—asplenia/complement deficiencies, end-stage renal disease/hemodialysis, heart/lung disease, alcoholism/chronic liver disease; diabetes; health care personnel; men having sex with men. Overall, it is to be noted that the CDC has given a "preferred" status to the recombinant vaccine over the live attenuated vaccine.

In "classic" immunocompromised states where protection against varicella zoster is highly desirable in view of the high frequency of infection and consequent morbidities, the live attenuated vaccine is contraindicated. Several trials have evaluated the safety and immunogenicity of recombinant (RZV) vaccine in compromised recipients such as autologous hematopoietic cell transplant (HCT) recipients, HIV patients, patients with solid tumors, and renal transplant patients [42–47]. Because of the required long-term follow-up, most trials did not address efficacy. When assessing for immunogenicity, both humoral and cellular immunity were measured. Each trial had predefined terms for cell-mediated immune response and humoral immune response. Immune surrogate for protection is not known; hence, duration of protection is uncertain. Humoral immunity was evaluated by measuring the anti-gE antibody concentration by gE-specific enzyme-linked immunosorbent assay, and cellular immunity (gE-specific CMI response) was measured in peripheral blood mononuclear cells by flow cytometry after stimulation with gE peptides. This assay, which measured 4 activation markers (CD40 ligand [CD40L] interleukin-2 [IL-2], tumor necrosis factor alpha [TNF-alpha], and interferon gamma (IFN-gamma), defined a positive result as the co-expression of 2 or more of these markers by T cells.

ROLE OF RECOMBINANT ZOSTER VACCINE

Autologous HCT Recipients

A phase 1/2 randomized, observer-blinded, placebo-controlled study evaluated the safety and immunogenicity of Hz/Su in autologous HCT recipients (Table 2) [42]. The participants included 121 adults with non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, or acute myeloid leukemia who had undergone autologous hematopoietic stem cell transplant. The subjects were randomized to receive 3 doses of recombinant adjuvanted vaccine or saline shortly after (50–70 days) HCT. The study demonstrated that immune responses, both humoral and cellular, were strong and that the vaccine was immunogenic and response persisted for up to 1 year even when given shortly after hematopoietic cell transplant.

More recently, based on the outcome of the above study, the Zoster Efficacy Study in Patients Undergoing HSCT (ZOE-HSCT) was conducted [43]. It demonstrated significant efficacy of the RZV in adult autologous HSCT recipients. This phase 3 randomized, placebo-controlled trial enrolled 1846 patients with a median follow-up of 21 months. The first dose was

Table 2. Recombinant Herpes Zoster Vaccine Studies in the Immunocompromised Adult Population

Patient Population [Ref]	No. of Patients	Length of Follow-up Postvaccination, mo	Immunogenicity: Vaccine Response Rate, %	
			CMI	Humoral
Autologous HSCT recipients aged ≥18 y [37]	1846	23	93	67
Adults with hematological malignancies receiving chemotherapy [41]	602	13	67	80
Individuals with solid tumors at start of chemotherapy cycle [38]	262	13	50	94
Adults following renal transplantation [40]	264	13	80	71
HIV-infected adults [39]	123	18	90	92–98

Humoral-positive response: ≥4-fold increase in gE-specific antibody concentration after vaccination, compared with the prevaccination level. T-cell-positive response (CMI): ≥2-fold increase in frequency of T cells detected by 2 of 4 activation markers, compared with prevaccination frequencies. The markers are CD40 ligand, interleukin-2, tumor necrosis factor alpha, and interferon-gamma.

Abbreviations: CMI, cell-mediated immunity; gE, glycoprotein E; HSCT, hematopoietic stem cell transplantation.

administered 50–70 days after the transplant, and the second dose 1–2 months thereafter. During the follow-up period, there were 49 confirmed cases of HZ in vaccine recipients and 135 confirmed cases in placebo recipients. Vaccine efficacy in preventing HZ was estimated to be 68.2% in those who received 2 doses and 63.7% in those who received 1 dose. Efficacy was 89% against PHN. Remarkably, efficacy was noted despite the fact that the vaccine was administered within a short period after transplantation, when immune reconstitution is not expected to have occurred.

Patients With Solid Tumors (Prechemotherapy)

A phase 2/3 observer-blinded, multicenter study looked at the safety and immunogenicity of recombinant vaccine vs placebo in 262 patients with solid tumors (STs; the most common diagnoses were breast cancer and colorectal cancer) before or at the start of the chemotherapy cycle [44]. Participants received 2 doses of either recombinant vaccine or placebo 1–2 months apart and were followed for a median duration of 13 months. The study demonstrated that 2 doses of the recombinant vaccine were immunogenic in this population, with persistence of immune responses up to 1 year after the second dose. Vaccination given at the time of chemotherapy resulted in reduced immunogenicity. One case of suspected HZ was reported in the recombinant vaccine group at 1 month after enrollment; however, no cases were reported among those who received both doses of vaccine. Efficacy data were not addressed.

HIV-Infected Patients

Safety and immunogenicity of the recombinant vaccine in comparison with saline in 123 HIV-infected individuals were evaluated [45]. This study was a phase 1/2 randomized, placebo-controlled, multicenter study. Three cohorts of HIV-infected individuals were included: antiretroviral therapy (ART) recipients with a high CD4+ T-cell count (>200 cells/mm^3; n = 94), ART recipients with a CD4+ T-cell count between 50 and 199 cells/mm^3 (n = 14), and ART-naïve adults with a high CD4 T-cell count (>500; n = 15). Subjects enrolled in the study received 3 doses of either the recombinant vaccine or saline and were followed for 18 months postvaccination, with 1 reported case of HZ in the vaccination arm. This study showed that strong cell-mediated immune responses were elicited in the vaccine cohort, and the responses persisted above the vaccine response threshold for at least 1 year after the last dose.

RENAL TRANSPLANT RECIPIENTS

A phase 3, randomized, observer-blinded, placebo-controlled, multicenter trial evaluated recombinant vaccine during renal transplantation [46]. Renal transplant recipients were randomized 1:1 to receive either 2 doses of recombinant Hz/Su vaccine or placebo 1–2 months apart. Transplant recipients were eligible to participate if they were >18 years of age, between 4 and 18 months post-transplantation, had stable renal function, and had no allograft rejection in the 3 months before the first dose of study vaccine. Two hundred sixty-four participants (n = 133 in each arm) were included. This study demonstrated that the recombinant vaccine was immunogenic among the study patients, and both cellular and humoral immunities persisted at 1 year postvaccination. Commonly reported adverse events in the recombinant vaccine participants included injection site pain (87%), myalgia (49.6%), and fever (16%). Importantly, no increase in organ rejection was noted.

Patients With Hematological Malignancies

In this phase 3, multicenter, randomized, placebo-controlled study, adult patients with hematological malignancies were randomly assigned to 2 doses of the recombinant vaccine or placebo during or after chemotherapy treatments [47]. Six hundred six participants were enrolled, of whom 569 were randomized. The most common malignancy was multiple myeloma (23.4% participants), followed by Hodgkin lymphoma (17%), chronic lymphocytic leukemia (14%), non-Hodgkin B-cell lymphoma (14%), acute myeloid leukemia (14%), myelodysplastic syndrome (5%), and non-Hodgkin T-cell lymphoma (5%). The study demonstrated that the vaccine

induced robust humoral and cellular responses when administered during and up to 6 months after chemotherapy. A post hoc analysis revealed a vaccine efficacy of 87.2% against the development of herpes zoster.

Though limited by sample size and duration of observation, available data on the safety and immunogenicity of the recombinant zoster vaccine in several compromised states are promising. Efficacy data in different populations are awaited. Concern remains about the strong adjuvant system in the vaccine and consequent potential complications such as organ rejection in solid organ transplantation, frequency of autoimmune disease, and impact on malignancies. As several immunosuppressive drugs are rapidly entering the market for both malignant and nonmalignant disorders, the role of vaccine is unclear among patients receiving such drugs. Many questions remain. Conducting clinical trials evaluating vaccine efficacy/safety among each immunosuppressed population receiving such drugs may never take place, thus leaving clinicians to make individualized decisions under different circumstances, based on very limited data.

The recombinant vaccine is preferred over the live vaccine in immunocompetent individuals >50 years of age, regardless of a history of varicella zoster or receipt of live vaccine [32]. With a strong adjuvant component, RZV has considerable reactogenicity [33]. With a paucity of data in different immunosuppressed states, the standard practice of acyclovir prophylaxis among compromised hosts is likely to continue while the clinical use of recombinant zoster vaccine gradually becomes more commonplace.

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