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Varicella zoster virus and cardiovascular diseases

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Abstract

Varicella zoster virus (VZV) is a Herpesviridae family double-stranded DNA virus that only affects humans. The first clinical manifestation appears to be varicella, typical of childhood. VZV, on the other hand, becomes latent in ganglion neurons throughout the neuroaxis after primary infection. The VZV reactivates and travels along peripheral nerve fibers in the elderly and immunocompromised individuals, resulting in Zoster. It can, however, spread centrally and infect cerebral and extracranial arteries, resulting in vasculopathy, which can lead to transient ischemic attacks, strokes, aneurysms, cavernous sinus thrombosis, giant cell arteritis, and granulomatous aortitis. Although the mechanisms of virus-induced pathological vascular remodeling are not fully understood, recent research indicates that inflammation and dysregulation of ligand-1 programmed death play a significant role. Few studies, on the other hand, have looked into the role of VZV in cardiovascular disease. As a result, the purpose of this review is to examine the relationship between VZV and cardiovascular disease, the efficacy of the vaccine as a protective mechanism, and the target population of heart disease patients who could benefit from vaccination.

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Introduction

Varicella zoster virus (VZV) is a neurotropic alpha-herpesvirus that only infects humans and infects more than 95% of the world's population. Varicella is typically caused by a primary infection, which is followed by the virus establishing latency in neurons of the cranial nerves, dorsal root and autonomic ganglia along the entire neuroaxis, as well as the adrenal glands. When VZV-specific cell-mediated immunity declines in the elderly and immunocompromised individuals, defects in innate immunity (particularly natural killer cell defects), or the presence of anti-cytokine antibodies, the virus reactivates by one or more ganglia, travels peripherally from nerve fibers to the skin, and causes herpes zoster in the corresponding dermatomes. Post-herpetic neuralgia frequently complicates the secondary manifestation (zoster) [1-7].

Impact of VZV on cardiovascular disease

VZV infections were first linked to VZV neurological vasculopathy in 1919, when it was described as late contralateral hemiplegia after a stroke [8]. There have been numerous reports of heart attacks in the brain, cerebellum, and midbrain as a result of VZV infection since then [9]. The initial theory for vasculopathy was that it was caused by a varicella infection that resulted in granulomatous angiitis [10,11]. VZV has recently been identified as a risk factor for stroke, but there have been few studies on the link between VZV and other cardiovascular diseases, such as myocardial infarction (MI) or heart failure (HF) [12]. Yang *et al.* [13] demonstrated, through a meta-analysis of all relevant studies, that VZV is a cause of cardiovascular events, most likely due to VZV migration from neurons to the cerebral and coronary vascular systems. This can trigger a local inflammatory response, resulting in vessel occlusion and, eventually, ischemia. Indeed, herpes zoster infection can cause ischemia via a variety of mechanisms, including

the production of prothrombotic autoimmune antibodies such as IgM and IgG anticardiolipin and lupus anticoagulant [14]. Antiphospholipid antibodies, on the other hand, have been found in two patients with acute thrombosis of the deep femoral and tibial arteries following varicella pneumonia [15]. Second, delayed vasculopathy can develop as a result of VZV infection due to an autoimmune phenomenon induced by circulating immune complexes [16] (Figure 1). Finally, direct transaxonal VZV diffusion from the dorsal root ganglia can result in vasculopathy and subsequent ischemia characterized by internal elastic lamina rupture, intimal hyperplasia, and decreased smooth muscle cells in the medial layer [17].

Seo *et al*. [18] recently demonstrated that VZV patients who require hospitalization are at risk for cardiovascular disease (CVD), including myocardial infarction (MI), ischemic stroke, and heart failure (HF), and that patients with newly diagnosed CVD are also at risk of serious VZV infection manifestations. As a result, greater emphasis may be warranted in early treatment of patients with VZV and concomitant CVD [19-21].

Effects of the vaccine on cardiovascular disease

A vaccine to prevent VZV in immunocompetent elderly people was approved in 2006 [22]. The VZV vaccine, which was originally developed and licensed as a "varicella vaccine," is a live attenuated vaccine that prevents primary infection with wild-type VZV. However, preliminary research suggested that a higher titer of live attenuated virus would be required to elicit a significant and sustained increase in cell-mediated immunity in the elderly, possibly because the elderly are less responsive to vaccination in general. As a result, the Food and Drug Administration (FDA) approved the zoster vaccine for the prevention of herpes zoster in people aged 60 and up on May 25, 2006. The new commercially available vaccine VZV (Zostavax, Merck) specific for protection against shingles contains a minimum of 19,400 plaque-forming units per dose [23].

The preventive effect of Zostavax, a live zoster vaccine, is thought to be due to its potentiating effect on an elderly person's cell-mediated immunity to VZV, which mimics the immunological benefits of chickenpox exposure of an adult immune to VZV. This pharmacological push pushes cell-mediated immunity to a new set point above the "immunological threshold" below which a person is at risk for zoster [24].

In terms of side effects, varicella-like rashes at the injection site are more common in vaccine recipients within the first 42 days after vaccination. Other more common symptoms and signs at the injection site include erythema, localized pain or tenderness, swelling, and itching [22,25].

The reduced efficacy of the Zostavax vaccine, which reaches 37.6% in over 70s and 18% in over 80s, combined with the contraindication of use in most immunocompromised individuals as a live attenuated vaccine, necessitated the use of a vaccine with different characteristics, both in terms of type and desirable efficacy, considering the problems associated with using the live attenuated vaccine (ZVL).

The new RZV vaccine (Shingrix, GSK) is an inactivated adjuvanted recombinant vaccine indicated for the prevention of HZ and postherpetic neuralgia. It was approved by the FDA in the United States in 2017, and it received the most recent authorization in Europe in 2020 for the extension of use for IC subjects. It is currently available in Italy with indication from the age of 50 for immunocompetent subjects and from the age of 18 for IC subjects.

Shingrix is a non-live subunit vaccine composed of an antigen, the VZV surface structural glycoprotein E, and an adjuvant system AS01B designed to overcome the decline in cell-mediated immunity associated with immunosenescence. These aspects play a critical role in ensuring long-term efficacy and the possibility of use in vulnerable populations by providing broad overall protection to all subjects for which it is indicated.

In the phase III clinical studies ZOE-50 and ZOE-70, conducted on over 30,000 participants, the efficacy of the RZV vaccine exceeded 91.4% in the over 80 population. The two-dose schedule demonstrated protection against HZ in all subjects over 50 with no safety concerns reported.

Several studies have been conducted to assess the efficacy of the RZV vaccine in patients at high risk, and these populations included IC subjects of various types, including those with HIV, transplanted (HSCT), onco-hematological patients, solid tumors, and kidney transplants [26,27].

Discussion

Acute coronary syndrome (ACS) is significantly more common in older patients than in younger patients. This suggests that reactivation of VZV infection in the elderly is associated with more severe complications, including a higher hospitalization rate per case and a longer average hospital stay. As a result, reactivation of VZV infection in the elderly may lead to more complications and a worse prognosis [28]. Herpes zoster antiviral treatment successfully reduced the cumulative risk of ACS. Patients who received inpatient antiviral treatment did, in fact, have more underlying comorbidities and a higher intrinsic risk of developing cardiovascular disease than patients who did not receive antiviral treatment.

Furthermore, there was a higher incidence of comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and cerebrovascular

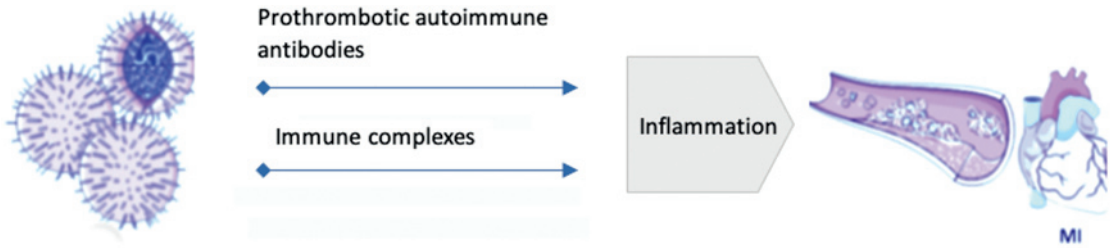

Figure 1. Mechanisms of cardiovascular events associated with varicella zoster virus infection.

events in patients requiring inpatient antiviral therapy. These risk factors are responsible for cellular immunity impairment, which results in both an increased risk of VZV reactivation with subsequent severe manifestations of the infection and an increased risk of cardiovascular disease [20,29].

Heymann *et al*. [30] discovered that people with diabetes mellitus had a significantly higher risk of herpes zoster infection, regardless of age.

Concerning the vaccine, Oxman *et al*. [31] demonstrated that it reduces the risk of VZV reinfection by 51.3% in people over 60, and that it is 66.5% effective in preventing postherpetic neuralgia in this age group, improving both humoral immune responses and the risk of cardiovascular disease due to severe clinical manifestations of VZV [32-34]. Even in patients with cardiovascular risk factors, particularly diabetes mellitus, the vaccine boosts VZV-specific immunity.

Furthermore, it has been demonstrated that the vaccine is more effective at preventing shingles in people aged 60 to 69 than in those aged 70 and older [22].

In an American cohort study by Yang *et al*. [35], administration of the Zostavax vaccine was associated with a 16% reduction in the risk of stroke compared to unvaccinated participants over a median follow-up of 5 years.

VZV vaccination is thus advised in patients with cardiovascular disease who have symptoms such as fatigue, dyspnea, angor, or heartbeat during less than ordinary physical activity (NYHA III) or symptoms at rest (NYHA IV). There is no scientific evidence, however, that vaccination cannot be recommended even in patients who have symptoms during normal physical activity (NYHA II) or no symptoms during normal physical activity (NYHA I) [36,37].

At a one-year follow-up, heart failure patients had a 2.07-fold increased risk of developing herpes zoster infection compared to the general population, according to a cohort study. The underlying mechanism is unknown, though the dysfunction of natural killer cells found in heart failure patients may be related to reactivation [38]. As a result, it can be assumed that herpes zoster vaccination is beneficial in patients with heart failure to prevent herpetic overinfection, which increases the risk of major cardiovascular complications and hospitalization. However, it must be taken into account that chronic heart failure induces an immense expansion of T cells, which contributes to an overall reduction in the pool of naïve T cells and, therefore, a greater degree of immunosenescence. This would account for the observed decrease in vaccine immunogenicity [39].

In addition, data from the literature showed a link between viral infections, including human herpesvirus-8, and angioproliferation and the development of pulmonary arterial hypertension in genetically predisposed subjects [40]. As a result, we can speculate that other Herpesviridae viruses, including VZV, may play a role in pulmonary hypertension. This research may support the use of VZV vaccination in patients with pulmonary arterial hypertension to prevent symptoms from worsening.

Furthermore, sympathetic-vagal discharges are common triggers for paroxysmal AF, and the intrinsic cardiac autonomic nervous system plays a critical role in the initiation and maintenance of atrial fibrillation (AF). Herpes zoster can cause autonomic dysfunction by affecting the nerve ganglia. As a result, patients with herpes zoster have an increased risk of atrial fibrillation, particularly in the severe forms [41].

As a result, given that patients with severe forms of VZV are at risk of CVD, including myocardial infarction and heart failure, and that patients with CVD are at risk of severe manifestations of VZV infection, the vaccination offer could be extended to a large population of cardiopathic patients (Table 1), regardless of NYHA class. The impact of VZV vaccination on the healthy population in the primary prevention of cardiovascular disease remains to be determined.

Table 1. Cardiovascular disorders that could benefit from varicella zoster virus vaccination.

Heart failure
Dilated heart disease awaiting heart transplant
Pulmonary arterial hypertension
Non-revascularized ischemic heart disease
Severe valvulopathies
Atrial fibrillation

Conclusions

Varicella zoster virus causes cardiovascular diseases such as heart failure, ischemic stroke, and myocardial infarction. Furthermore, patients with cardiovascular disease are more likely to develop severe forms of the varicella zoster virus. As a result, in patients with cardiovascular diseases, vaccination is available on active call. More clinical research is needed to determine which cardiovascular diseases would benefit the most from this vaccination and the impact of varicella zoster vaccination in the healthy population in primary prevention of cardiovascular diseases.

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