REVIEW ARTICLE

Herpes zoster infections: epidemiology, diagnostics, and prophylaxis in light of a growing clinical problem

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Hematology in Clinical Practice
2023, vol. 14, 69–79
DOI: 10.5603/hicp.96862

ISSN: 2720–1015
e-ISSN: 2720–2690

Received: August 7, 2023
Accepted: October 12, 2023

ABSTRACT

Herpes zoster (HZ) is an infectious disease that develops from reactivation of latent infection with the of the chickenpox and *varicella zoster* virus (VZV). Particularly vulnerable are the elderly and patients with weakened immune system function, including especially patients with cancers of the hematopoietic and lymphatic systems and lymphatic systems or solid tumors. HZ is often accompanied by complications, most often in the form of herpes zoster neuralgia, hearing or vision loss or vasculopathy. Antiviral prophylaxis reduces the risk of HZ in patients with impaired immune system function, but does not reduce the risk of developing complications, especially neuralgia. For this reason, the importance of immunization against the VZV, especially in groups at increased risk of contracting the disease. The article collects current data on the epidemiology of infection, the course of infection and current opportunities for prevention of HZ infections.

Keywords: *herpes zoster*, *varicella zoster* virus, immunosuppression, hematologic malignancies, vaccinations

INTRODUCTION

Herpes zoster (HZ) is an infectious disease developing due to the reactivation of latent infection with the *varicella zoster* virus (VZV; HHV-3, human herpesvirus-3). The average incidence of HZ in Europe is estimated at 5.23–10.9/1000 person-years. More than 90% of the world's population is carriers of VZV, of which more than 50% experience infection reactivation before the age of 85 [1]. Elderly people and patients with compromised immune systems, in particular patients with hematopoietic and lymphatic malignancies or solid tumors, are at risk of VZV infection reactivation and development of HZ. While the initial infection is usually mild, its reactivation is often accompanied by complications, most often in the form of postherpetic neuralgia (PHN), loss of hearing or vision, or vasculopathy. The mechanism of development of primary HZ infection and reactivation is presented in Figure 1.

ETIOLOGY OF HZ

The etiological factor of HZ is VZV — a virus that causes chickenpox upon first contact and then switches into a latent infection (the so-called latency phase), which may last for many years. Reactivation of VZV infection causes clinical symptoms of HZ. The VZV is able primarily to infect human cells [2]. The virus genome consists of a linear double strand of DNA with a size of approximately 125,000 base pairs. The VZV genome was sequenced for the first time in 1986, and it was determined that it encodes at least 71 unique open reading frames (ORFs) that are expressed during lytic infection [3]. For most VZV ORFs, transcription boundaries are not precisely defined, meaning that transcription start sites and polyadenylation sites are poorly separated. Since the first VZV genome sequencing, additional genes have been identified, including *ORF0*, *ORF9A*, *ORF33.5*, and the recently discovered VZV latency-associated transcript (*VLT*). An important feature of VZV is that the transcription of some genes (including *ORF0*, *ORF42/45*, *ORF50,* and *VLT*) requires activation of the host splicing machinery to remove introns from pre-mRNA, resulting in the synthesis of alternative proteins [4]. Therefore, it appears that the full transcriptional potential of VZV has not yet been revealed [4, 5]. The virion is an icosahedral nucleocapsid, which consists of 162 capsomers additionally covered

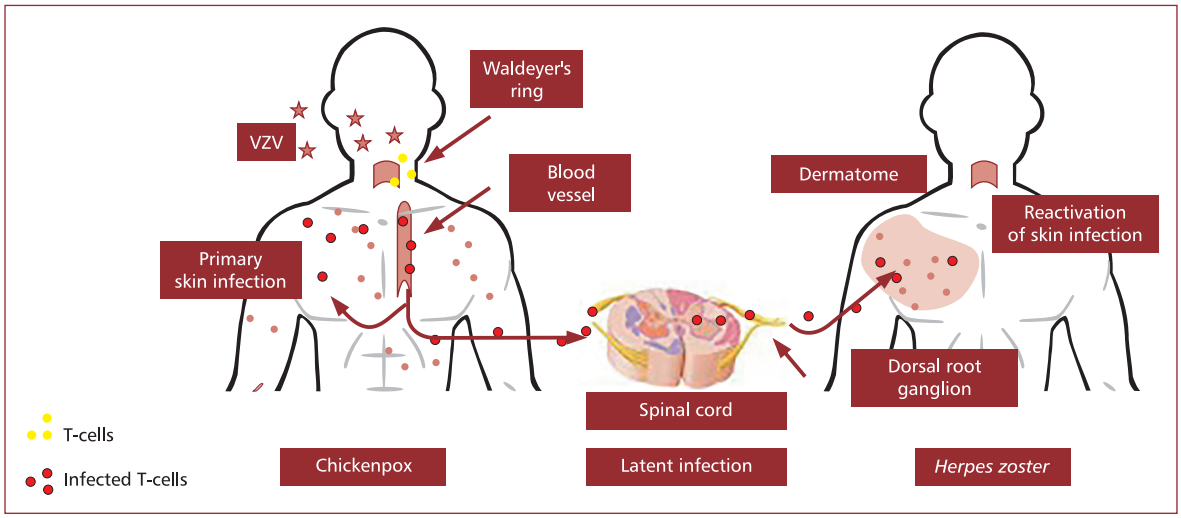

Figure 1. Primary infection and reactivation of *varicella zoster* virus (VZV) infection. In primary infection, VZV causes chickenpox with symptoms such as a vesicular rash that may be visible all over the patient's body. During this time, virions gain access to sensory nerve cells and switch into a latency state (latent infection), which may last for many years. In favorable conditions, mainly related to immunosuppression, the infection reactivates and *herpes zoster* develops. Unlike chickenpox, a rash is limited to one dermatome and is often accompanied by severe pain

with a lipid envelope. The virus particles are pleomorphic and have a diameter of 150 to 200 nm.

SPREAD OF INFECTION

Epidemiological observations indicate that primary VZV infection begins with replication in epithelial cells of upper respiratory tract mucosa, and after an incubation period of 10–21 days, a vesicular rash typical of chickenpox appears. The virus spreads to the tonsils and surrounding lymphoid tissue, from where infected T-cells can carry it through the bloodstream to distant parts of the body. During primary infection, virions gain access to sensory nerve cells through retrograde axonal transport from replication sites in the skin or are carried by infected T lymphocytes. The infection switches into latency status (latent infection) [6]. The VZV is highly associated with infected cells, making it difficult to obtain sufficient amounts of virus for molecular analysis [7, 8]. Under *in vitro* conditions in tissue cultures, VZV produces a cytopathic effect within approximately 3 days of entering cells. The formation of large multinucleated syncytia is observed without the release of significant amounts of stable infectious virions. This effect is mainly observed in the case of infected skin cells or epithelia. In other body cells, such as immune system cells, for which VZV also shows tropism, the formation of multinucleated cell syncytia is not observed, and the virus infects each cell separately [6]. This phenomenon is explained by the fact that VZV has a cell type-specific ability to inhibit cell fusion. The probable cause of this phenomenon is the preservation of the ability of T lymphocytes to move to other tissues, such as skin or sensory ganglia, which explains the development of diffuse skin lesions observed in the course of chickenpox or symptoms accompanying HZ [6, 9].

DIAGNOSIS

In typical cases, in people who have previously had chickenpox, HZ is diagnosed primarily based on characteristic clinical manifestation. When HZ is diagnosed in a person with an impaired immune system, it is advisable to perform additional tests. The causative agent can be identified by detecting the genetic material of the virus using the polymerase chain reaction (PCR), for example in vesicle fluid. It is also possible to identify VZV antigens in infected epidermal cells. Viral antigens are determined by direct immunofluorescence. Serological identification of specific IgG antibodies can also be performed using the enzyme immunoassay enzymatic (ELISA) technique, but this test is used to confirm the existence or acquisition of immunity, and not to establish the diagnosis [10,11].

IMMUNOLOGICAL MECHANISMS IN VZV INFECTION

Despite intensive research on animal models and *in vivo* human cells, the mechanism of VZV spread during infection is not fully understood. VZV was originally classified as a neurotropic alpha-herpesvirus, however, experiments conducted *in vivo* on mice with severe combined immunodeficiency (SCID) and *in vitro* on tonsillar T lymphocytes showed that the virus is also characterized by tropism for T lymphocytes and dendritic cells [6]. Dendritic cells are the first type of immune system cells to be infected by VZV, which occurs already in the respiratory mucosa, then through intensive contact with other immune system cells, mainly T lymphocytes in the tonsils and local lymph nodes, they enable the transmission of the virus to these cells [12, 13]. In light of current knowledge, it is believed that T lymphocytes play a key role in the spread of the virus in the

body. Data regarding the effects of VZV entry into immune system cells are contradictory. Some publications indicate that the entry of VZV into cells does not cause their death, on the contrary — it promotes their survival, among others, by activating the signal transducer and activator of the transcription 3 (STAT3) transcription factor. Flow cytometric studies, including on tonsil T-cells, showed increased expression of activation markers such as CD69, CD279, CD28, CD11a, and CD49d, and signaling molecules such as ZAP-70 and SLP76. Additionally, infected T lymphocytes showed high expression of the so-called homing receptors of CCR4 type (which is chemokines CCL17 and CCL22 receptor) and the cutaneous leukocyte antigen (CLA) molecule, which is a ligand for E-selectin appearing on the surface of skin vessels endothelium under the influence of local cytokine secretion [6, 9]. Other literature data indicate the activation of apoptosis pathways in some types of infected skin cells or immune system cells, such as T and B lymphocytes or monocytes. No activation of apoptosis was observed in neurons, which constitute the virus reservoir during the latency phase [12]. Overall, it is unclear whether specific VZV gene products induce apoptosis as a strategy to enhance viral spread, or whether apoptosis induction is an internal cell response to limit VZV replication and spread.

Efficiently functioning mechanisms of both specific and non-specific responses are necessary to control and alleviate the course of primary VZV infection and prevent its reactivation. Many factors have been identified by which the virus "defends itself" during VZV infection against elimination by the host's immune system, which allows the infection to switch into latent form. Mechanisms of non-specific immune response related to the activity of pattern recognition receptors (PRRs) are inhibited by at least three different viral proteins (*ORF47*, *ORF61,* and *ORF62* gene products). This leads to inhibition of the phosphorylation of interferon regulatory factor-3 (IRF3) and the nuclear factor κB (NFκB)-dependent signaling pathway [9, 14]. The presence of VZV in infected cells reduces the expression of ligands for NKG2D receptors, the binding of which is necessary to activate the functions of natural killer (NK) cells — a key cell population in controlling viral infections. Moreover, VZV reduces the secretion of interferons (IFNs), which are the basic cytokines of the antiviral response. Thus, there is no activation of, for example, NK cells, and the infected cell avoids death [12]. As mentioned earlier, VZV has tropism for dendritic cells. Penetrating inside them, it reduces the expression of co-stimulatory molecules such as CD80, CD83, and CD86, as well as molecules of major histocompatibility complexes (MHC) I and II, thereby inhibiting the process of viral antigen presentation, resulting in inhibition of T lymphocytes antiviral effect [14, 15].

LATENCY PHASE

Latency is the persistence of the complete viral genome in the host's body in an episomal form with limited transcription of viral genes and the ability to reactivate and produce daughter virions. The only confirmed sites where VZV can switch into latent status and reactivate under favorable conditions are the dorsal root ganglions (DRGs) and trigeminal ganglion (TG), where latent viral DNA is maintained as a form of circular episome. It has been shown that during latency, 2–5% of sensory nerve cells contain 5–7 copies of the VZV genome [9]. In autopsy studies in infected people, the presence of VZV was confirmed in the ganglia of the entire nervous axis, also in the ganglia of the autonomic nervous system, including the intestinal ganglia. After a symptom-free period, which may last up to several decades, VZV may reactivate from its latent state in the ganglia, causing the well-known HZ syndrome. The persistence of infection in the latency phase is multifactorial and not fully understood. An important factor is the function of the immune system, which has been confirmed by many observations related to the reactivation of infections in people with compromised immune systems. New light on this knowledge is shed by the results of molecular research in recent years, conducted on human autopsy material, but also on cultures of human neurons generated from pluripotent cells. It was noticed that most of the VZV genome remains inactive during the latency period, and only a small part of the genes retains transcriptional activity [16]. The functions of some of them were recognized; it is possible that the identification of a specific type of viral gene transcript that is expressed during the latency phase will provide clues as to its functional importance in this process, and in the future, it may constitute a potential prognostic factor or target for therapy. So far, it has been described that in the latency phase, the expression of transcripts derived from the *ORF21*, *29*, *62,* and *63* genes are detected. Additionally, cytoplasmic expression of the protein product of the *ORF63* gene has been demonstrated in sensory neuron cells [9]. The expression of the *VLT* transcript was also described, which was confirmed by ultra-deep RNA sequencing studies. It has been shown that the transcriptional activity of viral genes in human ganglia during the latency phase (assessed shortly after death, < 9 h after death is confirmed) is highly limited and is observed primarily in relation to *VLT* and *ORF63* [4]. Currently available data allow to speculate that *VLT* expression may maintain the latency phase by inhibiting *ORF61* gene transcription. Experimental studies on guinea pigs have shown that the expression of the IE61 protein encoded by the *ORF61* gene is necessary for the entry of the IE63 protein into the cell nucleus of enteric neurons, and this protein is most likely crucial for initiating the reactivation of VZV infection. This suggests that VLT-induced repression of *ORF61* transcription and translation may also retain the IE63 protein in the cytoplasm and thus prevent the reactivation of infection [5, 17].

From the immunological point of view, the T-cell response seems to be the most important for maintaining the latency phase, which was confirmed by observations

regarding the increase in the percentage of infection reactivation in the elderly or those with abnormal immune system function, as well as the emerging infiltration of T lymphocytes, mainly CD4+, in sensory nerves in patients during the period of reactivation of VZV infection. High concentrations of the chemokine CXCL10 are considered to be the factor inducing the recruitment of CD4+ lymphocytes to the sites of reactivation of VZV infection. It mainly attracts T lymphocytes and NK cells, which are numerously represented in the cellular infiltrate. During reactivation of VZV infection, a local increase in the concentration of pro-inflammatory cytokines was also observed, such as tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6), which additionally attract and activate B lymphocytes, NK cells, and monocytes [9].

FACTORS PROMOTING REACTIVATION OF VZV INFECTION

After the first infection, the virus lives in a latent form in the intervertebral ganglia, cranial ganglia, or peripheral nerves until conditions favorable for reactivation occur in the body. When the infection reactivates, the first symptom is usually pain in one dermatome (70–80% of cases). Pain episodes are of various natures (the pain may be continuous, intermittent, stabbing, burning, or pulsating) and usually appear a few days before the appearance of skin symptoms. Additionally, fever, malaise, or headaches (flu-like symptoms) may be present. The main factor in the reactivation of VZV infection and the occurrence of HZ is reduced immunity caused by factors such as age over 65 years, diabetes, immunodeficiencies [including infection with the human immunodeficiency virus (HIV)], cancer, especially lymphoproliferative disease, or immunosuppressive treatment leading to non-selective immunosuppression resulting in suppress both the cellular and humoral response [6, 18, 19].

In the course of cancer, impaired immune system functions are observed, which is particularly visible in the case of hematopoietic and lymphatic malignancies, which originate from immune system cells. Patients with hematological malignancies show impaired immune response, both specific and non-specific, which promotes cancer progression, but also manifests itself in greater susceptibility to all types of infections [20–22]. The frequency of viral infections in patients with cancer, especially hematological malignancy, is significantly higher than in healthy people, and their course is more severe and could be even fatal. Infections mainly concern clinical entities associated with the reactivation of herpes viruses, such as herpes simplex virus (HSV), VZV, cytomegalovirus (CMV), or Epstein-Bárr virus (EBV). Patients are also at risk of respiratory infections caused by influenza, parainfluenza, or respiratory syncytial virus (RSV) [23–25]. The main risk factor for the reactivation of a clinically significant infection is a profound disruption of the cellular response. The risk of viral infections increases primarily with the intensity and duration of T-cell functional suppression. This has been confirmed in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT) or in patients treated with monoclonal antibodies, e.g. alemtuzumab. The duration and depth of neutropenia are less important and have less impact on the risk of viral infections [23]. It has been shown that patients with cellular response deficiencies are much more likely to experience serious complications in the course of HZ, mainly PHN [26, 27]. McKay et al. [24] performed a meta-analysis regarding the risk of HZ in immunosuppressed patients in the US population. The study was based on the analysis of over 3,700 publications and assessed the cumulative risk of HZ and its complications in immunosuppressed patients divided into five groups: solid organ recipients, patients with solid tumors, patients with hematological malignancies, patients after HSCT and HIV carriers. The results of the pooled analysis indicated that the groups with the highest risk of HZ (and its complications) are patients after HSCT and patients with hematological malignancies [27]. Reactivation of VZV infection is reported in approximately 25% of pediatric allo-HSCT recipients up to 1 year after transplantation. In children whose reason for transplantation was acute leukemia, HZ developed significantly more often than in the case of other reasons for transplantation and occurred in as many as 38% of patients. This was associated with low pretransplant T-cell counts, especially in the CD4+ T-cell subpopulation [28]. In the case of autologous hematopoietic stem cell transplantation (auto-HSCT) adult recipients, the rate of VZV infection reactivation was estimated at approximately 25% [29]. However, after allo-HSCT, VZV reactivation occurred in 41% of patients on average 227 days after transplantation. Approximately 12% of VZV reactivation cases occurred in the first 100 days and 88% occurred in the first 24 months. Reactivation of VZV infection was the cause of death in approximately 10% of patients [30]. In the case of lymphoproliferative diseases, HZ occurs in approximately 25% of patients with plasma cell myeloma (PCM), Hodgkin lymphoma (HL), and chronic lymphocytic leukemia (CLL) and more than 6% of patients with non-Hodgkin lymphoma receiving immunosuppressive drugs [31]. A lower risk of reactivation of VZV infection has been demonstrated in solid organ transplant recipients, in patients with solid tumors, and then in HIV carriers. However, large differences in risk were observed within each of the five basic groups of immunosuppression causes. It can be noted that the risk of reactivation of VZV infection in HSCT recipients depends on the type of transplantation, type of underlying disease, rate of renewal of hematopoiesis, and the treatment used [24]. In patients after solid organ transplantation, the incidence of HZ is estimated at 8–11% in the first 4 years after transplantation [32, 33]. Also in this group, there is a dependence on the intensity and type of immunosuppressive therapy, as well as on the type of transplanted organ. In heart and lung transplant recipients, HZ occurs more often than in liver or kidney transplant recipients [24, 33]. The group of patients at risk of VZV re-

infection are HIV carriers. The incidence of HZ is estimated to be 12–17 times higher in people infected with HIV than in people not infected with this virus. Even after initiation of antiretroviral therapy (ART), the incidence of HZ remains 2–3 times higher among HIV-infected people, especially immediately after antiretroviral therapy (ART) initiation [34]. Overall, the risk of reactivation of VZV infection in patients with hematological malignancies is approximately 5 times higher than in the general population and 2 times higher in patients with solid tumors than in the general population. Moreover, the duration of infection in patients with hematological malignancies is longer than in patients with solid tumors, and the risk of HZ in both groups of patients is higher in patients undergoing chemotherapy-inducing immunosuppression [26, 27, 35].

REACTIVATION OF VZV INFECTION

Symptomatic reactivation of VZV, which leads to HZ and related pathologies, usually occurs only once or twice during the life of an infected person. Two events are probably necessary for it — bypassing existing immune protection mechanisms, which becomes possible when the immune system is compromised, and a stimulus from a latently infected neuron [4]. First, 70–80% of patients experience pain in one dermatome, which may be accompanied by itching, tingling, and other paresthesia — usually 3–4 days before the appearance of skin lesions. Additionally, fever, malaise, and headaches may be present. Then, skin eruptions appear in the form of a polymorphic rash located within one dermatome - small, erythematous, and spotted, and after 1–2 days they develop vesicles filled with clear or turbid serous fluid. After another 4–5 days, the blisters burst and leave behind painful erosions and ulcers, which then become covered with scabs. New skin lesions appear in waves; after 3–4 weeks, the scabs begin to fall off and the lesions heal, leaving discoloration and scars. Eruptions appear in clusters on the skin area innervated by branches of sensory nerves of the trunk or head in areas innervated by cranial nerves [18, 27]. Environmental factors and molecular mechanisms leading directly to the reactivation of VZV infection have so far been partially understood. Clinical observations of HZ occurring in patients after neurological injuries or neurosurgical procedures indicate that one of the elements triggering reactivation may be peripheral signals reaching nerve cells latently infected with VZV. Two main signaling pathways are involved in VZV reactivation: the phosphatidylinositol 3-kinase (PI3K)–Akt pathway and the mitogen-activated protein kinase (MAPK) pathway. Experimental models have shown that the activation of these signaling pathways is inhibited by the association of nerve growth factor (NGF) with its receptor (TrkA, tropomyosin receptor kinase A) in sensory neurons. Experimental removal of NGF leads to phosphorylation of proteins, mainly in the MAPK pathway, such as JNK (c-Jun, N-terminal kinase), which results in activation of lytic gene promoters and reactivation of VZV infection [4]. During lytic infection, over 70 VZV genes are activated in a cascade, including the so-called early (regulatory) and late (structural) genes, including genes encoding nine types of glycoproteins. One of them is glycoprotein E, which, together with glycoprotein I, is necessary for the infection of T lymphocytes, while glycoprotein B and the heterodimer formed by glycoprotein H and glycoprotein L are crucial in the process of cell–cell fusion and the formation of multinucleated syncytia in infected skin [9]. Glycoprotein E is highly expressed in VZV-infected cells and is immunogenic to the host immune system [8].

COMPLICATIONS IN PATIENTS WITH VZV REACTIVATION

The most common debilitating complication of HZ is PHN, characterized by the persistence of neuropathic pain and dysesthesia (impaired sensation) for weeks, months, and even years after the rash has resolved. The incidence of PHN increases significantly with age [27]. Globally, the incidence of PHN ranges from 5% to more than 30%, depending on the study, age distribution, and definition of PHN, with more than 30% of PHN patients experiencing pain lasting for more than 12 months. Immunosuppressed patients may develop chronic cutaneous VZV reactivation that persists for many months and sometimes even several years. Pain caused by acute neuritis and PHN are the most important complications of HZ in most patients, which, due to the high severity of the symptoms, significantly reduce the patient's quality of life. It is estimated that, depending on the patient group, PHN may occur in 25–50% of patients over 50 years of age [18, 27]. Both the mechanism of VZV-induced acute pain and progression to PHN remain unclear [18]. Other serious complications of HZ include ocular involvement that may lead to blindness and neurological complications resulting, for example, in hearing loss, vasculopathies, and associated strokes. In the United States, HZ is associated with the loss of over 60,000 years in terms of quality of life (QoL) $2.4 billion of direct medical costs, and loss of productivity [36].

PROPHYLAXIS OF VZV IN IMMUNOSUPPRESSED PATIENTS

Reactivation of latent infections is of great clinical importance, therefore antiviral prophylaxis plays an important role in patients who may develop immunosuppression as a result of cancer, anticancer treatment, or other factors that suppress the immune system. In immunocompromised patients, HZ usually has a more severe course than in healthy people. The skin eruption phase lasts longer and may be more extensive, and may also involve internal organs and develop pneumonia, hepatitis, or abnormalities in the nervous system, including PHN. The occurrence of HZ may cause the patient to postpone anticancer therapy, which

Table 1. Drugs used in the prevention of *varicella zoster* virus infections (sources [18, 39])

Drug	Dosage	Comments
Aciclovir	Adults:	
	• 5 × 800 mg/day (*p.o.*)	Limited bioavailability
	• 3 × 500 mg/day	In mild HZ
	• 3–5 × 10 mg/kg bw/day (i.v.)	In severe HZ in immunosuppressed patients (treatment lasts up to 10 days; usually 5–7 days)
	Children: 3 × 500 mg/m^2 BSA/day (*p.o.*)	Maximum daily dose 2.5 g
Brivudine	Adults: 125 mg/day (once, *p.o.*)	Administration for 5 days
Valaciclovir	Adults: 3 × 1,000 mg/day (*p.o.*)	Administration for 7 days
Famciclovir	Adults: 3 × 250–300 mg/day	In the 2nd-line of treatment in patients resistant to acyclovir

BSA — body surface area; bw — body weight; HZ — *herpes zoster*; i.v. — intravenously; *p.o.* (*per os*) — orally

further emphasizes the importance of antiviral prophylaxis [23]. The guidelines of the National Comprehensive Cancer Network (NCCN), the Infectious Diseases Society of America (IDSA), and the American Society of Oncology (ASCO) recommend antiviral prophylaxis in patients with immunosuppression due to the high risk of reactivation of VZV infection and its complications [27]. Drugs standardly used in prevention and their dosages are given in Table 1. All currently registered antiviral drugs used in the treatment of VZV infection have a mechanism of action based on blocking viral replication by inhibiting DNA polymerase or the viral helicase–primase enzyme complex [27]. The results of clinical trials indicate that prophylactic treatment with acyclovir in VZV-seropositive patients undergoing allo-HSCT significantly reduces the risk of VZV reactivation compared to placebo when implemented up to one year after transplantation [37, 38]. Low-dose acyclovir prophylaxis during the first year after transplantation has also been shown to be effective in preventing VZV reactivation in auto-HSCT recipients [35].

Anticancer therapy, through its immunosuppressive effect, also exposes patients to an additional increased risk of VZV reactivation. Prophylaxis is recommended for people treated with purine analogs, such as fludarabine, 2-chlorodeoxyadenosine (2-CDA), or pentostatin because they lead to CD4+ T-cells depletion. Antiviral prophylaxis should be started when the patient is affected by at least one of the following factors: age over 65 years, subsequent line of treatment, taking corticosteroids, CD4+ T-cell count below 50/μL, grade III or IV neutropenia [40]. The HZ has been reported in approximately 13% of CLL patients treated with fludarabine. A significant decrease in the number of CD4+ and CD8+T-cells persists in most patients for the first three cycles of fludarabine and then stabilizes. However, the percentage of HZ cases in this group of patients decreases over time after completion of fludarabine treatment, which is related to the normalization of the cellular composition and functions of the immune system [41, 42]. Similarly, in the case of therapy with a monoclonal antibody such as anti-CD52 (e.g. alemtuzumab), Janus kinase inhibitors (e.g. baricitinib, ruxolitinib, tofacitinib), anti-CCR4 drugs (e.g. mogamulizumab) and steroid, used for example for the treatment of graft-versus-host disease (GvHD), antiviral prophylaxis is also recommended [37, 43]. Drugs used to treat PCM directed against CD38 molecule (e.g. daratumumab) or proteasome inhibitors (e.g. bortezomib, carfilzomib, ixazomib) also increase the risk of reactivation of VZV infection. The study results indicate that the use of bortezomib in particular is associated with an increased risk of HZ. The recommendations of the NCCN and European working groups recommend antiviral prophylaxis in patients treated with these drugs [44, 45]. TNF-α inhibitors (e.g. adalimumab, certolizumab, etanercept, golimumab) may increase the risk of VZV reactivation [43]. Conflicting data are published regarding infliximab, which is also a TNF-α inhibitor. A survey conducted among over 2,000 participants treated with this drug did not show an increase in the incidence of HZ compared to those not treated with infliximab [18]. Anti-CD20 monoclonal antibodies (e.g. obinutuzumab, rituximab), anti-CD30 monoclonal antibodies (e.g. brentuximab vedotin), and PI3K inhibitors (e.g. idelalisib, buparlisib) also increase the risk of VZV reactivation, especially with concomitant use of other immunosuppressive drugs. Similarly, other biological drugs, such as anti-SLAMF7 antibodies (e.g. elotuzumab), IL-6 inhibitors (e.g. sarilumab, tocilizumab), or B-cell receptor (BCR) inhibitors, may increase the risk of HZ and in if they are used, the introduction of antiviral prophylaxis should also be considered on an individual basis [43, 46].

VACCINATIONS AGAINST HZ

Antiviral prophylaxis reduces the risk of reactivation of VZV infection in patients with compromised immune systems but does not reduce the risk of complications in the course of HZ, especially the risk of PHN. Similarly, in the case of treatment of patients with HZ, low effectiveness in preventing PHN is observed. It is estimated that this low effectiveness results, among others, from too late initiation of antiviral treatment (regardless of the drug used) or the need to modify doses depending on kidney function [39]. For many reasons, the use of vaccinations in people at increased risk of reactivation of VZV infection is an important option. Groundbreaking observations by Dr. Hope-Simpson in the 1960s [47] and the development of the live attenuated VZV *Oka vaccine* (*vOka*) by Takahashi et al. [48] led to the development and introduction of vaccines against HZ. Vaccinations against HZ have a different nature and functions than classic vaccinations. They are used in people who, in the vast majority of cases, have already had

Table 2. Main features of the Zostavax® and Shingrix® vaccines (sources [36, 39])

Characteristic	Zostavax® live attenuated vaccine (Merck)	Shingrix® recombinant vaccine (GlaxoSmithKline)
Vaccine ingredients	Lyophilizate containing the Oka strain and sterile diluent	Lyophilized gE antigen and a suspension containing AS01B adjuvant
Storage	From +2°C to +8°C	From +2°C to +8°C
Shelf-life	18 months	36 months
Dosage	1 dose for subcutaneous or intramuscular administration (0.65 mL)	2 doses for intramuscular administration at intervals 2–6 months; 2 × 0.5 mL
Efficacy against VZV reactivation	51.3%	97.2%
Efficacy in preventing PHN	66.5%	91.2%
Immune response stimulation	Weak	Strong

PHN — postherpetic neuralgia; VZV — *varicella zoster* virus

a primary VZV infection and have developed a response to it, but this response is insufficient and the remaining latent virus may be reactivated and cause HZ. To be effective, the vaccine must act as a so-called therapeutic vaccine — inducing a stronger specific response against VZV and preventing infection reactivation. An additional challenge is obtaining an effective response against VZV in patients with immunodeficiency, i.e. elderly people, patients with hematological malignancies and solid tumors, and other groups of patients with immunosuppression. Currently, two vaccines are registered for use against VZV reactivation; their characteristics are presented in Table 2. The former is the live attenuated Zostavax® vaccine (by Merck) intended for healthy people over 50 years of age. The presence of cancer and reduced immunity are contraindications to its use due to possible side effects, including death [27]. Clinical trial results indicate that the vaccine effectiveness is 70% in people aged 50–59 and decreases with age, being 64% in people aged 60–69 and only 18% in people over 80. Moreover, its effectiveness is limited in time, protecting 62% of vaccine recipients in the first year after vaccination and only 40% in the fifth year after vaccination [49, 50]. The effectiveness of the Zostavax® vaccine in preventing the occurrence of PHN was determined to be 66.5% in the group of patients over 60 years of age [51]. The second vaccine, Shingrix® (by GlaxoSmithKline), is the result of research aimed at developing a more effective and safer preparation that can also be used in immunosuppressed people — it is a recombinant vaccine containing VZV glycoprotein E, which has strong immunogenic properties and can effectively induce a specific immune response [36]. This is confirmed by published results of clinical trials. Cunningham et al. [52] assessed the effectiveness of the vaccine within 36 months of administration in a group of people over 50 years of age. It was shown that 97.9% of vaccinated people responded effectively to vaccination and developed a specific humoral response in the form of anti-gE antibodies directed against viral glycoprotein E. More than 99% of vaccinated people produced antibodies specific for glycoprotein E at the beginning of the study, and antibody titers were similar in each age group (> 50 years of age vs. > 70 years of age). The highest titers of anti-gE antibodies were observed 1 month after the second dose of vaccination, and then the concentrations decreased. This was especially noted in participants over 70 years of age when assessed 36 months after the second dose. However, in both age groups, antibody concentrations remained above the humoral response threshold in more than 75% of vaccinees 36 months after the second dose.

These clinical trials also assessed the cellular response to vaccination with Shingrix®. The percentage of CD4+ T-cells with the phenotype of memory cells and effector cells was assessed and the induction of the production of gE-specific CD4+ T-cells was demonstrated in over 90% of vaccinated people. Peak CD4+ T-cell levels were observed similarly to the humoral response 1 month after the second vaccine dose. The percentages then decreased until the 12th month after the second dose, after which the CD4+ T-cell level stabilized and remained until the end of the follow-up. Interestingly, better responses were seen in people over 70 years of age than in people under 70 years of age, but this may also be due to a lower baseline CD4+ T-cell percentage in people over 70 years of age, so the difference may be more pronounced. At 36 months after the second dose, CD4+ lymphocyte levels were still above the cut-off point in approximately 50% of vaccinated individuals [53]. The results of another study assessing the effectiveness of the immune response to vaccination with a recombinant vaccine confirm previous reports. The specific immune response against VZV glycoprotein E maintains at a high level (> 87%) and for a long time (4 years) [54]. The recombinant vaccine containing glycoprotein E stimulates the immune response, especially the humoral component, much more effectively than the live attenuated vaccine. A better response may result from the AS01B adjuvant system used, which enhances the antigen presentation process by increasing the number of activated antigen-presenting cells and stimulating the activity of T lymphocytes, macrophages, and secretion of gamma interferon (IFN-γ), which inhibits virus multiplication [52, 54, 55]. Due to the presence of an adjuvant that strongly stimulates the immune response and the use of one strong antigen, glycoprotein E, the recombinant vaccine is also recommended for immunosuppressed people. When using a recombinant vaccine, there is no risk of developing HZ, which happened in the case of a live attenuated vaccine used in people with compromised immune systems [56, 57]. Moreover, clinical trial results indicate that the

recombinant vaccine shows 67% effectiveness in PHN prevention [51, 53].

SAFETY AND EFFECTIVENESS OF RECOMBINANT VACCINE IN PATIENTS WITH COMPROMISED IMMUNE SYSTEM

The use of a live attenuated vaccine in patients with compromised immune systems is associated with the risk of HZ occurrence [56, 57]. Clinical trials with recombinant vaccines indicate its safety and high effectiveness also in patients with impaired immune system functions.

In 2019, the results of a phase III clinical trial on the immunogenicity and safety of the recombinant vaccine against HZ in adult patients with hematological malignancies during or after anticancer treatment were published. A total of 562 patients were enrolled in the study, including 23.7% with PCM, 17.3% with HL, 14.8% with CLL, 14.5% with B-cell lymphoma, and 4.6% patients with T-cell lymphoma. The remaining 25% were patients with other hematologic malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and myelodysplastic syndrome (MDS). Patients qualified for the group vaccinated with the recombinant vaccine received two doses, and then the effect of vaccination on humoral and cellular response in patients with hematological malignancies was examined. In all groups, the induction of a specific immune response was demonstrated, both humoral and cellular. In the case of cellular response, the percentage of CD4+ T-cells with intracellular expression of at least two of the following activation markers was assessed: IL-2 or INF-γ or TNF-α, CD40L. The level of cells assessed was comparable to that obtained after vaccinations in healthy people over 50 years of age. In the case of humoral response, the results obtained in patients with hematological malignancies were also satisfactory (the titer of antibodies specific to glycoprotein E was assessed), but not as good as for cellular response [31]. The weakest response to vaccination was observed in patients with CLL and B-cell lymphoma who were treated with anti-CD20 antibodies (e.g. rituximab). These results confirm previous observations [58, 59]. With regard to the effectiveness of HZ prevention in patients with hematological malignancies, the study showed an effectiveness of 87.2%, persisting 12 months after the second dose, and the number and severity of post-vaccination reactions were minor and similar to those in the placebo group. A separate analysis for each type of hematologic malignancy was not performed concerning the incidence of HZ in vaccinated persons due to the small overall number of HZ cases in the study cohort [31]. Parrino et al. [60] presents the results of a phase I clinical trial on the safety and effectiveness of live attenuated vaccine in patients with hematological malignancies treated with anti-CD20 antibodies. The study showed that the vaccine had an immunostimulatory effect by stimulating T-cells, but did not assess the humoral response. The study also showed that after four doses of the vaccine, 73.8% of patients experienced adverse events, including fever in 25% and diarrhea in 13.8%, but there was no increase in the number or severity of these events after administration of subsequent doses of the vaccine. One patient died, but this was not considered as vaccination-related. However, in the literature, there are descriptions of deaths in patients with hematological malignancies, which are associated with the administration of a live attenuated vaccine against HZ [56]. Comparing the results of both studies, the use of the recombinant vaccine brings more benefits, requires only two doses, and is associated with a lower risk of adverse events.

The risk of developing HZ increases after auto-HSCT due to a reduced number of T lymphocytes then decreases after 2–3 years as the immune system functions improve. During this period, antiviral prophylaxis is commonly used in patients after auto-HSCT to prevent HZ and its complications. The effectiveness of prevention depends on the patient's compliance regarding taking antiviral drugs. The duration of preventive treatment is not specified in the recommendations, therefore there is a high risk of HZ occurring if prophylaxis is stopped too early or in non-compliant patients. The best solution is vaccination, which can provide long-term protection against HZ. The use of a live vaccine is not recommended due to the risk of HZ. The results of the phase III clinical trial on the use of the recombinant vaccine in patients after auto-HSCT indicate its effectiveness in preventing HZ, which was estimated at 68.2% in patients who received two doses of the vaccine and 63.7% in patients who received only one dose [61]. The humoral response after vaccination was weaker than in people who had not previously undergone auto-HSCT [53, 61]. However, the cellular response was at a comparable level as in healthy people over 50 years of age [61]. This is related to the hematological disease, but also to the immunosuppressive treatment that patients receive before auto-HSCT. Despite this, the benefits of using a recombinant vaccine are significant compared to a live attenuated vaccine. The recombinant vaccine requires only two doses (not 4 as in the case of the live attenuated vaccine), moreover, in the case of vaccination with a live attenuated vaccine, the first administration should take place one month before the auto-HSCT procedure, which may be logistically difficult. When assessing the recombinant vaccine in allo-HSCT recipients, its effectiveness and safety were similarly demonstrated to be much better than that of the live vaccine. Koldehoff et al. [30] showed that the recombinant vaccine induced a much stronger cellular and humoral response than the live vaccine.

Even though organ transplant recipients are less exposed to HZ than patients with hematological malignancies undergoing HSCT procedures, the risk of HZ is approximately 9 times higher in this group of patients than in the general population. The results of observations of patients after kidney transplantation (taking daily immunosuppressive drugs) who were vaccinated with a recom-

binant vaccine indicate the safety and effectiveness of the preparation. In the study kidney transplant recipients were divided into two groups; the first received a placebo and the second received two doses of the recombinant vaccine. The cellular response (assessment of the percentage of antigen-specific CD4+ T-cells) and the humoral response (assessment of the titer of specific anti-gE antibodies) were assessed. In vaccinated patients after kidney transplantation, the percentage of CD4+ lymphocytes and the titer of anti-gE antibodies were significantly higher than in the placebo group, and the response persisted for at least 12 months after vaccination. No significant adverse events or impact of vaccination on the functioning of the transplanted kidney were observed [62].

The results of another clinical trial published by Vink et al. [63] indicate the safety and effectiveness of recombinant vaccines in patients with solid tumors. The vaccination was administered in two groups. The first group consisted of patients before starting chemotherapy, and the second group included those who had already started treatment. It was observed that vaccination was well tolerated in both groups and both groups responded positively to vaccination. However, patients vaccinated between 8 and 30 days before the start of chemotherapy showed a stronger humoral response than the group vaccinated after the start of anticancer treatment. Vaccinating a patient with solid tumors at least a week before starting immunosuppressive treatment was sufficient to develop an immune response and protect against HZ.

The incidence of HZ in people living with HIV in the era of ART is lower than before its introduction, but the risk is still 2–3 times higher than in the general population [64, 65]. The randomized phase I/II clinical trial analyzed the safety and immunogenicity of the recombinant vaccine compared to placebo. The results indicate the effectiveness of inducing a T-cell response in 64.5% of HIV-infected people, which lasted longer than 12 months. Similar results were obtained in the induction of the humoral response. HIV-infected patients, due to their immunosuppression, received three doses of the vaccine, but the study showed that the third dose did not change the titer of specific antibodies or the percentage of CD4+ T lymphocytes. The vaccine was well tolerated. Few mild symptoms were recorded, such as pain at the injection site or weakness, and there was no adverse effect on HIV load [66].

CONCLUSION

The results of many clinical trials indicate much greater safety of recombinant vaccine than the older live attenuated vaccine in the group of patients with compromised immune systems. The recombinant vaccine, by introducing one strong antigen in combination with an adjuvant system, effectively induces a specific immune response, both humoral and cellular, also in patients with immune system disorders resulting from hematologic malignancies, solid tumors, immunosuppressive treatment, or HIV infection. Study results confirm that immunity against HZ persists in some cases even 4 years after the second vaccine dose. Moreover, it has been shown that, apart from significantly reducing the risk of developing HZ, vaccination also reduces the incidence of complications, including PHN. The introduction of the recombinant vaccine to the Polish market took place in March 2023 and is an important option for the prevention of HZ in the group of immunosuppressed patients.

Article Information and Declarations

Acknowledgments: Not applicable.

Author contributions: PW — concept, writing the article. KG — concept, author of the article.

Conflict of interest: PW — no conflict of interest. KG — participation in the Advisory Board and fees from GlaxoSmithKline.

Funding: None.

Supplementary materials: None.

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