ARTYKUŁ PRZEGLĄDOWY REVIEW ARTICLE
DOI: 10.24292/01.OT.150724.1

Treatments of *Herpes zoster ophthalmicus*: an overview of current therapeutic and prophylactic strategies

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HIGHLIGHTS

Herpes zoster ophthalmicus can lead to many dangerous complications. Proper prevention and immediate initiation of treatment in case of the disease's onset are extremely important.

ABSTRACT

Shingles and its complications are a significant issue in medicine, primarily affecting the elderly. The condition is caused by the reactivation of infection by a virus, whose primary clinical manifestation is chickenpox. A particular form of shingles is the ocular type, where changes occur along the branches of the trigeminal nerve. During the course of the disease, numerous symptoms concerning the eyeball may occur, and the patient is exposed to many dangerous and troublesome complications. In the following article, we will present available therapeutic and preventive options aimed at treating and preventing *Herpes zoster ophthalmicus*.

Key words: shingles, herpes zoster ophthalmicus, ocular shingles, therapeutic options, preventing options, chickenpox

INTRODUCTION

Shingles is a secondary disease resulting from the reactivation of infection with the *Varicella zoster virus* (VZV). It can occur in individuals who have had chickenpox, regardless of the severity of the clinical course of the disease [1]. VZV resides in the cells of the dorsal root ganglia and cranial nerves for many years in a latent form. The reactivation of the virus mainly occurs in older people due to reduced immunity in this population. Conditions leading to immunosuppression, such as infections, medication intake or malignancies, can also trigger the reactivation of the virus [2]. Subsequently, the virus undergoes dynamic replication and travels along nerves to the skin. The most common location of shingles is the intercostal nerves, while involvement of the first branch of the trigeminal nerve can lead to a sight-threatening condition known as ocular shingles [1].

EPIDEMIOLOGY

Over time following chickenpox infection, the immunity determined by the level of memory T lymphocytes against the virus decreases, increasing the risk of developing shingles. Individuals with reduced immunity and impaired T lymphocyte response are more susceptible to shingles and a more severe course of the disease. This group includes individuals over 65 years old, organ and hematopoietic stem cell transplant recipients, patients receiving immunosuppressive treatment, and patients with lymphoma, leukaemia, or HIV infection. About 20% of individuals who have had primary infection experience later reactivation. After the age of 85, the risk increases to 50% [3, 4]. Furthermore, recent studies conducted in the United States of America highlight a correlation between COVID-19 infection and an increased risk of shingles [5]. Chickenpox is the most commonly reported infectious disease in Poland and is additionally characterized by high infectivity. It is estimated that over 90% of the Polish population over 40 years of age has had chickenpox, often without even realizing it. This implies that the majority of older individuals in Poland are at risk of developing shingles [1]. In approximately 10–20% of VZV infections, the ophthalmic branch of the fifth cranial nerve is affected. Without prompt antiviral treatment, ocular symptoms can occur in up to 50% of these patients [4]. Complications in patients with ocular shingles are particularly dangerous and can lead to blindness.

COURSE OF THE DISEASE

Ocular shingles, as a reactivation of latent VZV infection, causes inflammation of periocular and perineuronal tissues due to involvement of the ophthalmic branch of the trigeminal nerve (V1), which innervates the skin of the lateral aspect of the nose, as well as the face and head above the eyelid margin. The onset of shingles begins with systemic symptoms resembling flu-like symptoms, including fever. Their duration is estimated to be around 7 days. Subsequently, localized symptoms appear, including discomfort in the skin, eyeball, and resulting from nerve paralysis. More characteristic are the so-called prodromes within the dermatome. These include itching, tingling, numbness, and pain of varying intensity. Often accompanying these sensations is a feeling of pulsation or stabbing nerve pain characterized by stinging or burning sensations. It can affect the eyeball itself or other areas within the dermatome innervated by the trigeminal nerve. The pain occurs intermittently, often at night. Sometimes it persists for a long time, even after the resolution of other symptoms – this is known as postherpetic neuralgia (PHN). Approximately 2–3 days after the initial symptoms, skin eruptions appear in the eyelid, nose, and forehead area. They usually occur unilaterally. The maculopapular rash progresses to papules, then vesicles and pustules on an erythematous base, which may leave erosions, crusts, and scars. The eruptions usually resolve within a month unless bacterial or fungal superinfection occurs. Ocular symptoms typically appear a few days after the onset of the first skin eruptions but rarely dominate the clinical picture of the disease. The likelihood of ocular involvement increases if Hutchinson's sign is present – involvement of the nasociliary nerve, resulting in vesicles on the upper eyelid, lateral aspect, and tip of the nose [6]. The VZV can attack any structure comprising the eye. Inflammatory complications of ocular structures can even lead to vision loss, and the overall disease process with severe neuralgia can result in depressive disorders. According to virologists' research, an acute episode of shingles, including the ocular form, increases the risk of stroke or transient ischemic attack (TIA). The highest likelihood exists in the first month after onset, although it may persist for up to a year [7].

OCULAR SYMPTOMS AND COMPLICATIONS

Conjunctivitis

Conjunctivitis in the course of ocular shingles may affect over half of patients. It is almost always unilateral and resembles viral conjunctivitis, accompanying typical skin changes and systemic symptoms [8]. It often presents as mucopurulent conjunctivitis with accompanying vesicles on the eyelid margin. Typically, it lasts up to two weeks and is self-limiting. However, careful patient observation and cautious treatment are necessary, as it may develop into a chronic form.

Keratitis

Keratitis is one of the most common manifestations of ocular shingles. Patients with corneal involvement may experience a decrease in corneal sensation, and the disease process can affect each layer of the cornea. One of the

discussed types of keratitis is punctate superficial keratitis with pseudodendritic changes (acute epithelial keratitis). It occurs in over half of ocular shingles cases during the first week of ocular involvement. It usually resolves within a few days without treatment. Pseudodendrites are described as small, numerous star-shaped or dendritic lesions that stain with fluorescein and rose bengal. They are smaller and more elongated than "true" dendrites caused by the common herpes simplex virus (*Herpesviridae*). They do not have central ulcers and are pointedly terminated without bulbous swellings at the ends [9]. Discoid keratitis, on the other hand, occurs as a later change, usually in the second week of the disease. Characteristic are numerous, finely granular deposits surrounded by a halo of stromal haze, accumulating beneath Bowman's layer. After healing, residual "discoid scars" often remain. Untreated progressive discoid keratitis can lead to necrotizing interstitial keratitis. It is characterized by infiltrates in the stroma, thinning of the cornea, and the possibility of perforation. It may occur from 3 months to several years after the onset of the rash. Another described type is disciform keratitis (5% of cases) – it appears 3 weeks after the rash. It presents with the presence of disc-shaped opacities in Descemet's membrane, caused by cellular infiltration and oedema of the adjacent stroma and epithelium. The centrally affected proper substance of the cornea is surrounded by a ring of deposits of viral antigen-antibody complexes, known as Wessely ring. Untreated disciform keratitis can lead to secondary scarring and accumulation of lipid deposits in the corneal stroma. Additionally, changes occupying the central part of the cornea significantly worsen visual acuity [10]. Neurotrophic keratitis manifests as a damage to the corneal nerve, resulting in reduced or absent corneal sensitivity. It is a chronic form of keratitis, appearing as a late and very rare complication of ocular shingles. It causes permanent loss of epithelium, thinning, and even perforation. The last of the discussed – keratitis with the presence of mucous plaques, may develop between the third and sixth month after the onset of skin changes. Both loss of corneal sensation and severe pain can persist for months after the resolution of corneal changes [11].

Anterior uveitis

Develops within the first three weeks from the onset of skin changes, affecting 40–50% of patients (more often >50 years old) with ocular shingles. It involves the acute inflammation of the iris, ciliary body, and anterior chamber. Symptoms that may accompany patients include a sensation of a foreign body in the eye, blurred vision, eye pain, redness, and photophobia. The inflammation may take on a mild and asymptomatic form, but in some patients, it may present with fibrinous reaction, *hypopyon*, and elevated levels of white blood cells. Ophthalmic examination reveals conjunctival irritation, the presence of inflammatory cells, and deposits on the corneal endothelium. In severe cases, secondary iris atrophy may occur [6].

Acute retinal necrosis

A rare but highly dangerous manifestation of ocular shingles. In its initial period, it may affect one eye, although in most cases acute retinal necrosis is bilateral. It occurs in individuals with both normal and reduced immunity. Acute retinal necrosis, caused by VZV infection, more commonly affects older individuals, with both sexes equally affected [12]. It is characterized by varying courses – from mild vision disturbances with floaters to sudden and painful deterioration of visual acuity. The onset of the disease is marked by granulomatous anterior uveitis, vitritis, and retinal involvement in the form of multifocal, deep infiltrates and perivascular inflammation. The changes spread peripherally, leading to confluent necrosis, posing a risk of blindness. Involvement of the second eye typically occurs within the first 6 weeks, although it may also occur even after several years from the onset of the disease [13].

Secondary glaucoma

Glaucoma is a group of eye diseases characterized by progressive optic nerve atrophy, with typical changes in the appearance of the optic nerve head and progressive changes in the visual field. These changes are usually accompanied by elevated intraocular pressure due to impaired aqueous humour outflow. Secondary open-angle glaucoma is a rare consequence of ocular shingles. It is believed that the most likely mechanism of impaired aqueous humour outflow in VZV infection is swelling of the trabecular meshwork structures due to the ongoing inflammatory process [14].

Postherpetic neuralgia

Neuralgia is considered postherpetic when painful symptoms persist for more than 4 months after the onset of the rash [15]. Reactivation of the virus in the trigeminal nerve ganglia leads to inflammation and destruction of neurons. Active or smouldering VZV infection causes inflammatory reactions and sometimes necrosis within the dorsal root ganglia, sympathetic ganglia, and peripheral nerves. Central and peripheral sensitization occurs. Spontaneous discharges in neurons lower the pain threshold over time, and the pain response becomes disproportionate to the stimulus. Patients experience peripheral hyperalgesia or hypoesthesia. Significant loss of nociceptive afferent neurons is believed to be the cause of constant pain, while demyelination and reorganization of Aβ fibres result in paroxysmal pain. Allodynia may occur if nerves are completely damaged [16]. The likelihood of chronic neuralgia increases with age, especially in females. Additionally, the risk is higher in diabetic patients and individuals with immunodeficiencies. Strong pain preceding skin eruptions or involvement

of multiple dermatomes during the disease also increases the risk of this complication. In the literature, inflammation affecting the first branch of the trigeminal nerve is mentioned as a risk factor for more severe PHN. On the other hand, early initiation of antiviral therapy, within 72 h of the first signs of rash, reduces the likelihood and severity of PHN [17].

Ophthalmoplegia

Infection with ocular shingles may be associated with unilateral ophthalmoplegia due to paralysis of the eye muscles. Ophthalmoplegia, despite its clinical appearance, is a disorder of the nervous system rather than the visual organ. Symptoms primarily result from abnormalities within the oculomotor nerve. Damage to the motor fibres of the third cranial nerve results in outward and downward deviation of the eyeball and drooping of the upper eyelid due to paralysis of the *levator palpebrae superioris* muscle. Pathology of the parasympathetic fibres of this nerve leads to pupil dilation and loss of accommodation. The mechanism of spreading the inflammatory process is not fully understood; one hypothesis is the spread of infection through continuity in areas of neighbouring cranial nerves supplying the visual organ [18].

TREATMENT

Oral medications

The most popular choice for antiviral treatment is orally administered acyclovir (p.o., *per os*) at a dose of 800 mg 5 times daily for 7–10 days. Other options include oral valacyclovir at 1000 mg 3 times daily for 7 days or oral famciclovir at 500 mg 3 times daily for 7 days [19]. Currently available and used medications in Poland are acyclovir and valacyclovir. Studies show similar efficacy and tolerance for both drugs, but valacyclovir has a simpler dosing regimen [20]. The ocular form of shingles requires pharmacotherapy to be initiated promptly after the onset of the first symptoms. Prompt administration of antiviral drugs largely reduces the risk of complications, especially PHN, and influences the severity of the disease course. The optimal time to start treatment is within 72 h, which allows for the avoidance of late ocular complications even in 50% of patients. However, it has been proven that patients can still benefit from medication after this time [20, 21]. Oral corticosteroids may be added to antiviral treatment to reduce swelling and inflammation. An example is prednisone at 40–60 mg daily, with a gradual reduction in dose after 4 days of use [19]. Pain symptoms can be managed starting from paracetamol or nonsteroidal anti-inflammatory drugs, progressing to weak and strong opioids along with co-analgesics (gabapentin, pregabalin, amitriptyline) [22].

Intravenous medications

Intravenous treatment is required for patients with immunodeficiencies, malignant tumours, organ transplant recipients, or disseminated shingles [3]. An additional indication for hospitalization and intravenous treatment is the complication of ocular shingles in the form of acute retinal necrosis [13]. The most commonly used medication is intravenous acyclovir, with a recommended dose of 5–10 mg/kg body weight every 8 h for 7–10 days. If clinical symptoms resolve and the patient's condition improves, transitioning back to oral medication administration is possible [3].

Topical treatment

The use of antiviral ointments on skin lesions is not recommended. The primary focus should be on proper drying, disinfection, and applying cold compresses. Acyclovir ointment can be used for epithelial keratitis. In other forms of keratitis such as punctate epithelial keratitis, stromal keratitis, and disciform keratitis, or in anterior uveitis, topical corticosteroids are indicated [23]. For conjunctivitis, the use of 3% acyclovir eye ointment or 0.15% ganciclovir eye gel may be considered. Additionally, topical antibiotics in eye drops can be used to prevent potential secondary bacterial infections [8]. In cases of anterior segment involvement, the use of cycloplegics such as atropine or scopolamine is recommended. For secondary glaucoma complications, intraocular pressure-lowering medications may be utilized. In patients with immunodeficiency and acute retinal necrosis, intravitreal antiviral therapy may be indicated [3]. For PHN, surface-acting agents such as EMLA cream (a mixture of lidocaine and prilocaine), lidocaine patches 5% [24], or creams containing capsaicin 8% can be used. Additional pain relief options include lidocaine 1% nerve blocks, sympathetic nerve blocks, or extradural blocks. Their effectiveness is highest within the early period (1–4 months), and beyond 12 months, it is considered minimal. High-frequency current nerve ablation (RFA) is also mentioned for pain conduction cessation [17].

PREVENTION

The infectivity of herpes zoster is significantly lower than that of chickenpox, but potential risk of infection involves contact with the secretions from the blistering rash on the patient's body [19]. It's important to note the possibility of virus transmission to individuals who have not had chickenpox and have not been vaccinated against it [25]. Vaccination against VZV is a key element of prevention and can bring significant benefits to patients worldwide [1]. According to the Vaccination Schedule for 2024, varicella vaccination is not mandatory. However, exceptions are made for children and adolescents up to 19 years old who belong to high-risk groups for severe disease or complications, as well as for

those in close contact with particularly vulnerable individuals. In these cases, varicella vaccination is mandatory. There is also a group of individuals who have not had chickenpox and have not been previously vaccinated, but for whom vaccination is recommended. This includes women planning pregnancy, medical students, and healthcare workers [26]. Post-exposure prophylaxis is possible for healthy individuals susceptible to chickenpox, involving vaccination within 72 h of contact with an infected person. In Poland, there are two vaccines available containing live, attenuated VZV strains, recommended from the 9th month of life according to a two-dose schedule with a minimum interval of 6 weeks between doses [27, 28]. Since the second quarter of 2023, a newer vaccine has also been available, which is an inactivated and recombinant vaccine containing a fragment of the VZV (glycoprotein E) virus and an adjuvant system. Unlike its predecessors, it aims to prevent herpes zoster and PHN in individuals who have had contact with VZV, but it does not prevent primary chickenpox infection. Currently, it is recommended to administer two doses of the vaccine (2–3 months apart) to individuals over 50 years of age and adults at increased risk of herpes zoster. The dosing schedule may be modified in certain indications [29]. The vaccine's efficacy in preventing herpes zoster can last up to 10 years after vaccination, it is well-tolerated, and has minimal risk of adverse reactions. The vaccine has also been shown to be effective against PHN, one of the most common and debilitating complications of the disease [30].

CONCLUSION

Herpes zoster ophthalmicus is not the most common form of VZV reactivation, but it can lead to many distant complications. With the aging population, increasing incidence of cancer, more frequent use of immunosuppressive therapies, higher prevalence of lifestyle diseases, and the recent COVID-19 pandemic, an increase in shingles incidence can be expected. It is important to remember that early diagnosis and treatment of this disease are crucial in minimizing the risk of its severe course. The most effective method of protection against shingles is vaccination, both against varicella-zoster virus in children and against herpes zoster in older individuals.

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Authors' contributions:
All authors have equal contribution to the paper.

Conflict of interest:
None.

Financial support:
None.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.