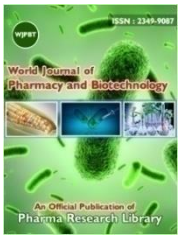

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A Review on Novel Pharmacotherapeutic Approaches for the Prevention and Management of Varicella-Zoster Virus Infections

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A B S T R A C T

Varicella-zoster virus (VZV), also known as human herpesvirus 3 (HHV-3) has a double-stranded DNA genome of 125 kb, encoding for approximately 71 open reading frames (ORFs). The herpesvirus family includes three subfamilies, α, β, and γ-herpesvirinae. VZV together with herpes simplex virus 1 and 2 (HSV-1 and HSV-2) belong to the α-herpesvirinae, characterized by establishment of latency in neurons. VZV is the causative agent of chickenpox (varicella), a common infantile illness. Like all herpesviruses, VZV undergoes a lifelong latent state following primary infection. During latency, the viral DNA persists in the dorsal root ganglia and cranial root ganglia. VZV reactivation produces skin lesions characteristic of herpes zoster (shingles), causing significant morbidity, but rarely mortality. Herpes zoster is characterized by a localized rash in a unilateral, dermatomal distribution and is often associated with severe neuropathic pain. VZV is highly infectious and enters the body via the respiratory tract, followed by rapid spread from the pharyngeal lymphoid tissue to circulating T lymphocytes. After 10–21 days, the virus arrives at the skin, producing the typical vesicular rash characteristic of varicella. In most individuals, VZV infection results in lifelong immunity. A potential anti-VZV drug candidate needs to be at least as effective and safe as the gold standard of treatment for HZ, i.e., valacyclovir. It will need to have also some advantages over valacyclovir, such as longer intracellular half-life allowing once a day dosing, superior efficacy, independence of TK for activation and/or target another enzyme than the DNA polymerase.

Keywords: Varicella-zoster virus, Skin lesions, Dermatomal distribution, Lifelong immunity, Gold standard of treatment

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Chickenpox is caused by primary infection with varicella zoster virus. In healthy people, it is usually a mild, self-limiting illness, characterized by low-grade fever, malaise, and a generalized, itchy, vesicular rash. However, severe disease can develop leading to pneumonitis, hepatitis, thrombocytopenia, or encephalitis. Risk of severe disease is higher in pregnancy, in neonates (<28 days of life), and in people who are immunocompromised due to medication or disease. In most people, infection is uncomplicated. The most common complication in immunocompetent people is secondary bacterial skin infection, often seen in children younger than 5 years of age. Less commonly, acute cerebellar ataxia can occur in older children. At all ages, infection can be complicated by soft tissue or deeper invasive group A streptococcal infection. Following primary infection, the varicella zoster virus remains latent in the body. Subsequently, it can re-activate to cause herpes

zoster[1-3]. Chickenpox, or varicella, is a contagious disease caused by the varicella-zoster virus (VZV). The virus causes chickenpox, typically a primary infection in nonimmune hosts, and herpes zoster, or shingles, which results from the reactivation of a latent infection. In 1767, Heberden first differentiated chickenpox from smallpox.

The word "chickenpox" has been thought to come from either the French word "chiche-pois," which means "chickpea" (referring to the size of the vesicles), or the Old English word "gigan," which means "to itch." The association between varicella and herpes zoster was initially identified in 1888, when von Bokay documented the onset of varicella in children after contact with individuals with herpes zoster illness. Kundratitz (1922) and Bruusgaard (1932) more conclusively established the correlation between the 2 diseases through the occurrence of varicella in susceptible infants implanted with vesicle fluid from patients with herpes zoster. The discovery of the same virus in both cases confirmed their identical etiologies.

Chickenpox is an airborne disease spread worldwide by coughing, sneezing, and contact with skin lesions. Symptoms begin 10 to 21 days after exposure; the average incubation period is about 2 weeks. Chickenpox results in a skin rash forming small, itchy blisters that scab over. The rash typically starts on the chest, back, and face and then spreads, accompanied by fever, fatigue, pharyngitis, and headaches, usually lasting 5 to 7 days. The virus may spread 1 to 2 days before the rash appears until all lesions are crusted over. Complications include pneumonia, brain inflammation, and bacterial skin infections. The disease is more severe in adults than in children.

Chickenpox is diagnosed based on the presenting symptoms and confirmed by polymerase chain reaction testing of the blister fluid or scabs. Tests for antibodies may be performed to determine if immunity is present. Although reinfections by varicella may occur, these reinfections are usually asymptomatic and much milder than the primary infection. Since its introduction in 1995, the varicella vaccine has significantly reduced the number of cases and complications, preventing about 70% to 90% of infections and 95% of severe disease. Routine immunization for children is recommended. Immunization within 3 days of exposure may still improve outcomes in children.

Etiology

Chickenpox, or varicella, is caused by VZV, a herpes virus with worldwide distribution. The virus establishes latency after primary infection, a feature unique to most herpes viruses. Chickenpox is acquired by inhalation of infected aerosolized droplets. This virus is highly contagious and can spread rapidly. The initial infection is in the mucosa of the upper airways. The virus enters the circulation after 2 to 6 days, and another bout of viremia occurs in 10 to 12 days. At this time, the characteristic vesicles appear. Immunoglobulin (Ig)A, IgM, IgG antibodies are produced, but the IgG antibodies confer lifelong immunity. After the primary infection, varicella localizes to sensory nerves and may reactivate later as shingles[4-8].

Risk factors for severe varicella in adolescents and adults are as follows:

- Steroid therapy: doses equivalent to 1 to 2 mg/kg/d of prednisolone administered for 2 weeks or longer are significant risk factors for severe illness. Even brief medication at these dosages shortly before or during the incubation period of varicella can result in severe or fatal varicella.
- Immunocompromised conditions (eg, cancer, antineoplastic agents, human immunodeficiency virus, other congenital or acquired immunodeficiency disorders). Cellular immunodeficiency, as compared to humoral immunodeficiency, is thought to predispose individuals to severe varicella.
- Pregnant women are at an elevated risk of developing severe varicella, particularly pneumonia. Moreover, maternal varicella accompanied by viremia can be transmitted transplacentally to the fetus. This results in newborn varicella. Infants born between 5 days before and 2 days after the onset of the varicella rash in the mother are at the highest risk for serious illness. The first month of a neonate's life is a vulnerable phase for severe varicella, particularly if the mother is seronegative. Delivery before 28 weeks of gestation predisposes a neonate to risk, as transplacental transfer of IgG antibodies occurs following this period.

2. Epidemiology

VZV has a global distribution, with 98% of the adult population being seropositive. Varicella occurs in all countries and is responsible for about 7000 deaths annually. Most cases occur in winter and spring. In the United States, VZV accounts for more than 9000 hospitalizations annually; its highest prevalence is in the 4- to 10-year-old age group. Following the implementation of the varicella vaccine in 1995, the overall incidence of varicella has diminished by approximately 85%, demonstrating evidence of herd immunity. The age of peak incidence transitioned from 5 to 9 years to 10 to 14 years, of age and an increased occurrence of breakthrough varicella among vaccinated children in the later age group prompted the inclusion of a second varicella vaccine dose in the standard childhood immunization schedule in 2006. Varicella is typically symptomatic, and before the introduction of the varicella vaccine, this condition affected 90% of children in the United States by the age of 10. Herpes zoster signifies the reactivation of latent VZV infection, occurring in around 20% of healthy adults and 50% of immunocompromised individuals, with considerable morbidity and mortality in the latter group. Secondary cases in household contacts tend to have more severe disease than primary cases. In the tropics, varicella tends to occur in older people and may cause more serious disease. A case has been recently reported in a patient who is 81 years old[9].

Pathophysiology

The causative agent, VZV, belongs to the human herpesvirus subfamily Alphaherpesvirinae and is a

deoxyribonucleic acid virus similar to all herpesviruses. The virus invades via the respiratory system (conjunctival or upper respiratory mucosa) and establishes itself in the upper respiratory tract. Viral replication occurs in regional lymph nodes within 2 to 4 days; then, 4 to 6 days later, primary viremia disseminates the virus to reticuloendothelial cells in the spleen, liver, and other locations.

After a week, a secondary viremia propagates the virus to the internal organs and skin, resulting in the characteristic skin lesions. This viremia disseminates the virus to the respiratory regions and facilitates the transmission of varicella before the onset of the rash. During this period, infections of the central nervous system or liver may arise, including encephalitis, hepatitis, or pneumonia.

Varicella can contribute to humoral and cell-mediated immune responses. These responses elicit enduring immunity. Individuals may experience recurrent subclinical infections; however, secondary episodes of chickenpox are exceedingly uncommon in immunocompetent individuals. Reexposure and subclinical infections may enhance the immunity developed following a chickenpox episode. Exposure causes the production of host IgG, IgM, and IgA. IgG antibodies persist for life and confer immunity. Cell-mediated immune responses are important in limiting the duration of primary varicella infection. After primary infection, varicella is theorized to spread from mucosal and epidermal lesions to local sensory nerves; it then remains latent in the dorsal ganglion cells of the sensory nerves. The immune system keeps the virus in check. However, reactivation can still occur later in life, resulting in the clinically distinct syndrome of herpes zoster.

3. Histopathology

Herpes simplex, varicella, and herpes zoster infections exhibit indistinguishable histological features. Intraepidermal vesicles often exhibit ballooning degeneration of keratinocytes together with the presence of multinucleated giant cells, which result from the fusion of infected keratinocytes. A hallmark is acantholysis, where individual keratinocytes separate and float freely within the blister space. These detached cells often display distinctive viral changes, including chromatin clumping at the nuclear edges, the presence of multiple nuclei, and inclusion bodies within the nuclei. Clinical correlation, immunohistochemistry, and viral culture or polymerase chain reaction are necessary to distinguish these viral infections[10-11].

History and Physical

The prodromal symptoms in adolescents and adults are aching muscles, nausea, decreased appetite, and headache, followed by a rash, oral sores, malaise, and a low-grade fever. Oral manifestations may precede the skin rash. In children, the illness may not be preceded by prodromal symptoms, and the initial sign could be a rash or oral cavity lesions. An eruption of pruritic, erythematous macules and papules ensues on the head and face before disseminating to the trunk and limbs. Lesions swiftly develop within approximately 12 hours into 1 to 3 mm clear vesicles encircled by narrow red halos. The quantity of vesicles ranges from a few to several hundred, frequently including the oral mucosa. Sparing of the distal and lower extremities is common. Older vesicles develop into pustules and crusts, with each lesion healing within 7 to 10 days. The existence of lesions at all developmental stages is characteristic of varicella. At the blister stage, intense pruritus is present. Blisters may occur on the palms, soles, and genital area. Commonly, visible evidence develops in the oral cavity and tonsil areas through small ulcers, which can be painful and itchy; this enanthem may precede the external exanthem by 1 to 3 days. These symptoms appear 10 to 21 days after exposure. Adults may have a widespread rash and more prolonged fever, and they are more likely to develop pneumonia, the most critical complication in adults. Because watery nasal discharge containing live virus precedes exanthems by 1 to 2 days, the infected person is contagious 1 to 2 days before recognizing the disease. In most cases, the infection resolves itself within 2 to 4 weeks.

Causes

Chickenpox is caused by the varicella-zoster virus, which is one of the herpes viruses. These viruses spread from one person to another through droplets or direct contact. When someone who is contagious breathes, coughs, sneezes or speaks, tiny droplets of saliva (spit) are released into the air. Chickenpox is usually spread when people breathe in those droplets. Fluid from inside the blisters is also contagious if they break open or are scratched off.

Prevalence

Chickenpox is most likely to affect preschool and school-age children between the ages of 2 and 10. Older children or adults who haven't been vaccinated can also become infected if they didn't have chickenpox when they were younger.

Complications

Chickenpox is often a mild illness in children; nearly all children recover without complications. Varicella in adolescents and adults is typically more severe than in children, characterized by more skin lesions. Significant complications may ensue in adults, immunocompromised individuals, and pregnant women as follows:

A common complication is a secondary bacterial infection that can present as cellulitis, impetigo, or erysipelas, leading to scarring. Adults get deep and more prominent scars. Varicella pneumonia has a 10% to 30% mortality risk if left untreated. Individuals with a history of varicella have a 20% lifetime probability of acquiring zoster. An immunocompetent patient reportedly experienced the simultaneous occurrence of chicken pox and herpes zoster, along with facial nerve palsy. Central nervous system consequences are infrequent (<1 per 1000 instances) and may encompass encephalitis, acute cerebellar ataxia, and Guillain-Barré syndrome. Varicella zoster can harm the arteries in the neck and head, resulting in a stroke. Reye syndrome, characterized by encephalitis and fatty liver, has become rare due to the avoidance of aspirin in children with varicella. Maternal varicella in the initial 20 weeks of gestation is linked to an approximately 2% incidence of

congenital varicella syndrome (varicella embryopathy). Potential congenital anomalies encompass low birth weight, cutaneous scarring, ocular abnormalities, cortical atrophy, psychomotor delay, and hypoplastic limbs. Children whose mothers contracted varicella during gestation may get zoster early in life without ever experiencing extrauterine varicella. Severe neonatal varicella, characterized by the absence of maternal antibody protection, may arise when maternal varicella manifests between 5 days before and 2 days following delivery. Maternal herpes zoster, on the other hand, constitutes little risk of neonatal complications or congenital varicella syndrome, probably because of established circulating maternal antibodies.

Varicella can result in serious complications and potentially fatal outcomes in immunocompromised individuals. These individuals commonly have a broader and unusual cutaneous eruption, sometimes accompanied by hemorrhagic or purpuric lesions. The lungs, liver, and central nervous system are primarily involved. Occasional complications include thrombocytopenia, hepatitis, glomerulonephritis, optic neuritis, keratitis, arthritis, myocarditis, pancreatitis, orchitis, and vasculitis[12-14].

Clinical Symptoms

People who get chickenpox generally feel ill at first. It causes muscle pain and headache, and your body temperature rises. The itchy rash typical of chickenpox develops next – usually on your face and torso first, and later spreading to your scalp, arms and legs. Sometimes mucous membranes and the genitals are also affected. The extreme itching is often the main problem, making it hard to sleep. Adults who have chickenpox may not develop a rash, or it may not spread over their body in the same way as it does in children.

The fever lasts three to five days, but is rarely higher than 39 °C (about 102 °F). The rash starts as small red spots and bumps, which then turn into blisters. The blisters contain clear fluid that later turns cloudy. They dry up after a few days. Scabs form and soon fall off. It usually takes about three to five days for the blisters to heal. Because the blisters on the skin are in different stages of development at any given time, their distribution is sometimes described as a "starry sky." The total number of blisters varies widely from person to person.

Prevention

The vaccination recommendations issued by the German Standing Committee on Vaccination (STIKO) apply to all children over eleven months of age, but also include the following groups, provided they have not had chickenpox already: teenagers, women hoping to get pregnant, and people who have certain other conditions such as severe eczema. In Germany, chickenpox vaccinations are covered by statutory health insurers. The vaccination consists of two injections given at least four to six weeks apart.

If you have never had chickenpox and are not vaccinated, you can still get vaccinated within five days of coming into contact with someone who is infected. Doing that can stop you from developing chickenpox, or at least help make the symptoms milder. Vaccinations should no longer be given during pregnancy. If a pregnant woman is at risk of infection, she can have treatment with antibodies to fight the viruses. This is called passive immunization, and it is also an option for newborns if their mother develops chickenpox a few days before or after the birth.

People who have been immunized can still get chickenpox. That rarely happens, though, and then the symptoms are usually milder. There is also a lower risk of complications. Chickenpox is classified as a notifiable disease in Germany. This means that all doctors must inform their local health authority even if someone is only thought to have chickenpox. If a child is infected, the health authority might then contact the parents to tell them to keep the child at home until he or she is no longer contagious[15-16].

Treatment

As a protective measure, those infected are usually required to stay home while infectious. Keeping nails short and wearing gloves may prevent scratching and reduce the risk of secondary infections. Topical calamine lotion may relieve pruritus. Daily cleansing with warm water helps avoid secondary bacterial infection. Acetaminophen may reduce fever; however, aspirin should be avoided as it may cause Reye syndrome.

Children:

Treatment is symptomatic relief**.** If taken within 24 hours of the start of the rash, acyclovir decreases symptoms by 1 day. Still, acyclovir does not affect complication rates and is not recommended for individuals with normal immune function.

Adults:

Infection tends to be more severe, and treatment with antiviral drugs (acyclovir or valacyclovir) is advised if they can be started within 24 to 48 hours of rash onset. Acyclovir, when initiated within 24 to 72 hours following the appearance of the cutaneous eruption, has demonstrated efficacy in reducing both the length and severity of varicella. Antivirals are typically indicated in adults, including pregnant women, because this group is more prone to complications. The preferred treatment is usually oral therapy, but intravenous antivirals are indicated for immunocompromised patients, especially those undergoing chronic systemic corticosteroid therapy, due to their heightened risk of severe illness and sequelae. Supportive care, such as increasing water intake and using antipyretics and antihistamines, is essential to management. Administration of varicella zoster immune globulin (125 U/10 kg, maximum 625 U) intramuscularly within 96 hours after varicella exposure is advised to offer passive prophylaxis to nonimmune immunocompromised adults, pregnant women, and high-risk neonates. Protection endures for around 3 weeks[17-21]. An alternative for postexposure varicella prophylaxis in these patient populations is the administration of intravenous immunoglobulin (intravenous immunoglobulin; ≥400 mg/kg), which possesses elevated concentrations of varicella-specific IgG. Prophylactic administration of oral acyclovir at standard varicella dosages for 1 week, commencing 7 to 10 days post-exposure, may also be contemplated. Finally, postexposure varicella immunization (given within 72 to 120 hours) may prevent or ameliorate

the disease in nonimmune individuals 12 months and older who are immunocompetent and eligible for this live attenuated vaccine[22-23].

New Antiviral Agents

Current antiviral drugs available for HZ treatment significantly decrease the incidence of new lesion formation, accelerate healing, and shorten the duration of viral shedding thereby reducing the incidence, severity and duration of pain, and limiting neuron damage. The effect on the resolution of pain is extremely important in the antiviral therapy of HZ. Pain associated with HZ can be measured in three ways: (i) pain at presentation (acute pain), quantified over the first 30 days; (ii) PHN (post-herpetic neuralgia), defined as "pain that has not resolved after 30 days of disease onset" or as "pain that persists after healing or pain 90 days after rash onset" and (iii) zoster-associated pain (ZAP), pain recorded from the time of acute zoster until its complete resolution. Acyclovir, valacyclovir and famciclovir are approved worldwide for the treatment of HZ in both immunocompetent and immunocompromised patients, brivudine is available in some European countries, and amenamevir is licensed only in Japan. Valacyclovir proved superior to acyclovir according to ZAP analysis from different clinical studies. Famciclovir and acyclovir were therapeutically equivalent in terms of healing rate and pain resolution in immunocompetent patients aged >50 years. Brivudine proved similar efficacy on pain and rash as well as a similar tolerability compared to famciclovir in a large multicenter study that enrolled patients with acute HZ aged ≥50 years. However, existing antiviral therapies are not completely effective in avoiding PHN, most likely because antivirals should be started within 72 h of rash appearance. The delay between onset of symptoms and start of treatment is likely the major cause of reduced efficacy of antiviral therapy. Clinical trials of antiviral drugs for HZ have enrolled patients within 72 h from rash onset; however, no well-controlled clinical trials comparing early-onset therapy with later therapy (>72 h) have been performed. Therefore, antiviral agents with a higher potency may achieve a more rapid decrease in viral replication consequently reducing neural damage and both acute and chronic symptoms of HZ. In addition, currently available antivirals require 3–5 times daily dosing regimens that need to be modified for patients with renal impairment. The medications used to treat the pain associated with PHN are only palliative, are often insufficient in terms of relief for the patients and do not provide a cure for HZ. Hence, drugs with superior anti-VZV activity, with the ability to prevent PHN, able to provide better pain relief, and with a more simplified dosing regimen are indeed needed. These drugs would also be very useful for the management of disseminated VZV primary infections and complications of VZV reactivation, including VZV vasculopathy, meningoradiculitis, cerebellitis, myelopathy, ocular disease, and zoster sine herpete[24-25].

Novel Anti-VZV Agents in Advanced Development

The gold standard for VZV therapy remains acyclovir and its prodrug valacyclovir. Other nucleoside analogues such as penciclovir, its prodrug famciclovir and brivudine can also be used. These antiviral agents rely on the viral TK for their first phosphorylation and have as target the viral DNA polymerase. VZV mutants arising under pressure with these nucleoside analogues bearing mutations in the viral TK can be treated with foscarnet, a direct inhibitor of viral DNA polymerases. However, foscarnet can be associated with significant renal toxicity and cannot be used for VZV DNA polymerase mutants emerging under acyclovir as most of them show cross-resistance to foscarnet. As cidofovir is a nucleotide analogue that bypass the activation by the viral TK and usually DNA polymerase mutants that are resistant to acyclovir and/or foscarnet remain sensitive to cidofovir, this drug can be used for VZV infections refractory to acyclovir, penciclovir and/or foscarnet. Unfortunately, cidofovir can also cause renal toxicity. Amenamevir, an helicase-primase inhibitor, has only been approved in Japan and its development was discontinued in United States due to toxicity concerns. The drawbacks of the currently available treatments for VZV-associated diseases highpoint the necessity for new, safe and highly effective anti-VZV agents. Drugs able to inhibit virus growth by targeting different steps of the VZV replicative cycle will be very useful for the management of drug-resistance infections in the clinic as well as for limiting the probability of emergence of antiviral drug-resistance and could also form the base for combination therapy.

Research should focus on the discovery and development of new anti-herpesvirus compounds having more potent activity than the currently available VZV antivirals. Besides, the search of new lead compounds able to block viral enzymes other than the viral DNA polymerase should be favored. In the last decade, only a few anti-VZV drugs were compared to valacyclovir in clinical trials to evaluate their efficacy in diminishing HZ associated pain and severity[26].

Bicyclic Nucleoside Analogues (BCNAs)

In 1999, the potent and selective anti-VZV activity of some unusual bicyclic nucleoside analogues (BCNAs) was reported by Mc Guigan and collaborators. For BCNAs with simple alkyl side-chain on the bicyclic base ring, the optimal carbon chain length for anti-VZV activity ranked between 8 and 10, with the 6-octyl-substituted derivative Cf-1368 being the most active and selective compound of this series of BCNAs.

Although BCNAs are structurally related to BVDU, they differ in their spectrum of antiviral activity as they exclusively inhibit VZV, in contrast to BVDU that possesses potent anti- HSV-1 and anti-VZV activity. Among BCNAs with an aromatic ring system (phenyl) in the side-chain, the n-pentylphenyl- and n-hexylphenyl-derivatives (Cf-1742 and Cf-1743, respectively) emerged as the most potent compounds with 50% effective concentration (EC_{50}) values as low as 0.0001–0.0005 µM against reference VZV strains as well as clinical isolates in vitro. A strong correlation between the length of the *n*-alkyl and *n*-alkylaryl moiety of the BCNAs and antiviral activity was observed. Cf-1743 was also able to reduce the replication and spread of VZV in organotypic epithelial raft cultures as measured by morphological changes induced by the virus and quantification of the viral DNA load. Similar

to acyclovir and brivudine, the BCNAs were inactive against TK-deficient (TK−) strains, pointing to a crucial role of the VZV-encoded TK in the activation (phosphorylation) of the BCNAs. VZV mutant strains selected in vitro under pressure of BCNAs showed mutations in the viral TK gene. Anti-VZV drugs in advanced development. Chemical structures of CF-1743 and its prodrug valnivudine hydrochloride (FV-100) and of omaciclovir (H2G) and its prodrug valomaciclovir stearate. BCNAs also strikingly differ from brivudine in their mechanism of activation. BCNAs are recognized by VZV TK as a substrate, but not by HSV-1 TK, nor by cytosolic TK-1 or mitochondrial TK-2 in kinetic studies with purified enzymes. VZV TK was demonstrated to phosphorylate the BCNAs not only to their corresponding 5′-mono- but also to their 5′-diphosphate derivatives due to the intrinsic dTMP kinase activity of the VZV TK. Thus, BCNAs are selectively phosphorylated to their 5′ diphosphates by the two successive enzyme activities of VZV TK (thymidine kinase and dTMP kinase). However, no clear-cut correlation between the antiviral potency of the compounds and their affinity for VZV TK could be demonstrated, pointing to a different structure/activity relationship of the eventual antiviral target of these compounds. In contrast to BVDU, human NDP kinase was unable to convert BCNAs to their triphosphate derivatives (BCNA-TP), in agreement with studies reporting no traces of BCNA-TP in VZV infected cells. These data clearly indicate that the mechanism of action of BCNAs differs from that of BVDU and suggests that BCNAs exert their antiviral effects via their monophosphate or diphosphate derivatives, virtually excluding the DNA polymerase as the molecular target of the BCNAs. The exact molecular target of the BCNAs could not be identified yet and is currently under investigation[27-31].

Activation, mechanism of action and catabolism of bicyclic nucleoside analogues (BCNAs). VZV TK converts BCNA's to the mono- and diphosphate forms although whether there is conversion to the triphosphate form and which is the active metabolite and mechanism of action remain unclear to date. Striking differences between BCNAs and BVDU exist regarding their catabolic pathways. In contrast to BVDU, human TPases do not recognize BCNA's as substrates and the free bases of BCNAs do not inhibit human DPD (dihydropyrimidine dehydrogenases) and thereof, there is a normal metabolism of Capecitabine/5-fluorouracyl. Dashed grey arrows indicate lack of activation.

Carbocyclic Nucleoside Analogues: H2G (Omaciclovir) and Its Prodrug (Valomaciclovir). Omaciclovir has a mode of action similar to that of acyclovir, but with less selectivity as a substrate for TK and resistance to omaciclovir maps to the TK. However, omaciclovir, in contrast to acyclovir, is not an obligate chain terminator, although incorporation of the triphosphate form (omaciclovir-TP) results in limited chain elongation. Omaciclovir-TP has a longer intracellular half-life than ACV-TP (providing dosing advantages over acyclovir) and is a potent inhibitor of VZV DNA polymerase though less active than ACV-TP. The anti-herpesvirus activity of omaciclovir can be markedly enhanced by the immunosuppressive agent mycophenolate mofetil.

Valomaciclovir stearate proved also effective against acute infectious mononucleosis due to primary EBV infection, for which there is no FDA-approved treatment. The findings of a randomized, placebo-controlled, double-blind trial of valomaciclovir stearate for infectious mononucleosis were reported in 2009 at a conference but data have not yet been published [97]. Omaciclovir produced a significant decrease in median EBV load in the oral compartment compared to placebo but no differences were found in clearance of EBV DNAemia, CD8:CD4 ratios, CD8 lymphocytosis, or CD8 responses to lytic and latent EBV tetramers in the valomaciclovir stearate vs. placebo group[32-36].

Brincidofovir

Brincidofovir is an orally bioavailable lipid acyclic nucleoside phosphonate (ANP) with the same broad-spectrum activity against DNA viruses as its parent compound cidofovir[37-39].

4. Conclusion

Varicella-zoster virus (VZV) is a pathogenic human alpha-herpesvirus that causes chickenpox (varicella) as a primary infection, which usually occurs in children in locales where vaccination is not practiced. Following the primary infection, this neurotropic virus becomes latent, primarily in neurons in peripheral autonomic ganglia throughout the entire neuroaxis including dorsal root ganglia (DRG), cranial nerve ganglia such as the trigeminal ganglia (TG), and autonomic ganglia including those in the enteric nervous system[40-41].

Despite the availability of a vaccine for the prevention of pediatric varicella in children and for the prevention of HZ in adults, there will continue to be a need for antiviral drugs. Some people in the elderly category are not able to mount a strong response to the vaccine. In immunocompromised persons, including patients with advanced HIV infection, varicella vaccination should be done exclusively with the subunit HZ vaccine as the life-attenuated vaccine is contraindicated for fear of disseminated vaccine-induced disease. New antiviral chemotherapeutics with a different mechanism of action are under development for the management of HZ, including valnivudine hydrochloride (FV-100), prodrug of the bicyclic nucleoside analogue Cf-1743, the helicase-primase inhibitor amenamevir (ASP2151) that got only approval in Japan because of toxicity issues, and the carbocyclic nucleoside analogue valomaciclovir stearate (EPB-348), the omaciclovir prodrug. Although the development of amenamevir has been halted due to problems of toxicity following a trial in United States, the results with valnivudine hydrochloride and valomaciclovir stearate indicated that these drugs are effective, well-tolerated, with once-daily therapy regimen in the treatment of HZ[42-43]. A potential anti-VZV drug candidate needs to be at least as

effective and safe as the gold standard of treatment for HZ, i.e., valacyclovir. Antiviral agents will still have a role in the treatment of VZV-associated diseases. A large percentage of the HZ at-risk population does not receive the vaccine. The currently FDA-approved antiviral drugs, including acyclovir, valacyclovir and famciclovir have low efficacy in the control of pain for HZ patients and a significant proportion of these patients (~20–40%) develops PHN. Novel antiviral chemotherapeutics with different mode of action than the currently available anti-VZV drugs are required for the treatment of ACV-resistant strains in the immunocompromised host.

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