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Review Article

Current scenario and future applicability of antivirals against herpes zoster

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ABSTRACT

Herpes zoster (HZ) is a common disease in the aging population and immunocompromised individuals, with a lifetime risk of 20%–30% that increases with age. HZ is caused by reactivation of the varicella-zoster virus (VZV), which remains latent in the spinal dorsal root ganglia and cranial sensory ganglia after resolution of the primary VZV infection. The main focus of HZ management is rapid recovery from VZV infection as well as the reduction and prevention of zoster-associated pain (ZAP) and postherpetic neuralgia (PHN). The use of antivirals against VZV is essential in the treatment of HZ. However, limited antivirals are only licensed clinically for the treatment of HZ, including acyclovir, valacyclovir, famciclovir, brivudine, and amenamevir. Fortunately, some new antivirals against different types of *Herpesviridae* have been investigated and suggested as novel drugs against VZV. Therefore, this review focuses on discussing the difference in efficacy and safety in the currently licensed antivirals for the treatment of HZ, the applicability of future novel antivirals against VZV, and the preventive or therapeutic effects of these antivirals on ZAP or PHN.

Keywords: Acyclovir; Amenamevir; Antiviral Agents; ASP2151; Brivudine; Famciclovir; Herpes Zoster; Herpesvirus 3, Human; Neuralgia, Postherpetic; Valacyclovir; Varicella Zoster Virus Infection.

INTRODUCTION

Herpes zoster (HZ) is a common disease in the aged population with a lifetime risk of 20%–30% that increases with age, and also in immunocompromised individuals with decreased cell-mediated immunity against varicella-zoster virus (VZV), immunosuppressive disorders, and immunosuppressive medications such as biologics, disease-modifying antirheumatic drugs, and/or corticosteroids [1–3]. HZ is caused by reactivation of VZV, which remains latent in the spinal dorsal root ganglia and cranial sensory ganglia after resolution of the primary VZV infection [1,4]. The replicated VZV spreads along the peripheral nerves to the skin and leads to a painful erythematous rash called HZ in the affected dermatomes [1,4].

The use of antivirals against VZV is essential in the treatment of HZ. Even though various antivirals have been developed for the treatment of alpha, beta, and gamma types of *Herpesviridae*, only a limited number of them can be used clinically for the treatment of HZ caused by VZV (alpha type of *Herpesviridae*) [4,5]. Only acyclovir, valacyclovir, and famciclovir have been approved for the treatment of HZ. Acyclovir was mainly used after approval for the treatment of HZ in 1982; how-

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Table 1. Current licensed and off-labeled antivirals for HZ

Classification	Antivirals	Dosing schedule	Characteristics
Nucleoside analogs			
	Acyclovir	5 × 800 mg/day P.O.	Limited bioavailability FDA approval for HZ Nephropathy Usually for 5–7 days
		3 × 500 mg/day I.V. followed by oral regimens for 10–14 days	
	Valacyclovir	3 × 1,000 mg/day P.O.	Prodrug of acyclovir with 54% bioavailability FDA approval for HZ For 7 days
	Famciclovir	3 × 250–500 mg/day P.O.	Prodrug of penciclovir with 77% bioavailability FDA approval for HZ For 7 days
	Brivudine	1 × 125 mg/day P.O.	Some Europe approval for HZ No renal toxicity For 5 days
Pyrophosphate analogs			
	Foscarnet	I.V. only	FDA non-approval for HZ Off-label acyclovir resistance Nephrotoxicity, electrolyte imbalance, genital ulcer
Nucleotide analogs			
	Cidofovir	I.V. only	FDA non-approval for HZ Off-label acyclovir or foscarnet resistance Nephrotoxicity, neutropenia
Helicase-primase inhibitor			
	Amenamevir	1 × 400 mg/day P.O.	Japan approval for HZ For 7 days

HZ: herpes zoster, P.O.: per oral, I.V.: intravenous, FDA: Food and Drug Administration.

ever, now famciclovir and valacyclovir are used instead of acyclovir [6]. Furthermore, since the number of antiviral drugs approved for HZ are very limited, the need for novel antivirals against VZV is increasing, and several antivirals for different types of *Herpesviridae* have been reported to have antiviral effects against VZV [5,7–10].

Antivirals against VZV reduce the incidence of new lesion formation, accelerate healing, and shorten the duration of viral shedding. Ultimately, it reduces the incidence, severity, and duration of pain and limits neuronal damage [1,8]. The replicated latent VZV leads to inflammatory sensory or motor neural damage of the peripheral and central nervous systems, resulting in zoster-associated pain (ZAP) or postherpetic neuralgia (PHN) [1,11]. In addition to the therapeutic effect of antivirals on HZ itself, the reduction and prevention of ZAP or PHN are also important clinical perspectives [1,12,13].

Therefore, this review focuses on the difference in efficacy and safety of the currently licensed antivirals for the treatment of HZ, the applicability of future novel antivirals against VZV, and the preventive or therapeutic effects of these antivirals on ZAP or PHN.

CLASSIFICATION OF ANTIVIRALS

1. Nucleoside analogs (Table 1)

Nucleoside analogs are phosphorylated to the active triphosphate form through three-step phosphorylation using viral thymidine kinase and host kinase [1,5]. Nucleoside analogs show highly selective antiviral effects by inhibiting viral DNA synthesis and targeting virus-encoded DNA polymerase [5].

Nucleoside analogs include acyclovir, penciclovir, ganciclovir, and derivatives of these drugs (prodrugs; valacyclovir, famciclovir, and valganciclovir, respectively) [5]. However, acyclovir, penciclovir, and ganciclovir have very

low oral bioavailability; therefore, they have a disadvantage in that they have to be administered in large doses and frequently administered each day for an inducible effect. In contrast, prodrugs such as valacyclovir, famciclovir, and valganciclovir have been developed with the improvement of oral bioavailability; they are able to obtain a treatment effect even with a small dose administered thrice a day or less and contribute to improvement of the patients' drug compliance [1].

1) Acyclovir and valacyclovir

Acyclovir remains the first-line treatment for HZ; however, it is disadvantageous in clinical use because of its low oral bioavailability (< 30%), thus requiring high doses and administration five times a day [5,14,15]. Valacyclovir was developed to overcome this limitation, which improved bioavailability to approximately 54% with longer dosing intervals, better compliance, and safety profiles similar to those of acyclovir [5,14,15]. Acyclovir and valacyclovir have favorable side effects and are well tolerated even with long-term administration [14]; the most common side effect is nephrotoxicity [5,14]. Acyclovir can be prescribed at 5 × 800 mg/day for oral administration and 3 × 500 mg/day for intravenous administration, whereas valacyclovir can be prescribed at 3 × 1,000 mg/day for oral administration [4].

2) Penciclovir and famciclovir

Penciclovir is not used in clinical practice because of its low bioavailability, but famciclovir is being used as a prodrug of penciclovir owing to its high oral bioavailability (77%) [5,8]. The side effects are nephrotoxicity, headaches, mental confusion, and nausea [5,15]. Oral famciclovir can be prescribed 3 × 250–500 mg/day [4].

3) Ganciclovir and valganciclovir

Ganciclovir is almost as active as acyclovir against VZV but is generally administered intravenously because of its very poor oral bioavailability (only 5%–10%) [5,14]. Ganciclovir has less favorable safety compared with acyclovir, including greater hepatorenal toxicity, requiring proportional dose adjustment in cases of renal impairment [5,14]. Valganciclovir is the prodrug of ganciclovir, with high oral bioavailability (60%) but has significant side effects including hepatorenal toxicity and myelosuppression [5,14]. Therefore, its clinical use is limited.

4) Brivudine

Brivudine is a nucleoside analog that has been approved and used for the treatment of HZ in some European countries [5,8]. This drug has a very high bioavailability (90%) and acts selectively against HZV [8]. Brivudine has efficacy and convenience similar to those of acyclovir, valacyclovir, and famciclovir [8]. In addition, although there is no difference in terms of pain reduction in patients with mild to moderate HZ, the time to decrease the intensity of pain is significantly reduced in patients with severe HZ receiving brivudine without significant differences in side effects [8,16].

In particular, brivudine has no renal toxicity, which is the most common side effect of nucleoside analogs [16]. Therefore, brivudine may be the first choice for patients with severe HZ and earlier pain control owing to its convenience of its once-daily administration (1 × 125 mg/day for 5 days) [16]. However, brivudine is contraindicated in patients receiving 5-fluorouracil or other 5-fluoropyrimidine compounds within the last 4 weeks because of drug interactions, resulting in significant bone marrow suppression [4].

2. Pyrophosphate analogs (Table 1)

Foscarnet, a pyrophosphate analog, exhibits antiviral effects by directly inhibiting the activity of viral DNA polymerase without undergoing a phosphorylation step, unlike nucleoside analogs [5,17]. Foscarnet has broad-spectrum antiviral activity against various types of *Herpesviridae* [5]. It can be used off-label as a second-line drug for the treatment of acyclovir or cidofovir-resistant HZ [14,17,18]. However, owing to its poor oral bioavailability, it is administered intravenously only [5,17]. Furthermore, it has significant side effects such as nephrotoxicity, electrolyte imbalance, and genital ulcers [15,18]. Therefore, close laboratory monitoring is recommended [14].

3. Nucleotide analogs (Table 1)

Cidofovir, a nucleotide analog, does not undergo phosphorylation by viral thymidine kinase, unlike nucleoside analogs, but only undergoes phosphorylation by host kinase to act on viral DNA polymerase, thereby exhibiting antiviral effects [5,14]. Even though cidofovir is approved principally for cytomegalovirus infections, it can be used off-label for the treatment of acyclovir or foscarnet-resistant HZ [5,18]. However, owing to its poor oral bioavail-

ability (5%–22%), it is administered intravenously [5]. The side effects of cidofovir are dose-dependent nephrotoxicity, neutropenia, and myelosuppression requiring intensive monitoring [5,18].

4. Helicase-primase inhibitor (Table 1)

Amenamevir, a helicase-primase inhibitor, is approved and used only in Japan for the treatment of HZ [5,8]. Unlike nucleoside analogs, such as acyclovir, the antiviral activity of amenamevir is not affected by the viral replication cycle and is exhibited by inhibiting viral helicase-primase activity after binding to the helicase-primase complex [8,19]. Amenamevir has a high bioavailability of 86% and can be prescribed as a once-daily dose [5,19]. It exhibits a non-inferior antiviral effect compared to valacyclovir with no serious side effects [19]. In particular, synergistic or additive effects can be demonstrated when used together with nucleoside analogs, such as acyclovir, which is recommended in patients with severe VZV infection [8,19].

COMPARISONS BETWEEN ANTIVIRALS

Evidence regarding the superiority or non-inferiority of antivirals in the treatment of HZ is lacking. Famciclovir was non-inferior to acyclovir with equivalent therapeutic effects and similar frequencies of side effects in patients with uncomplicated HZ, particularly in patients aged ≥ 50 years within 3 days of rash onset [20,21]. Valacyclovir is effective in reducing ZAP significantly and more rapidly than acyclovir [21–23]. However, Schuster et al. [24] reported that there was still uncertainty in cases of HZ ophthalmicus that valacyclovir was relatively beneficial or harmful compared with acyclovir. Brivudine was more effective (as a faster time to the cessation of new vesicles) than acyclovir, although the time to ZAP resolution was similar to that of acyclovir [21]. Brivudine also showed similar efficacy with ZAP and tolerability compared to famciclovir [21].

Brivudine, valacyclovir, and famciclovir can significantly reduce ZAP; however, there was no significant difference in pain score changes after antiviral treatment between each antiviral [16]. In patients with severe HZ, a significant reduction in pain score was observed on day 3 after brivudine, day 7 after famciclovir, and 2–3 weeks after valacyclovir [16]. However, no significant differences in vesicle formation severity during treatment were shown between brivudine, valacyclovir, and famciclovir [16,21].

The efficacy and safety of amenamevir have also been investigated in patients with HZ within 3 days of rash onset [25]. This study suggests that amenamevir has excellent pharmacokinetic and antiviral properties compared with acyclovir, and that amenamevir provided efficacy comparable to that of valacyclovir in a non-inferiority test.

The convenience of antiviral use is affected by the number of medications taken owing to differences in the oral bioavailability of each drug. Acyclovir needs to be administered five times a day; however, famciclovir and valacyclovir can be administered thrice a day, and brivudine and amenamevir can be administered once daily [4,5,16,19]. Therefore, brivudine and amenamevir are superior to famciclovir and valacyclovir, which are superior to acyclovir.

GENERAL RECOMMENDATIONS FOR ANTIVIRALS

In general, antiviral medication is recommended for HZ of the head and/or neck area, moderate to severe pain, any locations with multi-segment involvement, aberrant vesicles, and satellite lesions [26]. Antiviral treatment is also recommended for HZ of any localization in patients ≥ 50 years of age and for immunocompromised patients [26]. For adults aged < 50 years, intravenous acyclovir can be suggested when the trunk or extremities are involved without being at risk of or displaying signs of complicating courses [26]. Especially, intravenous acyclovir is recommended for serious patients requiring the administration of the above indications [26].

The required dose of antivirals increases depending on the duration of the VZV infection [19], and antivirals starting within 72 hours after the rash onset are most effective [27] Therefore, antivirals should be administered within 72 hours after the onset of symptoms as soon as possible [1,8,26,28]. However, even after 72 hours, the initiation of antivirals is suggested for all immunocompromised patients, in cases of new vesicles appearing in patients with significant complications or at risk of developing complications, and those with disseminated lesions invading the eyes and ears [1,8,26,28].

Generally, oral antivirals should be continued for 7 days but can be prescribed for more days until new lesions have not developed or symptoms of complications have improved [2,4,8,26,29]. Intravenous acyclovir administra-

tion should be continued until clinical improvement, and then an oral regimen should be initiated to complete a 10–14-day course when the formation of new lesions has ceased and the complicated signs and symptoms are improving [29].

As previously mentioned, the most common side effect associated with antivirals is renal toxicity. Therefore, careful monitoring of renal function is suggested in patients with known or suspected renal dysfunction [26]. Oral brivudine or intravenous acyclovir administration with proportional dose adjustment is recommended for patients with renal impairment [26].

EFFECT OF ANTIVIRALS ON PREVENTION OF PHN OR ZAP

Most studies have reported that acyclovir was effective in significantly reducing ZAP, while valacyclovir was more effective than acyclovir in reducing the duration of PHN [21]. Famciclovir and valacyclovir were equally effective at resolving ZAP [21]. A Cochrane review concluded that acyclovir had no effect on the reduction in PHN incidence, and evidence was insufficient to determine the effect of other antivirals [30].

A recent meta-analysis suggested that the prodrugs (famciclovir and valganciclovir) produced greater remission of PHN within one month after HZ than acyclovir, whereas acyclovir was no longer effective in reducing PHN incidence in this period compared to placebo or prodrugs [22]. They documented that the improved efficacy of these prodrugs may be influenced by greater bioavailability, better drug tolerance, and more favorable safety profiles than acyclovir [22].

A network meta-analysis reported that antivirals alone were not effective in preventing PHN; however, the combination of antivirals with interventions or steroids was effective in reducing PHN 1 month after HZ [31]. However, these combination therapies were ineffective in reducing the incidence of PHN after 3 and 6 months [31].

The evidence of antiviral benefits in the prevention of PHN is still conflicting, and antivirals are not completely effective in preventing PHN [8]. The main suspected cause is the delay between symptom onset and treatment initiation [8]. Therefore, to prove the effect of antivirals on the prevention of PHN, well-designed randomized control studies should be conducted.

NOVEL ANTIVIRALS FOR HZ

There are only a few studies on the antiviral effect and safety of HZ treatment, even though there are numerous antivirals against various types of *Herpesviridae* [5,7,9,10,14,32].

FV-100, a bicyclic nucleoside analog, has been suggested as a potent and selective VZV inhibitor to treat HZ [7]. FV-100 has the potential for the reduction in ZAP and the prevention of PHN, has tolerable safety profiles itself, and favorable safety profiles compared with those of valacyclovir [8,32]. FV-100 can offer more convenience than valacyclovir, with once daily *vs*. thrice daily dosing, respectively [8,32].

Valomaciclovir, a carbocyclic nucleoside analog, was investigated for antiviral activity against VZV in immunocompetent patients with acute HZ [9]. It showed greater convenience, with equal safety, than valacyclovir due to once-daily dosing and non-inferiority in terms of time required for healing HZ and complete pain resolution [9].

Brincidofovir, a nucleotide analog, is a prodrug of cidofovir; it overcomes the latter's poor oral bioavailability [5,10]. Brincidofovir reduced toxicity with no significant nephrotoxicity or myelosuppression and showed only minor side effects, such as diarrhea and other gastrointestinal problems [10,14]. However, no results of large-scale clinical studies have been reported in patients with HZ; therefore, no conclusions can be drawn regarding the efficiency of brincidofovir. Further research is needed to support its antiviral effects against VZV.

CONCLUSIONS

Currently, few antivirals are licensed for the treatment of HZ. Valacyclovir and famciclovir, compared with acyclovir, are non-inferior or superior in the therapeutic aspect of HZ and are superior in terms of convenience. Brivudine and amenamevir also have therapeutic effects similar to those of valacyclovir and famciclovir and are more convenient than valacyclovir and famciclovir. According to the existing literature, all antivirals claim to be ineffective in ZAP or PHN, and, owing to the diversity of research designs and criteria for selecting subjects, achievability of complete prevention or treatment of ZAP or PHN has not yet been proved. Therefore, further well-designed studies maintaining the recommendation for antivirals are required to demonstrate significant differences in the therapeutic effect on HZ and the preventive effects on ZAP or PHN between each antiviral. Foscarnet

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can be used in patients resistant to acyclovir, and cidofovir can be used in patients resistant to foscarnet. There are several novel antivirals against VZV; however, further research is required to verify their therapeutic effect on HZ and their preventive effect on ZAP or PHN.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed in this study.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

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