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Management of herpes zoster and post-herpetic neuralgia now and in the future

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SUMMARY

Herpes zoster (HZ; shingles) – a reactivation of the latent varicella zoster virus (VZV) – can cause significant morbidity. Its major complication is pain, particularly post-herpetic neuralgia (PHN). We will review the current management strategies available for the treatment of both acute HZ and PHN, including antiviral drugs, analgesic agents, anticonvulsants, tricyclic antidepressants and topical therapies. New molecules in development that show improved activity against VZV are also covered, and new drug targets are outlined. The role of translational neuroscience in moving towards a goal of finding disease-modifying treatments will be examined.

Abbreviations

HZ:	herpes zoster
PHN:	post-herpetic neuralgia
VZV:	varicella zoster virus
GP:	general practitioner
5-FU:	5-fluorouracil
TTP:	thrombotic thrombocytopoenic purpura
HUS:	haemolytic-uraemic syndrome
FDA:	Food and Drug Administration
ZAP:	zoster-associated pain
RR:	risk ratio
DPD:	dihydropyrimidine dehydrogenase
BVaraU:	bromovinyl arabinosyl uracil
BCNA:	bicyclic nucleoside analogue
SVV:	simian varicella virus
BVDU:	bromovinyldeoxyuridine
HPMPA:	9-(S)-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine
PMEA:	phosphonomethoxy-ethyl-adenine
TK:	thymidine kinase
TCA:	tricyclic antidepressant
ECG:	electrocardiogram
DRG:	dorsal root ganglion
PRF:	pulsed radio frequency
NE:	norepinephrine
APN:	aminopeptidase N
NEP:	neutral endopeptidase
CNS:	central nervous system

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1. Introduction

The objectives of treating herpes zoster (HZ) are to control acute pain, accelerate rash healing, minimize complications and reduce the risk of post-herpetic neuralgia (PHN) and other late-appearing sequelae. An additional objective, particularly important for immunosuppressed patients, is to reduce the risk of cutaneous and visceral dissemination of the varicella zoster virus (VZV).[1]

2. Current management of acute HZ

The diagnosis of HZ is generally evident at clinical presentation. However, there are situations where diagnosis is difficult, or the patient or physician had not recognized the symptoms and signs early enough. Several studies indicate potential hurdles in diagnosis. One seminal study tested the hypothesis that vaccination against VZV would decrease the incidence and/or severity of HZ and PHN among adults aged >60 years, including the burden of illness. This study involved >38,000 volunteers and demonstrated that 5–6% of the clinical diagnoses by academic physicians were not laboratory confirmed,[2] suggesting that even knowledgeable infectious diseases clinicians are occasionally wrong in their diagnosis. Similarly, a prospective study of HZ diagnoses by general practitioners (GPs) found 17% of diagnoses to be incorrect.[3] Furthermore, in a recent study of psychosocial correlates of HZ,[4] which used pain as an indicator of disease onset, 92% of 533 individuals with HZ had pain at presentation. However, only 46% sought medical attention within 72 hours of pain onset and 54% within 72 hours of rash appearance. Initial assessment was late, at a median time of 72 hours after the onset of rash. Importantly, >80% of the subjects reported prodromal pain, which in the majority of cases lasted 2 or 3 days.

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Table 1
Antivirals currently available for the treatment of HZ.

Drug	Dosage[a]	Comments, adverse events and contraindications	Reference
Oral acyclovir	800 mg five times daily for 7–10 days	• Adverse events similar to placebo	Prescribing information[5]
Intravenous acyclovir	10 mg/kg three times daily Adults and children over 40 kg: 800 mg four times daily for 5 days	• Indicated in immunocompromised patients • Adverse events include crystalluria associated with rapid infusion in patients with renal impairment • Rarely, CNS disturbances in elderly with renal dysfunction	Prescribing information[5]
Valacyclovir	1000 mg three times daily for 7 days	• Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnoea, pruritus, rash and urticaria • Contraindications: Hypersensitivity to valacyclovir (e.g., anaphylaxis), acyclovir or any component of the formulation • Pregnancy category B: Should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus • In two clinical studies, adverse events included nausea, headache, vomiting, dizziness and abdominal pain • TTP/HUS reported in AIDS and transplant patients during clinical trials	Prescribing information[6]
Famciclovir	500 mg every 8 hours for 7 days	• Contraindicated in patients with known hypersensitivity to famciclovir, its components and penciclovir cream • Pregnancy category B: Should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the foetus • In clinical studies, adverse events included headache, paresthesia, nausea and vomiting	Prescribing information[7]
Brivudin	125 mg once daily for 7 days	• Adverse events included nausea (incidence and type of potential adverse drug experiences were consistent with those known to occur with other nucleoside antiviral agents belonging to the same class) • Contraindicated in: – Patients undergoing cancer chemotherapy, especially if treated with 5-FU, including its topical preparations, its prodrugs (e.g., capecitabine, floxuridine, tegafur) and combination products containing these active substances or other 5-fluoropyrimidines – Immunocompromised patients such as those undergoing cancer chemotherapy, immunosuppressive therapy or therapy with flucytosine in severe systemic mycosis – Pregnant women or nursing mothers	Product characteristics[8]

Abbreviations: 5-FU, 5-fluorouracil; HUS, haemolytic-uraemic syndrome; TTP, thrombotic thrombocytopoenic purpura.
[a] Dosage of antivirals may differ between countries. Please refer to local prescribing information.

2.1. Current antiviral therapies

Three oral nucleoside analogues – acyclovir, valacyclovir (prodrug of acyclovir) and famciclovir (prodrug of penciclovir) – are approved worldwide for the treatment of HZ, including in immunocompromised patients. An additional antiviral drug, brivudin, is widely available in some countries but is limited to an indication for immunocompetent patients because of a potentially fatal interaction with 5-fluorouracil (5-FU) (see Table 1).

All of the antiviral drugs significantly decrease the incidence of new lesion formation and accelerate healing and the resolution of acute pain. In addition, antiviral therapy shortens the duration of viral shedding,[1] which hypothetically may limit neuron damage, thereby reducing the incidence, severity and duration of pain.

An essential component of antiviral treatment is its effects on the resolution of pain. There are three forms of pain defined as follows. First, pain at presentation is acute pain and the extent of its resolution can be quantified over the first 30 days. Second, and the most debilitating form of pain, is PHN. Several definitions of PHN have been used over the past 30 years, and all have different implications for clinical studies. PHN is defined by the US Food and Drug Administration (FDA) as 'Pain that has not resolved 30 days after disease onset'.[9] An alternative definition is pain that persists after skin healing. The third form of pain is that of zoster-associated pain (ZAP), whereby pain is viewed as a continuum from the time of acute zoster until its complete resolution, if it occurs.

To date, there is no consensus on the definition of PHN. Early studies used a wide range of definitions, including 'any pain that follows disappearance of the rash of herpes zoster', whereas other studies used the definition of 'pain present for more than 1 or 2 months after rash onset'.[10] However, recent models of pain resolution and statistical analysis suggest that the most appropriate definition of PHN is pain that persists 90 days or more after the onset of HZ rash.[11]

In early acyclovir studies, PHN was defined as 'persistence 30 days after disease onset or the healing of skin'. Thus, the early acyclovir trials and a large meta-analysis involving 691 patients suggested that acyclovir (800 mg five times daily for 7–10 days) was more effective than placebo in reducing pain.[12] Benefits were particularly noticeable for patients aged >50 years. Overall, the incidence and duration of PHN among patients receiving acyclovir were half those reported by placebo recipients, and fewer acyclovir-treated patients had PHN at 3 and 6 months.[12] However, this has not been proven in a sufficiently powered prospective study.

According to ZAP analyses from various clinical studies, valacyclovir (a prodrug of acyclovir) is more efficacious than acyclovir. One study comparing two different regimens of valacyclovir (1000 mg three times daily for 7 days, or 1000 mg three times daily for 14 days) with acyclovir (800 mg five times daily for 7 days) showed that the time to ZAP resolution was significantly longer with acyclovir therapy (median time to ZAP resolution: acyclovir, 51 days; 7-day valacyclovir, 38 days [$p = 0.002$]; 14-day valacyclovir, 44 days [$p = 0.03$]).[13] Valacyclovir therapy also had a faster time to ZAP resolution that had persisted for >30 days compared with acyclovir (HR 1.24; CI 1.04–1.48; $p = 0.01$ for the 7-day valacyclovir