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Review

Herpes zoster: focus on treatment in older adults☆

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1. Introduction

This is the second article in the series dealing with viral infections in the elderly population.

Over the past 25 years, application of the tools of modern molecular biology has greatly expanded our understanding of the pathogenesis and natural history of infections caused by varicella-zoster virus (VZV). Even more striking, however, have been advances in our ability to use antiviral chemotherapy to successfully treat both varicella (chickenpox) and herpes zoster (shingles) in immunocompetent as well as immunocompromised individuals. Since the incidence of herpes zoster is positively correlated with advancing age, clinicians can expect to encounter more patients with herpes zoster as the median age of the American population advances. Physicians now have access to a spectrum of potent antiviral drugs that can hasten the resolution of herpes zoster and improve the long-term outcome. This review will focus on the natural history of herpes zoster and treatment of the disease in older immunocompetent adults.

2. Epidemiology of herpes zoster

Primary VZV infection (varicella) occurs when a susceptible individual, usually a child, is exposed to airborne virus via the respiratory route. Over 90% of adults in the United States have serologic evidence of prior VZV infection (Choo et al., 1995). As VZV replicates in the skin during acute varicella, some virions are transported via sensory nerves to the corresponding dorsal root ganglia where latent infection is established (Meier and Straus, 1992). A presumptive decline

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in VZV-specific cell-mediated immune responses that occurs naturally with aging appears to be the most important factor predisposing to reactivation of latent VZV and development of herpes zoster (Burke et al., 1982; Cohen et al., 1999). This phenomenon has not been well studied and warrants further consideration, especially in the consideration of silent or abortive preactivation. The annualized incidence of herpes zoster is estimated to be 1.5–3.0 cases per 1000 persons in the population, which would project at least 500 000 cases of herpes zoster annually in the United States (Ragozzino et al., 1982; Donahue et al., 1995). These figures predict that an immunocompetent individual has a 10–20% risk of developing herpes zoster at some point during his or her lifetime. It has been estimated that 50% of individuals reaching age 80 will have experienced herpes zoster. Shingles appears with equal frequency in men and women and there is no seasonable association.

Notably, a vaccine has been licensed to prevent chickenpox in children. The immunity induced by the VZV vaccine is not as great as that following natural infection. As a consequence, with a decreasing incidence of chickenpox and less natural boosting, shingles may occur earlier in life. At the present, this is only speculation. In addition this vaccine is being tested to prevent shingles in older individuals (greater than 60 years of age).

3. Natural history and clinical course of herpes zoster

Herpes zoster typically presents as a painful cutaneous eruption in a localized dermatomal distribution. The inflammatory changes that occur with VZV reactivation in the sensory ganglion are manifest by a prodrome of discomfort in the corresponding dermatome. The patient may report sensations ranging from mild itching or tingling to severe pain that can precede the development of the vesicular rash by several days or occasionally by weeks. Skin changes begin with an erythematous maculopapular rash, followed by the appearance of clear vesicles. The cutaneous eruption, appearing in the skin segment innervated by a single sensory ganglion, is unilateral and does not cross the midline. Overlap of lesions into adjacent dermatomes occurs in 20% of cases. The most common sites for herpes zoster are the thoracic dermatomes (50% of cases), followed by cranial nerve (15%), lumbar (15%), and sacral (5%) dermatomes (Hope-Simpson, 1965). In older immunocompetent individuals, scattered cutaneous vesicles outside the primary dermatome are not uncommon. However, dissemination of VZV to visceral organs virtually never occurs in herpes zoster patients with normal cell-mediated immune function. New vesicles may continue to form for 3–5 days and evolve through stages of postulation and scabbing. Skin lesions heal within 2–4 weeks, and may leave skin scarring and permanent pigmentation changes.

In immunocompetent persons, pain is the most prominent manifestation of herpes zoster. During the acute phase of shingles, most patients experience dermatomal pruritus and pain (acute neuritis) that can be quite severe. Patients may also complain of headache, photophobia, and malaise, but significant fever is rare. Chronic pain following herpes zoster, traditionally termed *post-herpetic neuralgia* (PHN), can be a debilitating complication of shingles. The incidence (and possibly the duration) of PHN is markedly increased in elderly individuals (Ragozzino et al., 1982). In the absence of antiviral therapy, PHN may develop in as many as 50% of individuals over 60 years of age (Kost and Straus, 1996). In addition to age, the severity of the acute neuritis at the time of rash onset as well as the extent of disease in the involved dermatome also predict the risk for long-term pain (Dworkin and Portenoy, 1996; Dworkin et al., 1997; Whitley et al., 1999). More recently, the term *zoster-associated pain* (ZAP) has been used to describe the continuum of pain from onset through final resolution. In the opinion of many investigators, this description of pain more accurately reflects the natural history of herpes zoster and provides a more accurate basis for analyses of treatment effects.

4. Therapeutic agents

Clinical trials with vidarabine in the late 1970s provided a successful proof-of-concept for antiviral therapy of VZV infections. Over the last 20 years, a series of effective and well-tolerated antiviral compounds have been developed for treatment of herpes zoster (Balfour, 1999). Three oral antiviral drugs (acyclovir, valaciclovir, and famciclovir) are currently approved in the United States for treatment of herpes zoster in the immunocompetent host. Intravenous acyclovir is also available for therapy of complicated or disseminated VZV infections, including herpes zoster in immunocompromised individuals.

4.1. Acyclovir and valaciclovir

Acyclovir (Zovirax®) was the first oral antiviral compound marketed for treatment of herpes zoster. While widely and successfully prescribed, the efficacy of acyclovir for herpes zoster was somewhat limited by its poor oral bioavailability. Valaciclovir (Valtrex®), the L-valine ester prodrug of acyclovir has been developed to provide an orally administered drug with an improved pharmacokinetic profile.

4.1.1. Chemistry, mechanism of action, and antiviral activity

Acyclovir (9-{2-hydroxyethoxymethyl}guanine) is a synthetic acyclic purine nucleoside analogue which is a selective inhibitor of herpes simplex virus (HSV types 1 and 2) and VZV replication (Elion et al., 1977; Schaeffer et al., 1978). Acyclovir is converted by virus-encoded thymidine kinase (TK) to its monophosphate derivative, an event that does not occur to any significant extent in uninfected cells (Fyfe et al., 1978). Subsequent di- and tri-phosphorylation steps are catalyzed by cellular enzymes, resulting in acyclovir-triphosphate concentrations 40–100-fold higher in HSV- and VZV-infected cells. Acyclovir triphosphate inhibits viral DNA synthesis by competing with the deoxyguanosine triphosphate as a substrate for viral DNA polymerase (Derse et al., 1981). Because acyclovir triphosphate lacks the 3′ hydroxyl group required for DNA chain elongation, viral DNA synthesis is terminated. Viral DNA polymerase is tightly associated with the terminated DNA chain and is functionally inactivated (Furman et al., 1984). In addition, the viral polymerase has greater affinity for acyclovir triphosphate than does cellular DNA polymerase, resulting in little incorporation of acyclovir into cellular DNA. In vitro, acyclovir is most active against HSV-1 ($EC_{50} = 0.04$ μg/ml), HSV-2 ($EC_{50} = 0.3$ μg/ml), and VZV (Collins and Bauer, 1979).

Valaciclovir is cleaved to acyclovir by valine hydrolase, which then is metabolized in infected cells to the active triphosphate of acyclovir (Soul-Lawton et al., 1995). Because it is converted to acyclovir, it has the same in vitro spectrum of activity as the parent compound.

4.1.2. Absorption, distribution and elimination

For the treatment of herpes zoster, acyclovir is available in oral and intravenous formulations. Absorption of acyclovir after oral administration is slow and incomplete, with bioavailability of about 15–30% (de Miranda and Blum, 1983). After multidose oral administration of 200 or 800 mg of acyclovir, the mean steady-state levels are about 0.57 and 1.57 μg/ml, respectively (Laskin, 1984). Acyclovir plasma concentrations following intravenous doses of 5 or 10 mg/kg every 8 h are about 9.9 and 20.0 μg/ml, respectively. Acyclovir penetrates most body tissues well, including the brain. The terminal plasma half-life is 2–3 h in adults with normal renal function. Acyclovir is minimally metabolized and about 85% of the administered dose is excreted unchanged in the urine via renal tubular secretion and glomerular filtration. Acyclovir is readily removed by hemodialysis, but not by peritoneal dialysis. Acyclovir dosage adjustment is required in patients with impaired renal function. For herpes zoster patients with creatinine clearance (CrCl) of >25 ml/min the dose of acyclovir is 800 mg orally every 4 h (5 times daily). For CrCl of 10–25 or <10 ml/min, the acyclovir is given as 800 mg orally every 8 or 12 h, respectively.

Valaciclovir is only available as a tablet formulation. It is metabolized nearly completely to acyclovir within minutes after absorption

(Soul-Lawton et al., 1995). The subsequent oral bioavailability of acyclovir is about 54% (Perry and Faulds, 1996). Notably, plasma area-under-the-curve (AUC) levels of acyclovir which are achieved following 2 g of valaciclovir dosed orally four times daily approximate those achieved with acyclovir 10 mg/kg administered every 8 h intravenously (Weller et al., 1993). The recommended dose of valaciclovir for herpes zoster is 1000 mg orally every 8 h. Dosage reduction is required in patients with CrCl < 50 ml/min.

4.2. Penciclovir and famciclovir

4.2.1. Chemistry, mechanism of action and in vitro activity

Penciclovir, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine, is an acyclic guanine derivative that is similar to acyclovir in structure, mechanism of action, and spectrum of antiviral activity (Boyd et al., 1987). There are, however, differences between acyclovir and penciclovir in terms of activation and intracellular concentrations (Earnshaw et al., 1992). In HSV or VZV-infected cells, penciclovir is first monophosphorylated by virally-encoded TK and then further phosphorylated to the triphosphate moiety by cellular enzymes. Penciclovir triphosphate blocks viral DNA synthesis through competitive inhibition of viral DNA polymerase (Vere Hodge, 1993). Unlike acyclovir triphosphate, penciclovir triphosphate is not an obligate chain terminator and can be incorporated into the extending DNA chain. Compared with acyclovir triphosphate, intracellular concentrations of penciclovir triphosphate are much higher. However, this potential advantage is offset by a much lower affinity of penciclovir triphosphate for viral DNA polymerase (Vere Hodge, 1993). The in vitro activity of penciclovir against HSV-1, -2 and VZV is similar to that of acyclovir, with median EC_{50} values of 0.4, 1.5, and 4.0 μg/ml, respectively, in MRC-5 cells (Boyd et al., 1993). Compared with acyclovir triphosphate, penciclovir triphosphate has a much longer intracellular half-life in virus-infected cells (Earnshaw et al., 1992). For example, the half-life values for penciclovir triphosphate and acyclovir triphosphate in HSV-1-infected cells are 10 and 0.7 h, respectively. The clinical significance (if any) of the prolonged intracellular half-life is not known.

4.2.2. Absorption, distribution, and elimination

Penciclovir is very poorly absorbed (less than 5%) after oral administration. Intravenous infusion of a penciclovir dose of 10 mg/kg over 1 h yields a peak plasma concentration of 12.1 μg/ml (Pue and Benet, 1993). Plasma protein binding of penciclovir is $< 20\%$. The drug is cleared by renal tubular secretion and passive filtration. The plasma elimination half-life of penciclovir is about 2 h and approximately 70% of the administered dose is recovered unchanged in the urine (Fowles et al., 1992; Pue et al., 1994). The intravenous preparation of penciclovir has not yet been approved or commercially released.

Just as valaciclovir is a prodrug of acyclovir, famciclovir is a prodrug of penciclovir. Because penciclovir is very poorly absorbed, famciclovir (the diacetyl ester of 6-deoxy-penciclovir) was developed as the oral formulation (Vere Hodge, 1993). Famciclovir is well absorbed after oral administration. The first acetyl side chain is cleaved by esterases found in the intestinal wall. On first pass through the liver, the second acetyl group is removed and oxidation catalyzed by aldehyde oxidase occurs at the six position, yielding penciclovir, the active antiviral compound. When administered as the famciclovir prodrug, the bioavailability of penciclovir is about 77% (Pue and Benet, 1993). Following a single oral dose of 250 or 500 mg of famciclovir, peak plasma penciclovir concentrations of 1.9 and 3.5 μg/ml are achieved at 1 h (Pue et al., 1994). The pharmacokinetics of penciclovir are linear and dose independent over a famciclovir dosing range of 125–750 mg. Food slows famciclovir absorption and lowers the peak plasma penciclovir concentration, but does not alter the AUC value.

5. Treatment of herpes zoster

The goals of therapy of herpes zoster in immunocompetent adults are to accelerate the events of cutaneous healing, reduce the severity of acute neuritis, and, most importantly, to reduce the

incidence, severity, and duration of chronic pain. Three oral antiviral drugs are currently approved in the United States for treatment of herpes zoster. Acyclovir, valaciclovir, and famciclovir have all been demonstrated to reduce the duration of viral shedding, promote resolution of skin lesions, and limit the duration of pain when antiviral therapy is initiated within 72 h of shingles onset (Huff et al., 1988; Beutner et al., 1995; Tyring et al., 1995; Wood et al., 1996).

Oral acyclovir (800 mg 5 times daily for 7 days) accelerates cutaneous healing and reduces the severity of acute neuritis in immunocompetent adults with herpes zoster (Huff et al., 1988; Wood et al., 1988; Morton and Thomson, 1989). In placebo-controlled trials, acyclovir therapy reduced new vesicle formation by approximately 1.5 days and time to crusting by 2 days. Benefits are maximized when therapy is initiated within 48 h of appearance of lesions. Acyclovir therapy is also highly effective for prevention of ocular complications of herpes zoster ophthalmicus, including keratitis and uveitis (Cobo et al., 1986; Harding and Porter, 1991). Acyclovir does not alter the incidence of post-herpetic neuralgia, but can accelerate the resolution of chronic pain (Jackson et al., 1997). A recent meta-analysis of all of the placebo-controlled trials of acyclovir for herpes zoster demonstrated a significant reduction of zoster-associated pain among acyclovir recipients (Table 1) (Wood et al., 1996).

Valaciclovir (1000 mg 3 times daily for 7 days) was compared with acyclovir (800 mg 5 times daily for 7 days) in a study of 1141 immunocompetent patients over 50 years of age with herpes zoster (Beutner et al., 1995). The progression of cutaneous healing was similar in the two treatment groups. However, patients in the valaciclovir

Table 1
Efficacy of acyclovir in herpes zoster (Wood et al., 1996)

	Acyclovir versus Placebo		Studies analyzed
	Hazard ratio (95% confidence interval)[a]	P[b]	
Time to complete cessation of zoster-associated pain:			Morton and Thomson (1989) Huff et al. (1988) Harding and Porter (1991)
All patients	1.79 (1.34, 2.39)	<0.001	
Patients >50 years	2.13 (1.42, 3.19)	<0.001	
Time to complete cessation of moderate/severe zoster-associated pain	1.46 (1.11, 1.93)	0.007	Morton and Thomson (1989) Huff et al. (1988) Harding and Porter (1991)
Time to first pain-free period	1.31 (1.08, 1.60)	0.007	Morton and Thomson (1989) Huff et al. (1988) Harding and Porter (1991) Wood et al. (1988)

[a] Hazard ratio — ratio of risk for achieving cessation of pain between treatment groups.
[b] Statistical calculations determined by Cox logistic regression analyses.

Table 2
Accelerated resolution of zoster associated pain (Beutner et al., 1995)

	Intent-to-treat analysis, hazard ratio[a]	P[b]
Valaciclovir 7 day versus acyclovir	1.34 (1.12, 1.60)	0.001
Valaciclovir 14 day versus acyclovir	1.22 (1.03, 1.46)	0.03
Valaciclovir 7 day versus valaciclovir 14 day	1.10 (0.92, 1.30)	NS

[a] Intent-to-treat analysis — analysis utilizes all subjects randomized.
[b] Statistical calculations determined by Cox logistic regression analyses.

treatment group had a shorter duration of zoster-associated pain (38 versus 51 days; $P = 0.001$). Extending valaciclovir therapy to 14 days did not result in any additional benefit (Table 2).

Famciclovir has also been evaluated for treatment of dermatomal herpes zoster in immunocompetent patients (de Greef and Famciclovir Herpes Zoster Clinical Study Group, 1994; Tyring et al., 1995). In a placebo-controlled clinical trial, famciclovir accelerated cutaneous healing and reduced the duration of both viral shedding and post-herpetic neuralgia (Tyring et al., 1995). In a subset of subjects over 50 years of age, the duration of post-herpetic neuralgia was reduced from a median of 163 to 63 days in the placebo and famciclovir treatment groups, respectively ($P = 0.004$) (Tyring et al., 1995). Successful treatment with famciclovir at a dose of 750 mg once daily for 7 days has also been claimed (Ashton, 1996). In the United States, the recommended dose of famciclovir for uncomplicated herpes zoster is 500 mg 3 times daily, while doses of 250 mg 3 times daily and 750 mg once daily are approved in Europe and the United Kingdom. The effects of famciclovir on pain are summarized in Table 3.

6. Adjunctive therapies

Appropriate supportive care can help make patients with herpes zoster more comfortable. Skin lesions should be kept clean and dry to reduce the risk of bacterial superinfection. Astringent soaks (e.g. Domeboro solution) may be soothing. Most patients with acute herpes zoster will have very significant pain and will require symptomatic therapy with narcotic analgesics. Clinicians should not underestimate the requirement for po-

Table 3
Hazard ratios

	Zoster-associated pain (intent-to-treat analysis of patients treated within 72 h of rash onset)	Zoster-associated pain (efficacy evaluable subgroup, treated within 48 h of rash onset with age as a continuous covariate)	Post-herpetic neuralgia
500 mg famciclovir or	–[a]	–	1.7 (1.1, 2.7) $P = 0.02$
750 mg famciclovir versus placebo (Tyring et al., 1995)	–	–	1.9 (1.2, 2.9) $P = 0.005$
250 mg famciclovir[b]	1.4 (na[d]) $P = 0.086$	1.62 (1.06, 2.46) $P = 0.025$	–
500 mg famciclovir[b]	1.8 (na) $P = 0.003$	1.51 (0.99, 2.29) $P = 0.053$	–
750 mg famciclovir[b] versus 800 mg acyclovir[c] (de Greef and Famciclovir Herpes Zoster Clinical Study Group, 1994)	1.4 (na) $P = 0.05$	1.39 (0.925, 2.09) $P = 0.113$	–

[a] –, not analyzed in publication.
[b] 3 ×/day.
[c] 5 ×/day.
[d] na, confidence intervals not provided.

Table 4
Disease resolution according to Cox regression model (Whitley et al., 1996)[a]

Dependent variable	Risk ratio (95% CI)[b] Acyclovir plus prednisone compared with placebo
1-month evaluation of cutaneous healing	
Time to total crusting	2.27 (1.46, 3.55)[c]
Time to total healing	2.07 (1.26, 3.38)[c]
1-month evaluation of quality of life	
Time to cessation of acute neuritis	3.02 (1.42, 6.41)[c]
Time to uninterrupted sleep	2.12 (1.25, 3.58)[c]
Time to return to 100% usual activity	3.22 (1.92, 5.40)[c]
Time to no use of analgesics agents	3.15 (1.69, 5.89)[c]
6 month evaluation of pain	
Time to cessation of zoster-associated pain	1.56 (0.92, 2.66)

[a] Prognostic variables included in the model were: sex, race, age, number and duration of lesions prior to enrollment surface area of lesions, and severity of pain at baseline.

[b] Risk ratio — ratio of the risk for achieving cessation of pain between treatment groups.

[c] $P<0.05$; statistical calculations determined by Cox logistic regression analyses.

tent analgesics in older patients with herpes zoster.

The controversial issue of corticosteroid therapy for herpes zoster has recently been addressed in two large controlled clinical trials (Wood et al., 1994; Whitley et al., 1996). These studies demonstrated that the combination of acyclovir plus corticosteroids accelerated healing of skin lesions, reduced requirements for analgesic use, and accelerated the times for return to usual activity and uninterrupted sleep. Despite these benefits on the acute symptoms of herpes zoster, neither study demonstrated any reduction in the incidence of PHN. In the study of acyclovir plus prednisone for herpes zoster conducted in the United States by the NIAID Collaborative Antiviral Study Group, the clinical trial was based on a randomized 2×2 factorial design (Whitley et al., 1996). Pain was assessed serially during the first month of study enrollment (acute neuritis) and also as a continuum extending from study enrollment through 6 months of follow-up (zoster-associated pain). In the study population of relatively healthy patients over 50 years of age, pain and quality-of-life endpoints (which included return to usual activities, ability to sleep uninterrupted, and cessation of analgesic use) were evaluated as functions of treatment and other covariates. Based on a step-wise Cox regression model, two covariates predicted the times to resolution of acute neuritis and ZAP. These symptoms resolved significantly faster in patients with no or mild pain at baseline, compared with those with severe or incapacitating pain. Furthermore, patients who had the fewest number of lesions at enrollment had accelerated rates of resolution of acute and long-term pain. These variables significantly predicted resolution of herpes zoster pain independent of the effects of treatment (Table 4).

Thus, a tapering dose of corticosteroids can be considered in older individuals who do not otherwise have contraindications to corticosteroid administration. Because of potential complications of corticosteroid administration, the use of prednisone in this setting is considered controversial by some physicians and should be limited to those older individuals at greatest risk for pain which are those with significant pain and large surface area involvement at the time of presentation (Whitley et al., 1996, 1998). No data are available to support combination therapy of prednisone with famciclovir or valaciclovir, but these regimens should theoretically be as efficacious as prednisone with acyclovir.

Treatments which will consistently and reliably reduce the risk of chronic pain remain an unmet need in herpes zoster management. Drugs such as tricyclic antidepressants (Watson et al., 1992) and gabapentin (Rowbotham et al., 1998) have beneficial effects for treatment of established post-herpetic neuralgia. The potential utility of these drugs in patients with acute herpes zoster has not yet been investigated.

7. Summary of treatment of herpes zoster

Acyclovir, valaciclovir, and famciclovir are currently available for treatment of uncomplicated herpes zoster in immunocompetent patients. These drugs are all well tolerated and appear to be approximately comparable in clinical efficacy, although data from comparative trials are limited. Specifically, no randomized clinical studies comparing valaciclovir and famciclovir for therapy of herpes zoster have been published. However, because of their improved pharmacokinetic profiles and simpler dosing regimens, valaciclovir and famciclovir have emerged as the drugs of choice for this indication. Immunocompetent individuals under 50 years of age who develop herpes zoster tend to have relatively benign courses and are at low risk for chronic pain. Many physicians elect to manage these patients with analgesics alone and consider antiviral therapy to be optional. Older patients, however, are at increased risk for more severe disease and long-term complications and should be more aggressively treated with antiviral drugs. The subpopulation of herpes zoster patients most likely to benefit from antiviral therapy are those over the age of 60 who present with significant pain at onset and who have a large number of lesions within the involved dermatome. Administration of an antiviral drug should be considered mandatory for patients presenting with active herpes zoster involving the first division of the trigeminal nerve, primarily to prevent ocular complications that are potentially sight-threatening.

Physicians frequently encounter patients who present beyond the 48–72-h window that is considered the optimal time for initiation of antiviral therapy for herpes zoster. Very little information from clinical trials is currently available to support the value of these drugs for herpes zoster that has been clinically apparent for >72 h. One clue that clinicians may find useful is to examine the cutaneous eruption carefully for evidence of ongoing new vesicle formation. The presence of new vesicles (that is, those that are clear and not yet pustular) correlates well with ongoing VZV replication and may suggest that the patient would still benefit from antiviral drug therapy.

Finally, as with all infectious diseases, prevention is preferable to treatment. Investigators have hypothesized that administration of a live VZV vaccine to older adults (who are already latently infected with VZV) may stimulate the waning cellular immune responses, thereby preventing herpes zoster during the last decades of life when patients are at highest risk for shingles (Levin et al., 1994). Controlled clinical trials are currently ongoing to determine whether administration of a VZV vaccine can reduce the frequency or severity of herpes zoster in older adults.

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