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Comparative study of the efficacy and safety of valaciclovir versus acyclovir in the treatment of herpes zoster

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Acyclovir, a specific and selective inhibitor of the replication of *Herpesviridae* family, has well-documented efficacy and tolerability in the treatment of herpes zoster. Its limited oral bioavailability and short half-life, however, necessitates frequent dosing. Valaciclovir, the *l*-valyl ester of acyclovir, could be rapidly converted to acyclovir after oral administration, resulting in a three- to five-fold increase in acyclovir bioavailability compared with oral acyclovir in humans. Valaciclovir allows less frequent dosing and maintains the safety profiles of the parent drug. During the period from October 1996 through May 1998, a randomized, prospective study was performed in the Kaohsiung Veterans General Hospital to compare the safety and efficacy of valaciclovir with acyclovir in the treatment of herpes zoster in Taiwanese patients. Patients presenting with herpes zoster within 72 h after the onset of rash were enrolled and randomized to receive one of the following treatments: 1000 mg valaciclovir three times daily for 7 days or acyclovir 800 mg five times daily for 7 days. Patients were followed up for 29 days beginning with the start of therapy. A total of 57 patients were enrolled and randomized to receive valaciclovir (n = 32) or acyclovir (n = 25). Five patients in the valaciclovir group and three in the acyclovir group did not complete the study. The intent-to-treat analysis (57 patients) showed that valaciclovir significantly accelerated the resolution of herpes zoster-associated pain compared with acyclovir; on day 29, the valaciclovir group was 23% superior to the acyclovir group. There was no clinically significant difference in the nature, frequency or severity of adverse events between these two groups, although one and three adverse events were reported in the acyclovir and valaciclovir group, respectively. Thus, we conclude that in the management of herpes zoster, valaciclovir accelerates the resolution of pain and offers a simpler dosing, and maintains the favorable safety profile of acyclovir.

Key words: Acyclovir, valaciclovir, herpes zoster

It is estimated that between 60% to 95% of the total population worldwide has been infected with one or more viruses belonging to the *Herpesviridae* family [1, 2]. Herpes zoster (shingles) remains an important medical problem throughout the world. Its occurrence was caused by the reactivation of the varicella-zoster virus, a virus that has developed a complex survival strategy that allows it to remain latent in sensory or autonomic ganglia and avoid destruction by the immune system following a primary infection of varicella or chickenpox, usually in childhood [1,3-7].

Although herpes zoster may occur at any age, in the otherwise immunocompetent individuals, the reported incidence in the general population has ranged from 0.8 to 4.8 per 1000 persons [8]. An increase in incidence is observed in individuals older than 50 years, and it has been estimated that 50% of individuals who reach the age of 85 years will have suffered at least one attack of herpes zoster [6,7,9-11]. Acute herpes zoster presents with skin rashes distributed over one or more der-matomes usually resolve within approximately 4 weeks; however, in the untreated patient the associated pain, or post-herpetic neuralgia, can persist for several months or even years and can be a serious disabling condition, particularly in the elderly [10,12, 13]. The pain is often accompanied by abnormal sensations such as allodynia, tingling or numbness [10]. Replication of varicella-zoster virus in the ganglion of the involved nerve results in destructive inflammation and/or nerve dysfunction [7,13]. This may partly explain the pain, although the full pathogenesis of the syndrome is not clear [13].

For the management of herpesvirus infection in the otherwise healthy individuals, antiviral drugs must be

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effective, well tolerated and specific for virus-infected cells if they are to be of clinical use [14].

Acyclovir is the first antiherpetic drug developed that exhibits efficacy and tolerability. When administered orally (800 mg 5 times daily for 7-10 days), which is the most widely used treatment for acute herpes zoster during the acute stage, it halts or slows down viral replication, thus reducing the risk of viral induced neurological or eye damage [1,15,16]. It speeds the healing of the rash, reduces the formation of new lesions, and decreases the severity of zoster-associated pain [1,10,15-18]. In some studies, acyclovir therapy initiated early in the course of acute zoster (within 72 h at the onset of rash) reduced the incidence, severity, and duration of chronic zoster-associated pain [1,10, 15,19]. Studies in patients with zoster ophthalmicus showed that acyclovir reduces the incidence and severity of intraocular complications such as uveitis and keratitis, as well as the severity of chronic pain [20]. The limited oral bioavailability of acyclovir, however, necessitates frequent dosing to achieve a better therapeutic concentration in plasma for the treatment of acute herpes zoster [10,18,21].

Valaciclovir (Valtrex), the *l*-valyl ester of acyclovir, could be rapidly and completely converted to acyclovir in the body after oral administration, and results in an acyclovir bioavailability three to five times greater than that of oral acyclovir in humans. It has also been shown to provide an effective and well-tolerated treatment for herpes zoster [10,18].

This study compared the efficacy and safety of valaciclovir with acyclovir in the treatment of herpes zoster in Taiwanese patients in the Kaohsiung Veterans General Hospital using rash and zoster-associated pain as the endpoints for efficacy assessment.

Materials and Methods

This randomized, parallel and controlled study of valaciclovir versus acyclovir for the treatment of acute herpes zoster was carried out in the Kaohsiung Veterans General Hospital during the period from October 1996 through May 1998.

Patients

Patients aged 18 years or older, who were otherwise healthy, and presented with clinically diagnosed localized herpes zoster within 72 h after the onset of rash were considered eligible for participation in the study. Acute herpes zoster was clinically diagnosed in patients who met the criteria for enrollment based on the presence of unilateral dermatomal rash. Written informed consent was obtained from each patient prior to enrollment.

Drug administration

Patients were randomized to receive either 1000 mg of valaciclovir three times per day from the day of presentation for 7 days or oral 800 mg of acyclovir five times per day for the same period.

Efficacy assessments

The outcome measures of treatment response included the severity of zoster-associated pain up to day 29, presence or absence of zoster-associated abnormal sensation up to day 29, and the proportion of patients who reached healing of 50% or 100% of the surface area of the original rash (ie crusts lost) on day 8.

The investigator evaluated the zoster rash at presentation, including the proportion of the total lesion area consisting of macules/papules, vesicles, crusts and healed rash. The percentage of rash was determined in 10% increments. Definitions of lesion stages were as follows:

1. Maculopapular. Reddened and/or raised above the surface of the surrounding skin; solid and not containing fluid;
2. Vesicular. Blister-like, raised above the surface of the surrounding skin and containing fluid. Includes pustules, which contain cloudy or darkened fluid and ulcers, which may be present when the roof of the vesicle is lost, before a crust forms;
3. Crusted. Dry, scab-like layer that forms after the vesicular fluid is lost. Includes ulcers, which may be

Table 1. Demographic characteristics of herpes zoster patients by treatment group

	Acyclovir (n = 25)	Valaciclovir (n = 32)	*p*
Age (yr, mean ± SD)	63.3 ± 11.63	63.6 ± 12.86	0.927
Sex ratio (male:female)	18:7	19:13	0.322
Pain at presentation before day 1	22 (88%)	30 (93.8%)	0.448
Average days to onset of pain (day, mean ± SD)	4.1 ± 0.97	3.8 ± 0.85	0.256
Abnormal sensations before day 1	5 (20%)	3 (9.4%)	0.253
Average days to onset of abnormal sensations (day, mean ± SD)	2.6 ± 1.14	3.0 ± 1.00	0.500

present after the crust is lost, before re-epithelialization occurs;
4. Healed. Dry, non-glistering, re-epithelialized skin after the crust falls off. Erythema and scarring may be present.

A further assessment of the rash was made on day 8, when progression to a 50% or 100% loss of crusts was determined. To evaluate the pain and abnormal sensations, patients were asked to record these sensations daily on a diary card (day 1-28). Assessment of the severity of pain and abnormal sensations were conducted in both the valaciclovir and acyclovir arms. Furthermore, the impact of pain on daily activities was determined using a numerical scale with six levels as follows:

No pain	0 = no pain or discomfort
Just noticeable	1 = pain can easily be ignored
Mild	2 = pain does not interfere with daily activities
Moderate	3 = pain interfered with concentration or sleep
Severe	4 = pain interfered with all but basic needs
Very severe	5 = pain required rest or bed rest.

Concomitant use of medications to control pain, including analgesics, was recorded at each assessment. All adverse experiences were recorded during the treatment phase.

Statistical analysis

Analysis was conducted using SPSS software (Version 6.1). The difference in the severity of zoster-associated pain between the two treatment arms was compared using likelihood ratio chi-square test. Because of the small number of patients involved, other outcome measures were only evaluated descriptively. These include whether data was obtained on the presence or absence of abnormal sensations, and the proportion of patients who had reached the 50% or 100% healing over the rash surface area.

Table 2. Comparison of herpes zoster patients without zoster-associated pain and/or burning post-antiviral treatment

Day	No. (%) of patients		*p*
	Valaciclovir group (n = 32)	Acyclovir group (n = 25)	
1	0	0	
8	9 (28.1)	5 (20.0)	0.477
15	15 (46.9)	9 (36.0)	0.408
22	18 (56.3)	11 (44.0)	0.352
29	23 (71.9)	12 (48.0)	0.006[a]

[a]The rate of resolution of pain in the valaciclovir group was significantly higher than in the acyclovir group.

Table 3. Comparison of herpes zoster patients without zoster-associated abnormal sensation post-antiviral treatment

Day	No. (%) of patients		*p*
	Valaciclovir group (n = 32)	Acyclovir group (n = 25)	
1	27 (84.4)	21 (84.0)	0.969
8	20 (62.5)	20 (80.0)	0.147
15	21 (65.6)	18 (72.0)	0.606
22	28 (87.5)	18 (72.0)	0.142
29	27 (84.4)	18 (72.0)	0.257

Results

A total of 57 patients with acute herpes zoster were enrolled in the study. They were randomized into valaciclovir (n = 32) and acyclovir (n = 25) treatment groups. Among these patients, 49 (86%) completed the 4-week study according to the study protocol. Five patients in the valaciclovir group and three patients in the acyclovir group did not complete the study as planned due to protocol violation (6 patients from the acyclovir group), adverse events (1 patient from the acyclovir group), and withdrawal of consent (1 patients from the valaciclovir group). None of these patients were withdrawn because of serious adverse events. The data was analyzed based on the intent-to-treat basis.

Demographic and baseline characteristics were similar in the two treatment groups (Table 1). Overall, there were 20 (35.1%) women and 37 (64%) men, and the mean age was 63.6 ± 12.9 years in the valaciclovir group and 63.3 ± 11.6 years in the acyclovir group.

As for the patients whose crusts had fallen in over 50% of the affected area, those in the valaciclovir group had a slightly quicker healing rate than those in the acyclovir group, but this difference was not sig-nificant ($p = 0.805$).

Table 2 shows the outcome of zoster-associated pain after treatment. On day 29, the rate of pain cessation in the valaciclovir group (71.9%) was higher than that in the acyclovir group ($p < 0.05$).

The results concerning reports of abnormal sensations are shown in Table 3. Although on day 15, a higher percentage (72%) of patients in the acyclovir group than in the valaciclovir group (65.6%) reported an absence of abnormal sensation, at the end of study (day 29), 84.4% of patients in valaciclovir group reported an absence of abnormal sensation compared with 72% in the acyclovir group ($p = 0.257$).

Three patients in the valaciclovir group and one patient in the acyclovir group developed adverse effects.

Adverse effects in the valaciclovir group included skin rash, constipation, and dizziness. One patient in the acyclovir group developed diarrhea. No serious adverse effect were observed in either groups.

Discussion

This 4-week, randomized, parallel and controlled study has demonstrated that treatment with valaciclovir three times daily is effective in treating patients with herpes zoster.

Valaciclovir provided a faster resolution of pain, with 28.1% resolution of pain on day 8 as compared with 20% in the acyclovir group. Pain is the most debilitating feature of herpes zoster [7,11,13,22]. The majority of patients experience pain immediately before and during the acute rash phase. However, a more important clinical concern is to prevent or reduce the possibility of persistent pain [23]. In several previous studies, acyclovir was shown to have a beneficial effect on chronic herpes zoster-associated pain. In the current study, analysis of the zoster-associated pain showed significantly better pain resolution in the valaciclovir group than in the acyclovir group, and this trend persisted throughout the study period. In a multicenter (1141 patients) trial, Beutner *et al* [23] demonstrated that valaciclovir for 7 days significantly shortened the duration of herpes zoster-associated pain ($p < 0.005$) compared with acyclovir; and the median time to cessation of pain for valaciclovir and acyclovir was 38 days and 51 days, respectively. As a result, patients treated with valaciclovir had a more satisfactory outcome in pain control than those treated with acyclovir. In this study, the treatment effect in the valaciclovir group was slightly superior to that of the acyclovir group according to direct assessment of the rash. This finding is similar to results from other studies [5-7,10,11,13,22,24,25]. To achieve the same level of therapeutic effect, acyclovir needs to be taken five times (total 4 g) daily; however, valaciclovir needed to be taken only three times (total 3 g) daily.

The less frequent dosing needs of valaciclovir is mainly due to its enhanced bioavailability of 65%, compared to 15% to 20% for acyclovir. Valaciclovir, the *l*-valyl ester of acyclovir, produces higher plasma levels of acyclovir, allowing more convenient dosing [18,21,23,26], and resulting in better patient compliance and a lower incidence of adverse events [7,11,13,22].

The safety profile of acyclovir has been carefully established during more than 12 years of clinical use. In the current study, there were no clinically significant differences in the nature, frequency, or severity of adverse events between the two treatment groups. Although there were three adverse events reported in the valaciclovir group, all of them were mild. Previous placebo-controlled trial of oral acyclovir and valaciclovir in immunocompetent adults with herpes zoster have shown that adverse events are typical features of this disease rather than the result of therapy with acyclovir or valaciclovir [10]. Similarly, in this study, none of the adverse events were directly related to the treatment.

In conclusion, this study demonstrates that the administration of valaciclovir three times per day is an effective and safe treatment for acute herpes zoster. Valaciclovir treatment has the benefits of rapid resolution of the signs and symptoms of herpes zoster and an equivalent safety profile to acyclovir. Furthermore, using valaciclovir has the convenience of a three-times daily dosing, thereby ensuring better patient compliance, which makes this regimen an excellent choice for the treatment of herpes zoster.

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