Factors Influencing the Effect of Valaciclovir in Treating Acute Herpes Zoster

Dr. T. S. Au, Dr. K. K. Lo, Dr. L. Y. Chong, Dr. K. M. Ho, Dr. K. H. Lau and Dr. C. N. Look
Social Hygiene Service (Dermatology), Department of Health, Hong Kong

ABSTRACT

We conducted an open multicentre study to examine the factors that may possibly influence the effect of valaciclovir in treating acute herpes zoster. Forty-two patients were enrolled and 36 of them completed the study. They received valaciclovir 1000mg three times per day for one week. The median duration of zoster-associated pain was 21.5 days. Forty-two per cent of patients had pain lasting more than 28 days and 11% had pain longer than 24 weeks. Age of the patient was found to be an important predictor of the duration of zoster-associated pain; older patients tend to have chronic pain. Weight, body mass index, duration of rash before starting treatment, duration of pain before starting treatment, duration of abnormal sensation before starting treatment, sex and body region involved were not found to have statistically significant association with the outcome of treatment.

Keywords: Herpes zoster, Valaciclovir, treatment, age, zoster-associated pain

INTRODUCTION

Herpes zoster is caused by reactivation of Varicella-zoster virus which remains latent in sensory or autonomic ganglia following primary varicella infection usually in childhood.[1] Thoracic dermatomes are most commonly involved (50-56% patients). The cervical and cranial dermatomes are involved in 24-34% of patients.[2]

Persistent pain after the acute rash has subsided is the most common complication of herpes zoster. In recognition that most patients experience continuous pain with herpes zoster and to escape the arbitrary divisions of acute pain and post-herpetic neuralgia, the term 'zoster-associated pain' has been proposed to describe the continuum of pain associated with shingles.[3] Adoption of this concept facilitates the analysis of pain data from various clinical trials that evaluate antiviral treatment of herpes zoster.

It has been shown that aciclovir (800mg five times daily for 7-10 days) can accelerate rash healing, reduce new lesion formation and reduce severity of zoster-associated pain in patients suffering from herpes zoster.[4-6]

Valaciclovir, the L-valyl ester of aciclovir, is a prodrug that is rapidly metabolised to aciclovir and L-valine, an essential amino acid. Thus, the antiviral activity of valaciclovir is that of aciclovir. The absolute bioavailability of aciclovir delivered by oral valaciclovir is greater than that achieved after oral aciclovir administration; this is an important characteristic of the drug.[7] Valaciclovir is better absorbed through the gut wall than orally administered aciclovir, probably because of more rapid uptake into intestinal brush border membranes by an active saturable transporter.[8]

There has been a relative lack of published data in using valaciclovir to treat herpes zoster in Hong Kong. We thus performed an open study to examine the factors that may possibly influence the effect of valaciclovir in acute herpes zoster.

MATERIAL AND METHODS

Patients

The study was approved by the Ethical Committee of the Department of Health in Hong Kong. Inclusion criteria included patients who were eighteen years of age or older, with a clinical diagnosis of localised acute herpes zoster and willing to give written informed consent. Pregnant or lactating women, as well as

Correspondence address:
Dr. T. S. Au
Social Hygiene Service Headquarters
3/F, Sai Ying Pun Jockey Club Clinic
134 Queen's Road West
Hong Kong

sexually active women of childbearing potential not employing adequate contraception were excluded.

Study design

This was an open multicentre study of valaciclovir for the treatment of herpes zoster. Three clinics were involved, namely Yaumatei Dermatology Centre, Sai Ying Pun Dermatology Clinic and Yung Fung Shee Dermatology Clinic. Patients presenting with acute herpes zoster were given 1000mg valaciclovir three times per day for seven days. They were followed up for 24 weeks. Zoster-associated pain and abnormal sensations were assessed from presentation till the end of week 24. All concomitant medications taken by the patients were recorded. Systemic or topical agents with anti-Varicella-zoster virus activity, capsaicin or other topical applications to the rash that would obscure evaluation were not allowed.

Efficacy measures

The primary efficacy parameter of a treatment response was determined by time to complete cessation of zoster-associated pain while the secondary efficacy parameter was determined by time to complete cessation of zoster-associated abnormal sensations. Patients were given a diary to note the days of pain and abnormal sensations. Patients were assessed on day 1, 8, 29 and then 4-weekly till week 24.

Adverse experiences

All adverse experiences were recorded. A serious adverse experience is defined as any event that is fatal or life-threatening, permanently or significantly disabling, requires or prolongs hospitalisation.

RESULTS

The data presented in this study are part of the international study "VIZA: an open multicentre study to examine the influence of age and body region involved on the effect of valaciclovir in acute herpes zoster" designed by Department of Clinical Virology, the Wellcome Research Laboratories.

Forty-two patients were enrolled in the study. Eleven were female and 31 were male. The mean age was 49 years (range, 23-78). Twenty five (59.5%) patients had thoracic dermatomes involvement. Eight (19.0%) had cranial involvement and seven of them had zoster ophthalmicus; seven (16.7%) had cervical involvement and two (4.8%) had lumbar involvement. All patients were Oriental.

Thirty-six patients completed the whole study. Five defaulted follow up after finishing the one-week course of valaciclovir. They claimed that they were too busy to record the pain and abnormal sensation in the diary. One patient could not finish the medication because of experiencing nausea and headache after taking the drug.

The median duration of zoster-associated pain was 21.5 days (range six days to more than 24 weeks). Fifteen patients (41.7%) had zoster-associated pain longer than 28 days and four (11.1%) had zoster-associated pain longer than 24 weeks.

The continuous variables that may affect the effect of treatment include age of the patient, weight, body mass index, duration of rash before starting treatment, duration of pain before starting treatment and duration of abnormal sensation before starting treatment. Linear regression was used to correlate these factors with the duration of zoster-associated pain and abnormal sensations. Oneway analysis was performed to assess the categorical variables (sex and body region involved) with zoster-associated pain and abnormal sensations.

It was shown by linear regression that the age of patients significantly correlated with the duration of zoster-associated pain (Figure 1). Older patients tended to have longer zoster-associated pain (r=0.474 at 0.01 significance level).

Weight, body mass index, duration of rash before starting treatment, duration of pain before starting treatment, duration of abnormal sensation before starting treatment, sex and body region involved were not found to have statistically significant

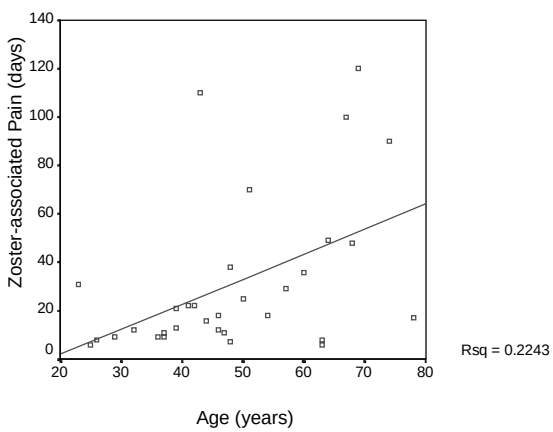

Figure 1: Zoster-associated Pain with Age

association with the outcome of treatment (Tables 1-3).

All except one patient finished the one week course of valaciclovir. Twenty-five percent of the patients experienced adverse events. They included headache (11.1%), dyspepsia (8.3%), nausea (2.8%) and thirst (2.8%). All were mild in severity. The patient who could not finish the medication complained of nausea and headache.

DISCUSSION

Between 1985 and 1991, there were four published placebo-controlled, double-blind trials evaluating the efficacy of oral aciclovir in immunocompetent patients with acute herpes zoster.[4,5,6,9] The trials showed that aciclovir therapy significantly reduced the duration of rash and pain during the acute phase. Three out of the four studies showed that aciclovir could reduce the incidence of chronic pain with the most significant effects in the first 3 months after the onset of the rash.[5,6,9]

In our study, we confirmed that age is an important predictor of the outcome of herpes zoster. Even with anti-viral treatment, older patients are more prone to have chronic pain. Although weight, body mass index, duration of rash before starting treatment, duration of pain before starting treatment, duration of abnormal sensation before starting treatment sex, body region involved and presence of zoster ophthalmicus were not found to have statistically significant association with the outcome of treatment, we must admit that the sample

Table 1. Correlation of weight, body mass index, duration of rash before starting treatment, duration of pain before starting treatment, duration of abnormal sensation before starting treatment and outcome

	Duration of zoster-associated pain	Duration of zoster-associated abnormal sensation
Weight	Pearson correlation = 0.249 Significance = 0.170	Pearson correlation = 0.249 Significance = 0.170
Body mass index	Pearson correlation = 0.249 Significance = 0.170	Pearson correlation = 0.125 Significance = 0.497
Duration of rash before starting treatment	Pearson correlation = -0.217 Significance = 0.234	Pearson correlation = -0.051 Significance = 0.780
Duration of pain before starting treatment	Pearson correlation = -0.121 Significance = 0.548	Pearson correlation = 0.039 Significance = 0.843
Duration of abnormal sensation before starting treatment	Pearson correlation = -0.119 Significance = 0.546	Pearson correlation = 0.120 Significance = 0.553

Table 2. Oneway Analysis

Sex with zoster-associated pain and abnormal sensation

	sum of squares	df	mean square	F	significance
Zoster-associated pain					
between groups	17.510	1	17.510	0.017	0.899
within groups	31834.958	30	1061.165		
total	31852.469	31			
Zoster-associated abnormal sensation					
between groups	128.714	1	128.714	0.176	0.678
within groups	21962.754	30	732.092		
total	22091.469	31			

Table 3. Oneway Analysis

Body region involved with zoster-associated pain and abnormal sensation

	sum of squares	df	mean square	F	significance
Zoster-associated pain					
between groups	9230764	3	307. 921	0.267	0.848
within groups	32233.111	28	1151.183		
total	33156.875	31			
Zoster-associated abnormal sensation					
between groups	811.319	3	270. 440	0.356	0.785
within groups	21280.150	28	760.005		
total	22091.469	31			

size of our study was not large enough. This drawback might lead to failure to detect less intense association between the variables and the effect of valaciclovir in acute herpes zoster.

From our study, valaciclovir is a well tolerated drug and its side effects are usually mild. Forty-one out of 42 patients were able to complete the one-week course treatment. The only patient who failed to finish the drug complained of nausea and headache. However, it must be noted that she had pre-existing anxiety neurosis being followed up in a psychiatric clinic. The psychiatric condition might contribute to her perception of side effects.

The treatment of post-herpetic neuralgia is difficult.[10] Supportive analgesic for acute pain should be considered: paracetamol and nonsteroidal anti-inflammatory drugs are often used. The use of long term opiates should be avoided as these may lead to physical dependence.[11] Amitriptyline is useful, especially for hyperaesthesia and constant burning pain, an effect independent of any antidepressant activity.[12] For stabbing pain, sodium valproate or other anticonvulsant may be tried. The starting dose should be low in elderly patients. Topical capsaicin 0.025% is a substance P depleter. It relieves pain in many patients although it may cause a burning sensation by itself.[13]

A large randomised trial has compared oral valaciclovir with oral aciclovir in 1141 immunocompetent patients with herpes zoster.[14] It showed that valaciclovir 1000mg three times per day for seven or 14 days significantly accelerated the resolution of zoster-associated pain by, on average, 34% and 22% (on the basis of hazard ratios), respectively, compared with aciclovir ($p<0.03$). Valaciclovir treatment initiated within 48 hours of rash onset appeared to confer no additional benefit over treatment started within 72 hours. The more rapid resolution of pain after valaciclovir therapy might be explained by the better absorption and thus bioavailability.

CONCLUSION

Prolonged zoster-associated pain is the most common complication of acute herpes zoster in immunocompetent patients. Even with active treatment with valaciclovir, age is still an important predictor of the outcome of herpes zoster. As valaciclovir is administered in a more convenient oral dosage regimen, it may ultimately succeed aciclovir as a first-line treatment for herpes zoster.

It has to be noted that the data collected in the larger international multicentre study are still in the process of analysis. The findings presented in this paper do not represent those of the international multicentre study.

Acknowledgment

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Learning points:

Age is an important predictor of the occurrence of prolonged zoster-associated pain. Even with anti-viral treatment, older patients are more prone to have chronic pain.

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