

Double-blind, randomized, acyclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster

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This randomized, double-blind, parallel-group study compared the efficacy and safety of famciclovir administered at 250 mg thrice daily with acyclovir 800 mg 5 times daily for the treatment of acute uncomplicated herpes zoster in immunocompetent adults. A total of 55 patients participated in this trial. Twenty seven patients (49.1%) were randomized into the famciclovir plus placebo treatment group and 28 (50.9%) into the acyclovir plus placebo group. Six of the 55 patients did not complete the study. Two of these patients were in the famciclovir plus placebo group and dropped out due to deviation from the study protocol. Four patients in the acyclovir plus placebo group did not complete the study protocol due to adverse events (n = 2), deviation from the protocol (n = 1), or loss to follow-up (n = 1). Treatment was initiated within 72 h of onset of the zoster rash and was continued for 7 days. When treatment was initiated within 72 h, famciclovir was as effective as acyclovir for healing the cutaneous lesion, as indicated by the time to full crusting, loss of acute phase pain, loss of vesicles, and loss of crusts. Famciclovir was well tolerated and had a more favorable adverse event profile compared to acyclovir. Constipation, hematuria, and glycosuria were the most commonly reported adverse events, but only constipation was considered to have a possible relationship to the treatment. In conclusion, famciclovir, administered less frequently and at lower unit doses than acyclovir, is an effective treatment for uncomplicated herpes zoster.

Key words: Acyclovir, famciclovir, herpes zoster, randomized controlled trial

Famciclovir is a new member of the guanine nucleoside family of drugs. It has recently been approved for the treatment of herpes zoster in the United Kingdom, the United States and several other countries. Famciclovir is a well absorbed oral form of penciclovir (77% bioavailable) [1]; a novel, selective, antiviral agent with activity against varicella-zoster virus (VZV) [2,3], herpes simplex virus (HSV) type 1 and 2, and Epstein-Barr virus. Both the relative and the absolute potency of penciclovir and acyclovir are dependent on the host cell and assay method used, and inhibitory concentrations are generally comparable in vitro [2,4,5]. However, the active triphosphate form of penciclovir has a prolonged intracellular half-life in both HSV- (10 to 20 h) and VZV-infected cells (9.1 h) compared with acyclovir-triphosphate (<1 h for both HSV- and VZV-infected cells)

[6-8]. These findings indicate that famciclovir has the potential to be administered at a lower dose and less frequently than acyclovir without compromising therapeutic efficacy. The safety and efficacy of famciclovir are not well documented in Taiwan.

The aim of this study was to compare the efficacy and safety of famciclovir at a dosage of 250 mg 3 times daily for 7 days with acyclovir at a dosage of 800 mg 5 times daily for 7 days in Taiwanese patients with uncomplicated herpes zoster.

Materials and Methods

Study design

A randomized, double-blind, parallel-group design was used to compare famciclovir and acyclovir in domiciliary or hospital-based patients suffering from herpes zoster who were over the age of 18 years. Patients enrolled in the study satisfied the inclusion criteria during the screening visit (day 1), and were randomized in a

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double-blind fashion to receive either 250 mg famciclovir thrice daily or acyclovir 800 mg (2 capsules) 5 times daily in a 1:1 ratio for a period of 7 days.

Study population

Only immunocompetent patients over the age of 18 with uncomplicated herpes zoster, characterized by localized, cutaneous lesions (papules, macules or vesicles), presenting within 72 h of the onset of rash, were eligible for inclusion in this study. Patients with complications of herpes zoster, including ocular or visceral involvement, severe disseminated infection (more than 20 lesions outside the primary affected dermatome), motor neuropathies, encephalitis or cerebrovascular complications were excluded. Pregnant or nursing women, patients with concurrent malignancy receiving chemotherapy, patients receiving chronic steroid therapy, patients with hematological malignancy, patients with autoimmune disease under immunosuppressive therapy, or patients known to be human immunodeficiency virus (HIV) seropositive at enrollment were also excluded.

Efficacy assessments

Patients were evaluated for pain and healing of the cutaneous lesions on each of the 7 days while receiving treatment and every other day for 7 days post-therapy, then every 7 days for at least a total of 28 days. The assessment of efficacy included a primary efficacy variable and secondary efficacy variables. The primary efficacy variable was defined as the time to full crusting of all herpes zoster lesions. Lesions were defined to be fully crusted when all the papules and vesicles in the primary affected dermatomal region had resolved and crusts had appeared. Secondary efficacy endpoints were defined as time to loss of acute phase pain (pain experienced up to the point when all crusts were lost) and time to loss of vesicles, ulcers and crusts.

Safety assessments

The number and percentage of patients reporting at least 1 adverse event during the treatment protocol were assessed. The intensity of the adverse events was coded according to the World Health Organization Adverse Drug Reactions Preferred Terms. Drug-related adverse events were defined to be those adverse events the investigator assessed as related or possibly related to the study therapy or as being of unknown causality. The complete blood cell count, urinalysis, and serum biochemistry test at baseline and at the end of treatment were monitored.

Statistical analysis

Two patient populations were examined in the statistical analysis: the intent-to-treat population and the safety population. The intent-to-treat population included all randomized patients who had returned for at least 1 post-randomization visit. The safety population included all randomized patients who had received at least 1 dose of treatment. Continuous variables were described by mean, standard deviation (SD) and range. Categorical data were summarized by counts and percentages. Time-to-event data were described by Kaplan-Meier curves. Ninety five percent confidence intervals (95% CI) were calculated when appropriate [9]. Differences in means of continuous variables were evaluated by Student's *t* test. Differences in proportions were evaluated by chi-squared or Fisher's exact test. Differences in 2 groups of time-to-event data were evaluated by log rank test. All tests were 2-sided and a *p* value of less than 0.05 was considered statistically significant.

Results

Patients and baseline information

In total, 55 patients were enrolled in the study and randomized into the 2 treatment groups. Twenty seven patients (49.1%) were randomized into the famciclovir plus placebo treatment group and 28 (50.9%) into the acyclovir plus placebo group. Six of the 55 patients did not complete the study. Two of these patients were in the famciclovir plus placebo group and dropped out due to deviation from the study protocol. Four patients in the acyclovir plus placebo group did not complete the study protocol due to adverse events ($n = 2$), deviation from the protocol ($n = 1$), or loss to follow-up ($n = 1$). The intent-to-treat population consisted of all 55 patients and the safety population consisted of the same 55 patients. The male-to-female ratio in the famciclovir plus placebo treatment group (1.1:1) was significantly less than in the acyclovir plus placebo group (3.71:1) [2-sided Fisher's exact test, $p=0.0496$]. The overall mean age was significantly less in the famciclovir plus placebo group (55.28 ± 18.8 years) than in the acyclovir plus placebo group (64.18 ± 13.83 years) [Student's *t* test, $p=0.0497$]. All patients in both treatment groups were Taiwanese (Table 1). The treatment groups were comparable with respect to height (average height, 163 cm for both treatment groups) and weight (average weight, 60.93 kg and 63.98 kg for the famciclovir plus placebo and acyclovir plus placebo groups, respectively). A history of significant medical/surgical conditions was reported

Table 1. Demographic data of the treatment groups (intent-to-treat population)

Variable	Famciclovir plus placebo n = 27 (%)	Acyclovir plus placebo n = 28 (%)	<i>p</i>
Gender			
Male	14 (51.9)	22 (78.6)	0.0496 ^a
Female	13 (48.1)	6 (21.4)	
Age (years)			
Mean	55.28	64.18	0.0497 ^a
SD	18.80	13.83	
Minimum	19.10	32.60	
Maximum	83.90	86.20	

Abbreviation: SD = standard deviation

^a*p*<0.05.

in 55.6% and 78.6% of the patients in the famciclovir plus placebo and acyclovir plus placebo groups, respectively, including diabetes mellitus, hypertension, minor stroke, peptic ulcer disease, benign prostate hyperplasia, urinary tract infection, previous appendectomy, and previous lower leg fracture. The difference in the prevalence of these conditions between the 2 groups was not significant (2-sided Fisher's exact test, *p*=0.09).

For the majority of patients in both treatment groups, the duration of rash at the start of treatment was between 48 and 72 h (85.2% for the famciclovir plus placebo group and 89.3% for the acyclovir plus placebo group). The distribution of the dermatomal region most affected was similar in both treatment groups. None of the patients in either group had bilateral involvement of the primary affected region. As for the dimension of the primary affected dermatomal region upon screening (day 1), the mean width and mean length of the region was not significantly different between the acyclovir plus placebo group (25.7 cm × 11.8 cm) and the famciclovir plus placebo group (23.2 cm × 11.4 cm) [Student's *t* test, *p*=0.6 for difference in length and *p*=0.85 for difference in width]. The mean area (length × width) of the affected dermatomal region was not significantly different between the famciclovir plus placebo group (379.6 ± 570.0 cm²) and the acyclovir plus placebo group (370.6 ± 388.3 cm²) [Student's *t* test, *p*=0.94]. The total number of lesions present in the primary affected dermatomal region at the screening visit is shown in Table 2. Fewer patients reported development of >50 papules or >50 vesicles in the famciclovir plus placebo group (>50 papules, 6 patients; >50 vesicles, 9 patients) than in the acyclovir plus placebo group (>50 papules, 10 patients; >50 vesicles, 11 patients), but the distribution of the number of lesions was comparable. Few ulcers and crusts

Table 2. Number of lesions present in the primary affected dermatomal region at screening visit (day 1) by treatment group (intent-to-treat population)

Variable	Number	Famciclovir plus placebo n = 27 (%)	Acyclovir plus placebo n = 28 (%)
Papules	<5	3 (11.1)	3 (10.7)
	5-10	6 (22.2)	5 (17.9)
	11-15	3 (11.1)	1 (3.6)
	16-20	3 (11.1)	5 (17.9)
	21-25	3 (11.1)	1 (3.6)
	26-50	3 (11.1)	3 (10.7)
	>50	6 (22.2)	10 (35.7)
Vesicles	<5	7 (25.9)	6 (21.4)
	5-10	3 (11.1)	2 (7.1)
	11-15	1 (3.7)	2 (7.1)
	16-20	1 (3.7)	0
	21-25	2 (7.4)	1 (3.6)
	26-50	4 (14.8)	6 (21.4)
	>50	9 (33.3)	11 (39.3)
Ulcers	<5	26 (96.3)	26 (92.9)
	5-10	1 (3.7)	1 (3.6)
	11-15	0	0
	16-20	0	0
	21-25	0	0
	26-50	0	1 (3.6)
	>50	0	0
Crusts	<5	22 (81.5)	21 (75.0)
	5-10	3 (11.1)	3 (10.7)
	11-15	0	2 (7.1)
	16-20	0	0
	21-25	0	1 (3.6)
	26-50	2 (7.4)	0
	>50	0	1 (3.6)

were found in either treatment group at the screening visit. Total number of lesions was comparable between the 2 groups (40.3 ± 21.3 in the famciclovir plus placebo group, 44.8 ± 15.0 in the acyclovir plus placebo group). No patient in the famciclovir plus placebo group had any lesion outside the primary affected dermatomal region. Three patients (10.7%) in the acyclovir plus placebo group had involvement of at least 1 distant dermatome at the screening visit. The mean number of lesions outside the primary affected dermatomal region was 1.0 ± 2.9 at each visit.

All patients in both treatment groups experienced pain at the time of screening and the distribution of pain intensity was comparable in the 2 groups. Most patients had moderate pain at the time of screening. No clinically significant difference was found in the results of urinalysis, hematology and serum biochemistry examination at baseline between the treatment groups.

Table 3. Analysis of time to full crusting, time to loss of acute phase pain, and time to loss of vesicles, ulcers and crusts

	Estimated rate (95% confidence interval) at day 28 (%)		Log rank test <i>p</i>	Median time (days)		Range (days)	
	Famciclovir plus placebo (F)	Acyclovir plus placebo (A)		F	A	F	A
Full crusting	73.1 (56.0-90.1) ^a	80.3 (64.8-95.7) ^a	0.761	11	10	4-28	5-28
Loss of acute phase pain	46.2 (27.0-65.3) ^a	59.3 (40-78.6) ^a	0.683	20	27	6-28	7-28
Loss of vesicles	100 (86.8-100) ^b	100 (86.8-100) ^b	0.696	6	6	2-28	2-28
Loss of ulcers	100 (87.2%-100) ^b	100 (87.2-100) ^b	0.487	1	1	1-13	1-28
Loss of crusts	84.6 (70.7-98.5) ^a	88.0 (75.2-100) ^a	0.558	20	27	7-28	11-28

^a95% confidence interval calculated by Greenwood's formula.

^b95% confidence interval calculated by the exact binomial method.

Efficacy

Analyses of the primary and secondary efficacy parameters are summarized in Table 3. In all Kaplan-Meier curves, the x-axis represents time since day 1 (screening). For example, there were 27 days since day 1 if an event was observed at the last visit (day 28). Kaplan-Meier curves of the distribution of time to full crusting in the 2 treatment groups are shown in Fig. 1. The median time to full crusting was 11 days in the famciclovir plus placebo group and 10 days in the acyclovir plus placebo group. The difference in the incidence of full crusting during the 28-day observation period was not significant (log rank test, $p=0.761$). Estimated rate of full crusting at day 28 was 73.1% (95% CI, 56.0%-90.1%) in the famciclovir plus placebo group and 80.3% (95% CI, 64.8%-95.7%) in the acyclovir plus placebo group. Since the baseline distribution of age and gender was not comparable between the 2 treatment groups, Cox's proportional hazards model was used to assess the potential impact of age and gender on the difference in treatment effects. Regression coefficients

of the 3 variables in the model were not significant: p values were 0.804 for treatment, 0.975 for age, and 0.522 for gender.

The loss of acute phase pain was generally comparable between the 2 treatment groups during each visit at which it was assessed. The median time to loss of acute phase pain was 20 days in the famciclovir plus placebo group and 27 days in the acyclovir plus placebo group. The difference in the incidence of loss of acute phase pain during the 28-day observation period was not significant (log rank test, $p=0.683$). The estimated rate of loss of acute phase pain at day 28 was 46.2% (95% CI, 27.0%-65.3%) in the famciclovir plus placebo group and 59.3% (95% CI, 40.0%-78.6%) in the acyclovir plus placebo group.

Kaplan-Meier curves of the distribution of time to loss of vesicles in the 2 treatment groups are shown in Fig. 2. The median time to loss of vesicles was 6 days in the famciclovir plus placebo group and 6 days in the acyclovir plus placebo group. The difference in the incidence of loss of vesicles during the 28-day

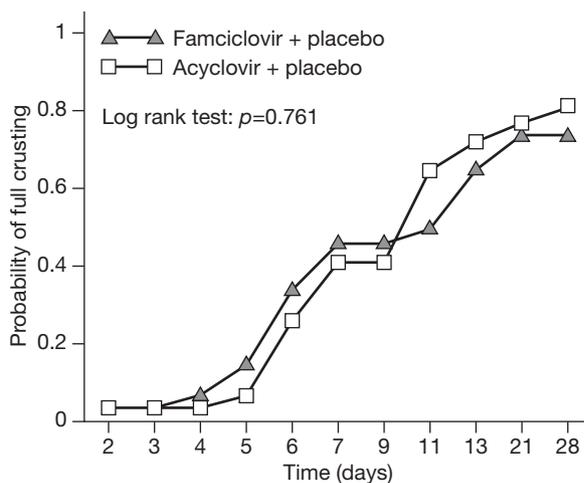


Fig. 1. Comparison of time to full crusting in the famciclovir and acyclovir groups.

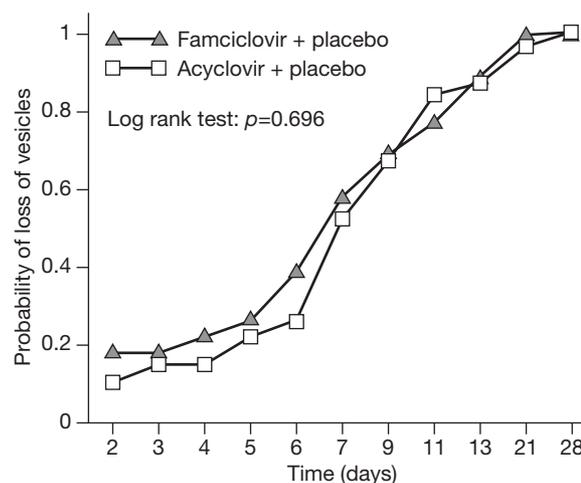


Fig. 2. Comparison of the time to loss of vesicles in the famciclovir and acyclovir groups.

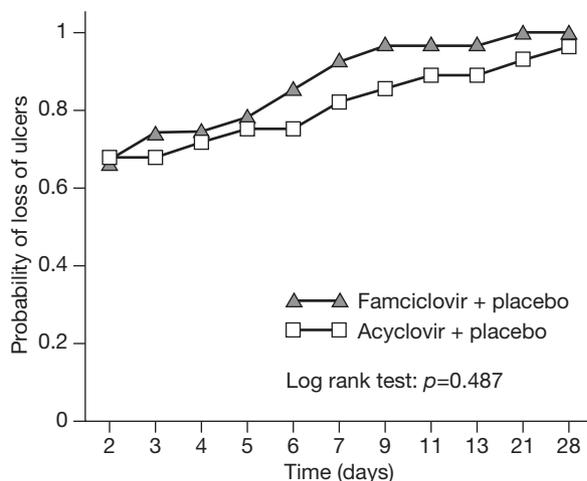


Fig. 3. Comparison of the time to loss of ulcers in the famciclovir and acyclovir groups.

observation period was not significant (log rank test, $p=0.696$). The estimated rate of loss of vesicles at day 28 was 100% (95% CI, 86.8%-100%, by the exact binomial method) in the famciclovir plus placebo group (26 patients had loss of vesicles by day 28 and 1 patient was dropped out before day 28). The estimated rate of loss of vesicles at day 28 was 100% (95% CI, 86.8%-100%, by the exact binomial method) in the acyclovir plus placebo group (26 patients had loss of vesicles by day 28 and 2 patients dropped out before day 28).

Kaplan-Meier curves of the distribution of time to loss of ulcers in the 2 treatment groups are shown in Fig. 3. The median time to loss of ulcers was 1 day in the famciclovir plus placebo group and 1 day in the acyclovir plus placebo group. The difference in the incidence of loss of ulcers during the 28-day observation period was not significant (log rank test, $p=0.487$). The estimated rate of loss of ulcers at day 28 was 100% (95% CI, 87.2%-100%, by the exact binomial method) in the famciclovir plus placebo group, and all 27 patients had loss of ulcers by day 21. The estimated rate of loss of ulcers at day 28 was 100% (95% CI, 87.2%-100%, by the exact binomial method) in the acyclovir plus placebo group (27 patients had loss of ulcers by day 28 and 1 patient dropped out before day 28).

Kaplan-Meier curves of the distribution of time to loss of crusts in the 2 treatment groups are shown in Fig. 4. The median time to loss of crusts was 20 days and 27 days in the famciclovir plus placebo group and the acyclovir plus placebo group, respectively. The difference in the incidence of loss of crusts during the 28-day observation period was not significant (log rank test, $p=0.558$). The estimated rate of loss of crusts at

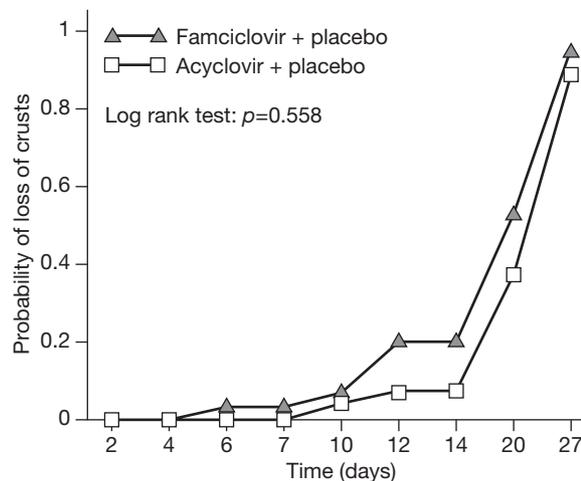


Fig. 4. Comparison of the time to loss of crusts between the famciclovir and acyclovir groups.

day 28 was 84.6% (95% CI, 70.7%-98.5%) in the famciclovir plus placebo group and 88.0% (95% CI, 75.2%-100%) in the acyclovir plus placebo group.

At day 28, 14 patients (53.8%) in the famciclovir plus placebo group and 10 patients (40.7%) in the acyclovir plus placebo group reported pain since the last assessment. This difference was not significant (chi-squared test, $p=0.32$). Among those who reported pain at this visit, more patients in the famciclovir plus placebo group had mild pain than those in the acyclovir plus placebo group (13/14 vs 6/10), although this difference was not significant (2-sided Fisher's exact test, $p=0.12$).

At the last visit (day 28), there was no significant difference in the mean area of the primary affected dermatomal region between the famciclovir plus placebo group ($254.9 \pm 604.8 \text{ cm}^2$) and the acyclovir plus placebo group ($161.7 \pm 293.4 \text{ cm}^2$) [Student's t test, $p=0.474$]. The mean decrease in area of the primary affected dermatomal region was not significantly different between the famciclovir plus placebo group ($124.7 \pm 238.7 \text{ cm}^2$) and the acyclovir plus placebo group ($208.9 \pm 380.2 \text{ cm}^2$) [Student's t -test, $p=0.33$]. None of the patients in either treatment group developed secondary infections. Marked improvement and healing were noted in all types of lesions. There was no lesion in 23 of 26 patients (88.5%) in the famciclovir plus placebo group and 23 of 25 patients (92%) in the acyclovir plus placebo group who had lesions evaluated and the results recorded at the last visit.

Concomitant medications that began during the treatment phase included analgesics, antacids, antidiabetic therapy, antihistamines, antihypertensives, laxatives, antibiotics, and tricyclic antidepressants. There

was no significant difference between the number of patients in the famciclovir plus placebo group (19, 70.4%) and the acyclovir plus placebo group (23, 82.1%) who started concomitant medications in the treatment phase (chi-squared test, $p=0.3$). Fifteen of the patients (55.6%) in the famciclovir plus placebo group and 13 (46.4%) in the acyclovir plus placebo group received analgesics.

Adverse events

During the treatment protocol and up to 30 days after, more adverse events occurred in the acyclovir plus placebo group (17/28, 60.7%) than in the famciclovir plus placebo group (5/27, 18.5%). A significantly higher proportion of patients in the acyclovir plus placebo group (14/28, 50%) had adverse events than in the famciclovir plus placebo group (4/27, 14.8%) [2-sided Fisher's exact test, $p=0.009$]. Significantly more patients in the acyclovir plus placebo group (7/28, 25%) than in the famciclovir plus placebo group (1/27, 3.7%) developed drug-related adverse events (2-sided Fisher's exact test, $p=0.05$).

Of the 17 adverse events reported by 14 patients in the acyclovir plus placebo treatment group, 9 (in 7 patients) were drug-related. One death due to intracerebral hemorrhage occurred in this treatment group. Only 1 out of 5 events (in 4 patients) reported in the famciclovir plus placebo treatment group was drug-related. This adverse event was glycosuria which was neither severe nor serious. The intensity of the adverse events grouped according to body system is shown in Table 4.

The 2 severe adverse events in the acyclovir plus placebo group were intracerebral hemorrhage resulting in death and asthenia. Thus, only 1 type of drug-related adverse event (glycosuria) occurred in greater than 5% of the patients in the famciclovir plus placebo group during the active treatment phase and up to 30 days after discontinuation of the study medication. In contrast, 4 types of drug-related adverse events (constipation, glycosuria, dysuria, hematuria) occurred in greater than 5% of the patients in the acyclovir plus placebo group during the study period.

Table 4. Summary of adverse events by body system and by treatment group and intensity, occurring during the active treatment phase and up to 30 days after discontinuation of the study medication (safety population)

Body system preferred term ^a	Intensity							
	Famciclovir plus placebo (n = 27) ^b				Acyclovir plus placebo (n = 28) ^b			
	n (%) ^c	Mild	Moderate	Severe	n (%) ^c	Mild	Moderate	Severe
Body as a whole general	1 (3.7)	1	0	0	2 (7.1)	1	0	1
Asthenia	0	0	0	0	1 (3.6)	1	0	0
Cellulitis	1 (3.7)	1	0	0	0	0	0	0
Fatigue	0	0	0	0	1 (3.6)	0	0	1
Central and peripheral nervous system	0	0	0	0	2 (7.1)	1	1	0
Dizziness	0	0	0	0	1 (3.6)	1	0	0
Headache	0	0	0	0	1 (3.6)	0	1	0
Gastrointestinal system	1 (3.7)	1	0	0	4 (14.3)	3	1	0
Constipation	1 (3.7)	1	0	0	3 (10.7)	2	1	0
Gastric ulcer hemorrhage	0	0	0	0	1 (3.6)	1	0	0
Hearing and vestibular	0	0	0	0	1 (3.6)	1	0	0
Tinnitus	0	0	0	0	1 (3.6)	1	0	0
Metabolic and nutritional	2 (7.4)	2	0	0	2 (7.1)	2	0	0
Glycosuria	2 (7.4)	2	0	0	2 (7.1)	2	0	0
Urinary system	1 (3.7)	1	0	0	5 (17.9)	4	1	0
Albuminuria	1 (3.7)	1	0	0	0	0	0	0
Dysuria	0	0	0	0	2 (7.1)	1	1	0
Hematuria	0	0	0	0	3 (10.7)	3	0	0
Vascular extracardiac	0	0	0	0	1 (3.6)	0	0	1
Intracerebral hemorrhage	0	0	0	0	1 (3.6)	0	0	1

^aWorld Health Organization Adverse Drug Reaction Preferred Terms.

^bn = total number in treatment group.

^cn = total number of patients with a particular adverse event, or number of patients with 1 or more adverse events in a particular body system.

Discussion

Famciclovir significantly reduced the duration of viral shedding ($p=0.0001$) and accelerated resolution of the lesion compared with placebo. Famciclovir was comparable to acyclovir in terms of these acute parameters [10,11]. In this study, the famciclovir dosage of 250 mg 3 times daily was as effective as acyclovir 800 mg 5 times a day in the healing of cutaneous zoster lesions (as indicated by median time to full crusting, loss of vesicles and loss of ulcers). Patients' assessment of loss of crusts suggested that famciclovir produced earlier healing than acyclovir (day 7 versus day 11), although this difference was not significant. The median time to loss of crusts was 20 days in the famciclovir plus placebo group compared to 27 days for the acyclovir plus placebo group.

Reports on safety from other ongoing and completed clinical studies have shown that famciclovir, a well-absorbed oral form of penciclovir, has been well tolerated by more than 3000 individuals worldwide [12]. The frequency of adverse events and laboratory abnormalities (hematology, clinical chemistry, and urinalysis parameters) was similar in patients receiving famciclovir or placebo [12]. In this study, tolerability data from the 27 patients who received famciclovir plus placebo indicates that famciclovir is well tolerated and had a more favorable adverse event profile than acyclovir plus placebo. The proportion of patients who reported adverse events was 14.8% (4/27) and 50% (14/28) in the famciclovir and acyclovir groups, respectively. The most common adverse events in the acyclovir plus placebo group were constipation (10.7%) and hematuria (10.7%). Glycosuria was the only type of adverse event occurring in greater than 5% of patients in the famciclovir plus placebo group during the active treatment phase and up to 30 days after discontinuation of the study medication. In both groups, glycosuria and hematuria were considered to be unrelated to the study drug, and more likely to be related to the advanced age of the patients. The only adverse event considered to be possibly related to the study drug was constipation (10.7% for acyclovir and 3.7% for famciclovir).

In conclusion, this clinical study indicates that famciclovir is as effective as acyclovir in the treatment of patients with uncomplicated herpes zoster. Famciclovir was well tolerated and had a safety profile comparable or more favorable to that of acyclovir. In addition, acyclovir had poor oral absorption and unfavorable pharmacokinetics, requiring a relatively

high dosage (800 mg) at 5 times a day for clinical efficacy. Famciclovir can be administered at a lower dose and dosing frequency, which may result in better compliance.

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