MAJOR ARTICLE

Single-Day, Patient-Initiated Famciclovir Therapy versus 3-Day Valacyclovir Regimen for Recurrent Genital Herpes: A Randomized, Double-Blind, Comparative Trial

Mohammed Abudalu,[1] Stephen Tyring,[2,3,4] William Koltun,[5] Neil Bodsworth,[7] and Kamal Hamed[6]

[1]Clayton Research Institute, St. Louis, Missouri; Departments of [2]Dermatology, [3]Microbiology and Molecular Genetics, and [4]Internal Medicine, University of Texas Health Science Center, Houston; [5]Medical Center for Clinical Research, San Diego, California; [6]Novartis, East Hanover, New Jersey; and [7]Taylor Square Private Clinic, Darlinghurst, New South Wales, Australia

Background. Recurrent genital herpes is a major problem for patients worldwide. Early episodic treatment with short-course therapy is effective, often stopping progression of outbreaks. This study is the first head-to-head comparison of single-day famciclovir (1000 mg administered twice daily) versus 3-day valacyclovir (500 mg administered twice daily) for episodic therapy in immunocompetent patients.

Methods. In this multicenter, multinational, double-blind, parallel-group study, 1179 adults with a history of recurrent genital herpes were randomized 1:1 to receive either famciclovir or valacyclovir. Patients initiated treatment within 6 h after a recurrence. The primary objective was to establish noninferiority of single-day famciclovir, compared with a 3-day course of valacyclovir, in time to healing of all nonaborted lesions in a modified intent-to-treat population.

Results. This study established that single-day famciclovir therapy was noninferior to 3-day valacyclovir therapy in reducing time to healing of all nonaborted genital herpes lesions (median time to healing, 4.25 days vs. 4.08 days). Approximately one-third of patients in each treatment group had aborted genital herpes episodes, suggesting that both treatments have similar efficacy in preventing outbreaks or progression of lesions beyond the papule stage. There was no significant difference in time to resolution of symptoms associated with recurrence. The overall incidence of adverse events was similar (23.2% for the famciclovir group vs. 22.3% for the valacyclovir group), with headache, nausea, diarrhea, vomiting, and abdominal pain reported most often.

Conclusions. Single-day famciclovir (1000 mg administered twice daily) was similar to 3-day valacyclovir (500 mg administered twice daily) in both efficacy and safety, representing a more convenient treatment for immunocompetent adults with recurrent genital herpes.

Genital herpes is a sexually transmitted disease most commonly caused by herpes simplex virus type 2 (HSV-2), although infection due to type 1 (HSV-1) has been increasingly implicated as oral-genital sexual behavior has increased [1, 2]. Approximately 17% of adults in the United States are seropositive for HSV-2 [3], with prevalence rates approaching 30% worldwide [4]. The vast majority (>90%) of HSV-2–infected patients who experience an initial classic genital herpes outbreak report at least 1 lifetime recurrence, and approximately one-third experience frequent recurrences (⩾6 episodes per year) [4, 5]. Although genital herpes is invariably non–life threatening and is often asymptomatic, it remains an incurable but treatable infection. Overall, genital herpes negatively impacts patient quality of life [6, 7] and constitutes a major public health problem.

Episodic therapy, a common management approach for recurrent genital herpes, has evolved in recent years from a traditional 5-day treatment regimen to short-course antiviral schedules that are effective and convenient [8–12]. Clinical trials have demonstrated the effectiveness of 3-day therapy with valacyclovir [8, 9],

Received 5 March 2008; accepted 18 April 2008; electronically published 18 July 2008.

Reprints or correspondence: Dr. Kamal Hamed, One Health Plaza, East Hanover, NJ 07936 (kamal.hamed@novartis.com).

Clinical Infectious Diseases 2008; 47:651–8

1058-4838/2008/4705-0010$15.00
DOI: 10.1086/590561

2-day regimens with high-dose acyclovir (800 mg administered 3 times daily) [10] and famciclovir (a 500-mg initial dose, followed by 250 mg administered twice daily) [11], and high-dose single-day famciclovir therapy (1000 mg administered twice) [12]. Single-day famciclovir was approved in the United States for treatment of recurrent genital herpes in 2006.

Because recurrent genital herpes outbreaks in immunocompetent individuals commence following a rapid burst of viral replication, with peak viral loads in the first 24 h [13], there is a brief and early therapeutic window that is best managed by patient-initiated therapy. Recognition of prodromal symptoms (e.g., pain, itching, tingling, and burning) by many patients [14] provides an opportunity for prompt treatment intervention. A recent study of single-day famciclovir treatment, started within 6 h after the onset of prodromal symptoms or recurrent genital herpes lesions, demonstrated an accelerated time to healing of lesions, compared with placebo [12]. This study also found that progression to a full outbreak was halted or prevented in nearly one-fourth of patients who used famciclovir.

The current study is the first head-to-head comparison of patient-initiated, single-day famciclovir therapy versus an active antiviral agent. We hypothesized that single-day, high-dose famciclovir therapy (1000 mg administered twice daily) would be noninferior to 3-day valacyclovir therapy (500 mg administered twice daily) in reducing time to healing of nonaborted recurrent genital herpes lesions (i.e., lesions that progressed beyond the papule stage).

PATIENTS AND METHODS

Study design. This multicenter, multinational, randomized, double-blind, noninferiority study assessed the efficacy and safety of patient-initiated single-day famciclovir versus 3-day valacyclovir as episodic treatment in immunocompetent adults with recurrent genital herpes. Approval of the study protocol and a consent form was obtained from each investigator's independent ethics committee or institutional review board, and all study activities were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All screened and enrolled subjects provided written informed consent prior to any study-related procedures. This study was registered at http://www.ClinicalTrials.gov. The trial registration number was NCT00306787.

Treatments. Patients who met the study entry criteria were randomized in a 1:1 ratio to receive either famciclovir (1000 mg given twice daily for a single day) or valacyclovir (500 mg given twice daily for 3 days). Famciclovir and valacyclovir placebos, matching in size, color, and formulation, were given to maintain blinding.

Study procedures. Patients were instructed to initiate therapy within 6 h after the onset of prodromal symptoms and/or genital herpes lesions associated with their next recurrence. They were to return to the clinic for medical evaluation within 24 h after initiating therapy and then daily for 3 days. Patients with unhealed lesions were subsequently evaluated every other day until all lesions healed or up to day 14 after initiation of the study drug. Type-specific HSV serological testing (by enzyme immunoassay) was performed at screening if there were no positive results in the patient's medical record. Routine hematological and serum chemistry tests were performed for safety assessment at randomization and on day 7 after initiation of the study drug. Toxicity was graded using a standard scoring system (Modified Division of Microbiology and Infectious Diseases Toxicity Tables, version 2.0). A negative pregnancy test result was required for women of childbearing age before initiating treatment with the study drug.

Study assessments. The time of healing was assessed by the investigator on the basis of clinical observations and patient diary entries. Healing was defined as complete loss of all crusts and reepithelialization of genital herpes lesions. Patients were to complete a diary starting from the time of prodromal symptoms or genital herpes lesions and to make entries twice daily after initiation of study drug treatment, recording the precise time of onset of genital herpes recurrence, the presence of symptoms, and the status of lesion stages until the investigator confirmed lesion healing.

Eligibility criteria. Immunocompetent men and women aged $\geqslant$18 years were considered to be eligible if they had previously received a diagnosis of genital herpes, had a history of lesions located on the external genitalia or anogenital region, and had laboratory evidence of HSV infection. Each patient was to have experienced at least 4 recurrences of genital herpes in the preceding 12 months or in the 12 months prior to undergoing suppressive antiviral therapy. Patients who received suppressive antiviral therapy had to be willing to discontinue this therapy at study entry.

Exclusion criteria included patients with a history of renal disease requiring adjustments of famciclovir or valacyclovir dosage, decompensated hepatic impairment, gastrointestinal malabsorption, or conditions resulting in immunosuppression (including HIV infection or chronic oral steroid use). Female patients of childbearing age were excluded if they were pregnant, breast-feeding, or using an unreliable form of contraception. Use of concomitant cimetidine and/or probenecid therapy was disallowed.

Safety and tolerability assessments. Safety assessments consisted of monitoring and recording all adverse events (AEs), serious AEs, vital signs, physical conditions, and routine hematological and serum chemistry test results. AEs were any adverse physiological events occurring from the initiation of study medication until the conclusion of the study. Investigators were asked to rate AEs according to severity (mild, moderate,

or severe), relationship to study drug (suspected or not suspected), and whether the AE resulted in discontinuation of study medication or other remedial action. Serious AEs were defined as AEs that were fatal, life threatening, or disabling; that resulted in hospitalization; or that required medical or surgical intervention to prevent one of these outcomes.

Analysis populations. The safety population included all patients who had initiated treatment with the study drug and had at least 1 postbaseline safety assessment. All patients who initiated treatment using study medication with the intention of treating genital herpes recurrences were included in the intent-to-treat (ITT) population. A modified ITT population—the primary efficacy population—included all patients who developed nonaborted genital herpes lesions during the treated recurrence. The per-protocol (PP) population included all patients from the modified ITT population who did not have major protocol deviations (e.g., noncompliance with study drug treatment).

Statistical analysis. The primary efficacy end point was investigator-assessed time to healing of all nonaborted genital herpes lesions. Secondary end points included the proportion of patients with investigator-assessed aborted lesions, investigator-assessed time to healing of all genital herpes lesions (nonaborted and aborted), and patient-reported time to resolution of all genital herpes–associated symptoms and specific genital herpes–associated symptoms.

Sample size calculations were based on the following assumptions: median time to healing of 4.5 days for both treatment groups, with the distribution of time to healing similar to that from a previous study [12], a censoring rate of 10%, and a noninferiority margin of 1.0 day. A total of 260 patients with nonaborted lesions (including dropouts) in each treatment group was required to have 90% power for establishing noninferiority. The sample size was estimated using SAS and StatXact Procs for SAS simulations (SAS).

The primary analysis was performed for the time to healing of nonaborted lesions for the modified ITT population and presented as the 2-sided Hodges-Lehman 95% CI of the median of the treatment difference (famciclovir minus valacyclovir). The noninferiority of single-day famciclovir compared with the 3-day valacyclovir regimen was confirmed if the upper bound of the 95% CI was less than the predefined noninferiority margin of 1.0 day. To assess the robustness of the primary analysis result, a similar 95% CI was constructed for the PP population and the modified ITT population without missing values. The primary efficacy end point and other secondary time-to-event variables were analyzed using a proportional hazards model, with treatment, sex, and study center as explanatory variables; hazard ratios (famciclovir:valacyclovir) were estimated, and their 95% CIs were constructed; and the Kaplan-Meier method was used to present distributions. The proportion of patients with aborted lesions was compared between treatment groups using the Cochran-Mantel-Haenszel test, stratified by sex and study center. All hypothesis tests were performed as planned and evaluated at a .05 level of statistical significance. No adjustments for multiplicity were performed for secondary analyses. Rates of AEs and laboratory test abnormalities were summarized descriptively.

RESULTS

Patient disposition. Of 1179 randomized patients, 756 received at least 1 dose of study medication (the safety population), and 751 comprised the ITT population. A total of 5

Table 1. Demographic and baseline medical characteristics of the intent-to-treat population in a trial comparing single-day famciclovir therapy with 3-day valacyclovir therapy for recurrent genital herpes.

Characteristic	Famciclovir (n = 370)	Valacyclovir (n = 381)
Age, median years (range)	39 (18–73)	41 (18–85)
Female sex	245 (66.2)	243 (63.8)
Race		
White	260 (70.3)	253 (66.4)
Black	94 (25.4)	111 (29.1)
Median no. of years in which patient experienced recurrent genital herpes (range)	7 (0–35)	8 (0–48)
Median no. of genital herpes recurrences during previous 12 months or in the 12 months immediately preceding suppressive treatment (range)	6 (3–40)	5 (4–20)
Received episodic antiherpes therapy	262 (70.8)	275 (72.2)
Received suppressive antiherpes therapy in previous 12 months	72 (19.5)	67 (17.6)
Herpes simplex virus serotype		
Type 1 only	32 (8.6)	26 (6.8)
Type 2 only	165 (44.6)	186 (48.8)
Both type 1 and type 2	173 (46.8)	169 (44.4)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Table 2. Time to healing of lesions for famciclovir and valacyclovir recipients with recurrent genital herpes.

Efficacy parameter	No. of patients	Median days to healing of lesions, by Kaplan-Meier method	Median days of difference in time to healing between treatments (95% CI)[a]	Hazard ratio (95% CI)[b]	P[b]
Nonaborted lesions					
Modified ITT population with imputation (primary)[c]					
Famciclovir group	249	4.25	0.16 (−0.15 to 0.60)	1.08 (0.88–1.32)	.48
Valacyclovir group	253	4.08			
Modified ITT population without imputation[d]					
Famciclovir group	218	4.07	0.06 (−0.28 to 0.45)	ND	ND
Valacyclovir group	230	4.02			
PP population[d]					
Famciclovir group	182	4.45	0.18 (−0.14 to 0.55)	1.09 (0.87–1.37)	.44
Valacyclovir group	196	4.14			
Nonaborted and aborted lesions					
ITT population[c,e]					
Famciclovir group	370	3.07	0.00 (0.00–0.00)	1.07 (0.91–1.25)	.42
Valacyclovir group	381	3.01			

NOTE. ITT, intent-to-treat; PP, per-protocol; ND, not done.

[a] Median of difference between treatments (famciclovir minus valacyclovir) was estimated using Hodges-Lehman shift model.

[b] Hazard ratio and P value were based on Cox proportional hazards model with treatment, pooled center, and sex as exploratory variables.

[c] For patients with nonaborted lesions who discontinued the study before healing of nonaborted lesions was confirmed and for patients who completed the study at 21 days after treatment initiation without nonaborted lesions and without a final assessment of aborted lesion status, the time to healing was censored at the time of the last clinical lesion observation for the Kaplan-Meier estimation and Cox model; for Hodges-Lehman estimation, the missing data for time to healing were imputed using the larger value of either the maximum value of time to healing observed in the study plus 1 day or time to censoring plus 2 days.

[d] Patients with missing data for time to healing were excluded.

[e] Patients with aborted lesions were assigned a time to healing of 0 days.

patients, including 4 patients who received the study drug to treat a condition other than genital herpes and 1 patient whose positive HSV serological test result was unavailable, were excluded from the ITT population. Twenty-six (7.0%) of the 370 famciclovir-treated patients and 26 (6.8%) of the 381 valacyclovir-treated patients discontinued the study. Primary reasons for premature discontinuation in both groups were protocol deviation (18 patients), loss to follow-up (15), and withdrawal of consent (11). The modified ITT population included 502 ITT patients who developed nonaborted genital herpes lesions; the PP population included 378 patients with nonaborted genital herpes lesions who did not have major protocol deviations.

Baseline demographic and clinical characteristics were similar for the 2 treatment groups in the ITT population (table 1). The median number of genital herpes recurrences per year was 5, with more than two-thirds of patients having received prior episodic therapy. The rate of seropositivity for HSV-2 was 92.3% (including 45.5% seropositivity for both HSV-2 and HSV-1); 7.7% of patients had serological evidence for HSV-1 alone.

Time to healing. In the modified ITT population, the time to healing of nonaborted lesions was similar for patients who received single-day, 1000-mg, twice-daily famciclovir (4.25 days) and patients who received 3-day, 500-mg, twice-daily valacyclovir (4.08 days). A median treatment difference (0.16 days) and its 95% CI for the modified ITT population demonstrated that famciclovir was noninferior to valacyclovir with respect to time to healing of all nonaborted genital herpes lesions. The upper bound of the 2-sided 95% CI (0.60 days) was well within the predefined noninferiority margin (famciclovir minus valacyclovir, <1.0 day). Consistent results were obtained for the PP population, showing that the median treatment difference was 0.18 days and that the upper bound of the 2-sided 95% CI was 0.55 days. Similar findings were reported for the modified ITT population with no missing values. The results were further confirmed by a secondary analysis using a Cox proportional model (table 2; $P > .05$ for all populations) and were found to be consistent with the time to healing estimated using the Kaplan-Meier method. Figure 1 shows a nearly identical time profile for the modified ITT population in both treatment groups. In addition, the time to healing of all lesions (including nonaborted and aborted lesions) in the ITT population was similar for the famciclovir and valacyclovir groups (table 2). A similar proportion of patients in both treatment groups comprising the ITT population experienced aborted lesions, including 32.7% (121 of 370 patients) in the famciclovir group and 33.6% (128 of 381) in the valacyclovir group.

Time to resolution of symptoms. In the ITT population, patients receiving single-day famciclovir had similar median times to resolution of all symptoms associated with recurrent genital herpes, as well as similar median time to resolution of

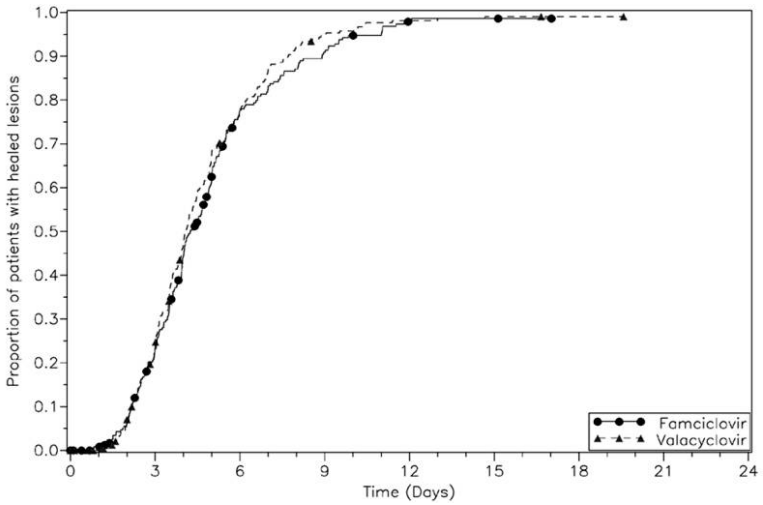

Figure 1. Kaplan-Meier plot of time to healing of all nonaborted genital herpes lesions (modified intent-to-treat population)

each individual symptom (i.e., pain, itching, tingling, burning, and tenderness), compared with the 3-day valacyclovir group (table 3).

Safety and tolerability. Adherence to study medication as prescribed was excellent, with 97.6% of famciclovir-treated patients (362 of 371 patients) receiving 2 doses on day 1 and 92.2% of valacyclovir-treated patients (355 of 385 patients) receiving all 6 doses over 3 days. Regardless of study drug causality or severity, the overall incidence of AEs was 23.2% (86 of 371 patients) for the famciclovir group, compared with 22.3% (86 of 385 patients) for the valacyclovir group. The most commonly reported AEs in either treatment group were headache (29 [7.8%] of 371 patients in the famciclovir group vs. 17 [4.4%] of 385 patients in the valacyclovir group), nausea (23 [6.2%] of 371 vs. 18 [4.7%] of 385), diarrhea (8 [2.2%] of 371 vs. 5 [1.3%] of 385), vomiting (5 [1.3%] of 371 vs. 3 [0.8%] of 385), and abdominal pain (1 [0.3%] of 371 vs. 4 [1.0%] of 385). Most AEs were mild or moderate in intensity, did not require remedial action, and resolved within 1–2 days after onset. All other individual AEs were reported in <1% of the safety population. Suspected drug-related AEs were reported in 11.3% of the famciclovir-treated patients (42 of 371 patients) and 9.1% of the valacyclovir-treated patients (35 of 385 patients), with headache (17 [4.6%] of 371 vs. 12 [3.1%] of 385), nausea (17 [4.6%] of 371 vs. 12 [3.1%] of 385), and diarrhea (3 [0.8%] of 371 vs. 5 [1.3%] of 385) reported most frequently.

Serious AEs were reported in 2 patients in the famciclovir group (myocardial ischemia and a suicide attempt) and in 1 patient in the valacyclovir group (polysubstance abuse requiring hospitalization). One famciclovir-treated patient discontinued therapy prematurely because of headache and nausea, and 1 valacyclovir-treated patient discontinued therapy secondary to pregnancy.

The percentage change from baseline in hematological and serum chemistry laboratory values was small. For serum chemistry in patients with normal baseline values, 12 tests shifted to grade 3 or 4 toxicity, including tests for serum glutamate pyruvate transaminase (grade 3 valacyclovir toxicity in 1 patient), amylase (grade 3 famciclovir toxicity in 2 patients; grade 3 valacyclovir toxicity in 1 patient), serum lipase (grade 4 famciclovir toxicity in 1 patient; grade 3 valacyclovir toxicity in 2 patients), and hypoglycemia (grade 4 valacyclovir toxicity in 3 patients; grade 3 valacyclovir toxicity in 1 patient; grade 4 famciclovir toxicity in 1 patient). The toxicity grade in 1 valacyclovir-treated patient with an abnormal serum lipase level at baseline worsened to grade 3. For hematological tests, there were no reports of grade 3 or 4 toxicity after initiation of study medication for patients with normal baseline values; the toxicity grade in 1 valacyclovir-treated patient with an abnormal baseline hemoglobin value worsened to grade 3.

DISCUSSION

This randomized, double-blind study demonstrated that single-day high-dose famciclovir (1000 mg administered twice daily) provided effectiveness similar to that of 3-day valacyclovir therapy in time to healing of all nonaborted lesions, time to healing of nonaborted plus aborted lesions, proportion of patients with aborted lesions, and time to resolution of common symptoms. The time to healing of all nonaborted lesions, which was the primary efficacy end point, was nearly identical between patients treated with famciclovir and patients treated with valacyclovir (4.25 vs. 4.08 days), thus establishing that single-day

Table 3. Time to resolution of symptoms associated with recurrent genital herpes lesions (intent-to-treat population).

Symptom	No. of patients whose symptom(s) resolved (uncensored data)	Median hours to resolution (interquartile range)[a]	Hazard ratio (95% CI)[b]	P^b
All symptoms				
Famciclovir group	236	72.9 (47.8–137.4)	1.03 (0.86–1.24)	.75
Valacyclovir group	238	72.0 (46.2–131.9)		
Pain				
Famciclovir group	182	18.0 (0.0–52.7)	1.00 (0.85–1.17)	.96
Valacyclovir group	177	20.1 (0.0–46.2)		
Itching				
Famciclovir group	229	43.9 (12.2–76.7)	1.02 (0.86–1.20)	.84
Valacyclovir group	209	42.3 (11.5–85.3)		
Tingling				
Famciclovir group	217	23.8 (0.0–58.0)	1.13 (0.96–1.33)	.13
Valacyclovir group	226	23.0 (0.0–50.5)		
Burning				
Famciclovir group	176	16.1 (0.0–50.5)	1.08 (0.92–1.26)	.35
Valacyclovir group	179	12.6 (0.0–47.5)		
Tenderness				
Famciclovir group	210	55.2 (20.4–106.0)	1.06 (0.90–1.26)	.47
Valacyclovir group	223	47.9 (14.3–87.3)		

[a] The Kaplan-Meier method was used to estimate the time to resolution at quartiles. Median time to resolution of all symptoms and individual symptoms was estimated using both uncensored and censored data. Uncensored data were obtained from 474 patients who reported at least 1 symptom after initiation of treatment and had a known resolution time for all symptoms (i.e., actual time of resolution was recorded) and 7 patients who reported no symptoms (i.e., time of resolution was set as 0 h). Censored data were obtained from 241 patients with at least 1 persistent symptom (i.e., time of resolution was set as the last valid entry after first dose) and 29 patients with no valid data available (i.e., time of resolution was set as 0 h).

[b] Based on Cox proportional hazards model with treatment, pooled center, and sex as explanatory variables. Hazard ratio for time to healing was defined as the hazard rate of famciclovir group/hazard rate of valacyclovir group.

high-dose famciclovir was noninferior to the 3-day valacyclovir regimen. This active-controlled study corroborates an earlier report in which treatment with single-day famciclovir significantly reduced time to healing of all nonaborted lesions, compared with placebo (4.3 vs. 6.1 days) [12].

This study also demonstrated that approximately one-third of patients in each treatment group had aborted lesions. The findings reported here for famciclovir are similar to the proportion of patients who received famciclovir versus patients who received placebo with aborted lesions in the earlier trial (23% vs. 13%) [12]. Moreover, examination of the population with positive PCR results revealed that 21% of patients who received single-day high-dose famciclovir had aborted lesions, compared with 5% of placebo recipients [15]. Although detection of HSV DNA by PCR testing was not performed in the current trial, these collective data imply that 1 in 3–5 patients who receive single-day famciclovir for recurrent genital herpes may experience an aborted episode.

Time to resolution of common genital herpes symptoms was ~3 days after both treatment with single-day famciclovir and treatment with 3-day valacyclovir. Pain, tingling, and burning tended to resolve most rapidly after initiation of either treatment (median time to resolution, 0.5–1 days). Resolution of itching and tenderness occurred nearly 2 days after initiation of famciclovir (median time to resolution, 1.8 days and 2.3 days, respectively) and valacyclovir therapy (median time to resolution, 1.8 days and 2.0 days, respectively). These findings parallel those reported after single-day famciclovir treatment in the placebo-controlled trial, which showed complete symptom resolution after a median of 3.3 days (0.9 days for pain, 1.0 days for tingling, 0.7 days for burning, 1.6 days for itching, and 2.0 days for tenderness) [12].

Overall, the effectiveness of single-day high-dose famciclovir for episodic treatment of recurrent genital herpes in the current and previous trial [12] is comparable to other reports of short-course oral antiviral therapy [8–10], including a 2-day famciclovir regimen [11], with similar benefits for healing and relief of symptoms. It is also well recognized that recurrent episodes of genital herpes follow a rapid burst of viral replication that reaches maximum threshold within 24 h after an outbreak [13]. In both the present study and the previous famciclovir study [12], patients were instructed to self-administer therapy within 6 h after experiencing prodromal symptoms or the first appearance of a genital lesion. We hypothesize that "hitting the

virus early and hard," when viral titers are highest [16], may be responsible for the effectiveness of single-day high-dose famciclovir and the fact that, in approximately one-third of patients, the outbreak did not progress beyond the papule stage.

The present study demonstrated that single-day high-dose famciclovir therapy was safe and well tolerated (overall AE rates, 23.2% for famciclovir vs. 22.3% for valacyclovir), with gastrointestinal and nervous system disorders reported most commonly. The majority of AEs were of mild-to-moderate severity, with little need for remedial treatment. Only 1 famciclovir-treated patient discontinued medication prematurely, after experiencing headache and nausea. These findings, coupled with earlier observations [12], suggest that single-day famciclovir has an acceptable tolerability profile.

In summary, this multicenter, multinational, double-blind, active-controlled study demonstrated that a patient-initiated single-day famciclovir regimen (1000 mg administered twice) was as effective and safe as a 3-day valacyclovir regimen (500 mg administered twice daily) in reducing the time to healing of nonaborted lesions in immunocompetent adults with recurrent genital herpes. The fact that nearly one-third of patients who were treated with single-day high-dose famciclovir had aborted episodes is encouraging and demonstrates that effective short-course therapy can significantly reduce the undesirable sequelae associated with recurrences. Single-day famciclovir is a simple and convenient treatment regimen for adults with recurrent genital herpes.

THE FAMCICLOVIR STUDY GROUP

United States. Dr. Mohammed Abudalu, St. Louis, Missouri; Dr. Keith Aqua, Boynton Beach, Florida; Dr. Charles Barker, Jonesboro, Arkansas; Dr. Stephan Bart, Baltimore, Maryland; Dr. Cristian Breton, Miami, Florida; Dr. Corey Casper, Seattle, Washington; Dr. Thomas Cherpes, Pittsburgh, Pennsylvania; Dr. Teresa Coats, Austin, Texas; Dr. Marcus Conant, San Francisco, California; Dr. Adnan Dahdul, Springfield, Massachusetts; Dr. Waymon Drummond, Dallas, Texas; Dr. Steven Elliott, Evansville, Indiana; Dr. David Ferrera, Sacramento, California; Dr. Kenneth Fife, Indianapolis, Indiana; Dr. Larry Gilderman, Pembroke Pines, Florida; Dr. John Gnann, Birmingham, Alabama; Dr. Carl Griffin, Oklahoma City, Oklahoma; Dr. Micah Harris, Phoenix, Arizona; Dr. Richard Hedrick, Winston-Salem, North Carolina; Dr. Helen Henry, Portland, Oregon; Dr. Walter Hood, Atlanta, Georgia; Dr. Campbell Kemp, Little Rock, Arkansas; Dr. Tracy Klein, Wichita, Kansas; Dr. Howard Knapp, Billings, Montana; Dr. William Koltun, San Diego, California; Dr. John Kreisel, Salt Lake City, Utah; Dr. Patricia Lee, Houston, Texas; Dr. Peter Leone, Raleigh, North Carolina; Dr. Myron Levin, Denver, Colorado; Dr. Thomas Malon, Simpsonville, South Carolina; Dr. Thomas Marbury, Orlando, Florida; Dr. John Marshall, Florence, South Carolina; Dr. John McGettigan, Tucson, Arizona; Dr. John Moore, Columbia, South Carolina; Dr. Lawrence Parish, Philadelphia, Pennsylvania; Dr. Prescott Prillaman, Richmond, Virginia; Dr. Lawrence Ratcliff, Dayton, Ohio; Dr. Daniel Rowe, West Palm Beach, Florida; Dr. Talha Shamin, Omaha, Nebraska; Dr. Teresa Sligh, Burbank, California; Dr. Howard Sofen, Los Angeles, California; Dr. Pamela Steams, Pembroke Pines, Florida; Dr. Dow Stough, Hot Springs, Arkansas; Dr. Michael Twede, Sandy, Utah; Dr. Stephen Tyring, Houston, Texas; Dr. Edward Williams, Tacoma, Washington; Dr. Bret Wittmer, Madisonville, Kentucky; Dr. Gail Womack, Lakewood, Colorado; Dr. Douglas Young, Sacramento, California; Dr. Edward Zbella, Clearwater, Florida.

Canada. Dr. Fred Aoki, Winnipeg, Manitoba; Dr. Robert Bissonnette, Montreal, Quebec; Dr. Alain Brassard, Montreal, Quebec; Dr. Brian Conway, Vancouver, British Columbia; Dr. Francisco Diaz-Mitoma, Ottawa, Ontario; Dr. David Gratton, Montreal, Ontario; Dr. Charles Lynde, Markham, Ontario; Dr. Stephen Shafran, Edmonton, Alberta; Dr. Sylvie Trottier, Sainte-Foy, Quebec.

Australia. Dr. Mark Bloch and Dr. Neil Bodsworth, Darlinghurst, New South Wales.

Germany. Dr. Andreas Clad, Freiburg; Dr. Gerd Gross, Rostock; Dr. Karl-Gustav Meyer, Berlin; Dr. Ulrich Petry, Wolfsburg; Dr. Georg Popp, Ausburg.

Novartis. Dr. Kamal Hamed; Maria Roberts; Dr. Wenchun Zhou.

Clinical Research Organization (Medpace). Norma Roebker; Dr. Rong Zhou; Dr. Lyon Gleich.

Acknowledgments

We thank the volunteers for their participation in this study.

Financial support. Novartis.

Potential conflicts of interest. Famciclovir is manufactured by Novarits under the brand name Famvir. M.A. has received research funding and speakers' honoraria from Novartis. S.T. has received research funding and speakers' honoraria from Novartis and GlaxoSmithKline. W.K. has received research funding and speakers' honoraria from Novartis, Bayer, Biosante, Boehringer Ingelheim, Duramed, Dynogen, GlaxoSmithKline, Kanion, Merck, Neurocrine Biosciences, Nventa, Pharm-Olam International, Proctor and Gamble, Roche, Sanofi Aventis, Shionog, Tap Pharmaceuticals, Upsher Smith, Warner Chilcott, Wyeth, Xanodyne Pharmaceuticals, and 3M. N.B. has been a consultant for and has received research funding from Novartis and GlaxoSmithKline. K.H. is an employee of Novartis.

References

1. Malkin JE. Epidemiology of genital herpes simplex virus infection in developed countries. Herpes **2004**; 11(Suppl 1):2A-23A.
2. Mertz GJ, Rosenthal SL, Stanberry LR. Editorial response: is herpes simplex virus type 1 (HSV-1) now more common than HSV-2 in first episodes of genital herpes? Sex Transm Dis **2003**; 30:801–2.
3. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA **2006**; 296:964–73.
4. Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. J Infect Dis **2002**; 186(Suppl):S3–28.

5. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med **1994**; 121:847–54.
6. Brentjens MH, Yeung-Yue KA, Lee PC, Tyring SK. Recurrent genital herpes treatments and their impact on quality of life. Pharmacoeconomics **2003**; 21:853–63.
7. Patel R, Boselli F, Cairo I, Barnett G, Price M, Wulf HC. Patients' perspectives on the burden of recurrent genital herpes. Int J STD AIDS **2001**; 12:640–5.
8. Leone PA, Trottier S, Miller JM. Valacyclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. Clin Infect Dis **2002**; 34:958–62.
9. Strand A, Patel R, Wulf HC, Coates KM. International Valaciclovir HSV Study Group. Aborted genital herpes simplex virus lesions: findings from a randomised controlled trial with valaciclovir. Sex Transm Infect **2002**; 78:435–9.
10. Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. Clin Infect Dis **2002**; 34:944–8.
11. Bodsworth N, Bloch M, McNulty A, et al. 2-Day versus 5-day famciclovir as treatment of recurrences of genital herpes—results of the FaST study. Sexual Health [in press].
12. Aoki FY, Tyring S, Diaz-Mitoma F, et al. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double blind, placebo trial. Clin Infect Dis **2006**; 42:8–13.
13. Brown ZA, Kern ER, Spruance SL, Overall JC Jr. Clinical and virologic course of herpes simplex genitalis. West J Med **1979**; 130:414–21.
14. Beauman JG. Genital herpes: a review. Am Fam Physician **2005**; 72: 1527–34.
15. Aoki F, Tyring S, Diaz-Mitoma F, Gao J, Hamed K. Patient-initiated high-dose oral famciclovir for 1 day shortens the duration of recurrent genital herpes lesions [abstract V1839]. In: Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). Washington, DC: American Society for Microbiology, **2005**.
16. Spruance S, Aoki FY, Tyring S, Stanberry L, Whitley R, Hamed K. Short-course therapy for recurrent genital herpes and herpes labialis. J Fam Pract **2007**; 56:30–6.