A Randomized, Placebo-Controlled Comparison of Oral Valacyclovir and Acyclovir in Immunocompetent Patients With Recurrent Genital Herpes Infections

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Objective: To compare valacyclovir hydrochloride with acyclovir in the treatment of recurrent genital herpes infection.

Design: A multicenter, double-blind, placebo-controlled, randomized, parallel-design study.

Setting: University clinics (dermatology, gynecology, and infectious diseases) and private practices.

Patients: One thousand two hundred patients with recurrent genital herpes simplex infections.

Interventions: Patients self-initiated oral therapy with 1000 mg of valacyclovir hydrochloride twice daily, 200 mg of acyclovir 5 times daily, or placebo for 5 days.

Main Outcome Measures: Resolution of all signs and symptoms of recurrent genital herpes infection.

Results: Both drugs were significantly more effective than placebo in speeding resolution of herpetic episodes (median duration, 4.8, 4.8, and 5.9 days, respectively); the hazards ratios for valacyclovir and acyclovir vs placebo were 1.66 (95% confidence interval [CI], 1.38-2.01) and 1.71 (95% CI, 1.41-2.06) (both P<.001). Similarly, valacyclovir and acyclovir significantly hastened lesion healing (hazards ratios vs placebo were 1.88 [95% CI, 1.53-2.32] and 1.90 [95% CI, 1.55-2.34], respectively; P<.001).

Conclusions: Twice-daily valacyclovir was as effective and well tolerated in the treatment of recurrent genital herpes simplex virus infection as 5-times-daily acyclovir. Therefore, valacyclovir could prove a useful alternative to acyclovir when convenience of dosing or compliance issues are the prime considerations in treatment.

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PATIENTS AND METHODS

PATIENTS

Eligible patients included otherwise healthy, immunocompetent males or females aged 13 years or older who had experienced 4 or more recurrences of genital herpes within the 12-month period prior to their entry into the study. Patients who had received long-term, suppressive acyclovir therapy within 12 months before the study were also eligible if they had had at least 1 recurrence within 3 months after treatment and within 3 months before the study. Patients were excluded from study participation if they had hepatic impairment (aspartate or alanine transaminase more than 3 times the upper limit of normal); renal impairment (estimated creatinine clearance <0.58 mL/s at North American sites or a serum creatinine level >120 µmol/L at European sites); a history of hypersensitivity to acyclovir; a condition characterized by gastrointestinal malabsorption; were pregnant or were nursing mothers; received immunosuppressive, immunomodulatory, or other antiviral therapy; or were sexually active women of childbearing potential who were not using an effective contraceptive method.

STUDY DESIGN

This phase 3 multicenter, multinational clinical trial was double-blind, randomized, parallel-group, and 3-arm in design. It was conducted at 53 study centers, including 30 in Europe, 20 in the United States, and 3 in Canada. The study protocol was approved by the institutional review board at each study site, and written informed consent was obtained from all patients (or parents for patients younger than 18 years) after the nature of the procedures had been fully explained.

TREATMENT ALLOCATION AND PROCEDURES

At the screening visit, patients provided a medical history and underwent a physical examination, measurement of vital signs, clinical laboratory tests, and quantitative urinalysis of protein and blood. A pregnancy test was performed for women of childbearing potential. A blood sample was obtained and assayed for HSV antibodies. Eligible patients were assigned to receive 1 of the following treatments for 5 days according to a 3:3:1 randomization schedule: oral valacyclovir, 1000 mg twice daily; oral acyclovir, 200 mg 5 times daily; or placebo 5 times daily. The study drug was supplied as capsules containing valacyclovir base as the hydrochloride salt plus excipient, or acyclovir (each with matching placebo capsules).

Patients were instructed to self-initiate treatment within 24 hours of the first signs or symptoms of a recurrence and to return to the clinic within 24 hours of starting treatment. Herpetic lesions were evaluated by clinicians on days 1, 2, 3, 5, and 7. In addition, patients kept a daily diary documenting the occurrence of any prodromal symptoms, compliance with medication schedules, and their assessments of pain, discomfort, and lesion healing. Evaluation continued at twice-weekly intervals after day 7 until all lesions had healed and clinical symptoms had resolved. At each clinic visit, existing herpetic lesions were classified by clinicians as macule/papule, vesicle/pustule/ulcer, crust, or healed lesion. Pain was classified by patients as none, mild, moderate, or severe. Lesions that did not progress beyond the macule/papule stage (including prodrome only) to the vesicular/ulcerative stage were considered aborted lesions. Clinicians' observations in the clinic and data in the patient diary were used to determine end points, unless the results conflicted, in which case the clinic observations took precedence. Viral swabs for HSV cultures were obtained from lesions at each visit for determination of viral shedding.

Efficacy End Points

Primary efficacy end points included (1) length of episode, defined as the number of days between initiation of treatment and complete resolution of all symptoms and signs, including aborted episodes; and (2) time to lesion healing, defined as the number of days between initiation of treatment and complete reepithelialization of all lesions. With regard to the latter end point, residual erythema could still be present, but aborted episodes were excluded. Secondary efficacy end points included (1) viral shedding, in terms of the number of days between treatment initiation and the first negative lesion culture, with no subsequent positive virus concentration of 4.96±0.64 mg/mL (22 µmol/L) was reached, and an average area under the plasma acyclovir concentration vs time curve (AUC) of 15.70±2.27 h·µg/mL was obtained.16

The objective of this phase 3 multicenter, double-blind, placebo-controlled trial was to compare the clinical efficacy and safety of a twice-daily valacyclovir regimen with that of a 3-times-daily acyclovir regimen in the acute treatment of recurrent genital HSV infection in immunocompetent patients.

RESULTS

PATIENT DEMOGRAPHICS AND ACCOUNTABILITY

A total of 1725 patients were enrolled at 53 study sites and randomized to treatment. Of these patients, 1200 experienced signs and symptoms of an HSV recurrence and returned to the clinic having initiated treatment (intent-to-treat population); 525 patients had no recurrence and were excluded from analysis. There were no significant differences among the treatment groups with regard to demographic or baseline HSV characteristics (Table 1) or baseline hematology, blood chemistry, or urinalysis values (data not shown). Within the intent-to-treat group, 128 patients prematurely discontinued from the study primarily because of unavailability for follow-up (69 patients) or major protocol violations (26 patients) (Table 1). Overall, there were 230 patients in the intent-to-treat group with major deviations or violations from the protocol, including 114 (9.5%) who failed to initiate treatment within 24 hours, 57 (4.8%) who failed to take more than 80% of their study medication, 29 (2.4%) who failed to initiate treatment with a full dose of medication, 27 (2.3%) who took other antiviral or immunomodulatory drugs, and 3 (1.3%) with other protocol violations.

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culture and proportions of patients never having a positive culture; (2) duration of pain, defined as the number of days between treatment initiation or the start of pain or discomfort and its complete resolution; (3) severity of pain and discomfort (categorized as none, mild, moderate, or severe); and (4) proportion of patients with aborted episodes.

**QUANTIFICATION OF ACYCLOVIR IN PLASMA SAMPLES**

Blood samples (5 mL) for determination of plasma acyclovir concentrations were taken on days 2 and 3 of the treatment period. Acyclovir concentrations were assayed by scintillation proximity radioimmunoassay. The area under the plasma acyclovir concentration vs time curve was calculated for patients receiving each active treatment to estimate comparative acyclovir exposure.

**HSV ISOLATION**

Swabs from genital lesions were passed in virus transport media, and an aliquot of this medium was used to inoculate monolayers of cultured cells at each participating study center. The cells were incubated at 37°C and examined daily for evidence of characteristic HSV cytopathic effects.

**SERUM ANTIBODY ASSAY**

Serum samples obtained at the time of the screening visit were frozen at −20°C and assayed for HSV type 2 antibodies as necessary, for patients for whom there was no documented history of a positive HSV culture and no positive culture during the treatment period. The assays were done by the Western blot procedure.

**SAFETY ANALYSIS**

Safety evaluation included adverse event reporting at each visit and laboratory testing (hematology, blood chemistry, and urinalysis) at screening and on days 1 and 5. Investigators classified adverse events as to their seriousness, intensity, and possible causal relationship to study drug.

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**PRIMARY EFFICACY END POINTS**

**Length of Episode**

Both valacyclovir and acyclovir treatments significantly decreased the length of HSV episode compared with placebo (P < .001). The median times to episode resolution were 4.8 and 4.8 days for valacyclovir and acyclovir, respectively, compared with 5.9 days for placebo (Table 2 and the Figure). The episode had resolved in an estimated 79% of patients within 6 days with active drug treatment compared with 8 days with placebo. Hazards ratios (Table 2) indicated that episodes resolved 1.66 and 1.71 times faster in the valacyclovir and acyclovir groups, respectively, relative to placebo. No differences between valacyclovir and acyclovir were detected with regard to this efficacy parameter (HR, 0.98; 95% CI, 0.85-1.12).

Exploratory analysis of prognostic factors showed that patient sex did not markedly affect the length of episode (HR, 0.90; P = .13), although age did (HR, 0.99; P < .001). In younger patients, HSV episodes resolved faster than in older patients, eg, a patient 20 years younger than another could expect episodes to resolve about 23% faster. Analyses also suggested that earlier treatment was more beneficial in resolving episodes (HR, 0.99; P < .01), eg, patients initiating treatment within 6 hours after the prodrome achieved 11% faster episode resolution than those starting after 24 hours. In patients who experienced 8 or fewer recurrences within the previous year, episode resolution appeared to be 19% faster than in those experiencing 9 or more recurrences per year (HR, 0.81; P = .003).

**Lesion Healing Time**

Both valacyclovir and acyclovir significantly reduced time to lesion healing compared with placebo (P < .001). Median healing times were 4.8 and 4.8 days,
were no statistically significant differences between the outcomes for the 2 active treatment arms. HR indicates hazards ratio; CI, confidence interval.

Than in male patients (HR, 0.85; 95% CI, 0.85-1.15). That healing time was 15% shorter in female patients than in male patients (HR, 0.99; 95% CI, 0.85-1.15). No differences between valacyclovir and acyclovir were detected with regard to this efficacy parameter.

Lesions healed 1.88 and 1.90 times faster in patients treated with valacyclovir and acyclovir, respectively, than in patients treated with placebo. No differences between valacyclovir and acyclovir, respectively, compared with placebo (median duration, 2 days for both vs 6.0 days (Table 2 and Figure). Hazards ratios indicated that the duration of viral shedding was 2.55 and 2.24 times longer in patients treated with placebo than in patients treated with valacyclovir and acyclovir, respectively (P<.001). Viral shedding tended to cease earlier in female patients than in male patients (HR=0.85, P=.12).

SECONDARY EFFICACY END POINTS

Aborted Episodes

The proportion of patients with aborted episodes was higher in the valacyclovir and acyclovir groups (25.9% and 24.8%, respectively) than in the placebo group (19.8%), although the differences did not attain statistical significance. The frequency of aborted episodes in males and females in the valacyclovir group was similar (24.8% and 27.0%, respectively); however, in the acyclovir treatment group, more females than males had aborted episodes (28.4% vs 20.9%). More male patients who received valacyclovir had aborted episodes than males who received placebo (24.8% vs 13.5%).

Viral Shedding

At least 1 virus culture was obtained from approximately 90% of patients in each treatment group. Culture results were negative in 49% of the valacyclovir and acyclovir treatment groups, respectively, compared with 29% of the placebo group (Table 3). One or more positive HSV culture results were obtained from a greater proportion of placebo recipients compared with those receiving valacyclovir or acyclovir. For patients with at least 1 positive viral culture, both valacyclovir and acyclovir significantly reduced the duration of viral shedding compared with placebo (median duration, 2 days for both vs 4 days for placebo), with no differences between the 2 active agents (Table 4 and Figure). Hazards ratios indicated that the duration of viral shedding was 2.55 and 2.24 times longer in patients treated with placebo than in patients treated with valacyclovir and acyclovir, respectively (P<.001). Viral shedding tended to cease earlier in female patients than in male patients (HR=0.85, P=.12).
Duration and Severity of Pain and Discomfort

Valacyclovir and acyclovir significantly decreased the duration of pain and discomfort compared with placebo (P < .05) in both males (median duration, 2, 2, and 3 days, respectively) and females (median duration, 3, 3, and 4 days, respectively) (Table 4). At day 3, there was strong evidence to suggest differences in proportions of patients with pain in each severity category among valacyclovir- and acyclovir-treated patients compared with placebo-treated patients (P < .001 and P = .001, respectively). Only 12% and 15% of patients in the valacyclovir and acyclovir groups, respectively, reported moderate or severe pain or discomfort compared with 25% of patients receiving placebo. By day 7, only 9% of patients in the valacyclovir and acyclovir groups reported pain or discomfort compared with 17% of patients in the placebo group (P = .05 and P = .06, respectively). No differences were detected between valacyclovir and acyclovir at day 3 or 7.

PLASMA ACYCLOVIR CONCENTRATIONS

For patients receiving 1000 mg of valacyclovir, the maximum average plasma acyclovir concentration was 4.29 µg/mL (19.0 µmol/L) and the estimated average single-dose AUC was 20.6 h·µg/mL (91.5 h·µmol/L).

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5-times-daily acyclovir administration, the AUC values corresponded to average daily acyclovir AUCs of 41.2 h·μg/mL (183 h·μmol/L) and 11.35 h·μg/mL (50 h·μmol/L) for the valacyclovir and acyclovir regimens, respectively.

ADVERSE EFFECTS AND LABORATORY FINDINGS

The most frequent adverse events were headache, nausea, diarrhea, and abdominal pain, and these were reported in a similar proportion of patients in each treatment group (Table 5). Of 6 serious adverse events reported, only 3, which occurred in 1 patient treated with acyclovir (poor concentration, feeling “spaced,” and feeling “tired”) were considered possibly attributable to study medication. Of the 9 treatment-limiting adverse events (events resulting in premature discontinuation of study drug) reported, 4 were noted in the valacyclovir group (headache, nausea and stomach cramps [2 patients]), 4 in the acyclovir group (nausea, diarrhea, vomiting, and gastritis, in 1 patient each), and 1 in the placebo group (pain at lesion site). No significant treatment-related change from baseline occurred in any clinical chemistry, hematology, or urinalysis parameter.

Our results indicate that the treatment of recurrent genital HSV infections with a twice-daily regimen of valacyclovir or a 5-times-daily regimen of acyclovir, administered for 5 days, is significantly more effective than placebo in decreasing the overall length of an episode, lesion healing time, duration of pain and discomfort, and the duration of viral shedding, with no significant differences between the 2 treatments. With a study population of 1200 patients, this, to our knowledge, the largest clinical trial conducted to date to assess the efficacy and safety of antiviral agents as episodic treatment for patients with recurrent genital HSV infections.

The pattern of clinical improvement noted in the valacyclovir treatment group in this study was similar to that previously reported by Spruance et al19 in their large-scale, multicenter, placebo-controlled clinical trial, in which 987 otherwise healthy patients with recurrent genital herpes infections were treated with the same 1000- or a 500-mg valacyclovir 5-day dosing regimen. As patients in both studies had very similar demographic and disease characteristics, and treatment was initiated at approximately the same time following onset of signs and symptoms (≤24 hours), major differences in study results would not have been expected. However, there were differences in the magnitude of changes in certain parameters. Spruance et al19 found that treatment with valacyclovir, 1000 or 500 mg twice daily, was associated with a more dramatic reduction in the length of the herpetic episode (median duration, 4.0 days vs 4.8 days in the present study) and lesion healing time (median, 4.1 days vs 4.8 days). As for secondary efficacy parameters, the findings of the present study were in close agreement with those of Spruance et al19 with respect to increase in the frequency of aborted episodes (25.9% vs 28.0%), decreasing the duration of pain in females (median, 3.0 days in both studies), and decreasing the duration of virus shedding (median, 2.0 days in both studies). However, we found that the valacyclovir 1000-mg regimen more markedly reduced the duration of pain in males (median, 2.0 days vs 2.6 days) (the median in the placebo group was 3.0 days in both studies).

The pattern of improvement in the acyclovir group was comparable to that reported in previous placebo-controlled clinical trials in which a 5-day regimen of acyclovir, 200 mg 5 times a day, was evaluated in immunocompetent patients with recurrent genital HSV infection.9-12,20 In contrast to the present study, these clinical trials involved smaller numbers of patients treated with acyclovir (31 to 106 patients vs 506 patients in the present study), examined fewer efficacy parameters, analyzed and reported treatment differences in efficacy parameters in terms of means instead of medians, and were inconsistent or unclear with regard to time of initiation of treatment (which varied from “at the earliest sign of a recurrence”9 to within 48 hours of signs and symptoms10). In only 3 of the 5 clinical trials was treatment initiated by patients, as it was in our study. Patient-initiated treatment has been shown to lead to a significantly faster healing time in recurrent genital HSV infections than clinic-initiated therapy.9,11 In all of the studies in which acyclovir treatment was patient initiated, the mean lesion healing time was reduced by approximately 1 to 2 days compared with placebo.9,11,20 In the present study, the median lesion healing time was likewise reduced by approximately 1 day (4.8 days vs 6.0 days with placebo) in the acyclovir treatment group. Reichman et al11 found that the duration of virus shedding in patients treated with acyclovir was reduced by a mean of 1.7 days below the placebo value of 3.9 days, which is in agreement with the 2-day median reduction shown in the present study. The present study showed a significant reduction in the duration of pain with acyclovir treatment, in contrast to the smaller-scale study by Reichman et al,11 who found that the change with treatment was not statistically significant.

There may be several reasons why no differences were detected between the valacyclovir and acyclovir treatments for the primary efficacy end points. The exact influence of peak or trough acyclovir plasma concentrations, frequency of high peak plasma acyclovir concentrations, or the overall daily AUC in terminating vi-
ral replication are not well understood. Although pharmacokinetic data in this study show that acyclovir plasma concentrations are substantially higher after administration of valacyclovir than acyclovir, such high concentrations may not be necessary because HSV types 1 and 2 are the most sensitive of all the human herpesviruses to acyclovir, the inhibitory concentration (IC50) values averaging 0.02 µg/mL (0.1 µmol/L) and 0.22 µg/mL (1.0 µmol/L), respectively. Additional increments of antiviral efficacy may, therefore, be difficult to detect beyond what have already been achieved with acyclovir exposure from the standard oral regimen.

The exploratory investigation in this study also permitted an assessment of the effect of age, HSV recurrence frequency history, and patient sex on efficacy parameters. Age and HSV recurrence history (number of recurrences in the previous year) significantly influenced the overall length of episode and lesion healing time, with resolution times being longer in older patients and those experiencing more frequent recurrences. The time to treatment initiation after prodrôme or first sign of a recurrence was only important in relation to length of episode, the parameter that included data from patients with aborted lesions. Previous studies have shown that early acyclovir treatment is preferable, which is supported by the exploratory results of the present trial. Both valacyclovir and acyclovir decreased the duration of pain and discomfort most markedly at study day 3, and the effect was more pronounced overall in male patients. The sex effect on pain and discomfort is consistent with that seen in previous studies. The greatest difference between valacyclovir and placebo with respect to the percentage of patients with aborted episodes (24.8% vs 13.5%) was also observed in male patients in this study.

One of the major goals of antiviral chemotherapy of recurrent HSV disease is to abort lesions. In this study, aborted episodes occurred in marginally more patients treated with valacyclovir and acyclovir than in those treated with placebo, but these differences did not attain statistical significance (P = 0.10). Previous investigations similarly found only trends for more aborted episodes of genital herpes in patients treated with the same acyclovir regimen that was evaluated in the present study. However, Spruance et al found that 5 days’ treatment with either 1000 or 500 mg of valacyclovir twice daily significantly increased the overall frequency of aborted episodes by 40%, from 21% in the placebo arm to 28% to 31% with active treatment. The disparity among studies may be due to differences in baseline disease characteristics of the populations evaluated (eg, recurrence frequency or disease severity) or to design differences (eg, whether patient-initiated early therapy was possible).

In this study, the daily acyclovir AUC estimates of 41.2 and 11.35 h-µg/mL (183 and 50 h-µmol/L) for the valacyclovir and acyclovir regimens, respectively, allowed the conclusion that the oral bioavailability of acyclovir from 1000 mg of valacyclovir is 2.62 times greater than that from 200 mg of oral acyclovir. Using the historical estimate of 20% for bioavailability from 200-mg oral acyclovir, this implies that the acyclovir bioavailability from 1000-mg valacyclovir dosing was approximately 52% in this study, which is similar to previous estimates. Interestingly, however, this higher systemic exposure of patients to acyclovir following valacyclovir administration did not change the quality or quantity of adverse events, nor did it alter laboratory findings.

In conclusion, as twice-daily valacyclovir is as effective and well tolerated in the treatment of recurrent genital HSV infection as 5-times-daily acyclovir, it could prove a useful alternative to acyclovir when convenience of dosing or compliance issues are the prime considerations in treatment.

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REFERENCES