Oral Famciclovir for the Suppression of Recurrent Genital Herpes

A Randomized Controlled Trial

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**Context.**—Recurrent genital herpes simplex virus (HSV) may be treated episodically, but this may not be sufficient for patients with frequent recurrences.

**Objective.**—To determine the efficacy and safety of famciclovir in the suppression of recurrent genital HSV infection.

**Design.**—A randomized, double-blind, placebo-controlled, parallel-group study.

**Setting.**—Thirty university, hospital, or private outpatient referral centers in Canada and Europe.

**Patients.**—A total of 455 patients (223 men, 232 women) aged 18 years or older with a history of 6 or more episodes of genital herpes during 12 of the most recent 24 months, in the absence of suppressive therapy, received study medication.

**Intervention.**—Oral famciclovir, 125 mg or 250 mg 3 times daily or 250 mg twice daily, or placebo for 52 weeks.

**Main Outcome Measures.**—Time to the first recurrence of genital HSV infection; the proportion of patients remaining free of HSV recurrence at 6 months; frequency of adverse events.

**Results.**—In an intent-to-treat analysis, famciclovir significantly delayed the time to the first recurrence of genital herpes at all dose regimens (hazard ratios, 2.9-3.3; \(P<.001\)); median time to recurrence for famciclovir recipients was 222 to 336 days compared with 47 days for placebo recipients. The proportion of patients remaining free of HSV recurrence was approximately 3 times higher in famciclovir recipients (79%-86%) than in placebo recipients (27%) at 6 months (relative risks, 2.9-3.1; \(P<.001\)); efficacy was maintained at 12 months. Famciclovir was well tolerated with an adverse experience profile comparable to placebo.

**Conclusions.**—Oral famciclovir (125 mg or 250 mg 3 times daily or 250 mg twice daily) is an effective, well-tolerated treatment for the suppression of genital HSV infection in patients with frequent recurrences.
METHODS

Study Sites

The study was conducted at 30 university, hospital, or private referral centers located in Belgium (2 sites), Canada (9 sites), France (12 sites), Iceland (1 site), Sweden (1 site), and the United Kingdom (5 sites). The protocol and statement of informed consent were approved by an institutional review board (or ethics committee) prior to each center’s initiation.

Study Population

Otherwise healthy male or female patients, aged 18 years or older, with a history of recurrent genital herpes, confirmed by serology, culture, or both, were eligible for inclusion. Written informed consent was obtained from each patient prior to entry into the study.

Patients who had not been treated with suppressive acyclovir in the year prior to study entry were eligible for inclusion if they had experienced 6 or more recurrences in the preceding 12 months. Patients who had been treated with suppressive acyclovir in the preceding 12 months were eligible if they had a history of 6 or more episodes during any 12-month period in the 2 years prior to study entry while not receiving suppressive acyclovir.

Patients were excluded if they were pregnant or breast-feeding, were immunocompromised, or had received antiviral therapy during the previous 14 days.

Study Design

The study was double blind and placebo controlled. Eligible patients were sequentially allocated a unique patient number at each center according to a computer-generated randomization code; the patient number determined the assignment to 1 of 3 famciclovir regimens (125 mg 3 times daily, 250 mg twice daily, or 250 mg 3 times daily) or to placebo. Tablets containing placebo were identical to those containing each dosage of famciclovir, and there were no reports of compromised blinding by vision or taste. The study medication was blister packed, and packs were labeled with the patient number. To maintain the study blind, patients were instructed to take tablets 4 times daily at the times indicated on the blister packs (0700, 1500, 1900, and 2300). Patients randomized to the twice-daily regimen (every 12 hours) received placebo tablets only at 1500 and 2300; patients randomized to the 3-times-daily regimens (every 8 hours) received only placebo tablets at 1900. Patients took 7 tablets daily during each regimen.

The patient, the investigator, and the sponsor personnel directly involved in monitoring the study or reviewing the data had no knowledge of what treatment had been allocated until the code was unblinded and the data were analyzed. The medication code for a particular patient was only to be broken in the event of a serious adverse experience that the investigator felt could not be adequately treated without knowing the identity of the study medication; the treatment blind was kept intact and was not broken for any patient during this study.

Patients were requested to take tablets each day at the times and in the sequence presented on blister packs. Treatment continued for 52 weeks.

Patients were required to attend the clinic for a scheduled visit every 28 days. If the patient suspected a lesional episode, he or she was required to return to the clinic within 24 hours of the start of the recurrence for confirmation of the episode.

Patients were encouraged to continue in the study despite recurrences of genital herpes. However, after patients had experienced either 2 virologically confirmed or 3 clinically confirmed recurrences, they were given the option of receiving open-label famciclovir (250 mg 3 times daily) for the remainder of the 52 weeks of the study.

Efficacy Assessments

Data for the analysis of both primary and secondary efficacy parameters were provided from investigator assessments of lesional episodes, patient self-assessment of episodes (using a diary card), and viral culture of lesions during recurrences. Isolation of HSV was performed at laboratories local to the research sites using standard cell-culture isolation procedures.

Safety Assessments

Adverse experiences were identified by the investigator or elicited from the patient in response to the question, “Have you felt different in any way since starting the treatment or since your last assessment?” Because patients who were experiencing confirmed recurrences were given the option of withdrawing from the double-blind phase of the study and receiving open-label famciclovir, the period for safety monitoring for placebo recipients was considerably shorter than that for famciclovir recipients (mean duration of exposure range from 277 to 287 days for famciclovir recipients compared with 170 days for placebo recipients). The number of adverse events reported correlated with the length of time

The favorable biological properties of penciclovir and famciclovir and the results of this dose-ranging study to evaluate suppression highlight the potential therapeutic value of famciclovir in the suppression of recurrent genital herpes. The current multicenter, double-blind, randomized, placebo-controlled trial therefore was conducted to determine the efficacy and safety of famciclovir at doses of 250 mg twice daily, 125 mg or 250 mg 3 times daily in the suppression of recurrent genital herpes. Although a high degree of efficacy was established for the 250-mg twice-daily regimen of famciclovir in the preliminary dose-ranging suppression study,13 a minority of patients still experienced HSV recurrences. To explore whether the efficacy of famciclovir could be further improved, the 3-times-daily regimens were incorporated into the design of this study.

The efficacy of famciclovir in the suppression of recurrent genital herpes was investigated in a preliminary, placebo-controlled, dose-ranging study in women with frequent recurrences. Patients were treated for 4 months with oral famciclovir, 125 mg once daily or twice daily, 250 mg once daily or twice daily, or 500 mg once daily, or with placebo. Results from this study indicated that 250 mg given twice daily for 4 months was an effective, well-tolerated treatment for the suppression of genital herpes, with 90% of patients remaining free of HSV recurrence for the duration of the study. Once-daily dosing with famciclovir produced less complete suppression with approximately 60% to 70% of patients remaining free of HSV recurrences. These data are consistent with the results of a dose-ranging study of suppressive oral acyclovir that suggests that twice-daily or 3-times-daily regimens may be more effective than once-daily treatment using equal or higher cumulative daily doses.14

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A total of 457 patients were randomized to the study (Figure 1); 2 patients that a patient participated in the double-blind phase of the study. Thus, to compare the incidences of adverse events between famciclovir and placebo groups in a consistent and unbiased fashion, data from those patients receiving long-term suppressive therapy (≥10 months of double-blind study medication) have been summarized. At each visit, blood samples were taken for measurement of hematologic and clinical chemistry parameters; urinalysis was also performed.

### Sample Size

A sample size of 73 patients per treatment group was required to detect a 30% difference compared with placebo in the proportion of patients who remained free of HSV recurrence for at least 6 months. This assumed at least 90% power and testing at the 1.67% significance level (using the Bonferroni adjustment to ensure that the type I error did not exceed 5%). With 73 patients per group, the study also had 90% power to detect a ratio of 1.185 for the median time to the first recurrence following the start of study medication.

A target enrollment of approximately 120 patients per group was set to provide 73 patients per group with evaluable data.

### Statistical Methods

Statistical analyses were based on data recorded during double-blind treatment only. All analyses were performed on an intent-to-treat population (ie, those patients who were randomized to and received at least 1 dose of study medication). Statistical tests were 2 sided, and 3 pairwise comparisons (ie, each active group vs placebo) were made.

The primary efficacy parameters were the time to the first recurrence after the start of study medication and the proportions of patients who remained free of HSV recurrences (culture confirmed) for at least 6 months after the start of study medication. The proportions of patients who remained free of HSV recurrences for at least 12 months after the start of study medication were evaluated as a secondary efficacy parameter. In addition, the median number of recurrences per year was evaluated.

The times to first recurrence were analyzed using the Cox proportional hazards regression model stratified by center; 95% confidence intervals for the hazard ratio (famciclovir:placebo) and median times were also presented. The comparisons of the proportions of patients free of HSV recurrence were summarized by relative risks (famciclovir:placebo) and analyzed using the Cochran-Mantel-Haenszel test stratified by center. The median numbers of recurrences were expressed as yearly recurrence rates and analyzed using the Wilcoxon rank sum test, stratifying by investigational center.

All patients who received at least 1 dose of double-blind study medication were included in the analyses of time to first event and frequency of events. Recurrence-free proportions were based on the population known either to have experienced at least 1 recurrence or to have been recurrence free during the entire reference time interval.

Clinical laboratory results were evaluated by calculating mean differences from baseline and by identifying laboratory values of potential clinical concern (values that had changed from baseline by more than a specified amount and were outside the sponsor-defined extended normal range).

### RESULTS

A total of 457 patients were randomized to the study (Figure 1); 2 patients...
did not take any study medication; thus, the 455 patients who received double-blind study medication constituted the intent-to-treat population. A total of 223 patients were male (42%-55% in each treatment group), and the mean age ranged from 35 to 38 years (Table 1).

Between 92% and 96% of patients in each group had documented laboratory confirmation of their recurrent genital herpes at enrollment; between 69% and 77% of patients had their infection confirmed by culture and between 22% and 28% by serology. The mean duration of genital herpes was approximately 7 years, and 405 (85%) of the 455 patients had experienced at least 10 recurrences in the 2 years prior to study entry. Sixty-eight patients (15%) had received suppressive therapy with acyclovir in the previous 12 months, and 177 patients (40%) had received episodic acyclovir treatment.

A total of 218 patients withdrew from the study while receiving double-blind medication (Figure 1). The withdrawal rate for placebo recipients (88 [77%] of 114) was approximately double the rate overall for famciclovir recipients (130 [38%] of 341). Furthermore, the proportion of patients withdrawing due to lack of efficacy in the placebo group (63 [55%] of 114) was approximately 3-fold higher than the proportion in the famciclovir groups (56 [16%] of 341). The proportions of patients who withdrew while still free of HSV recurrence were similar in each treatment group (22%-31% in the famciclovir groups, 23% in the placebo group). Other reasons for withdrawal included adverse events, lack of compliance, protocol violations, and loss to follow-up (Figure 1).

The majority of patients (more than 92% in each treatment group) were compliant (≥80% of patients) with double-blind medication.

**Efficacy Results**

The time to the first recurrence (Table 2) was significantly prolonged for patients who received famciclovir (hazard ratios, 2.9-3.3; \( P < .001 \)). The median time to the first recurrence was more than 7 months for the lowest-dose regimen of famciclovir (125 mg 3 times daily) and more than 10 months for the famciclovir 250 mg twice-daily or 250 mg 3-times-daily regimens compared with approximately 7 weeks for placebo recipients.

The proportion of patients remaining free of HSV recurrence was significantly higher for famciclovir recipients (Figure 2), with approximately 3 times more famciclovir recipients (125 mg 3 times daily, 69 [81%] of 85; 250 mg twice daily, 81 [79%] of 102; 250 mg 3 times daily, 74 [86%] of 86) than placebo recipients (25 [27%] of 91) remaining free of HSV recurrences at 6 months (relative risk, 2.9-3.1; \( P < .001 \)). This difference was maintained at 12 months; again, approximately 3 times more famciclovir recipients (125 mg 3 times daily, 55 [71%] of 77; 250 mg twice daily, 65 [72%] of 90; 250 mg 3 times daily, 65 [80%] of 81) than placebo recipients (19 [22%] of 88) remained free of HSV recurrences (relative risk, 3.3-3.6; \( P < .001 \)).

The median number of patient-reported recurrences per year ranged from 1 to 1.8 episodes for famciclovir recipients compared with 5.1 episodes for placebo recipients. The median number of investigator-reported recurrences per year ranged from 0 to 1.0 episode for famciclovir recipients compared with 4.4 episodes for placebo recipients (Table 3). These differences were statistically significant for all 3 famciclovir groups (\( P < .001 \)).

For both of the primary efficacy variables, the 3 famciclovir regimens were comparable; treatment with famciclovir, 250 mg twice daily, 125 mg 3 times daily, and 250 mg 3 times daily had similar efficacy. There was no difference in efficacy for either male or female patients (data not shown).

### Table 1.—Demographic Characteristics by Treatment Group

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Famciclovir, 125 mg 3 Times Daily (n = 112)</th>
<th>Famciclovir, 250 mg Twice Daily (n = 116)</th>
<th>Famciclovir, 250 mg 3 Times Daily (n = 113)</th>
<th>Placebo* (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>35 (19-67)</td>
<td>38 (20-76)</td>
<td>37 (20-66)</td>
<td>37 (20-68)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>52 (46)</td>
<td>64 (55)</td>
<td>59 (52)</td>
<td>48 (42)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>2.9</td>
<td>3.3</td>
<td>3.2</td>
<td>. . .</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>2.0-4.0</td>
<td>2.3-4.8</td>
<td>2.2-4.6</td>
<td>. . .</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*Ellipses indicate data not applicable.

### Table 2.—Time to First Recurrence by Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Famciclovir, 125 mg 3 Times Daily (n = 112)</th>
<th>Famciclovir, 250 mg Twice Daily (n = 116)</th>
<th>Famciclovir, 250 mg 3 Times Daily (n = 113)</th>
<th>Placebo* (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median No. of days</td>
<td>222</td>
<td>336</td>
<td>307</td>
<td>47</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>2.9</td>
<td>3.3</td>
<td>3.2</td>
<td>. . .</td>
</tr>
<tr>
<td>95% Confidence interval</td>
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<td>2.3-4.8</td>
<td>2.2-4.6</td>
<td>. . .</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>. . .</td>
</tr>
</tbody>
</table>

Figure 2.—Proportion of patients who remained free of herpes simplex virus (HSV) recurrence. All comparisons are statistically significant (\( P < .001 \)).
Safety Results

Adverse Experiences.—Famciclovir was well tolerated during both the double-blind and open-label phases of the study, with an adverse experience profile that was comparable with placebo. The most common events occurring in the double-blind phase for patients receiving either famciclovir or placebo for at least 10 months were headache, viral infection (influenza, flulike symptoms, cold symptoms), and upper respiratory tract infection (Table 4).

Only 20 patients had adverse experiences classified as “serious” during double-blind treatment: 5 (4.5%), 3 (2.6%), and 7 (6.2%) in the famciclovir, 125 mg 3 times daily, 250 mg twice daily, and 250 mg 3 times daily, groups, respectively, and 5 (4.4%) in the placebo group. Only 2 patients experienced serious events that were considered by the investigator to be possibly related to study medication, and no patients experienced serious events considered to be related to study medication. The serious events considered to be possibly related were as follows: 1 patient in the famciclovir, 125 mg 3 times daily, group had elevated levels of bilirubin and lipase after 10 months of treatment, which resolved on therapy after 7 days and remained normal for the rest of the study; 1 patient in the placebo group developed severely increased amylase and lipase levels after approximately 3 weeks of treatment (clinical pancreatitis was not reported); study medication (placebo) was withdrawn, and the increased enzyme levels resolved 6 days later.

Laboratory Tests.—While there were isolated differences in laboratory parameters between treatment groups, no consistent pattern or dose response could be identified. In general, the incidence of laboratory abnormalities was comparable between the 3 famciclovir groups and the placebo group.

COMMENT

The objective of this study was to evaluate clearly the efficacy and safety of oral famciclovir in the suppression of recurrent genital herpes. In many patients, recurrent genital herpes can be successfully managed with episodic therapy; however, such management may not be considered sufficient for patients with frequent symptomatic recurrences. To illustrate this, when patients with a history of 6 or more episodes of genital herpes per year were offered a choice of either suppressive or episodic therapy after completing a 1-year study with acyclovir, 80% of patients opted for suppressive therapy.12 The results from the current study clearly demonstrate yearlong treatment with famciclovir to be effective in the suppression of lesional episodes of genital herpes at all 3 dose regimens examined (125 mg 3 times daily, 250 mg twice daily, and 250 mg 3 times daily). The time to the first genital herpes outbreak was approximately 3 times longer for famciclovir recipients than for placebo recipients (hazard ratios, 2.9-3.3; P < .001); the time differences generally equate to approximately 9 months’ delay compared with placebo. Similarly, approximately 80% of famciclovir recipients remained free of HSV recurrences at 6 months compared with only 27% of placebo recipients. This difference was sustained at 12 months with approximately 75% of famciclovir recipients remaining free of HSV recurrences compared with only 22% of placebo recipients. In addition, famciclovir-treated patients experienced approximately 80% fewer recurrences per year than placebo recipients.

It is not appropriate to make direct comparisons between the results obtained in our study and those obtained in trials of suppressive acyclovir that were initiated before the licensure of oral acyclovir and widespread use of suppressive therapy; the patient populations involved in these studies are likely to be different. Nevertheless, studies have demonstrated that acyclovir, at a dose of 400 mg twice daily or 200 mg 3 to 5 times daily, is effective and safe when used as suppressive therapy for recurrent genital herpes for up to 10 years in immunocompetent patients.8,10,11,13-22 In 1-year studies, approximately 45% of patients receiving acyclovir at a dose of 400 mg twice daily remained recurrence free for 12 months compared with fewer than 10% of placebo recipients.19,22 Acyclovir recipients experienced a marked decrease in the number of recurrences per year, with no emergence of toxic effects over time.5

No significant changes in resistance patterns in acyclovir recipients have been detected even after long-term suppressive therapy; the prevalence of acyclovir-resistant HSV isolates in immunocompetent patients is low (typically around 0.3% of isolates).23,24 Similarly, no resistant virus was detected in any virus isolates obtained from famciclovir-treated patients in the current study; 1 resistant isolate was isolated from a patient receiving placebo. To date, no treatment-related HSV resistance has been detected in virus isolates from any clinical trial with famciclovir or penciclovir (R. Sarisky, MD, Smith-Kline Beecham, oral communication, May 25, 1998).

Famciclovir, 250 mg given twice daily, was found to be of similar efficacy to 3-times-daily regimens of famciclovir and provides convenience advantages that are particularly important for the long-term management of recurrent genital herpes. It has previously been demonstrated in women that the same total daily dose of famciclovir (500 mg) given once

Table 3.—Lesional Episodes per Year by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Median No. of episodes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famciclovir, 125 mg 3 Times Daily (n = 69)</td>
<td>1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Famciclovir, 250 mg Twice Daily (n = 81)</td>
<td>1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Famciclovir, 250 mg 3 Times Daily (n = 76)</td>
<td>1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Placebo (n = 30)</td>
<td>5.1</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*Ellipses indicate data not applicable.
†Patient-reported lesional episode following self-assessment and not necessarily clinically confirmed by the investigator.
‡Investigator clinically confirmed lesional episode.

Table 4.—Most Frequently Occurring Adverse Experiences in Patients Receiving Long-term Treatment by Treatment Group

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Famciclovir, 125 mg 3 Times Daily (n = 69)</th>
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<th>Famciclovir, 250 mg 3 Times Daily (n = 76)</th>
<th>Placebo (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>36 (52.2)</td>
<td>34 (42.0)</td>
<td>32 (42.1)</td>
<td>44 (46.7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (10.1)</td>
<td>9 (11.1)</td>
<td>15 (19.7)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>26 (37.7)</td>
<td>25 (30.9)</td>
<td>25 (32.9)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Injury</td>
<td>15 (21.7)</td>
<td>10 (12.3)</td>
<td>19 (25.5)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (10.1)</td>
<td>9 (11.1)</td>
<td>15 (19.7)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>12 (17.4)</td>
<td>13 (16.0)</td>
<td>11 (14.5)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 (5.8)</td>
<td>3 (3.7)</td>
<td>7 (9.2)</td>
<td>5 (16.7)</td>
</tr>
</tbody>
</table>

*Data from patients receiving at least 10 months of double-blind study medication. Adverse experiences are those occurring in 15% or more of patients within a treatment group. Viral infection included influenza, flulike symptoms, and symptoms of a cold.


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daily was clearly less effective than a twice-daily regimen. These data are consistent with the results of a dose-ranging study that investigated a number of different doses and dosing frequencies of suppressive oral acyclovir therapy, which suggest that twice-daily or 3-times-daily regimens of acyclovir may be more effective than once-daily treatment using equal or higher cumulative daily doses. To further support this, recent data with valacyclovir have also shown that a twice-daily regimen was more effective than a once-daily regimen in the suppression of frequently recurring genital herpes.

All regimens of famciclovir were well tolerated. No differences were observed in the frequency and severity of clinical adverse experiences between famciclovir and placebo recipients, and no evidence was seen of hematologic, renal, or hepatotoxic effects in any of the famciclovir groups. The safety of oral famciclovir has already been established for the acute treatment of genital herpes infections. References