Famciclovir Suppression of Asymptomatic and Symptomatic Recurrent Anogenital Herpes Simplex Virus Shedding in Women: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group, Single-Center Trial

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(See the editorial commentary by Corey and Whitley, on pages 1339–40.)

Genital herpes is most often transmitted while the patient is asymptomatic, presumably during episodes of viral shedding. To determine whether famciclovir is effective in reducing asymptomatic shedding, women with frequent, recurrent genital outbreaks were enrolled in a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 112-day trial of suppressive treatment with famciclovir for anogenital viral shedding. Sixty women received 125 mg of famciclovir 3 times daily, 59 received 250 mg of famciclovir 3 times daily, and 58 received placebo. Patients recorded symptoms and self-obtained cultures daily. Famciclovir reduced asymptomatic shedding, compared with placebo ($P<.0001$). The onset of asymptomatic shedding was also delayed ($P<.0001$). Famciclovir reduced symptomatic shedding in a dose-dependent manner (0.72% for 125 mg 3 times daily vs. 0.19% for 250 mg 3 times daily [ $P<.0001$ ] vs. 5.53% for placebo [ $P<.0001$ ]). In conclusion, suppressive treatment with famciclovir reduced both asymptomatic and symptomatic viral shedding and delayed the onset of asymptomatic shedding in women with frequently recurring genital herpes. Studies to examine the effects of suppression by famciclovir on the transmission of genital herpes are warranted.

Genital herpes simplex virus (HSV) infection may be caused by either HSV-1 or HSV-2 and is a significant public health problem associated with increased risks of transmission of HSV to the neonate [1] and of acquisition of HIV, if exposed [2]. Genital herpes is most often asymptomatic but may also present with atypical manifestations [3, 4]. In the United States, 45 million people have genital HSV-2 infection [5], and the rates continue to increase. Furthermore, genital herpes represents a global problem [6], undaunted by the safer-sex messages attendant with the HIV epidemic. Asymptomatic viral shedding is generally believed to be a major risk factor for transmission [7]. Famciclovir is the oral prodrug of penciclovir, a nucleoside analogue that shares the same antiviral spectrum as acyclovir, with similar potency and selectivity [8]. Oral bioavailability of penciclovir is $\sim$77% in volunteers following single-dose administration of famciclovir [9]. Famciclovir is highly effective in the acute, episodic treatment of recurrent genital herpes, reducing the time to cessation of viral shedding and lesion symptoms and the time to lesion healing, compared with placebo [10, 11]. In addition, famciclovir is effective in the suppression of recurrent genital herpes and, compared with placebo, delays the time to the first recurrence of genital herpes [12, 13].

Reduction in asymptomatic shedding has previously been demonstrated in women with early recurrent geni-
tal herpes who received suppressive acyclovir [14, 15]. The present report details the effects of famciclovir (125 mg and 250 mg 3 times daily) versus placebo on both symptomatic and asymptomatic viral shedding from the anogenital tracts of a cohort of Vancouver women with moderately frequent recurrent genital herpes.

PATIENTS AND METHODS

Patient population. Women who were ≥18 years old and in general good health were eligible for inclusion if they had a history of frequent (i.e., at least every 2 months for 6 months while not receiving treatment or monthly for 1 month after cessation of suppressive treatment) and recurrent genital HSV-2 infection (confirmed by culture or HSV Western blot serologic testing). Women of child-bearing potential had negative pregnancy tests before enrollment, were using an approved method of birth control for the duration of the study, and were not breast-feeding. All patients provided written, informed consent, and the study was conducted in accordance with Western Institutional Review Board (Olympia, WA) guidelines for clinical research. Study applicants with a history or clinical suspicion of renal, hepatic, cardiac, gastrointestinal, hematological, or immunological dysfunction were excluded. Patients with any other genital tract disorder or active genital herpes at the time of enrollment, those who were immunocompromised or receiving immunomodifying treatment, those who had a history of recent chronic alcoholism or drug abuse, those who were known to be hypersensitive to acyclovir, those who were receiving corticosteroids, those who had taken any other investigational new drug other than famciclovir within the previous 3 months, and those who had received any antiviral treatment within the previous 2 weeks were also excluded.

Study design. The present study was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-center trial to assess the efficacy and safety of famciclovir (125 mg 3 times daily and 250 mg 3 times daily) in the suppression of asymptomatic viral shedding for 16 weeks (112 consecutive days) in women with frequently recurring, culture-proven, genital HSV-2 infection. The study was conducted at Viridae Clinical Sciences (Vancouver, British Columbia, Canada).

Treatment assignment. Patients were randomized to receive 125 mg of oral famciclovir 3 times daily, 250 mg of oral famciclovir 3 times daily, or placebo for 16 weeks (112 days).

Clinical assessment and efficacy variables. During the study, patients were required to keep daily records of any symptoms of genital herpes and, each morning before rising or bathing, to self-obtain 1 individual “internal” swab for viral culture from the high vaginal mucosa, including the cervix wherever possible, and a second “external” swab from the external genitalia, including (in this order) the lower mons pubis, the clitoral hood, the labia minora (right then left), the labia majora (right then left), the perineum, and the perianal regions. Patients were required to attend the clinic every 28 days (or sooner if a recurrence was suspected) for collection of laboratory data and to assess compliance. After the onset of a symptomatic lesional recurrence, patients were required to have their lesions clinically verified and swabbed for viral culture by the investigator.

The primary efficacy variable was the proportion of days of asymptomatic viral shedding from any genital site. The key secondary efficacy variables were the proportion of days of asymptomatic viral shedding from vulvar and from vaginal sites, the time to the first asymptomatic HSV-positive culture, the time to the first HSV-positive culture, and the proportion of days of symptomatic HSV-positive shedding from any genital site.

Safety analysis. Adverse experiences were identified by the investigator or elicited from the patient in response to the following question: “Have you felt different in any way since starting the treatment or since your last assessment?” Blood samples were obtained at baseline and at each scheduled visit (every 4 weeks), for measurement of hematological and clinical chemistry variables.

Statistical analysis. Statistical tests were 2-sided, and 2 pair-wise comparisons between each famciclovir group and the placebo group were made. The modified Bonferroni correction was used to adjust for multiple comparisons, to maintain an overall significance level of 5% [16].

The proportion of days with asymptomatic shedding was based on the ratio of the number of days when the patients were asymptomatic but shed virus from any genital site to the number of days when a swab was taken and an assessment of lesions and symptoms was made. The proportion of days with symptomatic shedding was based on the ratio of number of days when a positive viral culture was obtained and signs or symptoms were observed to the number of days when a swab was taken and an assessment of lesions and symptoms was made. The efficacy variables listed above were analyzed by use of logistic regression (proportional odds model). Time-to-event variables were analyzed by use of the Cox proportional hazards regression model. Kaplan-Meier plots were used to summarize these variables.

RESULTS

Demographic and baseline characteristics. A total of 180 patients were randomly assigned to study treatment. Two patients (both assigned to placebo) withdrew from the study before taking any medication. A total of 169 patients (94%) completed the double-blind study plus 1 month of follow-up. The
mean age was ~32 years, and the majority of patients were white (table 1).

Fifty-eight patients (32%) had previously received episodic treatment with acyclovir, but treatment had ceased ≥14 days before entering the study. The majority of patients (160 patients [89%]) had not received suppressive treatment with acyclovir within the past year. The frequency of recurrences reported among patients who had not received suppressive treatment was similar among the 3 treatment groups. Sixty-two of these patients (39%) had at least 3 recurrences during the 6 months before the start of the study. Eighteen patients (10%) had received suppressive treatment during the year before enrollment, and all had discontinued treatment ≥30 days before entering the study.

**Proportion of patients with viral shedding.** Asymptomatic viral shedding from any genital site was recorded for a total of 73 patients, including 19 who received 125 mg of famciclovir 3 times daily, 16 who received 250 mg of famciclovir 3 times daily, and 38 who received placebo (table 2, “shedding from any site”). The percentage of days when asymptomatic viral shedding occurred was significantly lower among patients who received 125 mg of famciclovir 3 times daily (0.52% of days; odds ratio [OR], 6.1; 95% confidence interval [CI], 3.5–10.8; \( P < .0001 \)) or 250 mg of famciclovir 3 times daily (0.35% of days; OR, 7.7; 95% CI, 4.0–14.5; \( P < .0001 \)) than among those who received placebo (3.1% of days). Comparison of the 2 famciclovir doses showed no significant difference. External anogenital asymptomatic viral shedding accounted for a higher proportion of days—compared with asymptomatic, internal cervicovaginal shedding—for all treatment groups. Treatment with famciclovir significantly reduced the percentage of days of asymptomatic viral shedding, compared with placebo, for

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group</th>
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<tbody>
<tr>
<td></td>
<td>FCV 3 times daily</td>
<td>125 mg (n = 60)</td>
<td>250 mg (n = 60)</td>
<td>Placebo (n = 58)</td>
</tr>
<tr>
<td>Age, mean (SD) [range], years</td>
<td>32.4 (8.2) [20–61]</td>
<td>32.1 (7.0) [22–50]</td>
<td>33.0 (8.3) [19–53]</td>
<td></td>
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<tr>
<td>White, %</td>
<td>98</td>
<td>93</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Acyclovir treatment during previous year, %</td>
<td>27</td>
<td>28</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>8</td>
<td>10</td>
<td>12</td>
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**Table 2. Asymptomatic viral shedding in herpes simplex virus–infected women enrolled in a randomized, double-blind, double-dummy, placebo-controlled, parallel-group 112-day trial of suppressive treatment with famciclovir (FCV).**

<table>
<thead>
<tr>
<th>Site of shedding, parameter</th>
<th>Treatment group</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>FCV 3 times daily</td>
<td>125 mg (n = 60)</td>
<td>250 mg (n = 59)</td>
<td>Placebo (n = 58)</td>
</tr>
<tr>
<td>Shedding from any site</td>
<td>No. of patients with event</td>
<td>19</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>6.1 (3.5–10.8)</td>
<td>7.7 (4.0–14.5)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>( P^a )</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>External shedding</td>
<td>No. of patients with event</td>
<td>19</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>5.7 (3.2–10.0)</td>
<td>8.4 (4.2–16.8)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>( P^a )</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Cervicovaginal shedding</td>
<td>No. of patients with event</td>
<td>6</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>9.3 (4.2–20.6)</td>
<td>8.6 (3.9–19.2)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>( P^a )</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Only those days when a swab was taken and an assessment of lesions and symptoms was made were included. CI, confidence interval; OR, odds ratio.

\( ^a \) Logistic regression (proportional odds model).
both internal and external asymptomatic swabs (table 2, “external shedding” and “cervicovaginal shedding”).

The time to the first asymptomatic HSV-positive culture was significantly delayed for patients who received famciclovir, compared with patients who received placebo ($P = .0001$; figure 1). The median times were $>112$ days for both famciclovir groups, compared with 20 days for the placebo group. The hazard ratios (HRs) indicated that the rate of appearance of the first asymptomatic HSV positive culture for patients receiving famciclovir was 3–4 times slower than that for patients receiving placebo (125 mg 3 times daily: HR, 3.4 [95% CI, 1.9–5.9]; 250 mg 3 times daily: HR, 4.1 [95% CI, 2.3–7.5]). Comparison of the 2
Famciclovir suppression of HSV shedding

**DISCUSSION**

This is the first parallel-group clinical trial to examine the effects of antiviral suppressive treatment on HSV shedding during both asymptomatic and symptomatic time periods. In this 16-week study, it was found that this cohort of women with frequently recurrent HSV infection shed virus asymptomatically on ~3.1% of days on which symptoms were not noted. In contrast, they symptomatically shed virus on ~5% of days, overall. The present study has confirmed the findings of Wald et al. [17] that external shedding (separate rectal and vulvar swabs in her studies) is identified more frequently than is internal shedding and have demonstrated that both internal and external shedding, as well as both symptomatic and asymptomatic shedding, were significantly reduced by suppressive treatment with famciclovir at doses of 125 mg 3 times daily and 250 mg 3 times daily. Famciclovir also delayed the time to first viral shedding by nearly 3 months (median time, >100 days for the famciclovir groups vs. 19 days for the placebo group). The present study is also the first to demonstrate a dose effect against symptomatic shedding of HSV. Although a slightly higher viral shedding rate was seen in asymptomatic patients who received 125 mg of famciclovir 3 times daily, compared with 250 mg of famciclovir 3 times daily (0.52% vs. 0.35%), that dose difference was not significant.

The present study commenced before the famciclovir dose-ranging studies against symptomatic disease, which identified the approved suppressive dose of 250 mg twice daily [12, 13]. Because of that, I sought separately to confirm the efficacy of famciclovir twice daily in a small cohort of men with less frequent recurrences of genital herpes who were undergoing a 12-month, randomized, placebo-controlled treatment regimen of 250 mg of famciclovir twice daily designed to determine safety and effects on semenology parameters [18]. In that study, famciclovir reduced asymptomatic shedding from 1.09% of days to 0.08% of days (P < .05, vs. placebo) in a subset of men who participated in the asymptomatic shedding study. Although this cohort of men was smaller and the background shedding rates for men were lower, and although this small substudy cannot be quantitatively compared with the present study of women, these data demonstrate that men also benefit with respect to asymptomatic shedding and that they do so using a 250 mg twice-daily dosing format.

It is interesting to speculate on the mechanism underlying famciclovir’s dose-ranging effects on symptomatic disease without such an effect on asymptomatic disease. Indeed, the potential for differences in dose-ranging with famciclovir is well known in suppression of symptomatic disease, having been reported in both phase 2 [12] and phase 3 [13] studies. The 3-times-daily regimens used in the present study were included in the study by Diaz-Mitoma et al. [13] and were shown to be equivalent to the 250 mg twice-daily regimen. Of interest, the
125 mg 3-times-daily dosing format in that trial was associated with 1.8 patient-reported and 1.0 clinician-reported lesional episodes/year, whereas the 250 mg cohorts (either twice daily or 3 times daily) were each associated with 1.0 patient-reported and 0 clinician-reported lesional episodes/year. Any possible statistical differences were not mentioned. These observations point out, however, that efficacy results of suppressive treatment may look slightly different, depending on how any given parameter is defined in a study. In the present study, the suppressive efficacy of the lower dose against symptomatic shedding was clear, yet the degree of efficacy was modestly reduced. It may be that the large numbers of patients in the present trial were required to demonstrate such subtle differences in shedding. Mechanistically, it is possible to hypothesize that viral reactivations may be more likely to result in a symptomatic anogenital lesion in patients receiving the lower-dose regimen, compared with patients receiving the higher-dose regimen. In the present study, patients receiving the lower-dose regimen also shed virus asymptomatically slightly less frequently, although this difference was not statistically significant.

At the outset of the present trial, no treatment had been associated with a reduction of asymptomatic viral shedding, and polymerase chain reaction (PCR) assays of genital secretions were not well characterized. A crossover study of acyclovir was conducted at the University of Washington (Seattle), in which the frequency of both subclinical and symptomatic HSV shedding were examined [15]. In that study, acyclovir (400 mg twice daily) reduced the frequency of viral shedding from 6.9% of days to 0.3% of days over the course of a 70-day placebo-controlled crossover treatment study. Although that study measured a smaller cohort, the selection of patients in the post-primary phase of infection led to somewhat higher rates of shedding than were observed in the present study. Furthermore, the crossover design allowed those investigators to compare 1 patient to herself while receiving placebo and then acyclovir and vice versa. Those investigators also compared treatment effects of acyclovir measured by viral shedding with HSV PCR positivity [14], using a less formal treatment design. HSV DNA detection was reduced on acyclovir by a median of 80%, as measured by PCR. It is interesting to note the striking similarity between suppression of asymptomatic infection in Seattle and Vancouver. Koelle et al. [19] followed asymptomatic shedding from the onset of primary infection and, in subsequent follow-up studies, found a rate of 3.1% in women during the first year after the primary infection—precisely the same as that observed in the present study. In that study, rates decreased slightly, to 2.3% and 2.1%, in the second and third years of follow-up, respectively. In another study, Wald et al. [17] reported asymptomatic shedding rates of 2.0% for patients with established disease past the first year; patients with high symptomatic frequency rates had higher asymptomatic frequency rates. The present cohort had moderately high frequency rates of ≥1 every other month.

We now have almost 20 years’ experience with the safe and effective use of chronic antiviral viral treatment and, in the setting of increasing awareness of asymptomatic shedding and its likely role in transmission, the use of chronic suppressive treatment has become more commonly recommended [20, 21, 22]. Indeed, the proportion of reduction of asymptomatic shedding is ~80%–90%, similar to the degree of reduction of symptomatic infection. In contrast, episodic treatment cannot reduce the frequency of either symptomatic or asymptomatic episodes. It is not yet clear whether reductions in asymptomatic shedding correlate with concomitant reductions in transmission to susceptible partners. At least one study to that end is currently being analyzed and may provide answers regarding efficacy in this indication, along with specific data with which to make treatment decisions. People with herpes are seeking such solutions, especially in light of the disappointing results of vaccination with the Chiron gB-gD preparation demonstrating no protection [23] and vaccination with the GlaxoSmithKline gD preparation demonstrating partial protection in women only [24]. Further studies of the latter are under way, but it is clear that a blanket protection option from vaccination will not be available in the near future. In light of safety and efficacy against asymptomatic shedding, the choice for suppressive treatment may be compelling in many situations, especially where couples are known to be serologically and symptomatically discordant for herpes. In choosing treatment and management, clinicians will want to consider the HSV serostatus of the patient’s sex partners and the patient’s disease severity and frequency, lifestyle and relationship(s), relative risk for asymptomatic shedding, and ability to understand the requirements of drug dosing and compliance, in parallel and fully aligned with the patient’s specific expectations of treatment outcome. Famciclovir, like other antivirals, may be considered one potential suppressive tool in the reduction of asymptomatic and symptomatic viral shedding in people with recurrent genital herpes.

References

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