

# The Continuing Evolution of Antiviral Therapy for Recurrent Genital Herpes: 1-day Patient-initiated Treatment with Famciclovir

Fred Y Aoki, Medicine, Medical Microbiology and Pharmacology & Therapeutics, University of Manitoba, Winnipeg, Manitoba, Canada.

## KEY WORDS

■ RECURRENT GENITAL HERPES ■ ANTIVIRAL DRUGS  
■ PATIENT-INITIATED THERAPY ■ SHORT-COURSE THERAPY  
■ CONVENIENT REGIMENS

## SUMMARY

Increased understanding of the clinical and virological characteristics of recurrent genital herpes simplex virus infection in healthy adults, recognition of the critical importance of early initiation of therapy, which is best achieved by self-initiated therapy, and an appreciation of the excellent tolerance and safety of relatively high doses of available antiviral drugs have facilitated refinements to treatment regimens that are more convenient as well as efficacious and well-tolerated. This paper reviews the progressive convergence of these concepts to an efficacious, well-tolerated, 1-day, patient-initiated regimen for treating episodes of recurrent genital herpes.

## Introduction

IN 2006, IT was reported that patient-initiated, 1-day famciclovir therapy for recurrent genital herpes was efficacious and well-tolerated compared with placebo.<sup>1</sup> These results represented another step forward in the progressive development of convenient, simple and effective therapeutic regimens. This progress has been based on our increasing understanding of the biology of recurrent genital herpes infection and modelled on the concept of patient empowerment to enhance control of this recurring disease.

In one study, famciclovir 1000 mg ingested twice, 12 h apart, on the first day of an episode of recurrent genital herpes increased the proportion of recurrences that aborted, that is, did not progress beyond the papule stage, from 13% in the placebo group to 23% (a 1.9-fold increase), reduced the median duration of lesional symptoms by 33–41% and reduced the median healing time by 29% to 4.3 days.<sup>1</sup> Moreover, if one interpreted as aborted lesions only those in which herpes simplex virus (HSV)-DNA was demonstrated by polymerase chain reaction (PCR) in the swab obtained at the time treatment was initiated, the frequency of non-progression in the famciclovir group was increased from 5.3% in the placebo group to 20.9%, a 3.9-fold increase. The efficacy of this regimen might have been attributable to the rapid self-initiation of therapy after the onset of prodromal symptoms or a lesion and/or the relatively high dose of famciclovir administered. The

time between the onset of first lesional symptoms or signs and initiation of therapy was required by the protocol to not exceed 6 h. In fact, the actual median interval until therapy was started was 1.5 h (mean 2.5 h). The dose, 1000 mg, exceeded two-fold the largest doses of famciclovir previously evaluated as therapy for recurrent genital herpes.<sup>2</sup> Treatment with famciclovir was generally well tolerated but mild-to-moderately severe headaches lasting 1–3 days occurred more frequently in famciclovir recipients (13.5% versus 5.4% [ $P=0.01$ ]) and diarrhoea tended to be more frequent, at 4.9% versus 1.2% ( $P=0.06$ ). The evolution to this patient-initiated, higher-dose, short-course famciclovir regimen has been based on the following:

- Genital herpes due to HSV-2 recurs, on average, approximately four times per year.<sup>3</sup> Accordingly, brief treatments for episodes of recurrent genital herpes are more generally applicable to patients than continuous suppressive therapy. Suppressive therapy yields different therapeutic benefits, including reductions in recurrences and asymptomatic shedding and, in the case of valaciclovir, genital herpes transmission between discordant couples.<sup>4</sup> Suppressive therapy is generally preferred by, and recommended for, individuals experiencing six or more recurrences of genital herpes per year<sup>5</sup> or those who wish to reduce the risk of transmission to their sexual partner.
- Recognition by patients of prodromal symptoms facilitates early patient-initiated therapy (PIT), and such symptoms are experienced by 46% of patients.<sup>6</sup> Two-thirds of prodromal symptoms consist of localized paraesthesiae at the site of subsequent lesion formation. One-quarter of patients experience ipsilateral neuralgic prodromal symptoms, and approximately 5% of patients report systemic malaise and flu-like symptoms. Thus, approximately 50% of patients with recurrent genital herpes would potentially be able to initiate therapy during the prodromal phase of a recurrence.
- Langenberg *et al.*<sup>7</sup> reported that up to 40–65% of women with apparent asymptomatic HSV-2 genital infection diagnosed by serological testing can be successfully taught how to recognize genital herpes symptoms and signs. Thus, initiating therapy at the onset of prodromal symptoms or early in the course of a recurrence ought to be practicable in more than 50% of adults with recurrent genital herpes.

- The mean time to peak HSV concentrations in recurrent genital herpes lesions is only 1 day after lesion onset (Figures 1 and 2).<sup>6</sup> It follows that effective antiviral drug therapy needs to be initiated in the first 24 h after lesion onset. Theoretically, therapy initiated sufficiently early might arrest or limit local tissue injury and obviate lesion development or progression, i.e. abort lesion formation. This approach entails a small risk of unnecessary therapy; from 5% to 7% of recurrences are false prodromes as defined by non-progression in the absence of antiviral therapy<sup>6</sup> or the absence of HSV-DNA by PCR,<sup>1</sup> respectively.
- Genital herpes lesion virus concentration declines rapidly 2 to 3 days after lesion onset<sup>6</sup> so that therapy beyond 3 days may be unnecessary.
- Aciclovir, valaciclovir and famciclovir doses of 4000, 3000 and 1500 mg/day,<sup>8</sup> respectively, have been well tolerated for 5–10 days for treatment of adults with herpes zoster. These doses are larger than those initially approved for treatment of recurrent genital herpes (1000, 1000 and 250 mg/day, respectively). This tolerance has supported the recent evaluation of larger doses than were initially approved for treatment of recurrent genital herpes.

Based on the aforementioned facts, the quest for convenient, efficacious and well-tolerated oral antiviral drug regimens to treat episodes of recurrent genital herpes in healthy adults has evolved from initial studies reporting the efficacy and safety of aciclovir 200 mg five times per day for 5 days in the 1980s compared with placebo.<sup>9,10</sup> In those studies patients were enrolled with lesions of <24 h<sup>9</sup> up to 48 h<sup>10</sup> duration. The actual times to initiation of therapy in the studies were 21.6 h and 24.0 h, respectively. Therapeutic effects were modest and inconsistent in that mean healing times were reduced but not lesional pain duration. An effect of aciclovir in increasing the percentage of patients whose lesions were aborted was not reported.

In subsequent studies, all three dimensions of the antiviral drug therapy of recurrent genital herpes have been further evaluated: time to initiation of therapy; dose; and duration of treatment.

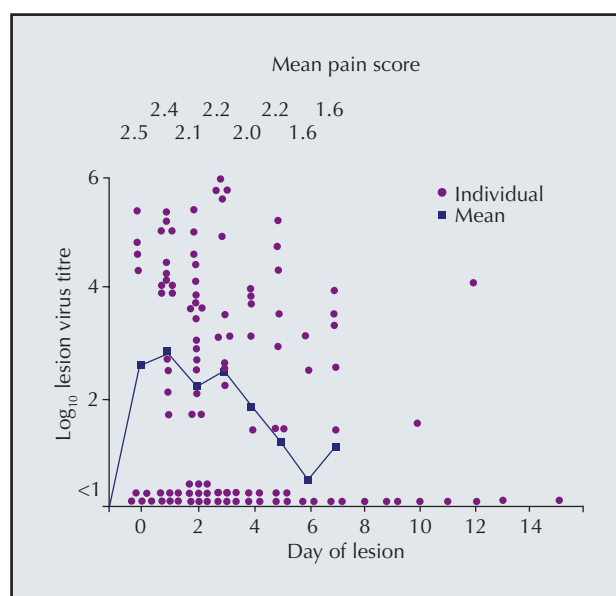


Figure 1: Mean pain score and individual and mean lesion virus titres in 52 women with recurrent herpes simplex genitalis.<sup>6</sup> Reproduced with permission from the BMJ Publishing Group.

## Effect of Early Initiation of Therapy

After a report that peak lesional HSV concentrations were observed 1 day after lesion onset,<sup>6</sup> three formal studies were undertaken to test the hypothesis that earlier initiation of aciclovir 200 mg five times per day would be advantageous.<sup>11–13</sup> Subjects were randomized to PIT with aciclovir or placebo, begun at the earliest symptom or sign of a recurrent genital herpes lesion, or clinic-initiated therapy (CIT) on arrival in the research clinic.

In one study, the mean time to PIT was 4.8 h, and to CIT 24.0 h.<sup>11</sup> The effects of treatment on the frequency of aborted lesions were not studied. Healing time was reported to be less in volunteers who self-initiated therapy but the difference was only significant ( $P \leq 0.05$ ) using a one-tail statistical test. The therapeutic effects of PIT and CIT with aciclovir compared with concurrent placebo were inconsistent, but the duration of HSV shedding was significantly shorter in aciclovir recipients who self-initiated therapy. The duration of virus shedding was not different between placebo groups.

Ruhnek-Forsbeck *et al.*<sup>12</sup> compared PIT and CIT treatment with aciclovir 200 mg or placebo five times a day for 5 days using a randomized cross-over design.<sup>12</sup> Mean times to initiate therapy after the onset of lesional symptoms were 6.0 h and 18.0 h in the two groups, respectively. The frequency of aborted PIT and CIT lesions tended to be greater with PIT with aciclovir compared with placebo (35% versus 19% [ $P=0.067$ ]) than CIT with aciclovir compared with placebo (26% versus 14% [ $P=0.172$ ]). However, there was no definite advantage of PIT aciclovir treatment at this dose compared with CIT aciclovir therapy.

Goldberg *et al.*<sup>13</sup> compared an increased dose of aciclovir 800 mg twice daily for 5 days and aciclovir 200 mg five times a day for 5 days with placebo. Patients were randomized initially to the different treatments in the clinic (CIT) within 48 h of lesion development, then to PIT for two episodes commenced at the first symptom (prodromal phase) of a recurrence. The aciclovir 800 mg dose was not more efficacious than the 200 mg dose in terms of lesion resolution and healing. PIT was efficacious in halting progression to lesion formation as

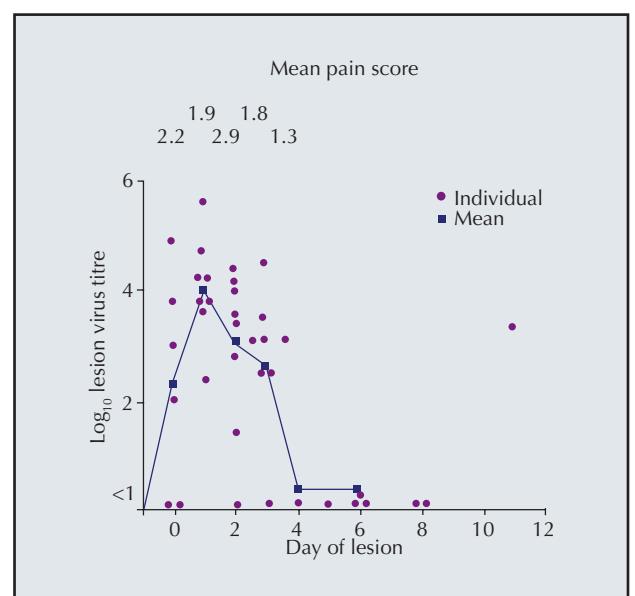


Figure 2: Mean pain score and individual and mean lesion virus titres in 22 men with recurrent herpes simplex genitalis.<sup>6</sup> Reproduced with permission from the BMJ Publishing Group.

11.3% of aciclovir recipients had aborted lesions compared with 3% of placebo recipients ( $P=0.05$ ) but the increased dose was not associated with more aborted lesions than the 200 mg aciclovir dose (11% and 12%, respectively).

Thus, the benefit of PIT with aciclovir 200 mg five times a day for 5 days (and perhaps 800 mg twice daily for the same duration) compared with CIT is modest and inconsistent. In one of two studies, PIT therapy was more efficacious than CIT in reducing lesion progression<sup>13</sup> and in one study, the duration of HSV lesional shedding with PIT was less.<sup>11</sup> There have been no studies directly comparing CIT and PIT with valaciclovir or famciclovir.

### Effect of Increasing Dose

The effect of an increased dose of aciclovir was indirectly tested by studies in which it was administered as the prodrug, valaciclovir, aciclovir being 55% and 15–26% bioavailable from valaciclovir<sup>14</sup> and aciclovir,<sup>15</sup> respectively. Spruance *et al.*<sup>16</sup> randomized volunteers to PIT with valaciclovir 500 or 1000 mg or placebo twice daily for 5 days. Seventy-five percent of volunteers started therapy within 12 h of the first symptoms or signs of a recurrence. Aborted lesions were observed in 31% and 28% of the valaciclovir groups, respectively ( $P=n.s.$ ); both rates were greater ( $P=0.05$ ) than in placebo recipients (21%). Lesional symptom resolution and healing duration were also better with valaciclovir. However, there was no difference in any treatment effect between these two valaciclovir doses, suggesting a flat dose-response curve with PIT over this range.

Bodsworth *et al.*<sup>17</sup> compared the effects of 5 days of aciclovir 200 mg five times per day or valaciclovir 500 mg twice daily with PIT begun at the first symptoms or signs of a recurrence. There were no differences in lesional symptom resolution, healing times, prevention of lesion progression beyond the papular stage or virus shedding between the two groups. Exploratory analysis of the regression of lesion resolution and healing on time revealed that patients who initiated therapy 6 h after onset of first symptoms or signs healed 13% and 15% faster, respectively, than those who started treatment 24 h after symptom onset.

Tyring *et al.*<sup>18</sup> subsequently reported that PIT in adult patients randomized to treatment with valaciclovir 1000 mg twice daily, aciclovir 200 mg five times a day or placebo five times a day begun within 24 h of the first symptom or sign of a recurrence yielded no difference in the percentage of aborted lesions.<sup>18</sup> Rates were 25.9%, 24.8% and 19.8% in the three groups, respectively. Exploratory analysis indicated that the time to resolution of an episode was 11% less in those patients who initiated therapy with either active agent within 6 h after the prodrome onset compared with those who initiated therapy at 24 h ( $P=0.01$ ).

Strand *et al.*<sup>19</sup> compared the therapeutic effects of PIT with valaciclovir 500 mg twice daily for 3 versus 5 days, commenced as soon as possible after onset of symptoms or signs of recurrent genital herpes but within 24 h.<sup>19</sup> Treatment effects were not different between groups but a *post hoc* analysis revealed that the odds of an aborted episode were 1.93 times higher for those patients who initiated therapy within 6 h of onset of the first symptom or sign of a recurrence, compared with those who started treatment later than 6 h after symptom onset ( $P=0.002$ ).

In conclusion, administering a larger systemic dose of aciclovir by treating patients with valaciclovir rather than the approved aciclovir dose of 200 mg five times a day for 5 days did not yield greater therapeutic effects with PIT initiated within 24 h after the onset of the first symptoms or signs of recurrent genital herpes. PIT commenced within 12 h of symptom onset increased the percentage of aborted lesions significantly compared with placebo.

The effect of large doses of famciclovir for treatment of recurrent genital herpes has been reported. Famciclovir 125, 250 and 500 mg or placebo was administered as PIT<sup>2</sup> or CIT<sup>20</sup> twice daily for 5 days. Therapy was initiated within 6 h or 6.5 h, respectively, of onset of first symptoms or signs of recurrence. No estimates of the percentage of aborted lesions were reported. In PIT or CIT recipients there were no differences among the three doses over the four-fold range studied, reflecting a flat dose-response curve. It is not possible to formally compare antiviral or clinical benefits of PIT versus CIT because the data were from different studies. However, lack of differences in analogous endpoints in both studies probably reflects the fact that times to initiate therapy and the doses studied were similar in both studies. A regimen of 125 mg twice daily was considered to be optimally efficacious and well tolerated in both studies (i.e. the largest dose was not more efficacious). Recently, the efficacy and safety of famciclovir given in an even larger dose (1000 mg) twice for only 1 day have been reported.<sup>1</sup>

### Effect of Reducing the Duration of Treatment with or without Larger Antiviral Drug Doses

Until 2002, all reports of drug treatment for episodes of recurrent genital herpes described results of 5 days of therapy. Data from a study on the clinical and virological characteristics of recurrent genital herpes<sup>6</sup> and data from placebo-treated persons in six controlled trials<sup>2,9,11,16,18,21</sup> in which the median duration of HSV excretion in genital herpes lesions was documented to range from 2.0<sup>21</sup> to 4.0<sup>16,18</sup> days, prompted researchers to evaluate shorter courses of therapy, sometimes with larger doses of antiviral drug.

In 2002, Strand *et al.*<sup>19</sup> and Leone *et al.*<sup>22</sup> reported no difference in outcome of PIT between patients treated for 3, compared with 5 days with valaciclovir 500 mg twice daily. Sample sizes of 259 and 402 patients plus 272 and 398 patients given 3 or 5 days of therapy, respectively, provided 80% statistical power to not miss any treatment difference >20%. Valaciclovir 500 mg twice daily for 3 days was approved for treating recurrent episodes. Subsequently, Wald *et al.* compared a 2-day PIT regimen of aciclovir 800 mg three times a day with placebo, initiated within 12 h of first symptoms or signs of recurrent genital herpes.<sup>23</sup> Aciclovir significantly increased the frequency of aborted lesions from 10.6% to 27%, and shortened lesion symptoms and healing time as well as the duration of HSV excretion. Prospective monitoring of the time to the subsequent recurrence was not significantly different between aciclovir recipients (median 48 days) and placebo recipients (median 40.5 days). This important observation indicated that this 2-day course of therapy was not associated with late relapse (i.e. early recurrence), a potential concern with short-course therapy. This high-dose, 2-day aciclovir PIT regimen is a convenient and efficacious off-label treatment. Subsequently, in 2006, 1-day PIT with

famciclovir 1000 mg ingested twice 12 h apart was reported to be efficacious and well tolerated.<sup>1</sup> It has been approved by the United States Food and Drug Administration.

## Conclusion

The paucity of comparative studies precludes definitive conclusions about differences in efficacy, tolerance, compliance or convenience among published reports. Nonetheless, their variety provides practitioners with a number of approved and off-label treatment options for PIT, which make it possible to select individualized, preferred options for patients. The Centers for Disease Control and Prevention (CDC) currently recommend seven different oral regimens for treatment of episodes of recurrent genital herpes:<sup>24</sup>

- Aciclovir 400 mg three times a day for 5 days;
- Aciclovir 800 mg twice a day for 5 days;
- Aciclovir 800 mg three times a day for 2 days;
- Famciclovir 125 mg twice daily for 5 days;
- Famciclovir 1000 mg twice daily for 1 day;
- Valaciclovir 500 mg twice daily for 3 days;
- Valaciclovir 1000 mg once a day for 5 days.

Whether the evolution in the antiviral drug therapy of recurrent genital herpes will continue and lead to the identification of an efficacious, tolerable, single-dose

treatment of monotherapy, or perhaps combination therapy, remains to be seen.

## Conflicts of Interest

Fred Y Aoki has received remuneration for participating in clinical trials on the management of genital herpes sponsored by GlaxoSmithKline and Novartis, manufacturers of valaciclovir and famciclovir, respectively. He holds memberships in genital herpes management advisory boards of both companies and receives honoraria for presentations on genital herpes management from both. He does not serve as a consultant. Neither he nor his family members owns any stocks or shares in either company.

### Address for correspondence:

Fred Y Aoki, MD, Professor of Medicine, Medical Microbiology and Pharmacology & Therapeutics, University of Manitoba, Room 510 – 730 William Avenue, Winnipeg, MB, R3E 0W3, Canada.

E-mail: nelsonak@ms.umanitoba.ca

Received for publication: 16 March 2007

Modified version accepted for publication: 20 August 2007

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