

## ORIGINAL ARTICLE

## Aborted genital herpes simplex virus lesions: findings from a randomised controlled trial with valaciclovir

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**Objectives:** In prospective trials, episodic valaciclovir significantly increased the chance of preventing or aborting the development of painful vesicular genital herpes simplex virus (HSV) lesions compared with placebo. We explored the clinical outcome of aborted lesions and its association with early treatment in a study designed to compare 3 and 5 days' treatment with valaciclovir.

**Methods:** In a randomised controlled trial, valaciclovir 500 mg twice daily for 3 or 5 days was initiated at the first symptoms of a genital herpes outbreak. The primary end point was length of episode with pain, HSV shedding, and aborted lesions secondary end points. The effect of time from symptom recognition to treatment initiation on aborted lesions was assessed in a post hoc analysis.

**Results:** In 531 patients, no differences were observed between 3 and 5 days' treatment in episode duration (median 4.7 v 4.6 days), loss of pain/discomfort (2.8 v 3.0 days), or lesion healing (4.9 v 4.5 days). Vesicular lesions were aborted in 27% of patients treated for 3 days v 21% of patients receiving valaciclovir for 5 days. The odds of achieving an aborted episode were 1.93 (95% CI: 1.28 to 2.90) times higher for those initiating treatment with valaciclovir within 6 hours of first sign or symptom.

**Conclusions:** There was no difference between 3 and 5 days' treatment in reducing episode duration or lesion abortion. Prompt treatment with valaciclovir can abort genital HSV reactivation episodes, preventing a vesicular outbreak. Maximum treatment benefit depends on prompt therapy after recognition of symptoms.

Genital herpes simplex virus (HSV) infection may manifest in a variety of ways. Some infected individuals experience frequent, classic recurrences characterised by painful lesions, while others have only mild symptoms, or are completely asymptomatic.<sup>1</sup> Accordingly, there is more than one treatment modality. Episodes may be treated acutely, or long term suppression therapy may be administered to reduce the frequency of genital herpes recurrences. Episodic or acute therapy is usually suitable for patients whose recurrences are mild, infrequent, and do not interfere greatly with the patient's lifestyle.

Episodic treatment of genital herpes with antiherpes agents for 5 days accelerates healing, resolution of pain, and cessation of viral shedding.<sup>2–4</sup> It is most successful when patients are educated to recognise prodromal symptoms and self initiate therapy as soon as they are first observed.<sup>5</sup> Retrospective analysis of early studies and an open label study in patients specifically taught to recognise the prodrome of a genital herpes outbreak introduced the possibility that therapy could prevent or abort the development of lesions.<sup>6–8</sup>

Prospective analysis of controlled clinical trials of valaciclovir as episodic treatment for genital herpes, and a meta-analysis of these studies, has shown that valaciclovir significantly increases the chance of genital herpes lesions aborting compared with placebo.<sup>9–11</sup> We aimed to determine if treatment duration could be reduced to 3 days without detriment to episode duration. An additional aim was to study the phenomenon of genital herpes lesion abortion more closely, including the associated viral shedding and the effect of treating soon after the recognition of symptoms.

## PATIENTS AND METHODS

## Study design

This was a multicentre, randomised, double blind parallel study comparing two treatment regimens of valaciclovir for

the episodic treatment of one recurrent genital herpes outbreak. The study was conducted at 55 study centres in Europe.

## Patient population

Healthy, male and female patients 18 years of age or older were eligible to enter the study if they had a history of recurrent genital herpes with six or more HSV recurrences in the year before enrolment (assessed over a minimum of 4 months). Those who had been receiving suppressive antiherpes treatment must have discontinued suppressive treatment for at least the last 3 months, and have experienced at least one genital HSV recurrence in that time. A history of genital HSV infection documented by HSV culture, direct antigen test, or written notice from a primary care physician was an entry criterion. Patients were not eligible if they had significant impairment of hepatic (liver transaminase values  $\geq 5$  times the upper limit of normal) or renal (estimated creatinine clearance  $\leq 15$  ml/min) function. Nor were they eligible if they were pregnant or nursing mothers, were known to be immunocompromised, were hypersensitive to aciclovir or valaciclovir, had malabsorption syndrome, or were receiving probenecid, immunomodulatory treatments, or other systemic antiviral or investigational drugs. Ethics committee approval was obtained at each study site before recruitment commenced and all patients gave full written, informed consent.

## Study procedures

At screening, a physical examination was performed, and patients were instructed on how to self swab to obtain a pre-treatment sample for HSV culture. Eligible patients were randomised at the screening visit in equal numbers to one of two treatment arms—oral valaciclovir 500 mg twice daily for 3 or 5 days. Patients received study medication for the first 2 days of treatment. The remaining doses for days 3–5 were provided

**Table 1** Demography, disease, and presentation characteristics

	Valaciclovir treatment		
	3 days (n=259)	5 days (n=272)	Total (n=531)
Male/female (%)	44/56	48/52	46/54
Median age (years, range)	34 (18–76)	36 (16–81)	35 (16–81)
Pain severity at treatment initiation (%)			
None/mild	52	58	55
Moderate/severe	48	42	45
HSV isolated pretreatment (day 0) (%)	35	36	35
Time from first signs/symptoms to start of treatment:			
≤6 hours (%)	50	46	48
Median (hours, range)	6.1 (0–291)	8.0 (0–187)	7.3 (0–291)

to patients on their return to the clinic with a herpes recurrence. Patients randomised to valaciclovir for 3 days received matching placebo tablets on days 4 and 5. Randomisation codes were kept by the sponsor and a copy contained in sealed envelopes held by the investigator or pharmacist for emergency use only.

At the first sign or symptom of a recurrence, patients self swabbed for pretreatment HSV culture (day 0) then started taking study medication as soon as possible but within 24 hours. Patients were required to return to the clinic for assessment within 24 hours of the first symptoms or signs of a recurrence (day 1). Clinical evaluation and lesion staging (no signs, macule/papule, vesicle/ulcer, crust/swab, or healed) were performed on days 1–5. Patients whose lesions had not healed and whose symptoms had not resolved by day 5 were required to return to the clinic every 2 days until all clinical signs and symptoms had resolved. Swabs for HSV culture were taken daily at each clinic visit as appropriate (that is, lesions still existing in macule/papule or vesicle/ulcer/pustule stage) until all lesions had scabbed or aborted. Virus was identified by cytopathic effect. Diaries were used throughout the treatment and follow up period for patients to record the date and time of prodrome/first signs of a genital herpes episode, date and time of each dose of study medication, the patient's assessment of lesion stage, and the pain/discomfort level (no pain, mild, moderate, or severe pain). Safety was assessed by adverse experience reporting at each clinic visit and at a follow up visit on day 9 for those patients whose lesions resolved by day 5 or day 7. Compliance was assessed by pill count of returned blister packs.

### Clinical end points

The primary end point was length of episode, defined as the number of days from treatment initiation to complete resolution of all signs and symptoms. Patients whose lesions aborted and those whose lesions developed or progressed through all stages to healing were identified. Patients having an aborted episode were those in whom prodromal symptoms were present, but the lesions never developed or never progressed past the macule/papule stage. Lesion healing was determined in those patients whose lesions progressed. Duration of pain or other genital discomfort was determined for all patients. Duration of HSV shedding was determined for those patients with one or more positive virus culture results at any time during the treated episode (day 0 to day 6). If patients did not reach an end point the event was deemed to have occurred on the last day that the subject was assessed.

### Statistical methods

This sample size of 400 patients provided 80% power to establish that the difference in median length of episode was less than 0.7 days. The value of 0.7 days was chosen as a conservative estimate of a 20% difference from the 5 day median healing time. Enrolment of 720 patients was estimated for

achievement of 400 patients reaching the end point of complete resolution of all signs and symptoms.

The intent to treat population for time to event analyses was defined as all patients randomised who returned to the clinic with a genital herpes episode and who had at least one post-baseline clinical assessment. This was the primary analysis population and was applicable to episode length and duration of pain analyses. The analysis of lesion healing excluded patients with aborted episodes. The analysis of duration of virus shedding was restricted to those for whom there was at least one positive virus culture result at any time during the treated episode (days 0 to 5). Statistical testing was not performed on the virus shedding end point as the number of subjects with at least one positive culture during the study (256/531) was considerably smaller than for the primary end point. The intent to treat population was used for the analysis of safety.

Equivalence of the 3 and 5 day valaciclovir regimens for episode resolution, lesion healing, and loss of pain was assessed using a Hodges-Lehman 95% confidence interval about the differences in medians between treatments, assuming that a difference of 20% or less is not clinically significant.<sup>12</sup> The Cochran-Mantel-Haenszel  $\chi^2$  test was used to test for treatment differences in the proportions of patients with aborted lesions.<sup>13</sup>

A post hoc exploratory analysis to investigate the effect of time of treatment initiation after onset of first signs and symptoms on the likelihood of lesions aborting was performed using the Cochran-Mantel-Haenszel  $\chi^2$  test.<sup>13</sup> The value of 6 hours was chosen as the cut off for analysing the frequency of aborted lesions because previous studies with famciclovir have required treatment within 6 hours of the first sign or symptom of an outbreak.<sup>3,14</sup> In patients with a virologically confirmed genital HSV episode, time to cessation of viral shedding was compared between patients whose lesions aborted and those in whom lesions progressed using a generalised Wilcoxon test.

### RESULTS

Of the 770 patients enrolled, 531 patients returned to the clinic with a genital herpes episode. The majority (73%) of the 239 patients who did not return to the clinic did not have an HSV recurrence during the study period. Consent was withdrawn by 12%, 8% were lost to follow up, 1% violated the protocol, and 5% withdrew for other reasons.

Demographic characteristics of the intent to treat population are summarised in table 1. The two treatment groups were very similar in demographic, disease history and presentation characteristics. A similar proportion of patients in the 3 day treatment group and the 5 day treatment group had a positive pretreatment culture for HSV (35% v 36% respectively). Overall, the median time from initial episode to entering the study was 4.8 years (range 0–47.3). Forty six per cent of patients had experienced nine or more recurrences in the

**Table 2** Proportion of genital herpes episodes aborting before vesicle formation

	Valaciclovir treatment		
	3 days (n=259)	5 days (n=272)	Total (n=531)
Vesicular lesions (% patients)			
Overall	73	79	76
Aborted episodes (% patients)			
Overall	27	21	24
Male (n=244)	23	19	21
Female (n=287)	30	23	26

previous year. Treatment was initiated within 6 hours of the first sign or symptom in 48% of patients, with a median time of 7.3 hours (range 0–291). Compliance with study treatment was good, with 96% of patients taking at least 80% of study medication. A total of 285 patients had a history of a positive HSV culture. Of these, 4% were HSV-1 positive, 54% were HSV-2 positive, 1% were seropositive for both HSV-1 and HSV-2, and 41% of cultures were untyped.

**Treatment differences**

Valaciclovir therapy for 3 and 5 days was equivalent for episode resolution (4.7 v 4.6 days respectively) and loss of pain/discomfort (3.0 v 2.8 days). Times to cessation of virus shedding were similar for the two groups (1.7 v 1.8 days), although no formal hypothesis testing was undertaken. The slight increase in lesion healing time observed for the 3 day group is not statistically significant and is not considered clinically meaningful (4.9 v 4.5 days).

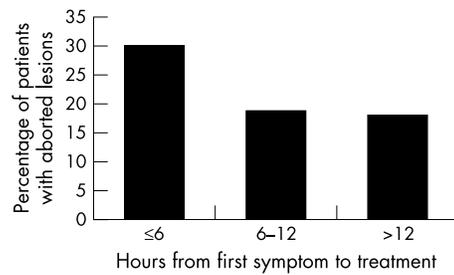
Since there were no differences between the 3 and 5 day treatment groups in demographic variables, treatment initiation time from onset of symptoms, key time to event analyses and the proportions of patients whose lesions aborted, HSV shedding data were pooled for analysis according to clinical outcome.

**Aborted lesions and early treatment**

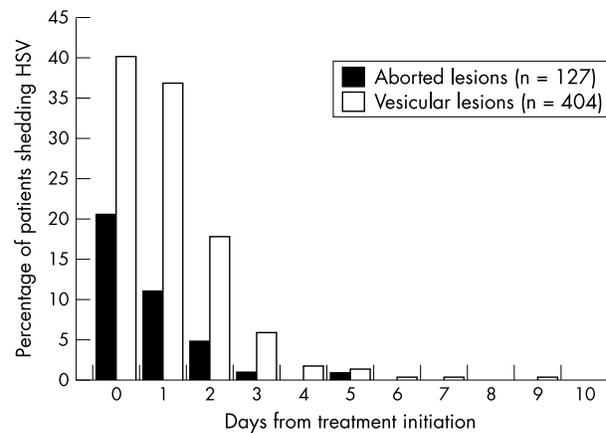
Overall, 24% of patients experienced prodromal symptoms that resolved without development of vesicular lesions (table 2). The percentage of patients treated for 3 days with aborted lesions was 27% and 21% of those treated for 5 days had aborted lesions. No statistically significant differences were observed between the 3 day and 5 day treatment groups in proportions with aborted lesions. The relative risk (95% CI), controlling for centre and sex for 3 day versus 5 day treatment groups, was 1.23 (0.92, 1.65); p=0.16.

The time from first signs or symptoms to treatment initiation was found to be important in determining clinical outcome. The median time from first symptoms to treatment initiation was 4.25 hours (range 0–216 hours) for patients with aborted lesions, and 8.50 hours (range 0–291 hours) for patients whose lesions progressed through all stages. Thirty per cent of subjects who started treatment within the first 6 hours had an aborted episode compared with 19% of subjects who treated 6–12 hours after the onset of signs and symptoms, and 18% who started treatment after 12 hours (fig 1). The odds of an aborted episode were 1.93 (95% CI: 1.28 to 2.90; p=0.002) times higher for those patients treated ≤6 hours compared with those patients treated >6 hours after first signs and symptoms. The relative risk of an aborted episode was 1.65 (95% CI: 1.20 to 2.25).

When only those patients with evidence of viral replication before treatment were considered (n=187), 20% of those patients treated within 6 hours had an aborted episode compared with 10% of those who treated after 6 hours. The effect of time to treatment on the chance of lesion abortion in this



**Figure 1** Clinical outcome with time from first signs and symptoms to treatment initiation.



**Figure 2** Proportion of patients shedding HSV by clinical outcome.

subgroup just failed to reach statistical significance at the two sided 5% level (p=0.051). The odds ratio was 2.30 (95% CI: 1.00 to 5.32) and the relative risk of an aborted episode was 2.05 (95% CI: 1.00 to 4.21).

**Virus shedding and clinical outcome**

Pretreatment swabs were obtained from 85% of patients with HSV detected in 35%. By day 6, a positive HSV culture had been obtained from 49% of patients, 49% of patients were culture negative for the duration of the study, and only 2% of patients did not have any culture results.

Among the 127 patients whose genital herpes lesions aborted, HSV reactivation was demonstrated by virus isolation in 29 (23%). A positive virus culture was obtained immediately before treatment in 26 patients (20%) (fig 2). Virus shedding quickly abated in these patients with treatment and the day after commencement of therapy, HSV shedding was observed in only 11% of patients. Virus was detected in 5% of patients on day 2 and less than 1% on day 3. After day 3, virus was detected in just one patient on day 5 only.

HSV was more likely to be isolated from patients whose lesions progressed. Of the 404 patients with vesicular lesions, 57% had a positive virus culture at some time during the episode. Forty per cent of these patients had a positive virus culture pretreatment. Shedding was slower to respond to therapy in patients whose lesions progressed and 37% of patients were still shedding HSV 1 day after treatment initiation. On day 3, virus was detected from 19% of patients and on days 4, 5, and 6 from 2%, 1%, and <1% respectively. HSV shedding was still detected in one patient on day 7 and another on day 9 post-treatment initiation.

In addition to reduced frequency of shedding, patients with aborted lesions experienced a significantly shorter duration of viral shedding than patients whose lesions progressed (median 1.1 v 1.6 days, p=0.042).

## Safety

Adverse events were generally mild and similar between treatment groups in frequency or severity. The most commonly reported adverse events and the percentage of patients in whom they occurred were headache (5%) and nausea (3%). Only a minority of adverse events were considered by the investigator to be drug related (2% headache and 2% with nausea).

## DISCUSSION

Aborted lesions, or non-lesional prodromes, are the most desirable outcome from episodic antiviral therapy for genital herpes outbreaks. This study has provided evidence that episodes that begin with prodromal symptoms, but do not progress to classic vesicular lesions, may be associated with reactivation of HSV virus. Additionally, the odds of lesion abortion are almost twice as high with early treatment with valaciclovir.

The time to clinical event outcomes for both the 3 day and 5 day treatment groups was similar in this study and in previous randomised controlled trials with the same dose of valaciclovir for 5 days.<sup>4,11</sup> The median episode length for the present study was 4.6–4.7 days versus 4.7–5 days for previous studies, lesion healing time was 4.5–4.9 days *v* 4.1–4.4 days, duration of pain was 2.8–3.0 days *v* 2.5–3.0 days, and duration of virus shedding was 1.7–1.8 days versus 2 days.<sup>4,11</sup> In previous studies, valaciclovir 500 mg twice daily has prevented lesion development in 22–31% of patients.<sup>4,11</sup> This compares favourably with the rate of aborted lesions reported in the current study (24% overall).

Early studies with aciclovir demonstrated the benefits of early, patient initiated therapy for recurrent genital herpes over delayed, physician initiated therapy.<sup>5</sup> A benefit of aciclovir for lesion abortion has also been suggested.<sup>6,7</sup> In studies of famciclovir using a protocol which required treatment initiation within 6 hours of first signs and symptoms of a recurrence, an effect on aborted episodes has not been reported.<sup>3,14</sup> Meta-analysis of three valaciclovir studies has demonstrated valaciclovir treatment within 24 hours of signs and symptoms significantly increased the odds of vesicular lesions being prevented by up to 44% compared with placebo.<sup>9</sup> The present study is consistent with this finding. Additionally, in those patients who experience a prodrome, early treatment (within 6 hours of the first signs and symptoms of a prodrome) improves the chance of aborting lesion formation.

By using pretreatment swabs to optimise the probability of detecting virus shedding, this study of valaciclovir provided evidence of HSV replication in 23% of aborted genital herpes episodes. As antiviral therapy has been shown to reduce the chances of detection of HSV<sup>3</sup> it is likely that virus was involved in a higher proportion of these episodes than 23%. The demonstrated effect of early therapy with valaciclovir on lesion abortion was more pronounced in subjects whose aborted episodes were shown to be virus associated (odds ratio 2.30 (95% CI: 1.00 to 5.32) in subjects with evidence of viral replication before treatment *v* odds ratio 1.93 (95% CI: 1.28 to 2.90) in all subjects). The smaller patient numbers in the group with evidence of viral replication meant that the comparison for the effect of time to treatment on the chance of an aborted lesion may not have been sufficiently powered to show a significant difference.

Although HSV shedding was detected in association with aborted lesions, HSV was isolated from less than half as many aborted lesions compared with vesicular lesions (23% *v* 57% patients shedding at any time during the episode). This, and the significantly shorter duration of shedding in patients with aborted lesions, suggests an association between reduced viral load and aborted lesions. A reduced viral load would be consistent with early treatment with valaciclovir effecting lesion abortion.

The findings of our study emphasise the importance of patient education and counselling for people with genital herpes. Patients should be taught to recognise the prodrome of a genital herpes episode, and empowered to treat early with effective oral antiviral therapy. The detection of HSV shedding from patients with aborted lesions suggests that transmission of infection is still possible and may help to explain why most genital HSV transmission occurs during apparently asymptomatic periods.<sup>15</sup> Patients need to be made aware of this.

This study did not identify differences in healing time or pain duration between valaciclovir therapy for 3 and 5 days for genital herpes episodes. The association of aborted lesions with prompt valaciclovir therapy was substantiated by analysis of clinical outcome in relation to HSV shedding and time to initiation of treatment. Observational studies have previously demonstrated that within and between individuals, variation in severity, duration and outcome of genital herpes lesions is broad and the outcome of aborted lesions is unlikely to be consistently achieved for any individual. We found that extended episodes resulting in development of vesicular lesions were associated with more prolonged HSV shedding and therefore risk of infectivity, and thus in clinical practice the duration of therapy should be considered carefully.

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## CONTRIBUTORS

AS, RP, and HW were involved in the design of the study and were responsible for data collection. KC interpreted the results and wrote the first draft of the manuscript; aAll authors commented on interim drafts, and all reviewed the final manuscript.

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