Corrigendum

2-day versus 5-day famciclovir as treatment of recurrences of genital herpes: results of the FaST study

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The published paper contained an error on page 225. Under the heading 'Investigators – Australia', the investigator's name, Philpot R, was omitted and should have been included.

2-day versus 5-day famciclovir as treatment of recurrences of genital herpes: results of the FaST study*

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Abstract. *Background*: The brief period of viral replication in recurrent genital herpes lesions suggests shorter therapeutic regimens may be as effective as standard 5-day courses. *Objective*: To demonstrate that a 2-day course of famciclovir 500 mg statim, then 250 mg twice daily was non-inferior to the standard 5-day course of 125 mg twice daily. *Methods*: Patients were randomly assigned either the 2-day or 5-day famciclovir course and initiated therapy within 12 h of onset of prodromal symptoms. They were instructed to complete daily questionnaires on herpes-related symptoms and functioning and to attend the clinic for assessment of healing 5.5 days after initiating therapy. *Results*: A total of 873 patients were randomised at least once and 1038 recurrences were treated. The proportion of evaluable recurrences with lesions present at 5.5 days was less in the 2-day arm (24%) than in the 5-day (28%) arm. The upper 97.5% confidence limit (CL) for this difference in favour of the 2-day arm was 2% in favour of the 5-day arm, well within the 10% predefined for non-inferiority. The upper 97.5% CL was similar in the intent-to-treat, evaluable and per-protocol recurrence populations and when adjusted for baseline differences (in gender, age, herpes history and HIV infection) or for clustering of recurrences within patients. Both treatments had similar side-effects; proportion of lesions aborted; time to next recurrence; patient-reported symptoms; and impact on daily functioning. *Conclusions*: The 2-day course was as safe and effective as the standard 5-day course and can only enhance patient convenience and compliance.

Additional keywords: episodic treatment, short course.

Introduction

Five-day treatments were examined in early trials of episodic therapy of recurrent genital herpes as this approximates the usual time to clinical healing. However, the period of actual viral replication in immunocompetent persons is much shorter, usually lasting just 1 or 2 days.[1] This observation has led to studies of shorter 2-day aciclovir[2] and 3-day valaciclovir[3] regimens both of which have demonstrated similar efficacy and toxicity as the standard 5-day regimens.

When the current study was designed there were no published or planned trials of short course famciclovir. We therefore conducted a double-blind, randomised, active-controlled study of a 2-day course of famciclovir compared with the standard 5-day course as treatment of a single episode of recurrent genital herpes.

Recurrent genital herpes can have profound social and psychological consequences, in addition to the impact of the physical symptoms of the infection.[4–6] The current study

consequently employed two validated questionnaires to assess herpes-related disability and to provide detailed temporal information on symptoms of genital herpes during acute episodes.[7]

Methods

Study design

This multinational, multicentre, randomised, double-blind, active-controlled study of patient-initiated therapy compared famciclovir 500 mg statim then 250 mg twice daily (bid) for 2 days (2-day course) with famciclovir 125 mg bid for 5 days (5-day course) in immunocompetent adults with recurrent herpes genitalis. The study was conducted at 59 centres in Australia and 7 in Canada. Patients were recruited and treated between January 2003 and February 2006. The 2-day regimen was chosen as it had the same total dose of famciclovir as the standard 5-day regimen but had a larger initial dose and was administered only during the time of anticipated maximal viral replication.

All participants gave written informed consent before being enrolled in the study and all study activities accorded with the Declaration of Helsinki. The protocol and consent forms were approved by the institutional ethical review board at each participating site.

Patients who met the entry criteria were randomised in a 1 : 1 ratio to receive either the 2-day or 5-day regimen. Randomisation was by consecutively numbered, sealed study medication kits held at each site. There was no stratification. Dummy tablets ensured that neither patient nor investigator was aware of treatment assignment. Each patient could treat up to two, independently randomised, episodes.

Patients were instructed to take a swab for polymerase chain reaction (PCR), carry out a urine pregnancy test as necessary and initiate therapy within 12 h of the onset of any sign or symptom. They were to attend the clinic within 24 h of initiating therapy ('confirmation visit') and as near as possible to 132 h (5.5 elapsed days) after initiating therapy ('follow-up visit'). Patients attending the first follow-up visit were re-randomised and supplied with medication for a possible second recurrence.

Patients completed two questionnaires each day between initiating therapy and the follow-up visit. In the Herpes Symptom Checklist (HSC) patients rated the following symptoms as 'none', 'mild', 'moderate' or 'severe': 'tingling'; 'burning'; 'pain'; 'aching (including backache)'; 'itching'; 'tenderness'; 'dysuria'; painful defecation'; 'penile or vaginal discharge'; 'headache'; 'tiredness'; 'urinary frequency'; and 'bowel frequency'. A total score of 0 to 39 was calculated. Patients also self-assessed lesions once a day and recorded the separate presence of 'redness', 'swelling', 'blisters', 'ulcers or sores', 'scabs or crusts' and 'cracked or torn skin'.

The Herpes Outbreak Impact Questionnaire (HOIQ) is a 14-item assessment of daily function (disability) specific to genital herpes outbreaks and relate to: 'leisure'; 'walking'; 'toileting'; 'travel'; 'socialising'; 'motivation'; 'hot places'; 'affection'; 'washing'; 'emotions'; 'transmitting concerns'; 'concentration'; 'sex' and 'uncomfortable'. Patients selected from four possible responses ('not at all', 'a little; 'a fair amount', and 'a great deal') to produce a score for that item.

Psychometric testing of the original instrument, concurrent with this study, determined that 12 of the items should be included in the calculation of a total score, which ranged from 0 to 36. A lower score indicates better herpes functioning, that is, lower herpes impact.

Both the HSC and HOIQ were developed by Galen Research (Manchester, UK) with funding provided by Novartis Pharmaceuticals. All patients completed the HSC but only Australian participants completed the HOIQ as it was not validated for Canadian language.

Patient population

Immunocompetent adults, aged ≥ 18 years, were eligible to participate if they had experienced more than two recurrences in the past 12 months; one recurrence in the past 6 months; or their first episode within the previous 6 months. Confirmation of diagnosis by either direct test of a genital site (PCR, culture, antigen detection) or herpes simplex virus (HSV)-2 specific serology was required. Patients with HIV infection were eligible if CD4 count ≥ 500 cells/μL and/or CD4 cells $\geq 25\%$ of total lymphocytes within previous 3 months and there were no change in antiretroviral therapy in the month before enrolment.

Patients were excluded if they had received probenecid or any investigational drug in the preceding 30 days. Patients were also excluded if: known to be immunosuppressed as a result of underlying disease or concomitant therapy; had a recent history of drug or alcohol abuse; women of child-bearing potential not taking adequate contraception; had significant genital abnormality or skin disease that would interfere with the assessment of lesions; or were allergic or hypersensitive to formulations containing aciclovir, penciclovir, famciclovir, or other nucleoside analogues.

Because each patient could treat one or two recurrences, the study populations were defined by recurrence rather than by patient. All recurrences in patients who initiated treatment with study medication were included in the intent-to-treat (ITT) recurrence population, which also acted as the safety recurrence population. The evaluable recurrence population comprised recurrences in patients who initiated treatment and also attended the follow-up (Day 5.5) clinical evaluation. The per-protocol recurrence population included all the recurrences in evaluable population patients without major protocol violations. Efficacy results are presented for the evaluable recurrence population unless otherwise stated.

Efficacy endpoints

The primary efficacy variable was the estimated probability of having lesions ('not lesion free') at 5.5 elapsed days after initiation of therapy as assessed by the investigator.

Secondary efficacy variables included: the proportion of recurrences that were aborted (failure to progress beyond the papule stage); the time between consecutive recurrences; the change from baseline in the scores for pain and other individual symptoms; and change in the total HSC and HOIQ scores.

Statistical analysis

This non-inferiority study examined the hypothesis 'that the 2-day famciclovir course would have ≤ 10 percentage-point

difference in the proportion of recurrences healed at 5.5 days when compared with the 5-day course'.

If the two treatments were equally effective, 650 treated recurrences, 325 per treatment group, would have 90% power of having the upper 97.5% confidence limit (CL) of the difference in proportions being ≤0.10. A difference of 10 percentage points in healing at 5.5 days was considered the maximal clinically acceptable difference and has been used in other non-inferiority studies of episodic treatment of genital herpes.[8,9] The study was event driven and recruitment was to cease after 700 treated per-protocol recurrences.

Because not all patients attended exactly 5.5 days after initiating therapy, a logistic regression model was used to model the relationship between the logit of the proportion of patients who were lesion-free at the follow-up visit and the time since initiating therapy and the treatment group. This model was then used to estimate the difference between treatment arms in the proportion lesion-free at 5.5 elapsed days.

Five sensitivity analyses were conducted on the primary efficacy endpoint to assess any effect of: clustering of recurrences by patient; clustering of recurrences by patients within each study centre; considering only the first recurrences; considering only PCR-positive recurrences; and adjustment for baseline demographic and clinical covariates.

The time between consecutive recurrences was analysed by Cox regression and unpaired *t*-test. The proportion aborted was compared by Fisher's exact test for a 2 × 2 table. For symptoms (HSC) and functional impact (HOIQ), the mean scores between Days 1 and 5 were calculated (area under the curve) and *t*-test statistics were used to compare treatment groups. Statistical analyses were performed using SAS Version 8 (SAS Institute, Cary, NC, USA).

The study was registered with www.clinicaltrials.gov (accessed 31 March 2008), trial identifier NCT00171990.

Results

Patients

A total of 873 patients were initially randomised to either the 2-day (*n* = 433) or the standard 5-day course (*n* = 440, Fig. 1). 29% did not experience a recurrence during the study. 616 patients had a recurrence, commenced study medication and were included in the safety (ITT) population. Of the 1038 treated recurrences, 1024 were assessed at the follow-up visit and included in the evaluable population. 278 recurrences occurred in patients with designated protocol violations leaving 760 recurrences (390 in the 2-day arm, 370 in the 5-day arm) for the per-protocol population. The most common protocol violations were failure to take study medication within 12 h of onset of symptoms (120 recurrences) and failure to attend the follow-up visit within the designated window of 108 to 192 h (115 recurrences).

Recurrences in the two treatment groups occurred in persons of similar age, sex, race, proportion with HIV infection and HSV disease characteristics (Table 1).

Primary efficacy endpoint

In the evaluable population, the proportion of recurrences with lesions present 5.5 days after initiating treatment was less in the
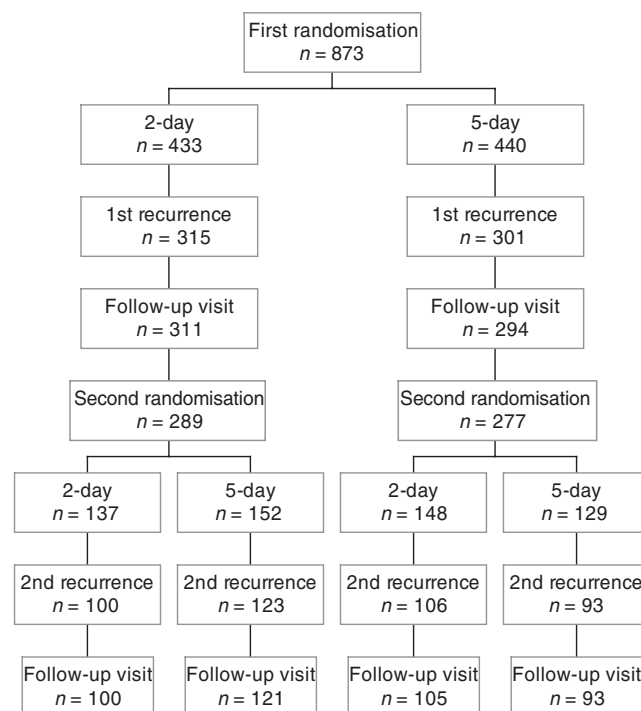

Fig. 1.   Flow of study participants.

2-day arm (24%) than the 5-day (28%) arm. The upper 97.5% CL for this difference in favour of the 2-day arm was 2% in favour of the 5-day arm, well within the 10% predefined for non-inferiority. The upper 97.5% CL was similar in the ITT, evaluable and per-protocol recurrence populations and when adjusted for baseline differences (in sex, age, herpes history and HIV infection); or when adjusted for clustering of recurrences within patients or clinics; or when restricted to first recurrences or to PCR-positive recurrences (Table 2).

Secondary efficacy endpoints

A similar proportion of recurrences was aborted in the 2-day arm (7.6%) as in the 5-day arm (9.5%, *P* = 0.31) (Table 3). There was no significant difference in time to next recurrence by treatment assignment of first recurrence. The resolution of symptoms and improvement in patient functioning was similar in both treatment groups, with little difference in the mean total HSC and HOIQ scores between Days 1 and 5. The mean scores for the individual HSC items at Days 1 and 5 are shown in Table 4.

Safety

Adverse events (AEs) in both famciclovir groups were similar. Overall, AEs were infrequent and of mild to moderate intensity. Headache was the most common AE being reported in association with 16% of 2-day treatments and 18% of 5-day treatments, followed by nausea (3%, 4%), back pain (3%, 2%), diarrhoea (2%, 3%), fatigue (2%, 3%), dizziness (2%, 2%) and abdominal pain (2%, 1%).

Table 1. Demographic and clinical characteristics (intent-to-treat population)
GH, genital herpes; HSV, herpes simplex virus

	2-day famciclovir (521 recurrences)	5-day famciclovir (517 recurrences)
Median age, years	40	40
Female gender	43.0%	45.1%
Caucasian	91.9%	90.7%
HIV-positive	7.9%	10.1%
Number of GH recurrences in previous year		
<3	10.9	10.7
3–9	62.6	64.8
≥10	23.6	21.5
Missing	2.9	3.1
Duration of GH, years		
<1	22.3	21.5
1 to <5	23.2	25.4
5 to <10	17.1	15.3
10 to <20	25.3	24.8
≥20	9.0	10.4
Missing	3.1	2.7
Type of HSV		
HSV-1 only	10.0%	9.5%
HSV-2 only	80.0%	78.7%
HSV-1 and HSV-2	8.6%	9.9%
HSV untyped	1.0%	1.4%
Missing	0.4%	0.6%

Table 2. Estimated probability of having lesions 5.5 days after initiating treatment
ITT, intent-to-treat; GH, genital herpes; CL, confidence limit

	Estimated probability	Difference (2-day–5-day)	Upper one-sided 97.5% CL of difference
Population			
Evaluable			
2-day	0.24	−0.03	≤+0.02
5-day	0.28	−0.03	≤+0.02
Adjusted for			
Sex		−0.04	≤+0.02
HIV		−0.03	≤+0.02
Age (years)		−0.03	≤+0.02
GH duration (months)		−0.03	≤+0.02
GH episodes per year		−0.03	≤+0.02
All of the above baseline covariates		−0.04	≤+0.02
Clustering of recurrences by patient		−0.03	≤+0.03
Clustering of recurrences by patient within each study centre		−0.03	≤+0.04
First recurrences only		−0.03	≤+0.05
Polymerase chain reaction positive recurrences only		−0.03	≤+0.05
ITT			
2-day	0.25		
5-day	0.29	−0.04	≤+0.02
Per protocol			
2-day	0.25		
5-day	0.30	−0.05	≤+0.02

Discussion

The present study was successful in its attempt to show that a 2-day course of famciclovir 500 mg statim, then 250 mg bid was non-inferior to the standard 5-day course of 125 mg bid. For the primary efficacy parameter of 'proportion with lesions 5.5 days after initiating treatment' there was a non-significant trend in favour of the short course and the upper 97.5% CL of this difference was well within the 10 percentage points predefined by the protocol to assume non-inferiority.

Table 3. Other clinical outcomes by treatment group (evaluable population)

CI, confidence interval; sd, standard deviation; HSC, Herpes Symptom Checklist; HOIQ, Herpes Outbreak Impact Questionnaire

	2-day famciclovir (515 recurrences)	5-day famciclovir (506 recurrences)	P
Lesions aborted[A] (%)	7.6	9.5	0.31
Time to next recurrence,[B] mean days (95% CI)	72.3 (61–84)	70.6 (60–81)	0.86
HSC, pooled mean total score over 5-day treatment period, mean (±s.d.)	4.77 (±3.76)	4.98 (±3.83)	0.40
HOIQ,[C] mean total score over 5-day treatment period, mean (±s.d.)	5.70 (±5.12)	5.78 (±5.29)	0.84

[A]Failure to progress beyond papule stage.
[B]By treatment assignment of first recurrence.
[C]Australian sites only.

Table 4. Herpes-related symptom scores[A] at baseline and at Day 5 by treatment group (evaluable population)

Symptom	2-day famciclovir, Day 1	2-day famciclovir, Day 5	5-day famciclovir, Day 0	5-day famciclovir, Day 5
Tingling	1.10 (0.83)	0.18 (0.43)	1.15 (0.87)	0.19 (0.47)
Burning	0.77 (0.86)	0.14 (0.42)	0.83 (0.89)	0.15 (0.44)
Pain	0.77 (0.81)	0.18 (0.49)	0.87 (0.89)	0.19 (0.49)
Aching	0.50 (0.80)	0.19 (0.52)	0.55 (0.84)	0.17 (0.47)
Itch	1.11 (0.92)	0.34 (0.64)	1.11 (0.93)	0.31 (0.59)
Tenderness	1.20 (0.86)	0.31 (0.58)	1.18 (0.88)	0.35 (0.61)
Dysuria	0.21 (0.56)	0.07 (0.29)	0.26 (0.62)	0.07 (0.35)
Painful bowel movements	0.14 (0.48)	0.05 (0.28)	0.17 (0.56)	0.05 (0.28)
Discharge	0.19 (0.51)	0.11 (0.39)	0.18 (0.50)	0.10 (0.41)
Headache	0.38 (0.71)	0.20 (0.51)	0.48 (0.78)	0.21 (0.56)
Tiredness	0.90 (0.93)	0.40 (0.69)	0.95 (0.94)	0.38 (0.69)
Urine frequency	0.27 (0.64)	0.11 (0.38)	0.27 (0.64)	0.10 (0.38)
Bowel frequency	0.12 (0.46)	0.05 (0.25)	0.10 (0.38)	0.05 (0.02)
Total score[B]	7.67 (5.18)	2.28 (3.49)	8.01 (5.21)	2.30 (3.66)

[A]Based on Herpes Symptom Checklist (see text for details).
[B]Pooled mean, s.d. = standard deviation, P > 0.05 for all comparisons.

The Famciclovir Short-Course Herpes Therapy (FaST) study recruited patients slowly over 3 years. During this time, the Aoki study of episodic famciclovir treatment compared famciclovir 1 g twice a day for 1 day with placebo,[10] and showed a 1.8-day treatment advantage in healing time of non-aborted lesions and a 1.5-day advantage for all lesions. Our study used a lower total dose of famciclovir than the Aoki study, 1250 mg *v.* 2000 mg, and so offers an alternative, while retaining good efficacy compared with the hitherto standard, 5-day famciclovir regimen.

In the Aoki study, 23.3% of episodes in famciclovir-treated patients failed to proceed beyond the papule stage, which was significantly greater than in placebo recipients (12.7%, $P = 0.003$). In contrast, we found much lower rates of aborted lesions with no significant difference between treatment arms, 7.6% and 9.5% for the 2-day and 5-day treatments, respectively. We believe that the reliance on patient self-assessment of lesions in our study is the principal cause of this difference; for example if a patient were to tick just one box in the HSC for say, 'cracked skin' in an otherwise sign-free recurrence then the lesion would not be counted as 'aborted'. In contrast, in the Aoki study, lesions were inspected by trial physicians every day through Day 5 and then every other day until healed.

The current study adopted a novel design in that lesion healing, the primary efficacy parameter, was assessed just once at the follow-up visit 5.5 days after initiation of treatment. Five and a half days was selected for three reasons: treatment is finished by 5.5 days; patients with lesions at 5.5 days are likely to re-present for assessment and further treatment; in other treatment studies the Kaplan–Meier plots of 'proportion healed' were generally furthest apart at 5.5 days which maximises the chance of detecting differences between treatment arms. The principal advantage of a single assessment is cost savings and reduced patient burden with little loss in statistical power. However, the current design does not quantify important outcome parameters such as 'time to healing' or 'duration of pain/discomfort' and would be inappropriate where a difference in these outcomes is to be quantified.

Allowing each patient to contribute up to two recurrences to the trial saves one visit for each second recurrence randomised (since re-randomisation was done at the first follow-up visit), reduced the cost of recruitment and increased the recruitment rate (because patients already recruited had no additional cost for the second recurrence and were likely to have several recurrences) and allowed assessment of the time between recurrences. A potential disadvantage was the clustering of

recurrences within patients, but the effect of clustering was slight; if there had been a large effect of clustering, future studies could exploit this using a 'crossover' design whereby successive recurrences receive different treatments.

Another unusual design feature was the inclusion of patients with HIV infection with no laboratory evidence of immune suppression (CD4 count $\geq$500 cells/μL and/or CD4% $\geq$25%). Nine per cent of recurrences occurred in HIV-infected persons yet there was no change at all in the primary efficacy parameter when adjusted for this covariate. HIV-infected persons with near normal immune parameters should not therefore be automatically excluded from future herpes drug trials.

Suppressive treatment of genital herpes using both aciclovir[11] and valaciclovir[12] has been associated with sustained improvements in patients' self-esteem, social and sexual functioning, personal relationships and mental health. The current study is the first to examine the impact of genital herpes on patient functioning in patients receiving episodic treatment for genital herpes and the first in any study of famciclovir. Both treatment arms were associated with substantial, albeit similar, improvements in herpes-related impairment and disability over 5 days, as measured by the HSC and HOIQ questionnaires, respectively. However, the relative contribution of natural history and study medication, if any, cannot be determined with the current study design. Validated, similar instruments should be used in placebo-controlled studies to determine the effect of drug treatment on these important patient-relevant parameters.

In summary, this clinical trial has added another abbreviated alternative to the previously standard 5-day treatments for episodes of recurrent genital herpes without compromise to either efficacy or safety.

Author Contributions

Study concept and design: Adena, Agnew, Bodsworth, Bonney. *Analysis of data*: Adena. *Analysis and interpretation of data*: Adena, Agnew, Bloch, Bodsworth, Bonney. *Drafting of the manuscript*: Bodsworth. *Critical revision of the manuscript for important intellectual content*: Adena, Agnew, Bloch, Bonney, Denham, Doong, McNulty, Trottier. *Study supervision*: Agnew.

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Conflicts of interest

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