Famciclovir for ophthalmic zoster: a randomised aciclovir controlled study

Stephen Tyring, Reinhard Engst, Christine Corriveau, Nicole Robillard, Sylvie Trottier, Steven Van Slycken, Rachel A Crann, Leslie A Locke, Robin Saltzman, Alan G Palestine, for the Collaborative Famciclovir Ophthalmic Zoster Research Group*

Abstract

Aims—To compare the efficacy and safety of famciclovir with aciclovir for the treatment of ophthalmic zoster.

Methods—Randomised, double masked, aciclovir controlled, parallel group in 87 centres worldwide including 454 patients with ophthalmal zoster of trigeminal nerve (V1) comprised the intent to treat population. Oral famciclovir 500 mg three times daily or oral aciclovir 800 mg five times daily for 7 days. Assessments included day 0 (screening), days 3 and 7 (during treatment), days 10, 14, 21, 28 and monthly thereafter, up to 6 months (follow up). Proportion of patients who experienced ocular manifestations, severe manifestations and non-severe manifestations; loss of visual acuity was the main outcome measure.

Results—The percentage of patients who experienced one or more ocular manifestations was similar for famciclovir (142/227; 62.6%) and aciclovir (114/196; 58.2%) recipients, with no significant difference between groups (OR 0.99; 95% CI 0.68, 1.45). The percentage of patients who experienced severe and non-severe manifestations was similar between groups, with no significant difference. The prevalence of individual ocular manifestations was comparable between groups. There was no significant difference between groups for visual acuity loss.

Conclusion—Famciclovir 500 mg three times daily was well tolerated and demonstrated efficacy similar to aciclovir 800 mg five times daily.

In 50%–72% of patients with ophthalmic herpetic zoster (HZO), involvement of the ocular structures leads to ocular manifestations ranging from self limited processes to chronic ocular inflammation or neuropathy which may lead to visual loss.4–6 The mechanism of ocular manifestations is thought to include active viral replication within the eye and ophthalmic trigeminal nerve, followed by vascular and neural inflammation and damage.

Aciclovir treatment for HZO has been shown to be beneficial to patients and is currently the standard of care among health practitioners.8–10 Oral aciclovir at doses of 600–800 mg five times daily for 10 days significantly reduced the acute signs and symptoms of the disease and the incidence of common ocular manifestations such as dendriform keratopathy, uveitis, and stromal keratitis.10 However, aciclovir has poor and variable bioavailability requiring high frequency dosing regimens which can lead to difficulties with compliance.11–15

Famciclovir is the oral form of penciclovir, a nucleoside analogue which shares the same antiviral spectrum as aciclovir for herpes viruses and has similar potency and selectivity. The oral bioavailability of penciclovir is 77% following administration of famciclovir,11 significantly higher than the bioavailability of aciclovir (10%–20%).12 In addition, the intracellular half life of penciclovir triphosphate is significantly longer than that of aciclovir triphosphate in cells infected with varicella zoster virus in vitro (1–11 hours for penciclovir triphosphate compared with <1 hour for aciclovir triphosphate).13

Famciclovir is currently approved in over 60 countries for treatment of acute uncomplicated herpes zoster. Previous studies have been undertaken to compare the efficacy and safety of famciclovir and aciclovir in the treatment of uncomplicated herpes zoster. In one study, famciclovir dosed at 250 mg three times daily for 7 days was as effective as 800 mg aciclovir dosed five times daily for 7 days in the treatment of the acute signs and symptoms of herpes zoster.14 When treatment was initiated within 72 hours of the onset of zoster rash, three doses of famciclovir (250 mg, 500 mg, and 750 mg three times daily) were all as effective as aciclovir (800 mg five times daily) in cutaneous lesion resolution. This includes the median times to loss of vesicles, full crusting, and loss of crusts.15 16 The time to cessation of new lesion formation and time to loss of acute pain was also comparable in patients receiving famciclovir and aciclovir. In patients who received treatment within 48 hours of rash onset, famciclovir significantly decreased the duration of zoster associated pain compared with aciclovir.15 17 In addition to accelerating the resolution of the acute zoster signs and symptoms, famciclovir has been proved to reduce the duration of postherpetic neuralgia.17

Famciclovir’s unique pharmacokinetic properties and demonstrated efficacy in acute uncomplicated herpes zoster prompted the investigation of famciclovir for the treatment of patients with HZO.

Materials and methods

Protocol.

Healthy male or female patients, aged 18 years or older, with clinically diagnosed localised zoster in which the dermatome primarily

*Members are listed at the end of the paper.
involved was the ophthalmic branch of the trigeminal nerve (V₃) were eligible for inclusion. Written informed consent was obtained from each patient before entry into the study.

Patients were excluded if their zoster rash was present for more than 72 hours at the time of receiving the first dose of study medication, if other significant, pre-existing, non-zoster associated pathology was present, if they were pregnant or breastfeeding, or had received antiviral therapy during the previous 14 days. Patients were also excluded if they were immunocompromised, were receiving immunomodifying therapy of any kind, or were known or suspected to be HIV seropositive at the time of enrolment. An HIV serology was performed if other significant, pre-existing, non-zoster associated pathology was present, if they were pregnant or breastfeeding, or had received antiviral therapy during the previous 14 days. Patients were also excluded if they were immunocompromised, were receiving immunomodifying therapy of any kind, or were known or suspected to be HIV seropositive at the time of enrolment. 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Patients were randomly assigned, in a double masked fashion, to one of two treatment regimens for 7 days at screening (day 0): famciclovir 500 mg three times daily or aciclovir 800 mg five times daily. Study visits occurred during treatment on days 3 and 7, during follow up on days 10, 14, 21, and 28, and monthly for months 2–6. An ophthalmic examination which included assessment of lines from the best visual acuity obtained at any previous visit during the study, were also performed. Although anterior uveitis and iridocyclitis are often used interchangeably, for this study a distinction was made in that anterior uveitis involved inflammation in the anterior chamber, whereas iridocyclitis involved inflammation in the vitreous.

### EFFICACY ASSESSMENTS

The primary efficacy parameter was the proportion of patients who experienced an ocular manifestation during the 6 month study period. Ocular manifestations were protocol defined (Table 1). Key secondary efficacy parameters included the proportion of patients who experienced severe ocular manifestations and non-severe ocular manifestations. The prevalence of individual ocular manifestations and the proportion of patients who experienced a loss of visual acuity during the study, defined as visual acuity at study end (month 6) demonstrating a deterioration of three or more lines from the best visual acuity obtained at any previous visit during the study, were also analysed. Although anterior uveitis and iridocyclitis are often used interchangeably, for this study a distinction was made in that anterior uveitis involved inflammation in the anterior chamber, whereas iridocyclitis involved inflammation of the anterior chamber combined with inflammation in the vitreous.

### SAFETY

Safety was assessed by recording reported adverse events and monitoring of haematological and clinical parameters. Only serious adverse experiences were to be collected 30 days or more after the last dose of study medication through the month 6 follow up visit.

Blood was taken for measurement of haematological and clinical chemistry parameters before the first dose on the day of enrolment and following completion of treatment on day 7. 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).

This is the largest controlled study of patients with HZO to date. Sample sizes were based on feasibility considerations. Notwithstanding this, the following figures gave an indication of differences that could be detected. A total of 130 evaluable patients per treatment group were sufficient to detect a 20% difference between the groups in the proportion of patients who developed ocular manifestations at some stage during the study. This assumed at least 90% power and testing at the 5% level.

It was considered that 200 patients per group were needed in order to obtain the required number of evaluable patients. However, target enrolment was revised to 479 patients (200 per treatment arm plus 79 additional) owing to the finding that the initial aciclovir recipients received study medication which was not bioequivalent to the commercial aciclovir formulation. Inclusion of the patients who received the non-bioequivalent aciclovir could have biased the results against the aciclovir treatment group. Thus, these non-bioequivalent aciclovir recipients were not included in the intent to treat population.

### STATISTICAL ANALYSIS

For the proportion end points, any patient who reported a particular symptom at baseline was considered unable to develop the condition during the study and was therefore excluded from the analysis. Any patient who had the symptom unassessed at baseline (that is, missing data) was excluded from the assessment of experiencing that particular symptom during the study as the presence or absence of any symptom could not be assumed. Analyses were performed on all observed data. The formal statistical analysis used logistic regression, based on odds ratios. The odds ratio for a proportion end point was constructed as the odds of famciclovir recipients developing an ocular manifestation(s) relative to the odds of aciclovir recipients developing a manifestation(s). Odds ratios are provided with the corresponding 95% confidence intervals.

### Table 1 Protocol defined ocular manifestations of herpes zoster

<table>
<thead>
<tr>
<th>Severe ocular manifestations</th>
<th>非-severe ocular manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroiditis</td>
<td>Iris atrophy</td>
</tr>
<tr>
<td>Deep keratitis</td>
<td>Subepithelial infiltrates</td>
</tr>
<tr>
<td>Esophthalmos</td>
<td>Non-vision interfering corneal scarring</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Retinitis</td>
</tr>
<tr>
<td>Keratic precipitates</td>
<td>Neuritis</td>
</tr>
<tr>
<td>Scleritis</td>
<td>Partial or complete nerve palsy III, IV, V, VI</td>
</tr>
<tr>
<td>Necrotising scleritis</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Synchiae</td>
<td>Cicatricial lid retraction</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Epitheliopathy</td>
</tr>
<tr>
<td>Non-severe ocular manifestations</td>
<td>Vision impairing corneal scarring or vascularisation</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Epitheliopathy</td>
</tr>
<tr>
<td>Episcleeritis</td>
<td>Subepithelial infiltrates</td>
</tr>
<tr>
<td>Epitheliopathy</td>
<td>Non-vision interfering corneal scarring</td>
</tr>
</tbody>
</table>

*Although anterior uveitis and iridocyclitis are often used interchangeably, for this study a distinction was made in that anterior uveitis involved inflammation in the anterior chamber, whereas iridocyclitis involved inflammation of the anterior chamber combined with inflammation in the vitreous.*
Each patient received one treatment box clearly marked with his/her patient number. Each box contained sufficient medication for 7 days’ treatment presented in daily cards. The study medication was blister packaged and each card displayed the times (07:00, 11:00, 15:00, 19:00, 23:00) and corresponding study medication to be taken.

**PATIENT RANDOMISATION AND BLINDING**

Famciclovir was provided as 500 mg white coated tablets and aciclovir was provided as 400 mg capsules. Tablets and capsules containing placebo were identical in appearance and taste to those containing the active study medication. Patients randomised to famciclovir treatment took famciclovir 500 mg tablets three times daily (07:00, 15:00, 23:00) and two placebo aciclovir capsules five times daily at 7:00, 11:00, 15:00, 19:00, and 23:00. Patients randomised to aciclovir treatment took aciclovir 800 mg (2 × 400 mg capsules) five times daily along with one placebo famciclovir tablet at 07:00, 15:00, and 23:00.

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 data was compiled and the data was analysed. The medication code for a particular patient was only to be broken in the event of a serious adverse experience which the investigator felt could not be adequately treated without knowing the identity of the study medication.

**Results**

Of the 499 patients randomised to the study, 497 patients received at least one dose of study medication (Fig 1). The intent to treat population comprised 454 patients. The demographic characteristics were comparable between treatment groups (Table 2). Slightly more than half of the population was female; mean age was 58 years (range 19–93 years). Zoster characteristics at baseline were also comparable between treatment groups (Table 2). More than half of the patients were enrolled within 48 hours of rash onset and approximately one third of patients had ≥25 lesions.

The presence of severe and non-severe ocular manifestations at baseline was also comparable between treatment groups (Table 3). The most frequent severe ocular manifestations at baseline included glaucoma (39/454, 9%), anterior uveitis (24/454, 6%), and iridocyclitis (21/454, 5%). The most frequent non-severe ocular manifestations at baseline included inflammation of the conjunctiva (242/454, 53%), punctate epithelial keratopathy (56/454, 12%), and episcleritis (44/454, 10%).

A total of 76 patients were withdrawn from the study (Fig 1). The withdrawal rates were comparable between famciclovir and aciclovir recipients (46/251, 18% and 30/203, 15%, respectively). No differences were noted between treatment groups in the percentage of withdrawals due to lack of efficacy or adverse events.

The majority of patients (≥95%) in each treatment group were compliant with study
manifestation post-first dose of study medication.

<table>
<thead>
<tr>
<th></th>
<th>Famciclovir 500 mg three times daily (n=245)</th>
<th>Aciclovir 800 mg 5 × daily (n=196)</th>
<th>Odds ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%)</td>
<td>142 (58.0%)</td>
<td>114 (58.2%)</td>
<td>0.99 (0.68, 1.45)</td>
</tr>
<tr>
<td>Severe</td>
<td>101 (41.2%)</td>
<td>78 (39.8%)</td>
<td>1.06 (0.72, 1.56)</td>
</tr>
<tr>
<td>Non-severe</td>
<td>110 (44.9%)</td>
<td>85 (43.4%)</td>
<td>1.06 (0.73, 1.55)</td>
</tr>
</tbody>
</table>

*Not statistically significantly different if 95% CI includes 1.0.

Table 5 Percentage of patients who experienced individual severe ocular manifestations of herpes zoster (>5% in either group)*

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Famciclovir 500 mg three times daily</th>
<th>Aciclovir 800 mg 5 × daily</th>
<th>Odds ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe ocular manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>25%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Keratitic precipitates</td>
<td>22%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Irido-cyclitis</td>
<td>16%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Overall keratitis†</td>
<td>13%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>11%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Disciform stromal keratitis</td>
<td>7%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Other keratitis</td>
<td>5%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Paralytic ptosis</td>
<td>5%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Stromal keratitis</td>
<td>5%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

*Each percentage is based on the number of patients in the treatment group minus those patients who had the manifestation in question at baseline and those patients who had no data for the manifestation post-first dose of study medication.
†Includes stromal and disciform stromal types of keratitis.

Table 6 Percentage of patients who experienced individual non-severe ocular manifestations of herpes zoster (>5% in either group)*

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Famciclovir 500 mg three times daily</th>
<th>Aciclovir 800 mg 5 × daily</th>
<th>Odds ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe ocular manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punctate epithelial keratopathy</td>
<td>26%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Inflammation of the conjunctiva</td>
<td>20%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Anterior subepithelial infiltrates</td>
<td>18%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Dendriform keratopathy</td>
<td>9%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Epithelial defect</td>
<td>8%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Episcleritis</td>
<td>8%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

* Each percentage is based on the number of patients in the treatment group minus those patients who had the manifestation in question at baseline and those patients who had no data for the manifestation post-first dose of study medication.

ADVERSE EXPERIENCES

Famciclovir was well tolerated with an adverse event profile comparable to aciclovir. The most common on-dose adverse events were nausea (10%), headache (5%), and vomiting (5%).

LABORATORY TESTS

While there were isolated differences in laboratory values between treatment groups no consistent pattern could be identified. In general, the prevalence of laboratory abnormalities was infrequent and comparable between the famciclovir and aciclovir groups.

Discussion

In view of the potentially serious long term complications of ophthalmic herpes zoster (HZO), appropriate and timely treatment is advocated. Aciclovir has poor and variable bioavailability requiring high frequency dosing regimens which can lead to difficulties with compliance. However, famciclovir has poor and variable bioavailability and a longer intracellular half life compared with aciclovir when dosed only three times daily, and has proved efficacy in the treatment of uncomplicated herpes zoster, both in aciclovir controlled and placebo controlled trials. This study was therefore set up to compare famciclovir and aciclovir for treatment of HZO.

The percentage of patients with ocular manifestations during the study was the primary efficacy parameter. Although powered to demonstrate superiority of famciclovir over aciclovir in the primary end point, the results demonstrated the two treatments were clinically equivalent (famciclovir, 58.0%; aciclovir, 58.2%; 95% CI for difference –9.47%, 9.06%) with no significant difference (OR 0.99, 95% CI for odds ratio 0.68, 1.45). As with the presence of ocular manifestations during the study, there were no significant differences between the treatments in the development of severe and non-severe ocular manifestations and the percentages were comparable.

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This is the largest controlled study of patients with HZO to date. Direct comparisons with the limited data in the literature are diffi-
cult owing to differences in study design, com-
posite end points, and definitions of ocular mani-
festations. However, the percentage of famci-
lovir recipients with ocular manifesta-
tions in this study is similar to that previously
reported for aciclovir treated patients with
HZO. Furthermore, the percentage of famci-
lovir treated patients with ocular manifesta-
tions is markedly reduced compared with that
reported for untreated patients.\textsuperscript{16} 18

Anterior uveitis, one of the most common
long term complications of HZO contributing
to vision loss, was the most frequently ob-
served severe ocular manifestation in the current
study (25\% in both groups). This result is
similar to the prevalence of anterior uveitis in
aciclovir treated patients in the study by Cobo
\textit{et al}.\textsuperscript{19} In that small (n = 71) placebo controlled
trial of oral aciclovir (600 mg five times daily
for 10 days), anterior uveitis was observed in
19\% of aciclovir recipients compared with 56\% of
placebo recipients, and the result was statis-
tically significant (p = 0.0020). The prevalence
of anterior uveitis in the current study is also
similar to the incidence observed in aciclovir
recipients in the study by Harding and Potter.\textsuperscript{20}

In that small (n = 46) placebo controlled study
evaluating oral aciclovir 800 mg five times daily
for 10 days, 30\% of aciclovir recipients (seven
patients) developed anterior uveitis compared
with 53\% of placebo recipients (10 patients;
p = 0.06). The percentage of famciclovir treated
patients who developed anterior uveitis in the
current study was lower than that reported for
untreated patients in the natural history study
by Harding (50\% with complications; anterior
uveitis observed in 92\%).\textsuperscript{16}

The prevalence of keratic precipitates, a
clinical indicator of anterior uveitis and the
second most frequently observed severe ocular
manifestation in the current study (22\% in
both groups) was comparable to that observed
in aciclovir recipients (19\%) and much lower
than that observed in placebo recipients (~50\%)
in the study by Cobo \textit{et al}.\textsuperscript{19}

Keratitis is another common long term com-
plexion of ophthalmic zoster contributing to
vision loss. In the current study, the prevalence
of overall keratitis (includes stromal, disciform
stromal, and keratitis classified as "other") was
slightly higher in aciclovir recipients (18\%)
compared with famciclovir recipients (13\%).
The prevalence of keratitis in the current study
was lower than that reported for aciclovir
recipients in the literature. In a small study (n
= 86) by Hoang-Xuan \textit{et al},\textsuperscript{16} oral aciclovir 800
mg five times daily was administered for either
7 or 14 days for treatment of ophthalmic
zoster. Topical aciclovir ointment was used
concomitantly by all patients. The most
common long term complication (appearing or
persisting after the first month of the onset of
herpes zoster) in aciclovir recipients was
stromal keratitis (27\%). In the study by Cobo
\textit{et al},\textsuperscript{19} stromal keratitis was also one of the most
common ocular complications, observed in
25\% of aciclovir recipients compared with 56\%
Famciclovir for ophthalmic zoster

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