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Evaluation of topical ophthalmic application of penciclovir cream in cats with experimental ocular feline herpesvirus-1 infection

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Objective
To determine the efficacy of topical penciclovir 1% cream for the treatment of cats with experimentally induced ocular feline herpesvirus-1 (FHV-1) infection.

Methods
A randomized, placebo-controlled trial was performed using 10 unvaccinated specific-pathogen-free cats with experimental FHV-1 infection induced by topical ocular inoculation. Cats received topical penciclovir 1% cream (n = 6 cats) or a placebo artificial tear gel (4) 3 times daily for 14 days. Cats were monitored after inoculation for 30 days. Ophthalmic examinations were performed every 2 days, and ocular disease scores were calculated. In vivo confocal microscopic ocular examinations were performed to quantify corneal leukocytes. Feline herpesvirus-1 quantitative PCR, viral titers, hemograms, and serum biochemistry panels were performed throughout the study.

Results
No significant differences in clinical ocular disease scores were observed between the penciclovir and placebo groups during the majority of the study period; however, penciclovir-treated cat scores declined more rapidly after study day 14. No significant differences were detected in corneal leukocyte infiltrates between study groups. Ocular viral loads determined by PCR were significantly lower in the penciclovir group on day 3 but were similar on all other sampling days. Hemogram and serum biochemistry values were unremarkable in all cats.

Conclusions
Topical penciclovir 1% cream administered 3 times daily was well tolerated and modestly reduced ocular viral shedding but had minimal effects on clinical ocular disease in cats with experimental ocular FHV-1 infection.

Clinical Relevance
Refinements in the topical penciclovir treatment strategies and optimization of penciclovir formulations are recommended before clinical applications in cats.

Keywords: antiviral, feline herpesvirus-1, herpes simplex virus type 1, keratitis, penciclovir

Feline herpesvirus-1 (FHV-1) is a common etiology of ocular surface disease in domestic cats that is associated with diverse clinical lesions including blepharitis, conjunctivitis, ulcerative keratitis, and nonulcerative keratitis.[1,2] Currently, there are few evidence-based topical antiviral treatment options available for ocular FHV-1 infections in cats. To date, only compounded cidofovir 0.5% ophthalmic solution and commercially available ganciclovir 0.15% ophthalmic gel have been demonstrated to be both safe and effective in cats with experimentally induced ocular FHV-1 infections.[3,4]

Penciclovir is a nucleoside analog with excellent in vitro activity against FHV-1.[5,6] Famciclovir,

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an oral prodrug of penciclovir, is an established and effective systemic antiviral for cats with ocular FHV-1 infections.[7,8] Subconjunctival penciclovir implants evaluated in a pilot study[9] of cats with experimental FHV-1 infection were well tolerated but provided minimal clinical benefits relative to placebo implants. A prior study[10] using 7 healthy cats without ocular disease evaluated twice daily topical ophthalmic application of a penciclovir 1% cream (Fenlips; Perrigo Pharma International DAC). This cream, available under several different trade names around the world, is labeled for the topical treatment of herpes labialis (ie, cold sores and fever blisters of the perioral region) in humans. Herpes labialis is a mucocutaneous infection caused by herpes simplex virus type 1, an alphaherpesvirus closely related to FHV-1.[11] In the feline tolerability study,[10] the penciclovir cream was not irritating and provided penciclovir tear concentrations that were above the expected minimal inhibitory concentration for FHV-1 for over 8 hours after application. A survey[10] of over 100 clients whose cats had been treated with penciclovir 1% cream also found a low incidence of local adverse reactions that were recognized and reported by the clients. Adverse effects were reported in 15% of treated cats and included ocular discharge, transient stinging sensation upon application, ocular redness, and mild periocular alopecia.

To the authors' knowledge, no controlled clinical or experimental studies have been published that evaluated the efficacy of topical penciclovir cream for the treatment of cats with FHV-1-associated ocular disease. The purpose of the present study was to evaluate the efficacy of a topical penciclovir 1% cream in cats with experimentally induced primary ocular FHV-1 infection. If found to be effective, penciclovir 1% cream could provide an additional and widely available evidence-based treatment option for cats with ocular FHV-1 diseases.

Methods

Animals

All protocols were approved by the IACUC of Cornell University (protocol No. 2023-0205) and were conducted in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. Ten 3-month-old, unvaccinated, specific pathogen-free (ie, FHV-1, FeLV, and FIV seronegative) domestic shorthair laboratory cats were used in the study. Five sexually intact male and 5 sexually intact female cats were included. Cats were single housed in an isolation animal housing facility, and direct contact among cats was prevented for the duration of the active study period. Strict bioisolation was maintained in the housing facility for all personnel in contact with the cats throughout the study, including the use of surgical isolation gowns, gloves, face masks, and boot covers. Cats were acclimated to the housing facilities for 4 weeks before the beginning of the study. All cats were adopted by private households after the study's completion.

Study groups and induction of primary FHV-1 infection

A randomized, 30-day placebo-controlled study was performed. Baseline study data were collected 1 day before initiation of the trial (study day 0). Ocular FHV-1 infection was then induced on study day 1 using the ocular drop method, as previously described.[12] Briefly, a 0.1-mL solution containing 10^6 plaque-forming units (PFU) of the FHV-1 strain FH2CS[13] was topically applied into the inferior conjunctival fornix of both eyes, and the eyelids were manually held closed for 1 minute. Cats were randomly assigned to 1 of 2 study groups using block randomization with an even ratio of males and females included in each group. The penciclovir group (n = 6 cats) received a 0.25-inch strip of penciclovir 1% cream (Penvir Labia; EMS Sigma Pharma) in both eyes 3 times daily at 8:00 AM, 2:00 PM, and 8:00 PM. The placebo group (n = 4 cats) received a 0.25-inch strip of artificial tear gel (Optixcare; CLC Medica) in both eyes 3 times daily at 8:00 AM, 2:00 PM, and 8:00 PM. Treatments were administered for 14 days, beginning 24 hours postviral inoculation (study days 2 to 15).

Clinical evaluations

Complete physical and ophthalmic examinations, including Schirmer I tear tests, slit-lamp biomicroscopy (Kowa SL-17; Kowa Co) before and after application of fluorescein stain (FUL-GLO fluorescein sodium strips USP; Moore Medical LLC), applanation tonometry (Tono-Pen XL), and indirect ophthalmoscopy (Heine Omega 600; Heine Optotechnik) were performed on both eyes of each cat on study day 0 (baseline examinations) and study day 30. Abbreviated ophthalmic examinations were performed on both eyes of each cat at 2-day intervals throughout the 30-day study. The abbreviated ophthalmic examinations included slit-lamp biomicroscopy before and after corneal application of fluorescein stain. A previously described ocular surface clinical scoring system[4] was used to quantify examination findings, with a minimum daily cumulative clinical score of 0 and a maximum daily cumulative score of 15. Clinical signs of blepharospasm, ocular discharge, conjunctival hyperemia, and chemosis were scored by means of the following classifications: 0, none; 1, mild; 2, moderate; and 3, severe. Corneal epithelial ulceration was scored by means of the following classifications: 0, none; 1, punctate ulcerations; 2, 1 or more linear or dendritic ulcerations; and 3, geographic ulcerations. When cats had multiple classifications of corneal ulcerations present during an individual examination, they were assigned the highest ulcer score present for that day. A single cumulative ocular surface disease score was calculated for each cat on each examination day, and a mean ocular surface clinical disease score for each group at each time point was calculated. All clinical ophthalmic examinations and ocular disease scorings were performed by a board-certified veterinary ophthalmologist (ECL).

Blood samples were collected from each cat by peripheral venipuncture on study days 0 (baseline samples), 15, and 30 for hemogram and serum biochemistry panel analyses.

FHV-1 virus isolation and real-time PCR

Following initial clinical ocular disease scoring, but before fluorescein stain application, conjunctival swab samples were collected from both eyes of each cat. Samples were collected for FHV-1 virus isolation and real-time quantitative polymerase chain reaction (qPCR) assays by gently brushing a sterile polyester-tipped swab across the superior and inferior conjunctival fornices. Conjunctival swab samples were collected at 3-day intervals throughout the duration of the study, starting on study day 0. Swabs were immediately placed in sterile tubes on ice containing virus transport media composed of 10% neonatal calf serum and 3X antibiotic/antimycotic solution in PBS. Tubes were incubated on ice for 4 hours and then vortexed for 15 seconds before viral transport medium was aliquoted and stored at −20 °C.

Viral titers were determined as previously described.[14] Briefly, 6 sequential 10-fold dilutions of virus were added to monolayers of Crandell Rees feline kidney cells in a 12-well plate for 2 hours. Inoculum media were then removed and replaced with media containing 1.88% carboxylmethylcellulose. Plates were fixed after 48 hours, and plaque-forming units per milliliter were calculated.

To assess viral genome copies by qPCR, DNA was isolated from 200 µL of virus transport media using the Qiagen DNeasy Blood and Tissue according to the manufacturer's protocol and diluted to 15 ng/µL. Viral DNA was quantified using a previously described plasmid standard and primers targeting the *US7* gene of FHV-1.[15] Feline genome equivalents in virus transport medium were quantified using a previously described plasmid standard and primers targeting feline albumin (*fAlb*).[12] Real-time PCR was performed using a QuantStudio3 Real-Time PCR System (Thermo Fisher Scientific Inc) using SYBR green reagents (Thermo Fisher Scientific Inc). The standard curves were used to interpolate the viral and host genome equivalents, and results were expressed as viral genome copies per 10 copies of *fAlb*.

In vivo confocal microscopy

In vivo confocal microscopy (IVCM) examinations of the cornea were performed with a Heidelberg Retina Tomograph 3 and Rostock Cornea Module (Heidelberg Engineering) using a 63X objective (Carl Zeiss Meditec AG). Examinations were performed on both eyes of each cat on study days 0 and 10. Examinations were performed after the application of a single drop of topical anesthetic (proparacaine hydrochloride 0.5% ophthalmic solution USP; Akorn). Several drops of contact gel (Optixcare gel) were applied to the front of the microscope lens and ocular surface. A sterile, single-use polymethyl methacrylate cap (TomoCap; Heidelberg Engineering) mounted on the microscope lens was positioned perpendicular to, and in slight contact with, the corneal surface. The polymethyl methacrylate caps were changed between each eye examined.

Following IVCM examination, digitized corneal images were analyzed for pathology. Images of a standardized anatomic location in the cornea were acquired and used for leukocyte infiltrate scoring. Images of the basal corneal epithelium in the axial cornea were collected, and leukocytes were quantified (cells per millimeter squared of tissue) in 3 noncontiguous corneal images from each eye using semiautomated cell counting software (HEYEX Software Version 2.5; Heidelberg Engineering).

Statistical analysis

A linear mixed quadratic model with fixed effects of treatment group and day, an interaction of treatment group by day, and controlled for the random effect of cat was used to assess the effect of treatment group (penciclovir cream or placebo artificial tear gel) and time on each continuous outcome of interest (ie, clinical ocular disease scores, viral load detected by virus isolation, and viral load detected by qPCR). A 2-sample Student *t* test was used to compare the mean corneal epithelial leukocyte count (leukocytes per millimeter squared corneal tissue) between the 2 treatment groups for the left and right eyes on day 10. A Fisher exact test was used to compare the number of cats with an inflammatory leukogram between the 2 study groups on day 30. All analyses were performed with statistical software, and values of $P < .05$ were considered significant.

Results

Baseline examinations

Baseline physical and ophthalmic examinations were unremarkable for each study cat. Schirmer I tear test results (mean ± SD; 15.1 ± 2.5 mm/min) and intraocular pressure measurements (mean ± SD; 14.4 ± 3.1 mmHg) were within normal ranges in both eyes of each cat. Results of all hemograms and serum biochemical analyses were unremarkable. In vivo confocal microscopy corneal examinations were unremarkable, and no leukocytes were detected in the cornea of any cat **(Figure 1)**. Feline herpesvirus-1 was not detected by virus isolation or qPCR analysis of ocular samples in any of the cats.

Clinical ophthalmic examinations

All cats developed clinical ocular disease consistent with FHV-1 infection by study day 6 **(Figure 2)**. Ocular disease was characterized in all cats by bilateral intermittent blepharospasm, mucopurulent ocular discharge, conjunctival hyperemia, chemosis, and corneal epithelial ulceration **(Figure 3)**. All cats from both study groups developed punctate and dendritic superficial corneal ulcerations between study days 10 and 26. Geographic superficial corneal ulcers were only detected in a single cat from the penciclovir

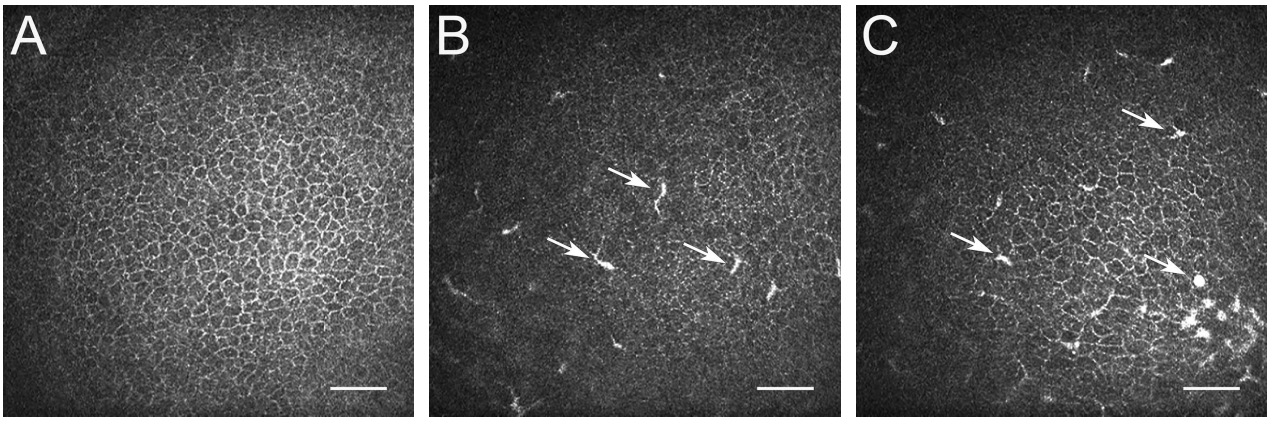

Figure 1—Representative in vivo corneal confocal photomicrographs of cats with experimentally induced ocular feline herpesvirus-1 (FHV-1) infection treated with topical penciclovir 1% cream or placebo topical artificial tear gel 3 times daily. Experimental ocular FHV-1 infection was induced on study day 1, and study medications were administered for 14 days starting on study day 2. In vivo confocal microscopy examinations were performed on study day 0 (baseline examination [A]) and study day 10 (artificial tear gel group [B] and penciclovir group [C]). Leukocytes (arrows) within the basal epithelium of the axial cornea were quantified on study day 10. No significant differences were detected in leukocyte infiltrate counts between the eyes of cats treated with penciclovir cream (C) versus the placebo artificial tear (B). Bars = 50 µm.

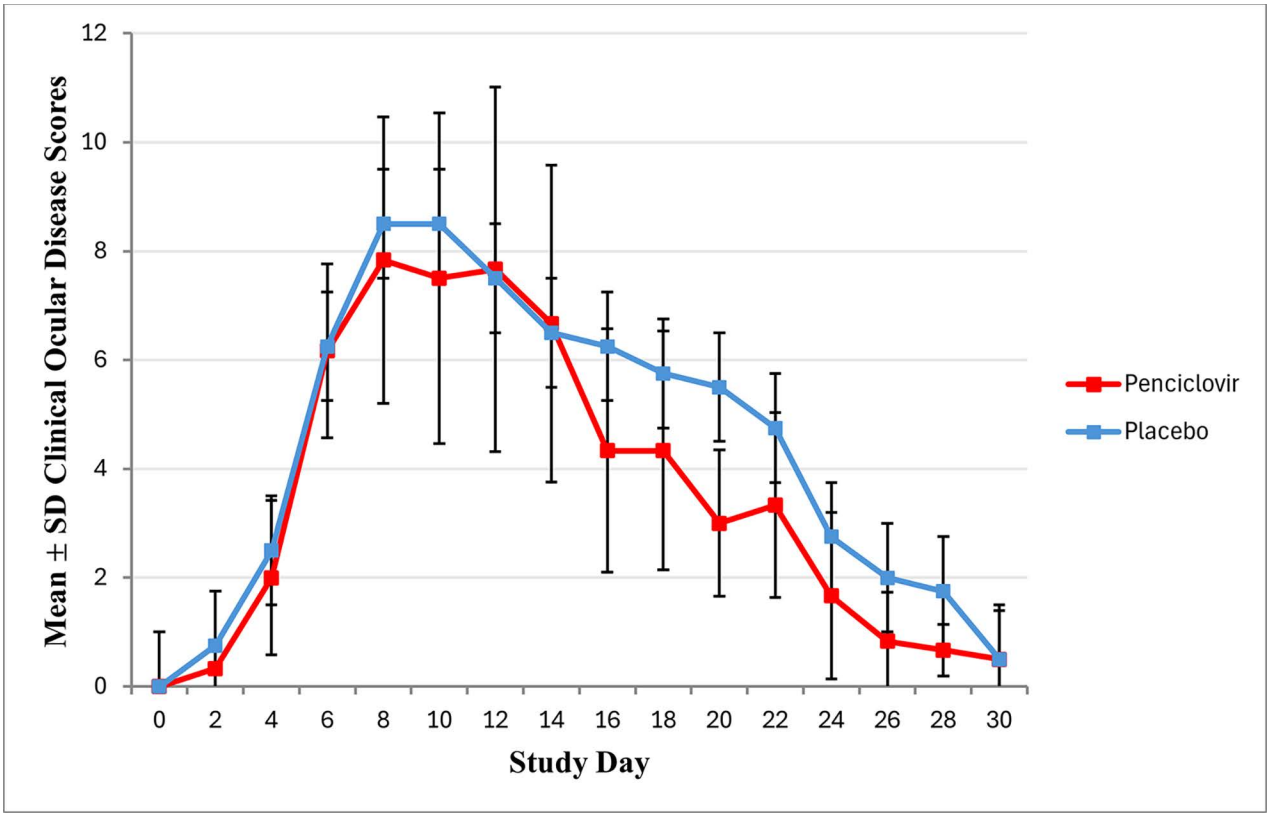

Figure 2—Mean ± SD clinical ocular disease scores for cats with experimentally induced ocular FHV-1 infection treated with topical penciclovir 1% cream (red line) or placebo topical artificial tear gel (blue line) for 14 days. Ocular FHV-1 infection was induced on study day 1, and study medications were administered for 14 days starting on study day 2. Clinical ocular disease scores were calculated every 2 days for 30 days. The ocular surface clinical scoring system used to quantify ophthalmic examination findings had a minimum daily clinical score of 0 and a maximum daily score of 15.

group on study day 12. Ocular disease clinical scores initially rose rapidly in both groups. Peak clinical ocular disease scores (mean ± SD) occurred on days 8 and 10 in the placebo group (8.5 ± 1.1 on day 8 and 8.5 ± 0.9 on day 10) and day 8 in the penciclovir group (7.8 ± 2.7). After peaking, clinical scores slowly declined until they reached 0, or near 0, by study day 30.

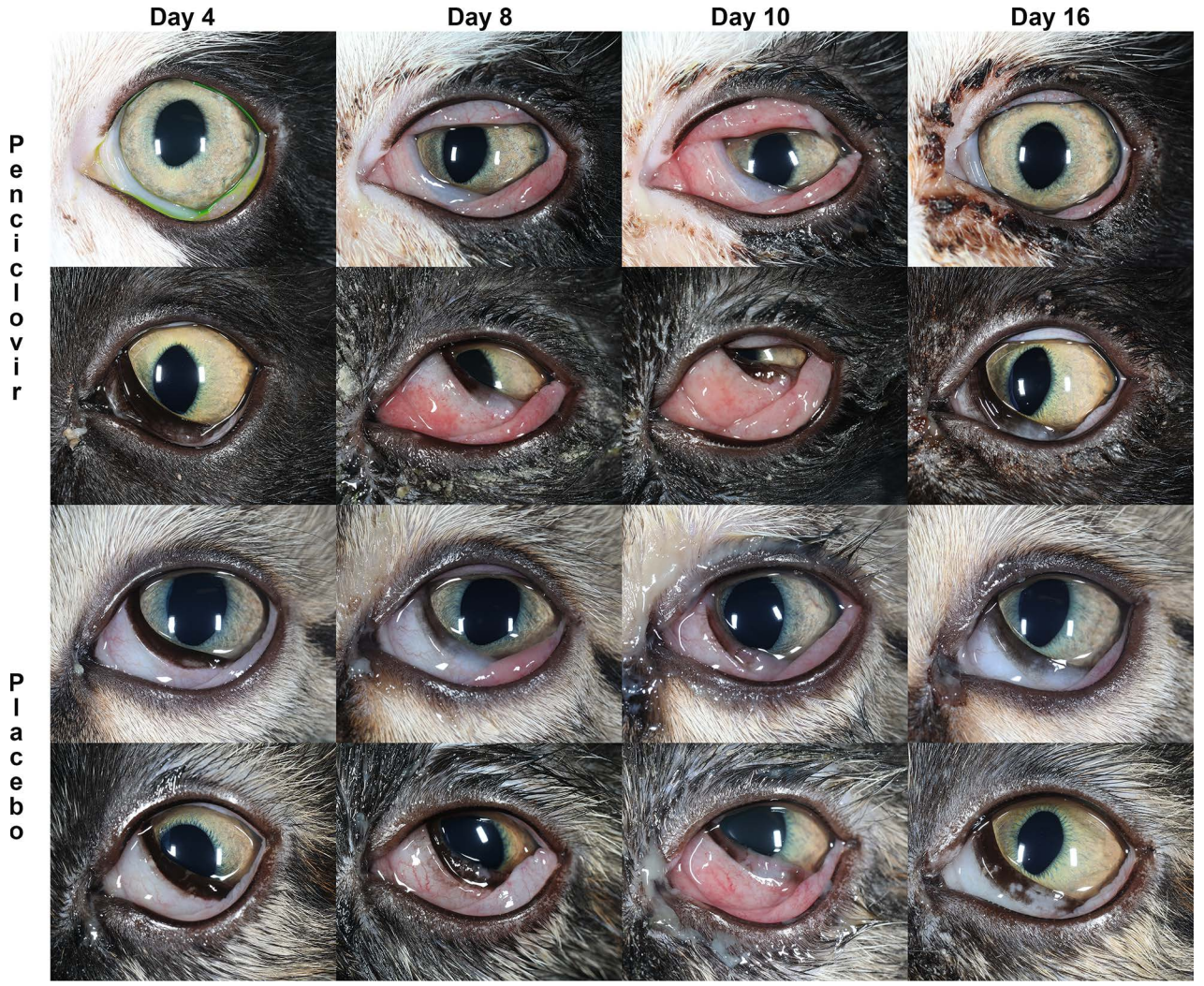

Figure 3—Representative clinical photographs of 4 cats with experimentally induced ocular FHV-1 infection treated with topical penciclovir 1% cream or placebo topical artificial tear gel for 14 days. Ocular FHV-1 infection was induced on study day 1, and study medications were administered for 14 days starting on study day 2. The first and second rows of photographs are serial images of 2 penciclovir-treated cats, and the third and fourth rows of photographs are serial images of 2 placebo-treated cats. Column 1 contains photographs taken on study day 4, column 2 is study day 8, column 3 is study day 10, and column 4 is study day 16.

No significant differences ($P = .24$) in clinical ocular disease scores were observed between the penciclovir and placebo groups when evaluated over the entire study period. Ocular disease scores in the penciclovir-treated cat group declined more rapidly after day 14 (Figure 2). When evaluating individual examination days after study day 14, ocular disease scores (mean ± SD) were significantly ($P \leq .04$) lower in the penciclovir group relative to the placebo study group on days 18 (penciclovir group, 4.3 ± 2.4; placebo group, 5.8. ± 1.8) and 20 (penciclovir group, 3.0 ± 1.2; placebo group, 5.5. ± 0.5). No additional significant differences between groups in ocular disease scores were detected on any individual examination days.

Virus isolation

Ocular viral shedding was first detected in all cats by infectious virus isolation on study day 3 **(Figure 4)**. The mean ± SD duration of viral shedding as detected by virus isolation was 21 ± 4.2 days in the placebo group and 16 ± 4.0 days in the penciclovir group. The mean ± SD daily viral load over the entire course of the study after day 0 was 63,280 ± 110,656 PFU/mL in the placebo group and 61,543 ± 121,800 PFU/mL in the penciclovir group. Ocular viral shedding was detected by virus isolation in the placebo group until study day 27 and the penciclovir group until study day 21. There were no statistically significant differences in ocular viral loads or duration of viral shedding as determined by infectious virus isolation between the study groups when evaluated over the entire study period; however, the ocular viral load (mean ± SD) was significantly ($P \leq .01$) lower in the placebo group (2.5^5 ± 124,818 PFU/mL) versus the penciclovir group (3.21^5 ± 75,851 PFU/mL) on study day 3. No additional significant differences in ocular

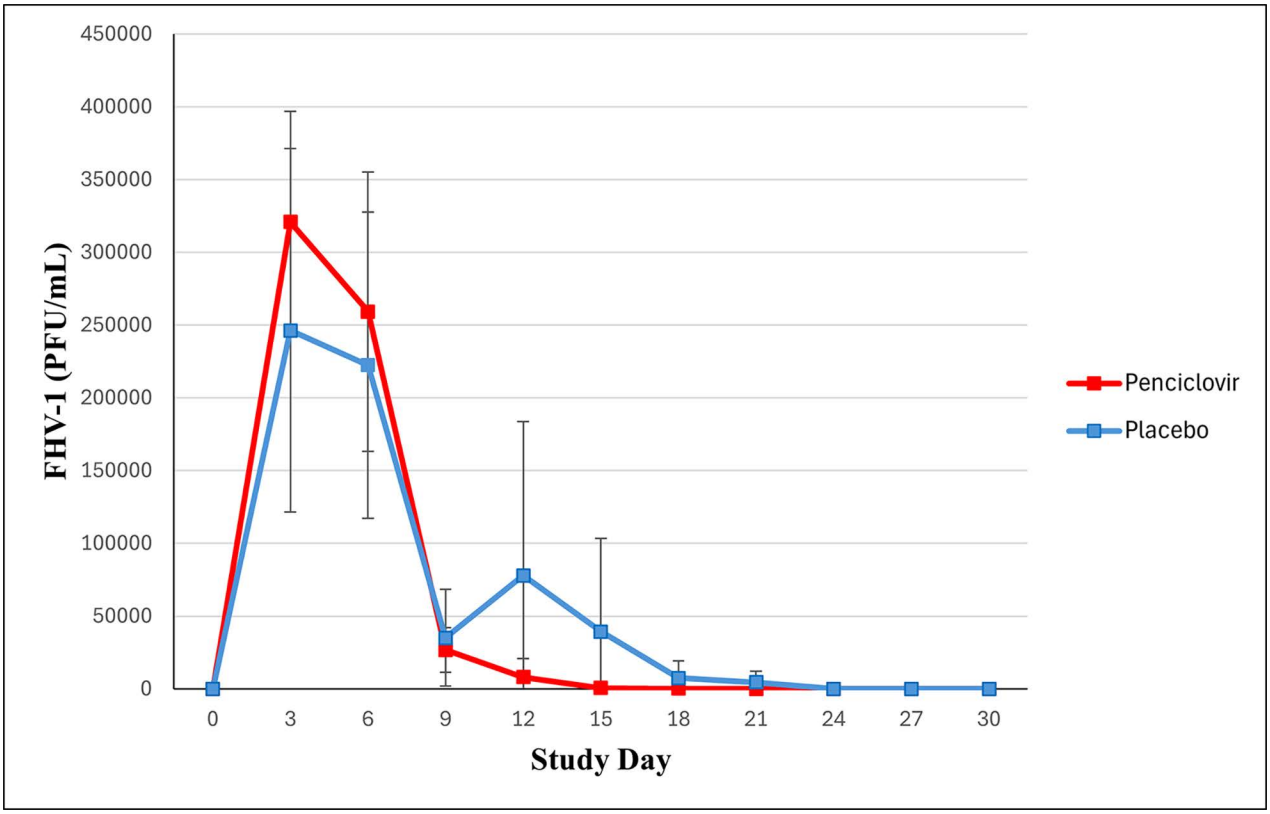

Figure 4—Mean ± SD ocular viral load (plaque-forming units [PFU] per milliliter) determined by virus isolation for cats with experimentally induced ocular FHV-1 infection treated with topical penciclovir 1% cream (red line) or placebo topical artificial tear gel (blue line) for 14 days. Ocular FHV-1 infection was induced on study day 1, and study medications were administered for 14 days starting on study day 2. Samples for the determination of ocular viral load were collected at 3-day intervals for 30 days.

viral loads measured by infectious virus isolation were detected between the groups on any individual sampling days.

FHV-1 real-time PCR

Ocular viral shedding was also first detected in all cats by qPCR on study day 3 **(Figure 5)**. Ocular viral shedding was detected by qPCR in all cats on each sampling day until the conclusion of the study on day 30. The mean ± SD daily viral load over the entire course of study after day 0 was 8.8^4 ± 255,693 FHV-1 copies/10 copies *fAlb* in the placebo group and 4.93^4 ± 177,045 FHV-1 copies/10 copies of *fAlb* cells in the penciclovir group. No significant (P = 0.24) differences in ocular viral loads as determined by qPCR were detected between the study groups when evaluated over the entire study period; however, the ocular viral load (mean ± SD) was significantly ($P \leq .001$) lower in the penciclovir group (4.1^5 ± 403,204 FHV-1 copies/10 copies of *fAlb* cells) versus the placebo group (7.4^5 ± 404,993 FHV-1 copies/10 copies of *fAlb* cells) on study day 3. No additional day-specific significant differences in ocular viral shedding measured by qPCR were detected between the groups.

In vivo confocal microscopy

Corneal epithelial leukocytes were detected by IVCM in all cats on study day 10 (Figure 1). The mean ± SD IVCM keratitis scores from study day 10 were 270 ± 140 leukocytes/mm^2 in the right eye and 297 ± 115 leukocytes/mm^2 in the left eye for the placebo group. Mean IVCM keratitis scores in the penciclovir group were 323 ± 212 leukocytes/mm^2 in the right eye and 280 ± 156 leukocytes/mm^2 in the left eye. No significant differences in leukocyte counts were detected between the penciclovir and placebo groups for the right (P = .35) or left (P = .73) eyes.

General diagnostic assays and examinations

All serum biochemistry panel results on study days 0, 15, and 30 were unremarkable. All hemogram results on study days 0 and 15 were unremarkable. Five cats, including 3 from the penciclovir group and 2 from the placebo group, displayed a mild leukocytosis on study day 30 (P = 1.0) consistent with primary FHV-1 infection.[12]

No adverse reactions to the study medications were observed in any cat at any time during the study. The penciclovir cream evaluated possessed moderate viscosity and was subjectively simple to administer but left a thick, white, opaque coating across the ocular surface for several minutes after each application. No clinical abnormalities were detected in any of the study cats during physical and ophthalmic examinations performed on study day 30, except for mild residual conjunctivitis in

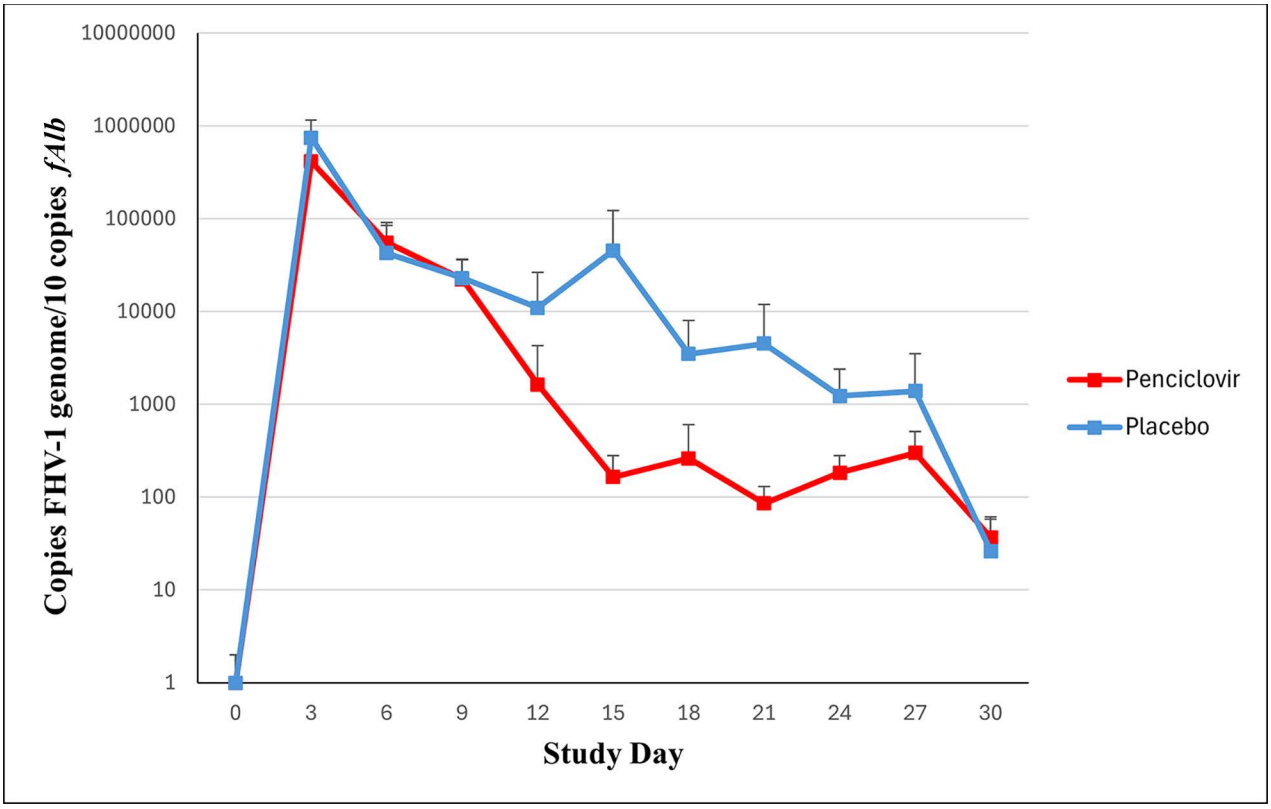

Figure 5—Mean ± SD ocular viral load (copies FHV-1 per 5 cells) determined by FHV-1 quantitative PCR for cats with experimentally induced ocular FHV-1 infection treated with topical penciclovir 1% cream (red line) or placebo topical artificial tear gel (blue line) for 14 days. Ocular FHV-1 infection was induced on study day 1, and study medications were administered for 14 days starting on study day 2 (administered on study days 2 to 15). Samples for the determination of ocular viral load were collected at 3-day intervals for 30 days. *fAlb* = Feline albumin.

half of the cats from each study group. Results of Schirmer I tear tests (mean ± SD; 16.7 ± 3.8 mm/min) and intraocular pressure measurements (mean ± SD; 13.2 ± 2.9 mm/min) were within normal ranges for all cats on study day 30.

Discussion

In the present study, daily application of topical penciclovir 1% cream 3 times was associated with a modest reduction in the detected severity of clinical ocular disease and a slightly faster clinical recovery after peak severity of ocular disease; however, improvements in the clinical lesions were relatively minimal when compared to several prior studies evaluating different antiviral treatment options in cats with experimentally induced ocular FHV-1 infection. Peak clinical scores were similar between penciclovir and placebo-treated cats, and the most severe manifestation of FHV-1 corneal infection (ie, geographic corneal ulceration) was only observed in a penciclovir-treated cat. The results of the present study are similar to what was previously reported[9] for the in vivo use of subconjunctival penciclovir implants in cats. In prior studies,[9,16] penciclovir displayed a high level of activity against FHV-1 in vitro, and the long-term release of penciclovir from a silicone implant was demonstrated in vitro. In cats with experimental ocular FHV-1 infection, however, the subconjunctival placement of the silicone penciclovir implant before disease induction resulted in inconsistent tear penciclovir concentrations that were only reliably above half maximal inhibitory concentrations for FHV-1 soon after implantation.[9] Clinical and histological scores, and conjunctival viral loads, were also similar between penciclovir and blank implanted cats, although cats with higher measured tear penciclovir concentrations developed fewer corneal ulcers.

It is possible that inflamed ocular tissues, altered tear film dynamics, or other changes in ocular surface physiology in cats with cytolytic FHV-1 infections modify the bioavailability, persistence, tissue absorption, release characteristics, or other pharmacological aspects of penciclovir treatments in vivo.[17,18] These physiologic and pharmacologic changes in cats with active viral infections could produce in vivo outcomes that are different than what is predicted by in vitro systems or observed in healthy cats. Collectively, these results suggest that refinements in the topical penciclovir treatment of cats (eg, physicochemical properties, concentration, application frequency) should be evaluated to optimize the efficacy of this antiviral medication for feline clinical applications.

There is minimal research evaluating the use of penciclovir as a topical ophthalmic treatment for ocular herpesvirus infections. A study[19] was

performed to evaluate the comparative effects of trifluridine 1% solution, cidofovir 0.2% solution, and penciclovir 3% ointment in rabbits with experimentally induced herpes simplex virus type 1 epithelial keratitis. All 3 antiviral medications reduced the severity of clinical disease in the rabbits relative to a placebo solution. Trifluridine and cidofovir displayed similar clinical efficacy in the rabbit model of herpetic keratitis.[19] Trifluridine and cidofovir treatment resulted in significantly lower keratitis scores than daily treatment with the penciclovir ointment either 2 or 4 times. The authors concluded that topical penciclovir was less effective than topical trifluridine or cidofovir therapy and that penciclovir offered no obvious advantages for the treatment of herpetic keratitis in their study.[19]

In contrast to ophthalmic applications, the efficacy of topical penciclovir 1% cream to speed healing times, reduce discomfort, and shorten viral shedding in humans with herpes labialis is well established.[20–23] The general application frequency recommended for herpes labialis is every 2 hours during waking hours for 4 days, which is more intensive than what was evaluated in the present study (ie, 3 times daily) or recommended in prior studies[24] evaluating tear penciclovir pharmacokinetics in healthy cats (ie, 2 times daily). More frequent application of the penciclovir cream in cats with ocular FHV-1 infections might yield different results than in the present study; however, the frequent application of topical ophthalmic medications in domestic cats can be challenging, and the induction of added stress in cats might have detrimental effects on the course of FHV-1 infections.[25] It should be noted that other topical antiviral medications have proven efficacy with relatively infrequent administration in cats with ocular FHV-1 infection, including twice daily cidofovir 0.5% ophthalmic solution and 3 times daily ganciclovir 0.15% ophthalmic gel, making these alternative medications potentially preferable in regions and situations where they are available.[3,4]

The potential advantages of the penciclovir cream evaluated in this study include its widespread commercial availability, relatively low cost in some markets, and the ease of administration of the moderate viscosity cream. In addition, the penciclovir cream was well tolerated after topical ophthalmic application in the current and a previous feline study.[10] The cream did produce a conspicuous and potentially vision-compromising opaque white film across the ocular surface immediately following application, but this film was generally much reduced after several minutes. It might be prudent to educate clients about this phenomenon when first prescribing the penciclovir cream to avoid unnecessary alarm or misinterpretation of the opaque ocular surface film.

The limitations of the present study include the relatively small size of the study groups. The inclusion of a higher number of cats in the study groups and the resultant increase in statistical power might have permitted the statistical detection of additional differences between the cat groups. The study group sizes for the present study were selected based on the established reproducibility of the experimental infection model used, the sample size calculations, and the results of previous studies evaluating antivirals in cats using similar group numbers.[4] Due to the opaque appearance of the evaluated penciclovir cream, the individual performing the clinical examinations was not masked to the cats' treatment group, which could have introduced bias in the examination findings. An ocular surface lubricant was used as the control study agent, which might have improved clinical disease and did not permit comparisons with the vehicle of the evaluated penciclovir cream. Penciclovir treatment was started 24 hours after FHV-1 inoculation in this study, which is earlier in the course of the infection than is likely to occur in many clinical scenarios. While initiation of antiviral treatment as early as possible during the course of an active herpesvirus infection is always considered preferable, ideally during the prodrome or early lesion phase, it has previously been shown that the topical penciclovir 1% cream maintains its clinical benefits in humans with herpes labialis even when started during the late stages of lesion development.[26] An experimental primary infection model using otherwise healthy young cats was used in this study due to its reliability and replicability, but this model may not adequately reflect all clinical situations requiring antiviral treatment in cats including older cats, those with recurrent ocular infections, shelter-housed cats, and immunosuppressed cats.[27,28]

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