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CASE SERIES

Treatment of feline herpesvirus-1 associated disease in cats with famciclovir and related drugs

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Background Feline herpesvirus 1 (FHV-1) is a common cause of ocular and upper respiratory disease in cats and kittens, and a potential cause of eosinophilic dermatitis.

Hypothesis The systemic anti-herpes drug, famciclovir (Famvir; Novartis), would be effective in the clinical management of disease attributable to FHV-1, including conjunctivitis, keratitis, corneal sequestra, rhinosinusitis and FHV-1 associated dermatitis.

Clinical outcome Oral famciclovir was used to treat signs considered referable to FHV-1 in 10 cats: four had primary ocular disease, two had rhinosinusitis and four had FHV-1 associated dermatitis. Patients treated in Australia (five cats) and Europe (one cat) were given 62.5 mg of famciclovir once or twice daily. Four cats treated in the USA were given 125 mg three times daily. Famciclovir was uniformly well tolerated and, in all cases, had a positive impact on the patient's condition. The apparent improvement in lesions was superior to what had been achieved previously using other therapeutic strategies. One cat with severe destructive rhinosinusitis was significantly improved by a 4-month course of famciclovir in combination with antibacterials. Corneal sequestra detached in two out of three cats treated; cats with ocular signs were qualitatively more comfortable, with reduced clinical signs and an improved appearance of the eyes. Critically, oral famciclovir therapy was considered more convenient than topical ocular therapy. All four cats with FHV-1 associated dermatitis improved substantially, although relapse occurred subsequently in three patients. A further cat with presumptive FHV-1 associated dermatitis responded to topical aciclovir cream before famciclovir could be sourced.

Conclusions Famciclovir appears to be a promising systemic drug for treating diseases associated with FHV-1 infection. More rigorous clinical trials are required to optimise the dosing regimen for safe and effective specific anti-herpes treatment in feline clinical medicine.

Feline herpesvirus-1 (FHV-1) is the major cause of upper respiratory and ocular disease in cats.[1–4] Infection of susceptible kittens with FHV-1 causes rhinosinusitis and conjunctivitis in virtually all exposed individuals, with lifetime persistence of virus in neural tissues (eg, trigeminal ganglia). This latency can result in recrudescent infections throughout the life of an affected cat.[5,6] A relapsing clinical course and persistence of residual clinical signs is quite typical of FHV-1 associated disease. An authoritative review on this feline pathogen has recently been published, with an exhaustive list of pertinent references.[4]

As well as rhinosinusitis and conjunctivitis, herpetic infection can result in keratitis, geographic or dendritic corneal ulcers, anterior uveitis, dermatitis and/or interstitial pneumonia.[2–4,7–12] Eosinophilic inflammation is often a feature of the inflammatory response observed in lesions of the eye[13] and skin,[11] whereas infection of the respiratory epithelium results in necrosis, neutrophilic infiltration and fibrin exudation.[14,15] Chronic ocular infection can result in the formation of corneal sequestra[13,16] or the development of stromal keratitis.[10]

One of the present authors, US veterinary dermatologist, Dr Helen Power, speaking at the Australian College of Veterinary Scientists' annual meeting in 2002,[11,12] discussed the 'rediscovered' syndrome of FHV-1 associated dermatitis, characterised by ulcerated lesions about the head, usually situated close to the nares or eyes, and the associated eosinophilic

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inflammation. Significantly, she mentioned therapy using the 'new' antiviral drug famciclovir (http://www.famvir.com/). Unlike first generation systemic anti-herpes agents (ie, the nucleoside analogues aciclovir and valciclovir), which had little clinical efficacy against FHV-1 in vitro and significant side effects in cats (myelosuppression, hepatotoxicity and nephrotoxicity),[17,18] this newer derivative was apparently well tolerated according to North American veterinary ophthalmologists.

On encountering our first case of presumptive FHV-1 associated dermatitis in Australia a few years later, we contacted Dr Power, who provided two empiric dosing protocols: (a) her own – 62.5 mg per cat orally once daily for 7 days, then every 48 h for 10 days; and (b) that of another of the present authors, Dr Carlo Vitale – 62.5 mg per cat twice daily for 21–30 days. Interestingly, we conducted Medline and CAB Abstract searches at that time, using the key words 'famciclovir' and 'cat(s)', and could find no peer-reviewed publications on the use of this drug in cats, or even any preliminary pharmacokinetic data. Ironically, our first patient (see later) was successfully treated with topical aciclovir before the famciclovir arrived from the drug wholesaler!

This experience, however, prompted us to learn more about the use of this drug in human patients. Famciclovir (Famvir; Novartis) has demonstrable in vitro activity against herpes simplex virus types 1 and 2 and varicella zoster. It is rapidly converted to penciclovir in vivo after oral administration. In cells infected by α-herpesviruses, virus-induced thymidine kinase converts penciclovir into penciclovir triphosphate, which competitively inhibits viral DNA polymerase, preventing DNA chain elongation. Consequently, viral DNA synthesis, and hence viral replication, are limited. Results in human patients with herpes simplex type 1 infection (cold sores), varicella zoster (shingles) and genital herpes simplex type 2 infections have been excellent, with improved lesion healing times, shorter duration of viral shedding and reduced recurrence rates, in both immunocompetent and immune-deficient patients.[19] Penciclovir has a very short plasma half-life in humans, dogs, rats and cats and is excreted in urine.[20–22] It does not cause renal toxicity, although patients with renal impairment need appropriate dosage adjustment. Side effects are otherwise very uncommon in human patients.

Since then, little has been recorded about the use of famciclovir in the cat, other than anecdotal comments, mainly by veterinary ophthalmologists, on various internet discussion forums and in unrefereed conference proceedings, where it generally receives a very favourable press. A recent study has, however, suggested that dosages of 62.5 mg per cat (approximately 15 mg/kg) q 8–12 h will produce plasma concentrations in the range of 0.2–0.6 μg/ml.[22] These levels are lower, by about an order of magnitude, than concentrations known to be most effective in vitro using plaque reduction or yield reduction assays (7–10 μg/ml),[22–24] although a 30–40% plaque reduction was observed at concentrations of 0.5 μg/ml in work done by another group.[25] Unfortunately, this pharmacokinetic data had not been published when we started an open clinical trial of famciclovir in a sporadic cohort of patients in which FHV-1 was thought to play an initiating or perpetuating role. Accordingly, we used doses recommended previously by our North American colleagues. Dr Vitale, in contrast, has used higher doses in recent cases under his care.

A relapsing clinical course and persistence of residual clinical signs is quite typical of FHV-1 associated disease.

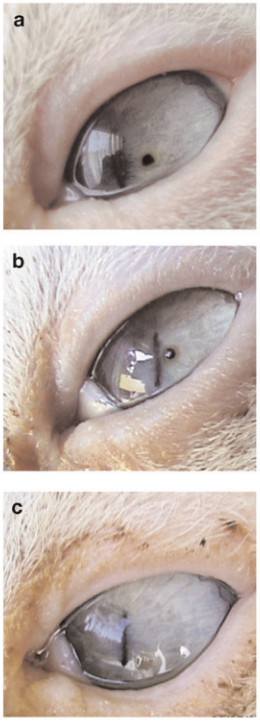


FIG 1 Affected eye of case 1, before (a), during (b) and immediately after (c) therapy with oral famciclovir. Photograph (c) shows a discernable defect in the cornea at the site where the corneal sequestrum had detached 8 days after starting famciclovir (Famvir) treatment. Excessive tearing is evident in all the photographs, despite therapy. The pigmented nature of the ocular discharge is especially obvious in (b) and (c)

As reported here, famciclovir was found to be very well tolerated, and to have apparent efficacy in cases with (a) ocular signs (conjunctivitis, keratitis, corneal sequestra), (b) cutaneous disease and (c) rhinosinusitis. We hope this preliminary case series will encourage other clinicians to share their findings in the peer-reviewed literature, and provide an impetus for academic clinicians to conduct more rigorous prospective clinical studies, including dose escalation trials and trials in kittens with primary FHV-1 infections.

Case reports

Case 1

A 5-year-old castrated Devon Rex (4.0 kg) was presented with a focal corneal lesion. The patient had a long history of presumptive FHV-1 infection dating back to a primary upper respiratory infection at 8 weeks of age. The cat also had urticaria pigmentosa, which had been confirmed histologically.[26] The

dermatopathy was controlled using a combination of ciclosporin (cyclosporin) (20–25 mg orally once daily) and an Ω-3 fatty acid supplement, while L-lysine (500 mg twice daily) was administered in an attempt to ameliorate signs referable to FHV-1 rhinitis and conjunctivitis.

On physical examination, a focal sequestrum (< 2 mm diameter) was noted in the centre of the cornea of the left eye, with concurrent bilateral conjunctivitis. Our assessment was that immunosuppressive therapy used to control the dermatopathy had exacerbated a chronic FHV-1 conjunctivitis, with excessive production of pigment resulting in formation of a focal sequestrum, perhaps at the site of superficial corneal erosion (Fig 1a). The lesion, in itself, did not appear to incite much additional ocular irritation.

On the presumption that the sequestrum was a consequence of chronic FHV-1 related inflammation and increased pigment formation, the cat was trialled on famciclovir, at 62.5 mg (half a 125 mg tablet) orally once daily for 7 days, then twice daily. The owner observed an immediate decrease in excessive tearing in both eyes on commencing therapy. Serous nasal discharge was also reduced. The cat developed diarrhoea, although this may have been related to the ciclosporin rather than famciclovir. Eight days after starting antiviral therapy, the sequestrum detached, leaving a small defect in the corneal surface (Fig 1c).

Therapy was continued for a total of 35 days. At the end of this period the eyes were substantially improved, and the defect in the corneal surface was less discernable. At the time of writing (18 months later), the cat continues to receive ciclosporin to control its dermatopathy, latterly in combination with ketoconazole, and a corneal sequestrum has not reformed.

Case 2

A 3-year-old castrated Persian cross (4.5 kg) was presented to a colleague with diffuse corneal ulceration and conjunctivitis affecting the right eye. Inexplicably, the cat was treated by scarification of the ulcer with dilute ferric chloride, followed by application of a third eyelid flap. This treatment was not successful, and after 'taking down' the third eyelid flap, diffuse corneal ulceration persisted, with a brown tinge to the superficial corneal surface suggesting an early corneal sequestrum. The cat was referred to a specialist ophthalmologist who made a presumptive diagnosis of FHV-1 infection and prescribed idoxuridine drops (every 6 h). The owner considered that the eye deteriorated further despite therapy, and sought yet another opinion 2 weeks later.

By this time, a sequestrum had formed on the central cornea (Fig 2a). A complete blood count and serum biochemistry profile did not demonstrate any pertinent abnormalities, and serology for FIV antibodies and FeLV antigen were negative. Famciclovir was commenced at a dose of 62.5 mg orally once daily, increasing to twice daily after 7 days. Medication was well tolerated, without any apparent side effects and with no effect on appetite. According to the owner, the cat's eyes appeared much more comfortable during the period of famciclovir administration.

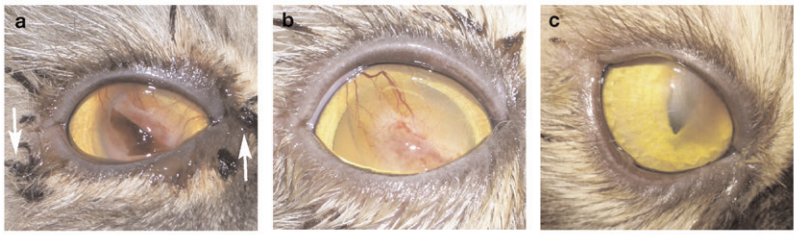


FIG 2 Affected eye of case 2 immediately prior to famciclovir (Famvir) therapy (a), after 23 days of therapy (b) and at the completion of a box of 40 tablets (c). The arrows in (a) highlight pigmented material deposited on the lid margins. As well as the clear improvement in the overall appearance of the corneal lesion, note the less pronounced swelling of the eyelid margins and the reduction in pigmented material in the vicinity of the eyelids

Twenty-three days after commencing systemic anti-herpes therapy, the pigmented plaque reportedly 'came away'. The owner continued to administer the drug for a total of 43 days (ie, until the box of 40 tablets had been used). Fig 2c shows the appearance of the eye at the completion of therapy.

Case 3

A 13-year-old spayed Burmese (3.0 kg) was initially presented for assessment of superficial ulceration of the cornea of the right eye. There was also superficial neovascularisation and a focal corneal sequestrum was present (Fig 3a). The owner reported that the cat had experienced previous episodes of blepharospasm and serous ocular discharge 'on and off' over a protracted period, sometimes associated with sneezing. As the owner had difficulty administering any medication orally, a topical antibiotic eye ointment (Opticin, Troy; chloramphenicol 10 mg/g, polymixin B sulphate 5000 units/g) was initially prescribed for twice daily administration. This had little or no impact on the ocular lesions.

One month later, the owner was encouraged to trial once daily oral famciclovir therapy (62.5 mg), with a veterinary nurse making a home visit daily to administer the medication. The cat was reportedly more comfortable immediately after commencing famciclovir, and there was a reduction in blepharospasm and ocular discharge (Fig 3b), but incomplete improvement in the appearance of the eye with persistence of the corneal sequestrum. We suspect a higher dose and/or more frequent administration may have made a more substantial impact, but further therapy was declined because of financial constraints.

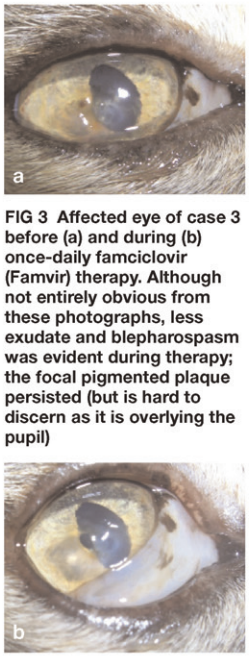


FIG 3 Affected eye of case 3 before (a) and during (b) once-daily famciclovir (Famvir) therapy. Although not entirely obvious from these photographs, less exudate and blepharospasm was evident during therapy; the focal pigmented plaque persisted (but is hard to discern as it is overlying the pupil)

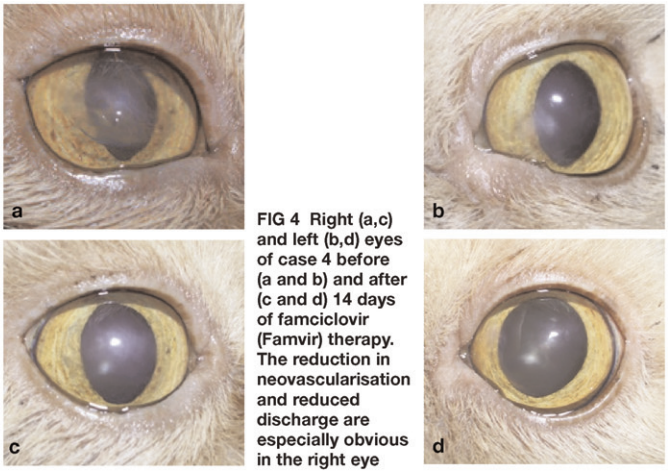


FIG 4 Right (a,c) and left (b,d) eyes of case 4 before (a and b) and after (c and d) 14 days of famciclovir (Famvir) therapy. The reduction in neovascularisation and reduced discharge are especially obvious in the right eye

Case 4

An 11-year-old castrated Persian (5.6 kg) was presented with extensive superficial corneal ulceration. This patient had experienced numerous 'flare ups' of presumptive herpetic ulceration over the preceding years. The cat had been referred to a veterinary ophthalmologist who concurred with the presumptive diagnosis based on the breed and the characteristic appearance of the corneal lesions. Treatments that had been trialled previously, with limited success, included idoxuridine drops, artificial tears containing five drops of concentrated povidone–iodine solution, and L-lysine (250 mg once daily).

During a subsequent 'flare up', oral famciclovir was trialled at a dose of 62.5 mg once daily for 7 days, then twice daily for another 7 days (Fig 4). Two weeks after commencing therapy, the eyes were apparently much improved, with the owners commenting how much more comfortable the cat seemed in terms of its ocular condition. In their opinion, this treatment was more effective and more convenient than any of the preceding treatments. Indeed, they declined a recommended further course of therapy because they were satisfied with the improvement. No side effects were noted during famciclovir treatment.

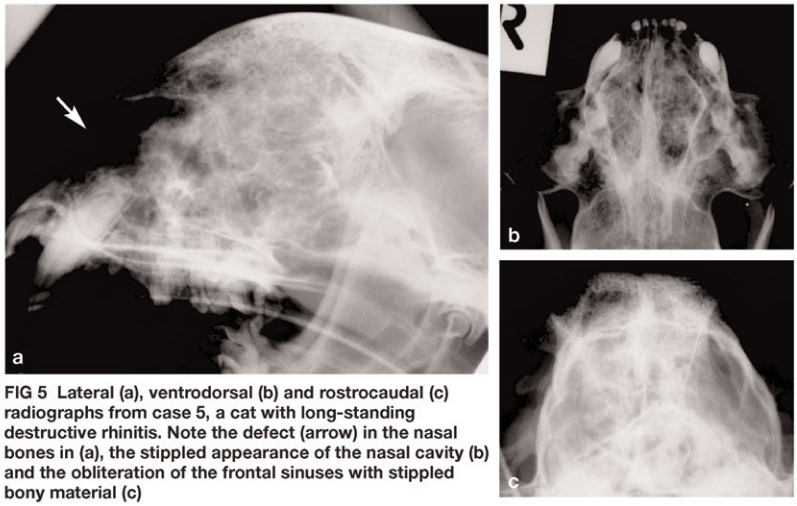


FIG 5 Lateral (a), ventrodorsal (b) and rostrocaudal (c) radiographs from case 5, a cat with long-standing destructive rhinitis. Note the defect (arrow) in the nasal bones in (a), the stippled appearance of the nasal cavity (b) and the obliteration of the frontal sinuses with stippled bony material (c)

Case 5

A 4-year-old castrated domestic crossbred cat (5.3 kg) was referred for rhinoscopic investigation of chronic upper respiratory disease. The patient had experienced signs of rhinosinusitis dating back to when he was 6 months old.

The cat had been treated with multiple courses of different antibiotics, and signs had invariably recurred once the antibiotics were stopped. Seven months prior to referral, signs had worsened, with the development of an open draining sinus on the bridge of the nose communicating with the nasal cavity. Mucopurulent material drained periodically through this sinus. The owner reported frequent severe sneezing 'fits', producing 'gobs' of mucopurulent material, stertorous breathing and an intermittent serous ocular discharge.

The wound on the cat's nose had finally closed 2 weeks prior to referral, in response to long term antimicrobial therapy (doxycycline monohydrate [Vibravet; Pfizer Animal Health] 25 mg orally twice daily for 6 months followed by amoxicillin clavulanate [Clavulox; Pfizer Animal Health] 125 mg orally twice daily for 1 month). The underlying circular defect in the nasal bone could be palpated through the overlying skin, being approximately 8 mm in diameter (Fig 5a). It was thought the draining sinus had developed as a consequence of localised osteomyelitis with erosion of the overlying nasal bone.

Haematology and serum biochemistry results were unremarkable. A serum latex *Cryptococcus* antigen test was negative, as were fungal cultures of nasal exudate. Radiographs demonstrated extensive bilateral loss of the normal turbinate pattern and its replacement by reactive bone with a 'stippled' appearance (Fig 5b). The frontal sinuses were almost completely replaced by bone (Fig 5c).

The cat was anaesthetised for rhinoscopic examination and the choanae examined using a retroflexed 5 mm bronchoscope. The right choanus appeared normal but the left was slightly obstructed by thickened mucosa. Anterior rhinoscopy was then performed with a 2.3 mm rigid arthroscope. There was a dramatic loss of normal turbinate architecture (Fig 6). The mucosa had lost its normal pink translucent appearance and was obviously thickened but only moderately inflamed. Only small amounts of exudate were present. Multiple biopsies were collected using 2.3 mm endoscopic cup biopsy forceps.

Histopathology demonstrated severe active chronic rhinitis with an apparent absence of normal glandular tissue in the biopsy

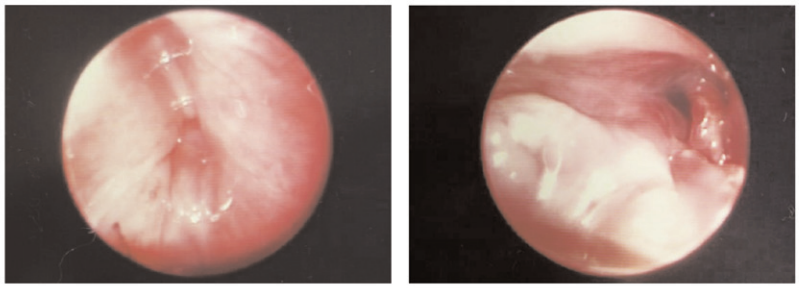


FIG 6 Anterior rhinoscopic images from case 5. Note the dramatic loss of normal tissue architecture, with turbinate atrophy and distortion

specimens. The tissues were heavily infiltrated with mixed inflammatory cells and in places there was considerable fibroplasia. Bone present in the sections was viable and displayed regenerative changes. Fungal elements were not seen in periodic acid Schiff-stained sections.

Our assessment was that the cat had long-standing destructive rhinitis most likely initiated and perpetuated by FHV-1, with secondary bacterial osteomyelitis/chondritis. Accordingly, famciclovir (62.5 mg orally once daily) was trialled in addition to conventional antimicrobial therapy (amoxicillin clavulanate 50 mg orally twice daily).

Within a month, the cat was substantially improved. It was no longer 'snuffling' or producing mucopurulent discharge, and sneezing was reduced to one or two episodes a day. This improvement was considered unequivocally to be greater than that observed during prior antibacterial therapy. The cat was maintained on the same dose of famciclovir and amoxicillin clavulanate for a total of 4 months. No side effects were noted. At the completion of this course of therapy the cat appeared happy and healthy, and exhibited only occasional minor sneezing.

Four months later the cat became unwell and inappetent, although the owner had not noticed any recurrence of upper respiratory signs. Until this time he had remained well and free of signs except for the occasional sneeze. On examination, there was a mild serous ocular discharge. No other significant abnormalities were noted. Further diagnostic tests were refused and, due to the owner's own health problems, the cat (5.7 kg) was euthanased 3 days later. Necropsy was not permitted.

Case 6

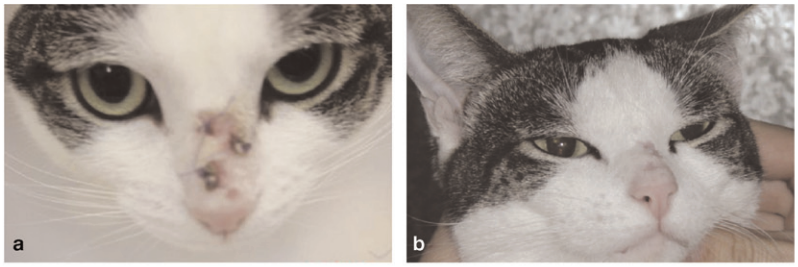
A 4-year-old castrated domestic crossbred cat (7.4 kg) was presented for management of chronic presumptive FHV-1-associated rhinosinusitis. The cat had been acquired as a stray in 2005 and, at that time, had bilateral serous ocular discharge. It subsequently developed typical signs of a viral upper respiratory infection. Nasal cavity signs persisted, developing into a 'chronic snuffler syndrome' associated with copious green/yellow nasal discharge. The cat eventually improved following courses of different antibiotics (amoxicillin clavulanate, enrofloxacin, clindamycin), but signs recurred some months later, and intermittently thereafter. An MRI study of the head demonstrated severe destruction of the nasal turbinates. The cat continued to be managed over a 2-year period with long courses of various antibiotics, L-lysine (250 mg once daily), oral interferon and periodic flushes of the nasal cavity under general anaesthesia.

In 2007, the cat was trialled on famciclovir at a dose of 62.5 mg once daily for 7 days, then twice daily for 4 weeks in combination with amoxicillin clavulanate (50 mg twice daily) and L-lysine. This produced an excellent response – 'enormous energy and basically no symptoms' according to his owners, and without any detectable side effects. Since then, and at the time of writing, recurrences had been less common and considerably milder, responding promptly to combination therapy with amoxicillin clavulanate and famciclovir.

Case 7

An 8-month-old castrated domestic crossbred cat (4.1 kg) was presented with three well circumscribed non-healing ulcers (approximately 2 mm diameter) on the bridge of its nose (Fig 7a). The ulcers were non-pruritic and did not discharge pus. No lesions were evident on the nasal planum or the pads and, although the cat had a history of recent upper respiratory infection, nasal discharge was not evident at the time of examination. Empiric treatment with cefalexin (20 mg/kg twice daily) for 4 weeks had no impact on the lesions.

FIG 7 (a) Three circumscribed ulcers on the nasal bridge of a young cat (case 7) that had recently recovered from an upper respiratory infection. (The picture was obtained following biopsy.) (b) The same cat after 10 days of topical therapy using aciclovir (Zolaten), showing complete healing of the lesions, with some scarring probably due to the biopsy procedure



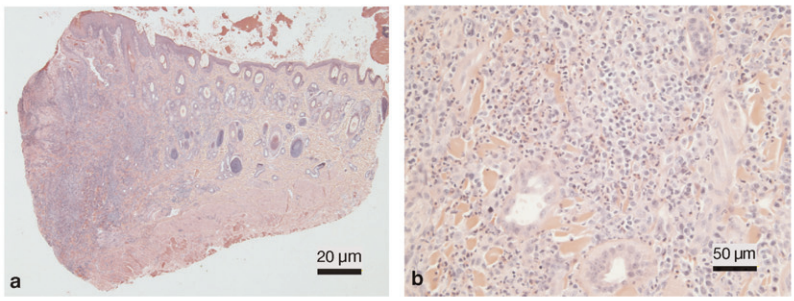


FIG 8 Low (a) and high (b) power photomicrographs of the biopsies obtained from case 7 (see Fig 7). Note the prominent eosinophilic inflammation. Haematoxylin and eosin

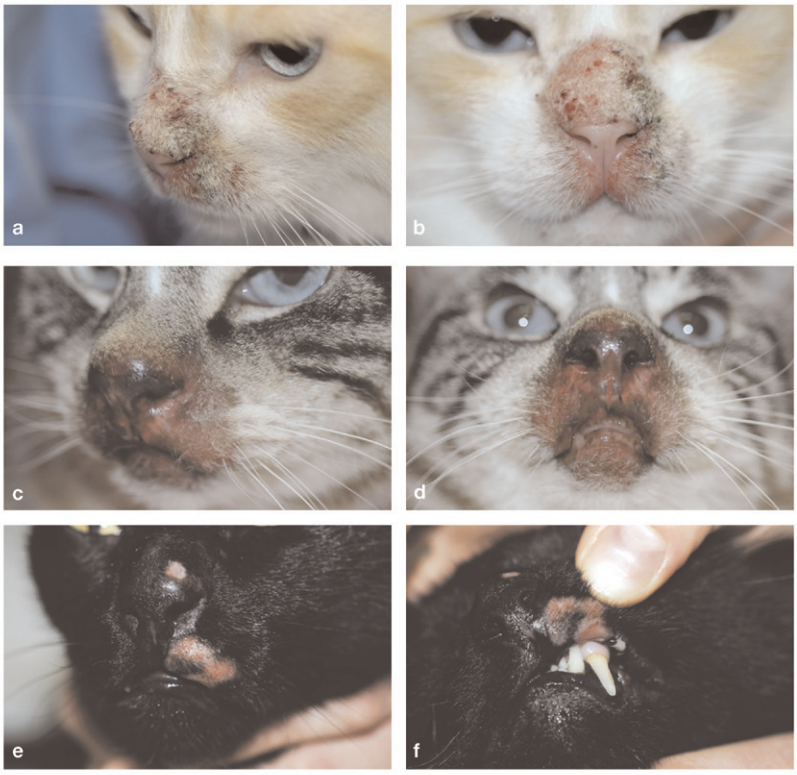


FIG 9 Dr Vitale's patients prior to therapy. (a,b) Case 8; note the punctate ulcers and the mild diffuse erythema of the nasal planum and surrounding skin. (c,d) Case 10; lesions consist of diffuse erythema and erosions, rather than ulcers. (e,f) Case 11; lesions resemble those seen with 'indolent ulcers'

Cytological examination of Diff Quik stained impression smears from the ulcers demonstrated neutrophils, red blood cells and eosinophils. Histological examination of skin biopsies from the margins of the lesions demonstrated a marked perivascular mixed inflammatory infiltrate within the dermis consisting of eosinophils, neutrophils, plasma cells and macrophages (Fig 8). This inflammation extended to surround occasional follicles, in which there was spongiosis of the follicular epithelial cells. Multiple foci of necrosis were associated with these inflammatory areas. On the surface, there was ulceration of the epidermis with parakeratotic hyperkeratosis. Although no intranuclear inclusions were observed, the microscopic findings were suggestive of FHV-1 associated dermatitis.[11]

We planned to treat this cat with oral famciclovir, as with other cases in this series. However, while waiting for the drug to be sourced from the veterinary wholesaler, it was elected to trial topical therapy using an over-the-counter 'cold sore' remedy. Thus, aciclovir cream 5% w/w (Zolaten; Sigma) was applied to the lesions three to four times a day. There was an apparently rapid response to this treatment (Fig 7b), with the lesions healing over 7 to 10 days. There was some residual scarring, although we considered this probably reflected the extent of tissue removal by the skin biopsy punch.

Cases 8, 9, 10 and 11

Cases 8–11 were diagnosed and treated by Dr Vitale in San Francisco, USA. Case 8 was a 2-year-old castrated male domestic shorthair cat (4.1 kg) presented with a 4-week history of sneezing and nasal discharge. It then suddenly developed pruritic skin lesions on its face (Fig 9 a,b). Case 9 was a 16-year-old spayed female domestic shorthair cat with pre-existing chronic renal insufficiency, which had been given repository steroids for 'feline asthma'. The cat subsequently developed cutaneous lesions that were found to be FHV-1 associated dermatitis with secondary *Staphylococcus aureus* infection. Case 10 was a 1-year-old intact female domestic shorthair cat with oral cavity lesions, which had been treated initially using oral prednisolone (dose unrecorded). The cutaneous lesions that developed subsequently consisted of erythema and erosions (Fig 9 c,d). The final cat (case 11) was a 10-year-old castrated domestic shorthair presented with lesions reminiscent of an 'indolent ulcer' (Fig 9 e,f).

In each case, FHV-1 associated dermatitis was diagnosed presumptively on the basis of the history of a recent upper respiratory infection and various characteristic physical findings; confirmation was obtained by demonstration of eosinophilic inflammation and viral inclusion bodies in haematoxylin and eosin stained biopsy sections. All patients were treated with 125 mg famciclovir three times daily for 2–6 weeks. The cat with secondary *S aureus* infection was also given sulfamethoxazole/trimethoprim for 21 days. Cats responded favourably to this therapy, although cases 8, 9 and 10 relapsed a variable time after discontinuation of treatment.

Discussion

Data from this preliminary case series needs to be interpreted with a number of limitations in mind. A definitive diagnosis of FHV-1 using viral isolation, immunofluorescence, immunohistochemistry or PCR studies was not obtained in the majority of cases.[9,11–13,27] Only in the cats from North America did the presence of viral inclusion bodies in skin biopsy specimens confirm the presumptive diagnosis. The extent of the clinical investigations was variable, and in several instances clinical data and follow-up were limited. It is also difficult to determine with certainty the efficacy of treatment regimens in a disease subject to periodic exacerbations and remissions.

These limitations mostly reflect the fact that cases were treated in general or referral prac-

tice, with some input from the senior author. Nonetheless, these observations, taken together, provide evidence that famciclovir is well tolerated, and of likely benefit in the management of FHV-1 associated disease (Fig 10).

In cats with ocular disease referable to FHV-1, famciclovir treatment reduced conjunctival inflammation, ocular discomfort, excessive tearing, and the amount of pigmented material present in the ocular discharge, resulting in re-epithelialisation of the cornea. Furthermore, in cases with corneal sequestra, the sequestrum would often detach some weeks after initiating therapy, in the absence of topical or surgical interventions. Most owners considered famciclovir therapy to have been more effective than other treatment regimens that had been attempted previously, including idoxuridine drops and/or L-lysine orally. Importantly, twice daily oral administration was easy to implement and well tolerated systemically, with no discernable effect on appetite or demeanor, which concurs with observations in healthy cats.[22] Theoretically, a further advantage of systemic famciclovir over topical antiviral regimens is that the active principal reaches not only the superficial cornea and conjunctiva, but also the anterior uvea and neural tissues harboring FHV-1.

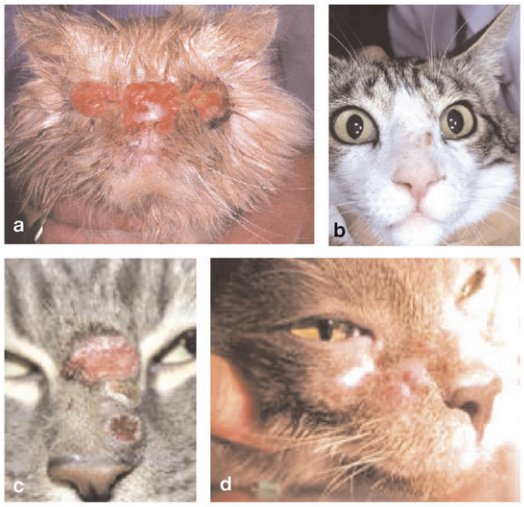


FIG 10 A variety of other cases of FHV-1 associated dermatitis. These cats would be good candidates for oral famciclovir therapy, probably in combination with topical therapy using creams designed for treating herpes simplex lesions ('cold sores') in humans. Lesions such as those in (c) must be distinguished by biopsy from those caused by saprophytic infectious agents[28] introduced following cat scratch injuries.[29] *Courtesy of Dr Helen Power and Dr Candace Sousa*

In vitro data suggests famciclovir, at doses used in most of our cases, should be of limited efficacy due to insufficient penciclovir concentrations obtained in vivo. However, levels having some activity may actually be achieved in virus-infected cells, or perhaps efficacy is contingent on the concurrent action of the normal host immune response directed against FHV-1. Considering that the doses of famciclovir used in our patients were mostly lower than those advocated on the basis of the pharmacokinetic data,[22] we suspect even better results may have been obtained using higher doses, such as those used in Dr Vitale's FHV-1 dermatitis cases. Another approach would be to combine famciclovir with topical inhibitors of herpesvirus replication, such as trifluorothymidine, idoxuridine, aciclovir or Ω-interferon.[4,25,30,31] In human patients, doses of up to 500 mg famciclovir twice daily are given; such high doses produce blood levels in the order of 3.3 µg/ml and are used in immunosuppressed patients (including those with AIDS) or where loss of vision is a possibility.[32]

Extrapolating from human and feline pharmacokinetic data, doses of 125 mg twice or three times daily may be required in cats to produce comparable blood levels. The in vitro data available indicates that these higher concentrations would have greater efficacy in inhibiting viral replication than those achieved in most of our patients. Indeed, in studies of embryonic and fetal development, doses of famciclovir as high as 1000 mg/kg/day have been given orally to rats and rabbits without ill effects (MIMS Prescribing information; http://mims.com.au); and, in rabbits, doses of 60 mg/kg have been used in experimental studies of herpetic keratitis.[33] The latter study makes a critical observation that famciclovir reduced the copy number of herpesvirus – not only in lesions, but also in ganglia, which may explain in part why this agent is effective not only in treating active lesions, but also in reducing the incidence of relapse.

Clearly, there is scope in future trials for assessing the use of higher doses of famciclovir, starting with 62.5 mg every 8 h, a dose already shown to be well tolerated in normal cats. Interestingly, Dr Vitale currently recommends using a 3-week course of 125 mg orally per cat three times daily for FHV-1 associated dermatitis, and has heard of colleagues who have used as much as 250 mg three times daily.

In two cases of presumptive FHV-1 associated rhinitis, famciclovir appeared to be beneficial when combined with conventional antimicrobial therapy. We have suggested the use of this agent to many practitioners confronted with chronic 'snuffler' cats that proved refractory to a variety of antibiotic agents and other strategies. Our feedback from colleagues and clients is that it is useful in some but not all cases, and in many of these cats concomitant ocular signs also improve during therapy (S. Pegrum and

In our opinion, famciclovir represents a substantial breakthrough in relation to the practical management of these frustrating FHV-1 associated cases, based on convenience of dosing, efficacy and absence of adverse side effects at the doses used.

D. Barfield, 2008, personal communication). Considering that the underlying pathologic process in 'post-viral rhinitis cases' may involve a loss of nasal mucosal integrity, coupled variously with contributions from active viral disease and chronic secondary bacterial infection of the turbinates and soft tissues, variability in the response to anti-herpes therapy would be anticipated. In the experience of one of the authors (Naomi Lessels) famciclovir also appears useful when recrudescent herpetic rhinitis and conjunctivitis develop after administration of corticosteroids, especially long-acting formulations. In the shelter situation, dosing of both queens and kittens with famciclovir has been considered greatly beneficial in shortening the period of active clinical disease in affected kittens, and in reducing mortality (G. Boobyer, 2008, personal communication). Studies have not yet involved the treatment of pregnant queens to determine potential teratogenic effects on unborn kittens.

It is our hope that these preliminary observations will encourage colleagues to formally document observations previously shared only through meetings and internet listservs. In a disease as difficult to chart as FHV-1 infection, it behooves us to be open to observations of practitioners in the field. Importantly, we would encourage clinicians in a supported academic environment to take this work further, by designing well constructed and, ideally, blinded prospective trials in which cases are diagnosed definitively, preferably with therapeutic monitoring of famciclovir concentrations in serum considering the complex non-linear pharmacokinetics.[22] Charting the effect of famciclovir on experimentally induced infection of specific pathogen-free kittens or adult cats[5] may also provide cogent information.

The veracity of our observations suggests the drug does indeed work in vivo, and sometimes with striking efficacy. In our opinion, famciclovir represents a substantial breakthrough in relation to the practical management of these frustrating FHV-1 associated cases, based on convenience of dosing, efficacy and absence of adverse side effects at the doses used. Although the medication is currently expensive (a box of 40 125 mg tablets costs $130 AUD wholesale), it is not prohibitive, and the drug will soon come out of patent, which may result in less expensive generic formulations becoming available. For FHV-1 associated dermatitis cases, famciclovir therapy (combined with topical anti-herpes ointment) is far more affordable than feline Ω-interferon used intra-lesionally,[34] and treatment does not require sedation or general anaesthesia. Another potential treatment option for FHV-1 associated dermatitis, which has been mentioned anecdotally[35] in conference proceedings, is the topical immunomodulator imiquimod (Aldara; 3M).[36]

Clearly, there is scope in future trials for assessing the use of higher doses of famciclovir, starting with 62.5 mg every 8 h, a dose already shown to be well tolerated in normal cats.

Finally, our view is that we may potentially prevent considerable suffering by trialling systemic anti-herpesvirus therapy using famciclovir in the setting of primary viral rhinosinusitis in kittens and young cats.[5,18] Given that the majority of these cases are likely to be caused by FHV-1, early treatment of such cats with famciclovir, in addition to currently recommended antimicrobials such as amoxicillin clavulanate or doxycycline monohydrate, will likely foreshorten the disease in affected individuals, and hopefully also reduce the likelihood of long term adverse sequelae such as the 'chronic snuffler syndrome', chronic conjunctivitis, chronic recurrent keratitis and stromal keratitis. Clinical trials in shelters could readily be designed to test this hypothesis.

Addendum

Since the submission of this case series, a colleague in Australia (Dr Aine Seavers) has reported treating three further presumptive FHV-1 infections using famciclovir (62.5 mg per cat daily for 7 days, then twice daily for 2 weeks). The first cat was a geriatric Persian with severe ocular disease; the two others were young adult cats with naso-ocular signs. All three showed marked improvement and were near normal after 3 weeks of therapy (unpublished observations). Additional data on famciclovir has been recently published in Abstract form by David Maggs' group at the University of California-Davis in the October 2008 Proceedings of the American College of Veterinary Ophthalmologists. Famciclovir (90 mg/kg q 8 h) was highly effective in the treatment of experimental infections in kittens (n= 10) and also in naturally occurring FHV-1 cases (n= 23) with nasal (43%), ocular (87%) and cutaneous (13%) lesions. Even at these high doses, side effects were rare, although anorexia and polydipsia with dilute urine were seen in a small number of cats. Recent human work has shown that high doses of famciclovir given for shorter periods may be as effective as lower doses given for protracted periods in treating 'cold sores' and genital herpes infections. Only time will tell what proves to be the most effective and affordable treatment regimen for our feline patients.

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