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Original article

Clinical evaluation of antiviral combination treatment in cats with feline herpesvirus-1 infection

Y. Ozkanlar[1], N. Ulas[2], I. Sozdutmaz[3], S. Ozkanlar[4]

[1] Department of Internal Medicine, Faculty of Veterinary, Ondokuz Mayis University, 55139 Atakum/Samsun, Turkey
[2] Department of Internal Medicine, Faculty of Veterinary, Ataturk University, 25240 Yakutiye/Erzurum, Turkey
[3] Department of Virology, Faculty of Veterinary, Erciyes University, 38280 Talas/Kayseri, Turkey
[4] Department of Biochemistry, Faculty of Veterinary, Ataturk University, 25240 Yakutiye/Erzurum, Turkey

Abstract

Feline herpesvirus-1 (FHV-1) can cause lifelong problems such as rhinotracheitis and ocular disease due to latency and reactivation in affected cats. The particular effects of antiviral drugs have been separately investigated in previous studies for decades and little is known about the combination treatment in active FHV-1 infection. Therefore, we aimed to evaluate the effects of antiviral combination on clinical effectiveness in cats with naturally occurring FHV-1 infection. 28 cats suffering from clinical signs of sneezing, nasal congestion, conjunctivitis, and eye/nose discharge were involved in this study following FHV-1 DNA detection by PCR assay in oculo-oropharyngeal samples. The treatment protocol was as follows: oral famciclovir and L-lysine, ophthalmic acyclovir, and subcutaneous amoxicillin plus clavulanic acid. The symptoms improved each day and total recovery success rate was 80% reduction in clinical scores at the end of the treatment on day 10 ($p<0.001$). Additionally, PCR was found to be negative for FHV-1 DNA in 82.1% of the samples after the treatment. There were mild decreases in neutrophil and monocyte counts ($p>0.05$). The arginine to lysine ratio decreased in favour of lysine ($p<0.01$). As a result, the antiviral combination treatment with famciclovir, L-lysine and ophthalmic acyclovir, and antibacterial drug appears to be clinically effective for the treatment of naturally occurring active FHV-1 infection in cats. In addition, any adverse clinical effect has not been determined associated with the antiviral combination during the study.

Keywords: acyclovir, antiviral treatment, famciclovir, feline herpesvirus, L-lysine

Introduction

Feline herpesvirus-1 (FHV-1) is one of the most common causes of feline viral ocular disease and rhinotracheitis in cats worldwide (Low et al. 2007, Wieliczko and Płoneczka-Janeczko 2010, Gould 2011, Fernandez et al. 2017). The cats are typically infected with the virus at a young age resulting in lifelong problems due to latency and reactivation (Stiles 2003). Feline herpes virus replicates in epithelial cells particularly in the conjunctiva as primary infection and tends to cause neuronal latency which may be reactivated throughout the life of the cat under the stress factors such as parturition, lactation, surgery, crowding, changes in housing

Correspondence to: Y. Ozkanlar, e-mail: yunusemre.ozkanlar@omu.edu.tr

or environmental conditions and corticosteroid treatment (Gaskell and Povey 1977, Stiles 2003, Maggs 2005). Clinical signs of the severe herpetic cases consist of conjunctivitis, ocular lesions, nasal discharge, sneezing, dyspnoea, fever, lethargy and inappetence in the cat. Mild herpetic cases may recover fully from symptoms with good care although medical treatment is necessary in the cats if the signs of active severe infection are present. Therefore, antiviral treatment of FHV-1 infection may limit epithelial replication, latency, reactivation and disease progression, and minimize frequency and severity of recurrences (Maggs 2005).

Feline herpes virus replication can be suppressed with antiviral agents (Hussein et al. 2008, Maggs 2010, Thomasy et al. 2011). Antivirals used for human herpesvirus have long been investigated in treatment of feline herpesvirus due to similarities between pathogenesis of FHV-1 infection in cats and herpes simplex virus (HSV) infection in humans. Antiviral medications are promising treatments for FHV-1 infection and potential drugs should be tested for safety before they are administered to cats (Maggs 2010). Famciclovir is a prodrug of penciclovir, it is an acyclic nucleoside analogue and inhibits viral polymerase and DNA synthesis (Sykes and Papich 2014). Famciclovir has been found to be very well tolerated in cats with herpesvirus (Maggs 2010, Thomasy et al. 2011, Reinhard et al. 2020, Ledbetter et al. 2022). In a recent clinical trial, famciclovir treatment has led to a significantly lower risk of worsening clinical signs in shelter cats with naturally occurring upper respiratory tract disease (Reinhard et al. 2020). Moreover, orally administered famciclovir has improved the outcomes of systemic, ophthalmic, clinicopathologic, virologic, and histologic findings in cats experimentally infected with FHV-1 (Thomasy et al. 2011). It is therefore noted that there is a necessity of researches to determine the effectiveness of famciclovir as part of treatment protocols for improving clinical signs and overall impacts in cats (Reinhard et al. 2020).

Early studies propose that lysine supplementation may suppress viral replication and results in less severe manifestations of conjunctivitis in cats experimentally infected with FHV-1 (Stiles et al. 2002, Maggs et al. 2003) and clinical recovery from herpes simplex infection in human patients (Griffith et al. 1987). Conversely, some studies report that dietary lysine supplementation 'alone' is not a successful means of controlling infectious upper respiratory disease although the trials have been tested in the cases with multiple aetiologies such as herpesvirus, calicivirus and chlamydophila in cats (Rees and Lubinski 2008, Drazenovich et al. 2009). It has been therefore referred from the previous reports that supplementary dose of dietary lysine is not effective to prevent becoming infected with upper respiratory disease and ocular manifestations (Gould 2011, Bol and Bunnik 2015). L-lysine supplementation appears to improve patients' subjective experience of herpes simplex virus (HSV) lesions in therapeutic doses while it may not be effective in low doses since lysine-arginine balance may affect herpesvirus expression and lysine competitively inhibits arginine-rich protein synthesis that is required for reproduction of herpesvirus (Mailoo and Rampes 2017, Pedrazini et al. 2022). Lysine is an essential amino acid for both humans and animals, besides there are similarities between HSV and FHV-1. Thus, data from previous studies and the clinical observations in cats and humans suggest that addition of lysine supplementation in therapeutic doses to treatment protocol of herpetic infections as an adjunctive support may help to treat the disease.

A topical antiviral treatment of conjunctivitis and keratitis may inhibit the viral replication of FHV-1 on the conjunctiva. Acyclovir is less effective on FHV-1-induced ocular lesions but beneficial effects can be seen if applied frequently (Williams et al. 2005, Gaskell et al. 2007). To prevent secondary bacterial infection, broad-spectrum antibiotic therapy is required to treat the infections (Gaskell et al. 2007, Thiry et al. 2009). Treatment of active disease is challenging and antiviral treatment with adjunctive therapy is promising. In previous studies, the particular effects of antiviral drugs have been separately investigated in naturally occurring and experimentally infected cats although little is known about the combination treatment in active FHV-1 infection. In this study, we have therefore used a combination treatment protocol for FHV-1 to evaluate the effects of famciclovir, L-lysine, amoxicillin plus clavulanic acid and topical acyclovir ointment on the clinical signs of FHV-1 infection in an open clinical trial.

Materials and Methods

Animals and treatment protocol

Twenty-eight cats with active clinical signs of FHV and diagnosed as PCR positive for FHV-1 DNA were used in this study. The cats were 2-10-month-old (median, 4.2) and 1.2-2.5 kg weight (mean, 1.8). All cats were non-vaccinated and referred to the animal hospital either from owners or from local animal shelters. Five non-vaccinated and PCR negative for FHV-1 DNA healthy cats that never had conjunctivitis history were also used to obtain control values for amino acid profile and leukogram. The treatment protocol of the cats with FHV infection was as follows: 125 mg/cat

famciclovir PO q 12 hr for 10 days (Famvir, Novartis Farmacéutica, Barberà del Vallès, Spain) 500 mg/cat lysine PO q 24 hr for 10 days (L-Lysine, Solgar Vitamin and Herbs, Leonia, NJ, USA), 7 mg/kg amoxicillin plus 1.75 mg/kg clavulanic acid SC q 24 hr for 10 days (Synulox, Zoetis/Pfizer, Istanbul, Turkey) and 3% acyclovir topical ophthalmic ointment to eyes q 8 hr for 5 days (Zovirax, Glaxo SmithKline – Glaxo Wellcome Operations, London, UK). All procedures were in compliance with the international ethical standards of National Institutes of Health Guide. This study was approved by the local ethics committee for animal researches of university (HADYEK, 2012/62).

Clinical scoring system

Clinical signs were scored according to the adapted clinical scoring system for FHV-1 infection (Lappin et al. 2006). Clinical symptoms were recorded at the time of enrolment once daily for up to 10 days. The animals were examined by the same veterinarian before the medication. Clinical signs of scoring system were conjunctivitis, corneal keratinization, corneal opacification, ocular discharge, nasal discharge, ocular ulceration, nasal ulceration, sneezing and dyspnoea. A clinical score for each clinical sign was assigned as 0 for absent, 1 for mild, 2 for moderate and 3 for severe on days abnormality present. A daily cumulative score was then calculated as a representative of all clinical signs.

Sample collection

Conjunctival and oropharyngeal (oculo-oropharyngeal) samples were obtained with a sterile Dacron swab before (day 0) and after (day 10) the treatment for virological analysis. The swab was gently rolled into the conjunctival sac of both eyes of the cat then in the oropharynx to represent an oculo-oropharyngeal sample for one cat (Kopecny et al. 2020). Blood samples were taken from the jugular vein into the tubes without anti-coagulants (Becton Dickinson, Rutherford, NJ, USA) and the tubes with anti-coagulants (K3 EDTA, FL Medical, Torreglia, Italy). Blood samples without anti-coagulants were centrifuged after clotting at 3500 rpm for 10 min at 4°C (Hettich 38R, Hettich Zentrifugen, Tuttlingen, Germany). The serum was separated into 1 ml aliquots and frozen at -20°C for biochemical analysis.

Virological analysis

Swab samples were scrutinized by PCR assay. The DNA of FHV-1 was extracted from the samples using a DNA kit (Qiagen, Valencia, Spain) in virology laboratory. The PCR assay was performed using primers for FHV-1 according to the method described previously (Sykes et al. 2001, Wieliczko and Płoneczka-Janeczko 2010). The primer sequences for FHV-1 were HerpF (5'-GACGTGGTGAATTATCAGC-3') and HerpR (5'-CAACTAGATTTCCACCAGGA-3') in thymidine kinase gene of FHV-1. Positive control was used from a commercial vaccine (Felocell, Pfizer Animal Health, USA) containing modified live virus of FHV-1. Reactions were performed in amplification mixture of 40 µL consisting of 2.5 U Taq DNA polymerase, 4 µL of Tris-HCl buffer, 2.4 µL of $MgCl_2$, 200 µM dNTP mixture, 1 µM of each primer and 2.6 µL of extracted DNA. The samples were subjected to 40 cycles with thermal conditions as described previously (Wieliczko and Płoneczka-Janeczko 2010). The product was visualized by colouring reagents into the microplates for the detection of the target DNA (Inouye and Hondo 1993). Absorbances of the samples were measured using a microplate reader (BioTek, µQuant, USA) at 450 nm (Vesanen et al. 1996).

Biochemical analysis

Amino acid profile was performed in Liquid Chromatography-Mass Spectrometry Tandem Gold Zivak LC-MS/MS. Zivak free amino acid LC-MS/MS analysis kit (ZV-3002-02C Amino acid biological fluids kit) was used in automatic Tandem Gold LC-MS/MS system (Zivak Technologies, Istanbul, Turkey) to determine serum amino acid profile. Serum lysine and arginine concentrations were evaluated within amino acid profiles of the cats before and after the lysine treatment. Arginine to lysine ratio was then calculated.

Haematological analysis

Complete blood counts were determined following the sample collection using a haematology analyser (Abacus Junior Vet 5, Diatron, Budapest, Hungary) in the blood samples with the anti-coagulant tubes before and after the treatment.

Statistical analysis

All data showed a normal distribution and coefficient variation was less than 20%. The data of the cats with FHV and healthy cats were compared using one-way ANOVA with Tukey's Post-Hoc test in the IBM SPSS 22.00 statistical program for Windows. A p value less than 0.05 is considered as significant difference. Pearson Chi Square analysis was used to compare the arginine to lysine ratio and the clinical recovery ratio (95%, CI). The data are presented as mean ± SEM.

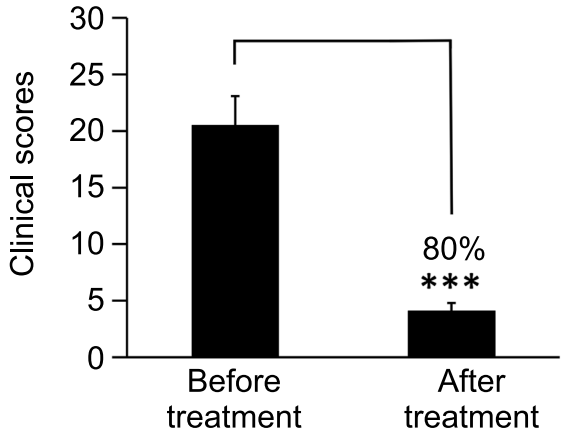

Fig. 1. Total clinical scores of the cats with FHV-1 infection before and after the treatment protocol (n=28). Scored clinical signs are conjunctivitis, corneal keratinization/opacification, ocular discharge, nasal discharge, nasal ulceration, sneezing and dyspnoea. A score is assigned to each clinical sign as 0 for absent, 1 for mild, 2 for moderate and 3 for severe by the same veterinarian. Bars represent standard error of the mean. *** $p<0.001$.

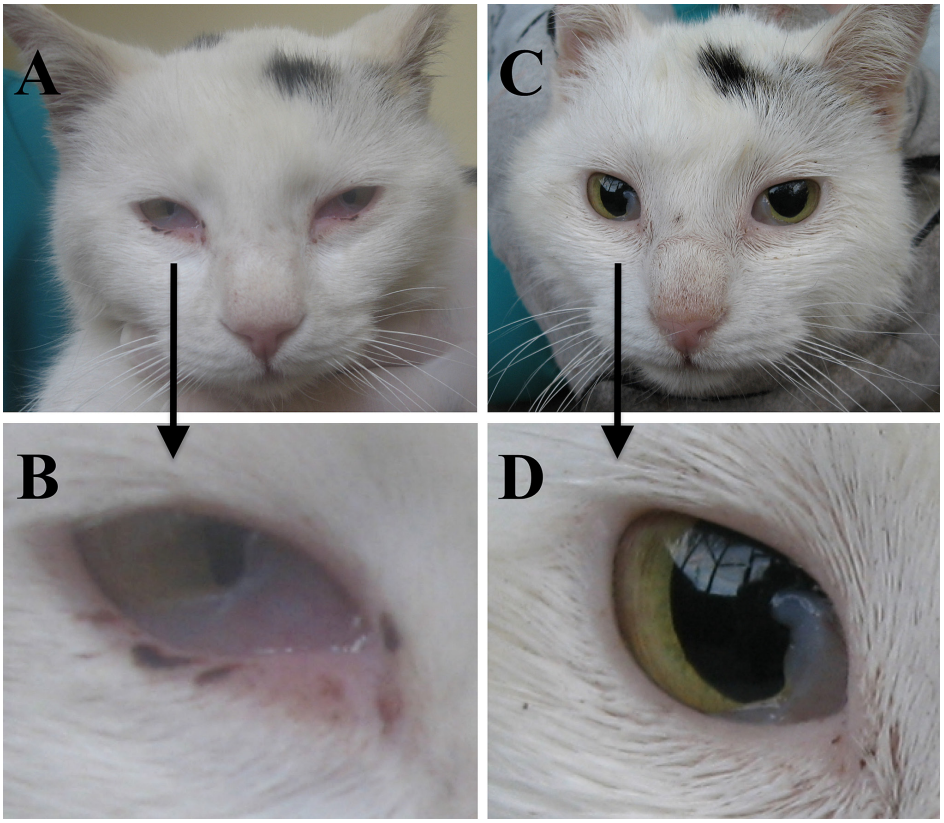

Fig. 2. Clinical appearance of a cat with FHV-1 infection. A and B: Conjunctivitis and conjunctival hyperaemia are seen in lining of lids and the third eyelid on both eyes along with sneezing and dyspnoea before the treatment. C and D: Conjunctivitis and conjunctival hyperaemia are not seen on both eyes after the treatment. FHV-1 was positive before the treatment and returned negative after the treatment on the day 10 in PCR analysis of the swab samples.

Results

The oculo-oropharyngeal swab samples were tested positive for FHV-1 DNA by PCR analysis for each cat at study entry. FHV-1 viral detection was found negative in 23 out of 28 cats on the day 10 of treatment compared with the time of enrolment (82.1%, $p<0.001$).

All cats presented conjunctivitis along with a sign of rhinotracheitis. The clinical symptoms of the affected cats were conjunctivitis, corneal keratinization, corneal opacification, ocular discharge, nasal discharge, ocular ulceration, nasal ulceration, sneezing, dyspnoea and lethargy. Conjunctivitis was determined as inflammation of lining of the lids and the third eyelid including front part of the eye. Clinical symptoms of the cats with FHV-1 infection improved with the treatment protocol

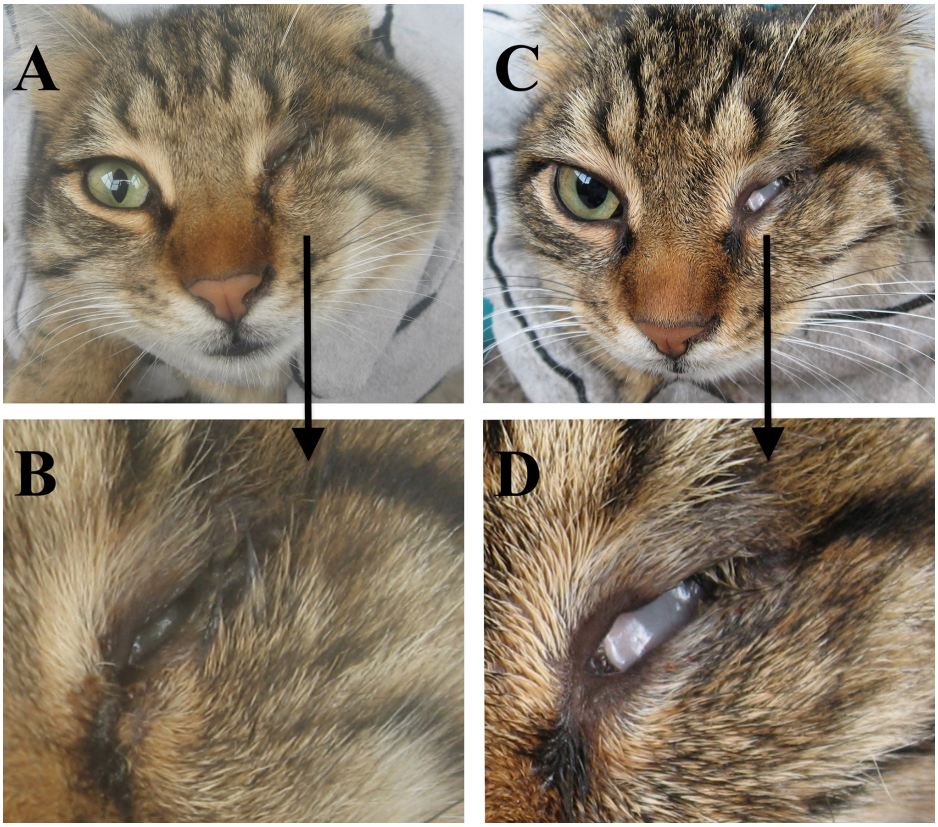

Fig. 3. Clinical appearance of a cat with severe FHV-1 infection. A and B: Serious injury is seen on one closed eye along with sneezing and dyspnoea before the treatment. C and D: Limited response is seen on the eye and the cat partly opens the eye after the treatment. FHV-1 was positive before the treatment and was still positive after the treatment on the day 10 in PCR analysis of the swab samples.

Table 1. Serum amino acid levels in the cats with FHV-1 infection (n=28) and healthy control cats (n=5).

	FHV-1		Healthy Control
	Before Treatment	After Treatment	
Arginine	165.1±15.6	170±12.4	164.9±23.8
Lysine	146.4±11.6[a]	292.1±31.9[b]	189.3±33.0[a]
Arginine/Lysine	1.13[a]	0.58[b]	0.87[a]

Different letters in the same row differ statistically ($p<0.05$). Results are mean ± standard error of the mean.

in each day. The mean values of total clinical scores of the cats before and after the treatment are presented in Fig. 1. Total clinical scores decreased significantly after the treatment and clinical recovery success was 80% reduction in the healing scores of the affected cats (20.5±2.6 vs 4.1±0.7, $p<0.001$). The rest of the cats responded with a limited healing to the treatment protocol due to the severity of infection in 10 days.

For illustration, a cat that presents conjunctivitis and conjunctival hyperaemia on lining of lids and third eyelid in both eyes along with sneezing and dyspnoea (Fig. 2AB) responded well to the treatment protocol and successful recovery was obtained on day 10 (Fig. 2CD). PCR analysis for FHV-1 was negative in this cat after the treatment. In another cat, however, one eye was seriously injured by the infection along with sneezing and dyspnoea (Fig. 3AB) and the response was limited in this cat (Fig. 3DC). This cat was still positive for FHV-1 virologically after the treatment.

Amino acid levels are presented in Table 1. Lysine level was relatively low before the treatment and the level increased significantly after the treatment compared with pre-treatment period ($p<0.01$). Lysine level at the post treatment time was found higher in the cats with FHV-1 than in the healthy control group ($p<0.05$). The arginine to lysine ratio decreased significantly in favour of lysine at the time point after the treatment in the cat with FHV-1 (1.13 to 0.58 ratio, 48.7 % reduction, $p<0.01$). The ratio of post-treatment period was also lower than the ratio of the healthy control (0.87 vs 0.58 ratio, 33.3 % reduction, $p<0.05$). Leukogram values did not change statistically after the treatment

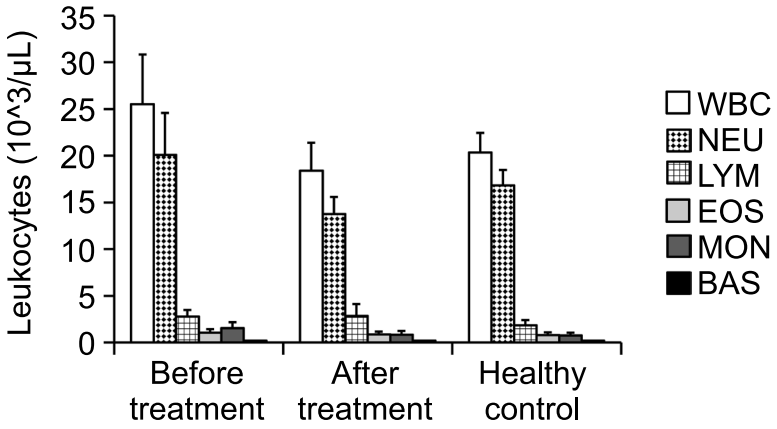

Fig. 4. Leukogram values in cats with FHV-1 infection before and after the treatment protocol (n=28) and healthy control cats (n=5). Leukocyte values tend to decrease after the treatment associated with neutrophil (20.1±4.3 vs 13.8±1.6, p=0.307) and monocyte (1.5±0.5 vs 0.8±0.2, p=0.269) counts with no statistical significance.

(Fig. 4). Leukocytes tended to decrease by the treatment especially neutrophils (20.1±4.3 vs 13.8±1.6, p=0.307) and monocytes (1.5±0.5 vs 0.8±0.2, p=0.269) values after the treatment compared with the values at the time of enrolment.

Discussion

The antiviral treatment appears to be effective against FHV-1 infection according to clinical healing scores. The antiviral drugs, used in this study, have been selected according to the findings of previous reports and further combined with an essential amino acid supplementation plus antibacterial therapy. Famciclovir treatment has been previously evaluated in spontaneous ocular, respiratory, or dermatologic disease in feline herpesvirus type 1 (Thomasy et al. 2016). The efficacy of drugs is variable in naturally occurring upper respiratory disease caused by viruses, indicating the effectiveness of treatment (Ozkanlar et al. 2012, Kopecny et al. 2020, Reinhard et al. 2020). Furthermore, there are consistent findings for antiviral efficacy in experimentally-infected cats with FHV-1 (Thomasy et al. 2011, Ledbetter et al. 2022). All cats were PCR positive for FHV-1-specific DNA in this study. Due to FHV-1 is common cause of chronic conjunctivitis in cats (Wieliczko and Płoneczka-Janeczko 2010), cats showing respiratory or ocular symptoms similar to herpesvirus were not included in the treatment protocol to evaluate clinical efficacy against herpesvirus infection. This clinical study, therefore, focuses exclusively on FHV-1 infection treatment with a combined drug protocol in naturally occurring cases.

Feline herpesvirus type 1 is a common cause of ocular surface disease, dermatitis, respiratory disease, and intraocular disease in cats and there is a need for effective antiviral treatment activity against FHV-1 (Thomasy and Maggs 2016). We evaluated a treatment combination – famciclovir, acyclovir, lysine supplementation and antibiotic – against FHV-1 infection and found clinically effective based on the findings of 80 percent improvement in the severity of clinical scores along with an 82.1 percent improvement in the negative PCR results of nasal and conjunctival swabs after the 10-day therapeutic period. Similar results are found in previous placebo-controlled experimental researches. Famciclovir administration alleviates systemic, ophthalmic, clinicopathological, virological, and histological changes in cats experimentally infected with FHV-1 (Thomasy et al. 2011). Topical use of ganciclovir or famciclovir treatment reduces the ocular disease scores and corneal inflammation in cats with experimental ocular FHV-1 infection (Ledbetter et al. 2022). There is limited report to compare our results with clinical outcomes in naturally occurring cases with FHV-1. Conjunctival FHV-1 shedding is reduced by 30-90 mg/kg famciclovir administration in 1-week although famciclovir administration alone may not enough to heal clinical manifestations of infectious upper respiratory tract disease (Cooper et al. 2019). The risk of worsening scores is low in famciclovir treatment of upper respiratory tract disease caused by multiple viral aetiology (Reinhard et al. 2020). Compared with previous reports, there is a satisfactory response in clinical manifestations of ocular and respiratory disease caused by FHV-1 infection. The dose of famciclovir is 125 mg per a cat which equals about 50-100 mg/kg dosage. The findings demonstrate that twice daily famciclovir for 10 days along with adjunctive support including acyclovir and L-lysine improves clinical symptoms and reduces the viral shedding. The reduction in viral shedding along with clinical healing in worsening scores should be particularly associated with the antiviral treatments. Thus, the findings

of this study and the previous researches may confirm the value of antivirals as part of the treatment protocol.

Acyclovir and its relevant prodrug forms are acyclic analogue of the purine nucleoside deoxy-guanosine commonly used to treat herpesvirus infections (Sykes and Papich 2014). Acyclovir is an effective drug for FHV-1 infection (Maggs and Clarke 2004) although it may be toxic at therapeutic levels for oral administration to cats (Gaskell et al. 2007). Topical acyclovir is safely used in the treatment (as eye drops or eye ointment) of herpetic conjunctivitis and keratitis with no toxic effect (De Clercq 2013). There found the use of topical acyclovir three times daily improves ocular lesions and conjunctivitis and is well tolerated in cats according to the clinical outcomes of this study. It is important to note herein that the therapy should be initiated as early as possible because the advanced ocular injuries may not be recovered fully in some cases due to the severity of lesions.

There was an increase in serum lysine level after the treatment of 500 mg lysine per a cat which equals about 200-400 mg/kg dosage. Lysine level at the pre-treatment time is partly low compared with the healthy control. Lysine supplementation may not change the arginine level while the arginine to lysine ratio decreases significantly in favour of lysine. Herpesvirus reproduction is bound to arginine-rich protein synthesis and high concentrations of lysine may competitively inhibit arginine synthesis (Mailoo and Rampes 2017). Arginine has growth-promoting effect on FHV-1. When plasma concentration of arginine is low and lysine is high, viral replication is inhibited. When arginine to lysine ratio is increased in favour of arginine, viral replication is increased. When the ratio is increased in favour of lysine, the viral replication is suppressed and virus's cytopathogenic effect is inhibited (Griffith et al. 1978). Lysine exerts this effect on FHV-1 replication only in condition of low concentrations of arginine. Thus, lysine may inhibit FHV-1 replication only in the presence of low arginine concentration (Maggs et al. 2000). Contrarily, there are reports that dietary lysine does not cause lysine-arginine antagonism (Fascetti et al. 2004). Researchers tested the hypothesis that increasing concentrations of L-lysine in media supplemented with L-arginine at concentrations compatible with supporting cell growth would inhibit FHV-1 replication in vitro. L-lysine does not inhibit in vitro replication of FHV-1 when L-arginine concentration is sufficient to maintain cell growth (Cave et al. 2014). It is clear that the use of lysine supplementation may not cause an inhibitory effect on the viral replication except for the conditions of low arginine level and high lysine level with a decreasing level of the arginine to lysine ratio.

There is evidence that the addition of lysine to the diets will reduce viral shedding, thereby reducing the risk of transmission to other cats in multi-cat house, shelters, and cat care homes, and have a beneficial effect on the frequency of recurrent outbreaks and the progression of disease symptoms. In one study, cats experimentally infected with FHV-1 were given 500 mg of L-lysine twice daily for 21 days. Consequently, FHV-1-induced conjunctivitis manifested less severe signs compared to cats receiving placebo suggesting that oral lysine administration could help the early treatment of FHV-1 infection by reducing the severity of the disease (Stiles et al. 2002). In another study, researchers administered L-lysine once daily to cats with FHV-1 for 30 days and evaluated the clinical signs of FHV-1 infection and ocular shedding of FHV-1 in latently infected cats. They proposed that oral administration of 400 mg of L-lysine once daily to cats infected with FHV-1 reduces viral shedding following changes in housing (Maggs et al. 2003). In an experimental study, it has been reported that high lysine concentrations reduce in vitro replication of FHV-1, but only in containing low concentrations of arginine, but clinical trials should be conducted to determine whether arginine-restricted or unrestricted lysine supplementation would be beneficial in the treatment of cats with FHV-1 infection (Maggs et al. 2000). Surprisingly, herpetic lesions have been suppressed by high dose L-lysine administration in a 60-year-old male subject with HSV reactivation after COVID-19 vaccination (Pedrazini et al. 2022). In the present study, L-lysine treatment combined with antiviral and the antibacterial drugs led to high lysine level and a relatively low arginine level with a decreasing level of the arginine to lysine ratio in the cats with FHV-1. Leukocytes, neutrophil and monocyte values, were also suppressed in these cats. Thus, addition of high dose lysine supplementation to anti-viral plus anti-bacterial protocol may be supportive to treat active herpetic infection based on the findings of this study and previous observations in cats and humans.

There are limitations of this study. The current study only reports a combination treatment of anti-viral, anti-bacterial and essential amino acids to improve respiratory and ocular symptoms caused by FHV-1 in cats. It is certain that the efficacy of each drug or in combination against naturally occurring infections should be determined in randomized and placebo-controlled groups. The effects of each drug should also be evaluated for systemic toxicity (Ozkanlar et al. 2005, Ozkanlar et al. 2014). In general, however, most of the diseases encountered in veterinary clinics and hospitals are being practically treated with drug combination protocols. The combination of the drugs used in the present

study has been proposed according to the previous reports mentioned above confirming the potentials of the drugs. The results of this combination protocol may particularly serve as a clinical report to direct further studies to evaluate separate contribution of each drug in naturally occurring cases. Our results do not determine or distinguish each drug efficacy when used alone rather than in combination. Although there may be difficulties in administering oral medication to cats in some cases, it is reported that oral administration of famciclovir is safe for cats (Thomasy et al. 2011). Because oral administration of acyclovir may be toxic to cats (Williams et al. 2005), the topical formulation of acyclovir should be used safely in the treatment of herpetic conjunctivitis without any systemic toxicity to provide an effective virutoxic level on the ocular surface in the treatment of herpetic conjunctivitis in cats (De Clercq 2013).

In conclusion, the combination of famciclovir, acyclovir, L-lysine and amoxicillin plus clavulanic acid improves the clinical manifestations of conjunctivitis and respiratory signs in naturally occurring FHV-1 infection in cats. The utility of systemic famciclovir and ocular acyclovir as part of the treatment protocol may be promising in active feline herpesvirus infection and antivirals with adjunctive therapy appear to be valuable medication in the treatment of challenging viral diseases. It is important to note here that further studies should be conducted in randomized and placebo-controlled clinical trials to evaluate the contribution of each drug in FHV-1 infection.

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