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Randomized, Placebo Controlled Study of the Effect of Propentofylline on Survival Time and Quality of Life of Cats with Feline Infectious Peritonitis

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Background: Currently there is no drug proven to effectively treat cats with feline infectious peritonitis (FIP).

Hypothesis: Propentofylline (PPF) can decrease vasculitis, and therefore prolong survival time in cats with FIP, and increase their quality of life.

Animals: Twenty-three privately owned cats with FIP.

Methods: Placebo-controlled double-blind trial. FIP was confirmed by histology or immunostaining of feline coronavirus (FCoV) antigen in effusion or tissue macrophages or both. The cats were randomly selected for treatment with either PPF or placebo. All cats received additional treatment with glucocorticoids, antibiotics, and low molecular weight heparin according to methods.

Results: There was no statistically significant difference in the survival time of cats treated with PPF (8 days, 95% CI 5.4–10.6) versus placebo (7.5 days, 95% CI 4.4–9.6). The median survival time of all cats was 8 days (4–36 days). There was neither a difference in quality of life (day 7, $P = .892$), in the amount of effusion (day 7, $P = .710$), the tumor necrosis factor-alpha (TNF-α) concentration (day 7, $P = .355$), nor in any other variable investigated in this study, including a complete blood count, and a small animal biochemistry profile.

Conclusions and Clinical Importance: This study did not detect an effect of PPF on the survival time, the quality of life, or any clinical or laboratory parameter in cats with FIP. Therefore, PPF does not appear to be an effective treatment option in cats with a late stage of the disease FIP.

Key words: FIP; Feline corona virus; Methylxanthine derivative; Vasculitis.

Feline infectious peritonitis (FIP) is one of the most frequent causes of death in young cats.[1–2] There is no proven record of cats with a confirmed diagnosis having recovered from FIP.[3] Thus, FIP is usually lethal; no controlled study has verified the success of any treatment used to date.[1,4–6] Therefore, providing objective evidence of the effectiveness of any treatment against this disease is important.

Several case reports can be found in the online Veterinary Information Network (http://www.VIN.com) that describe a positive effect of the methylxanthine derivative pentoxifylline (PTX) (Trental[a]) on the survival time in cats with FIP. Several veterinarians and well-known specialists in feline medicine have suggested that the use of PTX can be effective in treating cats with FIP.[4,6–8] According to those reports, PTX does not cure but is suggested to prolong the life of these cats.[4–5,8] In these reports it has been suggested that PTX is likely to decrease vasculitis, which is responsible for the majority of clinicopathological findings of FIP.[1] The mode of action of the methylxanthine derivatives is not fully understood, and the mechanism remains unknown.[9–10] The PTX inhibits several cytokines, such as interleukines and tumor necrosis factor-alpha (TNF-α).[9] There are studies in rats and humans (in vivo and in vitro) describing the inhibition of cytokines by PTX,[11–15] and PTX and other methylxanthine derivatives seem to suppress TNF-α synthesis.[15] These proinflammatory cytokines play a major role in the pathogenesis of vasculitis.[16] Therefore, it has been suggested that vasculitis may be effectively controlled with PTX because of its effect in neutralizing or suppressing these cytokines.[11–15] Propentofylline (PPF) and PTX have mainly been trialed for use in people with peripheral vascular diseases,[17–20] cerebrovascular diseases (such as Alzheimer's disease, brain ischemia, or cerebrovascular insufficiency),[9,20–22] endotoxemia,[14,23] and ischemic heart disease.[20,24] TNF-α also induces fibrinogen synthesis,[25–27] and is responsible for an increased production of free radicals

Abbreviations:

ALT	alanine aminotransferase
AP	alkaline phosphatase
CI	confidence interval
FCoV	feline coronavirus
FeLV	feline leukemia virus
FIP	feline infectious peritonitis
FIPV	feline infectious peritonitis virus
FIV	feline immundeficiency virus
IFAT	immunofluorescent antibody technique
PPF	propentofylline
PTX	pentoxifylline
RBC	red blood cells
SPSS	statistical package for the social sciences
TNF-α	tumor necrosis factor-alpha
TP	total protein
WBC	white blood cells

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which cause endothelial cell damage.[28] By inhibiting the synthesis of TNF-α by activated monocytes, PTX can probably decrease fibrinogen levels, a common component of the effusion in cats with FIP.[10,19] It was previously postulated that high fibrinogen levels could be an index of TNF-α levels. This finding is supported by a close correlation between decreased fibrinogen levels and clinical improvement.[19] A study into geriatric cachexia in humans additionally showed that PTX may decrease cachexia by down-regulating proinflammatory cytokines, such as TNF-α, interleukin 1 and 6, serotonin, and interferon-γ. Because cats with FIP are often anorectic, this was considered to be another positive effect of the methylxanthine derivatives on the well-being of cats with FIP.[24,29]

PPF, another methylxanthine derivative, is licensed in several European countries (including Germany) for veterinary use in dogs. It is very similar to PTX (which is not licensed in Germany for veterinary use) in its chemical structure as well as in its pharmacological effects.[30–31] Both PTX and PPF inhibit several cytokines, such as interleukins and TNF-α.[9] Furthermore, PPF has already been applied securely and effectively to cats with feline asthma.[32] Therefore, PPF instead of PTX was used in this study.

The aim of this study was to evaluate the efficacy of PPF on the survival time and quality of life in cats with a confirmed diagnosis of FIP in a placebo-controlled double-blind trial.

Materials and Methods

Sample Population

The study included 23 client-owned cats. Inclusion criterion to enter the study was the definitive diagnosis of FIP. All cats were presented to the Clinic of Small Animal Internal Medicine, LMU University of Munich, Germany. An informed consent of participation signed by the owners was obtained for all cats. This study fulfilled the general German guidelines for prospective studies with owners' consents and was approved by the ethics committee and the animal protection officials of the Regierung von Oberbayern, Germany (permission no. 55.2-1-54-2531-127-09). Consecutive cases of cats with confirmed FIP that had owners willing to participate in the study, presented to the clinic between April 2009 and December 2010, were entered into the study.

Diagnosis of FIP was either confirmed by detection of feline coronavirus (FCoV) antigen in macrophages in the effusion using direct immunofluorescence[33] (n = 9), by histopathological examination of tissue, positive immunohistochemical staining of FCoV antigen in macrophages[34] (n = 22), or by both. Cats with feline immundeficiency virus (FIV) or progressive feline leukemia virus (FeLV) infection were not included in the study (SNAP FeLV/FIV test[b]). Cats with severe clinical signs (Karnofsky's score[35] <30%) or a survival time less than 72 hours after treatment initiation were retrospectively excluded (2 cats). One cat had to be excluded in retrospect because of a lack of owner compliance.

Seventeen of the 23 cats (74%) were European Shorthair cats, 2 (9%) were British Shorthair cats, and there was one (4%) of each of the following breeds: Birman, Persian, Norwegian Forest cat, and Persian crossbred. The youngest cat was 13 weeks old and the oldest cat 2.8 years (mean, 0.9 years; median, 0.7 years; interquartile range, 0.42–1.25 years). Fifteen (65%) cats were younger than 12 months; 20 (87%) cats were younger than 2 years. Seventeen (74%) cats were male (5 neutered), and 6 (26%) female (2 neutered).

Study Design

The study was designed as a placebo-controlled, double-blind randomized trial. Cats were randomly assigned to the PPF (n = 7) or placebo group (n = 16). The dosage of PPF was based on the dosage used of PTX to treat cats with FIP in the literature and anecdotal case reports of different authors. In those reports, 10–15 mg/kg or 100 mg/cat every 12 hours was given PO.[6] According to studies in humans, PPF and PTX are used at the same dosage.[36] Cats in this study therefore received a median dosage of 18–25 mg/kg PPF[c,d] during the whole study period. Alternatively, cats received the similar amount of tablets of placebo[e] (containing lactose, magnesium stearate, and cellulose) every 12 hours PO. The PPF and the placebo pills were coded. Therefore, veterinarians and owners giving the pills were blinded to identity of the treatment. The code was broken after 23 cats had been treated. All results (including survival time, Karnofsky's score, blood and effusions variables, and volume of collected effusion) were obtained blinded.

All cats were also treated with glucocorticoids. In case of effusion at day of presentation (n = 21), dexamethasone[f] (1 mg/kg) was given intraperitoneally or intrathoracically (depending on the location of effusion) every 24 hours for 6 days after thoraco- or abdominocenthesis. Cats without effusion (n = 2) received dexamethasone[f] (1 mg/kg) SC for 6 days. After this period, all cats were treated with oral prednisolone[g,h] (2 mg/kg) every 24 hours until death. In addition, cats received amoxicillin/clavulanic acid[i] (12.5 mg/kg IV every 12 hours) for 7 days; dalteparin sodium[j] (75 IU/kg SC every 12 hours) for 5 days, which was gradually tapered within the next 2 days (day 6: 36 IU/kg, day 7: 18 IU/kg); as well as fluid and nutritional treatment if necessary during the hospitalization. If the cats were not properly vaccinated, they were treated SC with one dose (4 mL) of immunglobulins[k] (a product containing antibodies against feline panleukopeniavirus, feline herpesvirus, and feline calicivirus). This product was given to decrease the risk of acquiring an infectious disease because of immune suppression by glucocorticoid treatment and hospitalization. Glucocorticoids were given, because it is currently the only treatment thought to have a beneficial effect on cats with FIP although there are no controlled studies.[3,37] Antibiotics were administered to minimize the risk of bacterial infection because paracentesis was performed daily (if effusion was present), and because of the high dosage of glucocorticoid treatment. Cats also received low molecular weight heparin (dalteparid sodium) to minimize the risk of a disseminated intravascular coagulation (DIC), which is often observed in cats with FIP.[1,38–39]

Examination Schedule

All cats were either hospitalized during the 1st 7 days after treatment initiation or had to be presented to the clinic daily. Physical and ultrasound examinations were performed daily. The general condition was characterized by the Karnofsky's score. The index enables judgment of quality of life and well-being in cats by means of a score of 0% (dead) to 100% (absolutely healthy and happy).[35] On day 0 (day of inclusion in the study) as well as on the control days (day 7, 14, and 28), a complete physical examination was performed, and blood was collected. A CBC was performed with an automatic analyzer (Cell-Dyn[l]), the small animal biochemistry profile (see Table 1) was examined using an automatic analyzer (Hitachi[m]). Aliquots of the serum samples were preserved at –80°C for detection of TNF-α. If present,

Table 1. Variables on day 0 and *P*-values of all parameters showing or denying a significant difference between the cats of the propentofylline and the placebo group on days 0, 7, and 14.

			Day 0		Day 0		Day 0	Day 7	Day 14
			PPF group		Placebo group		PPF vs Placebo	PPF vs Placebo	PPF vs Placebo
Parameter	(RR)	Unit	Median	(1–3 quartile)	Median	(1–3 quartile)	(*P*-value)	(*P*-value)	(*P*-value)
Kamofsky's score		%	70	(55–80)	70	(70–80)	.405	.892	n.d.
Amount of effusion		Code*	2*	(1–4)*	2*	(1–4)*	.536	.710	.237
RBC	(5.00–1.00)	$\times 10^{12}$/L	8.83	(6.72–9.42)	7.38	(5.78–7.81)	.181	.572	.699
Hemoglobin	(5.60–9.30)	mM	5.88	(5.40–7.88)	5.94	(5.32–6.44)	.825	.396	1.000
Hematocrit	(0.30–.44)	L/L	0.31	(0.28–.40)	0.29	(0.20–.32)	.160	.570	.051
Platelets	(180–550)	$\times 10^9$/L	255	(220–310)	230	(154–311)	.673	.357	.076
WBC	(6.00–11.00)	$\times 10^9$/L	9.98	(8.16–19.80)	13.75	(11.73–17.70)	.316	.777	.245
Monocytes	(0.04–0.50)	$\times 10^9$/L	0.29	(0.14–.31)	0.37	(0.09–.59)	.786	.260	.683
Lymphocytes	(1.00–4.00)	$\times 10^9$/L	1.06	(0.53–1.54)	1.18	(0.70 –1.68)	.504	.396	.053
Band neutrophils	(0.00–.60)	$\times 10^9$/L	0.56	(0.07–2.39)	0.80	(0.24–1.05)	.905	.089	.245
Mature neutrophils	(3.00–11.00)	$\times 10^9$/L	7.39	(6.31–16.11)	11.53	(8.93–15.13)	.316	.888	.439
ALT	(0–114)	U/L	27	(26–65)	35	(23–55)	.640	.537	.348
AP	(0–94)	U/L	14	(12–23)	13	(9–18)	.402	.535	.100
Bilirubin	(0.0–4.7)	μM	13.5	(3.1–27.2)	15.5	(8.5–45.7)	.385	.877	.064
TP	(57.0–94.0)	g/L	82.5	(71.7–93.1)	69.6	(61.8–82.1)	.229	.758	.064
Albumin	(26.0–56.0)	g/L	24.6	(20.9–25.4)	22.5	(19.7–23.9)	.423	.439	.643
Alb/glob ratio	n.r.		0.46	(0.29–.57)	0.43	(0.35–.51)	.789	.279	1.000
Urea	(5.0–11.3)	mM	6.1	(5.1–6.7)	6.3	(5.5–7.9)	.815	.589	.165
Creatinine	(0.0–169.0)	μM	61.9	(51.5–68.0)	56.8	(38.8–82.0)	.947	.938	.355
Glucose	(3.7–6.9)	mM	6.1	(4.9–6.5)	5.5	(5.2–6.8)	.947	.643	.355
TNF-α in the serum	n.r.	pg/mL	8.48	(0.00–24.77)	15.09	(4.91–26.31)	.093	.355	n.d.

PPF, propentofylline; vs, versus; RR, reference range, n. d., not done; Karnofsky, Karnofsky's score, RBC, red blood cells; WBC, white blood cells; ALT, alanine aminotransferase; AP, alkaline phosphatase; TP, total protein; n. r., no reference values available.

*Code: 1 = 0–30 mL; 2 = 31–60 mL; 4 = >150 mL.

effusion was aspirated, and the amount was recorded. Depending on their health status, cats were returned to their owners after day 7. The owners were asked to fill in a provided diary recording temperature, respiratory rate, weight, general condition (duration of sleeping time, eating, playing, and grooming behavior) every day, as well as any problem noticed by the owners. Follow-up examinations in the clinic were scheduled on days 7, 14, and 28, including physical examination, examination of a CBC, a small animal biochemistry profile, and ultrasound to detect the presence of effusion.

Measurement of TNF-α

TNF-α was measured in the serum (on day 0, 7, 14, and 28) using an ELISA.[n] Because the ELISA is only validated for cell culture supernatants, a spiking experiment using serum samples was performed. Serum components can impact the accuracy of ELISA results and may interfere with antibody binding or show cross-reactivity. To assess recovery of serum samples and to assess accuracy of measured values, 200 pg TNF-α were spiked into a serum sample of a healthy cat. The sample was diluted in sample diluent (PBS[o] + 10% fetal calf serum[p]) 2-fold to yield samples containing 100, 50, and 25 pg. As a control, sample diluent was spiked and diluted accordingly. The spiked undiluted control yielded results in the expected range (89%). The spiked undiluted serum sample showed recovery of 65%, indicating inhibitors of detection in the serum. The serum at a 1 : 2 dilution showed recovery of 73% compared to 88% of the diluted control. The recovery loss of 15% was considered acceptable, and interference of inhibiting components appeared to be not severe; all serum samples were therefore diluted 1 : 2 for detection of TNF-α. The ELISA was performed according to the manufacturer's instructions. A 96-well microplate[n] was coated with capture antibody by overnight incubation. The next day, the wells were washed and samples (diluted 1 : 2) and standards[n] were incubated for 2 hours at room temperature. After washing, the detection antibody[n] was added and incubated for another 2 hours at room temperature. For detection, streptavidin-HRP[n] was used with tetramethylbenzidin[n] as a substrate solution. The reaction was stopped after 10 minutes with 0.5 M sulfuric acid.[n] The ELISA was measured with a Bio Tek Reader,[q] and the data analysis was performed using Gen5 Data Analysis software.[r]

Statistical Evaluation

All cats were randomly assigned to 2 groups, the PPF group and the placebo group. A power analysis had been performed before starting the study (using PASS, 2008; http://www.ncss.com/pass). For this analysis, a clinical relevant difference in median survival time was set at 21 days, assuming that animals treated with PPF would survive at least 21 days longer than animals receiving placebo. These differences could have been detected with 18 animals per group, using a power of 80% and a significance level of 5%. However, an interim analysis on the survival time was performed after 23 cats had been treated, because most cats in the study at that time point have survived for less than

29 days, and the median survival time was not significantly different between the groups (median survival time PPF: 8.0 days; placebo: 7.5 days). Therefore, it was decided to terminate the study prematurely for reasons of animal welfare, as the expected clinical relevant differences and the difference of the survival time were clearly not achievable.

Statistical analysis was performed using statistical software SPSS version 17.0 (http://www.spss.com). Variables compared between both groups (PPF or placebo group) included survival time, Karnofsky's score, red blood cells (RBC), hemoglobin, hematocrit, platelets, white blood cells (WBC), monocytes, lymphocytes, banded neutrophils, mature neutrophils, alanine aminotransferase (ALT), alkaline phosphatase (AP), bilirubin, total protein (TP), albumin, albumin to globulin ratio, urea, creatinine, glucose, and the volume of effusion. A difference in the survival time between both groups was evaluated using a log-rank test. Differences between the parameters of the 2 groups at day 0, day 7, and day 14 were investigated using a Mann Whitney *U* test. *P*-values <.05 were considered significant. A Bonferroni correction was performed to rule out multiple test interference. A 5% significance level was assumed for all variables, and thus the *P*-value of .05 was divided through the number of tests performed (n = 20). Therefore, a final value of $P \leq .0025$ for each variable was considered significant.

Results

There was no statistically significant difference in any blood parameter or in the amount of effusion at any time point between cats treated with PPF, and those that received placebo (Table 1). The Karnofsky's score of both groups also showed no statistically significant difference at the start of the study.

Cats survived between 4 and 36 days (median, 8 days). The median survival time of cats in the PPF group was 8 days (range 4–36; 95% confidence interval [CI] 5.4–10.6), and of cats in the placebo group the median survival time was 7.5 days (range 4–22; 95% CI 4.4–9.6). The difference in survival time between the 2 groups was not significantly different ($P = .665$) (Fig 1). Twenty-two of 23 (96%) cats survived less than 29 days. These 29 days were preset as expected minimum survival time in cats receiving PPF. In a previous study, a median survival time of 8 days was detected in cats with FIP.[3] In the present study, it was assumed that cats treated with PPF would live at least 21 days longer than those receiving placebo (with a median survival of 8 days), as this makes a relevant difference for the owners.[3]

No statistically significant differences of any blood parameter or of effusion were apparent after the 7 and 14 day period of treatment between the PPF group and the placebo group. The Karnofsky's score of both groups on the evaluated control days (day 7 and day 14) also showed no significant difference. On day 7, only 14 cats remained in the study. Two of them improved 10% in the Karnofsky's score, 5 cats showed no difference and the Karnofsky's score of 7 cats deteriorated for at least 70%. On day 14, only 4 cats remained in the study and the Karnofsky's score of all these cats had deteriorated for at least 80% compared to day 0. No statistical evaluation was performed after day 14 because only 1 cat was alive at day 28 (next control day).

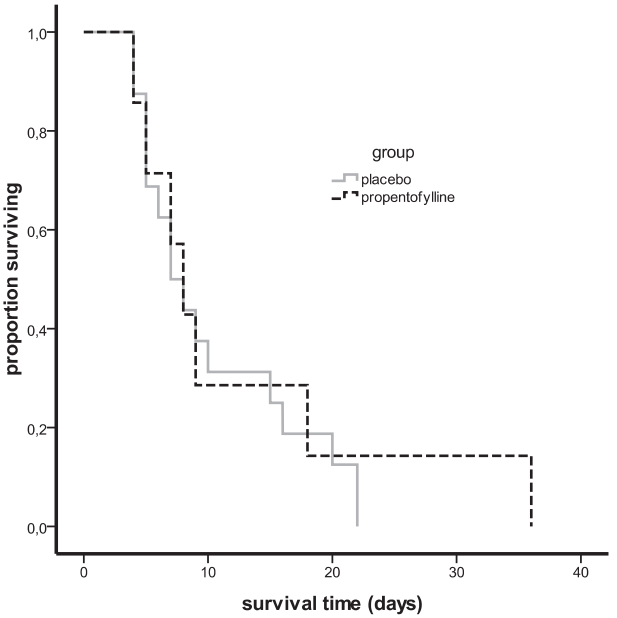

Fig 1. Kaplan-Meier survival curve of cats treated with propentofylline and cats treated with placebo; $P = .665$.

Only in 6 cats (4 of the PPF group, 2 of the placebo group) serum samples of more than one time point were available for the comparison of the TNF-α concentration during treatment with PPF. A significant decrease was not found in any of these cats; conversely, most cats even showed increased TNF-α serum levels during the study period.

Discussion

In this study, there was no statistically significant difference in the survival time of cats treated with PPF versus placebo. There was also no statistically significant difference in any other variable evaluated between both groups, including the CBC and a small animal biochemistry profile (as shown in Table 1).

The median survival time (8 days) of cats with FIP after definitive diagnosis in this study was nearly identical to the median survival of the study of Ritz et al.[3] There are no other reports on median survival times of cats after FIP was confirmed. However, in the study of Ritz et al,[3] several cats survived longer than 4 weeks, which was not the case in the present study.

Unfortunately, the desired effect of PPF was not observed. It has been proposed that PPF may decrease the volume of effusion, by inhibiting cytokines (particularly TNF-α) and thereby reducing resulting vasculitis. There was neither a significant difference in the amount of effusion between the PPF and the placebo group, nor a decrease in TNF-α in any of the cats in which serial measurement was performed. A cure was never the ultimate goal in the use of PPF in cats with FIP, because it is not an antiviral drug. However, because of the pharmacological features it was

assumed to have positive effects on the well-being of the cats and the survival time. PPF was meant to inhibit the TNF-α production,[9] which is involved in the development of vasculitis.[11–15] The TNF-α concentration, however, did not decrease in the cats treated with PPF, but increased instead. Most likely, PPF was not even able to exhibit its function within this short period of time, and the TNF-α increase mainly reflected severe progression of the disease.

Reasons for the lack of efficiency can be multifaceted. The most probable reason is that treatment may have been initiated too late. If signs of vasculitis were apparent, the immune-mediated process in cats with FIP might have been progressed too far to be delayed by PPF. In the present study, 21 of the 23 cats already showed effusion at the day of presentation. As shown in an experimental trial, signs of FIP become apparent 1–2 weeks after inoculation of the mutated feline infectious peritonitis virus (FIPV).[40] As the effect of PTX is described by the manufacturer information[a] to be seen after 2–4 weeks after treatment initiation, and it is an assumption that the same time frame would apply to PPF, most of the cats were already dead before an effect could be reached. A further reason for lack of PPF efficiency in this study could be that the treatment intervals could have been too long. An application of PPF every 12 hours was used in this trial following the anecdotal reports describing an effect of PTX in cats.[4,6,32,41] The manufacturer instruction recommends administration of PTX 3 times daily in human medicine,[20] because of a relatively short plasma half-life of 0.4–0.8 hours of the drug. A pharmacokinetic study in dogs indicated that PTX be administered every 8 hours.[42]

The reasons behind the reported beneficial effects of PTX described in case reports (http://www.VIN.com) are currently unknown. Treatment might have been initiated earlier in these cats. Alternatively, FIP was not confirmed by histopathology or immunofluorescent antibody technique (IFAT) in most of these cases; so, these cats could have suffered from other diseases. Some of the cats might have had a "non-effusive" form of FIP, which is considered to have longer survival times than in cats with effusion.[43]

Drug interactions between PPF and the other medications (especially the glucocorticoids) in this study are a possibility, but are not reported. In addition, in a recent study in cats with asthma, glucocorticoids and PPF were safely used in combination with no adverse interactions. The glucocorticoid dose can be reduced by addition of PPF to treatment.[32] Therefore, no adverse effects were expected with the combination PPF and glucocorticoids in the present study. Glucocorticoids are routinely used in cats with FIP,[1,3,44–47] as it is not the virus itself that causes major damage but the cat's own immune reaction that leads to the fatal consequences. There are no evidence based studies that glucocorticoids have a positive effect in cats with FIP.[37] The cats of the present study received an immunosuppressive dose of glucocorticoids (2 mg/kg). Together with the stress caused by hospitalization and daily paracenthesis, glucocorticoids might be a more confounding factor.[48–49] Potentially, a lower dose of glucocorticoids, or no glucocorticoids at all, might be better for "long-term" treatment. The beneficial effects of glucocorticoids in the treatment of FIP must be questioned given the median survival time is 8–9 days in the present and in the previous study,[3] both in treatment and placebo groups.[3] Therefore, future treatment study protocols should include a 3rd group of cats that receive no glucocorticoids. Alternatively a double-blinded study just evaluating glucocorticoids as treatment option for FIP could be performed.

There was no statistically significant difference in the Karnofsky's score during the treatment period between the two groups. Few cats showed an increased well-being shortly after participating in the study. This was most likely induced by the corticosteroids and was not the effect of PPF, because this phenomenon could be observed in both groups. However, the improvement in the general condition was not long-lasting, and cats deteriorated rapidly between 4 and 21 days after treatment initiation.

This study had several limitations. The 1st limitation is the unequal distribution of cats to the PPF and the placebo group. As this was a blinded, randomized trial, the distribution could not be influenced. Another limitation might be the small number of cats (only 2) without initial effusion. Definitive diagnosis in cats without effusion, however, is much more difficult to obtain.[33] The PPF might be more useful in cats without effusion, as it may have a chance to prevent vasculitis and therefore effusions

Footnotes

[a] Sanofi-aventis US, Bridgewater, NJ
[b] Feline Leukemia Virus Antigen/Feline Immunodeficiency Virus Antibody Test Kit; IDEXX, Wörrstadt, Germany
[c] Karsivan, 50 mg; Intervet, Unterschleissheim, Germany
[d] Karsivan, 100 mg; Intervet
[e] P-Tabletten, weiß, 7 mm; Lichtenstein, Winthrop, Fürstenfeldbruck, Germany
[f] Hexadreson; Intervet
[g] Prednisolon, 2 mg; GALENpharma GmbH, Kiel, Germany
[h] Prednisolon, 5 mg; CP-Pharma, Burgdorf, Germany
[i] Augmentan; Glaxo Smithkline, München, Germany
[j] Fragmin; Pfizer Pharma GmbH, Berlin, Germany
[k] Feliserin PRC; IDT Biologika GmbH, Dessau-Roßlan, Germany
[l] Cell-Dyn 3500; Abott Laboratories, IL
[m] Hitachi 911; Roche Deutschland Holding GmbH, Grenzach-Wyhlen, Germany
[n] DuoSet ELISA for feline TNF-α/TNFSF1A; R&D Systems, Inc, Minneapolis, MN
[o] PBS; Sigma-Aldrich, Taufkirchen, Germany
[p] Fetal Calf Serum; PAA Laboratories, Pasching, Austria
[q] Bio Tek Synergy HT Multi-Mode Microplate Reader; Bio Tek Germany, Bad Friedrichshall, Germany
[r] Gen5 Data Analysis Software; Bio Tek Germany

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