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TREATMENT WITH REMDESIVIR IN CATS WITH INFECTIVE PERITONITIS – CASE STUDY

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ABSTRACT

Feline infectious peritonitis (FIP) is common disease with wide spectrum of unspecific clinical signs, caused by feline coronavirus and is often with fatal outcome. Diagnosis can often be difficult and the test results should always be interpreted in conjunction with clinical signs, clinical examination findings and laboratory results. Lack of registered and available treatment for this disease is challenging for both owners and veterinary practitioners. The most recent promising treatment for cats with FIP is the use of the nucleoside analogue GS-441524, which is the active form of the prodrug Remdesivir. The goal of this study was to present successful treatment of 3 cats with different type of FIP. Clinical examination data, laboratory and rapid test results before and during treatment were evaluated. With this case study we present our positive experience with Remdesivir that can be used in all cats with FIP, regardless of the form of the disease.

Key words: Feline infective peritonitis, Remdesivir, treatment.

Introduction

Feline infectious peritonitis (FIP) is a highly contagious and fatal immune-mediated disease for cats. It is caused by a macrophage tropic mutant of feline coronavirus (FCoV), with oro-nasal transmission, and due to its survival time outside, can also be transmitted thought indirect contact (toys, clothes, grooming tools or iatrogenic). Most household disinfectants are effective in virus elimination. At high risk are cats under 3 years old and living in high density population (shelters, multiple-cat homes etc.) (Foley *et al.* 1998). Clinical manifestation varies depending on the form (wet, dry or mixed form) and fever refractory to antibiotics, lethargy, anorexia, weight loss are common non-specific signs. Abdominal and/or thoracic effusion are the most obvious manifestations of the effusive form. According to one study, approximately 13% of cats with FIP have neurologic signs, variating depending of the involved area of the CNS. Most common neurological clinical signs are ataxia, nystagmus, seizures, incoordination, behavioral changes etc. (Rohrer *et al.* 1994).

Difficulties in definitively diagnosing FIP arise from nonspecific clinical signs; lack of pathognomonic, hematologic, and biochemical abnormalities; and low sensitivity and specificity of tests routinely used in practice. Patients' history, clinical signs, laboratory findings and effusion analyses can help in further diagnostic test procedures. Hematological changes are often present in patients with FIP infection, including anemia, lymphopenia, neutrophilia and thrombocytopenia (Felten & Hartmann, 2019). The most common serum chemistry finding in cats with FIP is elevation in total protein levels, due to increased globulins, and decreased albumin to globulin ratio. It has been suggested that the albumin to globulin (A:G) ratio has better diagnostic utility than the gamma-globulin

or total protein concentration alone and several cut-offs have been suggested to potentially rule in (<0.4) or rule out (>0.6–0.8) FIP (Hartmann *et al.* 2003). The A:G ratio, as other hematological and serum biochemistry changes, should only be interpreted in conjunction with signalmen, history, other laboratory parameters and possibly molecular diagnostic methods. Other serum biochemistry parameters may be involved, depending of organic involvement, and they are usually not helpful in etiologic diagnosis (Rohrer *et al.* 1994). The majority of the cats with FIP have effusions (abdominal, thoracic or both). The Rivalta's test is a cheap and easy way to distinguish transudate from exudate and has good sensitivity for excluding FIP (91-100%). Rivalta's test can also be positive in effusions caused by bacterial peritonitis and lymphoma, in which cases cytology and/or culture can be used to confirm diagnosis. (Hartmann *et al*. 2003).

Rapid immunochromatographic tests are often used in every day clinical practice since they are rapid, noninvasive (they use blood, serum, plasma, effusion or feces), do not require special equipment, and are quite affordable in comparison of other diagnostic techniques (PCR, immunochistochemistry, etc.) (Novakov *et al.* 2023). The negative side of these tests is their sensitivity, which is low to satisfactory (Vojtkovská *et al.* 2022). In several studies, a large proportion of the cat population had serum antibodies against FCoV, but most of these cats never develop FIP. The significance of the presence of antibodies for diagnosing FIP in an individual cat therefore is very limited (Addie *et al.* 1995, Hartman *et al*. 2003, Giori *et al.* 2011). That is why the results of these test should always be interpreted in conjunction with clinical signs, clinical examination findings and laboratory results. Immunochistochemistry on histopathologically abnormal tissue (obtained postmortem or by laparotomy) still remains the gold standard of diagnosis (Felten & Hartmann 2019), but it is not available for everyday clinical diagnosis.

In many countries, there is currently no effective licensed treatment option for cats with FIP, although unlicensed compounds have been imported and used by cat owners. The most recent promising treatment for cats with FIP is the use of the nucleoside analogue GS-441524 (Roy *et al*. 2022, Cook *et al*. 2022, Coggins *et al*. 2023), which is the active form of the prodrug remdesivir. Remdesivir is the first Food and Drug Administration (FDA) approved anti-SARS-CoV-2 treatment for adult and pediatric patients. (Afshar *et al.* 2023). According to literature, parenteral administration of remdesivir for 12 weeks is effective and well-tolerated treatments for FIP (Coggins *et al.* 2023). Besides the availability of the therapy, treatment duration (~12 weeks) and expense can also be discouraging for the owners, so many owners decline treatment. The aim of this case study was to present successful treatment of 3 cats with different forms of FIP (wet and neurological).

Materials and methods

This study includes 3 cats, patients from VetCare veterinary medical centre in Dubai. Clinical examination was performed at the clinic, as well as follow up during treatment. The haematology analyses were performed on Idexx ProCyte DX (IDEXX Laboratories, Inc., US), while biochemistry was performed on Catalyst Dx Chemistry analyzer (IDEXX Laboratories, Inc., US). Rivalta's test was performed on the evacuated effusions from two of the cats with wet form of FIP (Rivalta 1985). Rapid antibody immunochromatography antibody test Speed Trio FELV/FIV/Corona (Virbac Diagnostics, France) was used for confirmation of the suspected FIP diagnosis. In the presented cases, cats were treated with Remdesivir GS 441524 (30mg/ml), subcutaneously (SC) 6-10mg/kg/day for 12 weeks.

Results

First case was a 7-month-old, 2.2 kg Scottish fold queen cat Lilly. She presented with sudden loss of coordination and rear limb balance (ataxia), reluctance to jump up or down from high. Incoordination is mostly noticeable at the rear legs. From the anamnestic data there was no history of trauma. The appetite was normal. On clinical examination vital signs were in referent ranges, there was loss of proprioception on both rear legs, preserved pain reflex and spinal reflexes. X-ray and ultrasound imaging were with normal finding. Serum Biochemistry results (Table 2) didn't reveal significant changes. Since she was not vaccinated, rapid immunochromatography antibody tests were performed, revealing positive for FCoV. Treatment protocol with Remdesivir 10mg/kg/day (0.7ml total) SC, 12 weeks was initiated. In the first week of treatment the cat was hospitalized and under observation. Since there were no side effects and clinical improvement of the patient was evident, the cat was released to continue the rest of the treatment at home (owner was previously instructed and trained to administer the drug under the skin). Due to financial issues, laboratory analyses were performed only at the end of the treatment (Table 1 and 2).

The second case is a 5-year-old Turkish van, 6.6 kg, tom cat named Namyra, presented in the clinic due to loss of appetite and lethargy. On clinical examination, mildly elevated body temperature was found (39.5°C) and a distended abdomen; ultrasound examination confirmed free fluid. Laboratory analyses revealed lymphopenia, thrombocytopenia, and hyperglobulinemia, with albumin/globulin ratio 0.4, indicative for FIP. Abdominocentesis was performed and Rivalta's test was positive, indicating FIP. The rapid antibody test was positive for FCoV. The cat was diagnosed with wet form of FIP and treatment with Remdesivir 6mg/kg/day for 12 weeks was initiated. The application of the medicine was performed every day at the clinic. Regular CBC, serum biochemistry and abdominal ultrasound were made during treatment (day 0, 46th and end of treatment day 84) (Table 1 and 2). There was evident clinical and laboratory results improvement after one week of initiation of treatment, and there were no side effects of the therapy.

Third case was 7-month-old Scottish fold tom cat, named Tommy presented at the clinic due to lack of appetite and abdominal distension. Clinical examination revealed fever and free abdominal fluid, positive on Rivalta's test. Rapid antibody test showed positive result for FCoV. Laboratory analyses revealed lymphocytopenia and eosinopenia, with low urea and creatinine levels, mild glycaemia and hypoalbuminemia, with albumin/globulin ratio 0.4. Therapy with Remdesivir was accepted by the owner and initiated at dosage 6mg/kg/day SC for 12 weeks. There was improvement of clinical condition in a week after initiation of treatment, while on the laboratory analyzes performed on day 64, the protein status was normalizing, as well as the lymphopenia and eosinopenia.

Table 1: Hematology results from the cats during treatment

Parameter Reference range/unit	Lilly[1]	Lilly[3]	Namira[1]	Namira[2]	Namira[3]	Tommy[1]	Tommy[2]	Tommy[3]
Red blood cells (6.8-10.5 M/μL)	-	12.08	8.17	7.84	8.48	10.82	12.38	13.44
Hematocrit (33.6-47.4 %)	-	49.6	31.5	30.1	32	34.8	47.4	50.9
Hemoglobin (10.5-14.6 g/dl)	-	16.1	11	10.2	10.6	12.5	16.2	16.8
White blood cells (5-15 K/μL)	-	5.8	11.81	8.2	9.38	11.12	7.02	8.15
Neutrophils (2.3-13.4 K/μL)	-	1.08	10.38	4.59	5.33	8.9	3.97	3.79
Lymphocytes (2-7.2 K/μL)	-	4.15	0.96	2.8	3.19	1.98	2.08	3.47
Monocytes (0-1 K/μL)	-	0.14	0.44	0.25	0.18	0.16	0.22	0.13
Eosinophils (0.3-1.7 K/μL)	-	0.38	0.02	0.51	0.63	0.01	0.55	0.62
Platelets (250-600 K/μL)	-	286	182	289	258	497	437	441

[1]beginning of treatment, [2]middle of treatment, [3]end of treatment.

Table 2: Serum biochemistry results from the cats during treatment

Parameter Reference range/unit	Lilly[1]	Lilly[3]	Namira[1]	Namira[2]	Namira[3]	Tommy[1]	Tommy[2]	Tommy[3]
Total protein (5.7-8.9 g/dL)	7.7	7.7	8.9	7.9	7.9	6.5	7.4	7.8
Albumin (2.2-4 g/dl)	3.4	3.4	2.6	2.8	2.8	**2**	3.2	3.2
Globulin 2.8-5.1 g/dl)	4.3	4.3	**6.3**	5.1	**5.2**	4.5	4.2	4.6
Albumin/Globulin	0.8	0.8	**0.4**	0.6	0.5	**0.4**	0.8	0.7
Urea (16-36 mg/dl)	**15**	26	16	22	24	**14**	24	28
Creatinine (0.8-2.4 mg/dl)	**0.5**	1	0.9	0.8	1	**0.6**	**0.6**	0.8
Alanine aminotransferase (12-130 U/l)	97	47	128	113	55	30	62	38
Alkaline phosphatase (14-111 U/l)	26	53	49	56	40	<10	67	46
Glucose (74-159 mg/dL)	156	102	110	93	90	165	101	95

1beginning of treatment, 2middle of treatment, 3end of treatment.
In bold are the parameters that were not in reference ranges.

At the end of treatment haematology and serum biochemistry were in reference ranges, with mild increase in red blood cells parameters (Table 1).

All cats to date are alive and healthy, occasionally visiting the clinic for regular check-ups.

Discussion

Feline infective peritonitis can be serious and fatal immune mediated disease, caused by oronasal infection with coronavirus (FCoV). Only 5% of infected cats develop disease. (Addie *et al.* 1995). There are challenges in definitive diagnosis. In this article, diagnosis was made using the available tests for every day clinical practitioners. The main consistent laboratory finding in cats with FIP is changes in serum protein status, mainly with increased globulin and decrease of albumin to globulin ratio (Rohrer *et al.* 1994). Two of our patients (with wet form of FIP) had hyperglobulinemia and decreased albumin to globulin ratio. Hematology findings in both of the patients with wet form were lymphopenia, while thrombocytopenia was present in one of the patients. Often lymphopenia and neutrophilia are stated as typical for FIP, but this changes can also be interpreted as a typical ‘‘stress leukogram’’that occurs in many systemic diseases in cats (Hartmann *et al.* 2003).

Regarding clinical findings, one of the patient was with neurologic signs and without protein status changes indicative for FIP infection. The other two cats were with wet form of FIP, decrease

in globulin/albumin ratio and positive Rivalta's test. Many cats with FIP have effusions (thoracic, abdominal or both), while smaller percent can develop the other forms (Kline *et al.* 1994).

Regarding therapy and prognosis of this disease in the past, only symptomatic treatment was prescribed with poor prognosis, while nowadays, there are many studies presenting results about off-label of commercially available formulations like Remdesivir or GS-441524. Remdesivir (GS-5734) is a prodrug of GS- 441524. Knowledge in several species including mice, rhesus monkeys, and humans suggests remdesivir undergoes rapid metabolic conversion *in vivo*, with GS-441524 the major circulating metabolite (Li *et al.* 2021, Warren *et al.* 2016). All of the patients in this study, were treated with Remdesivir with different dosage, depending of the form and previous experience in available literature. (Coggins *et al.* 2023, Krentz *et al.* 2021). The prescribed treatment was well tolerated by these cats, and the positive reaction was evident within one week of initiation of treatment, with evidence of improvement of clinical examination findings disappearance of neurologic signs, absence of effusions in abdomen, improvement of body weight) as well as laboratory results (improvement of serum protein status, improvement of hematology abnormalities). Our findings are in correlation with the study by Jones *et al.* 2021 and Coggins *et al*.2023, reporting good response of treatment.

Conclusion

With this case study we present our positive experience with Remdesivir and it is our opinion that it can be used in all cats with FIP regardless the form of the disease. This study should be continued on larger group of patients in order to gain statistical data analyzes that will confirm the efficacy of the treatment.

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