ESCOLA UNIVERSITÁRIA VASCO DA GAMA

MESTRADO INTEGRADO EM MEDICINA VETERINÁRIA

Feline Infectious Peritonitis Dry Form- case report

Nathan Delarre

Coimbra, Junho 2023

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Aluno do Mestrado integrado em Medicina Veterinária

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British Veterinary Center

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Abbreviations

FIP: feline infectious peritonitis

FCoV: feline coronavirus

RNA: ribonucleic acid

FECV: feline enteric coronavirus

FIPV: feline infectious peritonitis virus

CBC: complete blood count

Alb: albumin

Glob: globulin

PO: *peros*

BID: twice dose in a day

BAR: bright, alert and responsive

SC: subcutaneous

SID: single dose in a day

UK: United Kingdom

CMI: cell-mediated response

AGP1: alpha-1-acid glycoprotein

SAA: serum amyloid A

CSF: cerebrospinal fluid

NTP: triphosphate metabolite

S-gene: spike protein gene

WBC: white blood cell

PCV: packed cell volume

PCR: polymerase chain reaction

ELISA: enzyme-linked immunosorbent assay

RT-PCR: reverse transcriptase polymerase chain reaction

CRFK : crandell rees feline kidney

Feline Infectious Peritonitis Dry Form- case report

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Abstract

A 4-year-old male neutered Turkish Angora cat was presented for a second opinion of a suspicious feline infectious peritonitis (FIP) without evident clinical signs. After few months with non-specific clinical signs, an abdominal ultrasonography revealed mesenteric ileo-caecal lymph adenomegaly and liver masses. Histopathology of ileo-caecal lymph nodes and liver biopsies was suggestive of FIP. The animal was treated with GS- 441524.After the 12 weeks of GS-441524 administration, there was a resolution of the clinical signs and a normalization of all the altered blood analysis. This report describes a successful treatment with GS-441524 in a cat with the dry form of FIP.

Key words: Feline infectious peritonitis, coronavirus, GS-441524, lymphadenopathy.

Resumo

Um gato macho castrado de 4 anos de idade da raça Turkish Angora foi apresentado para uma consulta de segunda opinião de uma suspeita de peritonite infeciosa felina (FIP) sem sinais clínicos evidentes. Após alguns meses com sinais clínicos inespecíficos, uma ecografia abdominal revelou linfadenomegalia mesentérica ileocecal e massas hepáticas. A histopatologia de biópsias de linfonodos ileocecais e de fígado foi sugestivas de FIP. O animal foi tratado com GS-441524. Apos o período de tratamento de 12 semanas com GS-441524, observou-se a resolução dos sinais clínicas e normalização de todos os valores laboratoriais alterados. Este relatório descreve um caso clínico de um gato com FIP na forma seca que foi tratado com sucesso com GS-441524

Palavra chave: Peritonite infeciosa felina, coronavírus, GS-441524, lymphadenopathy.

Introduction

The family Coronaviridae includes four genera based on genotypic and serological characterization: Alpha, Beta, Gamma, and Delta. The feline coronavirus FCoV is an alphacoronavirus (Tekes & Thiel, 2016). FCoV is a fragile virus and is sensitive to the environment conditions and has both a high frequency of recombination and inherently high mutation rates Felten, S., & Hartmann, K. (2019). There are considered two pathotypes of the virus, feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV), which can cause different diseases in cats. Feline Infectious Peritonitis (FIP) is an ubiquitous disease found throughout the world, which was discovered in 1963 by Dr. Jean Holzworth (Thayer V and Gogolski S, 2022). Its prevalence is directly linked to the density of cats present in the considered area (Sherding R, 2006). The virus has a faecal-oral method of transmission, and its replication occurs in the columnar epithelial cells of small intestine Felten, S., & Hartmann, K. (2019). The mutation of FECV to FIPV is responsible for an alteration in the virus tropism, is random and it is possible that some cats are genetically predisposed to developing FIP after FCoV infection. The mutation allows the virus' replication in the lymphoid tissues and macrophages. The pathogenesis of FIP is based on the leukocytes infection (macrophage) (Pedersen,2009; Sherding, 2006b). The change between an avirulent FECV to a pathogenic FIPV is generated by the mutation of the S protein that acts at the level of cell entry (Rottier et al., 2005). The gold standard diagnosis of FIP is the detection of FCOV antigen in macrophages by immunostaining (Felten & Hartmann, 2019).

Previously the treatment was not efficient and was based on the combination of immunomodulating agents (enhancing and/or reducing the immune response) and antivirals (Izes et al., 2020b). However, the discovery of the GS-441524 molecule has made possible to cure FIP; and nowadays FIP can be considered as a treatable disease if diagnosed early (Izes et al., 2020).

Case description

This case report describes a 4-year-old male neutered Turkish Angora white cat diagnosed with the dry form of FIP, that was successfully treated with the new compound GS-441524. The cat was previously seen for a first opinion consultation at another practice due to acute vomiting and diarrhea in the last 2-3 days. The cat was previously a stray cat adopted recently, so his clinical history was unknown. Clinical information retrieved from the previous clinic was also scarce.

At the first veterinary clinic, the cat was diagnosed with FIP based on a positive coronavirus test and an increase in serum globulins. Amoxicillin, a liver protector and furosemide were prescribed to treat a suspected ascites. No abdominal ultrasound was performed.

First consultation day (June 13th,2022)

During the consultation, the cat showed a normal behaviour and was, bright, alert and responsive (BAR), without vomiting or diarrhea. On abdominal palpation the kidneys felt prominent. No alterations were detected in other parameters of physical examination. An abdominal ultrasound was performed evaluate the kidneys and presence / absence of ascites. A complete blood count (CBC) and serum biochemistry were also performed (figure 1).

	Value	Reference interval			Value	Reference interval	
RBC (x10^2/L)	11,57	6,54-12,20		GLU (mmol/L)	13,37	4,11-8,84	HIGH
HTC (%)	38,2	30,3-52,3		SDMA (ug/dL)	10	0-14	
HGB (g/dL)	12,9	9,8-16,2		CREA (umol/L)	59	71-212	LOW
MCV (fL)	33	35,9-53,1	LOW	UREA (mmol/L	6,4	5,7-12,9	
MCH (pg)	11,1	11,8-17,3	LOW	PHOS (mmol/L	1,19	1,00-2,42	
MCHC (g/dL)	33,8	28,1-35,8		CA (mmol/L)	2,48	1,95-2,83	
RDW (%)	38,2	15,0-27,0	HIGH	TP (g/L)	96	57-89	HIGH
RETIC (K/uL)	5,8	3,0-50,0		ALB (g/L)	25	22-40	
WBC (x10^9/L)	14,06	2,87-17,02		GLOB (g/L)	70	28-51	HIGH
NEU (x10^9/L)	10,88	2,30-10,29	HIGH	ALB/GLOB	0,4		
LYM (x10^9/L)	2,29	0,92-6,88		ALT (U/L)	26	12-130	
MONO (x10^9/L)	0,72	0,05-0,67	HIGH	ALKP (U/L)	15	14-111	
EOS (x10^9/L)	0,14	0,17-1,57	LOW	GGT (U/L)	0	0-4	
BASO (x10^9/L)	0,03	0,01-0,26		TBIL (umol/L)	6	0-15	
PLT (K/uL)	288	151-600		CHOL (mmol/L	2,92	1,68-5,81	
MPV (fL)	15,6	11,4-21,6		Na (mmol/L)	157	150-165	
PCT (%)	0,45	0,17-0,86		K (mmol/L)	4,3	3,5-5,8	
				Na/K	36		
				Cl (mmol/L)	119	129	

Figure 1: Blood analysis day 1 (Source: British Veterinary Center)

The results of the blood tests were interpreted as follows:

- ✓ Stress-related hyperglycemia
- ✓ Elevated globulin and albumin within the normal limits, Ratio Alb/Glob 0.4
- ✓ Stress leucogram

On abdominal ultrasound (figures 2 to 5), The liver and the kidneys were normal and lymphadenomegaly cranial and around the ileocecal junction was seen in a cluster of mesenteric lymph nodes.

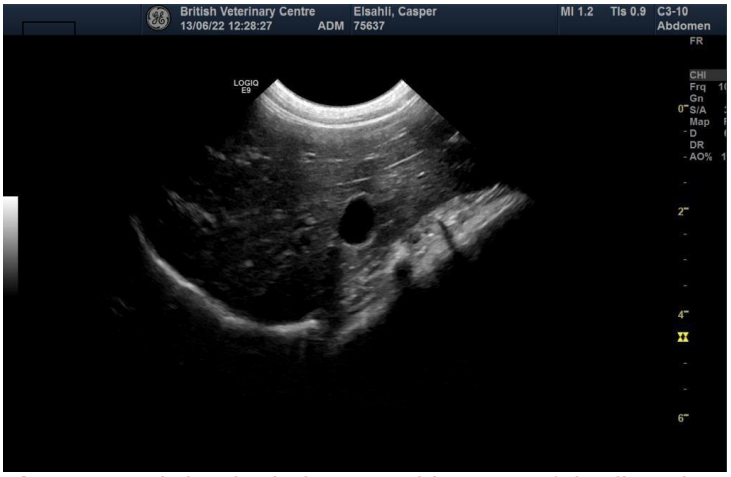
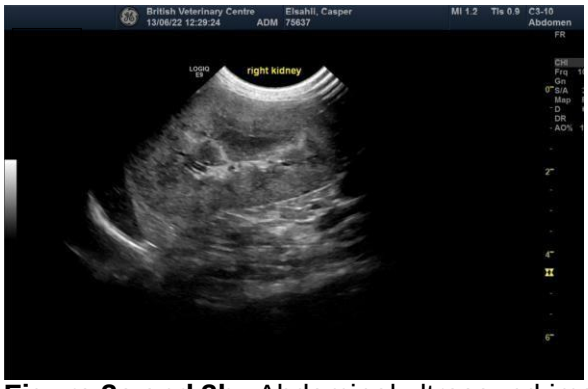


Figure 2 : Abdominal ultrasound images of the liver (Source: British Veterinary Center)



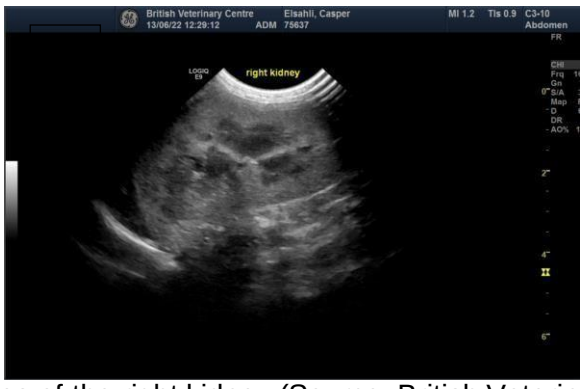
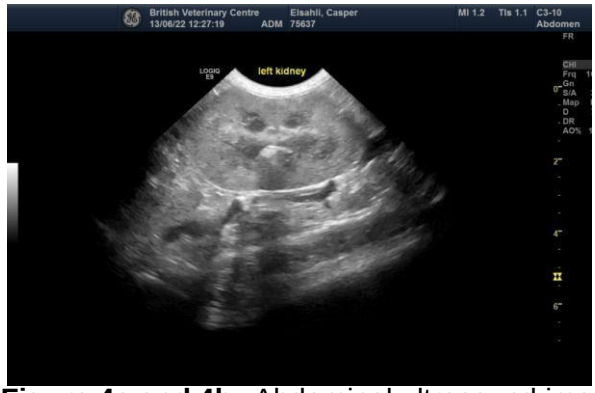


Figure 3a and 3b: Abdominal ultrasound images of the right kidney (Source: British Veterinary Center)



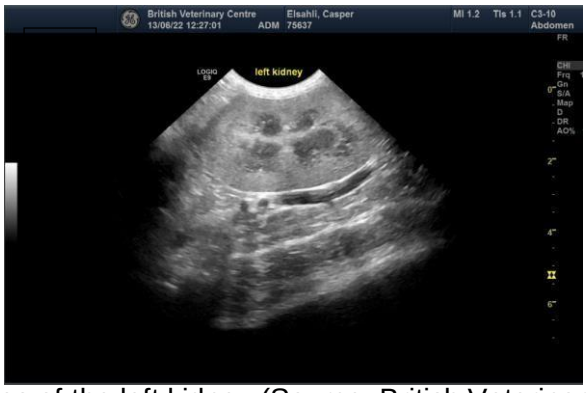
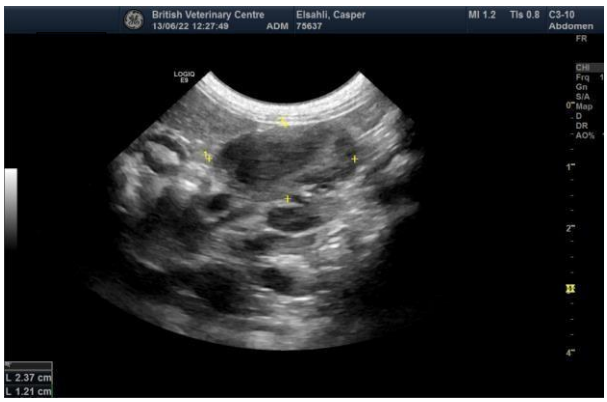


Figure 4a and 4b: Abdominal ultrasound images of the left kidney (Source: British Veterinary Center)



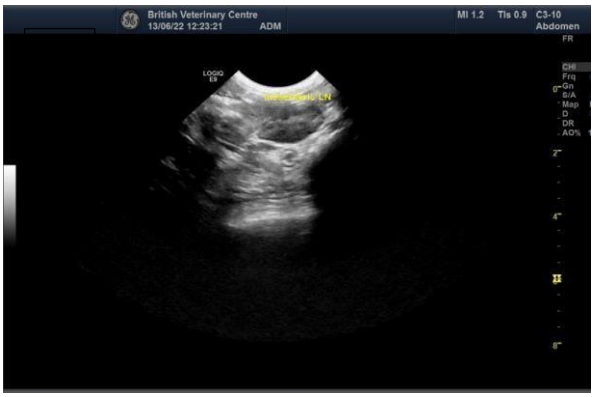


Figure 5a and 5b: Abdominal ultrasound images of the mesenteric lymph nodes (Source: British Veterinary Center)

Considering the clinical data available, lymphadenopathy due to inflammatory/infectious process, neoplasia (less likely as young cat, however still possible) and FIP were considered as the most probable differential diagnosis.

As previously stated, clinically the cat was stable, and treatment with prednisolone at 0.5 mg/kg PO BID during seven days and after half dose during the seven other days was prescribed, and an ultrasound of the lymph nodes was scheduled in two weeks.

Two weeks after the first visit, the cat was still bright, alert and responsive (BAR) and lost 200g weight (figure 6).. .A control abdominal ultrasound was performed (figures 6 to 7).

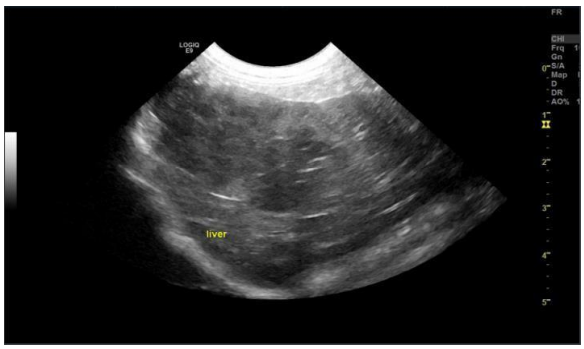


Figure 6: Abdominal ultrasound images of the liver (Source: British Veterinary Center)

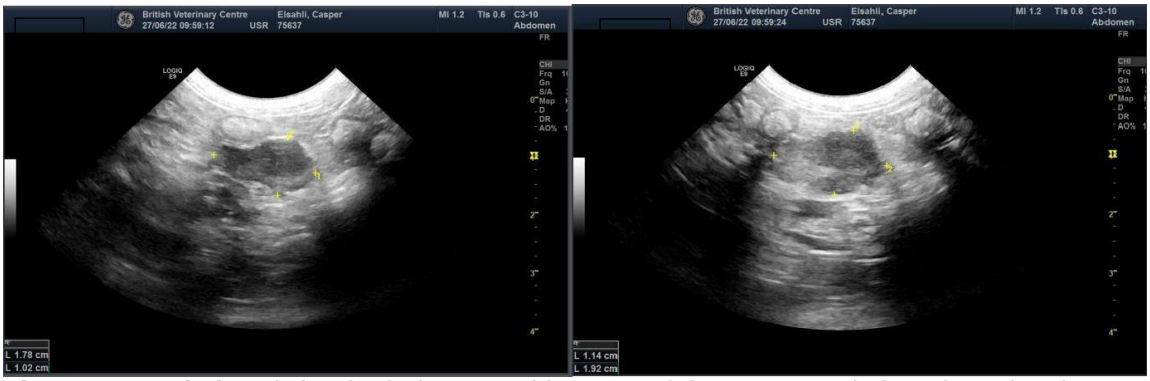


Figure 7a and 7b: Abdominal ultrasound images of the mesenteric lymph nodes (Source: British Veterinary Center)

The following changes were noticed: the ileocecal mesenteric lymph nodes were enlarged, and spherical nodules were visible on the surface of the liver. Based on these findings, the same treatment was prescribed as before, prednisolone at 0.5 mg/kg PO BID for 14 days and recommendedto come back for a control ultrasound after one month.

One month after the last visit, the third recheck was performed. The cat was BAR, active, playing and eating well.The rectal temperature was normal and during abdominal palpation nothing abnormal was found.

There was no vomiting or diarrhea. Weight loss of 200g was noted. Blood was sampled for analysis. The only alteration was a diminution of the PCV, at the limit of an anaemia.

	Value	Reference interval				Value	Reference interval
RBC (x10^2/L)	8,08	6,54-12,20			ALT (U/L)	26	12-130
HTC (%)	25,2	30,3-52,3	LOW		ALKP (U/L)	25	14-111
HGB (g/dL)	9,3	9,8-16,2	LOW		GGT (U/L)	0	0-4
MCV (fL)	31,2	35,9-53,1	LOW		TBIL (umol/L)	10	0-15
MCH (pg)	11,5	11,8-17,3	LOW				
MCHC (g/dL)	36,9	28,1-35,8	HIGH				
RDW (%)	32,5	15,0-27,0	HIGH				
RETIC (K/uL)	1,6	3,0-50,0	LOW				
WBC (x10^9/L)	8,68	2,87-17,02					
NEU (x10^9/L)	6,37	2,30-10,29					
LYM (x10^9/L)	1,61	0,92-6,88					
MONO (x10^9/L)	0,55	0,05-0,67					
EOS (x10^9/L)	0,12	0,17-1,57	LOW				
BASO (x10^9/L)	0,03	0,01-0,26					
PLT (K/uL)	245	151-600					
MPV (fL)	16,2	11,4-21,6					
PCT (%)	0,4	0,17-0,86					

Figure 8: Blood analysis day 44(Source: British Veterinary Center)

Abdominal ultrasound showed alterations similar to the ones observed at first abdominal ultrasound, namely moderate lymphadenopathy near the ileocecal junction and spherical nodules on the surface of the liver. The cat was not showing clinical signs and was fine from the owner'spoint of view.

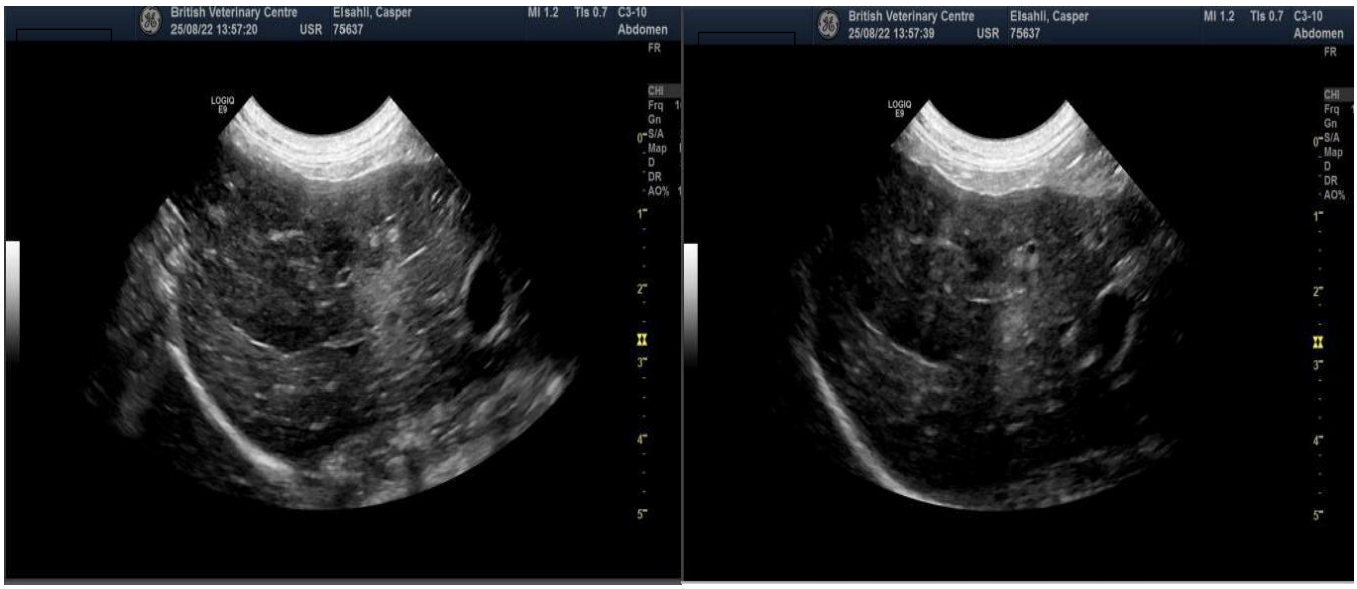


Figure 9a and 9b: Abdominal ultrasound images of the liver (Source: British Veterinary Center)

Following these observations, two options were proposed:

- ✓ Exploratory surgery was advised collection of biopsies of liver nodules and lymph nodes or,
- ✓ Monitoring of the animal's condition, with another abdominal ultrasound in a month.

The owners opted for monitoring the cat.

Five days later, the owners changed their opinion and decided to proceed with the exploratory surgery. At this time, the abdominal ultrasound showed no free fluid in the abdominal cavity, normal kidneys, spleen and pancreas. The mesenteric lymph nodes were still enlarged, even a little larger than when last observed. The cranial area of the liver presented a mottled pattern which was not previously observed.

Exploratory laparotomy for liver and ileocecal mesenteric lymph node biopsies was then performed. The liver was grossly abnormal with white nodular masses affecting a significant portion of the left midventral portion and adhesions to the omentum (possibly due to previous bleeding or inflammation). (Figures 10 -11)

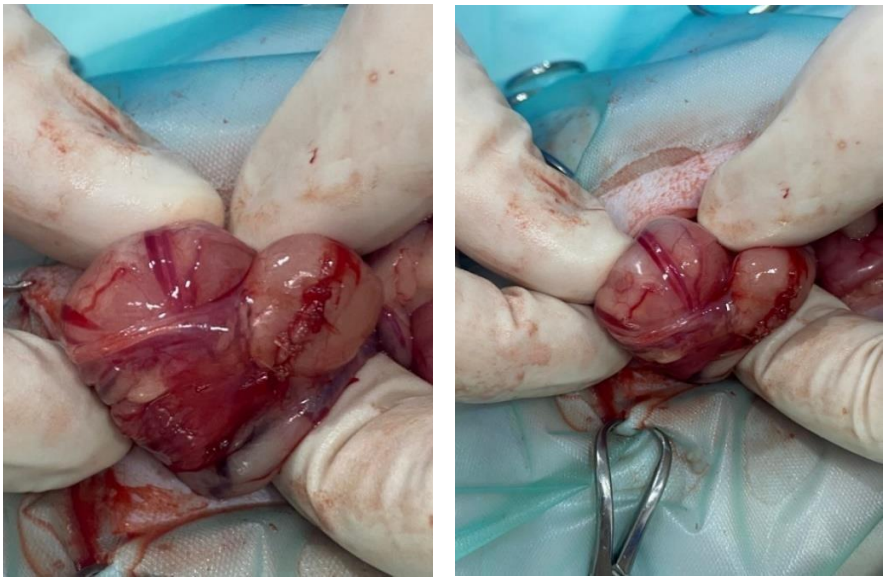


Figure 10a and 10b: Photo of mesenteric lymph nodes (Source: British Veterinary Center)

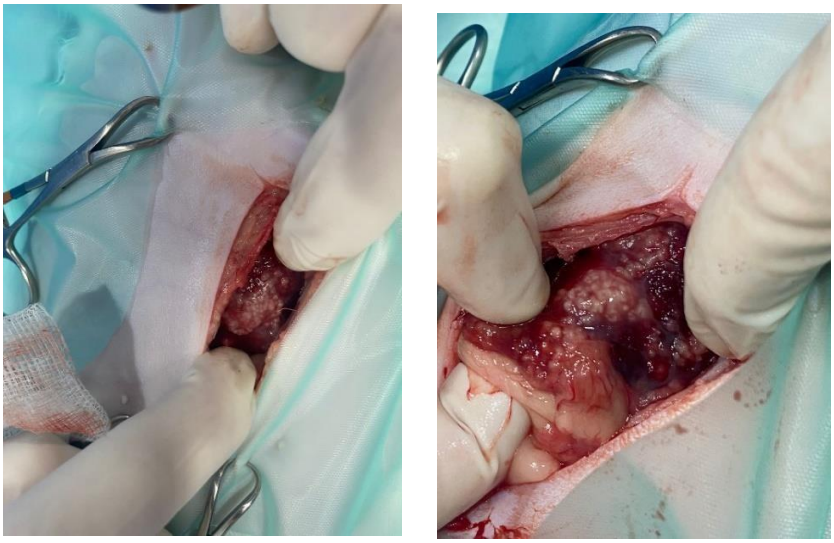


Figure 11a and 11b: Photo of pyogranulomatous nodules on the liver (Source: British Veterinary Center)

After the biopsies, ceftriaxone was administered IV at 25mg/kg, which was repeated 2 hours later, as prophylactic antibiosis. Subsequently, Cefovecine at 0.1 ml/kg SC and meloxicam at 0.2 mg/kg SC were administered for continuous antibiosis and post-operative pain relief, respectively. The cat went home on oral meloxicam at 0.05 mg/kg PO for 2 days. A post operative check was done 3 days later, and the biopsied materials were sent to IDEXX Laboratories in the UK for histopathology.

The histopathology results arrived 2 weeks later and revealed necrotizing pyogranulomatous hepatitis, but no pathogenic cause was found.
Therefore, an additional analysis was requested on the liver biopsy to confirm the presence of FIPV. A detection of FCoV antigen in macrophage by immunostaining was proceeded because it is a test with 100% of specificity and 97-100% sensitivity.
The result came on the same day and confirmed infection with FIPV.
Treatment with GS-441524 molecule was then prescribed (8 mg/Kg SID by SC injection for 84 days), which corresponded to 1ml of a commercially available GS-441524 preparation at 30mg/ml concentration. Following the first injection, the cat developed diarrhea, which was deemed to be a negative side-effect of the treatment, and as a precaution he was placed on a gastrointestinal prescription diet and probiotics for the following 4 weeks, and a recheck appointment scheduled in a month.

Four weeks later, the cat was doing very well at home, eating well with no vomiting or diarrhea. Gained approximately 700g bodyweight during this time. An abdominal ultrasound and a CBC were performed. (Figure 12 and figure 13 and 14)

	Value	Reference interval
RBC (x10^2/L)	8,42	6,54-12,20
HTC (%)	32,5	30,3-52,3
HGB (g/dL)	11,2	9,8-16,2
MCV (fL)	38,6	35,9-53,1
MCH (pg)	11,3	11,8-17,3
MCHC (g/dL)	34,5	28,1-35,8
RDW (%)	26,7	15,0-27,0
RETIC (K/uL)	25,3	3,0-50,0
WBC (x10^9/L)	7,94	2,87-17,02
NEU (x10^9/L)	2,61	2,30-10,29
LYM (x10^9/L)	4,52	0,92-6,88
MONO (x10^9/L)	0,24	0,05-0,67
EOS (x10^9/L)	0,48	0,17-1,57
BASO (x10^9/L)	0,09	0,01-0,26
PLT (K/uL)	270	151-600
MPV (fL)	15,5	11,4-21,6
PCT (%)	0,42	0,17-0,86

Figure 12 : Blood analysis day 91 (Source: British Veterinary Center)

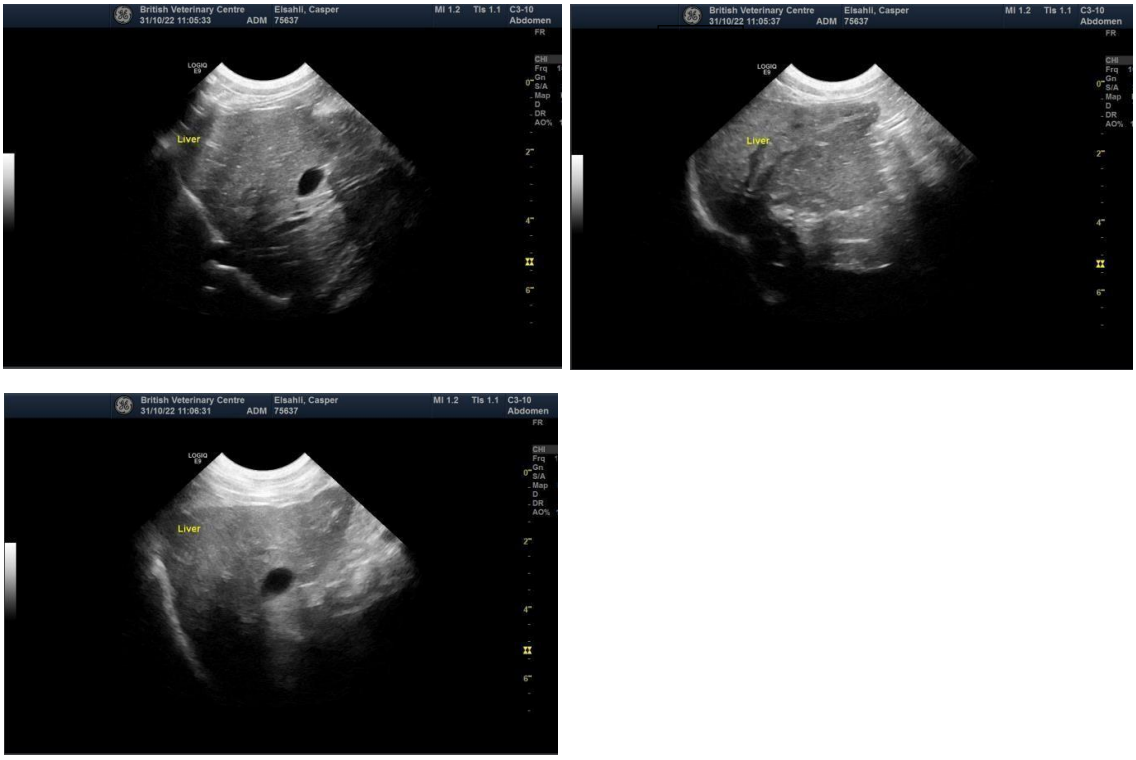


Figure 13a and 13b and 13c: Abdominal ultrasound images of the liver (Source: British Veterinary Center)

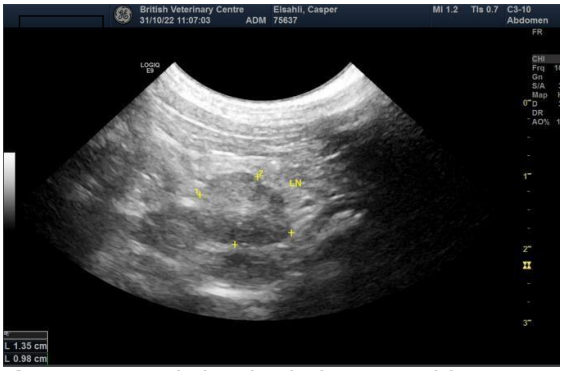


Figure 14 : Abdominal ultrasound images of the mesenteric lymph nodes (Source: British Veterinary Center)

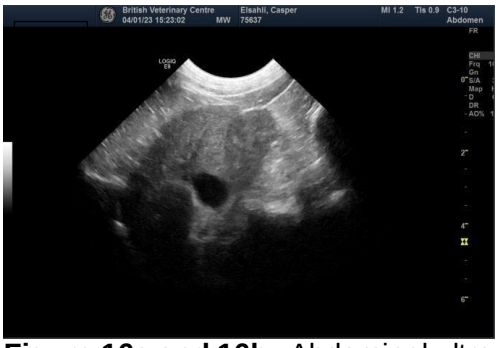
The abdominal ultrasound showed marked improvement in the liver, with minimal changes in echogenicity. The enlarged mesenteric lymphnodes were still visible but reduced in size significantly to approximately50%of their initial size. The CBC was normal at this point.

Overall the cat was doing very well, so it was decided to continue the GS-441524 therapy, but replacedthe daily injections for an oral formulation with capsule SID for cat with a weigh above 4kg.

Twelve weeks after 1st injection of GS therapy, the last recheck was completed. The animal showed no gastrointestinal signs. During the clinical examination, he was BAR, the mucous membranes were pink and moist, the oral cavity was normal, normal hydration status and rectal temperature of 38.6°C. Thoracic and abdominal auscultation were normal, and gained approximately 1.2Kg bodyweight during this time. An abdominal ultrasound and a CBC were performed. (Figure 15 to 17)

	Value	Reference interval				Value	Reference interval
RBC (x10^2/L)	11,32	6,54-12,20			GLU (mmol/L)	7,26	4,11-8,84
HTC (%)	38	30,3-52,3			SDMA (ug/dL)	13	0-14
HGB (g/dL)	13	9,8-16,2			CREA (umol/L)	98	71-212
MCV (fL)	33,6	35,9-53,1	LOW		UREA (mmol/L	9,9	5,7-12,9
MCH (pg)	11,5	11,8-17,3	LOW		PHOS (mmol/L	1,69	1,00-2,42
MCHC (g/dL)	34,2	28,1-35,8			CA (mmol/L)	2,35	1,95-2,83
RDW (%)	33,7	15,0-27,0	HIGH		TP (g/L)	79	57-89
RETIC (K/uL)	19,2	3,0-50,0			ALB (g/L)	27	22-40
WBC (x10^9/L)	6,59	2,87-17,02			GLOB (g/L)	52	28-51
NEU (x10^9/L)	1,95	2,30-10,29	LOW		ALB/GLOB	0,5	
LYM (x10^9/L)	3,84	0,92-6,88			ALT (U/L)	37	12-130
MONO (x10^9/L)	0,2	0,05-0,67			ALKP (U/L)	54	14-111
EOS (x10^9/L)	0,52	0,17-1,57			GGT (U/L)	0	0-4
BASO (x10^9/L)	0,08	0,01-0,26			TBIL (umol/L)	4	0-15
PLT (K/uL)	300	151-600			CHOL (mmol/L	3,61	1,68-5,81
MPV (fL)	17,3	11,4-21,6					
PCT (%)	0,52	0,17-0,86					

Figure 15: Blood analysis day 175 (Source: British Veterinary Center)



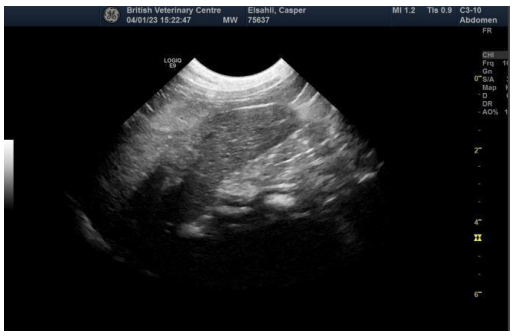
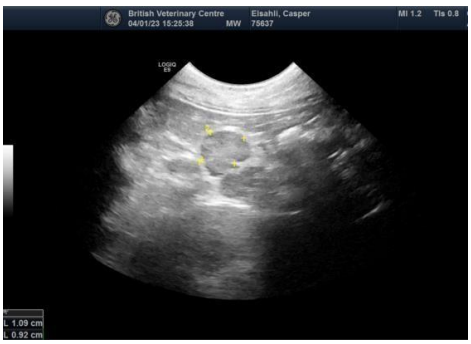


Figure 16a and 16b: Abdominal ultrasound images of the liver (Source: British Veterinary Center)



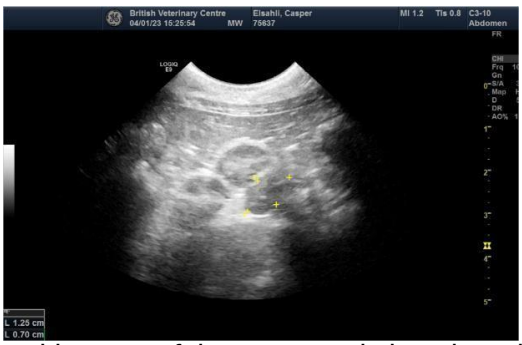


Figure 17a and 17b: Abdominal ultrasound images of the mesenteric lymph nodes (Source: British Veterinary Center)

The CBC was normal at this point. During the abdominal scan, no changes in liver were observed. The mesenteric lymphnodes were also normal.

Discussion

Feline Infectious Peritonitis (FIP) is a ubiquitous disease found throughout the world, which was discovered in 1963 by Dr. Jean Holzworth (Thayer V and Gogolski S, 2022). Its prevalence is directly linked to the density of cats present in the considered area (Sherding R, 2006). Feline infectious peritonitis virus is responsible for approximately 0.3% to 1.4% of feline mortality worldwide. The diagnosis of feline infectious peritonitis is complex, mainly the dry-FIP form, and the lethality was high, >95% (Sherding, 2006a), in all cases until recent years. FIP can be seen in two forms, “wet” and “dry” despond of which immune’s response appears.

The Cell-mediated immune (CMI) response to FIPV is the main characteristic that will indicate which forms of the disease the cat will develop. If the cellular immune response is weak, a type 3 immune complex response will develop, and a “wet” FIP will appear. It is due to the deposition of immune complexes in the walls of blood vessels and the subsequent activation of complement and other inflammatory mediators. This process leads to the exudation of fibrin-rich fluid into the body cavities causing fibrinous-granulomatous serositis (Tekes & Thiel, 2016). If there is a mild cellular response, the immune response is of type4 delayed response, and a “dry” FIP will occur. It is also known as granulomatous or non-effusive FIP. It is characterized by the formation of granulomatous lesions (composed by macrophages, lymphocytes and plasma cells surrounded by areas of necrosis and fibrosis) in organs like kidneys or liver (Haake et al., 2020; Pedersen, 2014b; Tekes & Thiel, 2016).

Table12: Table of clinical signs of FIP (adapted of Thayer V and Gogolski S, 202

System	Clinical signs
Non-specific	Lethargy, anorexia, weight loss, fever, jaundice, lymphadenopathy, pale mucous membranes
Abdominal	Abdominal distension, ascites, abdominal masses, diarrhea,lymphadenomegalia
Cardiac	Cardiac tamponade, heart failure
Neurological	Seizures, abnormal behavior, ataxia, anisocoria,tetra- or paraparesis,hyperesthesia
Respiratory	Dyspnea,tachypnea
Ocular	Anterior +/- posterior uveitis, blindness,hyphema,retinal vasculites, retinal detachment,hypopyon
Dermatological	Toxic epidermal necrolysis,intradermal papules,signs of vasculitis.
Reproductive	Scrotal enlargement,priapism

Definitive diagnosis of FIP is challenging since most existing diagnostic tests cannot differentiate between FECV and FIPV. It is based on a combination of characteristic signalment, history and laboratory test results (Lv et al., 2022).

There are several diagnostic methods for FIP, including:

1. Clinical signs and history: the clinical history and clinical signs might be suspicious of FIP (table 2)
2. Blood tests: Several blood test parameters can be helpful in the diagnosis of FIP, including:
    a. *Protein*: FIP typically causes an increase in total serum protein, particularly alpha-2 globulins and also a decreased in albumin levels. An albumin to globulin ratio (Alb/Glob ratio) <0.4is highly suggestive of FIP (Thayer V and Gogolski S, 2022).
    b. *White blood cell count*: FIP can cause leukopenia or leukocytosis, depending on the stage of the disease and the type of FIP (Pedersen et al., 2019).
    c. *Platelet count*: FIP can cause thrombocytopenia, which can lead to hemostatic disorders.
    d. *Acute phase proteins* (APP): increases in APP such as alpha-1-acid glycoprotein (AGP1), serum amyloid A (SAA) or haptoglobulin. Cats with FIP often have elevated serum levels of AGP1. However, elevated levels of AGP1 can also be due to inflammatory processes of different etiology in cats.
3. Effusion*:* If fluid has accumulated in the cats` abdomen or chest, or even the cerebrospinal fluid (CSF) or aqueous humour. The effusion is viscous, straw-coloured, clear to moderately cloudy, with elevated concentration of proteins, low Alb/Glob ratio (<0.4) and low total cell count. ARivalta's test can also be performed and has a good sensitivity (91-100%) (Fischer et al., 2012).
4. Detection of anti FCoV antibodies: it can be evaluated on blood samples, cavitary effusions and CSF. It is not accurate on serum due to the impossibility of the tests to differentiate between antibodies against FECV and FIPV. These antibodies can also be present in cats that have been exposed to the virus but have not developed the disease. It has a good sensitivity and specificity on effusion (86% and 85%).
5. Detection of immune complexes: It is not used (Felten & Hartmann, 2019).
6. Detection of FCoV antigen in macrophages by immunostaining; performed on tissue samples (sensitivity 97-100% and specificity 100%) and effusion. This is the gold standard for the diagnosis of FIP (Felten & Hartmann, 2019).
7. Detection of FCoV by RT-PCR: although both FIPV and FCoV can replicate systemically a high virus concentration by RT-PCR is suggestive of FIP.

8. Detection of viral mutation in the spike-protein gene (S-gene): S-gene determines the tissue tropism and virulence of FCoV and since both of FIPV and FCOV can spread systemically they both have the S-gene mutation. (Ouyang et al., 2022).

FIP treatment is based on two pillars, immunomodulating agents and antiviral molecules (Pedersen, 2014). Immunomodulating agents are used to either enhance the immune response with different treatments like staphylococcal A protein or interferon (Feline-ω or Human-α), or to reduce the inflammatory responseagainst FIP using drugs like glucocorticoids, cytokine inhibitors or cyclosporine A (Sherding, 2006b). Both strategies are usually used combined even though they have opposite effects. Antivirals target the viral genoma used in the infection or replication (Pedersen, 2014a). Interferon, ubiquitin-proteasome inhibitors or chloroquine (used against Malaria disease) are used as antiviral drugs.
Until recent years, protocols of combined treatment with immunomodulating agents and antiviral molecules presented lack of efficiency (Izes et al., 2020b). However recently, the use of GS-441524showed high efficacy in FIP treatment in cats.

GS-441524 is the active molecule of the Remdesivir. This antiviral was initially created as a treatment for Ebola disease (Lamb, 2020). In 2014, Remdesivir was tested in animal models of Ebola virus infection and showed promising results. In subsequent years, clinical trials were conducted in humans with Ebola virus disease, and the drug showed some efficacy in reducing mortality rates. However, it was not approved for widespread use as a treatment for Ebola due to a lack of conclusive evidence and the emergence of other treatments (Lamb, 2020).

In March 2020, with COVID-19 pandemia, scientists began investigating the potential use of Remdesivir as a treatment for COVID-19. Studies showed that the drug had activity against the coronavirus that causes COVID-19 *in vitro* and in animal models (Wang et al., 2022).

In June-July 2020, Remdesivir was approved in several countries (Europe, Singapore, and Australia among others) to be used as a treatment for hospitalized patients with severe COVID-19. Since then, numerous clinical trials have been conducted to evaluate the efficacy and safety of Remdesivir in COVID-19patients (Lamb, 2020).

GS-441524 is a 1-cyano-substituted adenine C-nucleoside ribose analogue, a small molecule that exhibits potent antiviral activity. It requires intracellular phosphorylation via cellular kinases to a nucleoside monophosphate and subsequently to the active triphosphate metabolite (NTP). The active NTP analogue is a competitor of the natural NTP in the viral RNA synthesis, causing its premature stop (Murphy et al., 2018).

To evaluate the safety and efficacity of the molecule, different studies in veterinary medicine showed that:

-GS-441524 was not cytotoxic *in vitro* (tested in Crandell Rees feline kidney cells (CRFK) at high

concentration) (Lawson et al., 2019; Murphy et al., 2018);

-It inhibits cytopathic effect in CRFK cells as well as RNA expression in naturally infected peritoneal macrophage and in CRFK cells (Krentz et al., 2021);

-Effective intracellular levels of GS-441524 with low concentration were sustained for three days in CRFK cells; (Lawson et al., 2019)

-Effective blood levels of GS-441524 were sustained over 24 hours following an intravenous or subcutaneous injection dose of 5mg/kg; (Lawson et al., 2019)

-Concentration of GS-441524 in CSF and aqueous humour is 1/5 than plasma (Dickinson, Bannasch, Thomasy, Murthy, Vernau, Liepnieks, Montgomery, Knickelbein, Murphy, Pedersen, et al., 2020).

GS-441524 molecule appears to be very safe as no toxicity was observed after disease remission (12-30 weeks after treatment) (Pedersen et al., 2019). Moreover, using scientific data collected in the field to demonstrate the efficacity of the molecule, (Dickinson, Bannasch, Thomasy, Murthy, Vernau, Liepnieks, Montgomery, Knickelbein, Murphy, & Pedersen, 2020; Jones et al., 2021a; Krentz et al., 2021; Pedersenet al., 2019) the probability of a successful treatment in cats with FIP is very high. However, due to the recent use of the molecule in treatment of diseased cats, the possible adverse effects in the very long term are still not known(Cook et al., 2022).

For most of the clinical parameters with are typically altered in cats with FIP (table 2), a normalization is observed during the first three weeks of treatment. Depending on the type of FIP (wet, dry, ocular or neurological) and the age and weight of the animal, the drug dose can change but the duration of the therapy should be of 12 weeks. An important parameter to consider for the effectiveness of the treatment is the severity of the disease at the time of treatment. Reported cases that did not survive with GS – 441524 treatment were detected and treated in advanced stages of the disease. As a matter of fact, necropsies and biopsies were carried out and were negatives of FIPV, so the cause of death wasn't due to FIP. (Pedersen et al., 2019).

However, the studies show that some cases do not respond to treatment with GS – 441524.

There is a new molecule - molnupiravir described last year by Roy et al., 2022, which is being used in FIP clinical cases refractory to treatment with GS - 441524. This molecule showed great results against coronaviruses and FIP. The molnupiravir acts at the level of the mutation rate of the virus, increasing its rate to inactivate the virus. Roy showed the efficacity of this molecule on 30 FIP cats that did not respond to GS - 441524 treatment. Of these, 28 cats responded successfully to treatment with molnupiravir. The described treatment period is of 12 weeks, with a normalization of most of clinical parameters within the 3 first weeks of treatment(Roy et al., 2022).

This is good news for the treatment of FIP because on some difficult case, instead of increasing GS-441524 dose, we can combine the two molecules or use the molnupiravir as a secondary line treatment(Cook et al., 2022).

Considering the current legal framework of the GS-441524 molecule (illegal on most of the countries), or lack of one available for most European countries, several ethical questions arise when considering its use in veterinary medicine.

The Hippocratic Oath is an oath traditionally taken by doctors, dental surgeons, and midwives in the West before starting to practice. In its historical form, this oath has no legal value, doctors being subject to regularly updated national codes. In its modern forms, the taking of a medical oath has retained its symbolic value. The Bourgelat Oath is to veterinarians what the Hippocratic Oath is to doctors.

Feline infectious peritonitis was still a fatal disease (Sherding, 2006a) before the discovery in 2019 of an effective treatment using an “unlabelled molecule”GS-441524. An unlabelled medicine is a medicine for a purpose other than that for which it has been specifically designed and approved (Izes et al., 2020c).

According to the veterinary code of ethics, the veterinarian is obliged to treat and perfect his knowledge but must refuse to use fraudulent means or methods without scientific value.(Sergio et al., n.d.).

The question of ethics is very controversial here since on one side the molecule is available on the black market, but it is not yet accepted and its long-term effects are not yet known (so can be considered as

fraudulent), while on the other side many scientific articles demonstrate its apparent curative effect on the disease and the clinical safety (Cook et al., 2022).

Ultimately, beyond the efficacy of the treatment with the molecule GS-441524 which seems to be confirmed, the ethical question of its use remains pertinent because the molecule is still unlabelled its long-term effects are not known today.

Conclusion

The diagnosis of feline infectious peritonitis is complex, mainly the dry-FIP form, and the prognosis was poor in all cases until recent years. Recently, a new molecule has emerged for treatment of FIP, GS-441524, showing excellent results in the treatment of FIP reported by different studies. However, the results are still scarce and the long-term prognosis of the cats treated with GS-441524 is still unknown. For these reasons are necessary more studies to support the use of GS-441524 in the treatment of FIP. Moreover, this molecule is still not approved in most countries.

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