UNIVET – University of Veterinary Medicine of Budapest

Department and Clinic of Internal Medicine

Novel therapies in cats with FIP (Feline Infectious Peritonitis): literature review and retrospective study with GS441524.

Linnéa Garrido-Andersson

Supervisor: Dr.Zsuzsanna Vizi
Clinical Veterinarian – Head of Intensive Care Unit
Graduate of ECVIM – Specialist in Internal Medicine

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List of abbreviations

CCoVs	Canine Coronaviruses
EC50	Half Maximal Effective Concentration
FCoV	Feline Coronavirus
FECV	Feline Enteric Coronavirus
FIP	Feline Infectious Peritonitis
FIPV	Feline Infectious Peritonitis Virus
FISS	Feline Injection Site Sarcoma
GS	GS-441524
HCoV-229E	Human Coronavirus 229E
HCoV-NL63	Human Coronavirus NL63
HR1, HR2	Heptad Repeat Regions 1/2
IL-1β	Interleukin 1 beta
MIS-C	Multisystem Inflammatory Syndrome in Children
ORFs	Open Reading Frames
PEDV	Porcine Epidemic Diarrhea Virus
PIMs	Pulmonary Intravascular Macrophages
RT-PCR	Reverse Transcriptase – Polymerase Chain Reaction
RT-nPCR	Reverse Transcriptase – nested Polymerase Chain Reaction
RT-qPCR	Reverse Transcriptase - quantitative Polymerase Chain reaction
RNA	Ribonucleic Acid
TGEV	Porcine Transmissible Gastroenteritis Virus

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Introduction

The Feline Infectious Peritonitis Virus (FIPV) is a virus from the genera Alphacoronavirus, closely related to other well-known viruses such as Canine Coronaviruses (CCoVs), Porcine Transmissible Gastroenteritis virus (TGEV), Porcine Epidemic Diarrhea Virus (PEDV), Human coronavirus 229E (HCoV-229E) and Human coronavirus NL63 (HCoV-NL63).
It is a pathogenic mutation of the Feline Enteric Coronavirus (FECV) which causes a widespread infectious disease called Feline Infectious Peritonitis (FIP).
FECV is mostly shed in feces and the infection can happen orally, nasally or trans-placentally. Existing evidence suggests that FECV is very contagious and that the majority of the global cat population is infected by it.
Critically, when felines are exposed to stress stimuli, FECV is capable of mutating to a very aggressive viral strain, which is observed to lead to a 100% fatality rate, when only treated with supportive therapy.
The diagnosis of this disease is also very problematic, since to this day there are no diagnostic methods or tools capable of facilitating a direct diagnosis of FIP.

Currently, there are no licensed drugs available in the veterinary pharmaceutical market. Several protocols with different medicines have been set up throughout the years, however none of them have shown truly successful results, with the exception of one; a nucleoside analogue antiviral drug developed by Gilead Sciences® called GS-441524.
Over years of new studies around this treatment, the data collected started showing very hopeful and convincing results. For that reason, and despite no official FDA approval, due to Gilead's refusal to license this drug for veterinary use, a lot of owners decided to acquire this medicine, sometimes illegally, in order to attempt saving their pets.

The aim of this thesis is to supply veterinary professionals, the pharmaceutical industry and FIP cat owners with a synthesis of the previous scientific articles and research around GS-441524; as well as provide further data, based on a retrospective study conducted with the help of cat owners who have treated their pets with the antiviral molecule.

Literature review

I. Feline Infectious Peritonitis Virus

FIPV is a mutated form of the Feline Enteric Coronavirus. It is estimated that 20-60% of the domestic cat population are infected by FECV due to the ubiquitous presence of this virus in the environment [1].

FECV is a single-stranded RNA virus, which has 2 different serotypes. Serotype I seems to be more present in Europe and America, while Serotype II was mostly observed in Asia [1]. The feline coronavirus genome is expressed in over 29 000 nucleotides together with 11 open reading frames (ORFs). These are encoding for accessory genes, as well as structural and non-structural ones [2]. Coronaviruses are named after the Latin word "*corona*" meaning "crown", because they have crown-like spike proteins on their surface. The spike protein "S" is the complimentary ligand of specific cell receptors throughout the body. When this surface protein attaches to the cell membrane, fusion happens thanks to the separate fusion domain, in which a fusion peptide contains two heptad repeat regions (HR1 and HR2). After this process, the virus being incorporated into the cell, will release single positive strand RNA into the cytosol that will further undergo changes in order for the virus to be able to use the cell's own organelles for viral protein synthesis purpose [2]. Mature virions will then be released by exocytosis from the cell, in order to spread throughout the body.

The FECV infection can occur orally, nasally or trans-placentally, after having been shed by a carrier from its feces usually, but shedding can take place through other body fluids too like the saliva, urine and respiratory secretions [3].
The infection is asymptomatic, clinically not apparent with no antecedent. With this enteric infection having no immune memory, a chronic low exposure to the virus seems to be keeping the cat's immunity working. This explains why kittens infected with FECV from the mother might start developing clinical symptoms, once the maternal immunity is fading at 5-6 weeks of age.
Direct transmission of FIPV have also been described based on an outbreak that occurred in a Taiwanese shelter, as explored by *Wang et al.* In fact, it seems that a horizontal transmission of the mutated FIPV is possible, since the identical type II FIPV recombination

sites were found in all 8 succumbed cats, especially when considering that there was no history of FIP in the shelter, before this group of 5 kittens was introduced [4].

It appears that FECV strives in multi-cat households and shelters, with an estimated seropositivity rate of up to 90% [1]. Its tissue tropism is primarily the apical epithelium of the intestinal villi, starting from the lower part of the small intestines until the caecum, which might therefore provoke mildly severe enteritis [5]. Although it is mostly associated with mild gastrointestinal tract symptoms, it is shown that it is also able to spread throughout the body via macrophage- and monocyte-associated viraemia [6]. In the study from *Kipar et al*. about the sites of feline coronavirus persistence in healthy cats, viral FECV antigens were identified in the scattered pulmonary intravascular macrophages (PIMs) in case of non-viremic cats with high viral titer in the lungs. This is raising the question of whether infected PIMs could contribute to the development of granulomatous vasculitis seen frequently in the lungs of cats with FIP [6].

In case of RNA polymerases, catalyzing the transcription of RNA polymer from DNA templates, there is an existing estimated error rate of 1/10 000 nucleotides [2]. In the study from *Chang et al.,* the estimated error rate was 10% of the genome, based on the whole virus sequencing of 11 FIPV-FECV pairs [7]. To this day, 3 different genes have been found to be in connection with the mutation of FECV into FIPV [2]. The first gene found to be linked with this conversion is the ORF3c accessory gene [2, 8]. It appears that cells not expressing the ORF3c-coded protein could induce a facilitated viral replication in macrophages [9]. Secondly, the most observed mutation in the study from *Chang et al.* were single-nucleotide mutations in the S gene encoding the fusion peptide, which might be involved in macrophage tropism as well [7]. Lastly, mutations in the level of S1/S2 cleavage site were shown to occur in the early conversion of FECV into FIPV, allowing better replication of the virus in monocytes and macrophages [10].

Ultimately, further studies need to be completed in order to conclude if these are the only 3 gene mutations affecting the conversion from FECV to FIPV, as well as understanding how they impact the disease's development. So far, it is believed that these mutations induce FECV mutates to lose their enterocytes tropism whilst acquiring tropism for monocytes and macrophages specific to endothelium of vessels in the omentum, pleura, serosa, meninges, and uveal tract.

II. Clinical signs, symptoms, and diagnostic of Feline Infectious Peritonitis

FIP has a very high mortality rate, and even though first described in the 1950s, it was only properly named in 1966. [11]. It induces a protein-rich serous effusion in the cat's body cavities, vasculitis, granulomatous lesions such as pyogranulomas, as well as fibrinous and granulomatous serositis [1, 11]. The difficulty in diagnosing this disease lies in the fact that the observed lesions are very idiomatic in their location, distribution, cellular composition as well as viral antigen expression level [1]. In fact, the clinicopathological fluctuations seen in FIP cases, such as lymphopenia, neutrophilia, anemia, hyperproteinaemia and hypergammaglobulinaemia, are seen in many other conditions [12, 13].

The course of this pathology seems to be associated with the infected monocytes/macrophages' as well as the host's immune system's response to the viral infection. The cytokines called tumor necrosis factor-α and IL-1β, as well as adhesions molecules called CD11b and CD18; are expressed by circulating activated monocytes. The latter molecules are responsible for the facilitated interaction between these monocytes and the activated endothelial cells in small and medium sized veins [1, 14, 15, 16, 17, 18, 19]. Furthermore, matrix metalloproteinase-9, also produced in increased amount by activated monocytes, result in extravasation of monocytes through endothelial barrier dysfunction [1, 11, 20]. The vascular endothelial growth factor, produced by infected monocytes/macrophages, was shown to increase the vessel's permeability leading to effusions in body cavities [1, 21]. Additionally, leukocytes which seem to become activated during FIPV infection, could be involved in the endothelial cell damage leading to FIP lesions [1, 22]. Finally, antibodies seems to enhance the macrophages infectiveness of the virus [2, 23].

Cats affected by FIPV will experience unspecific symptoms and clinical signs, making a definite diagnosis hard to establish since these findings are common to several different pathologies. The following symptoms and clinical signs have been reported to be associated with FIP cases:

<table>
<tr><th colspan="2">Symptoms and clinical signs</th></tr>
<tr><td colspan="2">Chronic fluctuating fever of unknown origin

Hypothermia

Lack of appetite

Weight loss - Anorexia

Poor haircoat quality

Runny nose

Lethargy

Failure to thrive in young cats – Stunted growth

Depression

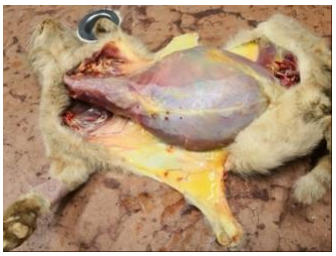
Pale or yellow mucous membranes

Dehydration

Polydipsia

Polyuria

Frequent sneezing</td></tr>
<tr><td>Constipation</td><td rowspan="3">If granulomas are present on the intestines.</td></tr>
<tr><td>Intestinal obstruction</td></tr>
<tr><td>Diarrhea</td></tr>
<tr><td>Vomiting</td><td rowspan="2">Most common finding in effusive FIP.

 
Figure 1 – Cat with effusive FIP form. Credits: Pathology Department of the University of Veterinary Medicine of Budapest</td></tr>
<tr><td>Abdominal distension/pot-bellied appearance with doughy feeling and painless when palpated

Ascites</td></tr>
<tr><td>Pericardial effusion</td><td>Uncommon.</td></tr>
</table>

Swollen chest cavity **Pleural effusion** **Palpable abdominal organ enlargement**	
Dyspnea – Open mouth breathing	Common in effusive FIP in case of pleural effusions.
Cyanotic mucous membranes **Muffled heart sounds** **Tachypnea** **Organ failure** (kidney, liver)	
Scrotal enlargement (due to extending peritonitis into the testes' tunics leading to edema)	In case of effusive FIP in intact males. Might lead to chronic fibrinous and necrotizing orchitis.
Hepatic lipidosis syndrome	[24]
Extreme fragility of the skin	
Jaundice **Cutaneous lesions**	
Non-puritic intradermal papules (over the neck and chest)	Observed in case of cat in terminal stage of non-effusive FIP progressing to the effusive form [25]
Pneumonia	In utero infection of FIPV by a wet-FIP positive queen to her kittens. The kittens developed these lesions [26]
Pleuritis	
Hepatitis	
Nephritis **Pericarditis**	
Synovitis (which might be found together with fever and lameness)	Due to the migration of the affected macrophages/monocytes into the synovial membrane or antibody-antigen immune complexes formation.
Pericarditis with cardiac tamponade (due to pericardial fluid accumulation)	[27]
Caeco-colic lymphadenopathy associated with signs of ulcerative colitis (soft bloody and mucinous stool)	A specific form of dry FIP.
Priapism	In case of dry FIP in castrated cats [28].
Syringomyelia	[29]
Myeloproliferative disorder	[30]

Vasculitis - Phlebitis **(Fibrinous) serositis** **Lymphoid necrosis** **Enlarged mesenteric lymph nodes**	
Ocular signs such as: - **Eye discharge** - **Blindness** - **Choroid lesion/plexitis with hydrocephalus** - **Cerebro-vestibular induced nystagmus** - **Uveitis** - **Chorioretinitis** - **Change in the iris' color** - **Swelling of iris** - **Focal lesions in the iris altering the pupil's shape.** - **Keratic precipitates in the caudal cornea/nictitating membrane** - **Aqueous flare** - **Cloudiness in the anterior chamber** - **Hemorrhage in the anterior chamber**	Most common in dry FIP
Neurological sign such as: - **Ataxia - Incoordination** - **Posterior paresis incoordination** - **Tetraparesis – Hemiparesis** - **Lameness** - **Hyperesthesia** - **Intention tremors** - **Seizures or convulsive disorders** - **Cranial nerve defects, leading to visual deficits and/or loss of menace reflex** - **Brachial/Trigeminal/Facial/Sciatic nerve palsy** - **Ependyma lesion/ependymitis with hydrocephalus** - **Dementia** - **Behavior change: aggressiveness, withdrawal, etc** - **Cerebro-vestibular induced head-tilt and/or circling** - **Encephalitis** - **Myelitis**	Most common in dry FIP

Figure 2 – Possible symptoms and clinical signs experienced during FIPV affection [1, 23, 12, 31, 32, 33].

FIP is very hard to diagnose ante-mortem non-invasively. There are mainly tools that allow to diagnose the presence of Feline Coronavirus (FCoV) antigen in macrophages and monocytes.

Tissue sampling for immunohistochemistry and histopathology seem to be the most efficient methods for diagnosing FIP [12, 34], but this method is much more invasive than other biopsy methods (c.f. fine needle aspiration, fine needle biopsy) which are less reliable FIP diagnostic-wise.

Detection of ongoing FCoV RNA (Ribonucleic Acid) secretion from the infected cats (via feces, tissues, body fluids) is possible through nested Reverse Transcriptase – Polymerase Chain Reaction (RT-nPCR) but is limiting the diagnosis of FIP since a majority of the cat population is healthy FCoV carrier-type. Although the use of this diagnostic tool is bound, it could be used as a screening method before introducing new cats into catteries and multi-cat households free of this virus, therefore preventing a potential hereafter mutation into FIPV [12].

Serology, widely used as a diagnostic tool, can be indicative of FIP if the immunofluorescence shows high titers (equal or above 400) [12, 35]. But since healthy cats are often healthy carriers of FCoV that develop high antibody titers against this virus, this method's results must be interpreted with caution [12, 13, 36, 37, 38, 39]. On the other hand, a seronegative result to FCoV antibody testing would rule out FIP with a predictive value of 97% [40, 41], allowing the focus on other differential diagnosis.

Gene susceptibility could also be used as a diagnostic tool in the future but is difficult to determine accurately.

A study from *Golovko et al.* demonstrated that Birman cats seem to be predisposed to developing FIP, after analyzing the DNA from a sample population of 199 Birman cats. Five regions on four different chromosomes, harboring genes involved in FIP predisposition, were found [42]. However, the extensiveness of this study can be questioned (Cf. Genetic lines more represented than others, 199 cats not representing the entire Birman cat population). Another extensive research by *Pesteanu-Somogyi et al.* suggested an increased risk of developing FIP in other purebred cats such as Abyssinians, Bengals, Himalayans, Ragdolls and Rexes. [43].

Further studies should be done on other breeds in which FIP seems to be recurrent to determine if a complex inheritance pattern is existing or not in certain cat breeds, or if this

FIP prevalence is more due to the confounding stress factors (Cf. catteries or multi-cat environment, breeding, regular welcoming of new kittens, weaning).

Two forms of FIP exist, both being interchangeable, each form having their commonly typical lesions and factors helping in the diagnosis of a specific form. The form acquired appears to be depending on the cellular-humoral immune response aberrant equilibrium.

A. Effusive or « Wet » form

According to *Dr.Pedersen*'s review from 2009 [2, 23], the effusive form appears to be more frequently seen than others, and usually develops during the terminal stage of a dry form.
The effusive form of FIP seems to result from a great intensity difference between T cell immunity and B cell response to the infection. In fact, the B cell immunity response was shown to be extreme, and the T cell one typically low [2, 23].
Typical lesions of this form involve pyogranulomas, containing accumulated macrophages, neutrophils, lymphocytes, and plasma cells. These inflammatory cells aggregate around the venules of the targeted tissues [2].
This form is accompanied by effusive protein-rich fluid in the abdominal and sometimes pleural cavities, hence its name [1]. The exudate fluid looks yellow-tinged, because of its bilirubin content, and cloudy with mucinous consistency. This effusive non parenchymatous form also includes an inflammation of the visceral serosa and omentum as well [23]. Ocular and CNS signs are not typically seen in this form. An estimation of 9% of cats with effusive FIP has been estimated to show these [23], making them more frequent in case of dry FIP form.
The incubation time of this form has been of 2-14 days in experimental conditions [23, 44, 45, 46, 47].
A study from *Longstaff et al.* from 2015 has shown that Reverse Transcriptase quantitative – Polymerase Chain reaction (RT-qPCR) could be used as a diagnostic tool in case of suspicion of effusive FIP. In fact, by using abdominal, pleural, or pericardial effusion samples, they reached a sensitivity of 85% to FIP in the cats confirmed FIP-affected, while no positive effusion samples were found in cats confirmed non-FIP infected [48]. However, with the sample size being limited to 20 confirmed FIP cases and 23 cases with other diseases, further studies needed be done to confirm the sensitivity and specificity of this diagnostic tool, including FCoV healthy carriers. In 2017, a study from *Felten et al*. on 63

cats with signs consistent with FIP, amongst which 38 were confirmed FIP cases and 25 were control-cats with a disease other than FIP, demonstrated a sensitivity of 68,6% with a confidence interval of 95% and a specificity of 95,8% to the disease when using effusion sample in RT-PCR [49].

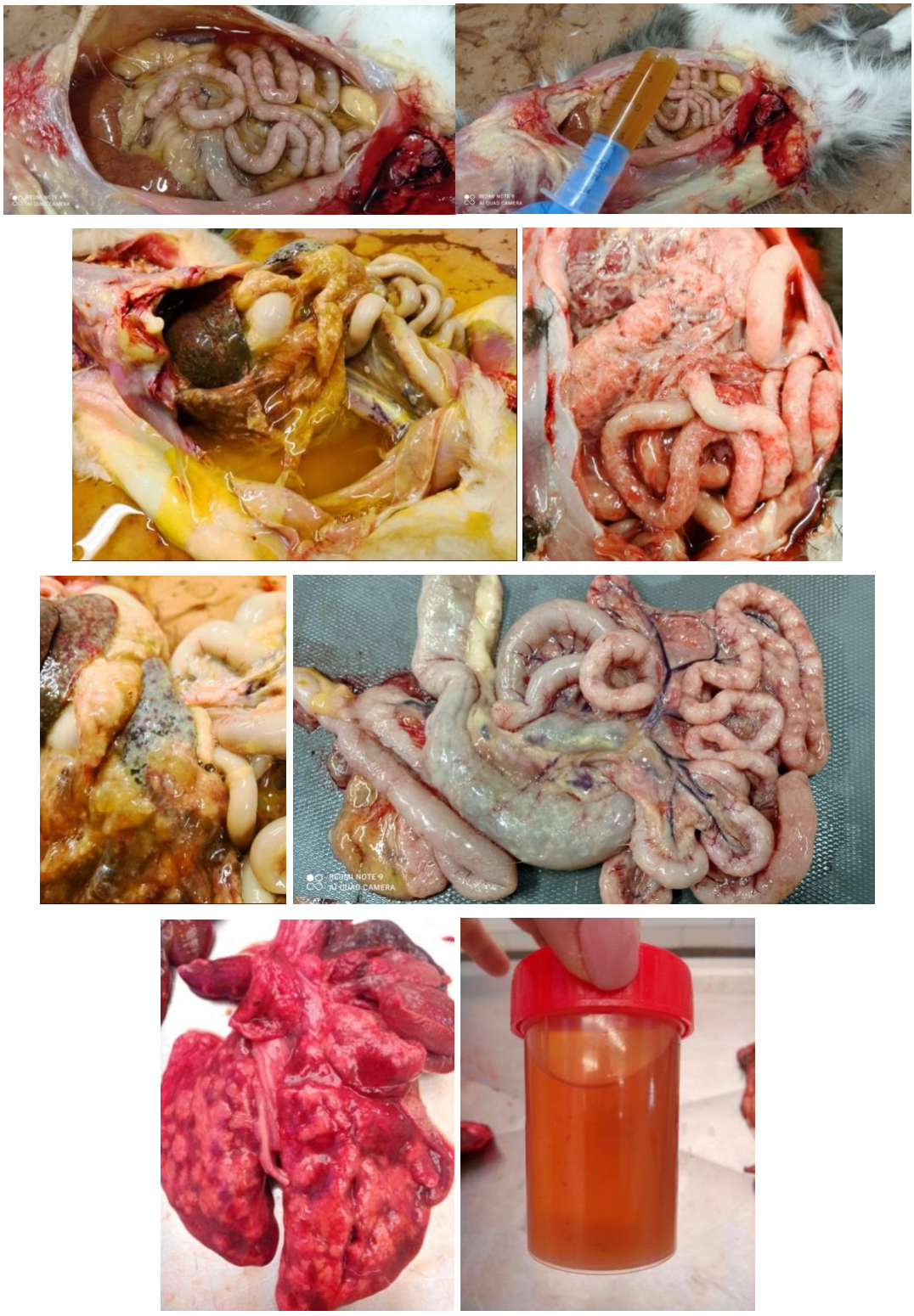


Figure 3-10 – Pathological findings in case of effusive FIP form.
Credits: Pathology Department of the University of Veterinary Medicine of Budapest

B. Parenchymatous or « Dry » form

The dry form of FIP appears to involve an intermediate cellular response, partially effective to keep the virus in small amount of macrophages, at a few focal sites [23].

This form is not accompanied by the typical protein-rich exudate seen in case of the wet form. Instead, typical lesions of this form involve granulomas in parenchymatous organs like the kidneys, mesenteric lymph nodes leading to their enlargement, bowel wall, liver, central nervous system and the eyes [23, 40, 41]. The granulomatous lesions are more often found in the kidneys and mesenteric lymph nodes than in the liver and hepatic lymph nodes. The central nervous system and the eyes are at 60% of the cases involved, while thoracic lesions are only seen in 10% of the cases and remain localized [23].

Birman and Burmese breeds are more commonly diagnosed with the dry/parenchymatous form of FIP than other breeds [34].

The incubation period of the dry form is estimated to several weeks [23].

The dry form of FIP has been proven to be more challenging to diagnose because of the incomplete information available about the FIP infection's pathogenesis [2]. Because of the lack of effusion and the few lesions, an explorative invasive laparotomy is usually needed in order to get biopsy samples for histopathology and immunohistochemistry [40].

A study from *Dunbar et al.* from 2018 has nevertheless demonstrated on a small cat population that Reverse Transcriptase quantitative – Polymerase Chain reaction (RT-qPCR) could be used to diagnose non-effusive form of FIP by using fine-needle aspirates from mesenteric lymph nodes. The results of this research led to an overall specificity of 96,1% and sensitivity of 90,0% to the disease, by associating the detection of FCoV in the mesenteric lymph nodes of a systemically ill cat to the diagnosis of FIP [40].

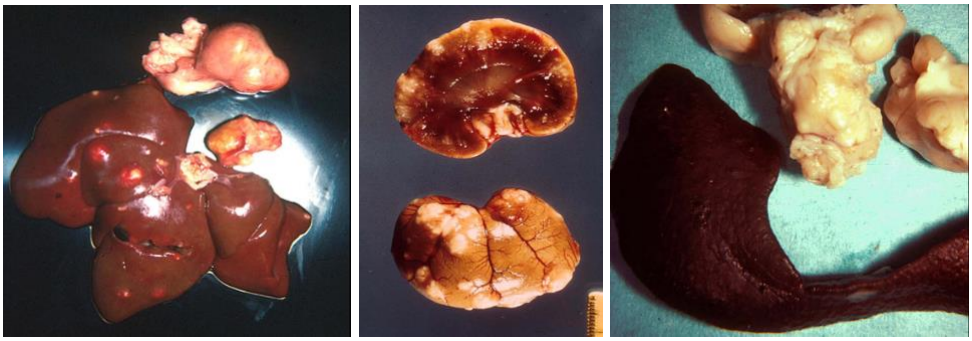


Figure 11 – Enlarged mesenteric and hepatic lymph nodes, granulomatous foci in the parenchyma of the liver, granulomatous lesions in the kidney and fibrinous capsules/plaques on the spleen of a cat with dry FIP. [23]

- Ocular form:

A supposition emitted in the study from *Dunbar et al.* (2018) poses the question on whether the previously mentioned RT-qPCR technique using mesenteric lymph nodes fine-needle aspirate could be used on aqueous humor samples in case of suspicion of FIP-associated uveitis [40].

Figure 12 – Right-eye uveitis in a cat with dry FIP [23].

- Neuropathic form:

The study from *Dunbar et al.* (2018) has shown that RT-qPCR with fine needle aspirates from mesenteric lymph nodes was limited to diagnose the neurological form of FIP, since the virus might not be present in the mesenteric lymph nodes but in the neural tissues [40]. Further studies should be done to determine whether this diagnostic tool could be used on cerebrospinal fluid samples, however this might be a challenging task. In fact, cerebrospinal fluid can be a relatively unspecific sample, since neuropathic FIP cats usually present ordinary results. This is due to the lower concentration of the virus in this body fluid [32].

III. The GS-441524 molecule and its administration forms

To this day, no legal cure has been found to fight the deadly condition that is FIP. Several immunosuppressive drugs, such as Cyclophosphamide and Glucocorticoids, have been prescribed when diagnosing FIP, but these were only delaying the unfortunate aftermath of the disease [23, 50].

Some cats are going into remission without treatment or with symptomatic therapy, but this could either be linked to a misdiagnosis or simply to an efficient natural immune response [23].

Vaccines have been thought of, and *Dr.Pedersen* supposed in 1989 that a live-attenuated vaccine would be ideal in order to develop a stable immunity to FIPV [51], but no successful vaccine was developed since this supposition [23].
In the past few years, the emergence of a small molecule, a 1'cyano-substituted adenine C-nucleoside ribose analog, has been shown to have repressive effects on the fatal disease that is FIP. This molecule is a molecular precursor of an active nucleoside triphosphate molecule that possesses antiviral effects and is called GS-441524 [52].

The GS-441524 molecule is activated by an intracellular phosphorylation, happening through the cellular kinases. A nucleoside monophosphate is then obtained, leading to an active triphosphate metabolite. The latest acts in the viral RNA synthesis by competing with the natural nucleoside triphosphate, causing premature termination of the RNA-polymerase-mediated transcription [57].

Two different administration forms exist; an injection (can be injected intravenously and/or subcutaneously depending on the product) and an oral tablet.

C. **Injection**

Injection of GS-441524 are the most well-known form of administration of that molecule.

In the research from *Dr. Pedersen et al.* from 2019 [53], 31 FIP-confirmed patients followed a protocol based on GS-441524 containing injection. The molecule's powder from Gilead Sciences was mixed in 10 or 15 mg/ml concentration together with 5% ethanol, 30% propylene glycol, 45% PEG 400, as well as 20% water at a pH of 1,5. The dosage administered was of 2,0mg/kg subcutaneously every 24h for 12 weeks (84 days). Amongst the 31 cats taking part in the trial, 4 were euthanized or simply died due to the severity of the disease from the start, and 1 was euthanized after 26 days of being unresponsive to the treatment. From the 26 remaining cats, 18 were cured with the primary uninterrupted treatment protocol. The final 8 cats experienced a relapse during the 84 days of treatment. When the relapse occurred for these patients, the dosage was increased to 4,0mg/kg. This upgraded dose worked efficiently in all 8 cats, except for 1 in which neurological relapse occurred and it needed to be euthanized. Ultimately, out of the 26 cats having completed the treatment, 25 were in sustained remission of FIP [53].

Unfortunately, this form of administration leads to side-effects such as pain and inflammation at the injection site in most cases, because of the acidic nature of the solution. According to the study from *Krentz et al.* of 2021, this side-effect could also be associated with Feline Injection Site Sarcoma (FISS) [54]. In fact, FISS is believed to emanate from fibroblasts and myofibroblasts in areas of chronic inflammation, especially at sites of injection [55].

Another disadvantage of this form seems to be the difficulty for the owners to perform an act that should be done by a veterinary professional, making these cats prone to injection site reactions [56]. According to a survey realized by *Jones et al*. about the administration of unlicensed crowd-sourced antiviral GS-441524, solely 8,7% of the 393 analyzed surveys have reported owners receiving help from their veterinarians in the administration of the treatment [57].

In a study from *Murphy et al.* from 2018, no significant toxic consequences have been noticed after treating the 10 cats of the experiment with subcutaneous GS-441524 in dosages of 5mg/kg/day (group A – 5 cats) and 2mg/kg/day (group B – 5 cats). The higher dosage reached 8-20 times the necessary EC50, letting us estimate that the lower dosage of this experiment could be used, and therefore reduce the potential toxic effects of the drug administration on longer therapy protocols. “Stinging” reactions were nevertheless noticed at the time of injection [52]. Additionally, in the research done by *Dr.Pedersen* in 2019 [53], liver and kidney parameters remained in normal ranges during and post-treatment.

In case of the neurological form, because the patients seem to develop a partial drug resistance, *Dr.Pedersen* advises to increase the protocol’s dosage, with a limit of 10mg/kg daily [56]. The study from *Dickinson et al*. from 2019 [58] of 4 different cases of neurological FIP forms supports this protocol. The increased dosage is also justified by the study from *Murphy et al.* from 2018, showing that the penetration of the GS-441524 molecule is limited at the level of the blood/brain and blood/eye barriers. In fact, in that experiment, the cats were given 10mg/kg of the GS-441524 subcutaneously, of which the level of the prodrug was equaling 22-23% of the plasma level in the aqueous humor and 7-21% of the plasma level in the cerebrospinal fluid [52]. In these cases, sticking to an injectable form of the molecule seems to be more efficient than opting for the oral form, because the oral absorption of the molecule is then limited at such high dosage [56]. Further

studies should be done to find out if the amount penetrating the blood/brain and blood/eye barriers would be enough to have a curing effect.

D. GS-441524 – Tablet

An oral form of the GS-441524 molecule was developed by Xraphconn®.
In the study from *Krentz et al.*, it was shown that this multi-component drug from Xraphconn® allowed the cats with FIP taking part in the trial to improve significantly in a short period of time. In fact, it was shown that this drug permits a drastic decrease in the viral loads within the first few days of the treatment. Additionally, the survival rate at the end of the experiment was 100% [54].
Slight side-effects were shown in this study, with a mild increase in liver enzyme activity in 11 of the 18 tested cats, as well as mild Heinz body anemia observed in one cat at the end of the advised 84-day-protocol. It has been demonstrated that these side-effects could be easily alleviated by respectively applying S-adenosyl-methionine and silymarin as supportive treatments. Lymphocytosis and Eosinophilia without any further clinical consequences were also seen.
In contrast with other studies, no acute renal toxicity has been proven during this trial [54].
However, it is not known whether the other components of this drug (Active ingredient: Radix scrophulariae; Inactive Ingredients: Platycodon grandiflorum, Phyllostachys pubescens, Forsythia suspensa, Anemarrhena asphodeloides) might have increased the efficacy of the GS-441524 molecule by synergistic effects. We could also question the extent of this study, since only 18 cats were selected for the trial, therefore not representing a big part of the FIP cat population. Nonetheless, the fact that all 18 cats of this study survived suggests this drug as a real option in the treatment against FIP – depending on the original health state of the patient [54].

This treatment form seems to be a good subsidiary to the injections since it appears to have little side-effects compared to the irritative nature of the injectable solution. This is explained by the GS-441524 being converted as an active nucleoside triphosphate directly in the liver and lung tissues.
However, due to the inactive nature of the intestinal tract in case of severely affected cats, the pharmacokinetic and pharmacodynamic of this drug seem compromised; therefore not

making of this medication the first treatment option if the patient is already rapidly declining [54].

E. Combination of both forms

An article written by *Richard Malik DVSc PhD FACVS FASM* [59] explains that an animal compounding pharmacy BOVA Australia managed to secure Remdesivir intravenous and subcutaneous drug stocks, allowing Australian veterinarians to experiment the efficacy of the GS-441524 – prodrug. A panel of 500 cats, having any kind of FIP forms, has been treated between October 2020 and November 2021, proving the treatment to be effective against FIP. These remdesivir injection forms seemed to provoke less painful administration as well as fewer injection-site reactions than other illegally-acquired GS-441524 – containing drugs.

The suggested dose was originally of 5-10mg/kg daily, but the results on the 500 treated cats showed that a higher dosage was needed. This might be explained due to the higher molecular weight of Remdesivir compared to pure GS-441524. Updated recommendations for an effusive form were of 10-12mg/kg SID diluted in 10ml of saline to provide a loading dose on the first 3-4 days. In case of the ocular form, the recommended dosage was 15mg/kg SID. In neuropathic forms, the recommended dosage was 20mg/kg SID. Opting for a more "aggressive" therapy from the start showed less recidivism in this 500-cat population, as well as no side-effects while giving the loading-dose except neurological signs such as seizures, that were associated to an undiagnosed subclinical neuropathic form.

The protocol suggests that after 2 weeks of daily injections (with the previously mentioned dosages) in case of the effusive and ocular forms, and after 2-4 weeks in case of the neuropathic form, oral GS-441524 tablets could be applied if no ascites was detected. This, allowed to lower therapy costs and limited the side-effects of the treatment. The dosages were the same as the IV/SC ones and given every 24h, except in case of neuropathic forms in which the high dosage was suggested to be given in 2 times, each at 12h apart. This oral route therapy was advised to be applied for 10 weeks.

Overall, the work of these Australian veterinarians shows very positive response from the treated patients to this therapy [59].

IV. The importance of considering legalizing this treatment

In the first instance, it is very clear that all the previous studies mentioned in the above parts show very positive clinical results of the GS-441524 applied on cats with FIP. *Dr. Pedersen* also mentioned in one of his studies that they are seeing a cure rate of 80% with this molecule, while considering FIP misdiagnoses, inadequate dosage, complicated disease conditions and drug resistance [56].

Remdesivir, a prodrug of GS-441524, is already readily available for veterinary use in the UK and Australia, allowing owners to finally rely on their veterinarian for the medical acts needed to be done on their pets (cf. subcutaneous injections). Veterinarians from other countries have also started accessing this drug from human pharmaceutical suppliers, especially in India, New-Zealand, Africa, and some European countries [59]. This shows that there is a real need for this cure to be marketed widely.

Additionally, these marketed drugs (Remdesivir products) are an insurance of the quality of the compounds they contain, which most probably influence the therapy's efficacy and the side-effects developed by the patients (less irritative, less injection-site lesions, less FISS). Marketed drugs could also mean regulated prices and less "illegal" purchases from the black-market, making this life-saving molecule more accessible to the distressed owners [56].

Furthermore, the idea of having FIP-cat models seems to arise nowadays when relating the clinical signs of FIP to the SARS-CoV-2 associated Multisystem Inflammatory Syndrome in Children (MIS-C). According to the study from *Krentz et al.*, MIS-C leads to gastrointestinal symptoms as well as persistent fever, ascites and pleural and pericardial effusion; similarly to FIP symptoms [54]. Researching about how the GS-441524 impacts cats affected with FIP could consequently serve not only veterinary medicine, but human medicine as well.

Retrospective study

I. Aims

The aim of this study is to build a solid base of information on the use of the GS-441524 molecule by FIP-cat owners.

In fact, since more and more owners found out about the potential positive impact this antiviral molecule has on cats suffering from FIP, there has been a breakthrough from owners trying to access the treatment. The dilemma is that these private trials are not being recorded by the scientific community. Therefore, with the help of an online questionnaire realized on Crowdsignal.com and based on the scientific data available we had on FIP and this treatment, we created a list of 21 questions addressed to owners having a cat that is undergoing or underwent treatment.

II. Materials and Methods

A. Questionnaire's structure

The questionnaire was translated into English, Hungarian and French. The questions were divided into 4 pages:

1) Cat's basic information:
    - Country
    - Name of the cat
    - Age
    - Breed
    - Sex
    - Neuter status
    - How many cats were there in the household?
    - Number of litters per cat
2) FIP diagnosis:
    - If the owner knows how the cat contracted FIP (cf. any stress that could have induced the mutation).
    - When was the diagnosis done?
    - Does the cat in question have any other pathologies?
    - Which form of FIP does the cat have?
3) Symptoms the cat experienced
4) Examinations and treatment received:
    - Examinations performed on the cat.
    - Therapy received prior to the treatment with GS-441524.

- How did the owners get to know about the possibility of a treatment with GS-441524.
- When did the treatment with GS-441524 start and which protocol was applied.
- How did the owners get access to the GS-441524-containing drugs.
- If they gave any other medication simultaneously with the GS-441524.
- If any side-effects were seen while the GS-441524 treatment was applied.
- If any positive signs were seen while the GS-441524 treatment was applied.
- What was the outcome of the treatment.

B. Questionnaire's spread

The questionnaire was opened from the 10th of January 2022 till the 30th of August 2022. The questionnaire was shared on several social media (Facebook) groups, whose aim is to help owners obtain information about the disease or access the GS-441524 treatment itself, both in injection and pill form. The admins of these groups had the ability to share the questionnaire further, to groups that may not have been contacted directly.

C. Questionnaire's basic data

With the help of the contacted FIP Facebook groups, the questionnaire was spread in a total of 24 countries, with France, the US and Hungary having the leading participation percentage.

By the 30th of August 2022, the questionnaire had received 503 complete answers.

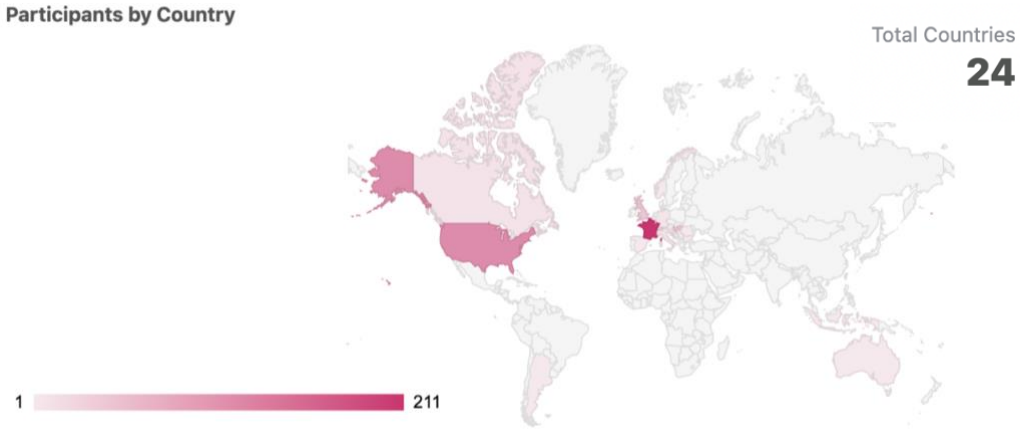


Figure 13 – Map of the 24 countries the questionnaire's answers were received from.

Country	Total	Rounded percentages
France	211	42%
United States of America	109	22%
Hungary	56	11%
United Kingdom	39	8%
Swiss Confederation	37	7%
Croatia	9	2%
Canada	7	1%
Italy	7	1%
Belgium	6	1%
Germany	5	1%
Slovenia	3	1%
Bosnia and Herzegovina	2	<1%
Luxembourd	1	<1%
Serbia	1	<1%
Romania	1	<1%
Norway	1	<1%
Monaco	1	<1%
Argentine	1	<1%
Indonesia	1	<1%
Spain	1	<1%
Bulgaria	1	<1%
Australia	1	<1%
Austria	1	<1%
Taiwan	1	<1%

Figure 14 – List of the 24 countries the questionnaire's answers were received from and their participation percentage out of the total 503 answers received.

III. Results

For the sake of making the data collected as accessible as possible to the engaged community of owners with FIP cats, an interactive dashboard was designed with the help of Giorgos Koursaros, Data scientist and expert in Tableau.
Link to the interactive dashboard:
https://public.tableau.com/app/profile/george.koursaros/viz/FIPCats/Overview?publish=yes

As shown below, out of the 503 cats mentioned in the questionnaire, 334 cats (66%) were males, and 169 cats (34%) were females. Additionally, 406 cats (81%) were already neutered, while 97 (19%) weren't. Finally, the cats diagnosed with the wet form of FIP were 295 (59%), whilst the ones with the dry form of FIP were 208 (41%).

Figure 15 – Sum up of the male/female ratio, the neutered/intact ratio, and the wet/dry form ratio.

A. Age

The data shows a tendency for young cats to develop FIP. In fact, 297 cats (59%) out of the 503 were less than 2 years old and already diagnosed with FIP at the time of answering the questionnaire. This information correlates with the usual FIP patient profile described in scientific researches.

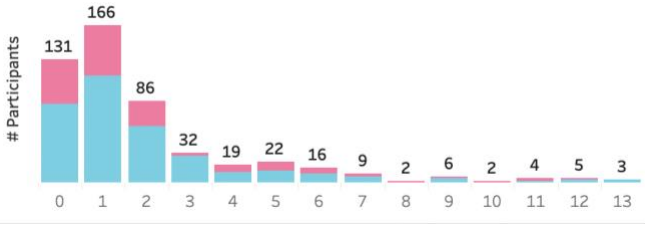


Figure 16 – Age in years of the FIP cats mentioned in the questionnaire's answers.

B. Breed

A majority of the cats mentioned in the questionnaire's answers were Domestic cats (265 cats – 52,7%). All the breeds mentioned previously in the literature part (Birman, Abyssinians, Bengals, Himalayans – cross between a Persian and a Siamese, Ragdolls, Rexes) were breeds represented in the data, although less than the domestic cats.

In this study, Maine coons, British shorthairs, Birmans, and Siberians were the most represented breeds after domestic cats.

The data does not support that potential complex inheritance pattern in certain cat breeds that would lead to a prevalence in FIP, since a majority of profiles were Domestic cats. It is however possible, that the questionnaire's sample is skewed in favour of domestic cats, just because it happened that the questionnaire reached more domestic cat owners, than pure-bred cat owners and it is therefore not conclusive that this a representative sample of the real FIP cat population.

Figure 17 – Male and female cats of the FIP cats mentioned in the questionnaire's answers, ordered according to their breed.

C. Sex

As shown by the data collected from the questionnaire, there appears to be a higher prevalence of FIP amongst male cats as compared to females. This is of course subject to

the possibility that there happened to be a higher participation rate from the male population's owners. These findings are nonetheless supported by previous studies.

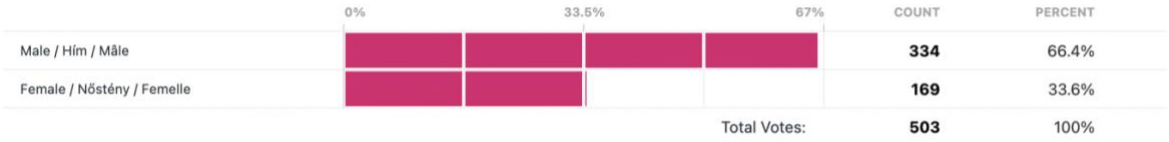


Figure 18 – Male-Female ratio of the cats mentioned in the questionnaire's answers.

D. Neuter status

It seems that the majority of cats which participated in the survey are neutered, as shown by the following graph. This poses the question of whether neutering could have an impact on the developing of FIP. Some owners mentioned the possibility of a stress factor induced by the surgery, that might have led to their cat contracting FIP. On the other hand, neutering is nowadays a common procedure advised by most practicing veterinarians for justified reasons, so it would be hard to prove scientifically a link between the neuter status and the course of developing FIP.

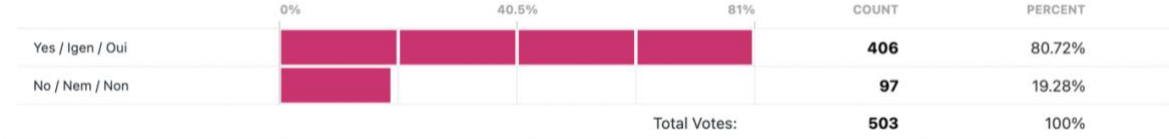


Figure 19 – Neutered-Intact ratio of the cats mentioned in the questionnaire's answers.

E. Symptoms of FIP

The data shows the most common FIP symptoms, which are unfortunately quite unspecific for most of them, partly rendering the diagnosis of this condition difficult.

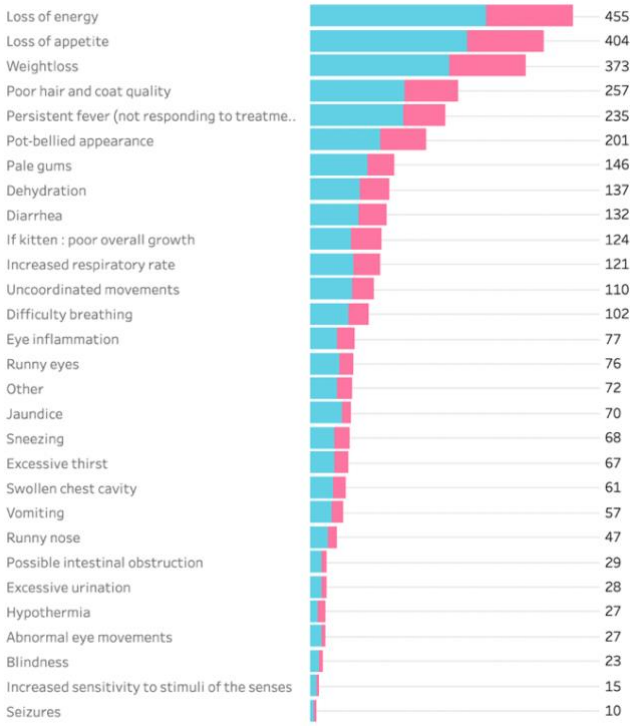


Figure 20 – Symptoms of the cats mentioned in the questionnaire's answers.

In the category “other”, 72 owners detailed the following additional signs:

General and dermatological signs:	Behavioral and neurological signs:	Gastrointestinal and abdominal signs:
- Cough - Drooling - Dry skin easy to wound. - Oral cavity ulcerations - Gingivitis - Fur loss - Otitis Ocular signs: - 3rd eyelid prolapse - Uveitis - Blood injected eyes - Anisocoria, Mydriasis - Change in iris color	- Head shaking/twitching - Tremors - Paralysis - Meningomyelitis - Depression/hiding/secluding behavior. Avoiding contact with owners and other cats of the household - Eating the litter material, licking metal objects and abnormal surfaces in the house (walls, windows, ground, doors) - Abnormal/unusual vocalization	- Severe gastrointestinal inflammation - Constipation - Anal prolapse - Ascites - Lymphadenomegaly - Neoplastic-like growth covering the intestines - Urinary and bowel incontinency - Liver failure - Hepatomegaly and nephromegaly

Figure 21 – Symptoms of the cats mentioned in the questionnaire’s answers.

F. Diagnosis

The following diagnostic tools and methods were selected by the owners.

Additionally, in the category “other”, 80 owners answered CT-scan (Computed Tomography), MRI (Magnetic Resonance Imaging), Cerebrospinal fluid aspiration and analysis/PCR, bone marrow biopsy, exploratory laparoscopy, PCR from lymph node tissues, fine needle aspiration - in some cases of the aqueous humor on the patient’s eye, gastroscopy, colonoscopy, bronchoalveolar lavage and consultations with specialists such as an Ophthalmologist in case of ocular FIP.

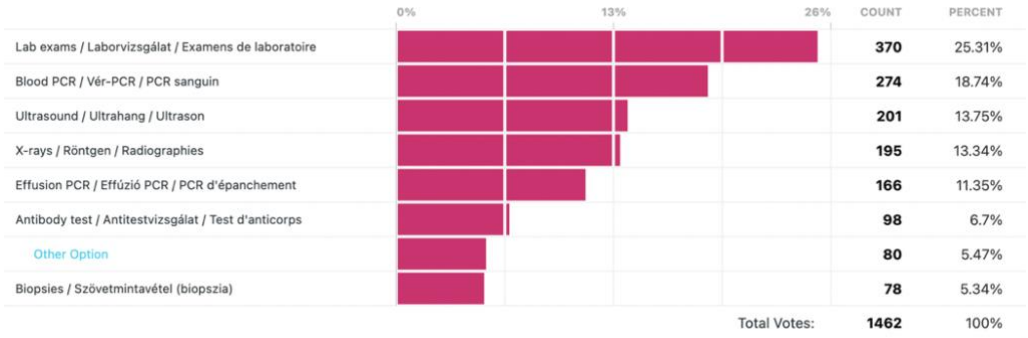


Figure 22 – Diagnostic methods used to diagnose the cats mentioned in the questionnaire’s answers.

G. Therapy received prior to the GS-treatment

Prior to initiating the GS treatment protocol, and in order to palliate the grave symptoms until a diagnosis is found, veterinarians seem to be prescribing anti-inflammatory drugs the

most. In fact, 326 cats (66,4 %) out of the 491 submitted patient profiles got treated with anti-inflammatory drugs. The second most popular therapy was the drainage of the fluid build-up in the abdominal cavity (87 cats – 17,7%). Environmental and nutritional changes come in the third place with 78 cat owners (15,9%) having been advised to change the feed of their cat, putting 1 liter per cat away from the feed, as well as sometimes completely separating the affected cat from the other cats of the household. Fluid therapy was realized in 67 cases (13,6%). Additionally, 20 cats (4,3%) received intravenous vitamin C therapy. The least employed therapies were blood transfusion (8 cats – 1,6%), homeopathic FIP nosodes (4 cats – 0,8%), cytokine therapy (3 cats – 0,6%) and Remdesivir – a prodrug of which the GS-441524 is an intermediate metabolite (2 cats – 0,4%).

In 58 cases (11,8%), an antibiotic treatment was given. This shows the lack of diagnostic tools to diagnose FIP, as well as the tendency to prescribe antibiotics prior to the final diagnosis for a febrile animal.

Other treatments were administered to some patients, such as: antipyretics, antiemetics (Maropitant), Mirtazapine/Diazepam as an appetite stimulant, pre/probiotics, diuretics, PERT (Pancreatic Enzyme Replacement Therapy), laxatives, antidiarrheals, dewormer, phytotherapy, surgery to remove mass in ileocaecal valve, Vit B12, liver protectants, Vetri DMG (a liquid formula supporting the immune system and helping in stress management– given per os), parrafin oil, ferritin supplementation and antiacids.

In solely 59 cases (12%), no therapy nor drugs were given prior to diagnosis FIP.

H. Treatment with GS-441524

Since the GS-441524 treatment is not on the pharmaceutical market, it is interesting to understand how it gets brought up to owners of FIP cats.

In 296 cases (58,8%), they got to know about it through social medias, especially through Facebook groups. In 226 cases (44,9%), the owners' veterinarian mentioned to them the existence of the GS-441524 without being able to prescribe it to them directly. In 172 cases (34,2%), they found information about this therapy on the internet (articles, forums, blogs, etc). Additionally, 45 owners (8,9%) got information from rescue shelters, breeders, animal organizations, friends and other people having already applied the treatment on their own cat previously. Lastly, solely 3 owners (0,5-6%) got information from magazines/papers.

Different suppliers, providing different packaging with different active ingredient concentration, are marketing their products mostly through Facebook groups and their admins. In the questionnaire, a majority of the owners were purchasing the medication

through the admins of these social media groups, while a minority ordered directly from the different supplying laboratories or bought from breeders/organizations/shelters/contact-persons. In some emergency contexts, owners of the same area in the world would drive to other owners who would have the drug in stock.

The protocol generally advised is a treatment based on 84 days of daily injections, then 84 days of observation period. During the treating period, one subcutaneous injection per day is typical given at the same hour every day; although in some cases the owners were advised to split the total daily dose into 2 injections per day in the first few days. In some cases, owners were advised to switch to the pill administration form from day 42, or day 30 – after having given injection for at least a month. These owners reported the easier administration mode as well as the avoidance of the tissue-irritating injections.

The advised dosages varied from 5 to 15 mg/kg body weight, the lower range being indicated for wet or dry FIP, middle range for ocular FIP and the higher range for neurological FIP. In specifically severe cases of ocular and neurological FIP, this dosage could be increased up to 20mg/kg body weight or simple doubled from the original wet FIP dose.

The cats were weighted daily so that the daily dose could be updated after the usual weight gain happening during the treating period.

PCR checkups are recommended at day 30, day 60 and day 82 of the first treatment phase.

A minority of other protocols consisted in giving a higher dose in the first few days, then doing a PCR as well as an Ultrasound check in order to see the disease's progression. If positive results such as no more effusion were seen, the dose was decreased (but still increased in time according to the weight gain).

When relapse was seen, another 84-day-protocol was started with generally a bigger dosage than the first round – often 5mg/kg more than the original dose.

Some owners found out that holding the cat and especially pushing their hand against the injection site would help in preventing the leakage of GS solution out, thus avoiding local skin irritation.

Simultaneously with the treatment, owners were giving other medications in order to try to palliate to the FIP symptoms as well as the GS-441524, such as:

- Gabapentin – 1-2h prior to injection to palliate to the pain at injection site
- Maropitant – as an antiemetic
- Mirtazapine – as an appetite stimulant
- Liver protectants (Silybin, Silymarin, Silybum, S-adenosyl-L-methionine)

- Supplementation in copper, essential vitamins (B1, B5, B6, B9, E, C), phosphorous, omega 3/6, lactoferrin, melatonin, krill oil; as well as Iron, vitamin B12 and Darbepoetin in case of anemia
- Immune booster such as thymic protein, spiruline
- Telmisartan – antihypertensive
- Eyedrops of antibiotics, anti-inflammatory drugs, Benzalkonium Chloride
- Antibiotics in case of skin lesions-skin infections, upper respiratory infections.
- Anti-inflammatory drugs – While in some cases they were completely stopped when the GS therapy was started, in other cases they were not discontinued.
- Levetiracetam – antiepileptic
- Diosmectite – Antidiarrheal
- Subcutaneous fluid therapy
- Probiotics
- Renal diet, convalescence diet
- Paraffine/Vaseline – laxatives
- Diuretics such as Furosemide, Spironolactone – Decrease edema
- Proton-pump inhibitors such as Omeprazole – help with inappetence and nausea
- Pancreatic dietary supplements such as pancreatic enzymes, UDCA
- Homeopathy, gemmotherapy, phytotherapy
- Skin ointments with Mallic acid, Benzoic acid, Salicylic acid, Arnica

These treatments were either advised by the admins/contact person concerning the GS treatment, or by the veterinarian.

Finally, out of the 502 owners who answered the questionnaire, 230 (45,8%) did not give any other treatment concurrently with the GS therapy.

I. Side-effects of the GS treatment

The major side-effects the owners noticed during the GS-441524 application were pain at the injection site (354 cats – 70,3%) and injection site reaction (218 cats – 43,4%). Skin reaction elsewhere than at the site of injection was noticed in 82 cats (16,3%), while liver damage or elevated liver enzymes as well as kidney damage were observed in respectively 39 cats (7,7%) and 18 cats (3,6%).

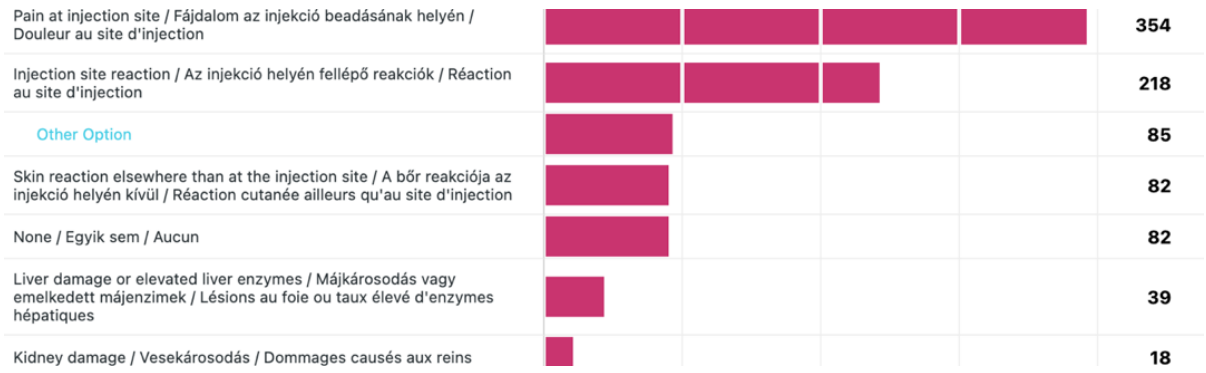


Figure 23 – Side-effects seen during the GS therapy.

In the category “other”, the owners mentioned the following additional side-effects:

General and dermatological signs:
- Ulcerations at injection sites.
- Food allergy developed.
- Appetite loss in a few cats (although the majority tends to the contrary).
- Abscess, especially when the product was injected intradermally instead of subcutaneously.
- 1 cat developed food allergy together with pododermatitis and eosinophilic granuloma complex in the buccal cavity.
- Local irritation if the product was getting directly in contact with the epidermis. Panniculitis.
- Fur loss, at some spots permanently.
- Fur thinning.
- Fur color change.
- Whisker loss/breakage, which usually never grew back to normal.
- Sores from the injections.
- Sores developing when switching to the pill format.
- Skin became tighter/harder with time and injections going on.
- Itchiness at site of injection.
- Drooling, supposed to be caused by the injecting act inducing stress in the cat more than the drug itself.
- Nausea.
- Skin necrosis at injection sites.
- Cutaneous hyperesthesia.

Behavioral and neurological signs:
- Pain leading to aggressiveness.
- Sleepiness/lethargy right after injection.

Ocular signs:
- Mydriasis during the 1min following injection.
- Temporary anisocoria.

Gastrointestinal and abdominal signs:
- Constipation.
- Diarrhea.
- Kidney values worsening periodically.

Figure 24 – Additional side-effects mentioned noticed by the owners during GS therapy.

J. Outcome of the GS treatment

During the 84-day treatment period, owners were able to notice a drastic change in health status in their cats.

In fact, it seems that the medical condition of the treated cats was remarkably improving in the first 12h to 48h after the first injection, from being lethargic for some cats to being playful again. Some owners were even able to notice a decrease of the fever in the few hours that followed the first injection, as illustrated by one of the cats mentioned whose temperature decreased to 38,4°C after the first shot, while having over 40°C meloxicam-unresponsive-fever for the 15 previous days.

The cats regained appetite very soon after the first shot, leading to a constant increase in weight throughout the therapy time, as well as the hindering of appetite stimulant supplementation. Their overall behavior came back to normal, showing during the first week of treatment playfulness, jumping, climbing, interacting again with the other cats of the household, seeking for owner’s affection, self-grooming again, etc. Furthermore, their fur was back to a healthy shiny state, stools and urination were normal again, and no vomiting nor nausea was noticed. A back-to-normal staturo-ponderal growth was noted in kittens.

Their blood work seemed to start normalizing at day 30 and on, with disappearing anemia and jaundice. In most of the cases normal results of the blood panel were seen and necessary to get into the observation period without treatment prolongation. Moreover, the

disappearing of the pot-bellied appearance, the pericardial/pleural/abdominal effusion, the mesenteric lymph node enlargement, as well as the dyspnea were remarked.

In case of ocular FIP cats, less ocular discharge and healing uveitis were noticed as well as a 3rd eyelid back in place and regain of eyesight, but in some cases other side effects weren't wearing off as well as other symptoms (E.g.: Nystagmus was persistent in one cat, although less pronounced). In case of neurological FIP, subsiding ataxia/tetraplegia was witnessed from 5h to 24h after the first injection. Seizures stopped as well.

In a few cats, the first few injections did not lead to such a great improvement, but the owners were questioning whether the treatment was started on time or too late. Euthanasia was needed in these cases.

Two cats were mentioned alive and thriving respectfully 2- and 3-year post-treatment. One cat improved so well that its veterinarians were able to perform a herniorrhaphy together with neutering following the 3rd week of treatment; no post-operative issues were noticed.

Out of the 494 cats mentioned in the treatment's outcome question, 58,9% (291 cats) were listed as completely recovered from FIP after the treatment, amongst which 2% (6 cats) could only recover after an increase in dose or treatment time compared to the initial protocol. Thereupon, an additional 1% (5 cats) recovered with sequels (seizure, neurological gait issue, urinary and/or bowel incontinence, blindness), but no details were mentioned about whether these sequels were caused by FIP, the GS treatment or other concomitant diseases. One of the cats mentioned recovered from FIP and died 1 year post-treatment due to unrelated reason. While 23,7% (117 cats) were still receiving the treatment and seeing positive improvement of the FIP symptoms at the time of the questionnaire, 11,3% (56 cats) had completed the usual 84 treatment protocol but were still in the observation period to monitor for any relapse – which at the time of the questionnaire was not present. Another 1,2% (6 cats) improved after starting the treatment but then relapsed and were still receiving the GS at the time of the questionnaire. Moreover, 3,2% (16 cats) had to be euthanized because of aggravating symptoms. Succinctly, from the 494 cats, 94% (464 cats) had a positive response to the therapy.

Discussion

This retrospective study was realized to disclose data from a panel of FIP positive cats whose owners purchased privately the GS-441524 treatment, still to this day not available on the veterinary pharmaceutical market. It resulted in, to this day, one of the largest collections of data from FIP cat owners using the GS molecule.

The survey received a majority of answers from France, the United State and Hungary.
In the final data collected, males were over-represented with a total of 334 cats (66%) – similarly to the 64,9% found in another major survey realized by *Jones et al* [57]. Additionally, just like in this study, 59% (297 cats) were found to be less than 2 years of age, corresponding to *Dr.Pedersen's* studies too [23]. About half of the panel (265 cats - 52,7%) were Domestic cats. The most cited breeds were Maine Coon (7,5%), British shorthair (5,2%), Birman (5%) and Siberian (4,6%).
Unlike the study from *Jones et al*. [57], the questionnaire's data showed 44,9% of the owners got told from their veterinarians about the possibility of the GS treatment, without being able to ensure the therapy itself for legal reasons; while 58,8% and 34,2% ensured respectively they had gotten awareness from social media groups and internet forums/blogs. Subsequently, they would get the drug provided by social media admins mostly, or more rarely by shelters, breeders, or directly from producing laboratories; and proceed to the administration themselves. *Dr. Pedersen's* 84-day treatment protocol and observation, with a daily injection at the same hour, was followed by almost all the owners answering the questions, although the dosage protocols mentioned differed from *Pedersen et al.* initial study [53]. In fact, as noticed in the report from *Jones et al*., the starting and ending advised doses were higher than in *Pedersen et al.*'s study, ranging from 5 to 15 mg/kg body weight according to the severity of the FIP form [53, 57]. In case of ocular and neurological FIP, some owners increased the dosage up to 20mg/kg body weight or doubled the original dosage. The subjectivity of each cat to the treatment, and the potential dose increase needed, or lengthened/renewed protocol could be explained by the treatment starting date in the course of the disease and/or the still-to-this-day unclear components marketed by these producing laboratories. In fact, generally no official information is displayed concerning the actual compounds of the sold medication. Even though it is suspected that these contain the molecule GS-441524, the "pureness" of the drug can be questioned, the excipients could have a positive/negative impact on the individual assimilation of the GS molecule, or the sold pharmaceuticals could potentially contain other active ingredients, such as the GC376 – another antiviral nucleoside analog [3, 54, 57, 60, 61].
Comparable to the result in the report from *Jones et al*., astounding outcomes were disclosed from the owners [57]. The population of completely recovered cats was 58,9%, out of which solely 2% needed an increase in dose and/or treatment time. An additional 1% recovered with persistent sequels (seizure, neurological gate issue, urinary and/or bowel incontinence, blindness). One cat recovered but died a year later due to another condition. Furthermore,

23,7% were still undergoing the 84-day treatment period and seeing major improvements in their health status and quality of life, 1,2% improved but then relapsed during the treatment period and underwent a change in protocol, while 11,3% were still going through the 84-day observation period for which no relapse was seen at the time of answering the questionnaire. Ultimately, 3,2% were mentioned having been euthanized because of exacerbating clinical status. Considering this data, 96,15% of the cats were still alive when replying to the questionnaire, correlating with the 96,7% found in the review from *Jones et al* [57]. Owners reported noticing a quick alleviating effect from the treatment seeing the first positive effects 12h to 48h after the first injection, as well as mostly pain and reaction at the injection site as a side-effect, in accordance with *Pedersen et al.* and *Jones et al.* writings [53, 57]. The efficacy of the treatment as well as the few side-effects mentioned by the owners most probably have been supported by the therapeutics applied concomitantly with the GS (Gabapentin, hepatoprotectants, anti-inflammatory drugs, etc).

Although the data collected is very promising of a treatment against FIP, it is important to note that this questionnaire, spread on social media platforms promoting the GS treatment, might have incidentally reached more FIP cat owners for whom the protocol is/was a success, and fewer the ones for whom it wasn't due to their decreased participation in these social groups. Moreover, this retrospective study was entirely based on a questionnaire with a limited number of participants who were employing diverse treatment strategies, consequently a standardized treatment protocol cannot be determined from this finite cat population. Just as importantly, it is necessary to mention that the owners treating their cat privately at-home might not have a veterinary medical background, therefore potentially generating side-effects when applying the treatment that could be avoided by a veterinary professional.

Conclusion

This retrospective study demonstrates the encouraging results of the GS-441524 treatment on FIP. This poses the question of using this molecule as a diagnostic tool until further diagnostic methods are found to dissociate FIP from other diseases. Although still not licensed in most countries, the black-market acquired medication shows a great interest and willpower from these owners to finally find a legitimate cure for FIP, formerly consistently considered a fatal disease.

Abstract in English

The Feline Infectious Peritonitis Virus, a pathogenic mutation of the Feline Enteric Coronavirus (FECV), causes a widespread infectious disease called Feline Infectious Peritonitis (FIP). Considered particularly lethal and originating from a very contagious widespread virus (FECV), this disorder, still to this day, does not have a proper diagnostic pathway since our current diagnostic methods and tools are not specific nor sensitive enough for this purpose. Furthermore, no official treatment protocol is available on the veterinary pharmaceutical market. Several protocols, both supportive and preventive-based have been tested throughout the years of fight against FIP, none of them having shown interesting results, except for the GS-441524, a nucleoside analogue antiviral drug. Several studies have shown the hopeful outcome of FIP cats treated with this molecule. However, the drug is not presently licensed for veterinary use and not available legally on the market.

The purpose of this research was to gather data from the owner of FIP cats, who privately purchased and treated their cats with the GS molecule, in order to provide fundamental insights on the effect of this drug has on these originally considered "lost" animals. This retrospective study was based on a questionnaire which received 503 answers from 24 different countries. Amongst the 494 answers to the question regarding the treatment's outcome, 57,7% (285 cats) were listed as completely recovered from FIP after the treatment, while 23,7% (117 cats) were still receiving the treatment and seeing positive improvement of the FIP symptoms. Additionally, 11,3% (56 cats) had completed the usual 84 treatment protocol but were still in the observation period to monitor for any relapse – which at the time of the questionnaire was not present. Lastly, in 2% of the answers (6 cats), the recovery was successful solely after an increase in dose or treatment time compared to the protocol advised originally, meaning that the actual number of cats recovered from the treatment is 58,9% (291 cats). The minor side-effects seen from the therapy are ones that could be palliated thanks to supportive therapy, unlike the original much graver FIP symptoms and clinical signs.

While additional research is needed on this drug molecule, the data reveals itself to be promising.

Abstract in Hungarian

A macskák fertőző hashártyagyulladása (FIP), a Feline Enteric Coronavirus (FECV) kóros mutációja, a fertőző hashártyagyulladás (FIP) nevű, széles körben elterjedt fertőző betegséget okozza. A különösen halálosnak tekintett és egy nagyon fertőző, széles körben elterjedt vírusból (FECV) származó betegségnek a mai napig nincs megfelelő diagnosztikai útvonala, mivel a jelenlegi diagnosztikai módszereink és eszközeink nem elég specifikusak és nem elég érzékenyek erre a célra. Továbbá az állatgyógyászati gyógyszerpiacon nem áll rendelkezésre hivatalos kezelési protokoll. A FIP elleni küzdelem évei során számos, mind támogató, mind megelőző jellegű protokollt teszteltek, de egyik sem mutatott érdekes eredményeket, kivéve a GS-441524, egy nukleozid-analóg vírusellenes gyógyszer. Több tanulmány is kimutatta, hogy az ezzel a molekulával kezelt FIP-es macskák reményteljes eredményt értek el. A gyógyszer azonban jelenleg nem engedélyezett állatgyógyászati felhasználásra, és legálisan nem kapható a piacon.

A kutatás célja az volt, hogy adatokat gyűjtsünk azok a FIP-es macskák gazdáitól, akik magáncélból vásárolták és kezelték macskájukat a GS-molekulával, hogy alapvető betekintést nyerjünk a gyógyszer hatására ezekre az eredetileg "elveszettnek" tekintett állatokra. Ez a retrospektív vizsgálat egy kérdőívre épült, amelyre 24 különböző országból 503 válasz érkezett. A kezelés eredményére vonatkozó kérdésre adott 494 válasz közül 57,7% (285 macska) a kezelés után teljesen meggyógyult a FIP-ből, míg 23,7% (117 macska) továbbra is kapta a kezelést, és a FIP tüneteiben pozitív javulást tapasztalt. Emellett 11,3% (56 macska) befejezte a szokásos 84 kezelési protokollt, de még mindig a megfigyelési időszakban volt, hogy figyelemmel kísérjék az esetleges visszaesést - amely a kérdőív kitöltésének időpontjában nem volt jelen. Végül a válaszok 2%-ában (6 macska) a gyógyulás kizárólag az eredetileg javasolt protokollhoz képest megnövelt dózis vagy kezelési idő után volt sikeres, ami azt jelenti, hogy a kezelésből gyógyult macskák tényleges száma 58,9% (291 macska). A kezelés során tapasztalt kisebb mellékhatások olyanok, amelyek a szupportív terápiának köszönhetően enyhíthetők, ellentétben az eredetileg sokkal súlyosabb FIP-tünetekkel és klinikai tünetekkel.

Bár még szükség van további kutatásokra ezzel a gyógyszermolekulával kapcsolatban, az adatok ígéretesnek mutatkoznak.

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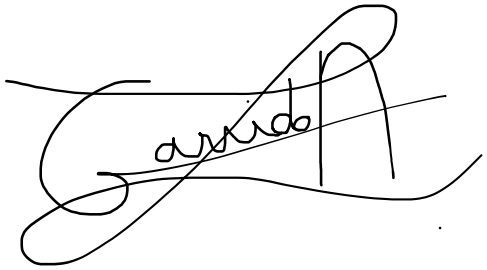

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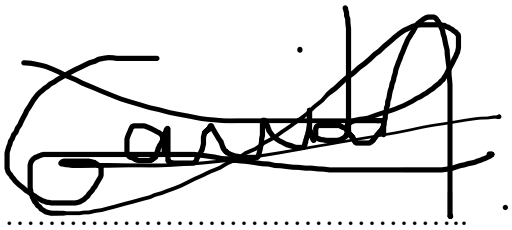
Appendix 5. Declaration regarding TDK research paper-thesis equivalence

DECLARATION

I hereby declare that the thesis entitled *"Novel therapies in cats with FIP (Feline Infectious Peritonitis): literature review and retrospective study with GS441524."*

is identical in terms of content and formal requirements to the TDK research paper submitted in 2022.

Date: 24/10/2023



(Name of student)