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This review accompanies the relevant episode of the Cutting Edge veterinary podcast. In each episode of this podcast, 3rd year students in the University of Calgary's veterinary medicine program fill you in on the most up-to-date literature and evidence-based practices on topics that matter to you, the practising veterinarian.

Remdesivir/GS-441524 as a Lifesaving Treatment Option in Cats with Feline Infectious Peritonitis (FIP): A Guide for Clinicians

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The goal of this proceedings paper is to give practitioners in Canada some background on GS-441524 and remdesivir and provide them with the current knowledge on these drugs to aid in therapeutic decision making.

The paper is organized as follows:

Background on Feline Infectious Peritonitis

FIP results from an initial infection with feline Coronavirus (FCOV) and its mutation in the host, although there have been cases where there has been direct transmission between individuals [2,4,6,10,19,21,22,23]. Approximately 20-50% of cats living in private households and 87-90% of purebred cats living in catteries tend to test positive for FCOV [6,19]. The high levels of FCOV in catteries explains the higher incidence of FIP in the purebred cat population[21].

There are two hypotheses for the development of FIP. The primary theory is the "Internal Mutation Theory" whereby a mutation occurs in the genome of FCOV resulting in a gained ability of the virus to replicate in macrophages. When cats become infected with FCOV through fecal-oral transmission (and rarely via inhalation) the virus replicates and infects the intestines[19]. Although there has been no consistent mutation that has been identified, mutations in the FCOV's spike protein, membrane protein, mutations in the S1/S2 locus and modulation in a furin recognition site as well as disruption in FCOV's NSP3c have been found to correlate with development of FIP. NSP3c is part of multi-domain non-structural protein 3 (NSP3) which is the largest protein encoded by coronavirus and plays a critical role in its replication/transcription complex[17]. Interestingly, viruses with an inactivated NSP3c region only rarely replicate in the intestines, which could explain the limited number of outbreaks. The second hypothesis for the development of FIP is the circulation of virulent and avirulent strains within the feline population[19]. In both hypotheses, there is massive replication of FCOV in macrophages and if the cat fails to clear the infected macrophages, FIP will develop.

Clinical signs of FIP include pyo-granulomatous vasculitis and/or serositis, high protein effusions, pyrexia, inappetence, lethargy, abdominal lymphadenopathy, ocular signs and/or neurological signs. FIP is generally distinguished into two clinical forms that often have overlap: "wet FIP" (effusive FIP/nonparenchymatous FIP) and "dry FIP" (noneffusive FIP)[19,21]. Effusive FIP is characterized by signs related to vasculopathy (i.e., leakage of serum protein/fluids into body cavities). Dry FIP is typically characterized by granuloma formation. Left untreated, FIP is almost always fatal, with most cats succumbing within weeks to months of diagnosis (median survival 9 days)[19,21]. While a definitive diagnosis of FIP usually relies on the detection of the FCOV antigen or FCOV RNA as well as typical FIP histopathological changes, other supportive findings from hematology, serum and/or fluid sample (e.g. effusion), biochemistry (e.g. hyperglobulinaemia, increased alpha-1-acid glycoprotein, serum amyloid A, hyperbilirubinemia, reduced albumin to globulin ratio), cytology (pyogranulomatous inflammation) can enable a presumptive diagnosis of FIP[21].

What are Remdesivir and GS-441524 and how do they work?

Remdesivir and GS-441524 are anti-viral drugs. Remdesivir (GS-5734) is the monophosphate prodrug of GS-441524. Knowledge from several species including mice, rhesus monkeys, and humans suggests remdesivir undergoes rapid metabolic conversion in vivo[4]. Remdesivir is metabolized within the host's cells to GS-441524 (the major circulating metabolite) via the enzyme carboxylesterase-1 before becoming the active triphosphate derivative GS-443902,

which can be used by viral RNA-dependent polymerases for genome replication[8,16]. GS-441524 is believed to have reduced antiviral activity compared to remdesivir because its diffusion into cells is rate-limited by the initial phosphorylation step, while remdesivir has higher cellular penetration[8,9]. The mechanism of action of both anti-viral drugs is delayed chain termination in the virus' replication process, through sterically interacting with the viruses RNA-dependent RNA polymerase[8]. Remdesivir's ability to induce delayed chain termination has been shown in vitro with multiple coronaviruses such as SARS, MERS, contemporary human COV and bat-COVs.

Background on initial research and history on unlicensed GS-441524/Remdesivir

Initial Studies

The first study on cultured cells determined that GS-441524 was non-toxic in feline cells at concentrations as high as 100uM (100uM was the highest concentration used in the study, so the toxic concentration is likely higher)[18]. In the same study, GS-441524 inhibited viral replication at as low as 1uM. This study included two cats with ocular/neurologic forms of FIP treated with GS-441524 10mg/kg and found that the levels of drug in aqueous humor and CSF averaged 21.4% of blood plasma. Initial studies of FIP used dosages of 2-5mg/kg of GS-441524 once per/day for 14-84 days and in some cases continued treatment if serum protein concentrations remained elevated[18,20]. Although the first two studies did not include FIP cases with ocular and neurological disease because of concerns about the ability of GS-441524 to penetrate the blood brain barrier, subsequent studies found success treating at a 5mg/kg dose [7,18,20]. Several subsequent studies soon followed, with many using the oral form of GS-441524.

Pharmacokinetics

Although you would expect the dose of GS-441524 to be half of the dose of remdesivir based on the molecular weight of GS-441524, most studies dose them equally on a mg/kg basis[5]. This is likely due to the poor bioavailability of remdesivir; data on the bioavailability of remdesivir in mice shows that remdesivir is unsuitable as an oral drug because it undergoes extensive hydrolysis and CYP-mediated metabolism in the liver. Meanwhile, GS-441524 exhibits favorable oral bioavailability (F=57%) and high plasma exposure[24]. GS-441524 and remdesivir at 25 mg/kg, and intravenously administered remdesivir at 7 mg/kg achieves plasma levels greater than the established corresponding EC_{50} values, which are sustained over 24h for GS-441524 and remdesivir.[5]

Treatment success & dose unreliability with unlicensed GS-441524

Although several studies demonstrate that treatment with GS-441524 is life-saving and efficacious, the content and purity of the drug is unknown in the unlicensed product due to the unlicensed GS-441524 being unregulated. Even the dose in these unlicensed forms can be questionable: one of the studies used a dose that was 1.8 times (18mg instead of 10mg) or 2.88 times higher (7.2mg instead of 2.5mg)[1]. The second study had 18 cats that were originally thought to have been treated with 5-10mg/kg but ended up being treated with a double dose accidentally; they all recovered from FIP and didn't experience any severe adverse effects[15,21].

Both studies sourced their drug from Mutian Life Sciences, a Chinese drug manufacturer. Despite the uncertainty with unregulated versions of the drug, the survival rate of cats treated with Mutian's formulation was 82.2% (116/141) in cats with effusive FIP, 85.1% (137/161) in cats with mixed FIP, and 93.9% (153/163) in dry FIP cats after 84 days of treatment [12,13].

Current Lack of Veterinary Involvement

Currently several social network groups help cat owners obtain GS-441524 or similar drugs. In such cases, this drug is purchased and administered with limited to no veterinary oversight. In Jones *et al* (2021) study on the efficacy of unlicensed GS-441524 survey results showed that of 393 owners using unlicensed GS-441524, only 8.7% of owners reported receiving help from their veterinarian administering the medication to their cat, 74.3% reported some help with monitoring, 25.7% received no help beyond the initial diagnostics[11]. This same study reported that almost one fourth of owners found out about GS-441524 through their veterinarian either directly (14.5%) or indirectly (12.0%), while 30.36% of owners said they found the information from searching online, and 23.21% from social media webpages for owners of cats with FIP. One example of this is "FIP Warriors" on Facebook; FIP Warriors is a Facebook group that connects cat owners with the unlicensed drug, provides treatment advice and peer support. This presents a real problem because not only do veterinary clients lose trust in veterinarians when we withhold information about treatment options, but it is a concerning welfare issue. Jone's *et al* study indicated that the administrators of FIP Warriors, the main provider of GS-441524 here in Canada, require a presumptive diagnosis of FIP based on clinical and laboratory data provided by a veterinarian. The administrators then track each cat's progress on a spreadsheet, monitoring parameters such as weight, hematocrit, white blood cell count, lymphocyte count, neutrophil count, monocyte count, albumin, globulin, serum A:G ratio (albumin globulin ratio), total bilirubin, BUN (blood urea nitrogen), creatinine, and ALT (alanine transaminase). While this is a commendable effort by the administrators, it presents a problem as they are not veterinary professionals and could be charged with practicing veterinary medicine without a license. More meaningfully, they could unknowingly cause harm. Until recently, veterinarians were unable to prescribe legal product due the North American manufacturers being unwilling to sell the drug for animal use. Since the unlicensed product was not approved for use in Canada and application for an Emergency Drug Release was not an option, veterinarians could not legally prescribe the drug[26]. Since veterinarians are legally able to administer, consult, monitor and treat the side effects resulting from the unlicensed product, veterinarians need to take on a more active role in monitoring the progress and health of these patients while they are treated with the unlicensed forms of these drugs. As of February 2024, Canadian veterinarians now have access to legal Remdesivir and GS-441524 from a drug company in the UK called BOVA, with the completion of an emergency drug release[29]. As a result, veterinarians also need to play a role in prescribing and sourcing these drugs. Unfortunately, once an emergency drug release is filled it will take about 7-10 days to receive the drug which is longer than the median survival time. Thus, if your clinic gets multiple cases of FIP a year (drug expiry ~18month) it is worth applying for a general emergency drug release, stocking a couple weeks' worth and applying for a second emergency drug release later. If your clinic does not see FIP often, knowing which clinics in your area keep the drug on-hand and temporarily sending those patients to those other clinics is an alternative option.

Unlicensed Distributors & Cost of Drug

MaxPaw is one of the main distributors of unlicensed GS-441524 in Canada and the United States. FIP Warriors Canada and FIP Warriors 5.0 are also sources of the unlicensed drug in Canada. Based on MaxPaw's pricing, it would currently cost $2,125.50 CA to treat an 8lb cat with wet FIP and $4,251 CA to treat a cat with neurological FIP for 84 days, with the injectable form not including the cost of needles. For an 8lb cat, the capsule and tablet cost approximately $40/day for wet or dry FIP and $80/day for ocular/neuro FIP leading to a cost of $3,360 and $6,720 for 84 days respectively. This price is considerably lower compared to the original studies. However, the cost of 4 days of injectable remdesivir and oral GS-441524 for 80 days is $2700 for a 4kg cat with the licensed drug from BOVA; this number accounts for weight gain over the course of treatment and presents a substantial cost savings[29]. Owners are also able to save money with the licensed drug when veterinarians dispense enough drug for a couple weeks and then dispense greater quantities of drug when the patient shows a positive response to therapy. In this way, should the patient die during treatment clients wouldn't have needlessly spent money. This cost savings can be used to encourage owners to use the licensed product. One benefit of MaxPaw though, is that they offer a lifetime guarantee which is beneficial considering that relapses do occur and that some cats need extensive treatment. Both MaxPaw and FIP Warriors 5.0 claim to have veterinarians and specialists available for consultation although there is no way to prove the veracity of those claims. MaxPaw is the only provider of unlicensed drug that presents straight-forward information on the product they are selling: they show their recommended treatment process, provide dosing recommendations, and show the factors they consider in their dosing recommendations. MaxPaw's policies and reviews are also available on their website. The other two Facebook groups are only accessible to members and at present the author of this paper is not a member of these groups. Although MaxPaw has a step-by-step process to obtain a diagnosis by a veterinarian and a consult with one of their administrators or veterinarians, there are no significant barriers to accessing the drug, as no validation of FIP was required when I investigated their checkout page. The only impediment to dissuade owners from buying the drug without a diagnosis by a veterinarian and a consultation is the need for the provision of lab work to get the lifetime guarantee. Currently, if you cannot get the licensed version of remdesivir or GS-441524 I would recommend MaxPaw to FIP cat owners due to its transparency and lifetime guarantee, with the caveat that, like with all unlicensed FIP treatments, there is no guarantee of the safety or efficacy of the product. I would only recommend using the unlicensed form if there is no other option and would get the cat switched to the licensed version as soon as you received it from BOVA. Either way, I would work with the owner to create a plan to monitor the cat's health during the treatment process and monitor for any side effects.

Routes, Current Dosage Ranges & Adverse Effects

Oral Administration

A small double-blinded non-inferiority trial indicates oral remdesivir and oral GS-442514 are equally efficacious in terms of survival, the results of other studies, although not direct comparisons, seem to agree with this[6]. Oral medication should not be used in patients with

gastrointestinal malabsorption, severe ileus, severe neurological signs, collapse, or if there is any risk of aspiration. Interestingly, it has been suggested that oral administration might be more effective than injectable formulations since it targets the major replication site of FCOV: the small intestine. However, in cases of FCOV moving beyond the intestine, the oral form is unlikely to provide a huge benefit. At this time, if the cat can tolerate the oral formulation, I would recommend the oral form given that it is more convenient. If a patient needs one of the injectable forms to start, I recommend switching to the oral form when the patient is stable enough to receive the oral form.

IV Administration

The recommendations for IV administration of remdesivir is to dilute the 10mg/kg dose in 10ml of saline and then administer it over 10–20mins[21]. It can also be diluted 50:50 with saline and given as a constant rate infusion over 1hr[9]. IV is mainly reserved for critically ill cats. Unless you stock the injectable form, given that the fastest that GS-441524 is available from unlicensed suppliers in Canada is 24hr using IV GS-441524/remdesivir is unlikely. Two situations where veterinarians may need to use IV remdesivir at a client's behest is if the cat rapidly deteriorates or if there is an attempt to keep the patient stable until the drug arrives.

SQ Administration

Subcutaneous administration appears to be less effective in large part because it is given to patients that are generally more ill and are unable to tolerate/absorb oral medication[21]. The most common adverse effect of subcutaneous injection is localized pain and discomfort (47.8%, 122/255)[21]. The degree of pain experienced by patients is evident due to the fact that 82% of cats vocalize, 76.1% show signs of pain, 51.7% of cats can have scarring or scabbing, and 8% can have an extremely aversive reaction such as biting owners and staff [4,11]**.** Pain was noticeable even with sedatives, anxiolytics and pain killers [4,9,21]. The pain experienced by the patients is another reason to recommend oral products in cases where patients can tolerate it. If the oral version is not available or the cat is not well enough to sufficiently absorb the medication, veterinarians are critical in demonstrating and/or administering the injections because clients may struggle with administration. Additionally, once a cat associates drug administration with pain, treatment compliance can decrease resulting in a potentially increased likelihood of euthanasia. Dosing the patient with gabapentin, buprenorphine or another sedative, anxiolytic or pain medication is advisable to help with pain prior to SQ administration[4,21]. Although, pain medication/anxiolytics may not eliminate pain, finding the right combination for that patient at a sufficient dose is necessary for the welfare of these patients.

Dosing

Most owners are administering both the SQ and oral medication once daily. With oral medications, as is common, rounding the dose to the nearest half tablet has been done. I would recommend tablets over capsules because the patient can be dosed more accurately[4]. In a large retrospective study using Remdesivir and GS-442514 the starting dose differed from the suggested dose on MaxPaw. In Taylor's *et al* study, the median starting dose when using GS-441524 alone for abdominal effusion was 12.3mg and 20mg for neurological[21]. For remdesivir

alone 10mg was used for all types of effusion and neurological cases. Despite the vast range of doses, most cats were treated with 10-15mg/kg, and 26.7% had their dose increased during the treatment period although it isn't noted what the doses were increased to. Some cats, in the study received as high as 27mg/kg as a starting dose. Given the information available to the authors of the study, it would have been beneficial to include what the doses were increased to, specifically if they were higher than 27mg/kg. The same study notes that over the course of the study, increases in doses and treatment duration occurred to try and optimize patient response and attempt to prevent relapses. Cats with ocular or neurologic FIP or with unstable FIP such as those with hypotension, hypoglycemia and severe pleural effusion should be on higher doses of remdesivir and GS-441524[9]. Based on current research, clients should follow the dosing provided by the treatment groups if they are using the unlicensed product. They need to follow the unlicensed providers dosing because the unlicensed products may contain substantially more drug than the label indicates. For clinicians, Weese's remdesivir and GS guidance for clinicians is supposed to be updated as treatment recommendations change, so use those recommendations as a baseline and check regularly for updates[29].

Clients need to have the option to increase the dose if the patient does not improve. Owners will need to consult you or/and the administrator of the licensed/unlicensed drug if they are to do this. Again, be sure to mention that if the unlicensed drug is being used that you can't guarantee that there will not be problems because the true dose is unknown and that they will need to bring the cat to an emergency if adverse effects are experienced. It is also essential to remind clients that the body weight of their cat will likely increase during the treatment period (most cats gain on average 30% of initial body weight by the end of treatment), so weighing the cat at home regularly is needed so their cat gets the right dose for its size, because underdosing increases relapse both during and after treatment completion[4]. A 5mg/kg increase has been noted in clinical trials if clinical signs persist and a full 84-days if relapse occurred at 5mg/kg higher than original course of therapy[4]. It was also mentioned that the presence of hyperglobulinemia beyond 6 weeks should prompt a dosage increase. It is important to note that should a patient require an increased dose, extension of treatment or need to be retreated that a new EDR needs to be completed[29].

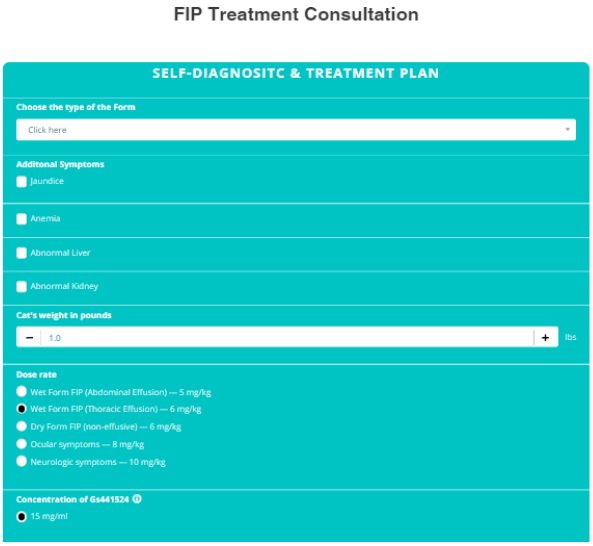

Figure 1. MaxPaw dosage consultation form

Adverse Effects

Less common adverse effects include sores/thickened skin at injection sites (3.5%), color change (black to white fur) at intrascapular injection site (1/255), brief period of subdued demeanor after injection (SQ/IV-2.5%), hypotension after IV administration (2%), period of diarrhea after starting oral (2%), pruritis (SQ/PO), persistent thrombocytopenia in one cat that responded to corticosteroids (GS-441524). Transient exacerbation of pleural effusion has been noted with IV administration. A serious but uncommon side effect is that GS-441524 can cause multifocal urolithiasis (cystic, renal and ureteral)[27,28]. These uroliths are a novel urinary calculus and are 98% consistent with GS-441524. In humans, both remdesivir and GS-441524 are recommended to be used with caution in patients with impaired renal function; given the potential for severe urolithiasis this caution should also be observed in veterinary patients[28]. Since medication-associated uroliths are rare in veterinary medicine, it is necessary to use patient factors such as a history of uroliths, obesity, urinary stasis, underlying metabolic abnormalities, and urinary abnormalities from human medicine as a guide on which patients to watch more closely. Hydration, dietary modifications (e.g. salt restriction) and alterations in urinary pH have been found to help in human medicine and are potential options in veterinary medicine. At the very least, given the limited solubility of GS-441524 (0.0004-0.1mg/mL), ensuring patients are adequately hydrated during treatment should be a priority. I also advise informing clients of the signs of urolithiasis and advising them that while development urolithiasis is rare on GS-441524/remdesivir that should those signs develop they need to immediately take their cat to the nearest emergency clinic as it can be a life-threatening emergency. Since the stones are visible on ultrasound, performing a quick ultrasound during patient check-ins in predisposed patients is an option. If a patient is azotemic or develops clinical signs of urolithiasis an ultrasound (or contrast radiography if ultrasound is unavailable) should be performed to check for urolithiasis.

Clinical Pathological Effects of Remdesivir/GS-441524 [4,9,21,25]

1. Increased ALT (47-1260 U/L- more common in cats treated with GS-441524 30% vs 8.3%). May or may not be an adverse effect of treatment as ALT is often high at time of diagnosis.
2. Eosinophilia (0.9-4.9X10^9/L- more common in cats treated with remdesivir 20% vs 3.9%). This might be a positive prognostic indicator as increased eosinophil counts are thought to hold positive prognostic value in humans with COVID-19.
3. Lymphocytosis (6.1-13.3X10^9 /L)-mild lymphocytosis can still be present over a year later. This might be a positive prognostic indicator considering lymphopenia is a poor prognostic indicator.
4. Increased ALP (55-155U/L)
5. Increased Creatinine (148-383 umol/L)
6. Increased albumin/globulin- continued increase 4,8,12 weeks
7. Other rare abnormalities: thrombocytosis

None of the clinical pathological findings resulted in discontinuation of the treatment and they all resolved without intervention. It is of note that once remdesivir/GS-441524 becomes used in clinics or even if your clients are using the unlicensed form, especially as doses start being titrated beyond 27mg/kg to watch for development or worsening of azotemia as remdesivir has been associated with AKI in humans[20].

Case Selection

In a study of 28 FIP cats with a survival rate of 86%, all 3 cats that were initially presented obtunded survived[4]. There is the potential to save these cats. These cats may be able to be saved if your clinic carries the injectable form, if you can refer the patient to a clinic that carries the injectable form or if you can prevent the patient from progressing to moribund in the 24hr period it takes to get the unlicensed drug. These, obtunded patients need to be treated in hospital. If the patient presents moribund, remdesivir is unlikely to save them. Both cats where this was attempted died within 48 hours, so, euthanasia is the best choice in those cases. In the same study, 96% of cats survived if they survived the first 48 hours. So, if a client has a cat not doing well at home, there is the potential to save these patients with hospitalization which can aid in their survival for the first 48 hours[4]. Cats that tend to die during treatment are those that are hypoglycemic (blood glucose <3.5mmol/L) or hypotensive (Doppler NIBP <80mmHg) on presentation and have azotemia/AKI prior to treatment[9]. Pre-treatment total bilirubin levels are an excellent prognostic indicator; 96.6% (28/29) of cats with effusive FIP whose T-bilirubin levels were below 0.5 mg/dL prior to the treatment were able to be saved, the survival rate of cats whose pre-treatment T-bilirubin levels exceeded 4.0 mg/dL was drastically low (14.3%: 1/7) [12]. Severe lymphopenia is a negative prognostic indicator[25].

Full Response, Partial Response & No response to Treatment

In the study of 307 cats, 88.6% were alive at the end of the treatment period and 84.4% were alive at the longest follow-up period[21]. Eleven of the 13 patients who died during the follow up period had signs consistent with FIP. In this study, 84.4% had a full response, 5.9% a partial response, and 9.8% no response. Cats with only a partial response still have a decent survival outcome; of 18 cats with a partial response 55.6% (10/18) survived past the longest follow-up point, although the ones who died accounted for approximately 72.7% (8/11) of the patients who died due to relapse after the treatment period. It is not unusual for surviving cats with a partial response to treatment to have persistent clinical signs; 4/10 surviving partial response cats were normal save for static neurological signs, 2 had persistent hyperglobulinemia, 1 had a persistent volume of fluid and lymphadenopathy, 2 had static ocular signs and one had stable azotemia as well as ultrasonographic changes to the kidney. The prognosis for non-responders to treatment is grave; 100% died or were euthanized 1-55 days following the start of treatment with a median of 3 days. If a cat achieves a complete response within 30 days of treatment it is much more likely to survive to the end of therapy and beyond (98.7% survival rate)[21]. However, only 28% will show a complete response to treatment at 30 days.

Relapse

Relapse usually presents as one of the following: neurological signs, weight loss, inappetence, pyrexia, effusions, uveitis, jaundice, abdominal mass, and severe anemia. Relapse can occur during and after the treatment period for all types of FIP; of the 10.8% of patients (33/307) who relapsed in one study, 45.5% relapsed during the treatment phase, and 54.5% after completion of the initial treatment[21]. Of the cats that relapsed after the completion of treatment, 83.3% (15/18) relapsed within the first 60 days of stopping treatment, and two relapsed over a year after the completion of treatment. Relapse is more common with lower doses of remdesivir /GS-441524[4]. This propensity for relapse before and after treatment means that these patients will need to be monitored closely both during and after treatment, especially in the first 60 days after stopping treatment. After relapse there is typically a good response (8/10 that completed initial treatment and 7/8 that relapsed during treatment) to restarting treatment at a higher dose; although there is the potential to relapse yet again[21]. My research made me think of one major question. What is the possibility of relapse several years down the line? FIP can be completely cleared as evident by the necropsy findings in a hit by car cat where there was no FCOV RNA or antigen or microscopic or gross evidence of FIP[15]. The current problem is getting the dose and length of treatment right as each cat differs in its response to treatment based on many factors including an individual's immune system and the type of FIP. The best we can do is use the most current research on dosing and titrate up to the effective dose in combination with other therapies for patient specific therapy. The patient's welfare during treatment needs to be a priority: provide all needed supportive therapies and be forward with owners at what point they will need to give up.

Monitoring Remission and Treatment Length

In some recent studies, treatment was given for a minimum of 84 days and treatment was continued until remission occurred or clients elected to discontinue treatment and euthanize[4,7,11]. In one prospective study, they administered the current minimum 84-day protocol and continued treatment for at least two weeks beyond remission date[4]. Since there is no existing protocol to monitor remission and resolution of FIP, the aforementioned study's definition of remission and monitoring can be used as a starting point. According to the study remission was defined as: a BCS≥ 5/9, achieving normothermia, complete resolution of the presenting signs of FIP, normalization of plasma total bilirubin concentration, plasma globulin concentration (with albumin: globulin ratio ≥0.6), neutrophil and lymphocyte count to within their normal reference intervals and a quality of life score ≥44/55 (average of 4/5 or higher for questions 1 to 11 in the owner assessment that is included in the supplemental section of this paper). Most owners will report a rapid improvement of QoL within two weeks. Note that in this prospective study, there was no untreated cohort as it was deemed unethical to withhold treatment given that the only alternative for these cats was death.

It is important to note that monitoring FCOV in feces of patients exposed to other cats is unhelpful, as many cats will be re-exposed to FCOV at home and start shedding FCOV again. Thus, you should not suggest restarting remdesivir or GS-441524 in response to fecal tests or suggest a fecal in long term monitoring of a cat in a multi-cat household[25].

Resolution of Clinical Signs and Normalization of Chemistry

A clinical response is typically able to be documented in cats in 2 days (1-5 days, in 28/32 cats) and very few require >3 days (3/28)[9]. Pleural effusion starts to improve within 3 days of treatment. An initial worsening of hyperglobulinemia before subsequent normalization is relatively common (26.7% of cats that had serum biochemistry reassessed within 30 days)[21]. Given that 75% of patients had normalization of temperature, clinical signs, bilirubin, effusion and hematocrit and ≥50% had an albumin to globulin ratio >0.4 and a normalization of globulin within 60 days, between 42-60 days would be a good time to do a full recheck to check the progress of the cat (see recommended monitoring schedule in list format on pg. 12). In a much smaller clinical trial, mesenteric lymphadenopathy, renomegaly, ileocecocolic mass effect tended to clear by 6 weeks, and anterior uveitis by 4 weeks[4]. In effusive cases do not be alarmed by a drop in body weight, a globulin concentration spike, and PCV drop that coincides with effusion reabsorption around week 2, as it is normal and likely has to do with systemic protein absorption and transient hemodilution due to fluid shifts. One case with the hypertrophic cardiomyopathy phenotype of FIP diagnosed at 4 weeks had all abnormalities resolve by week 12[9]. Some cats will have lymphadenomegaly during long term follow up, though the cause is unknown despite several theories[2,5]. Cats may also rarely develop signs like feline hyperesthesia, though this appears to be temporary.

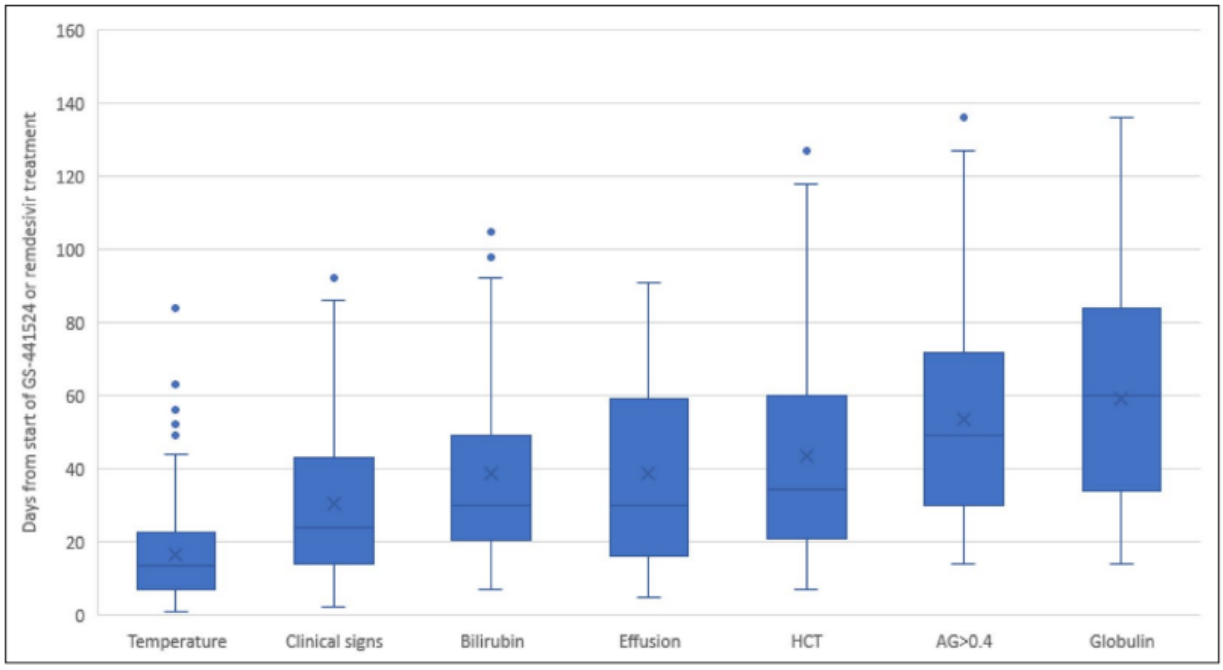

Figure 2: *Taylor et al.* Boxplot showing time to normalization in days of various clinical and clinicopathological parameters during treatment for feline infectious peritonitis. HCT=hematocrit; AG=albumin to globulin ratio. The blue boxes are edged by the 25th and 75th percentiles of the data, with the median (50th percentile) shown by a line within the box. The crosses indicate the mean of the data. The whiskers mark the 5th and 95th percentiles and values beyond these upper and lower bounds are considered outliers, marked with blue dots. HCT boxplots represent HCT or packed cell volume, depending on which was reported in the hematology profiles.

Based on the unknowns with these drugs, differences in response, potential for relapse and when chemistry starts to normalize, monitoring should be conducted at several time points. For at home patients, I would recommend:

1. A phone call/email 1-2 days after the start of treatment to monitor progress and screen for adverse effects.
2. Full recheck 2 weeks after the start of treatment (+ultrasound with effusive FIP).
3. Full recheck & blood chemistry at minimum 30 days after commencement of treatment.
4. Full recheck & blood chemistry at minimum 42-60 days after commencement of treatment.
5. Full recheck & blood chemistry within 60 days of stopping treatment.

Other Factors to Consider During the Treatment Period

Co-administering Other Drugs and Treatments, Vaccinations and Other Elective Procedures

Thoracocentesis is commonly needed prior to administration of GS-441524 in cats with pleural effusion. Likely 50% of those cats will require a second thoracocentesis within the first 24hr of

treatment. Currently, no cats need additional thoracocentesis 24 hours after treatment[9]. There is seemingly no negative effect on giving other drugs on treatment outcome. Corticosteroids were given to 19.9% of 307 cats (parenteral dexamethasone, oral prednisolone, topical ophthalmic preparations), antibiotics 48.2% (148/307), systemic NSAIDs 13.4% (41/307), mefloquine 4.6% (14/307) and feline recombinant interferon-omega to one cat (0.3%)[21]. Many patients require non-specific supportive therapy (174/307; 56.7%) with drugs such as mirtazapine (55/174; 31.6%), maropitant (45/174; 25.9%), gabapentin (35/174; 20.1%), opioid analgesia (24/174; 13.8%), IV fluid therapy (23/174; 13.2%), topical non-corticosteroid-containing ophthalmic preparations (21/174; 12.1%), ondansetron (8/174; 4.6%), blood transfusions (5/174; 2.9%), anti-seizure drugs (4/174; 2.3%), furosemide, norepinephrine, hydrocortisone, clopidogrel, cyclopentolate hydrochloride, ketorolac, latanoprost[9,21]. Cats with FIP often need treatment beyond solely remdesivir or GS-441524 in the form of other drugs and supportive treatment for both survival and general welfare. It is essential that veterinarians communicate to clients that other therapies and monitoring will be necessary during treatment with remdesivir or GS-441524.

Elective procedures (such as spaying or neutering, and vaccination) can still be conducted if pursued after the initial treatment period and if the cat is stable at the time. There has been no evidence of FIP relapse or other adverse sequelae following any procedure [4,21]. Currently, there is no evidence as to the safety of elective procedures before the end of the initial treatment phase besides a single enucleation and spay, so I would advise against any elective procedure during the initial treatment period. Vaccination during the treatment period is inadvisable for indoor pet cats due to the patient's already stressed immune response and potential interactions between the vaccine and the drugs. Instead of vaccinating, advise owners to keep patients away from possible sources of disease. For cats in catteries and shelters the benefits of core vaccines once the patient is stable outweighs the potential risks. These cats need to be vaccinated as soon as possible to protect them from the diseases in their environment.

Managing Risk to Housemates & Siblings During Treatment

In a large retrospective study of legal remdesivir and GS-441524, of the 257 patients which had data available for a housemate or siblings, 12.1% (31/257) were reported to have a housemate or sibling with suspected FIP (although the diagnosis was unconfirmed in most cases)[21]. Interestingly, 6 of the cats out of the 31 that were reported to have a housemate/sibling were from the same multi-cat environment; these 6 cats were confirmed to have FIP and likely represent an outbreak. Even though direct transmission of FIP is relatively uncommon, given that 10% of the cats in the aforementioned study (excluding the outbreak) had siblings/housemates with suspected FIP, I would recommend isolating the infected cat from other cats in the home throughout the treatment course[2,4,10,21,22,23]. The reasoning behind this recommendation is that although the risk of transmission to other cats is low and there are varying degrees of risk based on the genome mutation that enabled FIP to develop the current exorbitant price of treatment, makes isolating the infected cat preferable over not isolating and treating housemates should symptoms develop. This would be less of a financial and stressful burden on the owners.[22]. Due to the potential for transmission of FIP, it would be beneficial to mention to owners that there is a

slight risk to other cats in the household and to monitor other cats in the household for development of symptoms of FIP.

Future Drug Alternatives & Monitoring Aids

Nucleoside analogs GS-441524, remdesivir, molnupirvar, B-D-N-hydroxycytidine (NHC) and protease inhibitors GC376 and nirmatrelvir are strong inhibitors against feline infectious peritonitis virus serotypes I and II with EC50 values ≤1um[5]. GC376 was the drug with the best antiviral efficacy against FIP serotype I and NHC for FIP serotype II. For all the drugs, the EC50 value was higher in FIPII. This indicates that we should be treating at or higher concentrations that inhibit FIP II because in most cases the type of FIP a patient has is unknown. Combining antiviral drugs such as a nucleoside analog with a protease inhibitor appears to be the way of the future. Certain combinations of drugs have synergistic effects; remdesivir combined with GC376 appears to be especially promising. Combination drug therapy should help improve the efficacy of treatment as well as bring down the cost of treatment and make therapy more accessible to owners, as currently few owners have the means to pay for treatment and those that are paying to desperately try to save their cat could be putting themselves in a financial bind. Nirmatrelvir and molnuprivar are both found to hold potential for FIP due to their selectivity[3]. Having alternatives will be important should there be drug shortages or should resistance develop to remdesivir or GS-441524. Future drug resistance is a possibility as FCOV has already developed resistance to GC376, a protease inhibitor[25].
Tailoring drug dosing and therapeutic monitoring should soon become easier: a recent study validated a simple chromatography equipped with a fluorescence detector to quantify plasma concentrations of GS-441524; this will work for monitoring both remdesivir and GS-441524 as remdesivir is rapidly converted to GS-441524[14].

Conclusion

Remdesivir and GS-441524 are lifesaving drugs that are highly effective in treating the previously untreatable and invariably fatal disease, FIP. Veterinarians are needed in a multitude of ways to support FIP patients and their owners. Veterinarians need to be involved in diagnosing FIP, determining if the patient is a potential candidate for treatment, making clients aware that a treatment option exists, educating clients on the treatment, prescribing and obtaining the legal drug, monitoring the patient during treatment, and explaining the role of the veterinarian in the treatment/monitoring process. During the treatment process, veterinarians are essential to monitor for side effects, monitor patient progress, set end points with owners should therapy fail, and provide additional therapies/supports for these patients. Since this is a novel treatment, consent will need to be obtained from clients to protect the veterinarian when the unlicensed form is needed and when using licensed remdesivir/GS-441524 with an emergency drug release. Refer to the attached consent checklist based on the ABVMA member advisory as a guide on what pieces of consent to obtain when using the unlicensed drug. Additionally, refer to the supplemental section below for supplemental information created by OVC's Dr. Wiese on applying for an emergency drug release and information on creating an account with BOVA. As

more information on FIP treatments becomes available, it is essential that veterinarians remain up to date on these treatments.

Consent Checklist.docx

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Link to supplier pages

1.https://maxpawhealth.com/pages/fip-treatment-consultation-form
2.https://www.facebook.com/groups/fipwarriorsoriginal
3.https://www.facebook.com/groups/985604618443857/ (FIP warriors Canada)
4. https://bova.co.uk/ (licensed product)

Supplemental Information

1. Bova Account Form
   https://www.dropbox.com/scl/fo/jh2bnyanktn576omx6eju/h?dl=0&e=2&preview=BOVA+account+form_as+of+Feb+9_2024.pdf&rlkey=9xogpf5ldkfiopihcjxt7pl7c
2. Bova Order Form
   https://www.dropbox.com/scl/fo/jh2bnyanktn576omx6eju/h?dl=0&e=2&preview=BOVA+Order+form_as+of+Feb+9_2024.pdf&rlkey=9xogpf5ldkfiopihcjxt7pl7c
3. Emergency Drug Release Fee Form
   https://www.dropbox.com/scl/fo/jh2bnyanktn576omx6eju/h?dl=0&e=2&preview=EDR+fee+form.pdf&rlkey=9xogpf5ldkfiopihcjxt7pl7c
4. Examples of Emergency Drug Release Form for GS-441524 and remdesivir
   https://www.dropbox.com/scl/fo/jh2bnyanktn576omx6eju/h?dl=0&e=2&preview=EDR_GS_completed+example.pdf&rlkey=9xogpf5ldkfiopihcjxt7pl7c
   https://www.dropbox.com/scl/fo/jh2bnyanktn576omx6eju/h?dl=0&e=2&preview=DMU+Remdesivir.pdf&rlkey=9xogpf5ldkfiopihcjxt7pl7c
5. Supplementary Information for Emergency Drug Release application for remdesivir and GS-441524
   https://www.dropbox.com/scl/fo/jh2bnyanktn576omx6eju/h?dl=0&e=2&preview=Supplementary+Information+for+Emergency+Drug+Release+application+for+remdesivir+and+GS_updated_Feb+19_2024.docx&rlkey=9xogpf5ldkfiopihcjxt7pl7c
6. European Advisory Board on Cat Disease: Diagnostic tool for FIP
   file:///C:/Users/struc/Downloads/FIP_diagnostic_tool_Sept_2023.pdf
7. QoL questionnaire link: downloadSupplement (wiley.com)