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UPDATE ON C&T NO. 5896: A FELINE INFECTIOUS PERITONITIS (FIP) TREATMENT PROTOCOL

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Please note: Coronavirus titres or faecal analysis for the diagnosis of FIP are not recommended or required.

Please refer to the previous article C&T No. 5896 for a discussion on the disease and diagnostic options for FIP.

The Concord Veterinary Hospital Treatment Protocol

This article will discuss the use of a drug called remdesivir injectable liquid and the legally compounded GS-441524 tablets. Many clinicians will be familiar with GS-441524 from its use in Australia and overseas to treat FIP and a time when cat owners would have to source this drug independently and on the black market.

What are Remdesivir and GS-441524?

Remdesivir and GS-441524 are broad-spectrum antivirals. Remdesivir was originally developed to treat Hepatitis C and Ebola Virus; however, it was fast-tracked and given approval in many countries worldwide for the treatment of COVID-19. Its use in COVID-19 patients is somewhat controversial; however, it is showing amazing promise for the treatment of FIP in cats. GS-441524 was developed for human use; however, allegedly because of oral bioavailability issues, the manufacturer concentrated on other molecules, so its use is confined to coronaviruses in animals.

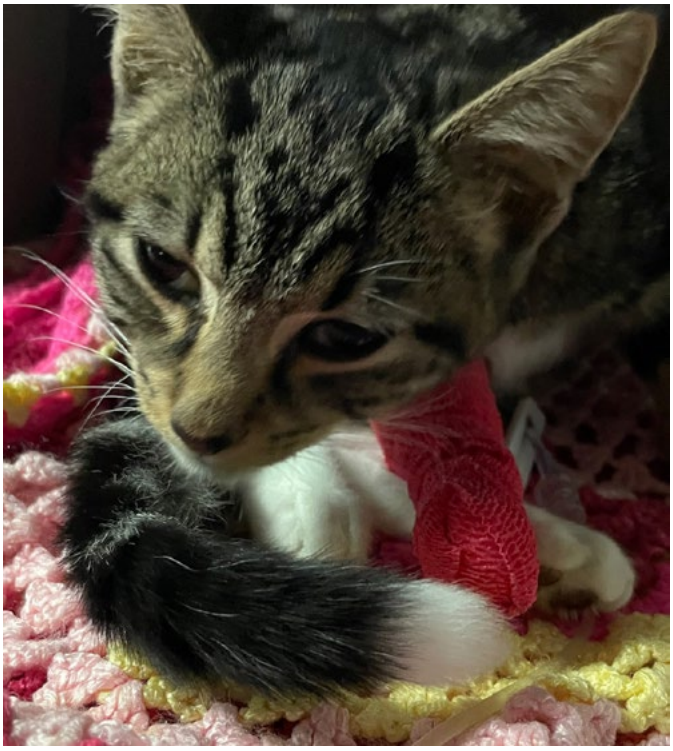

Figure 1. Before treatment

Figure 2. After treatment

Treatment With Remdesivir and GS-441524

Previously, treatment with remdesivir was for 84 days by subcutaneous injection. Remdesivir was the first commercially available anti-viral provided in Australia for treatment of FIP and it was highly successful in treating this disease; however, it was not completely effective in all cases—especially neurological and ocular FIP. We have driven many cats into permanent remission with remdesivir alone; however, there were a few patients where FIP remission was not achieved, or only achieved after many months.

Remdesivir can be obtained from BOVA Compounding who ship Australia-wide and usually overnight. The vials are $275/vial inclusive of GST and the final concentration is 10mg/mL. Dose recommendations range from 10–20mg/kg once to twice daily.

GS-441524 was available for owners to purchase on the black market as an injection and as tablets and capsules. In NSW at least, sourcing GS-441524 by a veterinarian was not permitted.

BOVA Compounding now produces a commercial supply of GS-441524 tablets. The tablets are 50mg, 10 tablets per bottle, at a cost of $660/bottle including GST. Dose range is 10–20mg/kg daily, either given as a single dose or divided and given twice daily. GS-441524 is slightly more economical than remdesivir to use. There are no injections and no need to purchase needles, syringes and EMLA cream.

The First 1 to 4 days

At this stage, Concord Veterinary Hospital is still using injectable remdesivir for 4-14 days prior to the introduction of GS-441524. The rationale behind this is that intestinal absorption of drugs is potentially limited in the first 2 weeks of treatment. A systemic route is preferred for this reason. However, GS-441524 is relatively cheaper when compared with remdesivir, so should a client be financially limited, it is certainly reasonable to commence with GS-441524 tablets.

The earlier treatment is commenced—the better the outcome—and this cannot be overstated. Most cases (there have been very few who have not made complete remission) that did not proceed to permanent remission were treated very late in the course of the disease.

Here are 3 options for commencing treatment. Like most things in life, it often comes down to budget.

1. **Subcutaneous Injections**
   If a patient is stable and eating, subcutaneous injections can be commenced at a dose rate of 10-20mg/kg once to twice daily, (wet FIP requires lower doses than dry FIP and abdominal FIP requires lower doses than neurological and ocular FIP). The patient is checked daily for the first 3–4 days. This is a perfectly acceptable routine for a well-hydrated patient who is eating and is the more financially sustainable option.

2. **The intravenous (IV) Route**
   If a patient is unwell, or where neurological or ocular FIP is suspected, then they should be hospitalised, placed on IV fluids run at a quarter to half maintenance rates (Hartmann's or similar is fine). The reason for such a low rate will become clear shortly.

   Remdesivir is administered SLOW IV (over 10 minutes is fine) once to twice daily for 3–4 days. We have found if you can maintain your catheter to a 4th day it is great to get a fourth intravenous dose into your patient; however, if there is pain at the cannula site or thrombophlebitis, then 3 days is also OK.

3. **The Oral Route**
   If a patient is stable and eating, or where finances dictate, oral GS-441524 can be administered from day 1 of treatment at a dose of 10-20mg/kg daily, given as a single dose or as divided doses. Once again—higher doses are required for dry, neurological, and ocular FIP.

Pros and Cons

The downside to administering remdesivir intravenously is:

- having to hospitalise the patient
- the added expense to the owner, which is not insignificant
- an increased risk (perhaps 10% risk) of developing or worsening of a pleural effusion with the use of intravenous remdesivir plus IV fluids

This is an issue mostly in wet forms of FIP, which then require close monitoring by either regular thoracic radiography or T-Fast ultrasonography daily or twice daily (we prefer twice daily radiographs).

The benefits of intravenous remdesivir are that;

- you get a high anti-viral dose to target the virus for the initial 3–4 days
- you get to observe your patient and often get to see the fever break within 1-2 days

and near moribund patients 'come back to life' and show signs of improvement daily

Obviously, this is a conversation to be had with each individual owner and for the clinician to make on a case-by-case basis. See below for other considerations before deciding which patients would or would not benefit from initial IV or subcutaneous remdesivir therapy *versus* oral GS-441524.

Cats receiving intravenous remdesivir do not need to be in a 24-hour facility—remdesivir could be administered intravenously in the mornings so a clinician then has the whole day to observe their patient, and then send home for overnight care with the indwelling canula in place for the following days treatment.

Days 5-14 to 84

Patients should ideally be switched from remdesivir to oral GS-441524 on day 4-14, depending on how systemically well they are. The minimum treatment course is 84 days in total, with some severe cases requiring longer. We would suggest that dry, ocular and neurological disease is dosed (GS-441524) at 20mg/kg and wet forms at 10-15mg/kg. In our experience there is a tendency for vets to reduce the dose of antivirals. We recommend not dosing to lean body mass or minus their effusion weight estimations.

Remember – kittens metabolise drugs faster and require a relatively higher dose on a mg/kg basis.

Monitoring

There is little point doing blood work on days 1–4 after commencement of treatment—nothing will have changed significantly.

We routinely perform blood work at weeks 4, 8 and 12 of treatment, and decide on cessation of treatment at the 12-week mark. We then perform blood work 4 weeks into the observation period and 12 weeks into the observation period.

If results are excellent (i.e., normal) then they are considered cured.

Ideally, we perform CBC and biochemistry panel including bilirubin and globulins. We are looking for improvements and resolution of anaemia, neutropenia, lymphopenia, hypoalbuminaemia, hyperglobulinaemia and hyperbilirubinemia. A mild peripheral eosinophilia is a favorable sign.

In theory, you could also perform a PCV, TPP and a globulin level. This will give you an idea of the anaemia, the colour of the serum to check if your patient is still jaundiced, the albumin and the globulin level by simple calculation.

Treatment ends when all analytes are normal and critically, globulin levels are well within the normal range.

A few patients have ended treatment when globulins are high upper end normal and have rapidly come out of remission.

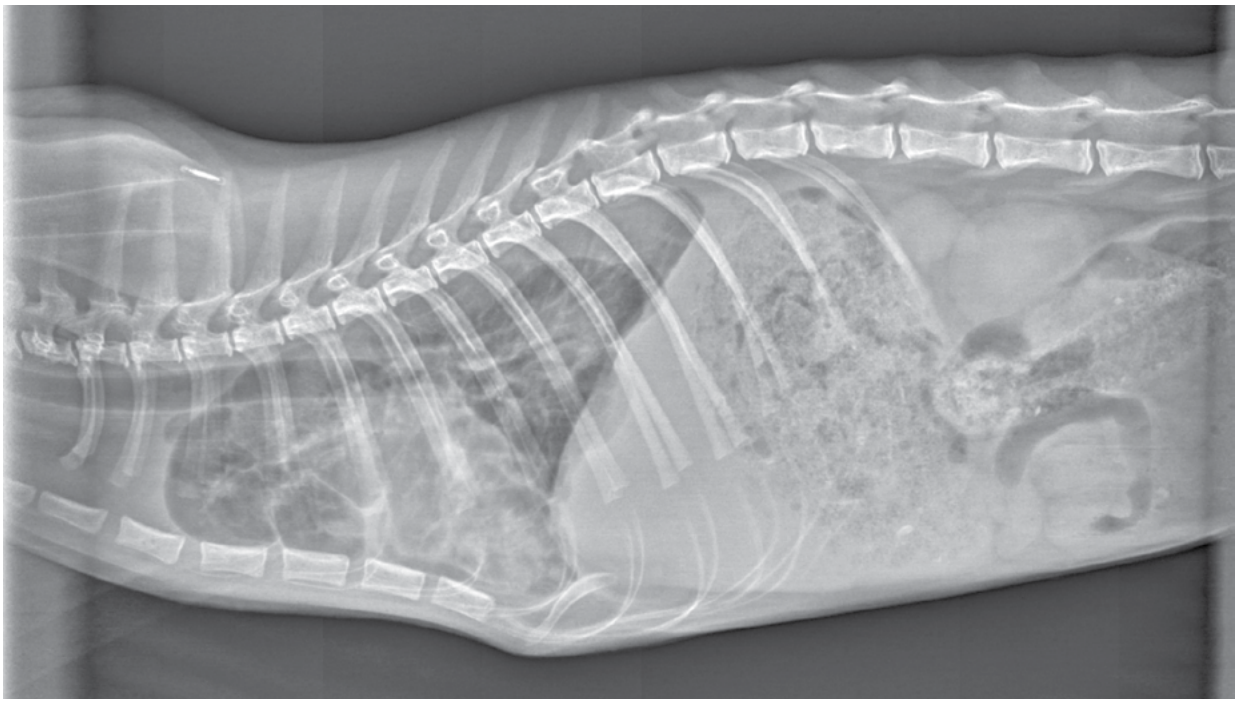

Figure 3. Radiograph showing patient's pleural effusion

But How Long Do They Last and How Many Have Died?

We get asked this a lot.

Since changing our protocol to include GS-441524—the remission rate is approximately 95%.

Timely diagnosis is vital. The cases that have not survived have presented to us moribund or have had comorbidities such as concurrent FIV or lymphoma.

It is worth noting—we have two cases currently, one ocular and one simple dry FIP—where we have been unable to reduce the globulins to a normal level beyond 84 days using remdesivir alone but once switched to oral GS-441524 both cats are now in full remission.

Other unsuccessful cases are predominantly ones we have seen as second opinions where the dose of antivirals has been too low.

To date, we have seen no side effects from remdesivir or GS-441524, although self-limiting increases in SDMA, urea, creatinine and ALT activity have been reported. Cessation of therapy is not normally required or recommended in these cases.

10 Important Points About the Use of antivirals in FIP cases:

1 THE MOST IMPORTANT POINT TO NOTE: 10% of cats receiving initial treatment (first 1–4 days) with intravenous remdesivir or oral GS-441524 can develop life threatening pleural effusion—especially in cases of wet FIP. These will require drainage. Therefore, it is recommended that cats receiving these antivirals should have serial radiographs and/or skilled T-Fast ultrasonography on a daily or bi-daily basis. If a patient is hospitalised for IV fluids and IV remdesivir, pleural effusions are more likely if a clinician pushes the intravenous fluid administration beyond maintenance—we prefer to keep the fluid rate below half maintenance. It is hard to resist the temptation to increase fluid rates in unwell and often dehydrated patients, but we would recommend against this.

2 Many patients will become quiet for 1–3 hours after receiving remdesivir intravenously—the exact mechanism is unknown.

3 There is no need to be alarmed if this occurs. It is generally a good sign. It is recommended to NOT drain the abdominal fluid unless to get diagnostic samples or for urgent therapeutic reasons (e.g., if dyspnoea is severe due to pressure onto the diaphragm). Also, somewhat bizarrely—pica has been reported in many cases of FIP where treatment has been suboptimal (usually dose related) or where remdesivir therapy is insufficient. Eating of cat litter is common, especially if they are anaemic. This is often the first sign that FIP is coming out of remission, and the dose should be immediately increased, and drug switched to GS-441524 if not already being administered.

4 Globulins will often go up at the first blood test before they begin to come down. Do not get disheartened. It's the protein in the fluids appearing in the circulation.

5 Many vets are concerned about the reports of elevations in kidney and liver analytes with the use of remdesivir. There have been a few reports of elevations in SDMA and occasional reports of elevation in ALT with doses of remdesivir as high as 15mg/kg that resolved once the dose was returned to normal. The authors have had 2 cats on 15mg/kg of remdesivir and has not personally seen elevations in ALT (but have not checked SDMA for various reasons).

6 Antibiotics: Often FIP cats have co-morbidities with infections which require treatment with antibiotics. Infections such as haematrophic Mycoplasmas are common. Antibiotics such as doxycycline or marbofloxacin are often a good choice. Other antimicrobials—if indicated—do not appear to be contraindicated. Some cats have translocated enteric bacteria in effusions.

7 NSAIDs to bring fevers down are often NOT required with the use of remdesivir.

8 The concurrent use of corticosteroids with remdesivir is not strictly contraindicated; however, it is not recommended. If your patient is already on corticosteroids, it is recommended you taper them off as quickly as possible.

9 Remdesivir and GS-441524 are well tolerated by cats and GS-441524 does not appear to be bitter when administered orally or crushed in food. Both can be obtained from BOVA Compounding and are usually shipped overnight Australia-wide.

10 Often it can be beneficial to a patient to commence a treatment trial of remdesivir to see if a presumptive diagnosis can be made of FIP or whilst waiting for further diagnostics to return from the lab. We would encourage early treatment and intervention prior to a formal diagnosis as the few days waiting for results can make or break a case ◆