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An update on treatment of feline infectious peritonitis in the UK

Introduction

The UK has had nucleoside analogue antivirals legally available to veterinarians for the treatment of feline infectious peritonitis (FIP) in cats since August 2021. During that time, many cats and kittens have been treated successfully; however, our knowledge is constantly evolving as are our recommended protocols. The antivirals available are from a specialist manufacturer in the UK and comprise oral GS-441524 (50 mg tablets) and injectable remdesivir (Figures 1 and 2). This article has been created to support practitioners in the use of these antivirals in the management of FIP. It is worth remembering that treatment needs to be tailored to the individual cat based on response, compliance and client finances. An information sheet on FIP is available for cat owners from International Cat Care describing treatments: https://icatcare.org/app/uploads/2022/05/FIP-pet-owner-brochure-FINAL-V2-1.pdf.

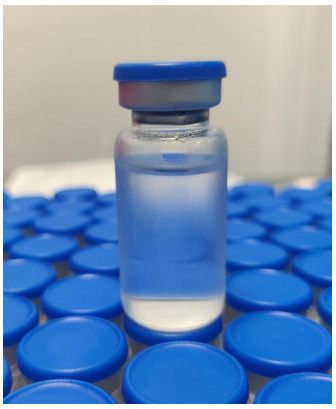

Figure 1: Remdesivir for intravenous or subcutaneous injection

Figure 2: Oral GS-441524 tablets

Treatment protocols (*updated January 2023*)

Initially, when only injectable remdesivir was available, protocols were based on using remdesivir for 12 weeks only. With the subsequent availability of oral GS-441524, protocols evolved to include an initial period of injectable remdesivir (from a few days to 2 weeks) before a switch to oral GS-441524 to complete the 12-week course. Although injectable remdesivir is still useful for the treatment of extremely dehydrated sick cats that cannot tolerate receiving oral GS-441524, treatment courses comprising only oral GS-441524 for the full 12-week course are now being increasingly used with success.

Reasons for the use of oral GS-441524 over injectable remdesivir include:

- Better compliance with oral medications over injectables owing to the ease of administration – pain can occur with subcutaneous remdesivir.
- Reduced cost of treatment, as oral GS-441524 is cheaper than remdesivir to purchase, and there are additional costs of giving injections in the cost of needles, syringes, sharps disposal, wastage, etc.
- Early recognition and treatment of FIP cases well enough to tolerate oral medication.
- Client and cat preferences for route of administration.
- When a cat has been started on injectable remdesivir but can be switched to oral GS-441524, this change can be made directly; remdesivir is given one day and GS-441524 tablets the next day
- There is no apparent difference in success between cats treated with only oral GS-441524 to those given a combination of remdesivir and GS-441524 or remdesivir only.

Suggested dosages, benefits and limitations of the drugs are provided below. Recommended drug dosages (Table 1) depend upon clinical presentation; that is, whether there is an effusion present or not and whether there is ocular and/or neurological involvement – this is due to variation in the tissue penetration of the drugs. Where there is doubt, use of the higher dosage is preferable.

ISFM Clinical Protocol

Please note that these dosages of oral GS-441524 are higher than quoted in some publications; this is because these publications have used illegal preparations of so-called GS-441524 in which the amount of active agent given to the cats was not confirmed and was likely to be higher than suggested by the manufacturers. The dosages provided below are based on experience using a reputable oral preparation of known GS-441524 content. Thus, extrapolation is not applicable to other oral preparations where the active component and/or its concentration are not known or given by the manufacturer.

Table 1: Summary of dosage recommendations for remdesivir and GS-441524

Clinical presentation	GS-441524 – oral	Remdesivir – by intravenous or subcutaneous injection
Cats with effusions and without ocular or neurological signs	10–12 mg/kg q24h	10 mg/kg q24h
No effusion and without ocular or neurological signs	10–12 mg/kg q24h	12 mg/kg q24h
Ocular signs present (effusive and non-effusive)	15 mg/kg q24h	15 mg/kg q24h
Neurological signs present (effusive and non-effusive)	10 mg/kg q12h (ie, 20 mg/kg/day given as a divided dose)	20 mg/kg q24h

Oral GS-441524-only treatment protocol:

Cat is deemed well enough to receive oral medications

An oral GS-441524 treatment only protocol is recommended if the cat can tolerate oral medications and/or injections are not tolerated and/or financial constraints exist:

1. Once (or twice if very high neurological dosage needed) daily **oral GS-441524** (see Table 1 for dosages) **continued until at least day 84 (ie, full 12-week treatment course).**

Combined injectable and oral treatment protocols:

Cat has very severe disease *(eg, anorexic, dehydrated, cat usually will be hospitalised to allow for appropriate supportive care to be given)*

1. Initial treatment can be given with once daily **intravenous remdesivir** (Table 1) for a few days. This provides a loading dose of the drug in cats that cannot receive oral medications or are too dehydrated to receive subcutaneous injections. On each day, dilute the remdesivir dose required to a total volume of 10 ml with saline and administer *slowly* over around 30 mins manually or with a syringe driver.
2. It is possible to change to once daily **subcutaneous remdesivir** at the same dosage (Table 1) once the cat is hydrated but still not able to accept oral medications
3. Remdesivir can be given for the number of days that medication using injectables is needed. More recently this has comprised just a few days early in treatment; for example, first 2–3 days of treatment.
4. Change to once daily (or twice daily if very high neurological dosage is needed) **oral GS-441524** (Table 1) as soon as oral medication can be tolerated and **continue until at least day 84.** However, injectable remdesivir (usually switching from intravenous to subcutaneous administration when cat is rehydrated) can be given for the full 84-day treatment course, if this is the only antiviral available and/or oral medication is not possible.

Less severe disease *(normal hydration, eating)*

1. If an injectable is required but the cat has less severe disease, treatment can be started with once daily **subcutaneous remdesivir** (Table 1) and continued for the duration that injectables are needed. Subcutaneous remdesivir is given as the formulation in the vial – no dilution is required.

2. Change to once daily (or twice daily if very high neurological dosage is needed) **oral GS-441524** (Table 1) as soon as oral medication can be tolerated and **continue until at least day 84.**

Potential adverse effects of remdesivir
Remdesivir seems well tolerated; however, the following adverse effects have been reported:

- Transient local discomfort/stinging on injection (see later on prevention).
- Development/worsening of a pleural effusion (not always proteinaceous) in the first 48 h of treatment, sometimes requiring drainage.
- Cats may seem depressed or nauseated for a few hours after IV administration.
- Increases in alanine aminotransferase (ALT) enzyme activity have been reported (it is unclear if this is due to underlying FIP disease or an adverse drug effect) but seem to resolve when treatment is stopped.
- Mild peripheral eosinophilia has been reported.

NOTE ON WEIGHING CATS
It is very important to **weigh cats weekly** during treatment, using accurate scales – weight gain and/or growth in kittens will occur with successful treatment necessitating **an increase in dose** to ensure that the **dosage of antiviral administered is still appropriate** for the type of FIP being treated as in Table 1.

Options for cost-limited clients – please note that treatment must be given using the recommended formulations and dosages for the full 84 days to increase the likelihood of cure. Only take the options below if absolutely necessary, as relapse may occur, which then requires longer treatment, thus increasing costs:

- Give oral GS-441524 treatment only for 84 days, as outlined above.
- Give oral GS-441524 or injectable remdesivir for as many days as the owner can afford before switching to **oral mefloquine,** 62.5 mg 2–3 times weekly (for a large cat, give three times a week) or 20–25 mgs orally once daily if reformulation of tablets into 20 or 25 mg tablets is possible (eg, PCCA Ltd) for completion of an 84-day treatment protocol; mefloquine is cheaper than GS-441524 and remdesivir but more research is needed to judge its effectiveness in this situation.
- If an increase in GS-441524 or remdesivir dosage is required (eg, due to neurological disease appearing during treatment) but cannot be afforded, mefloquine treatment can be added as adjunct treatment, as this is cheaper, although more research is needed to judge the effect of this combination.
- Feline interferon omega or propenyl immunostimulant have been used in the period following the end of treatment with GS-441524 or remdesivir but further research is needed on this combination to judge if it is necessary. Currently there is no evidence to suggest they are needed.
- Mefloquine has sometimes been used in the period following the end of treatment with GS-441524 or remdesivir to try and reduce the chances of relapse occurring; further research is needed to judge if it is necessary. Currently there is no evidence to suggest it is needed and many cats do well after finishing treatment if they fully recovered during treatment.
- As ALT can rise during treatment with GS-441524 or remdesivir, some suggest the use of hepatoprotectants (eg, S-adenosyl-L-methionine [SAMe]) during antiviral treatment, but further research is needed on this combination to judge if it is necessary. Currently there is no evidence to suggest it is needed.
- Limit tests for monitoring – see below.

Are oral treatments given with or without food?

- **GS-441524** is given on an empty stomach after an overnight fast for a morning dose or after a few hours fast for an evening dose, washing down with a little water. Food can be given 1 h after treatment. GS-441524 can be given with a small treat or crushed into a small amount of Lick-e-Lix if this makes administration possible.
- **Mefloquine** is given with food, otherwise vomiting often results.

Do not forget to support clients giving oral medications, as this can also be challenging. Direct clients to the International Cat Care website for information and videos: https://icatcare.org/advice/how-to-give-your-cat-a-tablet/

What can I do to help the owners administer subcutaneous remdesivir?

Injection with remdesivir can cause transient local discomfort. If a switch to oral GS-441524 is not possible, the following may help reduce discomfort and improve compliance:

- Ensure owners use a new needle each time to withdraw the drug from the bottle (this will reduce the risk of bacterial contamination of the bottle, as well as alcohol swabbing the reusable seal top of the bottle before entry of the needle).
- Ensure owners change the needle after withdrawing the drug from the bottle and before injection (puncturing the reusable seal will blunt the needle).
- Needle size preference varies; some prefer a 21 G needle to make injecting quicker, others find a finer 23 G needle is better tolerated, so it may be worth trying both if problems arise.
- Rotate the injection sites.
- Have remdesivir at room temperature before administration.
- Oral gabapentin (50–100 mg per cat) may be helpful and/or transmucosal or subcutaneous buprenorphine given at least 30–60 mins before the remdesivir injection to induce mild sedation/analgesia.
- The area to be injected can also be clipped to help owners locate the appropriate site to inject and so that topical EMLA cream can be applied 40 mins before injection, although surface desensitisation may not help as it is usually the remdesivir under the skin that causes discomfort.
- Ensure the full dose of injection is administered at each time point and encourage owners to report any mishaps as this may influence decisions if relapse occurs.
- Encourage owners to make the injection experience more positive by using treats (eg, Lick-e-Lix, Dreamies) around the time of injection, or stroking, brushing or playing with the cat if they are less food motivated. Suggest owners spend time each day with their cat positively engaged to avoid any damage to cat–owner relationships, which can reduce compliance.

What should I expect during treatment?

- In the first 2–5 days you should see an improvement in demeanour, appetite, resolution of pyrexia and reduction in abdominal (Figure 3) or pleural fluid if an effusion is present (note that in some cases pleural fluid can transiently worsen in the first couple of days – if the cat is at home, advise the owner to measure resting respiratory rate, plus respiratory effort); effusion typically resolves by 2 weeks.
- If an effusion is still present at 2 weeks, consider increasing the dosage (by 3–5 mg/mg if possible) to one that is greater than that being used; for example, increasing the dosage from that used for cats with effusions only.
- Serum albumin increases and globulin decreases (ie, they normalise) over 1–3 weeks but note that globulins can initially increase when a large volume effusion is absorbed.
- Lymphopenia and anaemia may take longer to resolve, up to 10 weeks, and a lymphocytosis can be seen as a result of treatment.
- Mild peripheral eosinophilia is a common finding and may be a favourable marker for disease resolution, as it is in COVID patients.
- Mild elevations of ALT and, less frequently alkaline phosphatase, may be documented during treatment and should resolve once treatment is completed.
- Lymph node size reduces over a few weeks.
- If progress is not as expected, consider reviewing the diagnosis (see below) and/or increasing the dosage.

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Figure 3: A cat with FIP and ascites. Effusions should start to resolve over 3–5 days after starting treatment.

What do I need to monitor during treatment?

- Ideally, serum biochemistry and haematology after 2 weeks and then monthly; alpha-1 acid glycoprotein (AGP) may be useful to predict remission (by returning to normal if elevated before treatment).
- However, for cost limited clients, monitoring weight, demeanour, effusions (eg, by in-house scanning [although abdominal girth measurement is a crude alternative for monitoring abdominal effusions]), neurological signs and/or key biochemical abnormalities only (eg, measuring just globulin, bilirubin and/or spinning microhaematocrit tube for packed cell volume/total proteins/colour of plasma) is adequate.
- NB. ALT enzyme activity may increase – it is not clear if this is due to FIP pathology vs drug reaction, and it is not usually a reason to stop therapy. It is not known if the addition of hepatoprotective therapy (eg, SAMe) is helpful in these cases and currently there is no evidence to suggest it is needed.
- Point-of-care ultrasonography (POCUS) to monitor for effusion resolution and/or lymph node size is useful if available and affordable.

If I am seeing a positive response to treatment, when do I stop treatment?

- Not before 84 days (12 weeks).
- Confirm resolution of previous abnormalities (clinically, POCUS, serum biochemistry [including albumin to globulin ratio of >0.6 and normal AGP if possible] and haematology).
- Only stop treatment once the cat has been normal (clinically and on serum biochemistry and haematology) for at least 2 weeks.

If I am seeing no response or a partial response to treatment, what do I do?

- Ensure that you are still confident that the cat has FIP – review the diagnosis, look for additional pathology, consider repeat sampling (eg, external laboratory analysis of any fluid; cytology or biopsy of lymph nodes) and AGP.
- If biochemical abnormalities (hyperglobulinaemia in particular) remain present after 6–8 weeks, then increase dose as for relapse (below).

What do I monitor after treatment?

- Advise the owner to monitor the cat closely for any clinical relapse – this monitoring should continue for 12 weeks after completion of treatment.
- Ideally, repeat serum biochemistry and haematology 2 weeks and one month after stopping treatment (to detect any changes that could suggest early relapse).

- Note that relapse can occur with clinical signs but without any significant biochemical/haematological abnormalities.

In the event of relapse

For example, recurrence of effusion, pyrexia, development of ocular or neurological signs or return of hyperglobulinaemia:

- Ensure that you are still confident that the cat has FIP – review the diagnosis, look for additional pathology, consider repeat sampling (eg, external laboratory analysis of any fluid; cytology or biopsy of lymph nodes) and AGP.
- If relapse occurs during treatment, increase the dosage of GS-441524 or remdesivir by 3–5 mg/kg per day and monitor as above, ensuring treatment is not stopped before the cat has been normal for at least 2 weeks. The increased dosage used will depend on the dosage the cat is on at the time of the relapse, the nature of the relapse and finances but can be up to that recommended for neurological FIP (see Table 1).
- If relapse occurs after completion of treatment, restart treatment with GS-441524 or remdesivir at a higher dosage (3–5 mg/kg per day higher than used previously) and treat for another 12 weeks. The increased dosage used will depend on the dosage the cat is on at the time of the relapse and the nature of the relapse but can be up to that recommended for neurological FIP (see Table 1).
- If it is not possible to increase the dosage of GS-441524 or remdesivir (eg, the highest neurological dosage is already in use), consider adding in mefloquine as an adjunct treatment (see above).

Neutering, parasiticides and vaccination during or after treatment for FIP

- Neutering is ideally performed a month after treatment is completed if the cat has responded well. However, if leaving the cat unneutered is causing stress (eg, attempts to escape or distress when queens are on heat), neutering during therapy may be preferred, ideally when the cat is doing well on treatment with at least another 4 weeks of treatment remaining. Some measure AGP to confirm it is normal before neutering.
- There is no contraindication to routine worming and flea treatment for cats on GS-441524 or remdesivir.
- No information is available on vaccination of cats receiving treatment for FIP although analysis of treated cases suggests that cats can be safely vaccinated after or during successful treatment without causing relapse. Vaccines should be administered as is normally recommended for the cat depending on its environment and risk (see WSAVA Vaccination Guidelines for general guidelines on vaccination). If urgent vaccination is required while the cat is being treated owing to the risk of infectious disease, vaccines can be given if the cat is well as vaccination is still likely to be protective. If only two vaccines have been given, consider providing a third dose of vaccine after completion of FIP treatment.
- If veterinary visits and procedures are necessary, clinic stays should be minimised, and Cat Friendly Clinic protocols and handling implemented to reduce stress to the cat.

Adjunctive treatments

- If the cat is on prednisolone treatment, this should be stopped while giving GS-441524 or remdesivir, unless it is required for short-term management of specific immune-mediated disease arising as a result of FIP (eg, haemolytic anaemia).
- Supportive therapies such as antiemetics, appetite stimulants, fluid therapy and analgesics can be given with GS-441524 or remdesivir as required.

Trial treatment with GS-441524 or remdesivir?

Now that effective antivirals are available for the treatment of FIP, they can be used as trial treatments in cases in which FIP is highly suspected rather than confirmed. Although confirmation of a diagnosis of FIP is always preferable, the costs and invasive nature of some diagnostics (eg, collecting biopsies) mean that trial treatment is being increasingly used in the field, especially as treatment should be started as soon as possible.

Potential future updates

We are constantly learning about treatment with these drugs and advice may change in time. Other agents, for example, protease inhibitors (eg, GC374) and other nucleoside analogues (eg, molnupiravir) have also been trialled in cats but are not commercially available at this time. How these agents and other immunomodulatory agents (eg, polyprenyl immunostimulant, interferon omega) will fit into a future protocol is unknown at this time.

Further reading

Tasker S, Addie D, Egberink H, et al. ABCD guidelines feline infectious peritonitis – factsheets & diagnostic tools. 2022, accessed 16 January 2023. *https://www.abcdcatsvets.org/portfolio-item/factsheets-tools-for-feline-infectious-peritonitis-fip/*

Thayer V, Gogolski S, Felten S, et al. 2022 AAFP/EveryCat feline infectious peritonitis diagnosis guidelines. *J Feline Med Surg* 2022**;** 24: 905–933.

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The above specialists have come together to run the 'FIP advice' email address (fipadvice@gmail.com) answering queries on the new treatments on a voluntary basis and disseminating information to vets and vet nurses in the UK. So far, they have answered over 700 emails on the advice line.