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Fight FIP

Unraveling feline infectious peritonitis from the ground up

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Summary

- For those families living with a diagnosis of feline infectious peritonitis (FIP) and for the veterinarians involved in their care, we understand that the decision to pursue the use of unlicensed therapy for what is otherwise an invariable fatal disease presents an ethical dilemma.
- Due to concerns about the safety and efficacy of black-market imitators of GS-441524, combined with the fact that veterinary oversight of such use is fraught with legal and ethical dilemmas, we

cannot advise the use of such treatment at this time.

- We strongly caution against widespread use of single-agent antiviral therapy in catteries and shelters with endemic feline enteric coronavirus (FECV). Broad use in such settings is expected to generate antiviral resistant FIP strains.
- In cases where treatment is pursued, we recommend cat owners work with their veterinarian to ensure an accurate diagnosis (AAFP guidelines) and to have their pet monitored continually during the treatment process. Information on clinical trials can be found at: https://www.fipvetguide.com/studies

Position Statement

We have received many inquiries regarding the use of the GS-441524 in the treatment of FIP. The following is a summary of GS-441524 as well as our position on its current use. Research into the use of this compound was first published by Dr. Niels Pedersen of UC Davis in 2018. Dr. Pedersen's team published a follow-up study documenting the use of GS-441524 in naturally occurring FIP cases in 2019. The results of both studies were unprecedented with a 100% (10/10) recovery rate reported in experimentally infected cats and 84% (25/31) recovery rate in naturally infected cats. Of the recovered cats, owners reported that they returned to "near normal" within two weeks of treatment. Fever typically resolved within the first 12-36 hours, accompanied by a return in appetite. Effusions resolved over the course of 10-14 days and jaundice gradually receded over the course of 2-4 weeks. The conclusion of the 2019 study proposed the optimized treatment protocol for GS-441624 use as 4.0 mg/kg given as a subcutaneous injection once daily for at least 12 weeks.

Although natural infection proved more challenging to control than experimental infection, most cats in the study responded to treatment. Dr. Pederson is a pioneer in the field of FIP research and there is no question

about the legitimacy of his work. Unfortunately, there are many questions surrounding the current use of GS-441524. Most of these concerns relate directly to the fact that this drug cannot be purchased legally from a regulated source. While this has hampered consumer access, it has also blocked research into the best practices for use and marginalized the role of veterinarians in treatment decisions.

GS-441524 is owned by Gilead Sciences, an American biopharmaceutical company focused on the development of antiviral drugs. Gilead provided GS-441624 to Dr. Pederson for use in his 2018 and 2019 studies but declined to market the drug for use in cats due to its close relationship to another promising antiviral, remdesivir. Prior to the SARS-CoV-2 pandemic, remdesivir was being tested as a treatment for Ebola. In a story complicated by the challenges of licensing human drugs, it is speculated that Gilead had concerns that any adverse effects from GS-441524 reported in cats would hurt remdesivir in its FDA approval process declined to license it for use in cats.

This created a black-market for GS-441524 led by overseas entrepreneurs looking to capitalize on the desperation caused by a diagnosis of FIP. The treatment course is expensive, ranging anywhere from 1000, to upwards of 10,000 dollars. There is no formal regulation of these black-market suppliers or their products. Veterinary professionals may be in legal jeopardy for recommending, dispensing, or administering such unapproved drugs. This combination of factors may prevent cats under treatment from receiving optimal care. We understand that FIP is an otherwise fatal disease so these risks may seem worthwhile, but we caution that the unregulated use of GS-441524 has the potential to promote antiviral resistance and compromise the success of future FIP treatments.

GS-441524 is a nucleoside analog. When the viral RNA polymerase incorporates GS-441524 into the viral genome this jams up the replication machinery and causes premature termination of transcription, hampering the ability of the virus to replicate. We know from experience with nucleoside analogs designed to target HIV that these drugs do not completely suppress viral replication. Use of single-agent therapy leads to

the development of resistant strains. Our most successful experience with antiviral treatments involves combination therapies targeting different aspects of viral replication. Such combination treatments lead to superior viral suppression and decrease the incidence of antiviral resistance.

An oral nucleoside analog of GS-441524 is currently being marketed under the guise of a supplement to support the feline immune response. A preliminary study by Dr. Dianne Addie, reports that this treatment stops shedding of the parent enteric coronavirus, also known as FECV. This work investigates the prophylactic use of a nucleoside analog in multi-cat environments where cats are at high risk of developing FIP. While these results appear positive on face value, they raise deep concern for the development of antiviral resistance. While there is a precedent for pre-exposure prophylaxis in people at high risk of contracting HIV, it is important to point out that this medication, known as Truvada, is a combination antiviral therapy. Decades of experience with HIV has demonstrated that monotherapies are much more likely to result in antiviral resistant strains.

Dr. Addie makes a compelling argument for the involvement of veterinarians and researchers in the use of novel FIP therapies. We want to add that there is an obligation to discourage any use that is expected to lead to the development of antiviral resistance. From a one-health perspective, both wild and domesticated cats appear to be susceptible to SARS-CoV-2. This has implications for both the veterinary and human worlds: coronaviruses are well known for their ability to recombine within susceptible hosts and the possibility exists that we will find ourselves in uncharted territory with emergence of recombinant viruses generated under selective antiviral pressure.

One silver lining to the dark cloud of the SARS-CoV-2 pandemic is that we may soon be able to put concerns about the black-market use of GS-441524 aside. Its close relative, remdesivir, has recently received FDA approval for use in pandemic SARS-CoV-2 infection in humans. Now that the primary obstacle to licensing has been cleared, we are optimistic that this will pave the way for legal and science-based use of GS-441524 in cats. While the

initial studies of GS-441624 showed great promise, important research remains to be done in the setting of broader use. Early data on the efficacy of remdesivir for treatment of COVID-19 illustrated better outcomes than those seen in a larger WHO study, where the drug has at best a modest effect on outcomes.

In regard to combination therapy, there are other potential antiviral drugs in consideration for use against FIP, in particular the protease inhibitor GC376 has an entirely different mechanism of action and is a promising component of combination therapy. (Although not discussed here, use black market GC376 involves a situation very similar to that of GS-441524.) Research into treatment of COVID-19 in humans will undoubtedly lead to the development of therapies that also show promise in cats. Dr. Pedersen has published preliminary data on 25 such compounds, some of which showed potential for combination therapy. While waiting on approval for GS-441524, there will be questions about the off label use remdesivir in cats. We caution that the effects of drugs across species can be unpredictable and laboratory work is needed to determine parameters for safety and efficacy.

For those families living with a diagnosis of FIP and for the veterinarians involved in their care, we understand that the decision to pursue the use of a unlicensed therapy for what is otherwise an invariable fatal disease presents an ethical dilemma. We hope that this statement provides a useful frame of reference on the history of GS-441524 while highlighting the potential for antiviral resistance with unregulated use. Dr. Pedersen has published his own commentary on the unlicensed at home use of FIP antivirals which provides more detailed information on strategies for current use. In the Whittaker Lab, we continue to perform vital basic research into the mechanism's coronaviruses use to expand their cellular tropism with the goal of better understanding the factors that lead to emergence of diseases such as FIP and COVID-19. We are committed to working together in solidarity with our fellow researchers, veterinarians, and cat caretakers to create a future without FIP.