Neurological and ocular FIP

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Background

What is FIP? - FIP is caused by a common and a largely innocuous enteric coronavirus, like those causing colds in humans and diarrhea in foals, calves and poultry. Most cats are infected with the feline enteric coronavirus (FECV) at about 9 weeks of age and may be reinfected several times before reaching 3 years of age. FECV infections, like those of any other infections of cats, become less common after this time. In about 10% of cats, mainly kittens, the enteric coronavirus will undergo specific mutations that allow it to escape the cells lining the lower intestine and infect the most basic cell of the immune system, the macrophage. This macrophage infection is eliminated in all but 0.3-1.4% of cats, which for unknown reasons are unable to develop the required protective immunity. However, in some cases the infected macrophages leave the intestinal lymphoid tissues and migrate in the bloodstream to distant sites including small veins in the linings of the peritoneal cavity, the uveal tract of the eye, the ependyma and meninges of the brain and spine. The disease that occurs in about 1% of of cats can clinically manifest within days, several weeks, sometimes months, and rarely a year or more. The form of disease that is manifested is referred to simply as wet (effusive) or dry (non-effusive). These two forms are easily distinguishable, although there may also be transition forms between the two. Some cats may present with signs of dry FIP but later develop wet FIP, or vice versa. Overall, about one-half of cats will present with wet FIP and one-half with dry FIP. Less than 5% of diseased cats, usually those with milder forms of dry FIP to start, will survive longer than one year, even with the best symptomatic care.

FIP manifestations and forms

Clinical manifestations of FIP- The clinical manifestations of wet (Table 1) and dry (Table 2) FIP vary according to the site(s) of in the body where infected macrophages end up and cause inflammation. The intensity and character of the inflammation is responsible for the disease form. Wet FIP is the more acute and severe form of FIP and is characterized by accumulation of inflammatory fluid either in the abdominal cavity and/or chest cavity. Involvement of the central nervous system (CNS) and eyes is relatively uncommon in the wet form of FIP (Table 1). The dry form of FIP is characterized, not by diffuse inflammation and fluid effusion, but rather by less numerous and more tumor-like lesions (i.e., granulomas) in organs (e. g., kidney, cecum, colon, liver, lung, lymph nodes) within the abdominal or thoracic cavities, or in the eyes and brain (Table 2). Whereas the brain and/or eyes are only involved in 9% of the wet cases, neurological and-or ocular disease is seen as the main presenting clinical sign in 70% of cats with dry FIP.

Table 1. Variability in clinical signs of effusive (wet) FIP from cats necropsied at UC Davis

Signs referable to:	% affected
Peritoneal cavity	**58**
Peritoneal & pleural cavity	**22**
Pleural cavity	**11**
Peritoneal cavity, eyes	**2.8**
Peritoneal cavity, CNS*	**1.9**
Peritoneal and pleural cavity, CNS	**0.9**
Peritoneal and pleural cavity, eyes	**0.9**
Pleural cavity, CNS, eyes	**0.9**
Peritoneal cavity, CNS, eyes	**0.9**

***Central nervous system (brain, spine)**

Table 2. Variability in clinical signs of non-effusive (dry) FIP from cats necropsied at UC Davis

Signs referable to:	% affected
Peritoneal cavity	**30**
CNS	**22**
Eyes	**14**
CNS & eyes	**8**
Peritoneal cavity, eyes	**7**
Peritoneal & pleural cavities	**4**
Peritoneal & pleural cavities, CNS	**3**
Peritoneal & pleural cavities, eyes	**2**
Peritoneal cavity, CNS, eyes	**2**
Pleural cavity	**1**

The blood-to-brain and blood-to-eye barriers

Background- The eye and central nervous system (CNS) are protected from harmful substances/agents by what is called the blood-to-eye and blood-to-brain barriers. These barriers have great evolutionary significance because they protect both brain and ocular functions from the effects of systemic toxins and infectious agents. Such barriers evolved over millions of years by positive selection for the fittest. The blood-to-brain barrier in cats will exclude around 80% of most drugs, while the blood-to-eye barrier excludes about 70%. Therefore, if a given dose of drug such as GS-441524 achieves an effective blood (plasma) level of 10 uM, the levels in the brain (cerebrospinal fluid) will be only 2 uM and the level in the eye (aqueous humor) only 3 uM. However, higher levels are probably achieved in inflamed tissues and will decrease as the inflammation subsides. This may be one explanation for the rapid improvement often seen in the first few days of treatment.

There are several other aspects of these two blood barriers that need to be considered. First, their efficiency at excluding unwanted substances and agents varies between individuals. Second, the

efficiency of this barrier will decrease in inflamed tissues and increase as inflammation subsides. This is good for treatment in the early stages of disease but bad for treatment in the final stages when the inflammation is gone and only the virus is left. Thirdly, there is no simple, safe or effective means to decrease these barriers and the only way to increase drug levels in brain or eyes is to increase their levels in blood plasma by giving a higher dosage orally or parenterally.

How these barriers effect the forms of FIP- Paradoxically, the ocular and neurological forms of FIP are also a result of these same barriers, but in this case of neurological and/o ocular FIP, the impediment is to the entry of antibodies and immune lymphocytes. The phenomenon of neurological disease following a common systemic virus infection is well known in humans and animals. The prime example is polio-encephalomyelitis in people and canine distemper in dogs. The polio virus is a common enteric pathogen and usually causes an inapparent or mild intestinal infection. However, in some people the virus also escapes to the brain and spinal cord. People mount a vigorous systemic immune response to the polio virus, which is highly effective in eliminating the virus in parts of the body except for the nervous system, where the blood-to-brain barrier limits is an impediment to immunity. These unfortunate people will develop the classical neurologic form of the infection. A similar phenomenon occurs with canine distemper. The canine distemper virus, which is closely related to the human measles virus, causes an acute respiratory infection in young dogs that manifests 7-14 days after exposure and lasts for a week or two. Most of these dogs will completely recover, but a proportion will develop neurological disease three or more weeks later. This highly fatal secondary form of canine distemper is caused by virus that escaped into the brain and spinal cord during the respiratory phase of infection and is shielded from the host's immune system by the blood-to-brain barrier.

The compartmentalization of disease between CNS and other parts of the body may also explain why blood tests are less likely to be abnormal in cats presenting with primary neurological disease or that have relapsed to these forms either during or after treatment for non-neurological FIP. It appears that inflammation within privileged sites like the CNS or less likely to evoke a systemic inflammatory response and to cause significant changes in hematology, increases in total protein and globulin, and decreases in albumin and A:G ratio.

Preliminary diagnosis of ocular and neurological FIP

Preliminary diagnosis -The initial suspicion of neurological and/or ocular FIP is based on the age, origin and presenting clinical signs. FIP occurs mainly in cats under 7 years of age, three-fourths under 3 years and with the highest incidence between 16 weeks and 1-1/2 years. Common presenting signs with both ocular and neurological FIP were retarded growth in kittens and adolescent cats, weight loss in adults and vague signs of ill-health often associated with fever.

The diagnosis of FIP, especially the dry form, is assumed to be difficult. However, a preliminary diagnosis is relatively easy to make given the stereotypic signalment, clinical histories, and physical findings and the rarity of confusing diseases in the highest FIP risk group. The neurological and/or ocular forms of FIP can be confused with feline systemic toxoplasmosis, which is why so many cats with these forms of FIP are tested for toxoplasmosis and treated with Clindamycin. However, systemic toxoplasmosis is an exceedingly rare disease of cats, especially

when compared to FIP. FIP can be easily differentiated by a cat's origin (cattery, foster/rescue, shelter), signalment (age, gender, breed), and basic blood test results. Deep fungal infections (coccidioidomycosis, blastomycosis, histoplasmosis) can cause similar clinical signs to dry FIP but are still uncommon even in their endemic regions. Lymphoma may also be a differential diagnosis for dry FIP, but this disease is usually sporadic and in older cats.

Ocular FIP signs- Ocular disease occurs as a sole or primary presenting sign in about one-third of cats with dry FIP and in association with extra-ocular lesions in two thirds of cases (Table 2). Ocular disease is an uncommon manifestation in cats presenting initially with wet FIP (Table 1). The initial clinical manifestation is unilateral or bilateral anterior uveitis manifested by change in iris color, cloudiness and flocculant debris in the anterior chamber, keratic precipitates on the back side of the cornea, and anisocoria. Retinitis is an accompanying feature in a proportion of cats and manifested by focal tapetal hyporeflectivity associated with local inflammation, and microhemorhage of retinal vessels. Less then one-third of cats with ocular FIP will also manifest vague or definite neurological signs (Table 2). Glaucoma, usually unilateral, and panopthalmlitis occur in some cases and may result in enucleation.

Neurological FIP signs- The same prodromal signs were often seen in cats that manifested neurological disease, but include vague signs of dementia, aggressive behavior, compulsive licking at inanimate objects and other cats, reluctance to jump to high places, spontaneous muscle twitching, abnormal swallowing motions, and occasionally seizures. Later signs include posterior ataxia, inability to jump to high places, physical and auditory hyperesthesia, hyperreflexia, and cerebellar-vestibular signs (crossed-extensor reflex, loss of conscious proprioception), seizures, and increasing incoordination and dementia. Signs of spinal involvement often include fecal and/or urinary incontinence, paralysis of tail and hindlegs, pain over lower back. MRI

Confirmatory tests for ocular and neurological FIP

Background- A definitive diagnosis of FIP is by identifying the presence of viral antigen or RNA within macrophages within typical effusions or lesions by PCR or immunohistochemistry (IHC). A definitive diagnosis can be a difficult and expensive process in many cats and PCR/IHC may be falsely negative in up to 30% of specimens. However, it is not necessary in most cases to meet this level of proof. A strong collection of historical, physical, and less direct laboratory abnormalities can suffice to establish a diagnosis.

Laboratory signs -A diagnosis of ocular and neurological FIP can usually be made with linking characteristic changes in cerebrospinal fluid (CSF) and aqueous humor (high protein, high cells, neutrophils, lymphocytes, macrophages), with suggestive abnormalities in history, physical exam, CBC, serum chemistry panel, or MRI. Total protein concentration is often increased (mean, 9.4 g/L; median, 3.6 g/L; range, 0.85–28.8 g/L) as is the total nucleated cell count (mean, 196/μL; median, 171/μL; range, 15–479/μL). Neutrophils are the dominant inflammatory cell in most cats, while lymphocytes and a mixture of neutrophils and lymphocytes are observed in a smaller proportion.

MRI is a useful tool for diagnosis of neurologic FIP, particularly in combination common signalment/history, typical clinical signs, and CSF analysis. Three distinct clinical syndromes have been identified MRI findings were described in 24 cats with necropsy confirmed neurological FIP (Rissi DR, JVDI, 2018,30:392–399): 1) T3-L3 myelopathy, 2) central vestibular syndrome, and 3) multifocal CNS disease. MRI abnormalities including meningeal contrast enhancement, ependymal contrast enhancement, ventriculomegaly, syringomyelia, and foramen magnum herniation were detected in all cases. 15 cases and consisted of hydrocephalus (10 cases), cerebellar herniation through the foramen magnum (6 cases), cerebral swelling with flattening of gyri (2 cases), and accumulation of fibrin within ventricles (2 cases) or leptomeninges (1 case). Histologically, 3 main distinct distributions of neuropathologic changes were observed, namely periventricular encephalitis (12 cases), rhombencephalitis (8 cases), and diffuse leptomeningitis with superficial encephalitis (6 cases).

In one study, the most useful antemortem indicator of neurologic FIP was a positive IgG anti-coronavirus antibody titer in the CSF. Cats with CSF antibody titers of 1:640 or greater were found only in cats with FIP and were always positive by RT-PCR. Initial studies indicated that CSF antibody was produced, at least in part, within the CNS. However, antibody was detected only in cats with serum titers of 1:4,096 to 1:16,384 in another study and researchers concluded that CSF antibodies were passively acquired. In another attempt to measure local CNS antibody production in cats with FIP, an albumin quotient and IgG index were measured to determine whether proteins in the CSF were of blood or local origin. Neither the albumin quotient nor IgG index identified a pattern consistent with intrathecal IgG synthesis in cats with the CNS form of FIP. In conclusion, it seems that coronavirus antibodies enter the CSF at high levels when they are also at high levels in the serum. Indeed, serum coronavirus antibody titers by IFA in cats with ocular and neurological FIP tend to be among the highest for any form of FIP.

PCR, when done on CSF and aqueous humor with higher protein and cell counts, is highly sensitive and specific for ocular and neurological FIP. It is recommended, however, that only the PCR test targeting the FCoV 7b gene be used and not the less sensitive PCR for FIPV specific mutations in the S gene. The FCoV gene is often used for PCR because it is the most abundant viral transcript and most likely to be detected. The FCoV M gene has also been targeted in some PCRs, as it is highly conserved across all isolates, but transcripts are less abundant than for the 7b gene.

Immunohistochemistry on cells collected from spinal fluid is equally sensitive and specific to PCR on samples with higher protein and cell counts. Antigen is localized specifically to macrophage appearing cells.

The rapid response of FIP to GS-441524 is being used more frequently as a confirmatory test. However, this should only be used when other evidence is strong, but no simpler or less expensive means are available to aid the diagnosis.

Treatment of ocular and neurological forms of FIP

Difficulty in obtaining animal rights for human targeted products - Drug companies like Gilead Sciences and Merck have refused to compromise the development and approval processes of their promising human anti-coronavirus drugs such as GS-5734 (Veklury®/Remdesivir) and EIDD-2801 (Molnupiravir®), or their respective biologically active forms GS-441524 and EIDD-1931. Out of desperation, cat owners around the world turned to the Chinese black market

to obtain drugs like GS-441524. This black market was not entirely profit motivated - the FIP problem in China has also grown with increasing numbers of pet cats. Moreover, even if Gilead Sciences had allowed animal use of GS-441524, the need for an effective FIP treatment has outpaced the official approval and commercialization process, which takes many years. chemical companies and a dozen or more sellers of injectable and oral products have been able to meet the GS demand of tens of thousands of desperate cat owners around the world. The veterinary profession has been reluctant to force human pharmaceutical companies like Gilead to also grant animal rights for their promising antiviral drugs but has increasingly involved with assisting owners with the treatment. It appears, therefore, that the unapproved use of human-orientated drugs like GS-441524, which are also desperately needed for veterinary species, will be the norm for many years.

Viral specific inhibitors- Inhibition of viral genes regulating specific stages of infection and replication have become the mainstays of treatment for chronic RNA virus infections of humans such as HIV and hepatitis C virus. The only effective treatment for ocular and neurological FIP that is currently available is the adenine nucleoside analog GS-441524 (GS), a specific inhibitor of viral RNA synthesis.

A viral protease inhibitor, GC376, has also been proven effective in younger cats with effusive FIP and no ocular or neurological involvement. Other experimental drugs such as the cytidine nucleoside analog Molnupiravir (EIDD-2801) are also in development for severe coronavirus disease in humans and may prove effective in cats with FIP.

GS-441524 treatment- An injectable (SC) and oral form of GS-441524 are available from the unapproved Chinese market. The oral form is equally effective on forms of FIP requiring less than 10 mg/kg daily of injectable GS. The efficiency of absorption of oral GS diminishes at higher equivalent oral dosages. Therefore, the oral form is satisfactory for cats with wet and dry FIP and no ocular or neurological disease. It is also effective for cats with ocular FIP, but the fact that many cats with ocular FIP subsequently develop neurological FIP, can be a problem. Cats with neurological FIP usually require a dosage of GS equivalent to 10 mg/kg daily or higher if needed.

The starting dosage for cats with wet or dry FIP and no ocular or neurological disease signs is 4-6 mg/kg daily for 12 weeks, with the younger and wet cases tending to go toward the lower end and the dry cases toward the higher end. Cats with ocular lesions and no neurological signs start at 8 mg/kg daily for 12 weeks. Cats with neurological signs start at 10 mg/kg, daily for 12 weeks. If cats with wet or dry FIP at the beginning develop ocular or neurological signs they go to the appropriate ocular or neurological dosage. The GS dosage be adjusted weekly to account for weight gains. Weight gain can be tremendous in many of these cats, either because they are so wasted at the start or that they their growth has been stunted. Failure to gain a good amount of weight during treatment is considered a bad sign. The starting dosage is not changed unless there is significant reasons to do so, such as failure or blood tests to improve, slow improvement, poor activity levels, failure of original clinical signs to disappear, or change in disease form to include ocular or neurological signs. If there are good reasons to increase the dosage, it should always be from +2 to +5 mg/kg daily and for a minimum of 4 weeks. If 4 weeks extends the 12-week treatment time, the treatment time is extended to accommodate. One should expect a positive

response to any increase in the dosage and a failure to see improvement indicates that the dosage is still not high enough, drug resistance is occurring, the brand of GS is not what it should be, the cat does not have FIP, or there are other diseases confusing the treatment.

One of the most difficult decisions is to determine when to stop treatment. Although some cats, often younger ones with wet FIP, can be cured in as little as 8 weeks and possibly sooner, the usual treatment time is 12 weeks. Some cats may even require dosage adjustments and even longer treatment periods. Critical blood values such as hematocrit, total protein, albumin and globulin levels, and absolute lymphocyte counts usually normalize in cats destined for cures at 8-10 weeks, at which time there is often an unanticipated increase in activity levels. It is believed, but not proven, that 8-10 weeks in when the cat's own immunity to the infection occurs. This is a situation that occurs with hepatitis C treatment in people, which is also a chronic RNA virus infection that often requires up to 12 weeks or more of antiviral drug treatment.

Cats with ocular disease, and no neurological involvement, have a rapid response to GS and full recovery of vision with minimal or no residual damage in as little as two weeks is expected. Cats that present with neurological abnormalities, develop neurological disease during treatment for other forms of FIP, or manifest neurological signs during the 12-week post-treatment observation period, also rapidly improve but the dosage is much higher, the treatment period often longer, and the cure rate somewhat lower. Treatment failures in cats with neurological FIP are due either to inadequate treatment or the development of drug resistance.

Unfortunately, there is no simple test that will determine when a cure has occurred and the fear of relapse often drives owners, treatment advisors, and veterinarians to extend treatments beyond 84 days. Although a thorough ocular exam can clear an eye of active disease signs, only an MRI and CSF analysis can investigate the conditions in brain and spine. These procedures are expensive, not available to everyone, and may not provide definite evidence that the infection in the CNS has been eliminated.

Fear of relapses causes many people involved in GS treatment to be overly cautious about single blood values that are a little abnormal (e.g., slightly high globulin or slightly low A:G ratio), or terminal ultrasound findings suggesting suspiciously enlarged abdominal lymph nodes, small amounts of abdominal fluid, or vague irregularities in organs such as the kidneys, spleen, pancreas, or intestines. It must be remembered that a normal range for a blood value covers most animals, but that it is a bell-shaped curve and that there will be a few exceptional patients that will have values on the margins of these curves. Ultrasonographers need to consider the degree of pathology that can occur in a FIP diseased abdomen and how scarring and other residual effects can alter normal appearances in successfully treated cats. In situations where such questions arise, it is best to look more closely at the total picture and not just one small part. The most important result of treatment is the return to normal health, which has two components – outward signs of health and inward signs of health. Outward signs of health include a return to normal levels of activity, appetite, appropriate weight gain and/or growth, and quality of the coat. The latter is one of the best measures of health for a cat. Inward signs of health include a return to normal of certain critical values based on periodic complete blood counts (CBC) and serum chemistry profiles. The most important values in the CBC are the hematocrit and the relative and absolute total white blood cell, neutrophil and lymphocyte counts. The most important values in

the serum chemistry panel (or serum electrophoresis panel) are the levels of total protein, globulin, albumin, and the A:G ratio. Bilirubin is often elevated in cats with effusive FIP and can be useful in monitoring the severity and duration of the inflammation. There are many other values in a CBC and serum chemistry panels, and it is not unusual for some of them to be a little higher or lower than normal, and it is best to ignore these values unless they are significantly elevated and associated with clinical signs. For instance, a high BUN and Creatinine that is also associated with increased water consumption, excess urination, and abnormalities in the urinalysis. Platelet counts by machine are notoriously low in cats due to trauma from blood collection and platelet clumping and should always be verified by manual examination of the blood smears. The final decision to stop or extend treatment when confronted with vague doubts from various test procedures should always be based on the outward manifestations of health more than any single test result.

Relapses of FIP during the 12-week post-treatment observation period occur in spite of seemingly good responses and there is no simple blood test to predict them. Relapses usually involve infections that have escaped to the central nervous system (brain, spine, eyes) during treatment for wet or dry FIP not accompanied by neurological or ocular signs. The dosage of GS-441524 used to treat these forms of FIP are often insufficient to effectively overcome the blood-to-brain or blood-to-eye barriers. The blood-to-brain barrier is even more effective than the blood-to-eye barrier, which explains why eye lesions can be more easily cured than brain and/or spinal infections. Relapses that occur in the post treatment period, and that involve, eyes, brain or spine are usually retreated for at least 8 weeks at a starting daily dosage at least 5 mg/kg higher than the dosage used during the primary treatment (e.g., 10, 12, 15 mg/kg daily). It is recommended that oral forms of GS not be used when the dosage exceeds 10 mg/kg daily of the injectable form, as the efficiency of gut absorption is diminished at this point. Cats that cannot be cured of infection at dosages of as high as 15 mg/kg daily are likely to have developed varying degrees of resistance to GS-441524. Partial resistance may allow for control of disease signs, but not a cure, while total resistance is manifested by varying severity of clinical signs in the face of treatment.

Various modifications in the treatment have been created by different FIP treatment groups. Some groups will treat with an exceedingly high dosage of GS from the onset rather than escalating the dosage when indicated, capping off or extending the treatment with a high dosage during the last two weeks at a higher dosage on the hope that it may reduce the chances of relapse. Systemic prednisolone is often prescribed in addition to GS but should only be used temporarily to stabilize severe presenting disease. Systemic steroids will reduce inflammation but tend to mask the beneficial effects of GS and if used long enough, and at higher dosage, possibly interfere with the development of FIP immunity. It is believed that the re-establishment of FIP immunity is an important component of successful GS treatment. Therefore, some people advocate the use of interferon omega or non-specific immunostimulants to further stimulate the immune system, and some employ even different modifications. There is no evidence that capping the treatment with an extra high dosage will improve cure rates. Likewise, interferon omega and non-specific immunostimulants have no proven beneficial effects on FIP when given as sole treatments or as supplements to GS. The practice of adding another antiviral drug, GC376 viral protease inhibitor, to GS treatment in cats developing GS resistance is also emerging and needs research. Finally, it is common for owners, treatment groups, and veterinarians to add in

many supplements, tonics, or injections (e.g., B12) to bolster blood levels or prevent liver or kidney disease. Such supplements are rarely necessary in cats with pure FIP disease.

Causes of treatment failure

Improper dosage adjustments- It is important to start the treatment at the appropriate dosage and closely monitor it with frequent checks of temperature, weight and outward signs of improving health. A CBC and serum chemistry panel that includes basic protein values (total protein, albumin, globulin (TP - Albumin = globulin), and A:G should be done at least monthly. Instructions for adjusting dosage is included in the section on GS-441524 treatment. Expensive serum protein electrophoresis does not add much more useful information.

Poor quality GS-441524- GS-441524 is not approved for marketing in any country and the source is a small number of Chinese chemical companies who sell it to distributors as a pure powder. Sellers dilute it for injection or prepare oral forms for sale under their brand names. There is no independent mechanism to assure the quality of the final product that is being sold to cat owners. Nevertheless, major providers of diluted forms for injection and/or oral preparations have been surprisingly honest and some even offer limited guarantees if treatment with one of their products fails to cure the disease. However, batches sold by some providers have appeared to be adulterated and some are not at the stated concentration. This can also vary between batches, probably because of problems with sellers having intermittent problems with their supply of raw GS and difficulties in meeting owner's needs. Various FIP Warrior groups have good information on the most reliable brands.

Drug resistance- Resistance to GS-441524 can exist at the time of diagnosis, but this is uncommon. Rather, it tends to occur during treatment and is often partial at first and necessitates a higher dosage to accommodate for it. It can become total in some cats. Resistance is the biggest problem in cats with neurological disease, especially those that present with neurological disease or develop brain infections during treatment or within a few days or weeks after treatment has been completed. Many cats with partial drug resistance can be "treated" of their disease signs but will relapse as soon as the treatment is stopped, like HIV therapy. There have been cats successfully treated, partially or completely, for FIP disease signs for over a year with no cure. Resistance ultimately resistance becomes worse and disease signs worsen, the hardships of treatment on owner and cat becomes untenable, or the owner runs out of money.

GS side effects

GS-441524 treatment is amazingly free of systemic side effects. It can cause minor kidney damage in cats with no significant renal impairment, but this does not progress to overt renal disease or failure. Systemic drug reactions of the vasculitis type have been seen in a few cats and can be confused with injection site reactions. However, these drug reactions are at non-injection sites and are often self-limiting or respond well to a short-term low dose of steroids. The major side-effect of GS treatment is pain at the injection sites, which varies from cat to cat and according to the injection prowess of the person doing the treatment (usually the owner). Injection site sores are a problem with some owners and usually occur when the injection site is not moved around the body (stay away from between the shoulders) and not given into the

muscle and nerve layers below the subcutis. I recommend selecting sites starting an inch behind the shoulder blades, down the back to 1-2 inches before the tailhead, and one third to one-half of the way down the chest and abdomen. Many people use gabapentin before injections to help ease the pain. Injection site sores are cleared of surrounding hair and gently cleaned 4 or more times a day with sterile cotton balls soaked in 1:5 dilution of household hydrogen peroxide. They usually do not require any more sophisticated treatment and heal within 2 weeks or so.

GS-441524 treatment prognosis

Accurate data on GS-441524 cure rates are not yet available, but it appears that over 80% of cats with confirmed FIP can be cured. Treatment failures are due to incorrect diagnosis of FIP, inadequate treatment monitoring and dosage adjustment, complicating diseases, poor quality GS, GS resistance, or economic difficulties. The cure rate is somewhat lower in cats with neurological forms of FIP and in aged cats. Aged cats are more apt to have other chronic illnesses that either predispose cats to FIP or complicate overall health.

Cats with neurological FIP may suffer from permanent residual disease signs. This is most true for cats with spinal involvement and urinary and/or fecal incontinence or posterior paralysis. Hydrocephalus and syringomyelia are common complications of neurological FIP and they often persist to some degree even after the infection has been cured. Fortunately, most cats with neurological FIP will recover normal or near-normal function despite persistent MRI changes.

Legal treatments for FIP?

The current hope is that a legal form of GS-441524 will be soon available. A drug named Remdesivir is the best current hope, because Remdsivir it is immediately broken down to GS when administered intravenously in humans, mice, primates and cats. Remdesivir (Veklury®) has been given full approval by the US FDA and similar approval will probably follow in other countries. If so, it can be prescribed by any licensed human physician, and by default, by veterinarians. However, the use of Remdesivir in the US has been limited initially to a specific subset of Covid-19 patients and only under controlled conditions and with continued data collection. Until all restrictions are lifted, it will not be readily available for even human use. We have no experience with treating cats with Remdesivir instead of GS-441524. The dosage of Remdesivir on a molar basis is theoretically the same as GS-441524. GS-441524 has a molecular weight of 291.3 g/M, while Remdesivir is 442.3 g/M. Therefore, it would take 442.3/291.3=1.5 mg of Remdesivir to yield 1 mg of GS-441524. The diluent for Remdesivir is significantly different than the diluent used for GS-441524 and designed for IV use in humans. How diluted Remdesivir will behave when injected subcutaneously over 12 or more weeks of daily treatment is not known. Finally, mild signs of both liver and kidney toxicity have been seen with Remdesivir in humans. GS-441524 causes mild and non-progressive renal toxicity in cats but with no apparent liver toxicity. It is uncertain whether the renal toxicity seen in humans given Remdesivir is due to its active ingredient (i.e., GS-441524) or to the chemical additions meant to enhance antiviral activity.

GC376 approval for cats (and humans) is in progress by Anivive but is still two or more years away. GC376 is a viral protease inhibitor and works downstream from GS-441524, which

inhibits the earliest stage of viral RNA replication. Therefore, it is unlikely to have a significant synergistic viral inhibitory effect and will be much more important in inhibiting drug resistance when used in combination (such as in combination antiviral therapy for HIV/AIDS).

Inappropriate use of GS-441524

Certain veterinary researchers, in conjunction with a major Chinese supplier of GS-441524, are advocating its use to eliminate feline enteric coronavirus (FECV) infection. The rationale is to prevent the appearance of FIP-causing mutant virus (FIPV) and thus prevent FIP. Support for this approach was provided by limited and highly questionable studies with cattery cats naturally exposed to FECV. Although this approach is attractive at first consideration, it is a greatly misguided use of GS-441524 in cats. FECV infection occurs initially in kittens and is not associated with any notable disease signs. Shedding lasts weeks, months, and in some cases indefinitely, but in most cats, it will ultimately cease as immunity builds. Indeed, most cats over three years of age will no longer be shedders. It is highly unlikely that GS-441524 treatment will lead to a more permanent immunity than seen in nature and eliminate cycles of infection and reinfection in younger cats.

Even though our current knowledge of FECV infection brings into serious question this approach, there are even more compelling reasons not to treat healthy cats with GS-441525 or any other antiviral in the future. We already know from published field trials that some primary strains of FIPV are resistant to GS-441524 (and to GC376). We also know that drug resistance has become a growing problem in cats on long term GS-441524, especially for neurological forms of FIP. Therefore, the use of drugs like GS-441524 in large populations of healthy cats will undoubtedly lead to widespread drug resistance in enzootic FECVs. This resistance will also be seen in FIP-causing mutants (FIPVs) of FECV from these populations, making it impossible to use GS-441524 in more and more cats with FIP. Unfortunately, veterinary medicine does not have the resources of human medicine, or the profit incentives, for discovering, testing, and gaining approval for more and more antiviral drugs merely to circumvent natural and acquired drug resistance, such has been accomplished with HIV/AIDS treatment (at least for the time).