

## Summary of GS-441524 treatment for FIP

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We use the same criteria for monitoring treatment as described in the JFMS field trial paper. Owners are asked to keep track of temperature, weight, activity, appetite, clinical signs of original disease at daily or weekly intervals. Blood tests including at a minimum CBC (hemogram) and serum chemistry panel (including serum protein values -total protein, albumin, globulin, A:G ratio) at onset of treatment and every 4 weeks thereafter. It is always helpful when these values, along with weight, are updated in a graph form. The goal is to have a healthy, alert and active cat at the end of 12 weeks of treatment and with normal blood test values, especially for hematocrit, total protein, globulin, albumin and A:G ratio. A significant weight gain is also a good sign and some young or particularly wasted cats can more than double their weight during their treatment. Of course, this is an idealized treatment, and one must expect that dosage may need to be adjusted upward if response is slow or if complications such as ocular or neurological involvement should manifest during treatment.

Supportive (symptomatic) care may be needed to stabilize cats that are critically ill at the time of diagnosis or during the first few days of GS-441524 (GS) treatment. Abdominal effusion should not be removed unless it is compressing the chest and interfering with breathing, as it will just be rapidly replaced at the expense of the rest of the body. However, thoracic effusions are usually associated with varying degrees of dyspnea and should be removed. Thoracic effusions are much slower to recur. Symptomatic care also frequently includes fluids and electrolytes to counteract dehydration, antibiotics when a secondary bacterial infection is suspected, and anti-inflammatories (usually systemic corticosteroids), and rarely blood transfusion. Topical medications may also be needed to counteract severe inflammation and increased intraocular pressure (glaucoma) in some of the cats with ocular involvement.

Corticosteroids such as prednisolone should only be used for the first few days of GS treatment and then discontinued as rapid improvement in health occurs. Long-term use of corticosteroids with GS is strongly discouraged as it can mask improvement signs caused by the GS, especially in cats with neurological FIP, it has no curative power, and may interfere with the development of a protective immune response to the FIP virus. It is possible that this immune response plays a major role in the ultimate cure. If cats are on chronic steroid treatment, there is no need in cats to taper the dosage as there is no evidence that severe adrenal atrophy, such as occurs in humans on long-term steroid treatment, occurs in cats. Many owners, GS treatment advisors, and veterinarians will use various supplements advertised to improve liver, kidney or immune system health as well as vitamins such as B12. These substances have no proven efficacy and I consider them a waste of money.

The treatment with the injection form of GS, which is most common, can also be complicated by injection site sores. The treatment is also hard on both owners and cats, as injections can be painful. There is also a problem in some cats, especially those with neurological involvement, with

development of partial drug resistance, which requires an increasing dosage. Response to treatment is usually within 24-72h and most cats are back to normal or near normal within 2-4 weeks, which is a good sign. We feel that the cure rate for FIP with GS-441424 is over 80%, with treatment failures due to misdiagnosis of FIP, inadequate dosage, complicating disease conditions, and drug resistance. Young cats are easier to treat and have a higher cure rate than old cats >7 years of age, cats with wet or dry FIP not complicated by neurological or ocular disease are easier to cure than cats with neurological FIP.

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. There is an oral form of GS available from at least two sources out of China (Aura, Mutian) and I do not use it so am not familiar with the comparable dosage. However, I do not recommend it when the injectable dosage goes above 10 mg/kg daily, as the efficiency of oral absorption goes down at these high dosages.

I recommend that the dosage be adjusted with weekly weight checks. Weight gain can be tremendous in many of these cats, either because they are so wasted at the start or that they are growing, and/or both. If there is some weight loss at first of treatment, I stay at the original dosage and do not lower it. Failure to gain a good amount of weight during treatment is considered a bad sign. I do not raise a dosage unless there are 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. This is where the art comes into play, because you do not want to get stuck on single blood values that are not quite normal and neglect the overall health status of the cat. For example, the globulin may still be a little high, but other critical blood test values and health status are good. If there is significant reason 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 total WBC 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 is 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.

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. Fear of relapses will also cause those people involved in the decision process 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 often one of the best measures of health for a cat. Inward signs of health are manifested by 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.

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 only when indicated, or cap off the treatment during the last two weeks or in an added two weeks with a higher dosage of GS on the hope that it may reduce treatment time or the chances of relapse. Some 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.

Relapses of FIP during the 12-week post-treatment observation period do occur, and there is no simple blood test to predict when a cure has occurred or if a relapse will occur. 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 high oral concentrations. 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.

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 during a relapse after what appears to have been a successful treatment. Many cats with partial drug resistance can be treated for their disease signs but will relapse as soon as the treatment is stopped. There have been cats "treated" for FIP for over a year with no cure, but ultimately resistance becomes worse, or the owner runs out of money. GS-441524 treatment is amazingly free of systemic side effects. It can cause minor kidney damage in some cats, but this does not progress to overt renal disease. 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.

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 Remdesivir it is immediately broken down to GS when administered intravenously in humans, mice, primates and cats. Remdesivir 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 still limited 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. I have no experience with treating cats with Remdesivir instead of GS-441524. However, groups in Australia and some Asian countries are starting to use it and report identical results to GS-441524. The dosage of Remdesivir on a molar basis is theoretically the same as GS-441524. The free base form of GS-441524 has a molecular weight of 291.3 g/M, while Remdesivir is 602.6 g/M. Therefore, it would take twice as much Remdesivir ( $602.6/291.3=2.07$  mg) 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).