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Use of recombinant feline interferon and glucocorticoid in the treatment of feline infectious peritonitis

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Summary A total of 12 clinically ill cats previously diagnosed as feline infectious peritonitis (FIP) were treated with a combination of recombinant feline interferon and glucocorticoid. A complete remission (over 2 years) and a partial remission (2 to 5 months) were observed in four (33.3%) and four (33.3%) cases, respectively. Those that survived for more than 2 years were all older cats (6 to 16 years old) with the effusive form of FIP.

Feline infectious peritonitis (FIP), a feline coronavirus (FCoV) disease, has been recognized worldwide, and is considered to be a fatal disease of this species (Rohrbach et al., 2001). Generally accepted therapies include glucocorticoid with or without other immunosuppressive agents such as cyclophosphamide (McReynolds and Macy, 1997). Other documented therapies include use of human interferon and a *Propionibacterium acnes* preparation (Weiss et al., 1990), and ozagrel hydrochloride (Watari et al., 1998), but complete resolution of the disease was not reported.

Clinical diagnosis of FIP in the practice setting is a challenge to practitioners. To date, there is no single ante-mortem test both sensitive and specific for FIP, and Sparkes et al. (1991) state that the diagnosis of FIP should depend on the presence of multiple abnormalities which are compatible with this disease to increase the specificity.

Recently, a recombinant feline interferon (rFeIFN) has been marketed in Japan, the UK and EC countries with some feline (Japanese market) and canine (European market) viral infections as the label indications (Martin et al., 2002; Sakurai et al., 1992; Ueda et al., 1993). Although significant antiviral effect of rFeIFN against feline coronaviruses has not been demonstrated in vitro (Mochizuki et al., 1994), the immunomodulatory effects of interferon are generally accepted (Tompkins, 1999) and might be of some use in the treatment of immunologic disease such as FIP.

Clinical diagnosis of FIP was established for 12 cats presented at the hospitals. The cases included six males and six females with ages varying from 3 months to 16 years. The criteria of the diagnosis included: antibiotics non-responsive chronic fever, low normal PCV values or mild non-regenerative anemia (PCV <32%; normal range 29–48%), hyperglobulinemia with electrophoretic evidence of polyclonal gammopathy, non-septic inflammatory ascites/pleural effusion (effusive) with characteristic findings, cytologic or pathologic evidence of pyogranuloma (dry-type), and FCoV serum antibody titer by an immunoperoxidase method using infected cell antigen. The mandatory findings for

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Table 1 Clinical feline infectious peritonitis cases treated with recombinant feline interferon

ID	Breed	Sex	Age	Clinical diagnosis[a]	FCoV antibody[b]	Survival	Postmortem results
1	DSH	FS	1 year 4 months	Effusive, T	1:400	1 month	FIP effusive
2	Abyssinian	M	1 year 4 months	Effusive, P	1:3200	10 days	FIP effusive
3	Abyssinian	F	9 months	Effusive, T	1:6400	2 days	FIP effusive
4	Abyssinian	M	6 months	Effusive, P	1:6400	3 months	FIP effusive
5	DSH	FS	6 years	Effusive, T	1:400	>2 years	N/A
6	Persian	F	11 years 4 months	Effusive, P	1:3200	>2 years	N/A
7	DSH	M	12 years 3 months	Effusive, T/P	1:200	>2 years	N/A
8	DSH	M	3 months	Effusive, T	1:6400	4 months	FIP effusive
9	DSH	M	1 year 4 months	Effusive, T	1:3200	5 months	FIP effusive
10	DSH	MC	5 years 1 months	Effusive, P	1:6400	10 days	FIP effusive
11	DSH	MC	16 years	Effusive, T	1:12800	>2 years	N/A
12	Maine coon	MC	3 years 7 months	Dry, kidney	1:6400	2 months	FIP dry

[a]T: thoracic, P: peritoneal.
[b]Measured by an immunoperoxidase method at Idexx Laboratories, Tokyo, Japan.

effusion were: no evidence of bacterial infection, high specific gravity (SG>1.017), high protein content (TP>3.0 g/dl), low albumin/globulin ratio (A/G<0.8), low cellularity (<10,000 cells/microliter), mixed cell reaction with non-degenerate neutrophils, lymphocytes and macrophages (Sparkes et al., 1991). The diagnosis of FIP was established when the cat had either the characteristic effusion or needle biopsy-confirmed granuloma and all the other findings above.

After the patients were stabilized by general supportive therapies including thoracocenthesis, oxygen administration and fluid therapy, the medical treatment was initiated. For the treatment regimen, rFeIFN[1] was initially administered subcutaneously at 1 MU/kg every other day until remission, followed by weekly subcutaneous injections with the same dosage. Glucocorticoid was used either as intrathoracic injection of dexamethasone at 1 mg/kg once, in case of respiratory emergency, followed by oral doses of prednisolone at 2 mg/kg daily gradually tapering to 0.5 mg/kg every other day, or oral prednisolone only from the start.

Table 1 shows the summary of cases studied and the outcome. Case 5 was a 6-year-old spayed female domestic shorthair (DSH) cat presented with difficulty breathing and fever, and diagnosed as the thoracic effusive form of FIP. The FCoV antibody titer was 1:400 with a marginal low normal PCV of 32% and an elevated serum total protein of 10.8 g/dl with a marked polyclonal gammopathy. With rFeIFN at 1 MU/kg every other day and prednisolone at 1 mg/kg PO bid, the pleural effusion disappeared in 1 week. The maintenance therapy with the weekly doses of rFeIFN and prednisolone at 1 mg/kg PO every other day, the cat was healthy at 14 months from the diagnosis, when the treatment was terminated and the FCoV antibody was <1:100. The cat was still healthy at the end of the 2-year observation period.

Case 6 was a female Persian cat, 11 years and 4 months of age, presented with fever and abdominal distension. The cat had a FCoV antibody titer of 1:3,200, elevated total serum protein of 9.1 g/dl with polyclonal gammopathy, a marginal low PCV and proteinuria. With the induction therapy with rFeIFN at 1 MU/kg SC every other day and prednisolone at 1 mg/kg PO bid, the ascites decreased in 1 month and completely disappeared in 2 months. For the maintenance therapy, the weekly doses of rFeIFN at 1 MU/kg were continued until 2 years from diagnosis and prednisolone was not given. At 2 years, the FCoV antibody titer was 1:800 and the cat was healthy.

Case 7 was a male DSH cat, 12 years and 3 months of age, presented with difficulty breathing, anemia and fever. The thoracocenthesis revealed a characteristic non-septic effusion (TP=4.1 g/dl, A/G=0.47). The serum FCoV antibody titer was 1:200 and total protein was elevated (TP=8.6 g/dl) with polyclonal gammopathy. The induction therapy with rFeIFN at 1 MU/kg SC every other day alone was effective in completely removing the effusion and fever in 17 days, and the treatment was terminated on day 22 with no further maintenance therapy because of the cat owner's financial concern. The cat was reportedly healthy at 2 years from diagnosis.

Case 11 was a 16-year-old castrated male DSH cat with fever, pleural effusion (TP=3.4 g/dl, SG1.027, A/G=0.6) and anemia (PCV=27%).

[1] Intercat®, manufactured by Toray, Japan, marketed by Kyoritsu Seiyaku, Japan.

Although the serum total protein was not significantly elevated (TP=6.2 g/dl), a marked polyclonal gammopathy was noted and the serum FCoV antibody titer was 1:12,800. After thoracocenthesis, an intrathoracic injection of 1 mg/kg dexamethasone was given, and rFeIFN was started at 1 MU/kg SC every other day with daily oral prednisolone at 2 mg/kg. The pleural effusion disappeared in 1 week, when the maintenance therapy with weekly rFeIFN and daily oral prednisolone at 1 mg/kg was started. Prednisolone was then tapered to 0.5 mg/kg PO every other day, and the treatment was stopped at 12 months, when the serum FCoV antibody titer was 1:1,600. The cat was healthy at 2 years from diagnosis.

Those with partial remission included one dry-type and three effusive form FIP cases in relatively young ages. Their survival times were from 2 months to 5 months. The other four cases showed no response to the therapy and all died within 1 month.

The overall efficacy in this study was 33.3% complete response (remission >2 years) and 33.3% partial response (remission 2 to 5 months). Since those that survived for 2 years were all older cats (6 years or older), the disease progression in older cats may be slower or the immunologic pathogenesis may be different in those cats, so that the rFeIFN therapy may have a possible impact on the disease. Since the glucocorticoid therapy has not been proven effective in inducing complete remission of FIP (McReynolds and Macy, 1997), the present results may demonstrate apparent therapeutic effect of rFeIFN in some cases.

A possible criticism for the present study includes the experimental design with no matched case controls. Further controlled studies with confirmed FIP cases are warranted to prove the efficacy of rFeIFN therapy. Although the accuracy of the clinical diagnosis in the present study was in part confirmed by necropsy of the dead cases, there was no way to confirm the diagnosis in those that survived. Therefore, in future studies, immunofluorescence detection of FCoV antigen in the mononuclear cells in the effusion by using a monoclonal antibody may be a good alternative for invasive biopsy. Also, specificity and sensitivity of PCR detection of FCoV genome in the effusion should be established.

The concurrent use of glucocorticoid did not seem to interfere with the effect of interferon in the cases that survived. If the immunomodulatory effects of interferon involves enhancement of the anti-viral immunologic events, it is not compatible with the immunosuppressive effects, against both Th1 and Th2 responses, of glucocorticoid. If interferon exerts its effect through modulation of immunologic inflammatory process, it will be interesting to study optimal dosing schedule with glucocorticoid.

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