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Short survey

Treatment of cats with feline infectious peritonitis

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Abstract

Feline infectious peritonitis (FIP) infection resulting in clinical signs is invariably fatal despite clinical intervention. As FIP is an immune-mediated disease, treatment is mainly aimed at controlling the immune response triggered by the infection with the feline coronavirus (FCoV). Immune suppressive drugs such as prednisone or cyclophosphamide may slow disease progression but do not produce a cure. In nearly every published case report of attempted therapy for clinical FIP, glucocorticoids have been used; there are, however, no controlled studies that evaluate the effect of glucocorticoids as a therapy for FIP. Some veterinarians prescribe immune modulators to treat cats with FIP with no documented controlled evidence of efficacy. It has been suggested that these agents may benefit infected animals by restoring compromised immune function, thereby allowing the patient to control viral burden and recover from clinical signs. However, a non-specific stimulation of the immune system may be contraindicated as clinical signs develop and progress as a result of an immune-mediated response to the mutated FCoV.

Keywords: Feline infectious peritonitis; Cat; Treatment; Review

In the oldest report published, Disque et al. (1968) treated a cat suspected to have feline infectious peritonitis (FIP) with prednisolone, penicillin, and dihydrostreptomycin, and the cat remained alert. At this point of time, etiology of FIP was unknown and the diagnosis of FIP was not confirmed (Disque et al., 1968).

In addition to glucocorticoids, cytostatic drugs such as cyclophosphamide have been used to suppress the immune system. Bilkei (1988) used a combination of cyclophosphamine (4 mg/kg for 24 h), prednisolone (4 mg/kg for 24 h), and ampicillin (100 mg/kg for 24 h) in 151 cats suspected of having FIP that were followed-up for 6 weeks. Of theses 151 cats, 76 cats were regarded as ''healthy'' after therapy. Cats included in this study had no confirmed diagnosis, inclusion criteria were extremely vague, and no control group existed (Bilkei, 1988). Chang et al. (1995) treated 2 cats with glucocorticoids and antibiotics. One of the 2 cats received cyclophosphamide in addition. The cats died after 5 days and 9 days, respectively. FIP was confirmed in histopathology (Chang et al., 1995).

Watari et al. (1998) published a case report including 2 cats (10 months and 7 years old) that were treated with ozagrel hydrochloride, a thromboxane synthetase inhibitor (5 mg/kg or 10 mg/kg for 12 h, respectively), and prednisolone (2 mg/kg for 24 h). Ozagrel hydrochloride suppresses platelet aggregation by production of thromboxane A2 that is a strong platelet aggregating agent (Hiraku et al., 1986). The cat receiving the lower dose was clinically healthy by 2 weeks after initiation of therapy. After 12 months, treatment was discontinued. The cat still remained healthy for the next 6 months. The other cat (receiving 10 mg/kg) was in a good clinical

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condition after 12 days (effusion had also vanished) and stayed healthy until therapy was stopped after 9 months because of the occurrence of nasal bleeding. Ascites recurred and the cat died 11 months after initial remission. Although likely, FIP was not confirmed in these 2 cases (Watari et al., 1998).

Weiss et al. (1993b) administered the antiviral drug ribavirin (16.5 mg/kg for 24 h for 10–14 days orally, intramuscularly, or intravenously) to specific pathogen-free (SPF) kittens 18 h after experimental challenge exposure with a FIP-causing virus. Ribavirin, a nucleoside analog, prevents formation of viral proteins, most likely by interfering with mRNA processing. All kittens, including ribavirin-treated and untreated kittens, succumbed to FIP. Clinical signs of disease were even more severe in the ribavirin-treated kittens and their mean survival times were shortened. Although active against feline coronavirus (FCoV) *in vitro* (Weiss and Oostrom-Ram, 1989; Barlough and Scott, 1990), ribavirin was, therefore, not effective to treat cats with FIP due to the severe side effects (Weiss et al., 1993a). Weiss et al. (1993b) tried to decrease the toxicity of ribavirin by incorporating it into lecithin-containing liposomes and giving it at lower dosage (5 mg/kg) intravenously to cats challenged with a FIP-causing virus. However, a therapeutic concentration of the drug was not achieved with this regime (Weiss et al., 1993b).

Madewell et al. (1978) treated a cat with melphalan, an alkylating agent of the nitrogen mustard group that irreversibly interacts with DNA. This cat was a 3-year old male cat that was feline leukemia virus-positive and suspected to have FIP. The cat was treated with melphalan (starting at 1 mg/kg every 72 h for 9 months), prednisone (10 mg/kg every 12 h, that was reduced after 3 weeks over the next 6 weeks to 5 mg/kg every 48 h), ampicillin (10 mg/kg every 8 h per 10 days), and streptokinase (10^4 IU/cat intraperitoneally after abdominocenteses every 12 h for 4 days). Additionally, vitamins and minerals were administered. The cat responded well to treatment for 9 months, then developed a myeloproliferative disorder and died. Again, the diagnosis FIP was not confirmed in this case either; in histopathology, there was no evidence of FIP (Madewell et al., 1978).

Immune-modulatory drugs are widely used in cats with FIP, including tylosin (Robison, 1968; Colgrove and Parker, 1971; Robison et al., 1971). Tylosin belongs to the macrolide antibiotics, but, like other macrolides, also has immune-modulatory effects (Fraschini et al., 1986; Ras and Anderson, 1986; Katahira et al., 1991a,b; Baba et al., 1998). Robison (1968) used tylosin (22 mg/kg/day) in 10 cats and achieved a "temporary remission"; however, FIP was not confirmed in these cases. Colgrove and Parker (1971) treated 3 naturally occurring cases of suspected FIP with tylosin (starting at 88 mg/kg orally for 12 h) and prednisolone (starting at 4 mg/kg/day) as well as supportive treatment with fluids and vitamins. One cat died after 42 days, the others were still healthy after 180 days and 210 days, respectively. The diagnosis of FIP, however, was also not confirmed in these cats (Colgrove and Parker, 1971). Robison et al. (1971) treated one cat suspected to have FIP with tylosin orally (50 mg/cat for 8 h) as well as prednisolone (10 mg/cat) and tylosin (200 mg/cat) intraperitoneally after abdominocentis. This cat recovered within 2 months; several other cats treated in a similar manner, however, died (Robison et al., 1971).

In a report of Ford (1986), the immune modulator promodulin was used in 52 cats suspected to have FIP that responded favorably to treatment; a rapid remission of clinical signs associated with FIP (anorexia, fever, and effusion) was seen. FIP was also not confirmed, there were no control group, and no long-term follow up included in the study (Ford, 1986).

Bölcskei and Bilkei (1995) treated 29 cats suspected to have FIP in 5 groups over 6 weeks that received either ampicillin (100 mg/kg/day), prednisolone (4 mg/kg/day) and cyclophoshamide (4 mg/kg/day); dexamethasone (2 mg/kg at day 1 and day 5) and ampicillin (20 mg/kg every 8 h for 10 days); human interferon-α (6×10^5 IU/cat 5 days a week for 3 weeks); the paraimmunity inducer Baypamun® (0.5 ml/cat/week for 6 weeks); or nothing. The cats were followed-up for 3 years. Between 29% and 80% (depending on the group) of the cats died within 3 years. Again, FIP was not confirmed in these cats, and inclusion criteria were unclear (Bölcskei and Bilkei, 1995).

Weiss et al. (1990) performed a controlled treatment trial using human interferon-α, *Propionibacterium acnes* (an immune-modulatory compound), a combination, or placebo. Human interferon-α has a direct antiviral effect by inducing a general "antiviral state" of interferon-α-containing cells that protects against virus replication. *In vitro*, antiviral efficacy of human interferon-α against a FIP-causing FCoV strain was demonstrated (Weiss and Oostrom-Ram, 1989). Weiss et al. (1990) included 74 specific pathogen-free cats (52 treated, 22 controls) and induced FIP experimentally. Neither the prophylactic nor the therapeutic administration of high doses (10^4 IU/kg or 10^6 IU/kg) interferon-α, feline interferon-β (10^3 IU/kg), or *P. acnes* (0.4 mg/cat or 4 mg/cat) significantly reduced mortality in treated versus untreated cats. Only in cats treated with 10^6 IU/kg interferon-α in combination with *P. acnes*,

the mean survival time was significantly prolonged for a few days. This is one of the few study published in which the diagnosis FIP was confirmed (artificial induction of FIP, histopathology at the end of the study) and a control group was included (Weiss et al., 1990).

Recently, feline interferon-ω, was licensed for use in veterinary medicine in some European countries and Japan. Interferons are species-specific and the feline interferon differs from the human one concerning its antigenicity (therefore causing no antibody development in cats) and its antiviral efficacy in feline cells. FCoV replication is inhibited by feline interferon-ω *in vitro* (Mochizuki et al., 1994). Ishida et al. (2004) treated 12 cats older than 6 years of age suspected to have FIP with feline interferon-ω (10^6 IU/kg subcutaneously every 48 h initially until clinical improvement, and subsequently once every 7 days), glucocorticoids, and supportive care (Ishida et al., 2004). Of these 12 cats, 4 survived a period of 2 years despite initial presentation with effusion. The diagnosis in the 4 surviving cats was not confirmed and no control group existed in this study (Ishida et al., 2004).

In a recently performed randomized placebo-controlled double-blind treatment trial, 37 cats with FIP were treated with interferon-ω or placebo. In all cats, FIP was confirmed by histology and/or immunohistochemical or immunofluorescence staining of FCoV antigen in effusion or tissue macrophages. All cats received glucocorticoids, either as dexamethasone in case of effusion (1 mg/kg intrathoracic or intraperitoneal injection every 24 h) or prednisolone (2 mg/kg orally every 24 h). In addition, cats received either placebo or interferon-ω at 10^6 U/kg subcutaneously every 24 h for 8 days and subsequently once every week. There was no statistically significant difference in the mean survival time of cats treated with interferon-ω versus placebo. Cats survived for a period of 3–200 days before euthanasia with a mean survival time of 18 days. There was only one long-term survivor (>3 months) that was in the interferon-ω group (Hartmann, 2006; Ritz et al., 2007).

Although there are numerous studies describing treatment of cats with suspected FIP, this review demonstrates that the results of most studies have to be interpreted with caution. Evaluation of the data is hampered by the lack of well-controlled clinical trials in which new treatments are compared against a standard care or placebo. In most studies, presence of FIP was not confirmed before treatment was initiated, making an assessment of the outcome impossible. Also evident from this review of the literature is that there is currently no effective therapeutic regime for control of the FIP. Drugs that effectively control replication of FCoV *in vitro*, like ribavirin, are unfortunately toxic to cats *in vivo*. Starting antiviral treatment at a time point when clinical signs of FIP are already present may be too late as immune-mediated responses to the virus are already overwhelming. Treatment of cats with FIP remains frustrating and success is limited to a few cases that respond favorably within the first few days of illness.

Conflicts of interest

None declared.

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