11. Lichenstein A, Bick A, Cantrell J, et al. Augmentation of NK activity by Corynebacterium parvum fractions in vivo and in vitro. *Int J Immunopharmacol* 1982;58:257–262.

12. Lies M. Volume of opinion warrants merit: this DVM sends FeLV cats home well: his name is not David Copperfield. *Vet Forum*, 1990;9:42–43.

13. Lafrado JL, Mathes LE, Zack PM, et al. Biological effects of staphyloccal protein A immunotherapy in cats with induced feline leukemia virus infection. *Am J Vet Res* 1990; 51:482–486.

14. Hitt ME, McCaw DL. FeLV infection, hemolytic anemia and hypocellular bone marrow in a cat: treatment with protein A and prednisone. *J Can Vet Res* 1988;29:737–739.

Chemotherapy of feline immunodeficiency virus infection

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Feline immunodeficiency virus (FIV) was first isolated from a multiple cat household in Petaluma, California in 1986.[1] The virus has morphologic, physical, and biochemical characteristics similar to those of human immunodeficiency virus (HIV), the causative agent of acquired immune deficiency syndrome AIDS in human beings.[2] However, FIV is antigenically and genetically distinct from HIV.

During FIV infection, a transient primary illness can be recognized and is characterized by fever, neutropenia, and lymphadenopathy.[3] Fever and neutropenia may persist for a few days to weeks, and the generalized lymphadenopathy may last for 2 to 9 months. After a long, clinically inconspicuous period, a second stage develops, with signs of an immunodeficiency-like syndrome. The incubation period for this stage can be as long as 5 years, during which, impairment of immune function develops.[4,5]

The diagnosis of FIV infection may be missed when only vague signs of illness, such as recurrent fever, emaciation, inappetence, lymphadenopathy, anemia, leukopenia, and behavioral changes predominate.[3,6,7] If signs of chronic secondary or opportunistic infections are present, FIV infection is included in the differential diagnosis.

Disease signs observed most frequently are chronic stomatitis/gingivitis (50%), enteritis (20%), infections of the upper respiratory tract (20%) and of the skin (15%).[3,6,8] Neoplasia (lymphosarcoma, myeloproliferative diseases), and neurologic, immunologic, and hematologic disorders are seen in a smaller proportion (5 to 10%) of FIV infections.[9,10] The immunodeficiency-like syndrome is progressive; clinical signs of disease worsen over a period of months to years.

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Treatment

Most cats in the AIDS-like phase of disease respond to empiric and supportive treatment, especially in the early stages of the disease. However, FIV infection is persistent and lifelong and the effect of treatment decreases with time.

Antiviral drugs have been used successfully for treatment of human beings with AIDS.[11] These drugs exert their effect by interacting with crucial steps in the replication cycle of the lentivirus. Various steps can serve as a target for chemotherapeutics (ie, virion binding to the receptor on the target cell; entry into the cell; uncoating of the RNA genome; integration of DNA transcripts into the host genome; processing of the viral precursor proteins; and virion assembly and "budding"). At present, nucleoside analogs like 3′-azido-3′deoxythymidine (AZT) have been studied; these inhibit viral reverse transcriptase and operate at the level of synthesis of DNA from viral RNA. This drug has been shown to prolong the survival and improve the quality of life of AIDS patients.[11]

Because FIV has many properties similar to those of HIV, and infection in cats parallels that in people, with respect to cell tropism and pathogenesis, antiviral drugs were also studied in FIV-infected cats.[12,13] Also, the reverse transcriptase (RT) enzyme of FIV is similar to that of HIV-1 in its sensitivity to several antiretroviral compounds.[14]

Table 1—Inhibitory effect of phosphonomethoxyethyl adenine (PMEA) and 3′-azido-3′deoxythymidine (AZT) on feline immunodeficiency virus (FIV) replication in feline thymocytes

Compound	ED_{50} (μM)	CD_{50} (μM)
PMEA	0.60	80
AZT	0.05	120

ED_{50} = 50% effective dose; CD_{50} = 50% cytotoxic dose.

Table 2—Effect of PMEA and AZT on clinical signs of disease in some of the FIV-infected field cats

Cat	Age (yr)	Drug	Clinical signs: Before treatment	Clinical signs: After treatment
1	4	PMEA	Chronic diarrhea/emaciation retardation	Feces normal Weight gain
2	14	PMEA	Emaciation/gingivitis stomatitis	Stomatitis cured Weight gain
3	4	PMEA	Upper respiratory tract disease/stomatitis	Complete recovery
4	1	PMEA	Emaciation/growth retardation/rhinitis/gingivitis	No improvement Euthanatized
5	10	AZT	Stomatitis/conjunctivitis alopecia	No stomatitis/conjunctivitis, Alopecia improved
6	4	AZT	Upper respiratory tract disease	None

We have tested AZT and the acyclic purine nucleoside analogue 9-2[phosphonomethoxyethyl]adenine (PMEA) for their potential to inhibit FIV replication in vitro and in vivo.[13]

Effect of AZT and PMEA In Vitro

The FIV was grown in feline thymocytes that had been stimulated with concanavalin A (5 μg/ml) and recombinant interleukin 2 (100 IU/ml). The inhibitory effect was tested by adding different concentrations of the drugs to the cultures at 1 hour before infection. After 4 and 6 days of culture in the presence of the drugs, the medium was harvested and assayed for the presence of FIV (eg, by determining RT activity). The 50% effective dose (ED_{50}: the concentration of compound reducing RT activity by 50%, compared with control cultures) and the 50% cytotoxic dose (CD_{50}: the concentration of compound reducing the number of viable mock-infected cells by 50%) were determined.

Both AZT and PMEA emerged as potent and selective inhibitors of FIV infection in vitro (Table 1). The ED_{50} and CD_{50} were close to the values reported for HIV in infected MT-4 cells.[15] The ED_{50} of AZT is lower than that of PMEA, and its therapeutic index is broader. In a murine infection model the potency and selectivity of PMEA, with respect to Moloney sarcoma virus, was greater than that of other compounds including AZT.[15] This was the reason we initiated a study of PMEA in cats with experimentally induced FIV infection.

Effect of PMEA and AZT In Vivo

The prophylactic effect of PMEA on experimentally induced FIV infection was tested in cats. The half-life in vivo was determined in 4-month-old kittens. After IM injection of a single dose of PMEA, maximal plasma concentration was attained after 30 to 60 minutes. Concentration decreased within 6 hours,[13] indicating clearance and accumulation of the drug in cells.

The drug was administered IM twice daily over 35 days. Although infection could not be prevented, PMEA caused dose-dependent suppression of FIV replication. A delay of 3 to 7 weeks in antibody responses was observed, a consequence of the later and less pronounced antigenic stimulation.[13]

The therapeutic efficacy of PMEA and AZT was determined in FIV-positive field cats with signs of opportunistic infections. Both drugs (5 mg/kg of body weight/d PMEA and 10 mg/kg/d AZT) were administered SC twice daily for a period of 3 weeks. In one study,[13] PMEA had a pronounced effect on the opportunistic infections accompanying FIV persistence. Of 6 treated cats, 5 recovered from a variety of severe signs of disease (stomatitis, gingivitis, and diarrhea) and had general clinical improvement (Table 2). In one cat with pronounced stomatitis, the same PMEA treatment regimen was applied twice after recurrence of clinical signs of disease, at 2 and 10 months after initial treatment had been discontinued. After both treatment periods, local signs of disease had completely disappeared and the cat's general health had appreciably improved. In another study by one of us PMEA and AZT (KH), proved to have a therapeutic effect (data not shown).

In addition to inhibiting lentivirus replication, PMEA also restrains herpesvirus infection.[16] Recovery from stomatitis, which in cats is frequently caused by the herpesvirus that causes rhinotracheitis, may have been attributable to this dual effect of the drug.

Toxic side effects like megaloblastic anemia and development of drug-resistent strains have been noticed after AZT administration in people.[17] In cats, anemia can also develop during treatment with PMEA and AZT and treated cats should, therefore be monitored. Normally, anemia develops only at high doses of the drugs. The question of whether drug-resistent strains of FIV develop in vivo still needs to be addressed. In vitro development of AZT resistance has been documented.[18]

Although antiviral chemotherapy does not eliminate FIV from the cat's body, it is of clinical benefit. The cat should still be considered a potent carrier and transmitter of the virus. Long-term prognosis is probably poor. Similar to HIV infection, it can be expected that antiviral drugs extend the life of FIV-infected cats. Besides a possible application of these drugs in veterinary practice, the in vivo screening of these and other newly developed anti-lentivirus compounds in FIV-infected cats can be considered as a useful and readily available model for HIV infection in people.

References

1. Pedersen NC, Ho F, Brown ML, et al. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. *Science* 1987;235:790–793.

2. Yamamoto JK, Sparger E, Ho EW, et al. Pathogenesis of experimentally induced feline immunodeficiency virus infection in cats. *Am J Vet Res* 1988;49:1246–1258.

3. Yamamoto JK, Hansen H, Ho EW, et al. Epidemiologic and clinical aspects of feline immunodeficiency virus infection in cats from the continental United States and Canada and possible mode of transmission. *J Am Vet Med Assoc* 1989;194:213–220.

4. Ackley CD, Yamamoto JK, Levy N, et al. Immunologic abnormalities in pathogen-free cats experimentally infected with feline immunodeficiency virus. *J Virol* 1990;64:5652–5655.

5. Siebelink KHJ, Chu IH, Rimmelzwaan GF, et al. Feline immunodeficiency virus (FIV) infection in the cat as a model for HIV infection in man: FIV-induced impairment of immune function. *AIDS Res Hum Retroviruses* 1990;6:1373–1378.

6. Hopper CD, Sparkes AH, Gruffyd-Jones TJ, et al. Clinical and laboratory findings in cats infected with feline immunodeficiency virus. *Vet Rec* 1989;125:341–346.

7. Ishida T, Washizu T, Toriyabe K, et al. Feline immunodeficiency virus (FIV) infection in cats of Japan. *J Am Vet Med Assoc* 1989;194:221–225.

8. Ishida T, Tomoda I. Clinical staging of feline Immunodeficiency Virus Infection. *Jpn J Vet Sci* 52:645–648.

9. Kölbl S, Schuller W. Serologische Untersuchungen zum Vorkommen des Felinen Immunodefizienzvirus (FIV) bei Katzen in Österreich. *Wien Tierärztl Mschr* 1989;76:185–189.

10. Shelton GH, Grant CK, Cotter SM, et al. Feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) infection and their relationships to lymphoid malignancies in cats: a retrospective study (1968-1988). *J AIDS* 1990;3:623–630.

11. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo controlled trial. *N Engl J Med* 1987;317:185–191.

12. Smyth NR, Gaskell RM, Brown A, et al. Treatment for FIV? (letter). *Vet Rec* 1990;126:409–410.

13. Egberink HF, Borst M, Niphuis H, et al. Suppression of feline immunodeficiency virus infection in vivo by 9-(2-phosphonomethoxyethyl)adenine. *Proc Natl Acad Sci USA* 1990;87:3087–3091.

14. North TW, Cronn RC, Remington KM, et al. Characterization of the reverse transcriptase from feline immunodeficiency virus. *J Biol Chem* 1990;265:5121–5128.

15. Balzarini J, Naesens L, Hendewijn P. Marked in vivo antiretrovirus activity of 9-(2-phosphonylmethoxyethyl)adenine, a selective anti-human immunodeficiency virus agent. *Proc Natl Acad Sci USA* 1989;86:332–336.

16. de Clercq E, Holy A, Rosenberg I. Efficacy of phosphonyl methoxyalkyl derivatives of adenine in experimental herpes simplex virus and vaccinia virus infections in vivo. *Antimicrob Agents Chemotherap* 1989;33:185–191.

17. Landen BA, Danby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science* 1989;243:1731–1734.

18. Remington KM, Chesebro B, Wehrly K, et al. Mutants of feline immunodeficiency virus resistant to 3′-azido-3′deoxythymidine. *J Virol* 1991;65:308–312.