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FELINE VIRUSES INDUCING IMMUNODEFICIENCY (FIV, FeLV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV): COMPARATIVE THEORETIC SUBSTANTIATION, STUDY INITIATION AND PRELIMINARY RESULTS

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The key to unravelling the pathogenic mechanisms and therapeutic approach of the Human Immunodeficiency Virus (HIV) was the research of similar feline retroviruses, namely the Feline Immunodeficiency Virus (FIV) and the Feline Leukemia Virus (FeLV). Differing of the Acquired Immune Deficiency Syndrome (AIDS) treatments, medicines used for FIV and/or FeLV infections proved inefficient (Zidovudine), respectively with severe in vivo and/or in vitro side effects (Lamivudine). This preliminary study marks out the evaluation of the usefulness of standardized marketed chicken egg IgY administration in cats diagnosed with FIV and/or FeLV and to compare the related data with published reports regarding its effects in HIV/AIDS as base to initialise a larger research. The aim of the study was to evaluate the dynamics of their quality of life and of the main standard biochemical and haematological relevant parameters. Preliminary data showed that administering chicken egg yolk IgY to FIV and/or FeLV infected felines has a positive impact: weight gain, anaemia amelioration, white line immune cells boost, as well as slight improvements in appetite and social behaviour in all the treated cats. The product was also free of adverse reactions and therefore vouches for initializing a larger study questing for possible more intimate effects.

Keywords: HIV, FIV, FeLV, IgY

INTRODUCTION

Retroviruses represent a large group of RNA viruses that are found in all vertebrates. They share many common features, such as similarities in genetic organization and mechanism of replication, and in particular for their encoding for a reverse transcriptase. These viruses stand for a significant source of morbidity and mortality in both humans and animals[1].

The human immunodeficiency virus (HIV) is the causative agent of AIDS (Acquired Immune Deficiency Syndrome) - a worldwide pandemic that continues to be a significant cause of morbidity and mortality. Among retroviruses, human immunodeficiency virus type 1 (HIV-1) is the most extensively studied, particularly in terms of drug development. According to the US Food and Drug Administration (FDA), there are approximately 25 drugs currently approved for the treatment of HIV-1[2].

Feline immunodeficiency virus (FIV) and **Feline Leukemia Virus (FeLV)** are lymphotropic retroviruses[3] causing slow virus infections[4] with suppression of immune system of cats consequently and a wide range of clinical signs[3], being among the most important diseases of cats[4].

Feline immunodeficiency virus (FIV) is a retrovirus of the genus Lentivirus that is closely related to human immunodeficiency virus (HIV), sharing a similar structure, life cycle and pathogenesis[5] and distantly related to the feline leukemia virus (FeLV)[6]. FIV is an important viral pathogen worldwide in cats. FIV is transmitted primarily by parenteral inoculation of virus present in saliva or blood, presumably by bite and fight wounds. Clinical signs generally manifest in middle aged cats (4 to 7 years) that have harboured the virus for an extended period. These signs may include chronic gingivitis, periodontal disease, chronic anaemia and leukopenia, pustular dermatopathies, chronic upper respiratory syndrome and generalized lymphadenopathy[5]. Once inoculated into a bitten cat, FIV replicates in monocytes, macrophages and lymphocytes, and spreads throughout the body. The decrease in lymphocytes and macrophages targeted by FIV induces a progressive breakdown of the immune system, which may lead to death[7].

Feline leukemia virus (FeLV) is a retrovirus[8] belonging to the Retroviridae family, Orthoretrovirinae subfamily, *Gammaretrovirus* genus[9], first recognized in 1964[10] and is believed to cause widespread infections in cats throughout the world with prevalences of between 1% and 20% reported from all the major continents[9]. FeLV is comparable to HIV[10] because of its ability to cause persistent and slow virus infection [8] and to induce profound immune suppression in infected cats. In approximately 20% of infected cats, FeLV is capable of causing malignant transformation of lymphoid cells, in addition to profound immune suppression[10]. FeLV is passed vertically from infected queens to kittens *in utero* [9] or after birth through milk[10] and horizontally among cats with prolonged close contact through saliva [10,8], urine and other body secretions[10]. Leukemia is also the major consequence of the disease and cats commonly die as a result of immune deficiency. Cats exposed to FeLV may progress into any one of four categories: abortive infection (formerly 'regressor cats'), regressive infection (formerly 'transient viraemia' followed by 'latent infection'), progressive infection (formerly 'persistent viraemia') and focal or atypical infection. Abortive infection is likely to occur when certain immunologically stable cats are exposed to low doses of the virus, where viral replication may be terminated by an effective humoral and cell-mediated immune response such that neither FeLV antigen nor viral ribonucleic acid (RNA) or pro-viral deoxyribonucleic acid (DNA) are detected in blood. In regressive infection, transient viraemia (during which the virus is detected in plasma) is terminated within weeks or months of infection, but the cats cannot completely eliminate the virus, as the proviral DNA is present in the bone marrow. Cats that have progressive infection are persistently viraemic and develop FeLV-associated diseases, with most of them dying within a few years of infection. Progressive FeLV infection is associated with a variety of malignancies that are characterised by development of cytoproliferative and cytosuppressive disorders. It clinically manifests as severe immunosuppression, profound anaemia, immune-mediated diseases, reproductive problems and enteritis. Focal or atypical infection is associated with localised viral replication that leads to low-grade viral antigen production that produces a weak positive reaction[9].

Current Options of Treatment for FIV and FeLV. Despite the significant achievements and understanding of FIV and FeLV biology, these viruses are still a significant source of morbidity and mortality in felines and the treatment options for infected cats are ineffective, toxic, or cost-prohibited[1]. The lack of effective treatment options leads most owners to choose to euthanize[2] or provide palliative care for FIV/FeLV-infected cats. Palliative care may include medications to treat infections, pain management, nutritional support, or any other care having the goal of keeping the cats comfortable and improving their quality of life[1].

Antiviral Drugs

Table 1 represents a synthesis of the current antiviral drugs used in the treatment of HIV, FeLV and FIV and Table 2 shows the current immunomodulators used as therapeutic options for FIV, FeLV and HIV

Immunoglobulin Y (IgY) is the major antibody produced by chickens (*Gallus gallus domesticus*)[14-17], which corresponds closely, from the point of view of its function in the body and immunochemical use, to mammalian IgG. As early as 1962, IgY protein was identified by Williams as gamma-globulin in a gamma-livetin fraction of yolk[21]. It is continually synthesised at a large scale, secreted into the blood and transferred to the egg yolk, where it accumulates[14, 15, 17, 18]. IgY is produced by hens to provide their offspring with an effective humoral immunity against the commonest avian pathogens until full maturation of their own immune system. IgY (167,250 kDa), although prevalent in circulating blood (5–7 mg/ml of serum) and in egg yolk (100 mg/egg yolk), is also found in duodenal contents, tracheal secretions and in seminal fluid. IgY secretion in the young chick starts 6 days after hatching. The IgY secreted by mature B cells is delivered directly into the circulation, attaining a constant concentration of 1.0–1.5mg/ml of serum. The IgY stored in egg yolk, at the time of incubation, is the antibody source produced by the hen to protect the young chick during the first days after hatching. The IgY antibody concentrations range from 50 to 100 mg per egg yolk. Although IgY can be purified from serum or plasma, egg yolk is by far the indicated source for purification. Eggs can be collected daily from the same hen and processed either individually or, as desired, from hens belonging to a similar immunized group. Over 100 mg of purified IgY can be obtained from a single egg. As hens continue producing eggs along at least 10 months, it is possible to obtain enormous amounts of specific IgY directed to the same or related antigens. There are different methods currently used to isolate IgY from egg yolk. IgY, like mammalian IgG, is a reasonably stable protein. Diluted in saline-containing substances that preserve the protein structure, IgY antibody activity can be stored at 2–4°C. When lyophilized, the IgY antibody activity is not diminished even after several months of storage at temperatures of 20°C or less, or even for 1 month at 37 C. The IgY concentration in the serum of adult hens is approximately 5–7 mg/ml. One hen of a high egg-laying strain can produce around 20 eggs per month. Such amounts correspond to 2 g of IgY per month equivalent, therefore, to the IgY content of 300 ml of serum or 600 ml of total blood. Such amounts of blood only can be obtained from large mammals[15].

Drug	Infection	Efficacy in Vitro	Controlled Field Study in Vivo	Efficacy in Vivo	Observations
NARTIs					
Azidothymidine (Zidovudine, AZT, Retrovir)	HIV	Yes	Yes	Yes	It is used for the treatment of HIV and the prevention of HIV transmission from infected mother to her foetus.
	FIV	Yes	Yes	Yes	Effective in some cats (eg, with stomatitis, neurological disorders)
	FeLV	Yes	Yes	No	Not very effective
Stavudine (d4T)	HIV	Yes	Yes	Yes	It is used for the treatment of HIV infection.
	FIV	Yes	No	ND	Possibly effective but no data in cats available
	FeLV	ND	No	ND	Possibly effective but no data in cats available
Didanosine (ddI)	HIV	Yes	Yes	Yes	It is used for the treatment of HIV infection in adults and children.
	FIV	Yes	Yes	Yes	Effective in 1 experimental study but neurological side effects
	FeLV	Yes	No	ND	Possibly effective but no data in cats available
Zalcitabine (ddC)	HIV	Yes	Yes	Yes	Zalcitabine is used for the treatment of HIV infection.
	FIV	Yes	No	ND	Possibly effective but no data in cats available
	FeLV	Yes	Yes	No	Not very effective
Lamivudine (3TC)	HIV	Yes	Yes	Yes	Lamivudine is used for the treatment of HIV infection
	FIV	Yes	Yes	No	Not very effective &toxic in high doses
	FeLV	ND	No	ND	Possibly effective but also toxic
Receptor Homologs/Antagonists					
Plerixafor	HIV	Yes	Yes	Yes	It is a selective inhibitor of human immunodeficiency virus.
	FIV	Yes	Yes	Yes	Some effects in study in privately owned cats
	FeLV	ND	No	ND	Very likely ineffective

Table 1. List of antivirals tested for HIV, FIV and FeLV[11]

Drug	Infection	Efficacy in Vitro	Controlled Field Study in Vivo	Efficacy in Vivo	Observations
Cytokines & Growth Factors					
Filgrastim (G-CSF)	HIV	Yes	Yes	Yes.	It is used as a treatment strategy for HIV-associated neutropenia.
	FIV	ND	Yes	No	Contraindicated (may increase viral replication)
	FeLV	ND	Yes	No	Ineffective
IGF-1	HIV	Yes	Yes	yes	Increasing body weight and modest improvements in HIV-specific immune function.
	FIV	ND	Yes	Yes	Possibly effective in young cats
	FeLV	ND	No	ND	Likely ineffective
Diethylcarbamazine (DEC)	HIV	Yes	Yes	Yes	It decreases HIV load.
	FIV	ND	No	ND	Likely contraindicated
	FeLV	ND	Yes	No	Ineffective
Lactoferrin	HIV	Yes	Yes	Yes	It decreases HIV load.
	FIV	ND	No	ND	Possibly effective in cats with stomatitis
	FeLV	ND	No	ND	Possibly effective in cats with stomatitis
Nosodes	HIV	Yes	Yes	Yes	It decreases HIV load.
	FIV	ND	No	ND	Likely contraindicated
	FeLV	ND	No	ND	Very likely ineffective

Table 2. Immunomodulators tested for HIV, FIV and FeLV[11, 14, 15]

Immunotherapy using chicken immunoglobulin, termed IgY, may provide new modalities for the treatment of infectious diseases in humans and animals. IgY immunotherapy has been shown to be effective in the prevention and treatment of gastrointestinal diseases in both humans and animals[18].

Effective protection against *Salmonella enteritidis*, *Salmonella e. typhimurium*, *Campylobacter jejuni*[15], *Escherichia coli* ETEC[16,18], murine and bovine rotavirus, and bovine corona virus infections in mice, pig and calves has been obtained with the use of passively-administered egg yolk-derived antibodies[15]. Also these antibodies effectively prevent human dental caries caused by *Streptococcus mutans*, canine distemper infection and canine parvovirus (CPV)[17].

MATERIALS AND METHODS

14 cats diagnosed with FIV or FeLV (out of which only 12 survived the 10 days of treatment period) were included in the study that had the goal of determining the therapeutic results of administering chicken yolk derived IgY immunomodulator., mostly in respect to the life quality improvement and comparing the results to a similar study developed on patients with HIV while using a fairly congenerous IgY immunomodulator. The study was performed according to the in force ethic procedures.

Diagnosis assays Consequent the clinical and paraclinical examinations, the preliminary orientation diagnosis was based on fast tests. The tests used for disease confirmation were ELISA and PCR for FeLV and ELISA and Western Immunobloting for FIV.

Patient selection and anamnesis Following the certainty diagnosis of FIV or FeLV, the anamnesis dossier was compiled and contained the following data: age, sex, hormonal status (neutered or not), place of provenance, living environment (outdoor and/or indoor and the eventual presence of hazards), diet, if there other cats in the same environment (and if this is the case, the exact number), the last anti-parasitic treatment and vaccination, the moment when the disease has first shown clinical signs, the levels of appetite for food and water, prior treatments the cat has received and the nature of the pathology, past surgical interventions, social behaviour and any other specifications that may be of relevance to the ongoing investigation.

Other major pathologies that had the potential of interfering with the validity and precision of the study results represented an exclusion criterion (for example, neoplasms, decompensated cardiac failure, terminal stage kidney failure, pre-comatose or comatose stage, etc.). Two cases also were not accepted, due to the lack of ability from the owners to properly tend to their companion animals.

Clinical and paraclinical assays

The clinical examination was pointed at evaluating the general health status, temperature, approachable lymph nodes, respiratory, neurological and digestive pathologies, tumours, body weight, and any other relevant clinical manifestations.

Blood specimens were sampled, prior and after the treatment, in order to assess the haematological and biochemical relevant parameters for the two pathologies. The blood samples for the haematological assays were preserved on EDTA tubes and the samples for biochemical examinations were preserved in tubes containing Blood Coagulation Accelerator and Serum Separating Gel.

The paraclinical assays consisted of:

(1) complete blood count and blood smears for the entire lot of 14 cats, where the following parameters were targeted: White Blood Cells, Neutrophils#, Lymphocytes#, Monocytes#, Eosinophils#, Basophils#, Red Blood Cells, Haemoglobin, Hematocrit, Mean Corpuscular Volume, Mean Corpuscular Haemoglobin, Platelet Count, Mean Platelet Volume, Platelet Distribution Width, Procalcitonin

(2) biochemical assays, for the following parameters: alanine aminotransferase (ALT), albumin (ALB), amylase (AMYL), aspartate aminotransferase (AST), total bilirubin (Bil T), creatinine (CRE), alkaline phosphatase (ALP), gama glutamyl transferase(GGT), Glucose (GLU), Na, K, Cl, pancreatic lipase, total protein (TP), Urea.

The IgY used is a non-specific IgY, more exactly that obtained after inoculation in chickens of the following bacteria: *Acinetobacter baumannii, Streptococcus pneumoniae, Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Salmonella enteritidis, Salmonella typhimurium, Pseudomonas aeruginosa, Clostridium difficile-spori, Clostridium difficile-corpi bacterieni, Clostridium difficile-anatoxina, Candida albicans, Helicobacter pylori, Streptococcus mutans* and is labelled as a food-supplement. The IgY was administered daily for 10 days, at a dosage of 10 mg, PO.

Symptomatic and supportive therapies implemented for side pathologies:

- 1 patient confirmed with FeLV, due to severe anaemia, received a blood transfusion, which was well tolerated;
- 5 patients confirmed with FIV, due to the presence of bacterial infections, received antibiotics therapy; of the five cases, 4 responded well to the antibiotics, while one case failed to improve its respiratory condition;
- 2 patients confirmed with FIV received supportive respiratory treatment for their upper respiratory chronic syndrome;
- 1 patient confirmed with FIV received antidiarrheal therapy for its chronic digestive disorders;

- 2 patients confirmed with FeLV received renal supportive therapy, due to their conditions of chronic renal failure;
- 2 patients confirmed with FIV received local treatment for a dermatitis of bacterial origin;
- 1 patient confirmed with FIV received local treatment for an otitis of parasitic origin.

Crt.	Age	Sex	Hormonal status	FIV/FeLV confirmed
1	10	Male	Stray	FIV
2	6	Male	Neutered	FIV
3	5	Male	Neutered	FIV
4	2	Male	Neutered	FeLV
5	4	Male	Neutered	FeLV
6	5	Female	Neutered	FIV
7	14	Female	Neutered	FIV
8	9	Male	Neutered	FIV
9	10	Male	Neutered	FIV
10	8	Female	Neutered	FeLV
11	4	Male	Neutered	FIV
12	11	Male	Neutered	FeLV

Table 3. General info of the cats that survived the treatment period

Clinical sign	FIV patients (No/%)	FeLV patients (No/%)
Parasitic otitis	1/ 12.5	0/ 0
Weight loss	6/ 75	3/ 75
Lymphadenopaty	2/ 25	0/ 0
Diarrhea	2/ 25	0/ 0
Vomiting	0/ 0	2/ 50
Modified appetite	5/ 62.5	3/ 75
Respiratory upper chronic disease	3/ 37.5	0/ 0
Uveitis	1/ 12.5	0/ 0
Periodontitis	4/ 50	1/ 25
Fatigue	4/ 50	3/ 75
Abdominal pain	2/ 25	2/ 50
Fever	2/ 25	0/ 0

Table 4. Clinical manifestations (investigations and anamnesis)

RESULTS AND DISCUSSIONS

The aforementioned comparative human study - *Improvements in Quality of Life for HIV/AIDS Patients Using Hyperimmune Egg (Immune 26™) 2005—* The TASO Study by Dr. Francis B. Kizito, had the goal to verify the usefulness of a food supplement that could be used to improve quality of people living with HIV/AIDS where other strategies are currently unaffordable. The food supplement was IgY anti-HIV, which was administered on three groups of human patients during three months. The investigations included weight, haemoglobin, total WBC and differential count and urinalysis[19].

Evaluation/Study	HIV		FIV		FeLV	
	% with symptom	%with symptom improved	% with symptom	%with symptom improved	% with symptom	%with symptom improved
Anorexia	45	100	62.5	100	75	33
Diarrhea	23	88	25	100	-	-
Fatigue	49	93	50	75	75	33
Dyspnea	52	75	37.5	66	-	-
Abdominal pain	48	60	25	100	50	100
Fever	26	88	25	100	-	-

Table 5. Comparative percentages of patients that have shown particular improvements

	HIV			FIV			FeLV		
	I	W	U	I	W	U	I	W	U
Haemoglobin	63	26	11	50	0	50	0	50	50
Weight	30	51	19	25	0	75	0	75	25

**I – Improved, W – Worsened, U – Unchanged*

Table 6.Comparative percentages of patients that have shown particular improvements

Evaluation	FIV			FeLV		
	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged
White Blood Cells	50	12.5	37.5	75	25	0
Neutrophils#	50	12.5	37.5	75	25	0
Lymphocytes#	62.5	0	37.5	50	25	25
Monocytes#	12.5	25	62.5	25	0	75
Eosinophils#	37.5	12.5	50	0	25	75
Basophils#	25	0	75	0	0	100
Red Blood Cells	50	0	50	25	50	25
Haemoglobin	50	0	50	0	50	50
Hematocrit	50	0	50	0	50	50
Mean Corpuscular Volume	25	0	75	25	50	25
Mean Corpuscular Haemoglobin	12.5	0	87.5	25	25	50
Platelet Count	75	12.5	12.5	25	25	50
Mean Platelet Volume	50	0	50	50	50	0
Platelet Distribution Width	12.5	12.5	75	50	25	25
Procalcitonin	50	25	25	25	25	50

Table 7. Evolution of the feline haematological parameters (%)

Evaluation	FIV			FeLV		
	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged
Alanine aminotransferase	37.5	25	37.5	25	50	25
Albumin	0	0	100	0	0	100
Amylase	12.5	37.5	50	0	100	0
Aspartat aminotransferase	25	0	75	25	50	25
Total bilirubin	12.5	12.5	75	25	50	25
Creatinine	12.5	0	87.5	25	50	25
Alkaline phosphatase	50	0	50	50	25	25
Gamma glutamyl transferase	62.5	0	37.5	0	50	50
Glucose	37.5	0	62.5	25	25	50
Na	0	0	100	25	0	75
K	12.5	0	87.5	0	0	100
Cl	0	0	100	0	25	100
Lipase	0	0	100	0	50	50
Total proteins	37.5	0	62.5	0	25	75
Urea	37.5	12.5	50	50	25	25

Table 8. Evolution of the feline biochemical parameters (%)

During and following the treatment period, the evolution of the clinical status of the felines was fairly positive, namely highlighting an improvement of the general health status or maintaining that prior the treatment. The therapy was well tolerated by the cats, devoid of side effects and easy to administer, showing a high degree of palatability. In respect to the presented data of the IgY HIV human study, our study results are fairly similar, when concerning the general health status and quality of life. In specific veterinary terms, the results of our study are extremely different for the two pathologies. In the case of FIV, we can discuss about a considerable improvement of the quality of life, as well as specific improvements: increases in the levels of neutrophils, platelets, limphocytes, red blood cells, as well as liver parameters - alkaline phosphatase, gamma glutamyl transferase. In the case of FeLV, the therapeutic success was more modestly highlighted in

neutrophils, limphocytes and alkaline phosphatase. The series of parameters where the initial values worsened comprised alanine aminotransferase and amylase.

CONCLUSIONS

Preliminary data showed that administering chicken egg yolk IgY to FIV and/or FeLV infected felines has a positive impact, is free of adverse reactions and therefore vouching for initializing a larger study, comprising immunologic tests (interleukins 2, 6, 8) questing for possible more intimate effects of the aforementioned compound.

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