Veterinary Immunology and Immunopathology 143 (2011) 301–306

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Research paper

Use of recombinant interferon omega in feline retrovirosis: From theory to practice

Ana Doménech[a,*], Guadalupe Miró[a], Victorio M. Collado[a], Natalia Ballesteros[a], Leticia Sanjosé[a], Elena Escolar[b,1], Sonsoles Martin[b], Esperanza Gomez-Lucia[a]

[a] Departamento Sanidad Animal, Universidad Complutense, 28040 Madrid, Spain
[b] Departamento Medicina y Cirugía Animal, Facultad de Veterinaria, Universidad Complutense, 28040 Madrid, Spain

ARTICLE INFO

Keywords:
Feline retrovirus
Feline immunodeficiency virus
Feline leukemia virus
Interferon omega
Treatment

ABSTRACT

Type-I interferons (IFNs) are cytokines that have non-specific antiviral activity, participating mostly in innate defense mechanisms. Their administration has been proposed to treat several viral and immunomediated diseases as an immunomodulatory therapy. Due to its availability, recombinant human interferon-alpha (rHuIFN-α) has been studied in relation to feline retrovirosis, both in vitro and in vivo. However, IFNs are species-specific and antibodies have been shown to develop in response to the high rHuIFN-α doses necessary for an effective therapy. A recombinant feline IFN has been developed, which has been characterized as interferon-omega (rFeIFN-ω), designed to overcome these problems. Nonetheless, very few studies have been undertaken to evaluate its efficacy in cats naturally infected with FIV or FeLV. In an initial study, we here demonstrated that rFeIFN-ω can dramatically improve the clinical condition of infected cats, and induce improvement of hematologic parameters. Minor changes or no change was observed for hypergammaglobulinemia, CD4/CD8 ratio, proviral load, viremia and RT activity, suggesting that the overall effect of IFN was on innate immunity. More studies are needed in order to better understand its in vivo mechanisms.

1. Introduction

Feline retroviruses, notably feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), induce chronic infections which eventually lead to the progressive weakening of cats and the presence of various clinical signs. In advanced stages of the disease, the immune suppression established may contribute to the death of the animal (review in Hartmann, 2006; Sellon and Hartmann, 2006). Treatment of animal retroviral diseases is usually based on supportive and symptomatic therapy, such as rehydration when needed, control of secondary infections with antibiotics, antiparasitic and antifungal drugs, among others, while the administration of antiviral drugs is uncommon (Hartmann, 2006; Sellon and Hartmann, 2006; Dunham and Graham, 2008). Most of the antivirals used for feline retrovirosis are the same as used in human medicine, including AZT (zidovudine), ribavirin, zalcitabine and foscarnet, singularly or in combination. The use of these drugs in cats has several disadvantages: doses and protocols are not well established, and they can be toxic for animals as well as producing secondary effects (Caney, 2005; Hartmann, 2006; Sellon and Hartmann, 2006; Dunham and Graham, 2008). As these infections are accompanied by a wide array of clinical signs (anemia, gingivitis, anorexia, secondary respiratory infections, tumors, etc.), there is no preferred curative treatment. Thus, a reasonable

* Corresponding author at: Departamento de Sanidad Animal, Facultad de Veterinaria, Universidad Complutense, 28040 Madrid, Spain.
Tel.: +34 91 394 4087; fax: +34 91 394 3908.
E-mail address: domenech@vet.ucm.es (A. Doménech).
[1] Deceased.

0165-2427/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetimm.2011.06.008

alternative for treatment is the use of immunomodulators, particularly type-I interferons that have an additional antiviral effect. The aim of the present work was both to review the literature on the possibility of using interferon-omega (IFN-ω) for treating feline retrovirosis, and to describe the results of a preliminary study conducted on 11 cats infected either by FeLV or FIV, observing clinical, biopathological and virological effects.

Innate immunity plays a role in protection against retroviral infections (Lehner et al., 2008), and includes both intracellular innate antiviral factors, and extracellular factors, particularly interferon. Interferons (IFNs) are cytokines with important multiple biological functions. Interferons are classified into type-I and type-II IFNs (Pestka et al., 2004). Type-I IFNs are produced by virus-infected cells and have non-specific antiviral activity on adjacent non-infected cells. Thus, they are known as "viral IFNs" and are associated with innate immunity. These interferons include IFN-α, IFN-β, and IFN-ω, among others. Each them has a general mechanism of action based on interaction with specific cell surface receptors and the subsequent induction of expression of interferon-stimulated genes (Sen, 2001; Pestka et al., 2004). These cytokines also induce anti-proliferative and anti-inflammatory responses, and therefore, can also participate in adaptive immune responses (Gerlach et al., 2006, 2009). Thus the administration of type-I IFN has been proposed as a treatment for several viral diseases as immunomodulatory therapy (Truyen et al., 2002; Collado et al., 2006). These products have been used empirically and quite successfully in feline medicine, without a profound knowledge of their molecular mechanisms.

The efficacy of human IFN-α (HuIFN-α) in the feline clinic was the first to be evaluated, as it was the first one commercially available (recombinant HuIFN-α(2a), rHuIFN-α(2a), Roferon®), as well as being the one with the highest in vitro antiviral effect. Even though clinical improvement and lengthening of the life expectancy of infected cats was observed, several disadvantages soon became apparent, such as: its activity in vivo may be lower than expected as cytokine activity is often species-restricted (it would have less effect on feline cells than on human cells); when injected, the higher doses (100,000 U/kg/day) that are able to induce adequate serum levels may lead to the development of specific neutralizing antibodies that block the active ingredient (Zeidner et al., 1990; Müller, 2002) and may have adverse effects (Caney, 2005).

These disadvantages could be overcome with the administration of a species-specific feline IFN (FeIFN). Several subtypes of recombinant FeIFN-α (rFeIFN-α) have been described that could have potential benefits for treating chronic viral infections in cats, given their in vitro antiviral activity (Wonderling et al., 2002). However, to date no rFeIFN-α is available for clinical use, although a recombinant feline interferon omega (rFeIFN-ω) is commercially available and used with relative success in feline viral infections of various etiologies.

IFN-ω, a type-I IFN secreted by virus infected leukocytes, was identified by Hauptmann and Swetly (1985) and is one of the more recently characterized interferons (Adolf, 1995). It was initially described in humans and is encoded by multiple IFN-ω or IFN-ω-like genes, which are present across mammalian groups, including cats (Roberts et al., 1998). Like other type-I IFNs, IFN-ω has species-restricted biological activity in vitro. It is able to bind to the same type-I IFN receptor complex as other type-I IFNs and therefore exerts similar antiviral, antiproliferative and immunomodulatory effects (Adolf, 1995). However, its antigenic structure is distantly related to IFN-α, -β and -γ, as it does not cross-react with antibodies against them (Adolf, 1995).

The rFeIFN-ω that has been developed (Nakamura et al., 1992; Ueda et al., 1993a) has a 60–65% homology to human IFN-α1. Its amino acid sequence consists of 170 amino acid residues and an N-glycosylation site at amino acid position 79. This recombinant IFN has been characterized as omega on the basis of its amino acid identity and the processing pattern of the N-terminal sequence (Ueda et al., 1993a; Adolf, 1995). It has a proven antiviral effect, both in vitro (Mochizuki et al., 1994; Truyen et al., 2002; Ohe et al., 2008) and in vivo against canine and feline parvovirus, herpesvirus, calicivirus, coronavirus and rotavirus (Truyen et al., 2002; De Mari et al., 2004; Ishida et al., 2004; Paltrinieri et al., 2007). In addition, the pharmacokinetic properties of rFeIFN-ω are comparable to those of human interferons in that it does not have a residual accumulation in the body (Ueda et al., 1993b). It has been licensed for use in veterinary medicine (Virbagen®, Virbac) in Europe, Japan, Australia, New Zealand and Mexico, although there are few clinical studies that support its use, and its in vivo molecular mechanisms are not well understood. In general, an improvement in clinical signs has been described, justifying its use in infections in which other treatments are not fully effective, such as retroviral diseases.

The in vitro effects of IFN-I on human retroviruses have been extensively studied. Generally, results from most studies have shown that retroviral protein synthesis is not affected, and suggest that IFN affects the latter stages of the viral cycle, preventing correct assembly or the release of viral particles (review in Gómez-Lucía et al., 2009). Unfortunately, few studies have focused on the effect of this cytokine on feline retroviruses (Rogers et al., 1972; Jameson and Essex, 1983; Yamamoto et al., 1986; Tanabe and Yamamoto, 2001; Collado et al., 2007).

In reviewing the literature, only Collado et al. (2007) have compared the effect of rHuIFN-α(2a) (Roferon®) and rFeIFN-ω (Virbagen®) on persistently FeLV-infected feline cells. Their results have indicated that, as with other retroviruses, rFeIFN-ω affects the FeLV cycle at the post-transcriptional level, as protein synthesis was not altered, while RT activity (used to estimate the number of infectious particles) decreased in a dose-dependent manner. Given its IC_{50}, rFeIFN-ω appeared to be around 50–90 times more potent than reHuIFN-α(2a) in inhibiting RT. In addition, the study revealed that IFNs induced a decrease in the viability of FeLV-infected cells, enhancing apoptosis in infected cells that were treated. The significance of this effect on cell viability and its in vivo impact is, at present, unknown.

In the case of FIV, similar experiments with rHuIFN-α(2a) and rFeIFN-ω in infected feline cells have shown