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International Immunopharmacology 52 (2017) 253–260

Contents lists available at ScienceDirect

International Immunopharmacology

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

Review

Interferon-omega: Current status in clinical applications

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ARTICLE INFO

Keywords:
Application
Biological activity
Interferon omega
Type I IFN

ABSTRACT

Since 1985, interferon (IFN)-ω, a type I IFN, has been identified in many animals, but not canines and mice. It has been demonstrated to have antiviral, anti-proliferation, and antitumor activities that are similar to those of IFN-α. To date, IFN-ω has been explored as a treatment option for some diseases or viral infections in humans and other animals. Studies have revealed that human IFN-ω displays antitumor activities in some models of human cancer cells and that it can be used to diagnose some diseases. While recombinant feline IFN-ω has been licensed in several countries for treating canine parvovirus, feline leukemia virus, and feline immunodeficiency virus infections, it also exhibits a certain efficacy when used to treat other viral infections or diseases. This review examines the known biological activity of IFN-ω and its clinical applications. We expect that the information provided in this review will stimulate further studies of IFN-ω as a therapeutic agent.

1. Introduction

Interferons (IFNs) were first reported by Isaacs and Lindenmann as antiviral proteins that are generated by cells in response to viral infection [1,2]. IFNs are composed of three subgroups: type I, type II, and type III IFNs. The type I IFNs, including IFN-α, IFN-β, IFN-ε, IFN-ω, IFN-κ, IFN-δ, IFN-τ, and IFN-ζ, exert biological activity through common receptors (interferon-α/β receptor 1 [IFNAR1] and IFNAR2) [3,4]. Type II IFN, namely IFN-γ, is produced by T lymphocytes and natural killer cells in response to the recognition of infected cells [5]. Type III IFNs consist of IFN-λ1, IFN-λ2, and IFN-λ3, which regulate the immune response via a distinct receptor complex that uses a signaling pathway that is similar to that of type I IFNs [6,7].

IFN-ω genes were first found in humans in 1985 [8,9]. IFN-ω diverged from the IFN-α gene approximately 130 million years ago, and it is produced primarily in leukocytes [10]. Human IFN-ω genes include four pseudogenes and one full gene that is expressed in leukocytes, and human IFN-ω shares 62% amino acid sequence homology and similar functions with IFN-α, and 33% amino acid similarity with IFN-β [11]. Similar to other IFNs, IFN-ω is also produced by cells in response to viral infection, and it has biological activities because it binds to the same receptors and activates a pathway that is similar to that activated by IFNAR [12], while the activation of phosphoinositide-3-kinase/protein kinase B (P13K/Akt) signaling is also vital for biological responses mediated by IFN-ω [13]. However, its antigenic structure is distantly related to IFN-α, -β, and -λ, as it does not cross-react with antibodies against them [14]. As a result, treatment with IFN-ω can be effective for patients who are resistant to IFN-α [15]. Although IFN-ω has been studied extensively, our knowledge of IFN-ω is still limited compared with that of interferon IFN-α and -β. Here, we provide a broad review of what is known about the biological activities and potential clinical application of IFN-ω. Overall, we hope that the information provided in this review will stimulate further studies of IFN-ω as a therapeutic agent.

2. The characteristics of IFN-ω in different species

Until now, IFN-ω has been identified in humans [8], felines [16], pigs [17], horses [18], rabbits [19], serotine bats [20], cattle [21], and sheep [22], while it has not been found in canines and mice [21]; however, the characteristics of IFN-ω differ in different species. The characteristics of IFN-ω from different species are summarized in Table 1. Despite such differences, there are common characteristics that exist in these species. Generally, IFN-ω genes are intronless, and *N*-glycosylation sites (not present in felines) and transcription factor binding sites, such as IRFs, ISREs, and NF-κB, are present in the promoter regions of these genes [9,10,20,30]. In addition, all mammalian IFN-ω genes lack the proline codon that precedes the final conserved cysteine codon [24]. The IFN-ω protein contains several conserved residues, such as arginine at position 161, cysteine residues at positions 1

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http://dx.doi.org/10.1016/j.intimp.2017.08.028
Received 8 July 2017; Received in revised form 20 August 2017; Accepted 28 August 2017

Table 1
IFN-ω in different species and the characteristics of the IFN-ω gene and protein.

Species	Location	Characteristics of the IFN-ω gene and protein	Reference
Human	Human chromosome 9	Human IFN-ω has at least five members, but only one member of the human IFN-ω family is a functional gene that results in a functional and glycosylated protein. This protein has six additional amino acids located at its carboxyl-terminus (172 amino acid residues) and a single polypeptide chain comprising two disulfide bonds and an *N*-glycosylation-linked site at amino acid 80. In terms of the primary structures of the type I IFNs, there is approximately 75% amino acid sequence identity between IFN-α and IFN-ω.	[8,9,12,15,23]
Cat	No data	Felines IFN-ω (FeIFN-ω) includes 13 subtypes that contain an amino-terminal secretory signal sequence from residues 1–23. The mature sequence of IFN-ω contains four highly conserved cysteines (positions 1, 29, 100, and 140) and seven prolines (four of those at positions 4, 26, 39, and 117 of the mature protein), while the FeIFN-ω protein has six additional amino acids at its carboxyl-terminus compared with FeIFN-α. Among these subtypes, FeIFN-ω2 and FeIFN-ω4 contain a seven-amino-acid insertion at position 109, and the insert location is comparable to that of the FeIFN-α, while it has higher antiviral activity than the other subtypes. Interestingly, different from that in other mammalian subtypes, these 13 subtypes do not have an *N*-glycosylation recognition site.	[16,24]
Pig	Chromosome 1	Porcine IFN-ω (PoIFN-ω) contains seven or eight members with variable open reading frame lengths. The most extensive similarity of the PoIFN-ω sequences are to bovine leukocyte IFN-ω, and the lowest one is to equine IFN-ω. It contains an IFabd functional domain, multiple putative binding sites for type I IFN receptor subunits, and one putative *N*-glycosylation site (Asn/Asp-X-Ser/Thr). The subtypes of the IFN-ω protein, which have five alpha-helices, bear amino-terminal 20- to 30-amino-acid signal peptides and four conserved cysteine residues, Cys24, Cys52, Cys122, and Cys162, which are also found in IFN-α1. In addition, all IFN-ω subtypes, except IFN-ω1 (whose carboxyl-terminus is 11 residues shorter than the other PoIFN-ω subtypes), have 14 or 16 extended residues, while the pairs IFN-ω2/6 and IFN-ω3/5 share identical sequences.	[17,25,26]
Horse	Chromosome 23	Horse IFN-ω contains eight members plus four pseudogenes, which is a greater than the number of IFN-α genes and more diverse than the other type I IFN genes. The IFN-ω gene contains a putative glycosylation sequence, Asn-Thr-Thr, at positions 78–80. The IFN-ω protein has six alpha-helices and it contains IFabd (cd00095), interferon (pfam00143), and IFabd (smart00076) domains, and multiple putative binding sites for the type I IFN receptor subunit 1 and 2 and an *N*-glycosylation site. Notably, the length of the open reading frame of each IFN-ω subtype is invariant.	[18,27]
Rabbit	No data	The rabbit IFN-ω family comprises at least eight genes that display the highest degree of homology with human IFN-ω and the lowest with murine IFN-αII. There are two IRF-1 binding sites at nucleotide positions 85 and 55, the hexamer repeat sequence 5′–GAAANN–3′ in the 5′ noncoding sequence, and a repetition of the 5′–TTATTTAT–3′ motif, which is similar to many 3′ downstream regions of genes encoding inflammatory cytokines. In addition, the immediate promoter region of the rabbit IFN-ω genes has a high proportion of purine residues. An ATG sequence, (5′–GAAATG–3′), was found only in the promoter region of RbIFNW48 at nucleotide position 66. Similarly, IFN-ω includes four Cys residues at amino acid positions 1, 29, 99, and 139.	[19]
Cattle	Chromosome 8q15	The IFN-ω family in cattle (BoIFN-ω) consists of 24 members that contain two pseudogenes and 22 functional genes. Among these subtypes, the nucleotide similarity is 91.3%–97.2%, and the amino acid identity is 84.4%–95.4%. Most of these subtypes encode 195 amino acids, expect BoIFN-ω7 and BoIFN-ω11, which lack nine amino acid residues at their carboxyl terminus. In addition, 23 of the members have signal peptides. A glycosylation site analysis revealed that BoIFN-ω 1, 2, 3, 4, 7, 9, 10, 11, 12, 13, 17, 20, 23 and 24 do not have a *N*-glycosylation site, while BoIFN-ω 1, 2, 3, 7, 13, 17, 20, 23, and 24 have one *O*-glycosylation site; BoIFN-ω 4 and 10 have three *O*-glycosylation sites, and BoIFN-ω 9,11, and 12 have two *O*-glycosylation sites. There are four conserved cysteines at positions 1, 29, 99, and 139, and one conserved arginine at position 161 in the mature peptide sequences; the cysteines at positions 1 and 29, and 99 and 139 positions could form two disulfide bonds. The three-dimensional structure of BoIFN-ω3 includes five alpha-helices.	[21,28–31]
Serotine bat	No data	The serotine bat IFN-ω genes are intronless, and its open reading frame consists of 588 bp (encoding 195 amino acids), and *N*-glycosylation sites were identified. Transcription factor binding sites, such as IRFs, ISREs, ATF2/c-Jun, and NF-κB, were found in the promoter region sequences at bp 1071. The potential transcription start sites of the genes are located at bp 1071 of the esIFN-ω promoter sequences.	[20]
Sheep	No data	Sheep IFN-ω concludes as least five members. All the putative IFN regulatory motifs found in the BoIFN-ω gene promoter are also conserved in the promoter region of the sheep gene, such as the three 5′–GAAANN–3′ motifs (− 51 to − 46, − 57 to − 52, and − 67 to − 62), which overlap two potential interferon regulatory factor-1 binding sites “8” (5′–AAATGA–3′, positions − 55 to − 50 and − 66 to − 61), and a fourth 5′–GAAANN–3′ hexamer (− 97 to − 92) which overlaps a third less conserved interferon regulatory factor-1 site in the sheep clone (5′–AACTGA–3′, positions − 101 to − 96).	[22,32]

and 99 and 100, seven prolines (four of which are located at positions 4, 26, 39, and 117 of the mature protein), while positions 29 and 139 and 140 form two disulfide bonds. These residues are present at similar locations in type I IFNs, and they are vital for their biological activity [33]. Other conserved structural motifs, such as the regions between amino acid residues 29–41, 71–82, and 123–142, are highly conserved among IFN-α proteins, and they play a key role in the biological activity of IFN-ω [26,28,29]. In addition to having a structure that is similar to that of type I IFNs, IFN-ω also displays the same physicochemical characteristics as type I IFNs, such as high sensitivity to trypsin, insensitivity to temperature, and stability at pH 2 [28,29]. Some studies revealed that IFN-ω loses its antiviral activities after being treated with 0.25% trypsin. However, it retains high antiviral activity against vesicular stomatitis virus after exposure to pH 2 for 24 h at temperatures ranging from 42 °C to 63 °C [26,28,29]. Based on analyses of phylogenetic trees obtained from alignments of the IFN-ω protein sequences from these mammal species, it was proposed that all these proteins evolved from a common ancestor [20,28].

3. The biological activity of IFN-ω

3.1. Antiviral activity

3.1.1. IFN-ω exerts antiviral effects in vitro and in vivo

Type I IFNs, including IFN-ω and IFN-α, display a common mechanism of action. IFNs interact with specific cell-surface receptors, and then the expression of IFN-stimulated genes (ISGs) is induced, some of which encode antiviral effectors or molecules, such as signaling proteins, transcription factors, and apoptotic proteins, while chemokines further regulate IFN signaling and other host responses in a positive or negative manner [28]. IFN-ω is not an exception. It has been proposed that IFN-ω shares antiviral activities with IFN-α because it binds to the same type I IFN receptor complex. Studies have revealed that IFN-ω induces the transcription of the Mx1, ISG15, IFIT3, and ISG56 genes [20,28]. However, different from IFN-α, it shows certain degrees of cross-species activity; therefore, IFNs could exhibit different physiological functions in the host. For example, bovine IFN-ω (BoIFN-ω) protects Madin–Darby bovine kidney cells, primary embryo bovine lung

cells, feline kidney cells, porcine kidney cells, rabbit kidney cells, and primary bovine testicular cells from vesicular stomatitis virus challenge. However, the antiviral activities of BoIFN-ω are low in Madin–Darby bovine kidney cells, but high in porcine kidney and bovine testicular cells. Additionally, no protective effects were found on Madin–Darby bovine kidney cells and baby hamster kidney cells [28,29]. These results suggest that cells have a tendency to be insensitive to IFN-ω from distantly related species. The antiviral activities of IFN-ω also vary with the subtypes and viral strain used in challenges. In a previous study, the expression of PoIFN-ω2/-ω6, PoIFN-ω3/-ω5, and PoIFN-ω8 were upregulated, while PoIFN-ω1 (which has 11 fewer residues at its carboxyl terminus than the other PoIFN-ω subtypes) was not detected in porcine kidney cells challenged with pseudorabies virus or poly (I):poly(C). Interestingly, the level of PoIFN-ω1 also increased when peripheral blood mononuclear cells were challenged with pseudorabies virus, and PoIFN-ω2/-ω6 was upregulated the most in these studies [26]. Similarly, recombinant serotine bats IFN-ω can inhibit European bat lyssavirus type 1, European bat lyssavirus type 2, and rabies virus replication in a dose-dependent manner, and different biological activities were elicited (in the order of European bat lyssavirus type 1 < rabies virus < European bat lyssavirus type 2) [20].

The antiviral activities of IFN-ω have also been compared to those of other IFNs. When A549 cells were respectively treated with IFN-ω and type I and type III IFNs, the cells treated with IFN-ω at a concentration of 10 ng/ml obviously repressed the replication of influenza A virus in a dose-dependent manner, and it resulted in larger reductions in viral titers, compared with those obtained with IFN-α2 [34]. However, its activity was much lower than the activity of IFN-β1, and it was slightly lower than the activities of IFN-λ1 and IFN-λ2. Depending on the dose, pretreating Caco-2 cells with human IFN-ω significantly reduced the loads of the H1N1 influenza virus [35]. Interestingly, IFN-β and IFN-ω showed similar inhibitory activity against both Ca/04 and BJ/501 influenza viruses at every concentration tested. In addition, both were significantly more potent than IFN-α as far as the inhibitory effects on both stains at a given concentration. In addition to its in vitro activities, IFN-ω has been demonstrated to have antiviral activity in vivo as well. For example, a robust induction of Mx mRNA and the OAS-1A protein was found in animals treated by IFN-ω compared with controls [35]. Furthermore, following daily intravenous treatment with human IFN-ω (HuIFN-ω), the viral load of H1N1 influenza virus decreased significantly in the lung tissues of guinea pigs, and IFN-ω exhibited an identical inhibitory effect against the Ca/04 influenza virus compared with IFN-α [35].

3.1.2. Strategies to improve the antiviral efficiency of IFN-ω

Although IFN-ω has demonstrated promising antiviral activity against some viral infections in vivo and vitro, several factors could limit its antiviral efficacy, such as poor pharmacokinetics and a short half-life [36]. PEGylation, a covalent conjugation of nontoxic polyethylene glycol (PEG), has been demonstrated to improve the plasma half-life of a therapeutic protein and decrease its proteolytic sensitivity [37]. Recently, Yu et al. [38] found that PEGylation improved the poor pharmacokinetics of recombinant HuIFN-ω (rHuIFN-ω), despite the fact that its antiviral activity was decreased to some extent. It is worth noting that the bioactivity of PEGylated rHuIFN-ω was determined by examining its PEGylation sites, in which residues at the amino-terminus had higher activities compared with those of residues Lys^{134} and Lys^{152}, while the poor pharmacokinetics were determined by the conjugated PEG mass. In a previous study, amino-terminally PEGylated rHuIFN-ω with 40 kDa of linear PEG, which exhibited 21.7% of the rHuIFN-ω biological activity with a half-life of 139.6 h, allowed some viral diseases to be treated by fewer doses at longer dosing intervals [38]. The use of human IgG1 Fc fusion proteins has also been demonstrated to be a simple and effective method for prolonging serum half-life [39]. Some studies showed that compared with rHuIFN-ω expressed in yeast with a specific activity of 7×10^7 IU/mg, rHuIFN-ω-Fc had a lower activity of 1.6×10^7 IU/mg when it was expressed in Chinese hamster ovary cells. Furthermore, the terminal half-life of rHuIFN-ω-Fc was 35-fold higher than that of rHuIFN-ω, and it exhibited better pharmacokinetics characteristics [40]. Perhaps rHuIFN-ω-Fc will become a new alternative antiviral drug for the treatment of chronic viral infections.

Several studies also revealed that glycosylation has an essential effect on the activity of IFNs [41], and glycosylated IFN-ω was more potent than IFN-ω against bovine viral diarrhea virus, yellow fever virus, and West Nile virus [41,42]. A possible explanation for its potency is that glycosylated IFN-ω could induce the activation of the sterol regulatory element binding transcription factor, the activating enhancer binding protein 2-like YY1 site, the interferon consensus sequence binding protein, the erythroid Kruppel-like factor gene, the homeotic gene forkhead of *Drosophila* 8/hepatocyte nuclear factor 3/mouse forkhead lung protein, HNF-1α, the interferon conserved sequence-binding protein, and the lymphocyte-enriched DNA binding protein LyF, which are not induced by IFN-α [41]. Glycosylated IFN-ω also exhibits good clinical applications. Previous studies showed that glycosylated IFN-ω + ribavirin (RBV) had a synergistic effect in terms of its antiviral activity in hepatitis C virus (HCV)-infected patients [43]. Similarly, a synergy of the antiviral effects of glycosylated IFN-ω + RBV against bovine viral diarrhea virus was also obtained. Interestingly, an antagonism of the cytotoxic effects of RBV by glycosylated IFN-ω was observed [43]. Thus, the combination of glycosylated IFN-ω and RBV appears to be favorable for the synergy of antiviral activities and the antagonism of the cytotoxic effects of RBV.

3.2. Regulating the innate immune response

Increasing evidence suggests that IFN-ω may be associated with the nonspecific immune response based on increased survival time, the presence of acute-phase proteins (serum amyloid-A, α-1-glycoprotein, and the C-reactive protein), the phagocytic activities of whole blood cells and macrophages, natural killer cell activities, and reduced concurrent viral excretion [44–48]. In general, increasing the number of ISGs, Mx proteins, and ZAPS, which could enhance pathogen detection and innate immune signaling, indicates that IFN-ω elicits an immune response. When cells are treated with IFN-ω, Mx-1, ISG15, IFIT3, and ISG56 expression was upregulated in a dose-dependent or time-dependent manner [20,29]. More recently, studies from Leal et al. [49] showed that interleukin (IL)-6 production was affected considerably in feline immunodeficiency virus (FIV)-infected cats treated with recombinant feline IFN-ω (rFeIFN-ω) by subcutaneous or oral protocols. Specifically, IL-6 plasma levels decreased and proviral loads increased in FIV-cats treated subcutaneously with rFeIFN-ω, while IL-6 mRNA expression decreased in the oral group. However, the therapy did not affect viremia and the expression of other cytokines (IL-1, IL-4, IL-10, IL-12p40, IFN-γ, and tumor necrosis factor-α) [49]. Thus, IFN-ω appears to be involved in innate immunity, and it could further inhibit viral replication and exert its antiviral activity.

3.3. Anti-proliferation and antitumor activity of IFN-ω in bench study

IFNs have been demonstrated to have antiproliferative effects as a result of inducing cell-cycle arrest and apoptosis, which are independent pathways [50]. Similar to IFN-α, IFN-ω also inhibits cell proliferation in a dose-dependent manner [20,29]. However, IFN-α exhibits a higher antiproliferative activity than IFN-ω at elevated concentrations [29].

IFN-ω also exhibits antitumor activity in vitro in a cell-specific manner. Feline mammary carcinomas are among the most common feline tumors, and they represent an important cause of mortality. When used to treat feline and canine mammary carcinoma cells and derived putative tumor-initiating cells, rFeIFN-ω exhibited a dose-dependent, species-specific, target cell-specific action, and an additive effect was observed between rFeIFN-ω and conventional anticancer

drugs such as mitoxantrone, doxorubicin, and vincristine [51]. Thus, rFeIFN-ω may be used as a therapeutic agent in feline and canine mammary carcinomas. There is evidence showing that gene transfer would allow one to take advantage of the beneficial effects of type I IFNs without their undesirable side effects [52]. For instance, HuIFNβ gene lipofection produces an equal or even superior effect than that of high doses of exogenously applied HuIFNβ protein. Recently, a study conducted by Villaverde et al. [52] demonstrated that felines FeIFN-ω gene lipofection exhibited an equal or higher cytotoxic effect than rFeIFN-ω. This kind of effect was due to the induction of reactive oxygen species generation, mitochondrial membrane potential disruption, and calcium uptake, indicating that fFeIFN-ω lipofection is an alternative approach for treating both sensitive and resistant phenotypes with an equal or superior outcome and with fewer adverse effects than recombinant fFeIFN-ω therapy [52]. Similarly, injecting the gene encoding interferon ω1 via the tail vein into mice bearing a Hep-A-22 liver tumor via liposomal gene delivery also significantly decreased tumor weights [53]. Interestingly, this effect was greater (43% tumor inhibition) only when the plasmid contained human thymosin alpha 1 [53]. A DNA ladder (a hallmark of cells undergoing apoptosis) was observed in the tumor cells treated by IFN-ω. Interestingly, the antitumor mechanisms involve increasing the expression of Tα1 and IFN-ω, and a plasmid-liposome complex of IFN-ω and IFN-α together exerted greater potency in inhibiting the growth of Hep-A-22 tumor cells than either compound alone [53].

4. Clinical applications of IFN-ω

Because of its antiviral, immunomodulatory, anti-proliferation, and antitumor activities, IFN-ω has been explored as a treatment option for some diseases and viral infections in humans and other animals. HuIFN-ω displays antitumor effects in several models of human cancer in vivo. In addition, it has also been used to diagnose some diseases [54,55]. When produced in silkworm larvae using a baculovirus vector that includes the FeIFN-ω sequence, rFeIFN-ω, as an immunomodulator, has been registered in many countries (e.g., Japan, Australia, New Zealand, and Mexico) to treat canine parvovirus, feline leukemia virus (FeLV), and FIV infections (http://emea.europa.eu) [45,56]. Despite the fact that it is not licensed to treat other viral infections, it exhibits efficacy when used to treat other viral infections such as bovine enterovirus, infectious bovine rhinotracheitis virus, bovine viral diarrhea virus, vesicular stomatitis virus, pseudorabies virus, European bat lyssavirus, influenza virus, feline calicivirus (FCV), and feline herpesvirus-1 (FHV-1) [20,28,34,57]. The rFeIFN-ω licensed protocol consists of three therapeutic cycles of five daily subcutaneous injections (1 MU/kg), beginning respectively on days 0, 14, and 60 [58]. However, its widespread use is limited because this protocol is relatively expensive and time-consuming. Some alternative subcutaneous and topical protocols, such as oral and intralesional administration, have been suggested [59,60]. Interestingly, no adverse effects were found in cats treated with rFeIFN-ω following mucosal administration [58,61], while subcutaneous administration was accompanied by some mild adverse effects (e.g., fever, lethargy, vomiting, and diarrhea) in some trials [46]. Thus, rFeIFN-ω could become an option for treatment in veterinary clinical practice.

4.1. IFN-ω application in humans

4.1.1. HCV

HCV is a major public health problem with approximately 170 million infections worldwide [62]. Many HCV-infected individuals cannot eliminate the virus, and persistent infection with HCV causes chronic liver disease, including cirrhosis and hepatocellular carcinoma [63,64]. Until now, a combination of IFN-α and RBV has been the standard of care for chronic HCV infections [65,66]. However, it has many deleterious side effects. Furthermore, some HCV chronic carriers are not suitable for this therapy, and new antiviral approaches are needed. Some studies showed that IFN-ω was equally effective at inhibiting HCV replication compared to IFN-α and IFN-β. Interestingly, the combinations of IFN-ω and IFN-α or IFN-β exhibited primarily antagonistic interactions [67]. In addition, other studies showed that the activity of non-glycosylated IFN-ω was comparable to that of IFN-α, while glycosylated IFN-ω was more potent in repressing HCV RNA replicons. Thus, IFN-ω can be used as a prospective antiviral candidate for the treatment of HCV infections [41].

4.1.2. Autoimmune polyglandular syndrome type 1 (APS-1)

In addition to being a potential therapy for HCV, IFN-ω could also be used to diagnose some human diseases. APS-1 is a monogenic disease that is caused by mutations in the autoimmune regulator (AIRE) gene [68,69]. Currently, many autoantibodies, including those targeting aromatic acid decarboxylase, tyrosine hydroxylase, NACHT leucine-rich repeat protein 5, tryptophan hydroxylase, and IFN-ω, have been found in APS-1 patients [55]. A study has shown an anti-IFN-ω antibody was highly prevalent in APS-1 patients with mutated AIRE alleles, even though the presence of anti-IFN-ω antibodies preceded APS-1 clinical symptoms and the development of other autoantibodies [70]. Therefore, antibodies against IFN-ω have become an essential diagnostic tool for APS-1. Numerous available assays, such as immunoassays, radioligand binding assays, and antiviral neutralization assays, were designed to detect anti-IFN-ω antibodies [70–72]. However, all of them have drawbacks, including a lack of sensitivity, the use of radioisotopes, the requirement for facilities to grow viral cultures, as well as being time-consuming. Some novels diagnosed methods were also developed. Zhang et al. [73] reported that an IPA based on ^{125}I-labeled IFN-ω showed higher sensitivity to APS-1 than other anti-type 1 IFN antibodies when 48 APS-1 patients were examined. Similar to the study by Zhang et al., 48 APS-1 patients were also investigated in a study by Oftedal et al. [74], and these patients were also positive for anti-IFN-ω antibodies, as determined by an IPA based on ^{35}S-labeled IFN-ω, which also exhibit a greater correlation to APS-1 than other anti-type 1 IFN antibodies. These results suggest that out of the spectrum of anti-type 1 IFN antibodies, testing for anti-IFN-ω antibodies is more suitable for patients suspected of having APS-1. Recently, Larosa et al. [75] developed a novel, highly sensitive, and specific assay to measure anti-IFN-ω antibodies. They found that ^{125}I-labeled IFN-ω and ^{35}S assays resulted in 5/6 and 1/6 discrepant samples, respectively, which agrees with AIRE gene results [75]. Regarding the measurement of anti-IFN-ω antibodies in the studied patients, the ^{125}I assay seems to have a better performance, as it is disease-specific, more reliable, and more precise than the ^{35}S assay, making it possible to assess patients with APS-1 and patients suspected of having APS-1 prior to an AIRE gene analysis.

4.2. IFN-ω as a treatment for animal diseases and viral infections

4.2.1. FCV and FHV-1

FCV, a member of the *Caliciviridae* family, is an important and common pathogen for cats, which is characterized by clinical signs ranging from mild and severe oral ulcerations or upper respiratory tract disease to a severe fatal systemic disease [76,77]. Unfortunately, there are still no direct-acting antiviral drugs for the treatment of FCV. Previous studies demonstrated that rFeIFN-ω had a positive therapeutic effect in FCV-infected cats in some experiments or trials [46,57,78]. Combination antiviral therapy has become a common practice. Recently, researchers revealed that a combination treatment of rFeIFN-ω and mefloquine resulted in additive effects with a reduction in the half maximal inhibitory concentration [79]. Another study conducted by Lee et al. [80] showed that the relative expression of IFN-ω, Mx, and ZAPS mRNA in Crandell-Reese Feline Kidney cells was upregulated significantly in FCV-infected cats. Interestingly, after the cats were pretreated with a Korean red ginseng (KRG) extract or ginsenosides, the expression of these genes was higher than that in the group treated with

FCV alone [80]. It is desirable to find a combination of a KRG extract or ginsenosides and IFN-ω that effectively treats FCV-infected cats. Because of its similar structural characteristics and genomic structure, FCV could be a representative human norovirus surrogate [81]; thus, these therapies could also be used to treat human norovirus infections.

FHV-1, a double-stranded DNA virus that replicates in the nucleus of host cells and produces intranuclear inclusion bodies, is one of the foremost causes of feline upper respiratory tract disease [82]. It has been demonstrated that rFeIFN-ω has a dose-dependent inhibitory effect on the replication of FHV-1 in vitro [83]. Several studies showed conflicting results about the biological activity of rFeIFN-ω against these two viruses in cats. For instance, 160 cats suffering from FCV-associated feline upper respiratory tract disease were treated with an intravenous dose of 2.5 or 5 MU/kg rFeIFN-ω three times per day every other day [82]. While improved clinical signs were detected within 7 days, no control group was used in this study. In another study, 20 cats with FHV-1-associated ocular keratitis were treated five times per day with a dose of 0.5 MU/mL rFeIFN-ω, and although a significant improvement of ocular signs was observed after 3 weeks of treatment, no control group was included [83]. In 2007, using a placebo as a control group, the effect of rFeIFN-ω in cats that were pretreated with rFeIFN-ω before challenge with FHV-1 was investigated [84]. Unexpectedly, no beneficial effects were observed in these cats. Ballin et al. [85] reported a similar finding; they found that compared to a control group treated with a placebo, cats treated with rFeIFN-ω did not exhibit improved clinical signs of acute viral feline upper respiratory tract disease despite having lower FCV copy numbers than cats receiving rFeIFN-ω [85]. More studies are needed to verify that rFeIFN-ω has a therapeutic effect in vivo.

4.2.2. FeLV and FIV

FeLV, an endogenous retrovirus that belongs to the genus *Gammaretrovirus* of the family *Retroviridae* causes a variety of degenerative and immunosuppressive disorders such as severe anorexia, cachexia, and progressive weakness [86,87]. Studies indicated that rFeIFN-ω affects the FeLV cycle at the post-transcriptional level. However, it did not alter protein synthesis [88]. Treatment with rFeIFN-ω lowered reverse transcriptase activity, which is used to evaluate the amount of infectious viral particles, in a dose-dependent manner in FeLV-infected FL74 cells [88]. Furthermore, according to the half maximal inhibitory concentration, rFeIFN-ω was more potent than rHuIFN-α in inhibiting reverse transcriptase activity. In addition, this study showed that IFN-ω decreased the viability of FeLV-infected FL74 cells and increased apoptosis and mortality in infected cells [88].

FIV is a feline lentivirus that was first described in 1987, and many studies have focused on it because its complex genomic and immunopathogenic features that are similar to those of human immunodeficiency virus [89,90]. Furthermore, FIV coinfection was found to occur in 7% of FeLV-infected cats [91]. Previous studies showed that rFeIFN-ω significantly decreased clinical scores and rates of mortality, and improved abnormal hematologic parameters (red blood cell count, packed cell volume, and white blood cell count) in virus-infected cats [45]. These studies demonstrated that rFeIFN-ω had significant therapeutic effects on clinical signs. Evidence also showed that an effective immune modulation in FIV-cats could be obtained by treating them orally with rFeIFN-ω. In a previous study [45], FIV-infected cats that were orally administered rFeIFN-ω at a dose of 0.1 MU/cat gained weight, although no dramatic changes were obtained regarding viral loads and the $CD4^+/CD8^+$ ratio. However, this study did not assess any clinical benefits [45]. Recently, oral protocols were also used to administer rFeIFN-ω in naturally FIV-infected cats, and initial clinical scores were obtained that were similar to those obtained using the licensed subcutaneous protocol [92]. Interestingly, similar to the use of the licensed protocol, rFeIFN-ω also induced a significant clinical improvement of cats that were treated orally, despite viral excretion, while there were no significant variations in acute-phase proteins [92]. These results suggest that oral administration of rFeIFN-ω can be an effective alternative therapy for FIV-infected cats.

4.2.3. Feline chronic gingivostomatitis syndrome (FCGS)

FCGS is a multifactorial disease. Some infectious viral diseases, such as FIV, FHV-1, and FeLV, can also trigger FCGS by inducing immune suppression and dysregulation [93,94]. Some studies showed that oral treatment with rFeIFN-ω was a beneficial therapy for FCGS. A study conducted by Hennet et al. [55] found that the oral protocol correlated with an obvious clinical improvement of FCGS lesions (caudal stomatitis and alveolar/buccal mucositis). Furthermore, the only difference between rFeIFN-ω and corticosteroids were that better pain relief was obtained with the rFeIFN-ω treatment. Recently, two clinical cases showed that the use of oral rFeIFN-ω was also effective in type II diabetic cats with FCGS [95]. In this study, a clinical improvement of oral lesions and a concurrent reduction of the required insulin dose had a positive relationship with rFeIFN-ω therapy, which agrees with Hennet's work showing that there was an overall relief of pain in refractory cases of FCGS [55,95].

4.2.4. Parvovirus

Parvovirus, a small, non-enveloped, single-stranded DNA virus, infects humans and carnivores in a host-specific manner. Canine parvovirus type-2 (CPV), feline panleukopenia virus, and mink enteritis virus share approximately 98% homology in their nucleotide and amino acid sequences [96]. There are several therapies used to treat CPV infections; however, many of them have drawbacks [50]. Reports suggest that rIFN-ω has a significant therapeutic effect on CPV-infected dogs [97,98]. For instance, it improved parvoviral clinical signs (such as pyrexia, vomiting, anorexia, and diarrhea), and reduced severe parvoviral enteritis and mortality in CPV infections. A study by Kuwabara et al. [48] showed that continuous immunoenhancement after rFeIFN-ω treatment and whole blood cells counts $> 5 \times 10^3/\mu l$ in dogs might be essential for improving severe clinical symptoms caused by CPV infection.

4.2.5. Cowpox virus (CPxV)

CPxV, belonging to the *Orthopoxvirus* genus, is most frequently found in domestic cats with > 400 cases having been reported, and it is endemic in northern Europe and western areas of the former Soviet Union [99,100]. However, until now, no antiviral drugs have been licensed to cure cats of CPxV infection. A recent study conducted by McInerney et al. [101] showed that treatment with rFeIFN-ω had a certain protective effect in cats infected with CPxV, although two of the four cats in the study died. Nevertheless, rFeIFN-ω may be potentially useful for treating CPxV-associated pneumonia and dermatitis in cats. Of note, additional research is needed before this can be confirmed.

4.2.6. Fibrosarcoma

Fibrosarcoma, a common disease in cats, accounts for over 40% of all skin tumors in this species [102]. Currently, few successful treatments for fibrosarcoma have been reported in cats, although treatment of feline fibrosarcoma with rFeIFN-ω has been demonstrated to be safe, well tolerated, and easily performed. A study by Hampel et al. [103] revealed that rFeIFN-ω increased the expression of major histocompatibility I molecules on feline fibrosarcoma cells, while eosinophilia, neutropenia, and weight loss were remarkably reduced by rFeIFN-ω treatment. However, a placebo-controlled trial is needed.

4.2.7. Canine atopic dermatitis (CAD)

CAD is a common, allergic skin disease. Some therapeutic protocols have been reported, such as allergen-specific immunotherapy, the use of topical and oral glucocorticoids and calcineurin inhibitors, essential fatty acid supplementation, and bathing [104]. However, none of them were highly efficacious, and some severe side-effects were observed occasionally. Fortunately, a study showed that treating dogs with CAD

with subcutaneously administered rFeIFN-ω had a comparable efficacy to orally-administered cyclosporin [105]. In later studies [106], oral IFN therapy showed higher efficacy than the subcutaneous treatment in terms of the Canine Atopic Dermatitis Extent and Severity Index and total scores, although the improvement of pruritus and quality of life scores were not significant; however, in this study, serum antibodies against rFeIFN-ω were not detected in any of the dogs.

4.2.8. Feline infectious peritonitis (FIP)

FIP is a common immune-mediated disease that is triggered by infection with a feline coronavirus [107]. Previous studies showed that IFN-ω is a beneficial therapy in FIP-infected cats. However, these studies used fewer than 12 cats per group and did not include a control group. Furthermore, the effect of IFN-ω was not reliably confirmed in FIP [108,109]. For instance, in a study of cats suspected of having FIP, 12 cats were treated with 106 U/kg of feline FeIFN-ω every other day until remission, followed by injections every week; four of the 12 cats lived longer than 2 years [108]. In a subsequent study conducted by Ritz et al. [109], a control group was used, but there were no significant differences between the survival times of cats treated with FeIFN-ω and a placebo, although the FeIFN-ω treatment resulted in a significantly lower lymphocyte count. Interestingly, one cat survived > 3 months in the FeIFN-ω group. These results suggest that FeIFN-ω could also have a certain therapeutic effect in FIP-infected cats.

5. Conclusions

As an IFN, IFN-ω has been demonstrated to have similar levels of biological activities as IFN-α and IFN-β, which are limited by their toxicity and side effects; thus, IFN-ω may be a useful and alternative antiviral agent. Although rFeIFN-ω has only been registered to treat CPV, FeLV, and FIV infections, it shows comparable efficacy when used to treat other viral infections or diseases. However, its safety (e.g., toxicity and side effects) when used at a high dose has not been investigated extensively. In addition, the antiviral activity of IFN-ω in some fatal infectious diseases also needs to be evaluated. In our laboratory, we confirmed the antiviral activities of IFN-ω against foot and mouth disease virus (not published yet), although these antiviral activities in other viral infections remain to be investigated, and further studies are very important for evaluating its efficacy in more animal models and ultimately in human trials.

Acknowledgments

This work was supported by the National Key Research and Development Program (2017YFD0500902), the Key R & D Program of Gansu Province of China (Grant No. 17YF1NA070) and the National Pig Industrial System of China (CARS-36-06B).

Disclosures

The authors declare no conflicts of interest.

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