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Review Article

# Interferon administered orally to the bovine species helps treat diseases

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**Abstract**

The safety and efficacy of orally administered interferon (IFN) have been reported in cattle. Bovine respiratory disease (BRD) and other diseases of cattle can be successfully treated with oral IFN. Foot-and-mouth disease virus (FMDV) cannot replicate in the presence of IFN and has mechanisms to inhibit host cell IFN production. Clinical data suggest that orally administered IFN is a viable approach for providing antiviral immunity to livestock exposed to viruses such as FMDV.

The first publication on the safety and efficacy of oral interferon [IFN] was published in 1972 [1]. That publication reported that neonatal mice given oral IFN were protected against a lethal viral challenge. In the following 46 years, oral IFN has been reported to be safe and efficacious in dogs, cats, horses, hogs, cattle [2] and man [3].

Despite oral IFN clinical data from Asia [4], Africa [5], Europe [6], Australia [7] and North America [8, 9], oral IFN is seldom employed by clinicians. This is especially regrettable in cattle where the clinical data are reported to have important applications, perhaps even in control of foot-and-mouth disease [FMD].

IFNs are found in the body in nanogram quantities, particularly nasal secretions [10]. IFN was not developed for oral administration because IFN given orally could not be detected in the blood of Rabbits [11], dogs [12] or African Green Monkeys [13]. More than 20 years later, the expression of Thousands of genes was modified by low-dose oral IFN alpha [IFN-α] given to cattle [4].

IFN in the blood is rapidly removed by the kidney and catabolized [15]. Injecting IFN to produce a blood level of IFN in cattle does not result in a clinical benefit. Many studies [reviewed below] demonstrate that IFN given orally to cattle is safe and beneficial.

Neutrophil function, lymphocyte blastogenesis, mononuclear leukocyte subsets and blood cell numbers were evaluated in Holstein steers [n=35] weighing 250-350 kg. A significant [P<0.5] and consistent decrease in neutrophil oxidative metabolism [measured by cytochrome C reduction] was noted 4-8 days after a single oral dose of10 or 50 international units [IU], but not 200 IU, of natural human IFN alpha [HuIFN-α]/steer or placebo. There was a trend [P< 0.10] toward increased T cell numbers in calves given 10 or 50 IUHuIFN-α orally. The results indicate that a single oral dose of 10-50 IU HuIFN-α/steer has biologic activity in cattle which is manifest as changes in lymphocyte populations and alterations of neutrophil oxidative metabolism [15].

Calves [number=7,071] weighing 182-295 kg were enrolled into a placebo-controlled study of bovine respiratory disease [BRD] to assess the effect of a single oral dose of natural HuIFN-α at 73 IU/100 kgbody weight. TheHuIFN-α or placebo, along with standard antibiotic therapy was given when cattle were first diagnosed with BRD. A single oral dose of HuIFN-α treatment reduced feedlot-associated morbidity [P<0.0001] and mortality [P<0.001] attributed to BRD [8].

Bull veal calves [number=264] weighing 40-50 kg were enrolled in a placebo-controlled study. Recombinant HuIFN-α [500 IU/calf] was added to milk replacer once daily for 5 consecutive days significantly [P<0.05] protected against diarrhea and otitis media during the following 15 weeks. Calves given HuIFN-α had fewer days and less severity of diarrhea, compared to placebo-treated calves. The incidence of otitis media was reduced from 18.7% in placebo-treated controls to 8.9% [P <0.05] in HuIFN-α treated calves. The mortality was lower [1.6%, compared to 2.9%] and average weight gain/calf was 6 kg better in HuIFN-α treated calves [9].

Fifty-six [56] bulls and steers weighing an average of 231 kg were enrolled to assess oral placebo with natural or recombinant HuIFN-α in an infectious bovine rhinotracheitis [IBR] virus challenge study. Natural HuIFN-α at 0.05 IU/kg given orally for 4 days starting 2 days before IBR virus challenge improved[P<0.05] weight gain, reduced fever and reduced need for antibiotics. Higher doses of natural HuIFN-α at 0.5 or 0.5 IU/kg or any dose of recombinant HuIFN-α were not significantly better than placebo [16].

Eighty-four [84] IBR seronegative steers [weighing 182-227 kg] were enrolled in a dose titration study of placebo versus 40, 200 or 400 IU of HuIFN-α/calf in the treatment of IBR virus infection. All the calves were given HuIFN-α treatment at the time of challenge with IBR virus and half the calves additionally were given HuIFN-α treatment 1 day before IBR challenge. An oral dose of 40 IU HuIFN-α, but not 200 or 400 IU of natural HuIFN-α resulted in less fever [P<0.005] than in calves given placebo twice [17].

Two hundred steers and bulls [133 and 67, respectively] were purchased from 6 sale barns in Tennessee and North Carolina. The animals ranged in weight from 168-248 kg. The calves were treated for 3 consecutive days in Tennessee with placebo or 0.11, 1.1 or 11 IU of HuIFN-α per kg of body weight before shipment to Texas. Oral doses of natural HuIFN-α at 1.1 IU, but not 0.11 or 11 IU, per kg of body weight, had a significant beneficial effect on lowering fever [>104 F]. Calves with normal rectal temperatures when treated in Tennessee with doses of0.11 or 1.1 IU/kg body weight [but not 11 IU] had a significant [P<0.05] weight gain 21 days after arrival [18].

Steers [number=112] with a mean weight of 185 kg were purchased in Tennessee and shipped to Texas. Upon arrival in Texas, the steers were treated once orally with placebo or 48, 300 or 500 IU of natural HuIFN-α/calf. Calves given 48 IU upon arrival had improved [P<0.05] feed-to-gain ratio on day 14 compared to placebo-treated calves. At day 28 feed-to-gain ratios were significantly [P<0.5] better in all natural HuIFN-α-treated groups, compared to placebo. Calves with pre-treatment fever > 40 C responded better to 300 IU/steer but calves with pre-treatment < 40 C responded better to 48 IU when comparing weight gain. The data indicate that oral natural HuIFN-α given post marketing and transit to newly stressed steers may be beneficial [19].

Natural HuIFNα was tested orally in 24 one-year-old Friesian bulls challenged with virulent *Theileria parva.* In two experiments natural HuIFNα orally at 1 IU/kg body weight protected 11 of 12 bulls against fatal theileriosis compared to death of 5 of 8 placebo-treated or 1 of 4 HuIFNα–treated at 10 IU/kg body weight. An increase in the challenge dose of virulent *Theileria* parva overcame any benefit of natural HuIFNα treatment [5].

Low-dose oral natural HuIFN-α at 0.5 IU/kg body weight was registered in Japan to treat rotavirus diarrhea in calves. Treated calves had significantly [P<0.05] less severe diarrhea, shorter duration of diarrhea, better weight gain and reduced rotavirus excretion [20].

A study of eight age and sex-matched Japanese Black calves identified genes differentially regulated in bovine peripheral blood through the use of cDNA microarrays after oral therapy with 1.0 IU/kg of HuIFN-α. Thousands of genes were noted to be HuIFN-α regulated. Only 15.5% of modified genes were identified as involving the immune system [4].

Oral administration of 20 IU HuIFN-α/calf at birth and 5 days after birth induced an increase in the monocytes [MHC class II-CD4+] 3 weeks after oral administration of natural HuIFN-α in 7 Japanese Black calves, compared to 7 untreated control [21].

Eight Holstein periparturient, multiparous dairy cows were given 10 IU HuIFNα/kg body weight and compared to 10 untreated control dairy cows. The HuIFNα was given orally daily starting 15 days before the estimated calving date; HuIFNα treatment ceased upon parturition. In a nearly identical study, 4 dairy cows were given 0.5 IU/kg body weight of HuIFNα and compared to 4 untreated control cows. The authors reported that HuIFNα activity remained biologically active for 4-6 hours in anaerobic rumen fluids. The authors surmised that cattle have repeated and extended interaction of HuIFNα with oral lymphoid tissues during rumination. Compared with controls, natural HuIFNα-treated dairy cows sustained an inflammatory response and had notable metabolic changes [6].

Sixteen feedlot steers [mean weight 182 kg] were randomly allotted into four groups for a dose titration study of natural bovine IFN at 0, 50, 200 or 800 units per calf. The IFN was administered twice: time 0 and 8 hours later. While the safety and efficacy profiles of orally administered bovine IFN have been documented, the mechanism[s] that result in clinical benefits remain elusive. One approach to delineating the molecular pathways of IFN efficacy is through the use of gene expression profiling technologies. In this proof-of-concept study, different oral doses of natural bovine IFN were tested in cattle to determine if oral IFN altered the expression of genes that may be pivotal to the development of systemic resistance to viral infections such as foot-and-mouth disease [FMD]. Blood was collected at 0, 8 and 24h after the first IFN administration, and DNA isolated from peripheral blood mononuclear cells [PBMCs] was employed in quantitative polymerase chain reaction [qPCR] microarray assays. Within 8h, 50 and 200 units of oral IFN induced significant [P<0.05] changes in expression of 41 of 92 tested autoimmune and inflammatory response-associated genes. These data suggest that orally administered IFN is a viable approach for providing short-term antiviral immunity to livestock exposed to viruses such as FMD virus [FMDV] until such a time that an effective vaccine can be produced and distributed to producers [22].

These cattle studies, performed under various conditions, demonstrated that oral IFN was safe and had anti-microbial effects, modified expression of genes or had effects on metabolism in cattle. The optimal dose for these effects was 1 IU/kg body weight of IFN-α or less.

USDA scientists have reported that the FMDV establishes infection in susceptible cells/hosts by its ability to block key host defenses, specifically the inducible IFN response. FMDV inhibits production of IFNα and blocks a key IFN-inducible, antiviral pathway, i.e.- double-stranded RNA – dependent protein kinase R [PKR] [23-24]. Moreover, FMD virion protein 1 [VP1] has been identified as a viral-origin IFN suppressor by interacting with soluble resistance-related calcium protein, sorcin [25].

Since a FMDV control method of host cells is suppression of IFNα production by FMDV-infected cells then treatment with IFNα or induction of endogenous IFN may help control FMDV. This vulnerability of FMDV to IFN has led to a novel viral disease control strategy using recombinant replication-defective human adenovirus 5 vector containing various species IFN genes.

When the Ad5-pIFNα vectored porcine IFN delivery system was injected into cattle, Ad5-pIFNα provided partial *in vivo*

protection by delaying viremia for one day and decreasing vesicle formulation in challenged cattle [26].

Subsequently, the ARS identified bovine IFN lambda-3 [boIFNλ3] and demonstratedthat expression of this molecule using a recombinant replication defective human Ad5 vector, Ad5boIFNλ3, exhibited FMDV-antiviral activity *in vitro* and *in vivo* [27] Inoculation of cattle with Ad5-boIFNλ3 induced systemic antiviral activity and up-regulation of ISG expression in the upper respiratory airways and the skin. FMD disease could be delayed for at least 6 days when cattle were inoculated with Ad5-boIFNλ3 and challenged one day later with virulent FMDV [27].

The delay in the appearance of disease was significantly prolonged whentreated cattle were challenged by aerosol of FMDV; clinical signs of FMD-disease, viremia, or viral shedding in nasal swabs were not observed in Ad5-boIFN-λ3-treated cattle for at least nine days after challenge [27].

FMDV inhibition in vivo by IFN has been known for 40 years. IFN-induced in the nasal secretions [NS] of cattle by intranasal IBR virus given provided protection against FMDV challenge [28]. One or 2 days after intranasal vaccination with IBR virus, calves were challenged with FMDV. IFN was detected in the NS within 24 hours and for 10 days after IBR virus inoculation. Vaccinated calves had a milder course of FMD and greater than a 99% reduction in NS FMDV.

In the process of studying FMDV transmission from carrier to susceptible cattle, carriers of FMDV were inoculated intranasally with IBR virus to create a stress which might increase excretion of FMDV from carrier cattle. However, FMDV was not detected in esophageal-pharyngeal fluid of the 2 carrier animals a day after IBR virus inoculation and was not detected again during the 4-week sampling period [29]. NS IFN was induced in calves by modified live intranasal IBR viral vaccine [30].

Cattle given coital vesicular exanthema virus [CVEV] and then infected with FMDV developed a milder form of FMD and developed FMD later than control calves [31]. The induction of IFN by the CVEV was probably responsible for the protection against FMDV.

Besides intranasal IBR vaccine [30], another animal viral vaccine that can induce intranasal IFN is a bluetongue virus [BTV] vaccine approved for sheep. A safety study of the BTV vaccine was conducted in cattle. Given intranasally, the BTV vaccine was safe and induced NS IFN in cattle [32]. IFN induced in the NS probably trickles into the oral and pharyngeal cavities. When IFN was radiolabeled and given orally to mice, the IFN was retained in the posterior nasal cavity, posterior tongue, small intestine and rectum [33].

Viral inducers of IFN protection of cattle with FMD agrees with the successful use of oral synthetic IFN inducers protecting mice from infection with FMDV. An oral IFN inducer protected mice when given 2, 24 or 48 hours before FMDV inoculation and another inducer protected mice when given 18 hours before FMDV [34-35].

Summary: Oral IFN clinical data from thousands of cattle from Asia [4], Africa [5], Europe [6], Australia [7] and North America [8,9] report that oral IFN is safe and efficacious. At a cost of only pennies per dose of a unit of IFN activity/kg body weight, it is reasonable to use oral IFN. Moreover, because FMDV is so sensitive to IFN, it is reasonable to treat FMD with oral IFN.

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