Potential Use of Recombinant Bovine Interferon-Alpha$_I$1 in the Control of Bovine Respiratory Disease in Fattening Calves

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Introduction

Bovine respiratory disease (BRD) complex poses a major problem to the cattle industry. Enzootic calf pneumonia (ECP) prevails in housed and/or intensively reared calves usually during the first months of their life. Economic losses result from animal mortality, weight loss, suboptimal feed conversion, and general poor performance as well as from treatment and extra labor costs.

Stress caused by transportation, overcrowding and environmental changes is a major factor that favors a disease outbreak. The aetiology of BRD is complex and multifactorial and is known to involve various viral pathogens (IBR/BHV-1, BRSV, PI-3, BVD, etc.), mycoplasmas and bacteria (*Pasteurella haemolytica* and *P. multocida*). An initial viral infection aggravated by stress results in immunosuppression in the calves which, in turn, favours a secondary colonization of the lungs by bacteria. The clinical sequel is fibrinous bronchopneumonia.

The judicious use of vaccines and antibiotics in parallel with good herd management may help to prevent and control BRD. However, complete protective immunity against the causative organisms is usually only achieved by natural exposure to the pathogens. Thus, the use of an immunomodulatory compound active against a wide spectrum of viruses represents an alternative approach to the control of BRD, particularly if such a medicament is administered immediately prior to or following a stressful episode.

Interferons (IFNs) are a group of proteins which control virus replication, exhibit anti-proliferative effects on cells, and modulate immune effector cell functions. The results of five semi-field trials summarized in the present article demonstrate that rBoIFN-α_I1 affords significant protection to fattening calves against natural outbreaks of ECP. The product has proved to be similarly promising in the control of shipping fever under North American feedlot conditions.[1]

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Materials and Methods

Cross-bred dairy calves were brought in local markets at 2 to 3 weeks of age, mixed, and transported by truck to the trial site within 12 hours after purchase. The majority of the calves were males weighing between 45 kg and 70 kg. Only calves that were clinically healthy at the time of arrival at the trial site were admitted to the studies.

On the day of arrival (day 0), the calves were individually identified by ear tags, weighed, randomized according to body weight and sectioned into 3 comparable treatment groups (20 to 22 head per group), and placed in 2 replicate pens per group. The calves were fed with a milk replacer either unmedicated or containing a subtherapeutic level of antibiotics. The calves were weighed at the end of the study (day 21).

Each animal was checked daily and scored for the severity of clinical symptoms, i.e. from day 0 up to and including day 21 of the study. Six symptoms representative of BRD were rated according to an established protocol.[2] A weighting coefficient was attributed to every parameter scored to calculate an overall mean value (OMV) reflecting the composite health status of an animal with respect to BRD. All animals with a daily OMV of two or greater were considered sick and received a standard course of antibiotic treatment. Cumulative incidence of disease (CI) within a treatment group, an index of morbidity was calculated as follows:

$$CI = \frac{\text{No. of animals sick at any time during the study}}{\text{No. of healthy animals at the beginning of the study}}$$

The number of clinical relapses following antibiotic therapy was also recorded. Calves that died during the

experiment were subjected to a post-mortem examination immediately after death, and lung samples were taken for bacteriology.

Recombinant bovine interferon-alpha|1 (rBoIFN-α_I1) produced in *E. coli*, purified to homogeneity, and formulated as a lyophilized dry substance was reconstituted with water for injection. Preparations had a minimum specific activity of 10^7 laboratory units/mg protein as determined by plaque inhibition of VSV grown in MDBK cells.

Test animals received either 0.5 mg, 1 mg or 5 mg of IFN intramuscularly (i.m.) once on day 0 or twice, on days 0 and 7. Controls received an equivalent volume (2 ml) of placebo formulation. All studies were blind. The personnel involved in scoring were unaware of the type of treatment administered. In experiment 40/87, the animals in the control and one treatment group were vaccinated against PI-3 virus at housing (and 10 weeks of age) (Imuresp^R, Norden Labs.) in addition to the placebo and IFN treatment.

Results and Discussion

No treatment-related adverse clinical reactions were noted at any time throughout the entire 21-day observation period. Under the experimental conditions described above, severe outbreaks of BRD developed in all 5 studies reported here, with cumulative incidences ranging from 0.68 to 0.91 in the control groups. Compared to the control groups, disease incidence was reduced in the treatment groups of all 5 studies (Table 1). Pending full statistical analysis of these and further data, an i.m. dose of 5 mg per animal administered once, at housing, or twice, at a 7-day interval, appear to be the recommendable treatment regimens, although lowering the dose to 1 mg or 0.5 mg (Table 1) may occasionally be equally effective. In all studies to date where the percent advantage of IFN treatment over the controls was 10% or less by day 21, the incidence of disease was significantly reduced on day 7 post treatment (more than 20%).

Recurrence rates following antibiotic therapy were reduced to a variable degree, by 39–67%, in the treatment groups of the five studies (Table 2). In all studies but one, weight gain and feed conversion were not significantly different between experimental groups of calves. In study 40/87, animals treated i.m. with 5 mg of rBoIFN-α_I1 alone gained an average of 30% more than animals treated with a PI-3 vaccine alone, and feed efficiency was improved by 31%.

The results presented are derived from studies in which the young calves were handled like commercial cattle, including transportation, crowding conditions and processing, in order to ensure proper exposure to stress and pathogens. The observed outbreaks of BRD were severe. In a reproducible semi-field model such as the one used by us, variability was to be expected due to pathogen variation as well as differences in the genetic background, source and age of the calves.

TABLE 1. Efficacy of rBoIFN-alpha|1

Study	Treatment	Disease Incidence	% Advantage
1/87	Control	0.84	--
	0.5 mg i.m.	0.62	+ 26
	5 mg i.m.	0.61	+ 27
2/87	Control	0.83	--
	5 mg i.m.	(1x) 0.71	+ 14
	5 mg i.m.	(2x) 0.50	+ 40
4/87	Control	0.91	--
	5 mg i.m.	0.72	+ 21
14/87	Control	0.86	--
	1 mg i.m.	(1x) 0.83	+ 3
	5 mg i.m.	(2x) 0.67	+ 22
40/87	Control/PI-3 Vaccine	0.68	--
	PI-3 Vaccine &		
	5 mg i.m.	0.32	+ 53
	5 mg i.m.	0.35	+ 49

TABLE 2. Effect of rBoIFN-alpha|1 on Clinical Relapses

Study	Treatment	Recurrence Incidence	% Advantage
1/87	Controls	0.63	--
	0.5 mg i.m.	0.33	+ 48
	5 mg i.m.	0.33	+ 48
2/87	Controls	0.33	--
	5 mg i.m.	(1x) 0.19	+ 42
	5 mg i.m.	(2x) 0.20	+ 39
4/87	Controls	0.64	--
	5 mg i.m.	0.36	+ 44
40/87	Controls/PI-3 Vaccine	0.27	--
	PI-3 Vaccine &		
	5 mg i.m.	0.09	+ 67
	5 mg i.m.	0.09	+ 67

In our study, although rBoIFN-alpha$_I$1 did not eliminate ECP from treated calves, it significantly reduced the incidence and severity (including relapse rates) of BRD. To our knowledge, this is the first report of a beneficial effect of a bovine interferon on BRD under actual conditions of veal calf fattening practice.

Summary

A series of practice-like semi-field studies were carried out to eaxmine whether recombinant bovine interferon-alpha$_I$1 (rBoIFN-α_I1) was effective in protecting intensively reared veal calves against enzootic calf pneumonia (ECP). A single intramuscular dose of 0.5, 1 or 5 mg of interferon was administered to the calves on admission to a fattening unit. Compared to placebo-treated controls, interferon treatment reduced the incidence of respiratory diseases and the relative frequency of relapse following standard antibiotic therapy. A second dose given 7 days after the first injection further increased product efficacy. No treatment-related adverse reactions were noted in the experimental animals. The results demonstrate that under practical conditions prophylactic dosing with rBoIFN-α_I1 partially protects young fattening calves against ECP.

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References

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