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Oral treatment of transmissible gastroenteritis with natural human interferon alpha: A field study

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Abstract

During a natural outbreak of transmissible gastroenteritis (TGE), groups of piglets were treated orally for 4 consecutive days with placebo or 1.0, 10.0 or 20.0 international units (IU) natural human interferon alpha (nHuIFNα). Piglets that were 1–12 days of age and given 1.0, 10.0 or 20.0 IU nHuIFNα had significantly (P<0.01) greater survival rates than placebo-treated piglets; survival rates were the greater for the highest level of nHuIFNα treatment. In contrast, beneficial effects of nHuIFNα were not observed in piglets farrowed during the disease outbreak and given nHuIFNα within hours of birth. Oral nHuIFNα therapy modulates the natural course of high morbidity and mortality commonly seen with TGE.

1. Introduction

Transmissible gastroenteritis virus (TGEV), a coronavirus, causes an infectious disease of swine resulting in diarrhea and dehydration with high mortality in neonates (Saif and Bohl, 1986). The severity of clinical signs is inversely proportional to the age of the animal, with morbidity and mortality approaching...
100% in piglets less than 14 days of age. Dehydration which contributes to the high mortality of piglets with TGE is aggravated by TGE-associated agalactia in affected sows (Saif and Bohl, 1986).

Virus-specific gut-associated secretory IgA (sIgA) provides direct immunological protection (Sprino and Ristic, 1982). Both lactogenic IgA and IgG provide partial protection to suckling piglets. When antibody levels are high, infected piglets develop less severe disease and have reduced mortality rates (Saif and Bohl, 1986).

Vaccination of neonatal piglets induces active immunity, but protection develops too late to prevent the serious and possibly lethal effects of TGE (Sprino and Ristic, 1982; Saif and Bohl, 1986). The ideal approach to treatment of piglets in a TGE epidemic might be to provide immediate antiviral therapy while the immune response to TGE virus develops.

Although human interferon alpha (HuIFNα) preparations are approved for use in man for 3 defined clinical entities and are administered parenterally in pharmacologic doses (millions of IU), responses to therapy are often disappointing. In contrast, recent data demonstrate that low doses of IFNα administered into the oral cavity are beneficial in the treatment of a variety of diseases in several animal species including swine (Tompkins and Cummins, 1982; Cummins and Hutcheson, 1983; Cummins and Hutcheson, 1986; Hutchinson et al., 1990; Lecce et al., 1990). The objective of this study was to assess the efficacy of low dose oral IFNα therapy in piglets during a natural outbreak of TGE.

2. Materials and methods

2.1. Interferon

Crude natural HuIFNα (nHuIFNα) induced in pooled human leukocytes by Sendai virus was processed and purified by immunoaffinity chromatography, acidification, and gel filtration chromatography (Interferon Sciences Inc., New Brunswick, NJ, 1989) and diluted to 1.0, 10.0 and 20.0 IU per ml in buffered saline solution (BSS). The dilutions were assayed by plaque reduction and determined to contain <1, 30 and 40 IU, respectively.

2.2. Diagnosis

A preliminary diagnosis of TGE was made by the attending veterinarian in consultation with one of the authors (B.W.S.) and was based on general field criteria for TGE (Cross and Bohl, 1969). Infection was confirmed by necropsy and histopathologic examination of intestine and a fluorescent antibody test for TGEV antigen in frozen tissues by the Pennsylvania State Diagnostic Laboratory, Summerdale, PA (Morin et al., 1973).
2.3. Animals

The piglets in this study were hybrid stock from a farrowing facility with a natural outbreak of TGE. The sows were susceptible to TGE and showed clinical signs, but were not tested for the presence of viral antigen. A total of 1740 piglets from 203 litters, age newborn to 20 days, were treated during the outbreak. Piglet treatment and responses were recorded individually and by litter.

2.4. Experimental design and statistical analysis

The experimental design was a randomized block design. The four treatments were placebo (0), 1.0, 10.0 or 20.0 IU nHuIFNα per piglet per day. The experiment was conducted 'blind', with treatments identified by four color codes: red, blue, white or brown. The litters of piglets were blocked by four and the treatments assigned within each four litters. The TGEV outbreak was in progress and the age of the piglets at time of exposure to TGE varied with farrowing dates. Therefore, the age at beginning of treatment was grouped as follows: piglets from 13 to 20 days of age, piglets from 1 to 12 days of age and newborn piglets. Except for animals that died, piglets were treated for 4 consecutive days (1.0 ml final volume orally) regardless of clinical condition. Only litters with at least four piglets prior to initiation of treatment were included in the study.

The data were analyzed by χ² analysis with each dose compared with the placebo within age groups. The P values reported are less than 0.05. Other P values were not considered significant.

3. Results

The treatment groups with the respective number of litters and piglets and the survival rates of piglets farrowed during the 14 day study period are listed in Table 1. Animals treated with either 1.0 or 10.0 IU nHuIFNα had significantly

| nHuIFNα (IU) | Number of Piglets | Litters | Alive | Dead | Percent survival | P value (treatment group vs. placebo) |
|--------------|-------------------|---------|-------|------|-----------------|--------------------------------------|
| 0            | 413               | 49      | 173   | 240  | 41.9            | -                                    |
| 1.0          | 448               | 52      | 227   | 221  | 50.7            | 0.01                                 |
| 10.0         | 443               | 53      | 217   | 226  | 49.0            | 0.04                                 |
| 20.0         | 436               | 49      | 195   | 241  | 44.7            | -                                    |
| Total        | 1740              | 203     | 813   | 928  | 46.7            |                                       |
Table 2
Age at treatment and percentage survival of piglets given natural interferon alpha (nHuIFNα) or placebo and exposed to transmissible gastroenteritis virus

| nHuIFNα (IU per pig) | 13–20 days Alive | Dead | Percent survival* | 1–12 days Alive | Dead | Percent survival | Newborn Alive | Dead | Percent survival* |
|----------------------|------------------|------|------------------|------------------|------|------------------|---------------|------|------------------|
| 0                    | 76               | 6    | 92.7             | 12               | 67   | 15.2             | 85            | 167  | 33.7             |
| 1.0                  | 98               | 9    | 91.6             | 25               | 44   | 36.2b            | 104           | 168  | 38.2             |
| 10.0                 | 93               | 3    | 96.9             | 29               | 46   | 38.7c            | 95            | 177  | 34.9             |
| 20.0                 | 80               | 2    | 97.6             | 44               | 44   | 50.0d            | 71            | 195  | 26.7             |
| Total                | 347              | 20   | 94.6             | 110              | 201  | 35.4             | 355           | 707  | 33.4             |

* No significant difference compared with placebo.

b 1 IU per pig significantly greater than 0 IU per pig ($P=0.003, \chi^2$ test).

c 10 IU per pig significantly greater than 0 IU per pig ($P=0.001, \chi^2$ test).

d 20 IU per pig group had significantly greater survival than 0 IU per pig ($P=0.000002, \chi^2$ test).

greater ($P<0.05$) survival rates (50.7% and 49% respectively) than piglets given placebo (41.9%).

Survival data were analyzed by age at treatment (Table 2). The 367 piglets from 44 litters which were 13–20 days old at the time of first treatment had a significantly greater ($P<0.001$) survival rate (94.6%) than newborn piglets (33.4%). The 311 piglets, which were 1–12 days old when first treated, were probably exposed to TGEV within the first 8 days of age; regardless of treatment, these piglets had a mean survival rate of 35.4%. A similarly low overall survival rate (33.4%) was observed in 1062 newborn piglets from 107 litters in which treatment was begun on the day of farrowing. These piglets were likely exposed to TGEV at birth. The mean litter sizes for the three age groups (13–20 days, 1–12 days, or newborns) were 10.4, 10.4, and 10.5, respectively. However, because some piglets died before the treatment began, the mean treated litter sizes were 8.3, 6.0 and 9.9 piglets, for 13–20 days, 1–12 days and newborns respectively.

Survival of piglets within the 1–12 day age group was favorably affected by treatment. For piglets 1–12 days old, nHuIFNα increased survival rate from 15.2% (placebo) to 50.0% (20.0 IU nHuIFNα); all dosages of nHuIFNα improved survival rates ($P<0.01$). In contrast, oral nHuIFNα treatment of newborn piglets did not significantly improve survival rates compared with placebo treatment.

4. Discussion

TGE is a devastating disease in piglets. In high density farrowing facilities, prophylaxis is largely limited to prevention of infection by exclusion of TGEV-contaminated materials from the farrowing facilities. An alternative approach to prevention is vaccination or planned natural infections of pregnant sows. In this
case, specific immunological protection against the lethal effects of TGE in neonatal piglets is related to levels of TGEV-specific sIgA concentrations in the gut, as provided by passive maternal immunity in colostrum and milk (Bohl et al., 1972; Saif et al., 1972). This approach is successful when pregnant sows are immunized prior to farrowing so that sufficient lactogenic IgA is available to the suckling neonates. Sow vaccination reduces mortality rates, the morbidity within the herd remains high and unacceptable death loss rates may be observed.

The TGE epidemic described in this study is typical of the disease in a high-production closed-farrowing facility. None of the sows were vaccinated prior to the outbreak, and thus, pigs of all ages were immunologically naive and susceptible to TGEV. Although the exact start of the TGE outbreak could not be determined, the epidemic was well established by the time therapy was initiated. The survival data were collected and analyzed by three age groups at initiation of nHuIFNα therapy. The most beneficial effects of nHuIFNα therapy were observed in 1–12 day old piglets; all three dosages of nHuIFNα were effective. In contrast, newborns that were farrowed during the disease outbreak, and treated with nHuIFNα within a few hours of birth, did not demonstrate a significant treatment response.

The variable effects of therapy observed in this study are consistent with the modulating effects of many biological response modifiers, including IFNα. Factors influencing this variability include dose and route of IFNα therapy in relation to both age and time of exposure to the infectious agent. Others have observed that IFNα therapy after infection is beneficial whereas IFNα therapy prior to infection is contraindicated (Oppenheim et al., 1987). Similarly, high doses of IFNα are sometimes less beneficial than the lower doses (Cummins et al., 1988; Koech et al., 1990; Young et al., 1990). Thus, IFNα therapy for TGE may exhibit a dose-dependent effect and efficacy may also vary according to the age and time of exposure to TGEV. Both effects were observed in this field trial.

The mechanism by which low doses of oral nHuIFNα provides benefit to piglets during this TGE outbreak is unknown. However, porcine blood mononuclear cells are known to secrete IFNα after induction by TGEV (Nowacki et al., 1993) and that IFN production gradually increases with the age of the animal. The beneficial effects of oral nHuIFNα therapy observed in this study may be related to the immune responsiveness of oral IFN therapy. Studies in piglets with both experimental and natural rotavirus infection showed a significant weight gain benefit and a reduction in enteric disease (Lecce et al., 1990).

This report documents a novel therapy for TGEV infection. The data demonstrate that orally administered nHuIFNα provides a positive survival benefit to 1–12 day old TGEV-infected piglets. Further, as with other biological response modifiers, the magnitude of effect varies with the dose used, age of animals treated and the stage of the disease at the time of initial therapy. Although the mechanism has not been determined, the beneficial effects described here are consistent with data obtained in other species.
References

Bohl, E.H., Gupta, R.K.P., Olquin, M.V.F. and Saif, L.J., 1972. Antibody responses in serum, colostrum and milk of swine after infection or vaccination with transmissible gastroenteritis virus. Infect. Immun., 6:289–301.

Cross, R.F. and Bohl, E.H., 1969. Some criteria for the field diagnosis of porcine transmissible gastroenteritis. J. Am. Vet. Med. Assoc., 154:264–272.

Cummins, J.M. and Hutcheson, D.P., 1983. Effect of interferon on feedlot cattle. Proc. Am. Assoc. Bov. Pract., 5:109–115.

Cummins, J.M. and Hutcheson, D.P., 1986. Low dosage of interferon to enhance vaccine efficiency in feedlot calves. Proc. Am. Assoc. Bov. Pract., 18:135–138.

Cummins, J.M., Tompkins, M.B., Olsen, R.G., Tompkins, W.A. and Lewis, M.G., 1988. Oral use of human alpha interferon in cats. J. Biol. Resp. Mod., 7:513–523.

Hutchinson, V., Angenend, J.L., Mok, W.L., Cummins, J.M. and Richards, A.B., 1990. Chronic recurrent aphthous stomatitis: oral treatment with low dose interferon alpha. Mol. Biother., 2:160–164.

Koech, D.K., Obel, A.O., Minowada, J., Hutchinson Y. and Cummins, J.M., 1990. Low dose oral alpha-interferon therapy for patients seropositive for the human immunodeficiency virus type-1 (HIV-1). Mol. Biother., 2:91–95.

Lecce, J.G., Cummins, J.M. and Richards, A.B., 1990. Treatment of rotavirus infection in newborn pigs using natural human interferon alpha. Mol. Biother., 2:211–216.

Morin, M., Morehouse, L.G., Solorzano, R.F. and Olson, L.D., 1973. Transmissible gastroenteritis in feeder swine. Clinical, immunofluorescence and histopathological observations. Can. J. Comp. Med., 37:239–248.

Nowacki, W., Cederblad, F., Renard, C., LaBonnardiere, C. and Charley, B., 1993. Age-related increase of porcine natural interferon α producing cell frequency and of interferon yield per cell. Vet. Immunol. Immunopathol., 37:113–122.

Oppenheim, J.J., Ruscetti, F.W. and Faltynek, C.R., 1987. Interleukins and interferons. In: D.P. Stites, J.D. Stobo and J.V. Wells (Editors), Basic and Clinical Immunology, 6th edn. Appleton and Lange, Norwalk, CN, pp. 82–95.

Saif, L.J. and Bohl, E.H., 1986. Transmissible gastroenteritis. In: A.D. Leman, B. Straw, R.D. Glock, W.I. Mengeling, R H C. Penny and F. Scholl (Editors), Diseases of Swine, 6th edn. Iowa State University Press, Ames, pp. 255–274.

Saif, L.J., Bohl, E.H. and Gupta, R.K.P., 1972. Isolation of porcine immunoglobulins and determination of the immunoglobulin classes of transmissible gastroenteritis viral antibodies. Infect. Immun., 6:600–609.

Sprino, P.J. and Ristic, M., 1982. Intestinal, pulmonary, and serum antibody responses of feeder pigs exposed to transmissible gastroenteritis virus by oral and oral-intranasal routes of inoculation. Am. J. Vet. Res., 43:255–261.

Tompkins, M.B. and Cummins, J.M., 1982. Response of feline leukemia virus-induced nonregenerative anemia to oral administration of an interferon-containing preparation. Feline Pract., 12:6–15.

Young, A.S., Maritim, A.C., Kariuki, D.P., Stagg, D.A., Wafula, J.M., Mutugi, J.J., Cummins, J.M., Richards, A.B. and Burns, C., 1990. Low dose oral administration of human interferon alpha can control the development of *Theileria parva* infection in cattle. Parasitology, 101:201–209.