Human Recombinant Interferonα-2b for Management of Idiopathic Recurrent Superficial Pyoderma in Dogs: A Pilot Study

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The oral use of human recombinant interferonα-2b at 1,000 IU/ml/day appeared to provide only a transient benefit as compared with placebo for management of idiopathic recurrent superficial pyoderma in dogs. Further investigation using a larger population of dogs is needed to determine whether interferon is effective for long-term treatment of this condition.

INTRODUCTION

Recurrent bacterial pyoderma in dogs is frequently a source of frustration for both pet owners and clinicians. Although many canine patients with bacterial pyoderma respond appropriately and completely to initial therapeutic management, many relapse. When diagnostic tests fail to reveal an underlying cause of recurrent superficial pyoderma (e.g., allergic disease, hypothyroidism, occult neoplasia), veterinarians frequently rely on one of three treatment options: antibiotic therapy, antibacterial shampoos, or immunomodulatory therapy with products such as the polyvalent bacterial antigen (Staphylococcus aureus) Staphage Lysate (SPL, Delmont Laboratories) or killed Propionibacterium acnes bacterin (Immuno-Regulin, ImmunoVet). SPL is a bacterin prepared by bacteriophage lysis of human-origin S. aureus bacteria. Administration of SPL is by SC injection once or twice weekly, and killed P. acnes bacterin is administered once or twice weekly IV. One study reports that approximately 30% to 50% of dogs with recurrent pyoderma ultimately benefit from bacterin treatment with SPL. However, some owners object to giving SC injections at home or to the inconvenience and expense of multiple trips to
the veterinarian for IV injections, which leads to decreased owner compliance and treatment failure.

The interferons (IFNs) are one of the body’s natural defense responses to invasion by microbes, tumors, or protein antigens. The response begins with production of IFN proteins (α, β, and γ), which then induce the antiviral, antimicrobial, antitumor, and immunomodulatory actions of IFN. IFNs have been shown to restrict intracellular replication of Toxoplasma gondii and obligate intracellular bacteria through reduction of intracellular tryptophan pools.

IFN’s defenses against bacterial pathogens involve both immunoregulatory functions and direct effects on nonleukocyte cells to inhibit bacterial invasion and replication. IFNs enhance phagocytic activity and macrophage activation. The bacteriostatic and bactericidal actions of activated macrophages constitute a major mechanism of host defense to many bacterial pathogens.

The biologic effects of human recombinant IFNα following oral administration do not appear to involve small intestinal absorption and peripheral circulation. Rather, IFNα is degraded by digestive enzymes and cannot be detected in peripheral blood after intragastric administration to African green monkeys. Alternatively, oral administration of IFNα may impart systemic biologic effects by altering the function of oropharyngeal-associated lymphoid tissue. Lymphocytes exposed to IFNα can transfer enhanced biologic effects to naïve lymphocytes in the absence of IFNα. This transference mechanism allows the biologic effects of IFNα to reach tissues accessible to mobile lymphocytes.

The bioavailability of IFNα following intraperitoneal or PO administration in mice is about 100% and 1%, respectively, yet the therapeutic efficacy of orally administered IFNα against Semliki Forest virus challenge is superior to that of the intraperitoneal route of administration. The presence of IFNα in the blood may not be a prerequisite for activation of systemic host resistance mechanisms. Oral dosing potentially activates unique natural defense systems originating in oropharyngeal-associated lymphoid tissue that involves cellular communication and amplification of the biologic response.

Veterinarians have used IFN to treat recurrent pyoderma; however, to date there are no reported double-blinded, placebo-controlled studies to document its effectiveness. Based on anecdotal evidence and an understanding of the mechanisms of action of the IFNs, a pilot study was undertaken to determine whether orally administered human recombinant IFNα-2b would be effective for management of idiopathic recurrent superficial pyoderma in dogs.

**MATERIALS AND METHODS**

**Patient Selection and Initial Evaluations**

Eleven dogs were selected from the patient population presented at a dermatology referral center between September 2001 and December 2002. Each dog selected had a well-documented history of nonseasonal, recurrent superficial pyoderma (greater than 1 year duration), for which an underlying cause could not be determined. All 11 dogs entered into the study had a history of complete response to antibiotic administration (i.e., return to clinical normalcy), followed by relapse within 6 weeks after the use of antibiotics was discontinued. A thorough physical examination was performed for each dog at the time of entry into the study. Minimum diagnostic evaluation of dogs prior to selection for the study consisted of a complete blood count, serum biochemical analysis, urinalysis, measurement of baseline serum thyroxine and baseline serum thyroid-stimulating hormone concentrations, examination of skin...
scrapings for ectoparasites, and fungal culture. Cytology from an intact superficial skin pustule was performed to verify the suspicion that the infection was caused by a gram-positive cocci. A swab specimen was submitted for bacteriologic culture and antimicrobial susceptibility testing. All dogs were actively infected with superficial bacterial pyoderma at the time of admission to the study.

Before initiation of antibiotic treatment, *Staphylococcus intermedius* was isolated in pure culture from lesions present on all dogs. All isolates were sensitive to cephalexin according to bacteriologic culture and antimicrobial susceptibility testing. Repeat culturing (n = 16), performed during the study confirmed that all subsequent isolates were *S. intermedius* and were sensitive to cephalexin.

**Allocation and Treatments**

Treatment spanned an 18-week period, with clinical evaluation performed at Weeks 0, 6, 10, 14, and 18. All 11 dogs received cephalexin (22 mg/kg PO every 12 hours) or other appropriate antimicrobial therapy based on culture and sensitivity testing of material from an intact superficial skin pustule from Weeks 0 through 6. Benzoyl peroxide (OxyDex, DVM Pharmaceuticals) or ethyl lactate shampoo (Etiderm, Virbac) was used to bathe patients once or twice weekly throughout the entire study. Concurrent with oral antibiotic administration, dogs were given either human recombinant IFNα-2b (Intron-A, Schering-Plough; 1,000 IU/ml PO once daily) or a placebo (1 ml of the same sterile saline solution used as diluent for the IFN agent). Assignment to either the IFN group (n = 5) or the placebo group (n = 6) was random. Vials were identified by a code number and were identical in appearance so that neither the owner nor the study personnel knew which substance was being administered. The IFN or placebo was administered at home by the owner. The assigned treatment was continued for the initial 6-week course of antibiotic treatment and for 12 weeks after cessation of antibiotics (18 weeks total).

**Evaluations**

Each dog was evaluated by a veterinarian at the end of the antibiotic regimen (Week 6) and every 4 weeks thereafter for 12 weeks using a standard scoring system (Table 1).² The same veterinarian performed all scheduled evaluations. Scores (1 to 6) at each evaluation were assigned based on extent of recurrence, whether some response to treatment was evident, and the necessity for additional antibiotic therapy to keep the dog comfortable. If antibiotics were needed for patient comfort, cephalexin was prescribed at 22 mg/kg PO every 12 hours for 2 weeks. During each examination (Weeks 0, 6, 10, 14, and 18), dogs were assessed for the presence and extent of bacterial pyoderma, and a specimen for

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recurrence?</th>
<th>Control Observed</th>
<th>Antibiotics Required*</th>
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<tr>
<td>1</td>
<td>None</td>
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<td>No</td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>Mild</td>
<td>Yes</td>
<td>Yes</td>
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<td>4</td>
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<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Worse than ever</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Cephalexin at 22 mg/kg PO every 12 hours for 2 weeks.
bacteriologic culture and antimicrobial susceptibility was obtained if needed (clinical score \( \geq 3 \)). A final mean score below 3 was considered a favorable clinical response, and a score of 3 or higher was considered a poor response. At the conclusion of the 18-week study, the treatment code was broken for evaluating the benefit of treatment with IFN.

### Statistical Analysis

A general linear model with generalized estimating equations (GEE) for ordinal data was used to evaluate the significance of differences in the clinical score between IFN and placebo treatments.\(^{13}\) Comparisons were made at each time point as well as for all time points combined. A \( P \) value < .05 was considered statistically significant.

### RESULTS

Adverse clinical reactions to the placebo or IFN were not reported by any owner. Following 6 weeks of treatment with cephalexin, clinical signs of superficial pyoderma were resolved for all 11 dogs, and all dogs received a clinical score of 1 at that evaluation (Table 2). During the period following cessation of cephalexin (Weeks 7–18), four of six dogs (66\%) treated with placebo showed a favorable clinical response, and two had a poor clinical response (Table 2). Mean combined scores (Weeks 0–18) for dogs treated with placebo ranged from 2.2 to 3.2. The cumulative mean score for the placebo-treated group was 2.73 (Figure 1).

Four of five dogs (80\%) treated with IFN\(\alpha\)-2b had a good clinical response (Table 2). Mean clinical scores for individual dogs in this group ranged from 1.8 to 3.2, and the cumulative mean score was 2.32 (Figure 1). There was a significant \( P < .035 \) difference between the groups in terms of clinical improvement and control of recurrent pyoderma at Week 14 (Table 2); however, clinical scores were not significantly different between the groups at Week 18.

Two of five dogs in the IFN group required
antibiotic therapy during Weeks 7 through 18, compared with five of six dogs in the placebo group that required treatment during that period.

**DISCUSSION**

The purpose of this pilot study was to determine whether oral use of human recombinant IFNα-2b is effective for treatment of idiopathic recurrent superficial pyoderma in dogs. In these dogs, human recombinant IFNα-2b treatment provided an apparent, albeit transient, benefit over placebo treatment as demonstrated by improved clinical evaluation scores. Only two of five dogs in the IFN group required antibiotic therapy during Weeks 7 through 18, compared with five of six dogs in the placebo group. Owners of the two dogs in the IFN group that required antibiotic therapy considered the dogs’ relapses to be less severe than previous relapses.

Despite a perceived response to IFN treatment as compared with that for dogs in the placebo group, a significant ($P < .035$) difference between the groups in terms of clinical improvement and control of recurrent bacterial pyoderma was only observed at Week 14. The sample size in this pilot study was considered sufficient for statistical evaluation of the ordinal data; however, with the limited number of subjects available, even one successful outcome in a placebo-treated animal or one treatment failure in the IFN-treated dogs would preclude the finding of a significant treatment effect. Future studies would most likely consider using a larger sample size.

The dogs that participated in this study were client-owned animals, and despite the provision of various discounts and other incentives, many owners were not willing to participate in the study unless their dog would receive antibiotic therapy when needed, even if the dog was in the

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**Figure 1.** Mean clinical scores for dogs with recurrent superficial pyoderma treated with either placebo or human recombinant interferonα-2b. Individual scoring is based on a scale of 1 (clinically normal) to 6 (extensive clinical signs present). An asterisk next to a marker indicates the clinical score for the placebo group is significantly ($P < .05$) higher than that for the group treated with human recombinant interferonα-2b.
placebo group. The authors felt an ethical obligation to reinstitute antibiotic therapy when relapses of pyoderma occurred. In order to qualify for inclusion in this study, the condition had to be proven responsive to antibiotic treatment. Therefore, it is possible that the clinical evaluation scores of dogs in the placebo group that required antibiotic therapy during Weeks 7 to 18 would have increased further had no antibiotic therapy been initiated.

The scoring system used in this study was selected because the investigators wanted the study design to be similar to one previously conducted with SPL. In retrospect, a revised scoring system that would assess lesions with regard to type and severity, such as a modified Canine Atopic Dermatitis Extent Severity Index (CADESI), might have been more beneficial. Another factor not included in the scoring system was a method for acknowledging that the patient was receiving antibiotic therapy at the time of a particular scoring episode. One example of such a scoring modification could be to add 0.5 to the score at any evaluation period during which the dog required antibiotic therapy. This and other modifications will be considered for future studies.

There were factors in this study that could not be tightly controlled by the investigators, such as changes in the home environment, accuracy of dosing, spontaneous waxing and waning of the disease process, a perceived placebo effect by the owners, and the beneficial effect of prolonged antibiotic treatment. Every effort was made, however, to minimize these factors by giving clients detailed oral and written instructions outlining what was expected during the study.

Several questions need to be addressed in future studies, including the following: Would dogs in the IFN group have responded better to canine IFN as opposed to human recombinant IFN? Although IFN (especially IFNα) has optimal biological activity on homologous species cells, it has also been shown that certain IFN types also have pronounced effects on heterologous species cells. What happens to dogs that receive oral IFN over a longer period (e.g., 12–24 months)? Do they consistently require less antibiotic therapy, and are relapses less intense clinically than for dogs that do not receive IFN? What happens when the IFN is discontinued? Do the episodes of superficial bacterial pyoderma become more frequent and require longer treatment with antibiotics for resolution? How effective is oral IFN compared with bacterin therapy using SPL? Are the two treatments comparable in terms of owner compliance? What are the long-term effects of oral IFN on the immune system?

If oral IFN therapy is shown to be as effective as bacterin preparations in the management of idiopathic recurrent superficial pyoderma in dogs, this would provide owners and veterinarians with another treatment modality that is both easy to use (oral versus injectable), and relatively inexpensive.

CONCLUSION

In this pilot study, the oral use of human recombinant IFNα-2b at 1,000 IU/ml/day appeared to provide only a transient benefit as compared with placebo treatment for management of idiopathic recurrent superficial pyoderma in dogs. Further investigation in a larger population of animals is needed to determine whether IFN is effective for long-term treatment of idiopathic recurrent superficial pyoderma.

REFERENCES

2. DeBoer DJ, Moriello KA, Thomas CB, Schultz KT: Evaluation of a commercial staphylococcal bacterin for management of idiopathic recurrent superficial pyo-