Bovine lactoferrin and piroxicam as an adjunct treatment for lymphocytic-plasmacytic gingivitis stomatitis in cats

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A B S T R A C T
Feline lymphocytic-plasmacytic gingivitis/stomatitis (LPGS) or caudal stomatitis is an inflammatory disease that causes painful erosive lesions and proliferations of the oral mucosa. The disease is difficult to cure and can affect cats at an early age, resulting in lifetime therapy. In this study, a new treatment using a combination of bovine lactoferrin (bLf) oral spray and oral piroxicam was investigated using a randomized double-blind clinical trial in 13 cats with caudal stomatitis. Oral lesion grading and scoring of clinical signs were conducted during and after the trial to assess treatment outcome. Oral mucosal biopsies were used to evaluate histological changes during and after treatment.

Clinical signs were significantly improved in 77% of the cats. In a 4-week study, clinical signs were considerably ameliorated by oral piroxicam during the first 2 weeks. In a 12-week study, the combined bLf oral spray and piroxicam, when compared with piroxicam alone, exhibited an enhanced effect that reduced the severity of the oral lesions (P < 0.05), quality of life (P < 0.05), and weight gain (P < 0.05). The remission of oral inflammation was closely correlated with the decreased number of macrophages (OR = 4.719, P < 0.05). There was no detectable influence on liver or kidney function during a 12-week assessment. It was concluded that combining oral bLf spray and piroxicam was safe and might be used to decrease the clinical signs of caudal stomatitis in cats.

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Introduction
Feline lymphocytic-plasmacytic gingivitis/stomatitis (LPGS) or caudal stomatitis is an intractable oral disease with an incidence exceeding 3% (Harley, 2003). It is a devastating, chronic inflammatory condition that causes painful erosive lesions in the gingival, buccal regions, and caudal oral mucosa (Sato et al., 1996; Lyon, 2005). Cats may be affected at an early age and, as the disease is difficult to cure, it typically requires therapy for life (Dowers et al., 2010; Hennet et al., 2011). Clinical signs of LPGS include ptyalism, pain, pawing at the mouth, halitosis, bleeding, weight loss, dysphagia, and dysorexia. The condition may even require euthanasia because of poor quality of life (Arzi et al., 2010; Dowers et al., 2010). Abnormal immunological reactions caused by genetic predispositions, environmental stresses, physiological factors, nutritional factors (Tenorio et al., 1991; Lyon, 2005), or viral infection (Kobayashi et al., 2008) have all been correlated with LPGS.

The intractable nature and poor understanding of the aetiopathogenesis of LPGS have led to widespread use of empirirical or symptomatic treatment regimens in which the clinical response has been frequently unsatisfactory (Harley et al., 1999). Treatments with corticosteroids, antibiotics, interferon, cyclosporine and chemotherapeutic agents have been reported (Gullford, 1996; Hennet et al., 2011; Lommer, 2013). Clinicians have frequently used corticosteroid treatment and surgery to control clinical signs of LPGS, but these may become less effective with time (White et al., 1992). Extraction of teeth, including the molars and premolars, has shown better results, achieving clinical cure in 50–60% of cases (Hennet, 1997; Bellei et al., 2008).

Lactoferrin (Lf) is an 80 kDa glycosylated protein that contains approximately 700 amino acids, has strong iron-binding affinity, and has been reported to have multiple functions, including antimicrobial, immunomodulatory, anti-inflammatory and anti-carcinogenic...
Addie et al., 2003

2010

2012

score (LS) of oral mucosa was assigned a grade of 0–3 according to the criteria shown was delivered during anaesthesia. General anaesthesia was maintained with propofol at 0.3–0.5 mg/kg/min. Oxygen administered IV for induction. The endpoint for propofol administration was determined before general anaesthesia. Propofol (Fresofol, Fresenius Kabi) at 6 mg/kg was administered of 250 μg/m² (intramuscular; IM) or 125 μg/m² (intravenous; IV) approximately 10 min before the study if they had been administered steroids during the month before the study or during the study itself, had concurrent systemic diseases, or had a history of allergies to anaesthetics or non-steroidal anti-inflammatory drugs. This study was approved by the Institutional Animal Care and Use Committee of NCHU (IACUC number 100–45; 13 July 2011).

Medical information included sex, breed, bodyweight (BW), history of being a stray cat and the age at onset of clinical signs. Clinical examination included submandibular lymph node palpation, complete blood counts, and serological profiles. Full-mouth dental radiography and oral mucosa biopsy were performed under general anaesthesia. The histopathological features of LPGS are characterized by mucosal hyperplasia and infiltration, primarily with plasma cells, with fewer lymphocytes and macrophage-like cells in the oral submucosa. However, the numbers of neutrophils varies among animals (Harley, 2003; Baird, 2005; Arzi et al., 2010).

Fourteen of the 25 cats were diagnosed with LPGS, of which 13 were enrolled after obtaining the informed consent of their owners (the owner of one animal insisted on treatment with steroids only). The other 11 cats were diagnosed as follows: seven cases of gingivitis, one case of chronic-active gingivitis caused by tartar formation, one case of gingival ulceration, one case of periodontal disease, and one case of feline tooth resorption lesion.

**Materials and methods**

**Animals**

Twenty-five cats assumed to have LPGS at local clinics were referred to the Veterinary Medicine Teaching Hospital of National Chung Hsing University (NCHU). Animals that complied with inclusion and exclusion criteria were enrolled. The inclusion criteria consisted of a diagnosis of LPGS confirmed by histopathological examination of oral mucosa and the presence of clinical signs related to LPGS. Animals were excluded from the study if they had been administered steroids during the month before the study or during the study itself, had concurrent systemic diseases, or had a history of allergies to anaesthetics or non-steroidal anti-inflammatory drugs. This study was approved by the Institutional Animal Care and Use Committee of NCHU (IACUC number 100–45; 13 July 2011).

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**Study design**

The study comprised a randomized double-blinded controlled clinical trial. The veterinarian and owners were not informed about the grouping at the start of the study, but the veterinarian was informed following data analysis at the end of the study. Animals were anaesthetized the day before treatment (D0), and on weeks 2, 4, 8, and 12 (W2, W4, W8, and W12) so as to perform lesion inspections, oropharyngeal swab sampling, and biopsies.

**Double-blind grouping**

This study consisted of two stages: (1) from D0 to W4, and (2) from W5 to W12. Animals were randomly assigned to the two groups. During the first stage, bLf and piroxicam group was administrated two sprays of bLf oral spray (3 mg/spray, Oral relax, Happy Harvest Corporation) at 6 mg per cat, twice daily as modified from previous studies (Sato et al., 1996; Addie et al., 2003), and piroxicam (Pirocam, Swiss Pharmaceutical Co.) at 0.3 mg/kg orally on alternate days. The piroxicam group was given a placebo oral spray (buffer only) in bottles with the same appearance, and piroxicam in a similar dose. No antibiotics were used. During the second stage, both groups were administrated bLf oral spray and piroxicam. The study asked owners of both groups to maintain the cats’ usual meals and daily routines.

**General anaesthesia and examination of oral mucosal lesions and biopsy**

Cats were premedicated with dexmedetomidine (Dexdomitor, Pfizer) at a dose of 250 μg/m² (intramuscular; IM) or 125 μg/m² (intravenous; IV) approximately 10 min before general anaesthesia. Propofol (Fresofol, Fresenius Kabi) at 6 mg/kg was administered IV for induction. The endpoint for propofol administration was determined by obtaining sufficient jaw relaxation and suppression of pharyngeal reflexes. General anaesthesia was maintained with propofol at 0.3–0.5 mg/kg/min. Oxygen was delivered during anaesthesia.

Lesions were examined when the cats were under general anaesthesia. The lesion score (LS) of oral mucosa was assigned a grade of 0–3 according to the criteria shown in Fig. 1. A biopsy was performed, and this included the areas of normal-like mucosa.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gross appearance</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>1</td>
<td></td>
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<tr>
<td>2</td>
<td></td>
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<td>3</td>
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</table>

**Fig. 1. Oral lesion grades and corresponding gross appearances in cats with lymphocytic-plasmacytic gingivitis/stomatitis (LPGS).** The lesion characteristics in each grade are described in a sequence from mild to severe as following: Grade 0, inflammation is absent without proliferation of the buccal mucosa lateral to palatoglossal folds (caudal oral mucosa). No lesion is observed in the tongue or palatoglossal folds; Grade 1, mild inflammation can be seen at the caudal oral mucosa, or maxillary or mandibular gingiva; protruding proliferative lesions involve only bilateral oral mucosa, but not the palatoglossal folds; Grade 2, moderate inflammation involves the bilateral buccal mucosa, gingiva and caudal oral mucosa; erosive lesions may also be present; nodular proliferations are evident at bilateral oral mucosa and extend towards the buccal and gingival mucosa of the mandible or the tongue, but passage through the fauces is not affected; Grade 3, severe inflammation associated with deep ulcers or fistulas involving the mucosa near the mandible and caudal oral mucosa; erosive lesions can also be seen at tongue or maxillary or mandibular gingiva; extensive nodular proliferations affect the caudal oral mucosa, buccal mucosa, gingiva and even the tongue; passage through the fauces is obstructed incompletely.
and inflammatory or proliferative tissue. The specimen was fixed in 10% formaldehyde for 24 h and then embedded in paraffin wax for further histological examination.

**Histological and immunohistochemical (IHC) analyses**

Sections (5 µm) were cut and stained with haematoxylin and eosin (H&E) for histological examination, and with CD3 (dilution of 1:800; A4052, Dako Cytomation) and CD79a (dilution of 1:200; M7051, Dako Cytomation) antibodies for immunohistochemical (IHC) analysis. The IHC was performed according to routine procedures (see Appendix A: Supplementary material in the online version at doi:10.1016/j.tvjl.2014.06.006) and each batch included a positive control using a feline lymph node.

The histopathological scoring was assessed by three veterinarians (VPH, YPY and SCC). The numbers of plasma cells, lymphocytes, neutrophils, macrophages and eosinophils were determined via 10 randomized microscopic high magnification fields (hmf; 400 × magnification). The grading system was modified from a previous study (Arzi et al., 2010). Each cell type was calculated and graded as follows: 0 (negative), 0.5 (1–10 cells/hmf), 1 (11–50 cells/hmf), 2 (51–100 cells/hmf), and 3 (>101 cells/hmf). Oral mucosa granulation was scored as 0, 0.5, 1, 2, and 3 based on the numbers of fibroblasts and the amount of collagen and angiogenesis. For section immunolabelling, three to five representative hmf’s were assessed and the number of CD3+/CD79a+ cells was calculated.

**Evaluation of questionnaires on clinical signs and quality of life**

A questionnaire on the clinical signs of LPGS was modified from a previous study (Addie et al., 2003) (see Appendix A: Supplementary Table S1 in the online version at doi:10.1016/j.tvjl.2014.06.006), and included oral pain, ptalism, inappetence, inflammation of oral mucosa, bleeding, and halitosis. Clinical signs were graded as follows: 1, absent; 2, mild; 3, moderate, and 4, severe. The owners were asked to complete the questionnaire weekly. The clinical sign grades were summed and assigned as the symptom score (SS). Additionally, a quality of life score (QS) was assigned according to subjective owner observations, and was summed and assigned as the symptom score (SS). Additionally, a quality of life score (QS) was assigned according to subjective owner observations, and was scored from 1 to 10, where 1 denoted the worst quality of life, and 10 denoted the best.

**Statistical analysis**

The statistical analysis was performed using Statistical Package for the Social Sciences (v.10.0.7, SPSS). The difference in variables, including LS, SS, QS, and BW, between the bLf and piroxicam, and piroxicam groups was tested with the Wilcoxon rank sum test. The difference in variables, including LS, SS, QS, and BW, in the same group compared with D0 was assessed using the Wilcoxon signed rank test. The chi-square test and binary logistic regression were used to establish the correlation between the cell type or number and the LS or SS. Linear regression analysis was performed to assess the correlation between the number of macrophages and the LS. P < 0.05 indicated a statistically significant difference between categorized groups. All values are described as means ± standard error (SE) and median, with a range from the minimum to maximum values.

**Results**

**Animal characteristics**

Of the 13 cats, three (n = 3/13; 23.1%) were excluded because their owners claimed dissatisfaction with their response to treatment. Table 1 lists the characteristics of all animals, including the withdrawn cases. Ten cats completed the 12-week treatment, and all of these were neutered domestic short-hair cats, including eight males and two females. These animals had a mean age of 6.93 ± 4.21 (median, 5.5; range, 2–14) years. The average age of onset of clinical signs was 5.47 ± 3.47 (median, 4.5; range, 1.42–12.25) years. The mean BW was 4.43 ± 0.95 (median, 4.45; range, 2.93–5.60) kg. Seven out of 10 animals had a history of being a stray, with an average time spent roaming of 8.43 ± 3.41 (median, 7.5; range, 2–12) months. Consequently, five cats were assigned to the bLf and piroxicam group, and five cats to the piroxicam group. The two groups did not differ significantly on D0 (see Appendix A: Supplementary Tables S2 and S3 in the online version at doi:10.1016/j.tvjl.2014.06.006).

**Evaluation of the first stage from day 0 to week 4**

The values of SS, LS, QS, and BW were analyzed and compared between the two groups and are shown in Fig. 2. The bLf and piroxicam group showed a continuous reduction of SS, but elevated SS was observed in W4 in the piroxicam group. The LS was decreased in both groups, but the bLf and piroxicam group was more responsive to treatment. For QS and BW, improvement was observed in the bLf and piroxicam group compared with the piroxicam group. Positive responses were objectively observed in the bLf and piroxicam group, although there were no significant differences within or between the two groups.

**Evaluation of the first and second stage from day 0 to week 12**

To assess the longer term effects, changes in SS, LS, QS, and BW were assessed during the 12-week trial treatment (Fig. 3). From D0 to W2, the SS decreased markedly in both groups. Following W2, SS in the bLf and piroxicam group gradually reduced, and decreased significantly in W4 and W8 compared with D0 (P < 0.05). However, in the piroxicam group, the SS displayed no such reaction, and was elevated in W4 and W12. LS decreased significantly only in the bLf and piroxicam group in W2 compared with D0 (P < 0.05). The QS in the bLf and piroxicam group exhibited a

**Table 1**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Randomized group</th>
<th>Breed</th>
<th>Gender</th>
<th>BW (kg)</th>
<th>Age (years)</th>
<th>Onset age of LPGS (years)</th>
<th>Clinical sign duration (months)</th>
<th>Lesion grade</th>
<th>Roaming time (months)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>DSH</td>
<td>NF</td>
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<td>8.8</td>
<td>14</td>
<td>3</td>
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</tr>
<tr>
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<td>12</td>
</tr>
<tr>
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<td>DSH</td>
<td>NM</td>
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<tr>
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<td>NM</td>
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<td>7</td>
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<td>9</td>
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<tr>
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<td>DSH</td>
<td>NM</td>
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<td>4</td>
<td>3.4</td>
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<td>NM</td>
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<td>NM</td>
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<tr>
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<td>bLf and piroxicam</td>
<td>DSH</td>
<td>NM</td>
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<td>7</td>
<td>5.8</td>
<td>16</td>
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<td>9</td>
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</table>

BW, bodyweight; bLf, bovine lactoferrin; DSH, domestic short hair; NF, neutered female; NM, neutered male.

a Time between clinical sign identification and final diagnosis in this study.

b The withdrawn cases because of unsatisfied response to treatment from the owners.
continuous increase, and differed significantly in W12 compared with D0 (P < 0.05). The BW in the bLf and piroxicam group displayed a continuous increase, while the piroxicam group showed a gradual decrease. A significant increase (P < 0.05) in BW in the bLf and piroxicam group was exhibited in W8 compared with D0.

Accordingly, the bLf and piroxicam group achieved a significantly better outcome in terms of amelioration of clinical signs and oral lesions. Furthermore, the remission of clinical signs in cats with FLPS improved the appetite and BW. Quality of life also improved following the 12-week treatment.

**Correlation between cell type and lesion/symptom score**

The number of plasma cells (OR 4.09, P < 0.05) and CD79a+ cells (OR 7.49, P < 0.05) was significantly increased in the high LS cats (see Appendix A: Supplementary Fig. S1 in the online version at doi:10.1016/j.tvjl.2014.06.006). In the high SS cats, only the number of plasma cells (OR 4.558, P < 0.05) was markedly elevated. The immunolabelling results of CD79a and CD3 are shown in Appendix A: Supplementary Fig. 2. Binary logistic regression analysis showed a significantly increased the number of macrophages in the high LS cats (OR 4.719, 95% CI 1.05-21.20, P < 0.05). A positive correlation between LS and the number of macrophages was observed by the use of linear regression (r < 0.05). Fig. 4 shows that the number of macrophages increased or decreased with the LS over the 12-week observation period, except during week 2.

**Side effects**

Findings of serum chemistry profiles revealed no significant influence on hepatic or renal function (see Appendix A: Supplementary Tables S4 and S5 in the online version at doi:10.1016/j.tvjl.2014.06.006). Vomiting, diarrhoea or other clinical signs were not observed during or following the 12-week treatment trial. However, the oral spray agent was rejected by 20% (n = 2/10) of the animals in the piroxicam group, but bLf could still be administered by forced administration.

**Three withdrawn cats**

All three of the cats that were withdrawn from the study showed anorexia after being administered bLf oral spray or piroxicam for >1 month. The owners of these animals requested steroid therapy rather than trial treatment. The animals were withdrawn on W5 (number 8 in the bLf and piroxicam group), W8 (number 6 in the piroxicam group), and W9 (number 1 in the bLf and piroxicam group), respectively. The LS was higher (P = 0.076) in these three cats than in other cats (see Appendix A: Supplementary Table S6 in the online version at doi:10.1016/j.tvjl.2014.06.006).
Follow-up

After 12 weeks of treatment, it was suggested that the piroxicam treatment be discontinued, while the bLf oral spray was to be continuously administered. The owners were interviewed by telephone for more than 6 months, except for two cats (numbers 2 and 10), for which follow-up information was lost. Of eight cats, 50% (n = 4/8) maintained their appetite and quality of life; 12.5% (n = 1/8) needed combined piroxicam and bLf oral spray to maintain appetite, and 12.5% (n = 1/8) were switched to steroid therapy on the owner’s request. The remaining 25% (n = 2/8) of the cats were able to maintain most of their appetite and quality of life with bLf oral spray alone. Though clinical signs in both cats did recur once, they were followed by rapid remission after an additional 2-week treatment with piroxicam.

Discussion

During the first stage, the SS decreased significantly during D0 to W2 in both groups, which indicated that piroxicam significantly reduced the severity of clinical signs. Additionally, the bLf and piroxicam group showed improvement in SS, LS, QS, and BW compared with the piroxicam group from D0 to W4, which suggested that the combined treatment with bLf oral spray and
piroxicam displayed a better outcome than piroxicam alone. In the 12-week study, the clinical signs were well controlled in 77% (n = 10/13) of cats, and the bLf and piroxicam group exhibited a significant improvement in SS, QS, and BW following W8. This indicated a possible cumulative effect, and thus longer administration of bLf oral spray might be necessary for an improved response.

Amelioration of oral inflammation was closely correlated with decreased numbers of macrophages in the oral mucosa, which suggests that the combined oral bLf spray and piroxicam might reduce the number of macrophages, and thus down-regulate cytokine expression and inhibit inflammation. Cytokines such as INF-α, IL-1, IL-6, IL-12, and IL-18 are released simultaneously by macrophages to activate T cells and the inflammatory response (D’Andrea et al., 1992; Tizard, 2000). Furthermore, Lf has been reported to be an immune modulator and an anti-inflammatory agent that acts by inhibiting the proliferation of peripheral blood mononuclear cells and down-regulating cytokines that can stimulate an immune response (Kobayashi et al., 2008; Garcia-Montoya et al., 2012; Vogel, 2012). bLf has been reported to be beneficial in oral sanitation (Masson et al., 1969) because of its strong antimicrobial effects (Arnold et al., 1977; Ellison et al., 1988; Singh et al., 2002; Berlutti et al., 2011). Thus, bLf oral spray may inhibit excessive immune responses or control the recurrence of clinical signs of LPGS through its antimicrobial effects.

The age of onset of the LPGS cats in this study ranged widely from 1.5- to 12.3-year-olds, which was similar to previous studies (Hennet et al., 2011; Robson and Crystal, 2011). Because caudal stomatitis can affect animals at an early age, a lifetime of treatment may be required. Since long-term administration with bLf (Sato et al., 1996; Addie et al., 2003) or piroxicam (Bulman-Fleming et al., 2010) for periods exceeding 20 months has been well tolerated in cats, a treatment regimen that combines the two may be suitable for the long-term administration that is crucial for animals suffering from LPGS.

Initially, 25 cats were presumed to have LPGS based on their history, clinical signs and gross lesions. However, following histopathological examination, only 56% (n = 14/25) of the referred cats were confirmed to have LPGS. Therefore, oral mucosa biopsy is recommended in cases where it is necessary to confirm LPGS (Lyon, 2005; Harley et al., 2011).

Extracting teeth to reduce plaque-retentive surfaces has proven to be most effective in eliminating plaque and reducing oral inflammation (Hennet, 1997; Lyon, 2005; Bellei et al., 2008) because the immune system stimulated by plaque bacteria appears to contribute to ongoing inflammation (Lommer, 2013). However, recent studies showed that only approximately 60% of cats with LPGS improved without further medication, 20% needed additional medical therapy and the other 20% had relapses (Bellei et al., 2008; Hennet et al., 2011). In our study, two cats (numbers 7 and 8) displayed a recurrence of LPGS signs following dental extraction of molars and premolars. Because of the irreversible damage associated with surgical intervention, such operations must be considered only when animals are non-responsive to medical therapy, and/or suffer from pain and tooth damage (Lyon, 2005; Bellei et al., 2008).

Conclusions

Positive responses were demonstrated in cats with caudal stomatitis using a treatment combining bLf oral spray and oral piroxicam. Oral administration of the bLf spray reduced macrophage numbers, inhibited inflammation, and eventually ameliorated oral lesions, resulting in improved quality of life. The combination of the bLf oral spray and orally administered piroxicam was safe and might be used to decrease clinical signs in cats affected by LPGS with longer administrations recommended to improve outcomes.

Conflict of interest statement

Happy Harvest Corporation supplied the bovine lactoferrin oral spray agents used in this study, but played no role in the study design, in the collection, analysis and interpretation of the data, or in the decision to submit the manuscript for publication. This study was supported by a grant from the Happy Harvest Corporation. None of the authors has any financial or personal relationship with other people or organizations that could inappropriate influence or bias the content of the paper.

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Appendix: Supplementary material

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.tvjl.2014.06.006.

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