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Dietary Trial Using a Commercial Hypoallergenic Diet Containing Hydrolyzed Protein for Dogs with Inflammatory Bowel Disease

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Abstract

Six dogs with inflammatory bowel disease (IBD) received a commercially available hypoallergenic diet containing an enzymatically hydrolyzed defatted soy globulin as the only protein source. Five of the six dogs had been refractory to a variety of controlled diets, and four dogs had failed to respond to previous medical therapy. All dogs were fed the test diet twice daily for 10 weeks. Dogs not showing adequate improvement in clinical signs after 2 to 4 weeks on diet alone had appropriate medical therapy added to the dietary regimen. Gastroduodenoscopy and biopsy were performed on Day 0 and repeated at the conclusion of the study. Intestinal biopsies were evaluated by a pathologist using a numeric grading scheme to describe histologic alterations and mucosal architecture. Dietary therapy alone provided adequate clinical improvement in four dogs, and concurrent medical therapy was required in two dogs, one of which had exocrine pancreatic insufficiency. Mean fecal scores improved after therapy. Five dogs showed mild to moderate histologic improvement in duodenal biopsies after therapy. The clinical improvement observed cannot be solely attributed to the hydrolyzed nature of the protein source because the diet tested was highly digestible, contained cornstarch (rather than intact grains) and a source of medium-chain triglycerides (23% of fat), and had an altered ratio of w-6 to w-3 polyunsaturated fatty acids. Nevertheless, the resolution of clinical signs and improved biopsy scores demonstrate the importance of conducting further studies to critically assess the role of diets containing a hydrolyzed protein source for the management of dogs with previously refractory IBD.

Introduction

Inflammatory bowel disease (IBD) is the most common cause of chronic vomiting and diarrhea in dogs and encompasses a spectrum of idiopathic gastrointestinal (GI) disorders.[1] The causes of canine IBD are poorly understood, and most of the evidence for proposed causes in dogs is extrapolated from humans with ulcerative colitis and Crohn's disease.[2-6] Proposed causes for human IBD include defective immunoregulation of gut-associated lymphoid tissue, which may be precipitated by permeability defects,[2] infectious and parasitic agents,[3,4] or dietary allergies.[5,6] Evidence from clinical observations and animal models of intestinal inflammation incriminates normal luminal bacteria or bacterial products in the initiation and perpetuation of canine IBD.[7,8] The clinical response to hypoallergenic diets suggests that dietary factors may influence the pathogenesis.[9]

Therapy for IBD is usually directed at controlling any antigenic source of inflammation, followed by suppressing the cell-mediated inflammatory response in the GI tract. Antiinflammatory drugs, motility modifiers, antibiotics, and dietary manipulation have all been implemented in the management of canine IBD with varying degrees of success.[1,9-12] The utilization and specific nature of dietary manipulation is a controversial subject, with some dogs showing improvement on highly digestible controlled diets[1,9,12] and others benefiting from high-residue diets containing multiple protein sources. Dietary fat restriction is also important in the management of intestinal disease because unabsorbed fatty acids and bile acids can promote colonic secretion and increase colonic permeability.[11,13]

Antigenic determinants on proteins are incriminated in many cases of IBD, implying that the feeding of hypoallergenic diets containing a single, highly digestible, novel protein source might be beneficial for managing dogs with IBD.[1,9,12,14] The effectiveness of any novel protein in reducing symptoms associated with food sensitivity is due mainly to its novelty or lack of prior exposure. The ability to induce an antibody-mediated hypersensitivity response appears to be dependent on the size and structure of the protein. The allergens in soybean protein, for example, are between 20 and 78 kD,[15] suggesting that soybean proteins with a molecular weight below this threshold would be less likely to be immunogenic. Oligopeptide-based diets that have been used in Crohn's disease patients have a mean peptide chain length of four or five amino acids, which is too short for antigen recognition or presentation.[6] The objective of the study described here was to evaluate a commercial hypoallergenic diet (HA HypoAllergenic™ brand Canine Formula, Purina Veterinary Diets™, St. Louis, MO) containing an enzymatically hydrolyzed, defatted soy globulin as the only protein source for the management of dogs with IBD.

Materials and Methods

Case Selection

The following criteria were used to select dogs for this clinical investigation: (1) chronic signs of vomiting or diarrhea (greater than 3 months' duration); (2) fecal flotation and smears negative for intestinal parasites; (3) physical examination and endoscopic evaluation of the GI tract were negative for foreign bodies, masses, or intussusceptions; (4) endoscopically obtained biopsies showing histologic evidence of gastric or duodenal inflammation; and (5) owners willing to fill out a questionnaire every 2 weeks during the 10-week study and to return their pet for repeat gastroduodenoscopy and biopsy following the dietary trial. The questionnaire gathered information about each dog's appetite, body weight, coat condition, frequency of defecation, fecal consistency, presence of tenesmus, and presence of blood in the feces. Serum cobalamin and folate concentrations and serum trypsinlike immunoreactivity were measured at the beginning of the study to help isolate the location of mucosal involvement (either the proximal or distal small intestine) and to assess exocrine pancreatic function. Dogs were also evaluated at the initial examination for body condition and given a score ranging from 1 (emaciated) to 9 (obese). Six dogs presented over a 6-month period met all of the selection criteria and are the basis for this report. Five of the six dogs had been refractory to dietary management utilizing premium commercial or home-cooked diets containing novel, single-protein sources for at least 4 weeks, and one dog had failed to respond to a commercial dry diet containing multiple protein sources fed for 1 month.

Treatments

Initial therapy for all dogs was restricted to feeding the test diet. All dogs were fed the test diet twice daily for 10 weeks, with total intake calculated to meet energy requirements ($132 \times BW_{kg}^{0.75}$).[16] No other medical therapy was used in the initial management of the dogs, and considerable emphasis was placed on educating owners about the importance of feeding only the test diet with absolutely no treats. For patients not showing adequate improvement in clinical signs after 2 to 4 weeks on diet alone, appropriate medical therapy was added to the dietary regimen.

Clinical Evaluations

Fecal quality was assessed by owners on a daily basis using a score of 0 to 100, with 0 being very watery stool and 100 representing very firm stool. Illustrated guidelines were provided to the dog owners to help provide consistency in scoring. At the end of each 2-week period, owners observed the dog for one day and entered a score on the questionnaire to represent the average score for all feces passed by the dog on that day. Clinical outcome (based on the degree of improvement in fecal score) was determined at the end of the study. The term "moderate improvement" was used to reflect an estimated 50% improvement in fecal score or 50% reduction in frequency of vomiting. The term "complete resolution" reflected complete resolution of diarrhea characterized by well-formed feces and normal frequency of defecation.

Biopsies

Endoscopic biopsy samples from the stomach and duodenum of each dog were obtained prior to and at the end of the dietary trial (Week 10). Samples were fixed in 10% neutral buffered formalin, processed routinely, stained with hematoxylin and eosin, and examined retrospectively in blinded fashion by a single pathologist. Previously described criteria were used to evaluate cellular infiltrates within the lamina propria of the intestines, to evaluate morphologic features commonly described in inflammatory gastrointestinal disease,[17-20] and to generate semiquantitative, numeric scores reflective of inflammatory changes in examined tissues. Gastric and duodenal samples were evaluated separately using the same semiquantitative scoring scheme, and all of the samples collected during each endoscopic procedure were examined. In this scheme, points were assigned to each of the following histologic features: Zero points were given for lymphocytes and/or plasma cells occupying 20% or less of the lamina propria or submucosa; one point each was given for lymphocytes and/or plasma cells occupying 20% to 50% of the lamina propria or submucosa, villous blunting, villous fusion, mild infiltration of lymphocytes into the mucosal epithelial layer, erosion or necrosis, lymphangiectasia of the lacteals, fibrosis, or crypt or gland ectasia; two points each were given for lymphocytes and/or plasma cells occupying 50% to 75% of the lamina propria or submucosa, moderate infiltration of lymphocytes into the mucosal epithelial layer, or metaplastic changes of superficial epithelial cells; and three points each were given for lymphocytes and/or plasma cells occupying 75% to 100% of the lamina propria or severe infiltration of lymphocytes into the mucosal epithelial layer. Tissue with a score of zero was considered within normal limits. A total score between one and three was considered mild, a score between four and six was rated moderate, and seven or higher corresponded to severe alterations in the gastric or duodenal histology. Scores were subsequently used to compare the histologic changes before and after therapy.

Statistics

Data were analyzed for normality of distribution and the treatment effect was analyzed by paired t-tests, using SigmaStat® 2.0 (SPSS Science, Chicago, IL). Test criteria were set at a = .05 and b = 0.75.

Results

Six different breeds were represented in the study, and the dogs ranged from 1.5 to 9 years of age (mean = 3.3 years) (Table 1). The duration of vomiting or diarrhea before the start of the study ranged from 3 to 18 months with a mean of 9 months. Five dogs initially evaluated by private practitioners had been refractory to a variety of commercial and home-cooked elimination diets, and four dogs had failed to respond to concurrent medical therapy with metronidazole, metoclopramide, famotidine, amoxicillin, diphenhydramine hydrochloride, or pancreatic enzyme powder supplementalation (Table 1).

Fecal scores improved markedly from a mean of 42.5 before therapy to 91.7 after therapy (Figure 1). Dietary therapy alone provided adequate clinical benefit in four dogs, characterized by a marked increase in fecal consistency. Two of these four dogs achieved complete resolution of their diarrhea within 3 days of dietary therapy, whereas two others showed marked improvement in their fecal scores within 12 days of dietary therapy (Table 2). The clinical outcome of one dog (Dog 6) was not considered a complete resolution, despite the postdietary fecal score of 100. This dog had a history of having very soft feces approximately three times daily with occasional episodes of hematochezia and intermittent (every 2 months) bouts of severe diarrhea that would resolve with intravenous fluid and antibiotic therapy. Fecal cultures repeated twice for this dog were negative for *Salmonella* spp, *Campylobacter jejuni*, *Clostridium difficile*, and *Clostridium perfringens*. Despite the marked improvement in the dog's daily fecal consistency following dietary therapy, intermittent outbreaks of diarrhea persisted.

Two dogs in the study required additional medical therapy (Table 2). Dog 5 was diagnosed with IBD and concurrent exocrine pancreatic insufficiency; this dog required pancreatic enzyme replacement, prednisone, and metronidazole before its stools improved. Dog 3 was presented with vomiting associated with lymphoplasmacytic gastritis and showed a moderate reduction in the frequency of vomiting episodes following dietary intervention alone and complete resolution of vomiting following dietary therapy with metoclopramide.

The number of gastric biopsy specimens per endoscopic procedure varied from 3 to 11 (mean = 7.2), and the total number of gastric biopsy specimens collected from the six dogs before and after therapy was 86. The majority of the specimens (98.8%) included only mucosa, and most (74.4%) were oriented perpendicular to the long axis of glands. The number of duodenal biopsy specimens per endoscopic procedure varied from 6 to 15 (mean = 10.2), and the total number of duodenal biopsy specimens collected from the six dogs was 122. All specimens included mucosa only, and most (71.3%) were oriented perpendicular to the long axis of the villi. Significant histologic improvement occurred in duodenal biopsies after therapy (P = .015; Figure 2). Four dogs showed histologic improvement in their gastric biopsies; however, the overall effect of treatment did not reach statistical significance. Typical histologic changes observed in the duodenal biopsy specimens before and after dietary therapy in Dog 6 are illustrated in Figure 3 .

Discussion

This study documents apparent beneficial effects of a novel, hydrolyzed protein diet in a small group of dogs with IBD previously refractory to dietary therapy. Five of six dogs had failed to respond to dietary therapy with various commercial diets containing novel, single-protein sources fed for at least 4 weeks, and four of the dogs had also failed to respond to home-cooked diets consisting of chicken and boiled rice, hamburger meat and boiled rice, cottage cheese and boiled rice, and veal and boiled rice with potato. In addition, prior drug therapy with antibiotics, prokinetic agents, and H_2-receptor antagonists in three dogs had minimal effect in controlling the signs of IBD.

Although this study does not definitively establish a dietary antigen-induced, immune-mediated cause for the inflammatory gastroenteritis identified in these dogs, the resolution of clinical signs and improved biopsy scores following dietary therapy alone suggest a dietary role in the development of this condition. Challenge of the dogs with their original diet would have been helpful to substantiate the role of dietary change; however, the clinical benefits of the dietary regimen in the study resulted in universal rejection of this suggestion by the owners at the end of the 10-week study period. In one study,[9] only two of 13 dogs with idiopathic canine colitis that were stabilized on a hypoallergenic diet of boiled rice and low-fat cottage cheese tolerated a subsequent switch back to the diet they were being fed at the time of onset of colitis (i.e., did not have a relapse).

Several prospective, randomized trials have shown equivalent efficacy of purified diets compared with corticosteroids as the primary therapy for Crohn's disease in humans.[21-23] The mechanism by which controlled formula diets can induce remission in active Crohn's disease and the choice of type of diet are controversial; however, intestinal rest, reduction in dietary antigen load, changes to bacterial flora, immune modulation by changes in the fatty acid profile, and improved nutrition may all contribute to the clinical response.[21-23]

The test diet used in this study contained cornstarch rather than intact grains, potentially decreasing the allergenicity of the diet. In addition, manipulation of the ratio of w-6 to w-3 polyunsaturated fatty acids in this diet has the potential to reduce the inflammatory response in canine IBD, similar to human ulcerative colitis and Crohn's disease.[24,25]

Diets enriched in w-3 fatty acids can result in the incorporation of the w-3 fatty acids into biological membranes with a corresponding decrease in concentrations of the proinflammatory w-6 fatty acids such as arachidonic acid.

The semiquantitative scoring system used in this study was developed in an attempt to increase the objective criteria used in evaluating inflammatory disease in endoscopically obtained gastric and duodenal biopsies. Establishment of and adherence to established objective criteria is important because endoscopic biopsies often do not include architectural features such as the submucosa or muscular wall, which are often used to evaluate the extent and nature (e.g., inflammation versus neoplasia) of disease. This is not to imply that endoscopic biopsies lack utility. On the contrary, endoscopically obtained biopsies have been shown to provide a representative sampling of inflammatory changes in the intestines. In one report by Jacobs and coworkers,[17] lymphocytic and plasmacytic infiltration were limited to the lamina propria in more than 90% of full-thickness samples taken from the duodenum, jejunum, or ileum. In addition, when present, inflammation in endoscopically obtained duodenal biopsies was generally as severe in the lamina propria of villi as in the crypt regions.[17]

In this study, duodenal biopsies from five of six dogs showed evidence of histologic improvement when evaluated in a blinded fashion. Although follow-up biopsies may be helpful in patients whose clinical signs are refractory to medical therapy, there is a paucity of data documenting the results of rebiopsy in patients in clinical remission. The dog with the most dramatic improvement in its follow-up biopsy score had a severe infiltrate of lymphocytes and plasma cells in the lamina propria of the duodenum before dietary therapy and showed a dramatic and rapid response to the diet. In contrast, one dog in the study with mild duodenal inflammation showed the least amount of improvement in its posttherapy duodenal biopsies, despite therapy with prednisone and metronidazole. Although this dog had concurrent exocrine pancreatic insufficiency, clinical signs of diarrhea persisted for 3 weeks despite medical management. Performing follow-up biopsies in patients with IBD may help define prognosis for those patients with persistent subclinical GI inflammation.

In conclusion, the results of this pilot study indicate that the feeding of HA HypoAllergenic™ brand Canine Formula to dogs with IBD was associated with partial to complete resolution of clinical signs. Inherent weaknesses of this study include the relatively small group of dogs evaluated, the lack of a control group, and the fact that owners were not blinded to the test diet. Despite these concerns, the dramatic clinical improvement in five dogs following a previous lack of response to "hypoallergenic" diets and medical therapy, as well as the objective improvement in five of six duodenal and gastric biopsies suggest the product is clinically effective. A prospective, controlled double-blind study in a large group of dogs with IBD is warranted to confirm these findings. Ideally, such a study would compare the response to this hydrolyzed diet with the response to a control diet containing intact soybean protein.

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