

Comparison of Oral Prednisone and Prednisone Combined with Metronidazole for Induction Therapy of Canine Inflammatory Bowel Disease: A Randomized-Controlled Trial

A.E. Jergens, J. Crandell, J.A. Morrison, K. Deitz, M. Pressel, M. Ackermann, J.S. Suchodolski, J.M. Steiner, and R. Evans

Background: Although prednisone and metronidazole are commonly used to treat canine inflammatory bowel disease (IBD), no randomized-controlled trials have been performed.

Hypothesis: Combination drug therapy with prednisone and metronidazole will be more effective than prednisone alone for treatment of canine IBD. Reduction in disease severity will be accompanied by decreased canine IBD activity index (CIBDAI) scores and serum C-reactive protein (CRP) concentrations.

Animals: Fifty-four pet dogs diagnosed with IBD of varying severity.

Methods: Dogs were randomized to receive oral prednisone (1 mg/kg; n = 25) or prednisone and metronidazole (10 mg/kg; n = 29) twice daily for 21 days. Clinical (CIBDAI) scores and serum CRP were determined at diagnosis and after 21 days of drug therapy. The primary efficacy measure was remission at 21 days, defined as a 75% or greater reduction in baseline CIBDAI score.

Results: Differences between treatments in the rate of remission (both exceeding 80%) or the magnitude of its change over time were not observed. CRP concentrations in prednisone-treated dogs were increased because of many dogs having active disease. Both treatments reduced CRP in comparison with pretreatment concentrations. An interaction between CIBDAI and CRP was identified in 42 of 54 dogs (78%), whereas 8 of 54 dogs (15%) showed disagreement between these indices.

Conclusions and Clinical Importance: Prednisone is as effective as combined treatment with prednisone and metronidazole for induction therapy of canine IBD. CRP may be normal or increased in dogs with IBD and may be useful in assessing the response of individual dogs to treatment along with changes in the CIBDAI.

Key words: C-reactive protein; CIBDAI; Drug treatment; IBD.

Idiopathic inflammatory bowel disease (IBD) is a common cause of chronic gastrointestinal disease in dogs.^{1–3} Medical treatment for induction of clinical remission is largely empirical and consists of dietary management and use of nonspecific anti-inflammatory drugs, with corticosteroids providing the most consistent benefit.^{1,2,4} Accumulating evidence in human IBD and experimental colitis in animal models suggests that the resident microbiota contribute to the pathogenesis of chronic immunologically mediated intestinal inflammation.^{5–7} Dogs with IBD have distinctly different duodenal microbial communities compared with healthy dogs.^{8,9} Additionally, canine histiocytic ulcerative colitis now is recognized to be associated with adherent and invasive *Escherichia coli*,¹⁰ and affected dogs frequently

Abbreviations:

CIBDAI	canine IBD activity index
CRP	C-reactive protein
IBD	inflammatory bowel disease

respond to fluoroquinolone antimicrobial treatment.¹¹ Thus, there appears to be a sound rationale for evaluating canine IBD treatment protocols that target enteric bacteria and the harmful immune responses that they might evoke.

Clinical trials in human IBD (eg, patients with Crohn's disease and ulcerative colitis) consistently demonstrate response to 5-aminosalicylates (5-ASA) and corticosteroids as mainstays of treatment.^{12–14} Antibiotic treatment with metronidazole and ciprofloxacin is commonly used for Crohn's disease, although controlled trials to support this practice are limited.^{15,16} Many clinicians include metronidazole into the treatment protocol for canine IBD, and metronidazole often is combined with immunosuppressive drugs in dogs having moderate to severe clinical signs or histopathologic lesions.^{4,17,18} However, no controlled trials have evaluated the efficacy of prednisone in combination with metronidazole for the treatment of IBD in dogs. The objective of the present study was to compare the efficacy of prednisone and metronidazole combination therapy versus prednisone monotherapy for the treatment of canine IBD. Moreover, serum concentrations of C-reactive protein (CRP) were evaluated before and after induction drug therapy to assess their utility as therapeutic monitoring tools.

From the Department of Veterinary Clinical Sciences (Jergens, Crandell, Morrison, Deitz, Pressel) and Veterinary Pathology (Ackermann), College of Veterinary Medicine, Iowa State University, Ames, IA; the Gastrointestinal Laboratory and Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX (Suchodolski, Steiner); and the Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL (Evans).

Corresponding author: Albert E. Jergens, DVM, PhD, DACVIM, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA 50010; e-mail: ajergens@iastate.edu.

Submitted February 11, 2009; Revised September 22, 2009; Accepted November 4, 2009.

Copyright © 2009 by the American College of Veterinary Internal Medicine

10.1111/j.1939-1676.2009.0447.x

Materials and Methods

Dogs

The randomized-controlled trial was conducted at the Veterinary Teaching Hospital at Iowa State University (ISU) from January 2004 to February 2008. The protocol was approved by the ISU Institutional Animal Care and Use Committee. All clients gave written or verbal informed consent. Investigators were unaware of the treatment assignment until a final diagnosis was made.

All dogs were diagnosed with idiopathic IBD according to previously published clinical criteria.^{1,19} In brief, these variables included persistent (> 3 weeks) gastrointestinal signs; failed responses to dietary (commercial intact protein elimination diet) or symptomatic (parasiticides, antibiotics, anticholinergics, gastrointestinal protectants) therapies alone; thorough diagnostic evaluation with exclusion of other causes of gastroenteritis; and, histopathologic diagnosis of intestinal inflammation. Each dog was fed the elimination diet for a minimum of 3 weeks to eliminate adverse food reactions (ie, food-responsive enteropathy) as a cause for gastrointestinal signs. Additionally, metronidazole or amoxicillin with clavulanic acid was administered to every dog for 14 days if the dogs failed to respond to dietary intervention alone. The minimum diagnostic evaluation performed on all dogs included a CBC, serum biochemistry profile, urinalysis, trypsin-like immunoreactivity, direct (wet mount) and indirect (zinc sulfate flotation) examination of feces for nematode and protozoan parasites, survey abdominal radiographs, and histopathologic review of mucosal biopsy specimens obtained via gastroduodenoscopy, colonoscopy, or both. The performance of a particular endoscopic procedure was dictated by the history and predominant clinical signs (ie, small intestinal, large intestinal, or mixed clinical signs) exhibited by each dog. Intestinal inflammation was defined on the basis of recently described World Small Animal Veterinary Association histopathologic guidelines.²⁰ Additional tests such as abdominal ultrasonography (n = 14 dogs), pancreatic lipase immunoreactivity (n = 11 dogs), serum cobalamin and folate measurements (n = 32 dogs), or some combination of these tests also were performed in some dogs at the clinician's discretion. Furthermore, none of the dogs could show evidence of extra-alimentary tract inflammation (based on results obtained from initial diagnostic testing) nor could they have received immunosuppressive drugs (eg, corticosteroids, metronidazole, or sulfasalazine) or antibiotics within 14 days of clinical examination.

Baseline Studies

Dogs with IBD were assigned a pretreatment clinical disease severity score calculated by use of a numerical activity index, the canine IBD activity index (CIBDAI).¹⁹ This index incorporates the following items: general attitude and activity, appetite, frequency of vomiting, stool consistency, stool frequency, and weight loss. The overall score may range from 0 to 18, with disease activity interpreted as being clinically insignificant (score 0–3), mild (score 4–5), moderate (score 6–8), or severe (score 9 or greater). Only dogs having a baseline CIBDAI score of at least 4 were included in the trial. At the time of randomization, a blood sample was collected for measurement of serum CRP by a solid phase sandwich immunoassay^a validated for dogs.²¹ The reference range for CRP concentrations in healthy dogs by this assay is 0–7.6 mg/L.^b

Randomization and Drug Administration for IBD

The IBD dogs were randomly assigned, by means of a computer-generated schedule, to receive either oral prednisone (1 mg/kg q12h) or oral prednisone and metronidazole (10 mg/kg q12h) for 21 days. In some instances, a coin flip was used to determine which treatment arm was administered to a patient. The use of a coin flip was

reserved for 5 dogs whose biopsy results were returned after hours or on weekends, when the study technician and access to the randomization schedule were unavailable. All dogs were exclusively fed 1 of 2 commercial elimination (intact protein) diets^{c,d} during the 21-day induction treatment period. The elimination diets chosen were of similar composition with respect to high digestibility and low fat content, and clients additionally were instructed to avoid feeding dog treats or table scraps to their pets during the drug treatment period. All hypocobalaminemic dogs received SC cobalamin supplementation (500 µg cobalamin per injection in dogs 5–15 kg; 500–1200 µg cobalamin per injection in dogs > 15 kg) weekly during the trial. Those dogs exhibiting large bowel signs with histopathologic evidence of colitis additionally were treated with fiber supplementation^e (1–3 tsp) at each feeding. Owner compliance to drug and dietary recommendations was assured by weekly telephone consultations performed by the study technician.

Clinical Response and Measures of Outcome

Dogs were re-evaluated at the ISU clinic 3 weeks after initiation of drug therapy. Clinical assessment was performed by calculation of the posttreatment CIBDAI score, and blood was obtained for repeat CRP analysis. Study medications were continued or tapered based on the presence or absence of presenting gastrointestinal signs. The primary measure of response was clinical remission at 21 days posttreatment. Remission was defined as a 75% or greater reduction in posttreatment CIBDAI score as compared with its corresponding pretreatment value. Partial clinical remission was defined as a treatment response resulting in a posttreatment CIBDAI score < 75% but > 25% of its pretreatment determination. Secondary measures included the mean change in serum CRP concentration and any adverse drug reactions.

Data Analysis and Statistics

Two treatment groups (prednisone versus prednisone and metronidazole) were compared on 2 outcome measures (CIBDAI score and serum CRP) after 21 days of treatment. First, descriptive statistics and graphs (means, medians, standard deviations, box plots, and histograms) were used to evaluate the data distributions and provide data summaries for all variables. Change (posttreatment minus pretreatment) variables corresponding to CIBDAI and CRP were constructed. Two dogs with a CRP change > 4 standard deviations from the mean change were removed from the analysis because they were considered statistical outliers. Second, the treatment groups were compared on the change variables with Wilcoxon's nonparametric tests. Third, matched-pairs *t*-tests were used to test the change in outcome variable over time (ie, post-pre) by treatment group. Finally, the agreement of the change scores was summarized with Pearson's correlation. Statistical analyses were performed with the JMP software package.^f

It was estimated that 50% of dogs treated with prednisone alone would be in remission at 21 days. This hypothesis was based on results from previous canine IBD studies that showed that use of steroids (eg, prednisone or prednisolone administered at an identical dosage to that utilized in the present study) resulted in clinical remission (monitored by the CIBDAI) posttreatment in the majority of diseased dogs.^{17,19,22,23} A minimum clinically significant difference in the occurrence of this outcome was considered to be 25%. Therefore, a remission rate of 75% in the prednisone and metronidazole group was anticipated. Randomization of 15 dogs per group would give a power of 80% to detect this difference at the 0.05 significance level. Additional dogs were enrolled to allow for a noncompliance rate up to 25%.

Results

Study Population

The characteristics of the study populations generally were balanced for all factors examined (Table 1). Body weights in IBD dogs ranged from 6 to 48 kg and from 4 to 43 kg in prednisone-treated and prednisone and metronidazole-treated dogs, respectively. Disease severity based on CIBDAI scoring showed that the prednisone treatment group comprised 9 mild, 13 moderate, and 7 severe IBD dogs, whereas the prednisone and metronidazole treatment group contained 11 mild, 12 moderate, and 2 severe IBD dogs. Both groups had mean clinical (CIBDAI) scores indicative of moderate IBD, but disease flares (ie, presence of overt clinical signs within 24 hours of hospitalization) were reported in 75% of dogs assigned to prednisone versus 38% of dogs assigned to prednisone and metronidazole. Decreased serum albumin concentration^g was found in 31% (9 of 29; mean, 2.1 g/dL; range, 1.7–2.5 g/dL) and 36% (9 of 25; mean, 2.5 g/dL; range, 1.0–3.1 g/dL) of dogs treated with prednisone or prednisone and metronidazole, respectively. Hypocobalaminemia^h was observed in 39% (7 of 18; mean, 191 ng/L; range, 99–248 ng/L) of prednisone-randomized dogs and 21% (3 of 14; mean, 204 ng/L; range, 160–228 ng/L) of dogs randomized to prednisone and metronidazole. Survey abdominal radiography confirmed fluid-distended small intestinal bowel loops, suggestive of nonspecific enteritis, in 18 of 54 dogs. Abdominal ultrasound examination showed mild mesenteric lymphadenopathy and increased thickness of the intestinal wall in 3 of 14 and 5 of 14 dogs, respectively.

Endoscopy and Histology

Gastroduodenoscopy was the most commonly performed endoscopic procedure in both treatment groups (Table 2). Mucosal lesions of increased friability, granularity, erosions or some combination of these predominated

Table 1. Baseline characteristics of the IBD dogs overall with associated complications. Characteristics of the 54 dogs enrolled in the study.

Parameter	Prednisone Monotherapy	Prednisone/Metronidazole
Age (years)	6.8	6.5
Weight (mean, kg)	19.5	19.9
n (male/female)	29 (9/20)	25 (11/14)
CIBDAI score ^a	7.1	6.0
Organs ^b	SI, colon	SI, colon
Disease duration (mo)	5.0	6.3
Flare ^c	Yes (75%)	Yes (38%)
Complications	—	—
Hypoalbuminemia n (%)	9/29 (31)	9/25 (36)
Hypocobalaminemia n (%)	7/18 (39)	3/14 (21)

^aMean disease activity at diagnosis; range 0–18.

^bHistopathologic confirmation of mucosal inflammation.

^cActive gastrointestinal signs within 24 hours of presentation.

IBD, inflammatory bowel disease; CIBDAI, canine IBD activity index.

in the intestines of most diseased dogs. Histologically, all dogs showed variable infiltration of the lamina propria with lymphocytes, plasma cells, and eosinophils which were accompanied by morphologic and inflammatory changes in the mucosa.^{1,20}

Twenty-eight dogs had mild inflammation and 26 dogs had moderate to severe intestinal inflammation on histopathologic review of biopsy specimens. The severity of inflammation in the small intestine was similar for both treatment groups, with prednisone-treated dogs diagnosed as having mild (n = 14) or moderate to severe (n = 13) IBD in comparison with dogs receiving combination drug therapy, which were diagnosed with mild (n = 13) or moderate to severe (n = 12) enteritis. Colonoscopy with endoscopic biopsy was performed in 16 dogs that completed the study. Histopathologic lesions in the colonic mucosa were observed in 3 of 8 prednisone-treated dogs (2 dogs having moderate IBD colitis and 1 dog diagnosed with mild IBD colitis) and 4 of 8 combination treatment dogs (mild or moderate to severe IBD colitis diagnosed in 2 dogs each, respectively). Some dogs were observed to have histopathologic lesions of IBD in both the small and large intestines.

Randomization

During the study period, 101 dogs were screened for eligibility and 80 dogs were randomized into the drug trial (Fig 1). Twenty-one dogs were not enrolled because they had normal histology or were diagnosed with non-IBD causes for gastrointestinal disease, including parasites, *Helicobacter* spp. gastritis, lymphosarcoma, histoplasmosis, pancreatitis, idiopathic megaesophagus, or other illnesses. Of the 80 dogs enrolled, 45 were randomized to treatment with prednisone and 35 to prednisone and metronidazole. A total of 26 dogs (32%) did not complete the 3 weeks of study medications including 16 dogs (35%) in the prednisone group and 10 dogs (40%) in the prednisone and metronidazole group. In dogs treated with prednisone, 14 were excluded from final analysis because of noncompliance and 2 dogs were lost to follow-up. The reasons for exclusion in dogs treated with prednisone and metronidazole included noncompliance in 8 dogs, and 2 dogs were lost to follow-up. Overall, 54 dogs completed the full trial and reached week 3.

Primary and Secondary Outcomes

After 3 weeks of drug therapy, the proportion of dogs in remission was 24 of 29 (83%) in the prednisone and metronidazole group and 22 of 25 (88%) of dogs that received prednisone alone. Five (n = 2 prednisone-treated, n = 3 prednisone and metronidazole-treated) of 7 dogs with colitis that received fiber supplementation achieved full clinical remission. Two other dogs with colitis were treated with fiber and prednisone and metronidazole but achieved only partial remission (ie, at least 50% reduction in CIBDAI score pre- versus post-treatment). For the population as a whole, no difference ($P = .38$) was noted between the treatment groups in the rate of remission or its magnitude of change over time

Table 2. Endoscopic procedures performed in 54 dogs randomized to receive drug therapy for canine inflammatory bowel disease.

Treatment Group	Gastrointestinal Endoscopic Procedures		
	Gastroduodenoscopy	Gastroduodenoscopy + Colonoscopy	Colonoscopy
Prednisone (n = 29)	21	7	1
Prednisone + metronidazole (n = 25)	17	7	1

(Fig 2). All hypocobalaminemic dogs (n = 10) in both treatment groups achieved full remission by the end of the treatment period. Conversely, IBD dogs with hypoalbuminemia (eg, 9 of 29 prednisone-treated dogs and 9 of 25 prednisone and metronidazole-treated dogs) showed lower remission rates with 4 of 5 nonresponsive dogs in both treatment groups failing to achieve even partial clinical remission.

At the baseline visit, the mean CRP in prednisone-treated dogs was significantly ($P < .001$) higher than the mean CRP observed in dogs treated with prednisone and metronidazole, 22.5 and 7.5 mg/L, respectively (Fig 3). Both prednisone and prednisone and metronidazole groups showed significant ($P < .001$) reduction in CRP concentrations pre- versus posttreatment. However, prednisone-treated dogs showed a significantly ($P = .013$) greater magnitude of decrease in CRP concentrations over time as compared with CRP concentrations in dogs treated with prednisone and metronidazole. Collectively, the interactions between CIBDAI and CRP over the 3-week trial were in agreement in 42 of 54 dogs (78%), whereas 8 of 54 dogs (15%) showed disagreement between these indices. Four dogs had pretreatment and posttreatment CRP values of 0 mg/L.

Adverse Effects

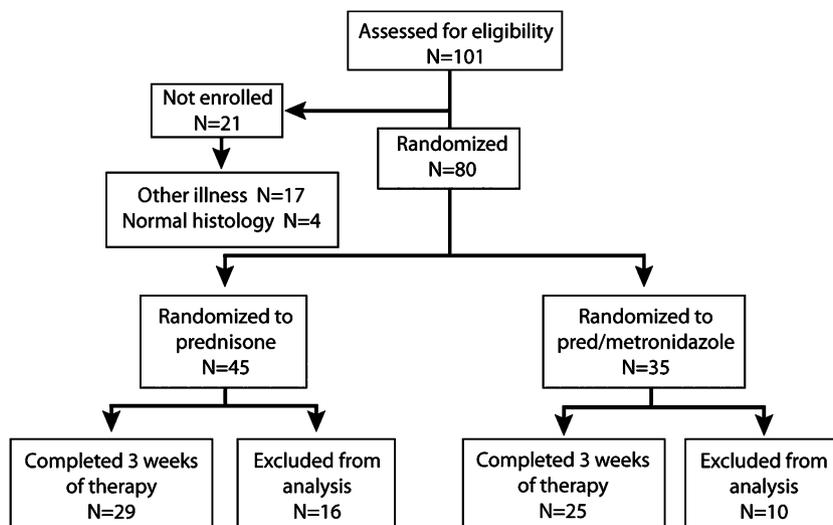
Overall, both treatments were well tolerated. Systemic adverse effects (ie, polyphagia, polyuria, and polydipsia, restlessness, panting) attributable to prednisone were noted in 6 of 54 (9%) of dogs in both treatment groups.

Anxiety and panting were observed in 3 large breed (> 27 kg) dogs. None of these signs were severe enough to cause owners to discontinue treatment and withdraw their dogs from the study. Adverse signs associated with metronidazole toxicity (eg, nausea, vomiting, diarrhea, neurologic disorders) were not observed in any dog receiving this medication.

Discussion

The limited understanding of the etiopathogenesis and disease course of canine IBD has prompted therapeutic decisions based on clinical experience and data derived from uncontrolled case series and trials. The present study represents the first randomized-controlled trial evaluating the efficacy of prednisone versus prednisone and metronidazole in combination for the treatment of canine IBD. The rate of remission after 21 days of treatment was similar for both treatment groups. Furthermore, drug treatment with either prednisone or prednisone and metronidazole was associated with significantly decreased mean CRP concentrations posttreatment, but the magnitude of CRP reduction was greatest in dogs receiving prednisone monotherapy. Because antibiotics are commonly used alone^{4,24,25} or in combination with glucocorticoids^{1,17–19,25} or aminosalicylates^{1,18,19,25} as treatment of canine IBD, the results of this study are highly relevant to the care of these patients.

It was the goal of this study to critically compare the hypothetically more potent treatment regimen of prednisone and metronidazole to treatment with prednisone

**Fig 1.** Study enrollment and drug treatment of canine inflammatory bowel disease dogs.

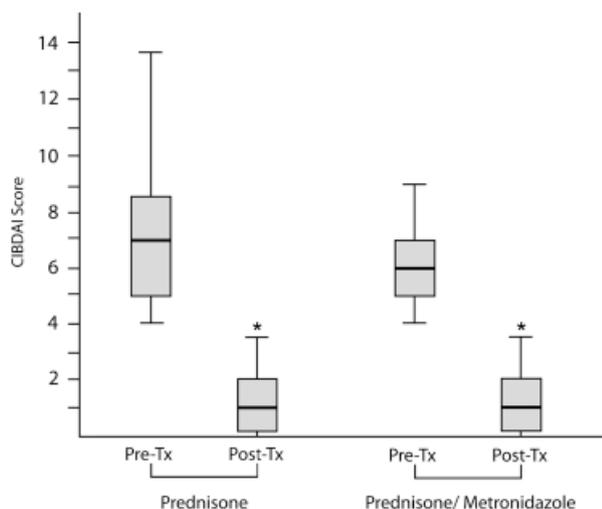


Fig 2. Effect of drug therapy on clinical remission according to canine inflammatory bowel disease activity index (CIBDAI) scores. Remission was defined by a 75% or greater reduction in the CIBDAI value posttreatment versus pretreatment. Box plots show the mean, range, 25 and 75% quartiles for CIBDAI scores. * $P < .05$ compared with pretreatment value. Tx, treatment. Data derived from analysis of 54 inflammatory bowel disease dogs.

alone in IBD dogs having clinically significant (ie, CIBDAI score ≥ 4) disease. The design of our trial excluded dogs with food-responsive enteropathy (ie, clinical signs that improved or resolved when fed an elimination diet for at least 21 days) and dogs that had received antibiotic or immunosuppressive drug therapy within 2 weeks of initial diagnostic evaluation. Clinical assessment of IBD activity was performed using both clinical (CIBDAI) and biologic (CRP) indices after histopathologic confirmation of idiopathic intestinal

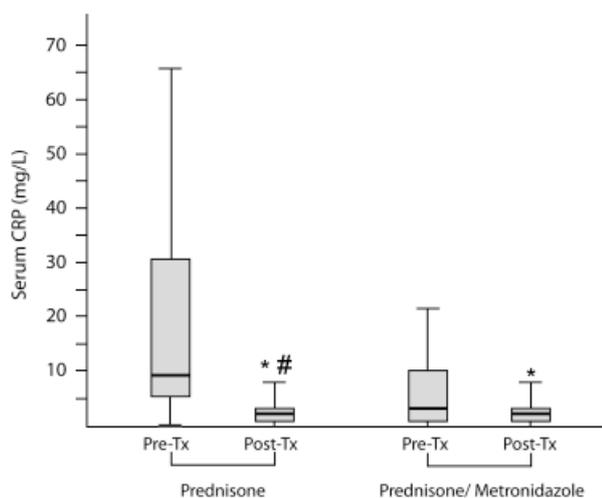


Fig 3. Effect of drug therapy on serum C-reactive protein (CRP) concentrations. Box plots show the mean, range, 25 and 75% quartiles for CRP concentrations. * $P < .05$ compared with pretreatment value. #Magnitude of prednisone group CRP change is significant ($P < .05$) compared with prednisone/metronidazole group. Tx, treatment. Data derived from analysis of 52 inflammatory bowel disease dogs.

inflammation. Furthermore, randomization was performed by computer generation of a randomization sequence to assign dogs to treatment groups, and clinicians were masked to the intervention until a diagnosis of IBD was made.^{26,27}

Practical guidelines for the treatment of human IBD are dictated by the disease (ulcerative colitis versus Crohn's disease), course (active versus quiescent, presence of flares), site (small intestine versus colon or rectum), and severity of clinical disease.^{12,28-31} Mild IBD is treated with 5-ASA, which function as a free radical scavenger and as an anti-inflammatory drug.^{32,33} Corticosteroids, such as prednisone, are potent, rapidly acting anti-inflammatory agents used for acute treatment of moderate to severe active disease.^{12,13} Induction dosing averages 7-14 days¹³ but long-term maintenance therapy is undesirable because of adverse effects (eg, Cushing's disease, osteoporosis, cardiomyopathy).^{34,35} Immunomodulators such as azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine are useful in the maintenance of remission in IBD patients with chronic active disease. Most recently, biological therapies, especially anti-TNF agents, have shown efficacy in treatment of Crohn's disease patients who have failed to respond to more conventional treatment options.^{13,36}

Antibiotics are used as a primary or adjuvant treatment option for active Crohn's disease and ulcerative colitis, although controlled clinical trials supporting use of these agents are lacking.³⁷⁻³⁹ The rationale for this selective therapeutic manipulation is based on animal model observations that the gut microbiota provide the stimulus for intestinal inflammation.^{5-7,38-42,i} There is presumptive evidence that metronidazole, ciprofloxacin, or the combination of these antibiotics are effective in Crohn's colitis and ileocolitis, but not in isolated ileal disease.⁴³⁻⁴⁶ The use of antibiotics as a primary treatment for ulcerative colitis currently is not justified based on available studies. However, other studies suggest that long-term administration of ciprofloxacin⁴⁷ or the non-absorbable broad-spectrum antibiotic rifaximin^j might have a possible benefit as an adjunct to standard anti-inflammatory treatment in these patients.

Several different combinations of glucocorticoids and antimicrobials have been used for treatment of canine IBD in different trials. In a retrospective analysis of 80 dogs with IBD, Craven et al¹⁸ reported that treatment with prednisolone, sulfasalazine, metronidazole, or tylosin was not associated with a favorable long-term outcome. The initial treatment chosen in this trial consisted of multiple drugs and various combinations were administered, which confounded interpretation of response rates. The authors characterized remission status as full (26%), partial with cyclical signs (50%), or incomplete (4%) at follow-up examination, but scoring indices were not utilized. Jergens et al¹⁹ reported that treatment with prednisone and metronidazole for 21 days significantly decreased the CIBDAI and CRP from baseline values in 58 IBD dogs, although sulfasalazine also was administered to some dogs with colitis. Similarly, the combination of prednisone and metronidazole administered at tapering doses over 90 days was associated with both

clinical (CIBDAI) and endoscopic improvement in dogs with nonhypoproteinemic lymphocytic-plasmacytic enteritis.¹⁷ In another study, Munster et al²⁵ evaluated the association among drug treatment, clinical response, and histologic severity of inflammation at the time of diagnosis. Dogs with IBD were treated with multiple drugs (metronidazole, prednisolone, azathioprine, sulfasalazine, or some combination of these) with efficacy assessed 3 times over a 12-week treatment period. Overall, 15 of 21 dogs with IBD of varying severity showed good therapeutic responses based on clinical (CIBDAI) scores. However, the effect of metronidazole treatment in a subset ($n = 5$) of IBD dogs with low disease activity was questionable. Moreover, there was no significant association between efficacy of treatment and age, CIBDAI score, or serum albumin concentration. Finally, Allenspach et al⁴⁸ showed that 10 of 21 dogs with chronic enteropathies that received oral prednisone responded to the initial treatment and failed to show any relapses for the next 3 years.

Other single and combination drug regimens have been reported to treat canine IBD effectively. Cyclosporine was a useful rescue agent in 11 of 14 IBD dogs that were previously refractory to prednisolone and intermittent antibiotic treatment.⁴⁹ Luckschander et al⁵⁰ reported that a 10-week trial of prednisolone reduced clinical (CIBDAI) scores in IBD dogs post treatment. Of interest, 54% of IBD dogs in this study were hypoalbuminemic at diagnosis, but the glucocorticoid responsiveness of these dogs in comparison with the nonhypoproteinemic IBD dogs was not reported. A small case series also suggested that tylosin may have a role in treating canine chronic diarrhea based on improved fecal consistency scores after antibiotic and dietary therapy.²⁴ Antimicrobials, such as tylosin or metronidazole, may exert their anti-inflammatory actions in IBD through one of several mechanisms. One theory is that changing the intestinal microbiota prevents colonization by pathogenic bacteria.⁴⁰ Another potential mechanism is that in genetically susceptible hosts there is a lack of tolerance to commensal bacteria in the intestines, leading to activation of the gut immune system.^{5,6,39,40} Suppression of the microbiota might lead to down-regulation of aberrant host responses directed against microbial antigens that trigger and perpetuate chronic mucosal injury. Antibiotics such as amoxicillin-clavulanic acid and metronidazole also might have direct anti-inflammatory effects independent of their antimicrobial activity, including suppression of cell-mediated immunity.⁵¹⁻⁵³

The clinical results of this study indicate a beneficial role for prednisone as part of an induction protocol in dogs with moderate to severe IBD. Both treatment arms resulted in significant reduction of CIBDAI scores after drug therapy with the greatest rate of remission observed in the monotherapy (prednisone) group. Furthermore, these data are in broad agreement with previous investigations in which glucocorticoids were of proven efficacy for treatment of canine IBD when used alone or in combination with metronidazole.^{1,17-19,25,50} Interestingly, both treatment groups in the present study contained numerous IBD dogs that had disease flares within 24 hours

of presentation. These dogs comprised 75 and 38% of prednisone-treated and prednisone and metronidazole-treated dogs, respectively, and represent new data of disease expression which has not previously been reported. Thus, our study lends further support to the utility of oral prednisone for treatment of dogs with active IBD. We did not study metronidazole as monotherapy and therefore cannot exclude the possibility that this drug is beneficial in canine IBD when used on its own.⁴

Hypoalbuminemia and low serum cobalamin concentration have been reported previously to be associated with negative outcome in canine chronic enteropathies.^{18,48} Both hypoalbuminemia and hypocobalaminemia were common clinicopathologic variables observed in the IBD dogs of this study. However, in contrast to earlier reports, IBD remission rates in both treatment groups exceeded 83% despite the presence of active clinical disease. The reasons for this difference in outcome between the present and earlier studies may be related to several factors. First, the magnitude of hypoalbuminemia in our dogs (mean, 2.3 g/dL) was not as severe as that (< 2.0 g/dL) noted in earlier reports. Secondly, ascites associated with overt protein-losing enteropathy was not a salient feature observed on physical examination in the dogs of this study. Thirdly, the short duration of clinical follow-up (ie, 21 days versus median long-term outcome assessments of 17¹⁸ and 36⁴⁸ months) may have biased our results toward a positive outcome because this 3-week time frame might have been too short to detect clinical relapse.

Serum CRP was used as an indirect marker of intestinal inflammation in IBD dogs of this study. CRP repeatedly has been shown to be a useful inflammation-sensitive biomarker to determine the acute phase response in humans with IBD, especially those with Crohn's disease.⁵⁴⁻⁵⁷ Our data showed that CRP concentrations were increased in 23 of 54 (43%) dogs on initial presentation, with the prednisone treatment group showing the highest mean CRP concentration. This finding of increased baseline CRP in a proportion of IBD dogs is in accordance with 2 earlier reports^{19,58} but is in disagreement with another report,⁴⁸ which categorized chronic enteropathy dogs into food-responsive, steroid-treated, and PLE groups. In this latter study, CRP was measured in less than half of the dogs described raising the possibility that high CRP concentrations may have been missed in some animals at the time of diagnosis. Interestingly, the increased CRP concentrations in these dogs decreased posttreatment to within the reference range. It should be noted that many human IBD patients have CRP concentrations within the normal range at diagnosis with wide overlap observed between values for patients with Crohn's disease and ulcerative colitis.^{56,59} CRP concentrations were significantly increased in the prednisone-treated dogs of this study, likely as a consequence of recent inflammatory activity (flare) which was observed in 75% of dogs in this group. Both interventions were associated with decreased serum CRP concentrations after completion of drug therapy, but the magnitude of change pre- versus posttreatment was greatest in dogs that received prednisone alone. This

difference (fold-change) in CRP concentrations of prednisone-treated dogs partially may have been because of their high baseline (eg, pretreatment) concentrations. A similar observation showing a positive response to treatment paralleled by decreased CRP concentrations was made by Jergens et al¹⁹ in a subset (n = 28) of dogs having moderate to severe IBD. Collectively, these observations suggest that CRP may be normal or increased in dogs with IBD and may be most useful in assessing the response of individual dogs to treatment along with changes in clinical indices.⁵⁶

The present study has some potential limitations. Although considered unlikely, we cannot conclusively exclude bacterial enteropathogens as contributing to intestinal inflammation in some IBD dogs because fecal cultures and bacterial toxin assays were not performed in all animals. Most of the IBD dogs had histopathologic lesions involving the small intestinal mucosa, which is different than human IBD where histopathologic inflammation typically involves the colon alone (ulcerative colitis) or less commonly involves the small intestine (Crohn's disease).^{5,6,31} The effect of prednisone in reducing gut inflammation may not have been entirely because of its anti-inflammatory actions, but also because of steroid-induced enhancement of small intestinal digestive and absorptive functions that could contribute to resolution of clinical signs.² Subtle variability in the specific novel protein source, extent of digestibility, relative fat content of the elimination diet fed to a given dog or some combination of these also may have influenced outcome to some extent. Although the use of elimination diets for treatment of food-responsive enteropathies is well established^{2,4,17,22,23,48–50} we are unaware of previous studies that have shown the superiority of 1 novel intact protein source over another in the dietary management of canine IBD. Fiber (eg, Metamucil, which contains psyllium seed husk as an active ingredient) supplemented to the elimination diets of dogs with colitis also could have provided a protective effect on intestinal health because of its prebiotic activity. Probiotics can stimulate the growth and metabolism of a beneficial enteric microbiota and stimulate the production of colonic short-chain fatty acids (such as butyrate) attributable to fermentation by colonic bacteria.^{60,61} Studies using prebiotics have been performed mostly in animal (rodent) models of intestinal inflammation, but not all studies using prebiotics have resulted in positive outcomes.^{62,63} To our knowledge, the use of prebiotics as primary treatment for canine IBD has not been reported.

Our clinical trial was designed to evaluate the effects of induction drug therapy for canine IBD. Reevaluations were performed after 21 days of diet and pharmacotherapy, which is standard practice at our institution and generally is adequate to assess response to medical treatment.¹⁹ Furthermore, this interval encouraged owner compliance. We observed very good to excellent control of gastrointestinal signs in most prednisone-treated dogs during the 3-week treatment period. However, additional studies are warranted to evaluate the effects of prolonged drug therapy because it is possible that gastrointestinal signs could recur when the prednisone dosage is tapered.

In this regard, metronidazole could have a prednisone-sparing effect that is only documented when prednisone is administered at a lower dosage.

Cobalamin deficiencies in some IBD dogs also may have affected the drug and dietary therapy in those animals. Not all dogs in our study had baseline serum cobalamin concentrations assessed. Some of the reasons for this included client financial constraints, previous cobalamin supplementation at the time of referral, and the fact that not all dogs had gastrointestinal signs (eg, cachexia with poor appetite, weight loss, watery small bowel diarrhea) indicative of severe small intestinal disease which might be associated with hypcobalaminemia and negative outcome.⁴⁸ The 10 dogs with hypcobalaminemia in this study were successfully treated with weekly cobalamin injections, which returned serum cobalamin concentrations into the normal range within 6 weeks after initiating vitamin treatment.

In conclusion, the results of this study show that oral prednisone monotherapy is as effective as combined treatment with prednisone and metronidazole for treatment of canine IBD. Adverse effects of either drug are uncommon, and both medications are well tolerated when used as part of an IBD induction therapy regimen. Although CRP may be normal or increased in dogs with IBD, a change in CRP concentration after treatment is useful to assess the effect of the drug therapy on the severity of clinical disease.

Footnotes

- ^a Tri-Delta-Phase, Tri-Delta Diagnostic Inc, Boonton Township, NJ
- ^b Gastrointestinal Laboratory, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX
- ^c Potato and duck formula, Royal Canin USA Inc, St. Charles, MO
- ^d Potato and whitefish formula, Royal Canin USA Inc
- ^e Metamucil, Proctor and Gamble, Cincinnati, OH
- ^f JMP 7.0.1, SAS Institute, Cary, NC
- ^g Iowa State University CVM reference range: 3.2–4.3 g/dL
- ^h TAMU GI Laboratory reference range: 252–908 ng/L
- ⁱ Kim SC, Tonkonogy SL, Albright CA, et al. Regional and host specificity of colitis in mice monoassociated with different non-pathogenic bacteria. *Gastroenterology* 2003;124:A485 (abstract)
- ^j Lukas M, Konecny M, Zboril V. Rifaximin in patients with mild to moderate activity of ulcerative colitis: An open labeled study. *Am J Gastroenterol* 2003;98:A434 (abstract)

References

- Jergens AE, Moore FM, Haynes JS, et al. Idiopathic inflammatory bowel disease in dogs and cats: 84 cases (1987–1990). *J Am Vet Med Assoc* 1992;201:1603–1608.
- Hall EJ, German AJ. Diseases of the small intestine. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*, 6th ed. Philadelphia, PA: Saunders; 2004:1332–1378.
- German AJ, Hall EJ, Day MJ. Immune cell populations within the duodenal mucosa of dogs with enteropathies. *J Vet Intern Med* 2001;15:14–25.

4. Jergens AE. Inflammatory bowel disease: Current perspectives. *Vet Clin North Am Small Anim Pract* 1999;29:501–521.
5. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007;448:427–434.
6. Sartor RB. Mechanisms of disease: Pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol* 2006;3:390–407.
7. Jergens AE, Wilson J, Dorn A, et al. *Helicobacter bilis* triggers persistent immune activation to commensal bacteria in C3H/HeN mice colonized with defined flora. *Gut* 2007;56:934–940.
8. Xenoulis PG, Palculict B, Allenspach K, et al. Molecular-phylogenetic characterization of microbial communities imbalances in the small intestine of dogs with inflammatory bowel disease. *FEMS Microbiol Ecol* 2008;66:579–589.
9. Glanemann B, Schonenbrucher H, Bridger N, et al. Detection of *Mycobacterium avium* subspecies paratuberculosis-specific DNA by PCR in intestinal biopsies of dogs. *J Vet Intern Med* 2008;22:1090–1094.
10. Simpson KW, Togan B, Rishniw M, et al. Adherent and invasive *Escherichia coli* is associated with granulomatous colitis in Boxer dogs. *Infect Immun* 2006;74:4778–4792.
11. Hostutler RA, Luria BJ, Johnson SE, et al. Antibiotic-responsive histiocytic ulcerative colitis in 9 dogs. *J Vet Intern Med* 2004;18:499–504.
12. Kuhbacher T, Folsch UR. Practical guidelines for the treatment of inflammatory bowel disease. *World J Gastroenterol* 2007;13:1149–1155.
13. Lichtenstein GR, Abreu MT, Conta R, et al. American gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006;130:935–939.
14. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: A systemic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007;5:103–110.
15. Thia KT, Mahadevan U, Fegan BG, et al. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: A randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009;15:17–24.
16. D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: A controlled randomized trial. *Gastroenterology* 2008;135:1123–1129.
17. Garcia-Sancho M, Rodriguez-Franco F, Sainz A, et al. Evaluation of clinical, macroscopic, and histopathologic response to treatment in nohypoproteinemic dogs with lymphocytic-plasmacytic enteritis. *J Vet Intern Med* 2007;21:11–17.
18. Craven M, Simpson JW, Ridyard AE, et al. Canine inflammatory bowel disease: Retrospective analysis of diagnosis and outcome in 80 cases (1995–2002). *J Small Anim Pract* 2004;45:336–342.
19. Jergens AE, Schreiner CA, Frank DE, et al. A scoring index for disease activity in canine inflammatory bowel disease. *J Vet Intern Med* 2003;17:291–297.
20. Day MJ, Bilzer T, Mansell J, et al. International standards for the histopathological diagnosis of gastrointestinal inflammation in the dog and cat: A report from the World Small Animal Veterinary Association Gastrointestinal Standardization Group. *J Comp Pathol* 2008;138 (Suppl 1):S1–S43.
21. Mischke R, Waterston M, Eckersall PD. Changes in C-reactive protein and haptoglobin in dogs with lymphatic neoplasia. *Vet J* 2006;174:188–192.
22. Schreiner NMS, Gaschen F, Grone A, et al. Clinical signs, histology, and CD3-positive cells before and after treatment of dogs with chronic enteropathies. *J Vet Intern Med* 2008;22:1079–1083.
23. Burgener IA, Konig A, Allenspach K, et al. Up-regulation of toll-like receptors in chronic enteropathies in dogs. *J Vet Intern Med* 2008;22:553–560.
24. Westermarck E, Skrzypczak T, Harmoinen J, et al. Tylosin-responsive chronic diarrhea in dogs. *J Vet Intern Med* 2005;19:177–186.
25. Munster M, Horauf A, Bilzer T. Assessment of disease severity and outcome of dietary, antibiotic, and immunosuppressive interventions by use of the canine IBD activity index in 21 dogs with chronic inflammatory bowel disease. *Berl Munch Tierarztl Wochenschr* 2006;119:493–505.
26. Brown DC. Reports of parallel group-controlled clinical trials: What needs to be there? *J Vet Emerg Crit Care* 2005;15:171–173.
27. Brown DC. Control of selection bias in parallel group controlled clinical trials in dogs and cats: 97 trials (2000–2005). *J Am Vet Med Assoc* 2006;229:990–993.
28. Hanauer SB, Myers S. Management of Crohn's disease in adults. *Am J Gastroenterol* 1997;92:559–566.
29. Rutgeerts PJ. Conventional treatment of Crohn's disease: Objectives and outcomes. *Inflamm Bowel Dis* 2001;7(Suppl 1):S2–S8.
30. Feagan BJ. Maintenance therapy for inflammatory bowel disease. *Am J Gastroenterol* 2003;98:S6–S17.
31. Hanauer SB, Present DH. The state of the art in management of inflammatory bowel disease. *Rev Gastroenterol Disord* 2003;3:81–92.
32. Camma C, Giunta M, Rosselli M, et al. Mesalamine in the maintenance treatment of Crohn's disease: A meta-analysis adjusted for confounding variables. *Gastroenterology* 1997;113:1465–1473.
33. Sutherland L, Roth D, Beck P, et al. Oral 5-aminosalicylic acid for inducing remission in ulcerative colitis. *Cochrane Database Syst Rev* 2000, CD 000543.
34. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis. Pathogenesis and management. *Ann Intern Med* 1990;112:352–364.
35. Chun A, Chadi RM, Korelitz BI, et al. Intravenous corticotrophin vs. hydrocortisone in the treatment of patients with Crohn's disease: A randomized double-blind study and follow-up. *Inflamm Bowel Dis* 1998;4:177–181.
36. Sandborn WJ. Current directions in IBD therapy: What goals are feasible with biological modifiers? *Gastroenterology* 2008;135:1442–1447.
37. Colombel JF, Cortot A, Van Kruiningen HJ. Antibiotics in Crohn's disease. *Gut* 2001;48:647.
38. Isaacs KL, Sartor RB. Treatment of inflammatory bowel disease with antibiotics. *Gastroenterol Clin North Am* 2004;33:335–345.
39. Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: Antibiotics, probiotics, and prebiotics. *Gastroenterology* 2004;126:1620–1633.
40. Sartor RB. Microbial influences in inflammatory bowel disease. *Gastroenterology* 2008;134:577–594.
41. Rath HC, Herfarth HH, Ikeda JS, et al. Normal luminal bacterial, especially *Bacteroides* species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. *J Clin Invest* 1996;98:945–953.
42. Sellon RK, Tonkonogy SL, Schultz M, et al. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10 deficient mice. *Infect Immun* 1998;66:5224–5231.
43. Greenblum SL, Steinhart AH, Greenberg GR. Combination ciprofloxacin and metronidazole for active Crohn's disease. *Can J Gastroenterol* 1998;12:53–56.
44. Steinhart AH, Feagan BG, Wong CJ, et al. Combined budesonide and antibiotic therapy for active Crohn's disease: A randomized control trial. *Gastroenterology* 2002;123:33–40.
45. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995;108:1617–1621.
46. Prantera C, Zannoni F, Schribano ML, et al. An antibiotic regimen for the treatment of active Crohn's disease: A randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996;91:328–332.

47. Turunen U, Farkkial MA, Valtonen V. Long-term treatment of ulcerative colitis with ciprofloxacin. *Gastroenterology* 1999;117:282–283.
48. Allenspach K, Wieland B, Grone A, et al. Chronic enteropathies in dogs: Evaluation of risk factors for negative outcome. *J Vet Intern Med* 2007;21:700–708.
49. Allenspach K, Rufenacht S, Sauter S, et al. Pharmacokinetics and clinical efficacy of cyclosporine treatment of dogs with steroid-refractory inflammatory bowel disease. *J Vet Intern Med* 2006;20:239–244.
50. Luckschander N, Allenspach K, Hall J, et al. Perinuclear antineutrophilic cytoplasmic antibody and response to treatment in diarrheic dogs with food responsive disease or inflammatory bowel disease. *J Vet Intern Med* 2006;20:221–227.
51. Grove DI, Mahmoud AA, Warren KS. Suppression of cell-mediated immunity by metronidazole. *Int Arch Allergy Appl Immunol* 1977;54:422–427.
52. Arndt H, Palitzsch KD, Grisham MB, et al. Metronidazole inhibits leukocyte-endothelial cell adhesion in rat mesenteric venules. *Gastroenterology* 1994;106:1271–1276.
53. Miller JJ. The imidazoles as immunosuppressive agents. *Transplant Proc* 1980;12:300–303.
54. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med* 2000;348:24–32.
55. Pepys MB, Hirschfield GM. C-reactive protein: A critical update. *J Clin Invest* 2003;111:1805–1812.
56. Vermeire S, van Assche G, Ruteerts P. Laboratory markers in IBD. Useful, magic, or unnecessary toys? *Gut* 2006;55:426–431.
57. Solem CA, Loftus EV Jr, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;11:707–712.
58. McCann TM, Ridyard AE, Else RW, et al. Evaluation of disease activity markers in dogs with idiopathic inflammatory bowel disease. *J Small Anim Pract* 2007;48:620–625.
59. Henriksen M, Jahnsen J, Lygren I, et al. C-reactive protein: A predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. *Gut* 2008;57:1518–1523.
60. Ewaschuk JB, Dieleman LA. Probiotics and prebiotics in chronic inflammatory bowel diseases. *World J Gastroenterol* 2006;12:5941–5950.
61. Cherbut C. Inulin and oligofructose in the dietary fibre concept. *Br J Nutr* 2002;87(Suppl 2):S159–S162.
62. Moreau NM, Martin LJ, Toquet CS, et al. Restoration of the integrity of rat caeco-colonic mucosa by resistant starch, but not by fructo-oligosaccharides, in dextran sulfate sodium-induced colonic inflammation in rats. *Br J Nutr* 2003;90:75–85.
63. Holma R, Juvonen P, As mawi MZ, et al. Galacto-oligosaccharides stimulate the growth of bifidobacteria but fail to attenuate inflammation in experimental colitis in rats. *Scand J Gastroenterol* 2002;37:1042–1047.