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Review

Treatment of inflammatory bowel disease (IBD) in dogs and cats

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Abstract

The treatment of inflammatory bowel disease (IBD) possesses numerous difficulties owing to the unclear etiology of the disease. This article overviews the drugs used in the treatment of IBD depending on the intensity of clinical symptoms (Canine Inflammatory Bowel Disease Activity Index and Canine Chronic Enteropathy Clinical Activity Index). Patients demonstrating mild symptoms of the disease are usually placed on an appropriate diet which may be combined with immunomodulative or probiotic treatment. In moderate progression of IBD, 5-aminosalicylic acid (mesalazine or olsalazine) derivatives may be administered. Patients showing severe symptoms of the disease are usually treated with immunosuppressive drugs, antibiotics and elimination diet. Since the immune system plays an important role in the pathogenesis of the disease, the advancements in biological therapy research will contribute to the progress in the treatment of canine and feline IBD in the coming years.

Key words: IBD, treatment, CIBDAI, dogs, cats

Canine and feline inflammatory bowel disease (IBD) is a group of chronic enteropathies characterized by persistent or recurring gastric symptoms with an unknown etiology which are related to histopathological changes in the mucosa of the small and large intestine, in the form of cellular infiltration in the lamina propria of the mucosa. The classification of IBD is determined by the dominant type of inflammatory cells in the lamina propria of the intestinal mucosa (German 2001, Craven 2004, Garcia-Sancho 2007, Day et al. 2008, Washabau 2008).

The pathogenesis of IBD involves various factors, and it has not been fully explained. The most predominant factors conditioning canine and feline inflammatory bowel disease include bacterial and environmental factors, genetic predispositions of selected breeds, allergens and side effects of certain drugs

(Garside 1999, German et al. 2000, Jergens 2002, German et al. 2003, Allenspach and Gaschen 2003, Bhatia and Tandon 2005, Hall 2007). In the light of the recent research, the key role in the pathogenesis of IBD is ascribed to the loss of tolerance for endogenous microflora, food antigens or endogenous antigens which leads to a chronic inflammation of the gastrointestinal tract (Allenspach et al. 2007, Xenoulis et al. 2008). The loss of permeability in the gastrointestinal mucosa and immunological aberrations in the gastrointestinal system produce an inappropriate immune response (German et al. 2001, Hall 2007, McCann et al. 2007, Sauter et al. 2007)

The diagnosis of canine and feline IBD is a difficult process which requires vast knowledge and involvement on behalf of the clinical physician. In addition to an unclear etiopathogenesis, the main obstacle

to correct IBD diagnosis is an absence of an unambiguous treatment scenario. The Gastrointestinal Standardization Group of the World Small Animal Veterinary Association (WSAVA) attempted to develop such standards and proposed the following procedure for diagnosing the disease:

- other causes of chronic diarrhoea should be eliminated, laboratory tests recommended in the diagnosis of gastrointestinal disorders should be performed (dogs: serum TLI, serum folate and cobalamin, intestinal permeability, fecal α -1- protease inhibitor; cats: T4, fTLI, FeLV and FIV, fTLI), laboratory tests ruling out the possibility of systemic disease that produces gastric symptoms should be carried out;

- the canine IBD activity index (CIBDAI or CCECAI) score should be determined;

- endoscopic examination should be performed, including sampling of gastrointestinal mucosa biopsies;

- intestinal mucosal biopsy specimens should be evaluated in a histopathological examination by WSAVA standards;

- if possible, the degree of cell-mediated and humoral immunity should be determined (Jergens 2002, Craven et al. 2004, Hall 2007, Sauter et al. 2007, Day et al. 2008, Dossin 2009).

An analysis of the severity of clinical symptoms is an important element of the diagnostic process. The Canine Inflammatory Bowel Disease Activity Index – CIBDAI was proposed by Jergens in 2003 based on an analysis of the most common clinical symptoms. The index relies on an evaluation of the six most frequently encountered clinical symptoms which are graded on a scale of 0 to 3 points, depending on severity. The following symptoms are evaluated: the patient's activity level, appetite, vomiting, stool consistency, stool frequency and weight loss. A new Canine Chronic Enteropathy Clinical Activity Index (CCECAI) includes hypoalbuminemia (serum concentrations <20 g/L), assessment of ascites, peripheral edema and pruritus in addition to the CIBDAI scores. CIBDAI and CCECAI supports a preliminary classification of the intensity of inflammatory changes, enabling the selection of the appropriate treatment, treatment monitoring and early relapse detection (Jergens et al. 2003, Allenspach et al. 2007).

Several therapeutic procedures for managing the disease have been proposed in the light of the recent research into the etiopathogenesis of canine IBD and a modified immune response to selected nutritional components and the bacterial flora of the gastrointestinal tract. Standard therapy combines elimination diet and antibacterial and immunosuppressive treatment. The majority of practical guidelines for the

treatment of IBD are based on the physician's individual experience and the progression of changes in the clinical and histopathological picture. Most research studies into the treatment of canine IBD recommend a staged approach whenever possible (mild to moderate changes based on the CIBDAI score).

Therapies based solely on dietary modification are possible only in dogs with a moderate (CIBDAI score 4-5) progression of the disease (Münster et al. 2006). The recommended diet contains a single protein source. IBD may be caused by reaction to food antigens, therefore, a restricted diet or an elimination diet containing proteins and carbohydrates previously not found in the animal's nutritional regime are recommended. Diets recommended for IBD patients could contain fructooligosaccharides (FOS), a nutritional substance for a healthy intestinal flora, manooligosaccharides (MOS) which support the elimination of pathogenic microorganisms as well as potato pulp, a source of nourishment for colonic mucosal cells (Swanson et al. 2002a,b, Zentek et al. 2002). The recommended diet has a low fat content and an optimal ratio of Omega-6 to Omega-3 fatty acids to alleviate intestinal inflammations. The addition of glutamine to the food may minimize the risk of intestinal villous atrophy and stimulates the recovery after gastrointestinal disorders. Glutamine is a source of energy for enterocytes of the intestinal mucosa, and also regulates hepatic detoxification processes (Elliott 2006). Hypoallergenic and low residue diets are usually recommended if the disease affects mostly the small intestine. High-fiber diets are administered when the inflammatory process affects the large intestine. Shortly after the onset of IBD treatment, inflammation is minimized and mucosal permeability to food antigens is increased, which is why some patients may become excessively sensitive to the new source of protein in the recommended diet. The above leads to a recurrence of gastrointestinal symptoms. If this is the case, a new source of protein is introduced six weeks after the onset of treatment when inflammation has been reduced. IBD therapy relying solely on diet modification is effective in cats. Dietary modification includes elimination or novel protein diet, or highly digestible diet. Dietary treatment should be associated at least initially with a course of antibiotics (Dossin 2009).

Probiotics may be included in the treatment if diet modification alone does not produce satisfactory results in patients with mild symptoms of the disease (Chrzastowska et al. 2009). The interactions between bacteria of the genera *Lactobacillus spp*, *Enterococcus spp* and *Bifidobacterium spp* and GALT lead to changes in the balance of pro-inflammatory and anti-inflammatory cytokines (Benyacoub et al. 2003,

Ghosh et al. 2003, Sauter et al. 2005). Probiotics decrease levels of the pro-inflammatory interleukin-6 and they stimulate an increase in the anti-inflammatory interleukin-10 (German et al. 2003, Chrzęstowska et al. 2009). Due to inflammatory changes in other organs, such as the liver or the skin, which often accompany IBD, the above could lead to a rapid improvement in the patient's condition. Probiotics suppress the development of pathogenic bacteria, and they modulate the immune response of GALT by stimulating innate phagocytic activity or the specific immune response through the production of IgA (Wagner et al. 1997, Mitsuyama et al. 2002, Macpherson and Harris 2004). The effectiveness of probiotics is determined by species consistency and, if possible, the use of live cultures. Freeze-dried products are characterized by lower therapeutic effectiveness.

Natural and synthetic immunomodulators may also be used in the treatment of canine IBD. β -glucans are the most commonly used natural immunomodulators in veterinary practice. β -glucans are polysaccharides that are a component of the cell walls of many fungal species. Some β -glucans are applied in human medicine in the treatment of neoplasms, viral infections, bacterial infections and diabetes. They effectively lower blood cholesterol levels (Chen and Seviour 2007). Water-insoluble β -1,3/1,6-D glucans obtained from *Saccharomyces cerevisiae* yeast are marked by the highest immunological potency (Li et al. 2005). In veterinary medicine, they are used as adjunctive agents in the treatment and prevention of contagious diseases (viral, bacterial and fungal) (Hunter Jr. et al. 2002, Hiss and Sauerwein 2003, Siwicki and Skopniewska-Różeńska 2003, Szymańska-Czerwińska and Bednarek 2008). There are few studies investigating the use of β -glucans in the treatment of IBD in humans, and the efficacy of these immunomodulators in the treatment of canine IBD has not been documented to date. The results of the study carried out by the Department of Clinical Diagnostics at the University of Warmia and Mazury in Olsztyn (Poland) indicate that in case of dogs affected by IBD and treated with levamisole, β -hydroxy- β -methyl butyrate (HMB) and β -1,3/1,6-D-glucan, the best therapeutic results were noted as regards the latter. Feed supplementation with beta-glucans in the amount of 7 mg/kg bw led to the most rapid suppression of the inflammatory process, graded on the CIBDAI scale, the greatest histopathological improvement of the intestinal mucosa, the highest drop in IL-6 levels and the greatest increase in IL-10 levels. Only the patients administered beta-glucans did not relapse over a period of six months (Rychlik et al. 2009). The mechanism of beta-glucans is as follows: the host's body recognizes

beta-glucans as foreign particles (antigens), the immune system is stimulated activating a non-specific immune response with the involvement of specific factors – antibodies. Antibodies interact with receptors found on the surface of macrophages, NK cells, B-lymphocytes, T-lymphocytes and other immunocompetent cells. Beta-glucans activate the complement and stimulate the production of pro-inflammatory and anti-inflammatory interleukins and TNF- α , thus activating the body's immune function (Pelizon et al. 2005, Wójcik et al. 2007, Chen and Seviour 2007). Beta-glucans may also be administered in moderate progression of the disease. The use of immunomodulators in severe disorders is not recommended as they may aggravate the disease, as observed in humans (Chen and Seviour 2007).

Topical non-steroidal anti-inflammatory drugs (NSAIDs) may be used in the treatment of moderate forms of IBD (CIBDAI score of 6 to 8) or in patients showing mild symptoms of the disease who were not effectively treated by other drugs or dietary modification alone. 5-aminosalicylic acid derivatives exert a bacteriostatic, anti-inflammatory and immunosuppressive effect by suppressing the synthesis of leukotrienes, prostaglandins and cytokines. They inhibit the migration of inflammatory cells and the production of immunoglobulins by B cells. They impair the adhesion and functions of neutrophils and macrophages, and they support the elimination of reactive oxygen species (Cipolla et al. 2002, Ransford and Langman 2002). To date, two types of substances have been used in canine therapy, depending on the site affected by the inflammatory process. Sulfasalazine, applied to manage canine IBD, is a prodrug with diazo bonds linking sulfapyridine with 5-ASA which is then released by colon bacteria as free 5-ASA that has a local effect in the colon. If administered over periods longer than six weeks, sulfasalazine may lead to the dry eye syndrome (kerato-conjunctivitis sicca – KSC), and Schirmer's test may be required. In dogs, the average sulfasalazine dose is 12.5 mg/kg every six hours p.o. over a period of 14 days, followed by 12.5 mg/kg every 12 hours for 28 days, and 10 mg/kg every 24 hours for 14 days. Some patients may require higher and more frequent doses. The majority of dogs respond to treatment within several days, but in some cases, the first noticeable signs of improvement may be observed only after four weeks of the treatment. Some clinical physicians suggest a combination of prednisolone and azathioprine if the patient's condition does not improve after one week of treatment. If clinical symptoms of the disease persist after four weeks, the IBD diagnosis should be revised. Mesalazine, olsalazine and the latest aminosalicylate derivatives affect the small intestine. In dogs, owing to more frequently ob-

served changes in this segment of the gastrointestinal tract (in 70-80% of dogs affected by IBD, changes are found in the small intestine), the above drugs seem to be more effective, and they prolong remission times (Rychlik et al. 2008). The recommended dose of mesalazine is 12.5 mg/kg b.w. twice a day for four to six weeks. Cats are susceptible to salicylate poisoning, which is manifested by anorexia and anemia, therefore salicylate derivatives are not recommended for the treatment of feline IBD.

The most effective form of therapy in patients affected by severe IBD (CIBDAI score higher than 9) is immunosuppression, which is also applied when previous treatment involving diet modification, probiotics, immunomodulators and non-steroidal anti-inflammatory drugs were ineffective. The most frequently used immunosuppressants are glucocorticoids, and the drug of choice is prednisolone administered at 1-2 mg/kg b.w. every 12 hours for two to four weeks, with a gradual dosage reduction of 25% every week or every two weeks, ending in a low maintenance dose administered every 48 hours. Glucocorticoid therapy may be discontinued in a very limited number of cases. In some patients, treatment may be discontinued after a period of remission of at least six months. Higher dosage is recommended in patients with hypoalbuminemia. Histopathological changes in the mucosa of intestines may persist despite clinical improvement (Allenspach et al. 2006, Garcia-Sancho et al. 2007). The side effects of glucocorticoids include iatrogenic hyperadrenocorticism (polyphagia, polydipsia, polyuria, muscle atrophy). Most side effects can be managed by dose reduction.

Modern steroids that deliver a local effect and influence the intestinal mucosa offer an alternative to prednisone or prednisolone treatment. One of such drugs is Budesonide which shows promise in the treatment of human IBD. After absorption, nearly 90% of the drug is metabolized by the liver already after the first pass. In comparison with prednisolone, Budesonid has a minimal suppressive effect on the hypothalamic-pituitary-adrenal axis. The recommended dose is 3 mg/animal/day for medium-sized dogs and 1 mg/animal/day for small breeds. The recommended dose for cats is 0.5 to 1 mg/animal/day. Some patients treated with Budesonid developed steroid hepatopathy (Stewart 1997, Tumulty et al. 2004).

Azathioprine (AZA) is popularly used in dogs when IBD cannot be effectively managed with glucocorticoids or when the glucocorticoid dose has to be reduced due to side effects. In most canine patients, the drug is administered daily (2 mg/kg once a day p.o.) for five days, later every other day, alternately with prednisolone. Cats are more sensitive to azathioprine, and the appropriate dose in feline pa-

tients is 0.3 mg/kg 2-3 times per day p.o. The drug may suppress the bone marrow activity, therefore hematological examinations should be performed every 2-4 weeks. Azathioprine therapy should be continued for three to nine months, and the first results are observed after two to three weeks. Vomiting, hepatic toxicity and myelosuppression is a common side effect of azathioprine treatment in dogs (Modigliani 2000, Salavaggione et al. 2002).

Cyclosporin A (dogs: 5 mg/kg once daily; cats: 1-4 mg/kg) is an alternative form of immunosuppressive therapy for IBD (Day 2004, Allenspach et al. 2006, Gaschen 2006). The drug inhibits IL-2 production and it probably shortens the lymphocyte life-span by inducing the apoptosis of T helper cells (CD⁴⁺ lymphocytes). Metronidazole may also be administered (dogs: 10-20 mg/kg twice a day p.o. for 10-14 days, then once a day for 10-14 days; cats: 7-10 mg/kg), including in combination with corticosteroids. The drug suppresses cell-mediated immunity, and it has an antiprotozoan and bactericidal effect on anaerobic bacteria (Jergens et al. 2010). Cyclosporin's effectiveness in the treatment of IBD has not been fully validated. Allenspach observed a noticeable clinical improvement in around 60% of dogs administered cyclosporin A. After four weeks of the treatment, the CIBDAI score of the studied animals was lowered to 0-2, i.e. to the level of clinically insignificant symptoms (Allenspach et al. 2006). In another experiment, a preliminary study on the use of cyclosporin A in the treatment of canine IBD pointed to the low efficacy of the drug (Hall and German 2005). The side effects of cyclosporin A include loss of appetite, sialorrhea, vomiting and, less frequently, ataxia, nystagmus and convulsions (at high doses).

Immunosuppressants may be gradually withdrawn when a period of remission lasts two to three months. If the patient relapses, the drug can be re-administered daily, and the treatment should be continued until symptoms disappear, followed by a gradual dose reduction. In patients showing a weak response to the treatment and patients that relapse after a positive initial response, an intestine biopsy should be performed to rule out lymphosarcoma. Chlorambucil, an immunosuppressive cytostatic drug, may be prescribed in cats that do not respond to steroid treatment alone, at 2 mg p.o. every 4 days (Gaschen 2006). Future progress in the treatment of canine and feline IBD is closely related to the use of new-generation drugs in humans. The aim of biological therapy is to reduce inflammation by neutralizing pro-inflammatory cytokines, using anti-inflammatory cytokines and inhibiting neutrophil adhesion (Sanchez-Muñoz et al. 2008). Biological treatment relies on pro-inflammatory interleukin antibodies, including IL-2 receptor

antibodies (daclizumab, basiliximab), IL-6 receptor antibodies (atlizumab, tocilizumab), IL-12, IL-17 and IL-23 receptor antibodies. Research studies are initiated into the use of anti-inflammatory interleukins, including recombinant IL-10 and IL-11 (Sandborn and Targan 2002, Kurtovic and Segal 2004). In a study of humans, selected immunosuppressants (Thalidomide, Oxypenthylline, anti-TNF- α monoclonal antibody) affecting the TNF- α (tumor necrosis factor) were found to be effective in IBD therapy. Thalidomide delivered promising results in the treatment of Crohn's disease in humans, but clinical research in dogs produced unsatisfactory results (German et al. 2003, Day 2004). Since CD⁴⁺ T cells participate in the pathogenesis of canine IBD, anti-TNF- α monoclonal antibodies may offer a viable alternative in the treatment of the disease, provided that species-specific monoclonal antibodies are available (German et al. 2003).

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