

Review

Inflammatory Bowel Disease and Current Treatment Options in Dogs

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Abstract: Inflammatory Bowel Disease (IBD) is an idiopathic and chronic gastrointestinal failure of cats, dogs and some farm animals such as horses. Since the long and difficult classical therapy of the disease has various side effects such as malignancy and lymphoma, new therapeutic methods are needed. However, a safe and standardized treatment protocol has not been developed, yet. Therefore, IBD treatment is still a big dilemma for both veterinary and human medicine. In this review, IBD and new possible therapeutic alternatives were evaluated for dogs.

Keywords: Inflammatory Bowel Disease, Novel Treatment, Dogs

Introduction

Inflammatory Bowel Disease (IBD) represents a group of chronic, inflammatory disorders in the gastrointestinal system in animals as well as humans (Haas *et al.*, 2014). It is a progressive disease with poorly characterized etiology (Jackson and Jewell, 2015). IBD is especially important for dogs, because large number of dogs suffer from chronic or recurrent gastrointestinal problems (Cerquetella *et al.*, 2010; Haas *et al.*, 2014).

The 'inflammatory bowel disease' term is applied in veterinary medicine to idiopathic inflammation which is characterized by infiltration of inflammatory cells in the intestinal mucosa and occurs in any area of the gastrointestinal tract (Jergens *et al.*, 1992; Suchodolski *et al.*, 2012). There are different types of diseases defined by affected intestinal region and observed inflammatory cells (German *et al.*, 2003).

The various forms of IBD are classified by anatomic location and the predominant cell type involved in animals. Lymphocytic-plasmacytic enteritis is the predominant form in cats and dogs, followed by eosinophilic inflammation. There are occasional reports of inflammation with a granulomatous pattern (regional enteritis). A neutrophilic predominance in the inflammatory infiltrate is rare. In addition, a mixed pattern of cellular infiltrate is described on many occasions. Certain unique IBD syndromes occur more often in some breeds, such as the protein-losing enteropathy/nephropathy complex in Soft-coated Wheaten Terriers, immunoproliferative enteropathy of

Basenjis, IBD in Norwegian Lundehunds and histiocytic ulcerative colitis in Boxers (Craven *et al.*, 2004; Defarges, 2016).

Pathogenesis

There are various genetic, environmental and immunoregulatory factors affected etiology and pathogenesis of IBD in dogs as well as humans (Hanauer, 2006; Minamoto *et al.*, 2015).

Routine hematology, parasitic and bacteriologic fecal analyses, dietary trials, radiographic imaging and histopathologic examination of intestinal biopsy specimens provide data to eliminate other causes of chronic enteropathy (Cerquetella *et al.*, 2010).

In dogs, IBD occur a consequence of a deregulation of mucosal immunity in predisposed animals. One of the most studied mechanism to explain development of chronic intestinal inflammation is the loss of tolerance to antigens (food, intestinal bacteria, etc.) that could justify the development of chronic intestinal inflammation. In the dogs with IBD, IgE is increased when compared with healthy dogs. This data could show the immune mediated basis of the disease and hypersensitivity reactions in the pathogenesis. In addition, it could explain the mode of action of immunomodulant drugs in the treatment (Slovak *et al.*, 2014).

Eosinophils and mast cells increase in many dogs with Eosinophilic Gastro-Enteritis (EGE) according to the mucosal barrier failure, independently of the primary cause (bacterial, chemical, etc.) of the inflammation can also lead to further antigen exposure, thereby the chronic

process becomes and is enforced by decreased apoptosis of lymphocytes, as demonstrated in dogs with IBD when compared to control dogs (Cerquetella *et al.*, 2010).

Genetically predisposition is an important risk factor for IBD. It is believed that IBD is caused by inappropriate and permanent inflammatory response to communal microorganisms in a genetically susceptible host. Recent studies showed the main mechanisms, relationships between the mucosal immunity and the disease, interaction of genetic factors with microbial and environmental reasons and different biological effects in different phenotypes (Khor *et al.*, 2011).

Incidence

There is no information about incidence for dogs and cats in IBD. Because, characterisation of many cases is still incomplete and detailed histopathological criteria for the differential diagnosis are needed (Hall, 2009).

The peak incidence of IBD in human population was observed between 1960s and 1980s in North America. It was reported that approximately 1 000 000 people have IBD and about 30000 new cases are defined annually in the U.S.A. (Hanauer, 2006). The incidence is evenly divided between UC and CD. For Europe, IBD incidence is at least three times higher in northern Europe than the southern part (Shivananda *et al.*, 1996).

Epidemiological researches showed that the incidence of IBD has dramatically elevated in the last 50 years. There are more than 160 genetic risk loci, most of them cannot be fully defined. IBD is getting more common especially in developing countries and in migrants populations. These findings also show the importance of environmental influences on the genetic predisposition. Another important predisposition factor is the smoking and CD incidence was reported higher in smokers in the West. However, appendectomy, tonsillectomy, breast feeding and antibiotic use are other indicated factors of high IBD incidence (Siew *et al.*, 2014).

Sex and Age

There is no apparent age, sex, or breed predisposition associated with IBD in animals; however, it may be more common in German Shepherds, Yorkshire Terriers, Cocker Spaniels and purebred cats. The mean age reported for development of clinical disease is 6.3 year in dogs and 6.9 year in cats, but IBD has been documented in dogs <2 years old (Defarges, 2016).

Intestinal inflammation has been reported usually in dogs and cats 6 month old and much younger. However, it is generally not evaluated as IBD and other reasons, such as *Trichomonas* infections, are considered the cause of this kind of inflammatory failures. In addition, IBD could be histologically confused with villus lymphoma (Hall, 2009).

More comprehensive information is present for human. Although IBD can be seen any age of individuals, its incidence is higher in young adults. It was reported that IBD is usually seen in people 15-30 years old. Approximately 10% of IBD cases has been observed in 18 years old. Minimum incidence of UC and CD is observed in humans 50-70 years old. CD is occurring frequently in females (1.8 times higher than males). However, UC is observed almost in equal ratio between females and males. Higher socioeconomic populations are under elevated risk for both diseases (Hanauer, 2006; Khor *et al.*, 2011).

Localisation in Gastrointestinal System (GIS)

A chronic, continuous or intermittent inflammation is the evident observation of Crohn's Disease (CD) and Ulcerative Colitis (UC) that are considered as IBD in humans. Although CD affects all parts of the intestinal tract, it generally locates in ileum and colon. Granulomas that could describe an ulcerative and inflammatory disease can involve in the whole intestinal part in CD (Khor *et al.*, 2011). The most common location is the ileocecal region, followed by the terminal ileum alone, diffuse small bowel, or isolated colonic disease in decreasing order of frequency (Hendrickson *et al.*, 2002). However, these signs are mostly restricted in the superficial layers of the colon (mucosa or superficial part of the submucosa) in UC (Khor *et al.*, 2011).

The localisation of IBD is very important for the diagnosis of the disease in humans. Relapses are more occurring in CD patients with ileocolitis than patients with ileitis or colitis alone. For UC, the symptoms and complications are more frequent and serious when colon is involved to the disease. The importance of the anatomical localisation of IBD is not clear in cats and dogs. It was reported that although histological changes may be observed in whole parts of GI tract, IBD frequently affects to the small intestine especially ileum and jejunum (Craven *et al.*, 2004; Suchodolski *et al.*, 2012).

Clinical Signs and Severity

There is no specific symptom for IBD in dogs. The common symptoms are weight loss, persistent or recurrent vomiting and/or diarrhoea. These findings generally associated with anaemia (if hypoalbuminemia is observed) or pallor of mucous membranes (if chronic gastrointestinal bleeding is occurred) (Cerquetella *et al.*, 2010).

Because of IBD is a very individual disease, it could be difficult to make comparison among patients. Numeric data is necessary to objective evaluation of the disease severity. Therefore an "Activity Index" was reported by Jergens *et al.* (2003) in dogs with IBD. The index useful to the management of clinical patients, in addition initial response to treatment could be evaluate and long term process would be detected (Jergens *et al.*, 2003).

Canine IBD Activity Index

“The Canine IBD Activity Index” (CIBDAI) is a simple scoring system. In this system, 6 remarkable gastrointestinal signs were evaluated based on healthy clinical situation of animals and scored 0-3 by the gastroenterology specialist Table 1. After that the scores are summed, a total cumulative CIBDAI score is obtained and the severity of IBD is evaluated Table 2 (Jergens *et al.*, 2003).

Diagnosis

For the diagnosis, all possible GI inflammation reasons should have been ruled out (Suchodolski *et al.*, 2012). Beside clinical signs and CIBDAI scores, endoscopy, biopsy and his to pathological investigation are used for the detection of IBD. GI endoscopy is an easy, relatively non-invasive and useful method for determination the active inflammation. The criteria have been developed for qualitative evaluation of endoscopic mucosal appearances Table 3 (Slovak *et al.*, 2014). In addition, his to pathological analysis is another method for the diagnosis of IBD and objective criteria are established in dogs Table 4 (Poullis *et al.*, 2002; McCann *et al.*, 2007; Magro *et al.*, 2013).

However, practical, cheap, sensitive and specific methods are needed for the diagnosis of the disease, still. Blood and faecal markers could fulfil these criteria and may be a good diagnostic alternative. CRP, Tumour Necrosis Factor Alpha (TNF α) and microalbuminuria have been identified as useful markers of disease activity in human patients with IBD (Poullis *et al.*, 2002; McCann *et al.*, 2007). Nevertheless, McCann *et al.* (2007) reported that there was no Correlation Between those parameters and clinical symptoms (CIBDAI) and his to pathological findings.

Anti-Neutrophil Cytoplasmic antibody (p-ANCA), Anti-*Saccharomyces Cerevisiae* (ASCA) were investigated a clinic-pathological diagnostic/monitoring markers in veterinary medicine for IBD. In addition, measurement of mucosal permeability after lactulose and rhamnose administration and IgG and nitrite concentrations in colonic lavage fluid could be important parameters for the diagnosis and monitoring of the IBD in dogs (Cerquetella *et al.*, 2010).

The serum folate and cobalamin concentrations were also investigated but they were considered as non-specific findings in IBD. However, these parameters could be important for supplementation during the treatment (Cerquetella *et al.*, 2010).

Recently, Fecal Calprotectin (FC) has been reported as a useful biomarker for evaluation of the intestinal inflammation and IBD in humans. FC is also known as L1 protein, Myoleoid-Related Protein 8/14 (MRP-8/14), calgranulin and cystic fibrosis antigen. FC is

excreted and stable for 7 days at room temperature in feces and can be measured with a commercially available ELISA immunoassay. FC levels have been found to be significantly elevated in patients with inflammatory and neoplastic conditions (von Roon *et al.*, 2007) and could be a new marker for differential diagnosis of IBD in animals, as well.

Treatment

The main aim of the treatment of IBD is to depress the inflammation regarding clinical symptoms and histological alterations. Although this approach is beneficial for long-term remission and reduced risks of complications, relapses of the disease are common in many patients. Therefore, recent researches tend to find more effective therapeutic methods to re-install intestinal immune tolerance in IBD (Di Giovangiulio *et al.*, 2015).

Treatments of Canine IBD are generally based on human therapies. Most general and primitive therapeutic procedure in canine and human IBD contains corticosteroids, other anti-inflammatory agents, such as 5-Amino Salicylic Acid (5-ASA) or immunosuppressant in the last decade (Farzaei *et al.*, 2015; Zhang *et al.*, 2016).

Corticosteroids are commonly first choice for the treatment of IBD in dogs. According to retrospective studies, prednisolone is the most used drug alone or in combination. Many studies showed that prednisone has good effects in the treatment of IBD in dogs. But, systemic corticosteroids caused some side effects, such as polyphagia, polyuria, polydipsia, restlessness, panting and behaviour changes in dogs. Long-time usage of corticosteroids can cause obesity, vacuolar hepatopathy, muscle atrophy and weakness, ligament rupture, urinary tract infection, pyoderma and development of diabetes mellitus (Dye *et al.*, 2013). Furthermore, corticosteroids and immunosuppressive drugs combinations caused extra short- and long-term side effects, such as increased liver parameters, allergic reactions, nausea, pancreatitis (Zhang *et al.*, 2016).

The knowledge about treatment alternatives of IBD are changing day by day according to the new experiences. Some researchers reported the malignancy of the therapeutics specifically. For example, immunosuppressive therapies used in IBD may increase the risk of lymphoma (Kotlyar *et al.*, 2015). Pasternak *et al.* (2013) reported that azathioprine usage was associated with an increased risk of overall cancer in IBD patients, although these data cannot establish causality. In addition, a meta-analysis study demonstrated that the use of thiopurines (azathioprine and 6-mercaptopurine) is associated with a 4-fold increased risk of lymphoma in patients with IBD (Kotlyar *et al.*, 2015).

Table 1. Evaluation criteria for clinical IBD (Jergens *et al.*, 2003)

Attitude/activity	0 normal
Appetite	1 Slightly decreased
	2 Moderately decreased
	3 Severely decreased
Vomiting	0 Normal
	1 Slightly decreased
	2 Moderately decreased
Stool consistency	3 Severely decreased
	0 None
	1 Mild (1 time/week)
Stool frequency	2 Moderate (2-3 times/week)
	3 Severe (3 times/week)
	0 Normal
Weight loss	1 Slightly soft feces or fecalblood, mucus, or both
	2 Very soft feces
	3 Watery diarrhoea
Weight loss	0 Normal
	1 Slightly increased (2-3 times/day)
	2 Moderately increased (4-5 times/day)
Weight loss	3 Severely increased (>5 times/day)
	0 None
	1 Mild (<5% loss)
Weight loss	2 Moderate (5-10% loss)
	3 Severe (>10% loss)

Table 2. Means of CIBDAI Scores (Jergens *et al.*, 2003)

0-3	4-5	6-8	9 and more
Clinically non-significant disease	Mild IBD	Moderate IBD	Intensive IBD

Table 3. Qualitative evaluation of endoscopic mucosal appearances (Slovak *et al.*, 2014)

Appearance	Score	Description
Friability	0	Absent
	1	Mild bleeding to touch
	2	Marked bleeding to touch
Granularity	0	Normal mucosal texture
	1	Mucosal texture increased
	2	Marked mucosal texture
Erosions	0	Absent
	1	Only few erosions
	2	Diffuse erosions
Lymphatic dilatation ^a	0	Absent
	1	Focal-multifocal white foci
	2	Diffuse white foci

^aDefined only during endoscopy

Classical Treatment

Medical treatment for induction of clinical remission is largely based on anti-inflammatory drugs (corticosteroids) and dietary management (Minamoto *et al.*, 2015). Jergens *et al.* (2010) carried out the first randomized-controlled trial evaluating the efficacy of prednisone versus prednisone and metronidazole in combination in dogs with IBD. The recovery ratio was similar in both treatment groups after 21 days. In addition, both treatment protocols caused significantly decreased mean C-Reactive Protein (CRP) concentrations post-treatment. However, the magnitude of CRP reduction was greatest in dogs receiving prednisone monotherapy. The results

of the study showed that oral prednisone immunotherapy was as effective as combined treatment with prednisone and metronidazole in the treatment of canine IBD.

In addition, recent studies focused on the close relationship between the GI microbiota and the host. Because, alterations in the GI microbiota (dysbiosis) has been determined in dogs with chronic GI inflammation as well as humans. This kind of changes and the status of GI microbiota are very important the therapy and the health status. Additionally, it was reported that histolytic ulcerative colitis in dogs has been associated with adherent and invasive *Escherichia coli* and fluoroquinolone antimicrobial treatment was frequently effective (Minamoto *et al.*, 2015).

Table 4. Objective criteria for histopathological evaluation of IBD in dogs (McCann *et al.*, 2007)

Epithelium (surface)	
Presence of bacteria/fungi	None noted +++
Integrity of epithelium	Normal or abnormal (if abnormal description of change and severity graded, + +++)
Goblet cell differentiation	None noted +++
Mononuclear (or other) cell trafficking	None noted +++ (and description of cell type)
Lamina	
Haemorrhage, congestion or oedema	None noted +++
Fibrosis	None noted +++
Cellular infiltration	Normal numbers +++ (and description of cell type)
Crypts	
Uniformity/symmetry	Symmetric or asymmetric
Deletion	None noted +++
Hypertrophy	None noted +++
Hyperplasia	None noted +++
Goblet cell differentiation	None noted +++
Mononuclear (or other) cell trafficking	None noted +++
Small intestinal villi	
Architecture	Normal or abnormal

Probiotics

Microbes in the GI tract have important roles for health in mammals. Intestinal microbiota provides a defensive barrier against pathogen agents, helps the digestion, stimulates the immune system and gives a nutritional support to enterocytes. Also, dysbiosis, alterations of GI microbes and presence of particular pathogen species (*Clostridium perfringens*, *Salmonella spp.*, *some viruses* and *parasites*) are associated with many GI disorders such as idiopathic IBD in dogs. Therefore, definition of specific microbial community entero types may open up new therapeutic approaches to companion animal health, by designing or prescribing appropriate diets for specific disease phenotypes (Suchodolski *et al.*, 2012).

Many researches have been evaluated harmful effects of microorganisms in GI disorders. However, there is a tendency to investigate helpful effects of beneficial bacteria. Recent studies defined the good effects of probiotics to manipulate the normal intestinal flora (Khor *et al.*, 2011).

Intestinal flora has a regulatory function to the inflammation and this function is probably lost or insufficient in IBD. Researches showed that probiotics may be helpful for restoration the microbial homeostasis in intestines (Khor *et al.*, 2011).

Khor *et al.* (2011) reported that a probiotic formulation caused a significant increasing of IgA levels in infants and probable enhancement of the intestinal mucosal resistance. Bibiloni *et al.* (2005) reported that a probiotic preparation (VSL#3) consisting of a mixture of eight lactic acid bacterial species (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii subsp. bulgaricus*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, *Streptococcus salivarius subsp. thermophilus*) is quite effective in maintaining clinical remission in UC. In another study, VSL#3 and kefir have provided

significant recover in the intestinal mucosa of rats with induced IBD (Arslan *et al.*, 2009).

In addition to human and experimental animal studies, although probiotics are used in veterinary medicine (especially in small animal practice) for a long time, there are few data regarding effects of probiotics in dogs. Suchodolski *et al.* (2010) showed that significant differences of the mucosa-adherent duodenal microbiota were observed between dogs with idiopathic IBD and healthy dogs. Rossi *et al.* (2014) investigated comparative effects of a commercial product (VSL#3) that is used in human CD and UC cases and contained different strains of *Lactobacillus*, *Bifidobacterium* and *Streptococcus* and combination of corticosteroid and metronidazol for the treatment IBD in dogs. The results showed that high dose probiotic combination was effective for clinical and histological recovery of IBD and normalization of symbiosis.

Arslan *et al.* (2012) evaluated therapeutic effects of probiotic bacteria, in comparison with single supportive and symptomatic therapy, in canine parvovirus infection. Only supportive and symptomatic therapy was applied in group I, whereas VSL#3 was used as adjuvant oral therapy in the group II. The study indicated that probiotics have been shortened the recovery time, under optimal care conditions.

Budesonide

Budesonide is a non-halogenated glucocorticoid that was developed for IBD in humans. Budesonide has fewer side effects than systemic corticosteroids. In dogs budesonide is used for treatment of allergic dermatitis (topically), chronic inflammatory airway disease (aerosol) and IBD. But there is no controlled studies evaluating the efficacy of oral budesonide treatment for canine IBD (Dye *et al.*, 2013). According to Pietra *et al.* (2013), budesonide can rapidly absorb and metabolize

in dogs with IBD. The drug gradually accumulated and it is shown an adequate therapeutic response and no adverse effects occurred.

In another study, 40 dogs were divided into two treatment groups. One group treated with prednisone and second group treated with budenisonone. After 3 weeks, complete blood count, biochemical profile and urinalysis were examined. Gastrointestinal endoscopy and biopsies of the intestine with histopathology were performed at Week6. Thereseults showed that budisonide is 15 times more potent than prednisolone and may be an effective alternative to prednisone therapy (Dye *et al.*, 2013).

In contrary, Rychlik *et al.* (2016) reported that budesonide was not effective for treatment of IBD in dogs. The tested drug failed to alleviate clinical symptoms of the disease, decrease the CIBDAI scores or improve the macroscopic appearance of intestinal mucosa. The highest efficacy of budesonide treatment was observed in the histopathological picture of duodenal, jejunal and colonic mucosa.

Mesenchymal Stem Cell Treatment

Mesenchymal Stem Cells (MSCs) are isolated from various adult tissues and can modulate the immune system. Also, MSCs cause the inhibition of release of pro-inflammatory cytokines (TNF- α , Interleukin (IL)-1 β , IL-6 and interferon) and support the damaged cells, after in-vivo administration (Uccelli *et al.*, 2008).

The application of MSCs is recent concept in treatment of IBD in humans. This technique enhances epithelial proliferation and coordinate re-modelling during the healing process. MSCs have been used in animal model of colitis successfully in pre-clinical studies (González *et al.*, 2009). MSCs have shown immunomodulatory and anti-inflammatory effects in experimental colitis and successful clinical results have been achieved in humans with CD and UC (Pérez-Merino *et al.*, 2015).

Also, MSCs is one of the current therapies in canine IBD. In veterinary medicine, a recent study of the use of intravenous MSC therapy in spontaneous feline enteropathy was showed a positive and safe clinical response (Pérez-Merino *et al.*, 2015).

In another study, MSCs were obtained from abdominal adipose tissue and used for treatment of IBD in dogs. The study showed that after 2 weeks of therapy, digestive symptoms (vomiting, diarrhoea, soft stools) disappeared and all animals increased activity, appetite and started gaining weight (González *et al.*, 2009).

Thelper-17 (Th17) cells are a group of T helper cells and cause the secretion of cytokines that are members of IL17 family. IL17 cytokines are very important in the inflammation process and promote the production of other pro-inflammatory cytokines, chemokines, hematopoietic growth factors and prostaglandins. Th17 cells have been defined in various inflammatory and autoimmune disorders such as CD, multiple sclerosis,

rheumatoid arthritis and psoriasis. Th17 cells consider as responsible for morbidity and mortality of those diseases (Kol *et al.*, 2016).

There are experimental studies regarding determination exact pathways, inhibition of Th 17 polarization and development of potential application protocols to direct therapeutic targets in dogs. The results showed that MSCs may inhibit Th17 polarization in animal models (Kol *et al.*, 2016).

Chondroitin Sulfate and Prebiotics

Chondroitin Sulfate (CS) is a natural glycosaminoglycan existing in the extracellular matrix and utilized as a substrate by the bacteroid inhabitants of the colon. CS inhibits pro-inflammatory cytokines that producing high levels and characterized by the 'hyper activation' of immune effector cells via their toll-like receptors, particularly macrophages and causing colonic mucosa damage in IBD (Rubinstein *et al.*, 1992; Linares *et al.*, 2015).

Prebiotics are non-digestible food ingredients which support health and helpful for selective stimulation of beneficial bacterial growth (one or limited number of bacteria) in the colon (Geier *et al.*, 2007). Prebiotics could reduce intestinal inflammation, oxidative stress and gut symbiosis (Segarra *et al.*, 2016).

Therefore, there is a new approach with oral CS and prebiotics for the treatment of canine IBD. For instance, Segarra *et al.* (2016) used a dietary supplement containing CS and prebiotics in dogs with IBD over 180 days. The study showed that long-term oral administration of the combined administration of the supplement with hydrolyzed diet was safe and beneficial for treatment of IBD in dogs.

Polyphenols

Polyphenols are the secondary plant metabolites which are only present in vegetables and fruits. Apple, bilberry anthocyanin, curcumin, green tea, naringenin, olive oil, pomegranate and ellagic acid, quercetin and resveratrol are regarded as the most commonly used polyphenols (Farzaei *et al.*, 2015). They have antioxidant, anti-inflammatory and immunomodulatory biological effects. In addition, polyphenols have marked ability to modulate inflammation (Biasi *et al.*, 2011). Investigations showed that dietary polyphenols possessed protective properties against various chronic diseases, including cardiovascular and degenerative diseases, diabetes, osteoarthritis and gastrointestinal diseases (Farzaei *et al.*, 2015). In addition, studies on experimental models indicated that polyphenones were able to reduced colonic injury (Biasi *et al.*, 2011). Polyphenones as dietary supplements can metabolite and help to improving intestinal microbiota and suppressing the inflammatory reactions in the intestinal lumen. Recent years, polyphenones have been revealed for the treatment of IBD in humans (Farzaei *et al.*, 2015).

Infliximab and Biosimilars

The introduction of biologic therapeutics for treatment of IBD has significantly improved recent years. However, their use is associated with much higher cost compared with traditional treatment options. Therefore, new studies have been carried out regarding cheaper and practical alternatives to biologic therapies. Biosimilars, which are a biologic therapeutic products, similar to the licensed reference product in terms of its quality, safety and efficacy, are getting popular for IBD (Kang *et al.*, 2015).

TNF- α is a pro-inflammatory cytokine and associates many chronic inflammatory autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, CD and UC (Kang *et al.*, 2015). Infliximab (IFX), a biologic TNF- α antagonist, is effective for treating patients with CD and UC (Van de Castele and Gils, 2015). After the expiration of the patent on IFX, its biosimilars are now available in the market. The first biosimilar of IFX, CT-P13 was developed by Celtrion, Inc. (Republic of Korea) and authorized in Europe in September 2013 (Sieczkowska *et al.*, 2016).

CT-P13 were used a case series to indicated the clinical efficacy, safety and inter changeability in the treatment of IBD compared with its originator. As a result, the researchers reported that CT-P13 may have biosimilarity and interchangeability with its originator in IBD (Kang *et al.*, 2015).

Edible Ginger-Derived Nanoparticles

Ginger, the rhizome of *Zingiber officinale*, is a widely used natural product. It is consumed as a spice and used as a medicine for the treatment of digestive tract problems like nausea, colic, flatulence, diarrhoea and dyspepsia. In addition, ginger and its active components, including 6-gingerol and 6-shogaol, are anti-oxidative, anti-inflammatory and anti-cancer agents. Recent studies showed that that nanoparticles derived from edible ginger (GDNPs 2) could be a natural and safe alternative for treatment of intestinal inflammations (Zhang *et al.*, 2016).

Conclusion

IBD is a very important health problem for either human or veterinary medicine. Due to unclear etiopathogenesis and obligatory life-long treatment, the disease seems to a big black hole. In addition, there is a big dilemma, while a life-long treatment is necessary, this classical treatment receipts can cause life-threatening risks in patients, such as malignancy and lymphoma. Therefore, new, safe, easily accessible and cheap treatment alternatives should be improved for animals as well as humans in IBD.

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Author's Contribution

Handan Hilal Arslan: Designed, wrote, developed and published the manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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