Journal of Veterinary Science & Animal Husbandry
Volume 8 | Issue 1
ISSN: 2348-9790

Review Article Open Access

An Adjuvant Approach to Alleviate Reoccurring or Treatment Resistant Symptoms of IBD in Companion Animals

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Citation: Bottley A (2020) An Adjuvant Approach to Alleviate Reoccurring or Treatment Resistant Symptoms of IBD in Companion Animals. J Vet Sci Ani Husb 8(1): 105

Received Date: March 09, 2020 Accepted Date: August 12, 2020 Published Date: August 14, 2020

Abstract

Inflammatory bowel disease (IBD) is a common yet distressing condition afflicting tissues of the gastrointestinal (GI) tract in companion animals; symptoms include vomiting, diarrhoea, loss of appetite and weight loss. Pathogenesis of IBD may link to both diet and parasitic or bacterial infections of the gut. Although current treatments may provide some relief to the animal, unfortunately recurrent flaring of symptoms is not uncommon. Therapeutic interventions available to the veterinarian include those that focus on treating any underlying infection and or a change in diet, both employed with the aim of reducing inflammation. It is thought that pro-inflammatory genes such as TNFα drive the symptoms of IBD and it is therefore not surprising most treatments target these proteins. However, given that recurrence is common during or after treatment, it is likely that a complex polygenic network of genes also contributes to promote or maintain aberrant immune signalling within the gut. In order to limit flare-ups, it may also be necessary to target different aspects of the immune system linked to IBD e.g. VCAM / TNFα / IL-8. Interestingly recent research originating from a number of groups has identified that bio actives present in fruit obtained from the genus *Cucumis* may act on these genes. Additionally, *in-vivo* canine clinical trialling has identified extracts derived from *Cucumis* may stimulate beneficial responses in inflamed ileus tissue in IBD afflicted animals; effects confirmed using histopathological tests. Collectively this data suggests that a combination of existing treatments together with adjuvant treatments may be more efficacious for animals presenting with IBD.

Keywords: Inflammatory bowel disease; Adjuvant; *Cucumis*

Introduction

New strategies for treating inflammatory bowel disease (IBD) have achieved some success in recent years. Therapeutic targets have been identified and proof of concept research has been translated into clinical success for both humans and companion animals. A once difficult to treat condition is now manageable for most patients and although may not be curative, symptoms can be managed to some degree through the implementation of an appropriate treatment plan. However not all interventions are successful and after recovery, relapses are common. Current treatments for human IBD are focussed on inhibiting the activity of the pro-inflammatory signalling protein TNFα, although the relationship between TNFα and IBD is complex [1]. Similarly, a number of widely used veterinary treatments for this condition also act on TNFα [2].

In addition to proteins such as TNFα it is likely there exists a network of ancillary genes and pathways that collectively or individually act to exacerbate the symptoms of IBD. Genome-wide association studies (GWAS) together with meta-analysis has collectively identified in excess of 200 distinct loci that correlate with IBD [3,4], suggesting a complex polygenic condition with many different risk factors. A number of associated variants identified in screening correlate with expression changes in response to immune stimulus [3], functioning as both positive and negative regulators of the immune response. It has yet to be fully established how genes identified via genetic analysis link with current therapeutic targets such as TNFα, however this data may be useful in establishing a more personalised approach to treatment.

Although primary treatments for IBD have met with some success, effectiveness varies on a patient by patient basis; it could be hypothesised that targeting secondary targets or sub-pathways would further improve clinical outcome. Recent research conducted using extracts sourced from plants of the genus *Cucumis* have reported effective downregulation of IBD ancillary genes [5]; it should be noted that to date these effects have been reported for one study and additional confirmatory research is needed to determine the extent to which genes linked to IBD may be regulated by treatment. Interestingly, preliminary results from *in-vivo* testing suggest amelioration of pathogenesis of IBD; effects of treatment include the reversal of IBD induced damage to the GI tract mucosal membrane structure. Collectively therefore targeting these genes may provide benefit to animals suffering from chronic IBD.

IBD in Animals

Companion animal species including dogs and cats may develop chronic inflammation within the gastrointestinal tract (GI). Although comparative differences have been recorded in GI tract physiology e.g. rates of motility and gastric or intestinal pH [6], symptoms of IBD remain similar in animals and humans. IBD in animals may be defined by persistent symptoms induced by chronic irritation of the GI tract tissue, leading to recurrent vomiting, diarrhoea and reduced appetite [7]. IBD is classified by veterinarians depending of the site of inflammation within the GI tract and the cell type linked to pathogenesis.

Research into the causes of IBD has identified hypersensitivity responses provoked by a range of different antigens (e.g. bacteria); responses that occur within the intestinal lumen or mucosa [8]. Although there is no specific link between IBD and age, sex, of the animal, it presents more frequently in some canine breeds such as German shepherds and specific breeds of cats [9]. This may not be surprising, different breeds possess different anatomical and physiological GI tract characteristics [10] e.g. transit time through the intestine, features which may determine either susceptibility to IBD and or explain relative severity of symptoms [11]. Variation in GI tract morphology may therefore link to breed susceptibility; as yet however, no conclusive evidence has been presented linking animal size with IBD. It could be suggested that genetic variation at loci associated with IBD-associated genes could also explain prevalence among breeds e.g. German Shepherds [12]. However, the identification of any genetic component linked to an aberrant immune-response may allow for new breed optimised strategies for treatment.

Prevalence in Animals

IBD is a commonly reported condition in companion animals such as canines, and symptoms can negatively affect quality of life [7]. It is therefore unsurprising that IBD results in both animal owner distress and is responsible for a large number of veterinarian consultations. Although symptoms are alleviated to some degree by existing treatments, some discomfort can remain and may be refractory to additional treatment. The causes of reoccurring or treatment resistant symptoms in treated animal cohorts are to date not obvious, however recent research suggests environmental factors such as diet may be in-part responsible [13].

Secondary Drivers of Disease

In order to better understand conditions under which recurrent or treatment resistant symptoms of IBD may occur e.g. symptoms not directly due or alleviated by the targeted mechanism of action being treated, it is important to understand those secondary processes that occur within the GI tract that link with disease. Our current understanding of IBD suggests a model in which symptoms and the result from dysregulated hypersensitive responses to bacteria or other immune-stimulants such as parasites present within the GI tract [8]. The GI tract may play host to many different organisms and accordingly a number of different local immunological pathways are engaged to scan and monitor for potential threats; responses which if incorrectly regulated may lead to a hypersensitive effects [14]. It is thought that the pro-inflammatory mediator TNFα may act as a central conduit in this process, converging different aspects of the immune system into a unified response, thus placing this signalling protein at the centre of IBD pathogenesis.

Inhibiting TNFα has proven effective as a therapeutic strategy for treating IBD in humans. However, immunogenicity, cost, safety profile and duration of treatment are all factors that can determine treatment recommendations in veterinary medicine. First line treatment options available to clinicians may not therefore be suitable for veterinarians. Testing diseased tissue has also identified different pathways in play, such as those linked to IL-8 and VCAM, these also contribute to pathogenesis; it is likely that the activity of these genes should also be considered alongside TNFα.

VCAM-1 has been implicated in a number of different immunological disorders [15]. This protein is a member of the cell adhesion molecule family which acts to facilitate the adhesion of immune cells such as lymphocytes and monocytes to the vascular endothelium [15]. Upon cell binding, VCAM activates endothelial cell signal transduction thereby altering endothelial cell shape allowing leukocyte migration [16]. Microvascular expression of VCAM-1 is upregulated in human patients afflicted with IBD and links with chronically inflamed micro-vessels; ultimately the effect of leukocyte recruitment mediated by VCAM-1 is continued or exacerbated symptoms of IBD [17]. Interestingly Gu *et al.* (2017) noted increased expression of VCAM-1 in biopsied colonic tissue from patients in remission yet reporting subsequent flaring; VCAM may therefore function in events that lead to recurrence of symptoms after treatment [18]. Suppression of VCAM may present as an option to prevent or limit the severity of flare-ups in animals after treatment.

Interleukin-8 (IL-8) is a cytokine produced in a range of cells types [19]. Unlike other members of the interleukin family, this protein has target specificity acting to attract neutrophil cells [19]. Neutrophils are known to accumulate in inflamed mucosa [20] and as Neutrophils are among the first immune cells recruited to the site of inflammation it is thought that this may at least in-part initiate signalling leading to the progression of disease [20]. Neutrophils cells however are also essential in the resolution of inflammation and if dysregulated, can lead to a positive feedback amplification of the immune response. TNFα is known to induce IL-8 expression in some cell types [21]; therefore, initiation via TNFα may lead to symptoms independent of TNFα i.e. driven by IL-8 feedback alone. These effects could at least in-part explain persistence of disease after treatment with agents targeted at TNFα and suggest that strategies for ameliorating IL-8 may be useful adjuvants when used alongside existing treatments.

Collectively, published data suggests members of the VCAM / TNFα / IL-8 (via Neutrophil) axis can function either collectively or independently to drive pathogenesis of IBD and contribute to flare-ups or reoccurrence of IBD symptoms after treatment.

Primary Treatment Options For IBD

The primary aim of treatment is to reduce symptoms such as diarrhoea and vomiting while restoring appetite and importantly decreasing inflammation within the GI tract (see msdvetmanual.com for a treatment overview). As IBD is commonly linked to parasitic or bacterial infection, a first step in any treatment program may include agents targeted at these pathogens e.g. Fenbendazole or Tylosin; treatments aimed at ameliorating cause of disease. Fenbendazole drug is effective against a range of gastrointestinal parasites [22], while Tylosin is an antibacterial feed additive [23].

The design of any treatment program may vary depending on the site of the inflammatory response (see msdvetmanual.com for a detailed description of treatment options). Steroidal treatments have shown some success when IBD presents in either the large or small intestine [24]. Corticosteroids influence the expression of many different pro-inflammatory pathways, including TNFα [25]. However, research has shown TNFα levels may be refractory to treatment with corticosteroids depending on cell type. Key IBD linked cell types such as Mast cells show expression of TNFα refractory to treatment with corticosteroids [26], and as mast cells function as a surveillance system for pathogens it is unsurprising that their activity is a feature of IBD linked to infection [27]. Targeting TNFα using corticosteroids may however have limited success due to retained mast cell signalling. Unfortunately, steroidal interventions may also result in adverse side-effects including vomiting and diarrhoea rendering any treatment counterproductive (see msdvetmanual.com).

When inflammation due to IBD is limited to the large intestine, other anti-inflammatory treatments become viable options e.g. drug such as Sulfasalazine which also inhibit TNFα via its receptor [28]. It should be noted that in companion animals, the use of this drug is limited to canines; feline specific toxicity is a limiter for its use in cats. In addition to administering anti-inflammatories, it may be desirable to also cycle-in treatments options to suppress the immune system, however unless the initiator of the hypersensitive immune response e.g. parasite or bacterial growth has successfully been treated, it is unlikely this strategy will be successful.

As the pathogenesis of IBD may also link with diet, a change in food may also be recommended. Veterinarians may recommend sequentially excluding certain types of feed and or a switch to hypoallergenic alternatives (see msdvetmanual.com). Changes in diet may include different sources of protein and or levels of fibre; decisions that depend on the type of IBD diagnosed. Although a relatively easy method of intervention, changes in diet can yield some success. This however may depend on the severity of IBD [29].

Cucumis Sativus L Extract as an Adjuvant for IBD

Cucumis sativus L. (Cucumber) is a widely cultivated crop species. Cucumber fruit contain many different phytonutrients such as flavonoids [30]; compounds that possess known antioxidant and importantly anti-inflammatory properties [30]. Patil *et al.* (2012) sought to elucidate if treatment with a water based extract of this fruit would result in beneficial or restorative effects in an acetic acid induced colitis rodent model; interestingly this research established that the immune-suppressive effects demonstrated *in-vitro* [31] ameliorates induced GI tract inflammation *in-vivo*; reported reductions in areas of ulceration, in addition to reduced neutrophil infiltration.

Preparations consisting of water/ethanol extract of *Cucumis sativus L.* have also recently been tested by Bernardini *et al.* (2018) for effects linked to the suppression of inflammatory responses associated with IBD in a porcine cell-based model (Aortic Endothelial Cells). *In-vitro* testing of *Cucumis sativus L.* identified decreased secretion of the pro-inflammatory cytokine IL-8, alongside elevated levels of the protective Hemeoxygenase (HO)-1 protein [5]; HO-1 protein has been shown to mediate anti-inflammatory and anti-apoptotic effects in a number of studies [32]. This model is highly relevant to IBD. Endothelial cells (ECs) are the major constituent of the microvasculature that line blood and lymphatic vessels in the GI tract. These cells are highly sensitive to elevated levels of IBD related cytokines and they may also respond by secreting IL-8 [33]. Interestingly follow-up research has identified suppressive effects on levels of expression of both TNFα and VCAM in a lipopolysaccharide induced inflammation model after treatment with *Cucumis sativus L.*; data also obtained using the porcine aortic endothelial cell model [34].

Cucumis Sativus F. Extract as an Adjuvant for IBD (Cuvrex™)

Interestingly, additional *in-vitro* testing has identified suppressive effects on the expression of pro-inflammatory genes after treatment with extracts prepared from *Cucumis sativus F*; data obtained from a canine trial to determine effects on markers of inflammation present in faeces [35,36]. A further *in-vivo* study, a 90-day open-label evaluation has since been undertaken to evaluate the effects of *Cucumis* extract (marketed by Naturalea as Cuvrex™, see 37, pers. Comm.) on inflammation-linked blood-borne and histological markers in canines (see www.naturalea.ch, unpublished). Dogs were randomized into two groups; the extract (Cuvrex™) group (n = 15) received 1 capsule of extract for 60 consecutive days; the control group (n = 15) received a placebo treatment. Biopsy specimens were obtained directly from mucosal lesions of increased granularity, friability, or erosions as well as areas of normal-appearing mucosa. Treatment with Cuvrex™ alleviated a range of IBD related markers in a number of test subjects, including in those cases presenting as idiopathic IBD with no previous response to any therapeutic protocol. The most significant aspect of this trial is the partial structural repair of mucosal damage after treatment (Figure 1); relative improvements in the morphology of the intestinal villi were observed in animals treated with *Cucumis* extract when compared to the untreated control group. This suggests damage resulting from long term chronic IBD may be reversed to some degree by the effects of bio-actives present in this extract.

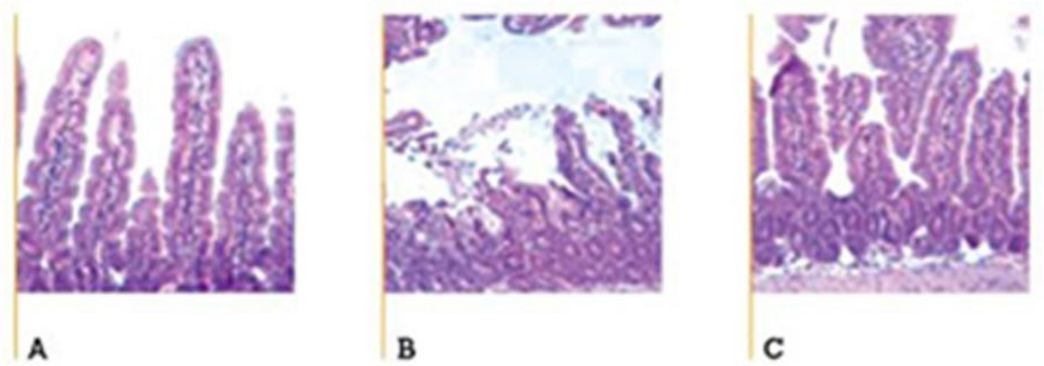

Figure 1: Curvex and reduction of the histological and structural damage of the inflamed intestine **(A)** normal ileus; **(B)** inflamed ileum; **(C)** inflamed ileum treated with Cuvrex

Conclusion

It is highly likely that some new adjuvant approaches to treatment may enhance existing therapeutic effects, limiting flare-ups and recurrent symptoms currently refractory to treatment. Combinatorial benefits may be due to additive suppressive effects on genes such as TNFα, and or via effects on other pro-inflammatory pathways linked to symptoms of IBD. Preparations of *Cucumis sativus* have been shown to attenuate the effects of different drivers of IBD, effects confirmed by a combination of *in-vitro* testing and histological analysis of diseased tissue in canine test subjects. It should be noted that beneficial effects observed in canines resulted from treatment with this extract only. It will be interesting to observe the effects of combination supplementation alongside existing therapeutics targeting TNFα and other clinical therapeutics currently in development. It may be hypothesised that ameliorating a broader spectrum of pro-inflammatory pathways will better treat this condition.

Conflict of Interest

The author reports that he has received a prior research funding from Naturalea, although this funding is not connected with the development of Cuvrex™.

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