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Inflammation as a Potential Therapeutic Target in IBS

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<http://dx.doi.org/10.5772/66193>

Abstract

The pathogenesis of irritable bowel syndrome (IBS) has been intensively researched, and despite a long journey for unraveling all the structures and the pathways involved, it still remains partially obscure. Inflammation was the first to be hypothesized as a potential pathway for the pathogenesis of IBS. It remains a keystone in the complex machinery of the pathogenesis that is currently considered multifactorial. Elucidating the pathogenesis of IBS is crucial for a targeted therapy of the disease. In this chapter, we review information regarding gut inflammation in IBS, underlining some of the newest data or the cornerstones. Additionally, our aim was also to review treatment currently available and future perspectives regarding anti-inflammatory treatments for IBS. Newer techniques allow detection and research of mediators involved in inflammation, as well as their potential role to be targeted by pharmacological agents. Recent data supports not only further research of the newer agents that are currently being developed but also some of the available ones that do not have sufficient evidence. Emerging therapies that target inflammation are under evaluation, in trials. A multidrug or a multidisciplinary approach needs to be considered in some cases that fail to respond to current treatment.

Keywords: anti-inflammatory, inflammation, irritable bowel syndrome, IBS treatment, postinfectious

1. Introduction

Despite the intensive research on irritable bowel syndrome (IBS) is being conducted, the pathogenesis still remains partially obscure. Since the description of this syndrome, many researchers have questioned the cause of IBS, which is currently being considered as

multifactorial [1–3] with increasing evidence that support the concept [4, 5], since there are multiple mechanisms that could trigger the clinical complaints.

Not just one structure or system is involved in the occurrence of IBS, and there is a complex network already described and currently referred to as brain-gut axis [6–9] with multiple directions and ways to communicate or interrelate between these structures and paths [10] that are reflected also in the heterogeneity of the subtypes of IBS.

Although IBS is a functional gastrointestinal disorder [11] with no structural or biochemical abnormalities, there is some evidence suggesting that in some subtypes of IBS, inflammation might play a key role in generating a low-grade inflammatory response and a spectrum of symptoms that sometimes overlap with those of inflammatory bowel diseases in remission [12, 13], leading to difficulties in establishing the diagnosis in clinical practice.

In this chapter, we will review literature data concerning inflammation and its relation to IBS underlining some of the newest data or the key ones. Our aim was also to review treatment currently available and future perspectives regarding anti-inflammatory treatments for IBS.

2. Inflammation in IBS

Inflammation, defined as the answer of the immune system to various triggers, was first described by Celsus [14], who has assigned to it the four signs: *dolor* (pain), *rubor* (redness), *tumor* (swelling), *calor* (heat), and to which Rudolf Virchow [15] added *functio laesa* (functional impairment). All the characteristics that define inflammation are induced by a complex set of mediators [16]. In addition, the triggers that could initiate inflammatory responses are numerous and diverse [17]. The inflammatory responses may be acute or chronic [16, 17].

Inflammation was one of the first hypothesised causes of IBS [18]. Intestinal inflammation was proposed as a potential mechanism involved in the pathogenesis of IBS since 1960s, when Hiatt et al. [18] described mast cells in the muscularis externa of the terminal colon and cecum. Discovered by Paul Ehrlich, mast cells are the precursors of CD34+ hematopoietic stem cells [19]. Due to the diversity of functions of mast cells, they have been a cornerstone in the study of multiple conditions, being intensively researched in the last decades. Mast cells have multiple functions [20], some of them involving the gut: neuroimmune interactions, epithelial secretion and permeability, and visceral sensation [20, 21]. In addition, it can express receptors for several cytokines that are involved in immunity [19] or release key mediators [22]. Numerous studies assessed the presence and/or the role of mast cells in IBS [23–25]. There are also rigorous papers that reviewed studies investigating mast cells and/or the mast cell mediators in IBS [26].

Other types of mediators, such as immunoglobulin (Ig) E and atopia, have been investigated in IBS and linked to mast cells [27, 28]. Degranulation of mast cells and, subsequently, the release of mast cell mediators can also be induced by IgE [28]. There are few data regarding IgE levels in IBS. Vara et al. [29] showed higher levels of IgE in IBS compared with healthy controls.

Besides mast cells, there are data indicating that inflammatory cells are present in colonic mucosa in IBS patients [23]. They showed on colonic biopsies multiple types of cells such as neutrophils and T lymphocytes besides mast cells, all of which may support the role of the immune system in the etiopathogenesis of IBS [23, 30]. If most of the studies examined mucosa of the rectum [31, 32], there are few studies that assessed also the deeper layers of the enteral wall [33]. There is a complex local response when triggers are detected [16, 34].

The balance of pro-inflammatory and anti-inflammatory responses and the mediators that are involved in the complex interactions have also been the subject of many studies. There is evidence of sustained inflammation in IBS supported by numerous studies that have detected low anti-inflammatory cytokines in IBS patients [35] or others that found high levels of those pro-inflammatory ones or a misbalance of the pro- and anti-inflammatory cytokine proportion [36, 37]. The complex dialogue between the structures involved in maintaining the homeostasis includes interrelation of nervous, immune, and endocrine systems [30, 34], where a pivotal piece is the brain that governs the humoral and neurological systems [34, 38, 39], in a complex network with multidirectional communicating systems [10]. Not only the anatomical integrity but also the functional status of all the systems is of major importance [40].

Psychological factors can participate in this mechanism, maintaining a state of low inflammation [41]. Inflammation in the gut might be responsible also for hyperalgesia [42] present in some patients with IBS contributing to the maintenance of the complaints.

2.1. Postinfectious IBS

Postinfectious IBS (PI-IBS) is a more recently coined type of IBS, initially identified as post-dysenteric IBS (PD-IBS) [43]. PI-IBS is defined as a subset of IBS in which the onset of IBS symptoms develops after an infectious episode and was first described by Chaudhary and Truelove [43]. This entity was confirmed by other studies [44]. The incidence of PI-IBS varies between 4 and 32% [45–47]. More frequently, PI-IBS was described and studied after an enteral infection [44, 48]. Pathogens already recognized to be involved in enteral infections are the following:

- bacteria: *Campylobacter jejuni* [31], *Salmonella enterica* [45], *Shigella* [49], *Escherichia coli* [50–52], *Clostridium difficile* [53]
- viruses: *Norovirus* [50, 54]
- parasites: *Giardia lamblia* [50, 55], *Blastocystis* spp. [56], *Dientamoeba fragilis* [57]

This subset of IBS patients offers a strong support emphasizing the importance of inflammation as one of the main paths to IBS. Enteral pathogens may induce pathological changes [31]. Spiller et al. [31] reported an imbalance of the enteroendocrine cells and of T lymphocytes, these two being assessed by histopathological examination of the rectal biopsies of the PI-IBS when compared with controls. There can be at least three scenarios: a prolonged normal inflammatory response, an augmented pathological inflammatory response in these patients, or there is a certain group of patients with particular characteristics that have a higher susceptibility [44, 58–60]. Anyway, there is not yet a firm conclusion.

2.2. Barrier function

The gut barrier function is important in modulating the gut inflammation [26, 61]. The barrier has multiple roles and its integrity is essential for a normal functionality of the digestive system [61]. An impaired barrier could facilitate the passage of inflammatory triggers that might induce changes in the gut. An increased permeability of the barrier might expose various structures to antigen contact [31].

2.3. Cholinergic system

There is another important piece in the complex domino of Inflammation – the so-called “cholinergic anti-inflammatory pathway” [34, 62, 63]. We did not intend to review the data regarding this system as there are multiple reviews [34] that have already analyzed the evidence, but to find the studies that support the interrelation with inflammation in IBS. Dinan et al. [64] investigated several cytokines, such as interleukin (IL): IL-6, IL-8, IL-10, and the growth hormone in the two arms of the study. They found that only IL-6 and the growth hormone in the group of IBS patients were overproduced when compared with controls after the administration of pyridostigmine that might suggest the implication of the cholinergic system [64].

2.4. Low-grade inflammation

More and more data sustain the hypotheses of a low-grade inflammation in IBS [65–67]. The fine line between normal to a pathological inflammatory response is still difficult to set. There is a low-grade inflammation of the gut that has been already acknowledged and literature data supports the putative role of the low-grade inflammation in IBS [65–68]. Several articles addressed this issue, some authors investigated tissue samples [23], while others assessed blood or stool samples [69–72] in order to detect and determine the inflammation status in IBS patients.

There are already numerous studies that assessed erythrocyte sedimentation rate, C-reactive protein (CRP) from blood sample, fecal calprotectin, and/or lactoferrin in order to detect their presence in IBS and/or to calculate their predictive values [71–73]. Valuable information was provided by a meta-analysis, although that assessed their cut-off values in order to exclude inflammatory bowel diseases [74].

There are limited data regarding the presence of high-sensitivity CRP [69] in IBS, but results indicate that when compared with healthy subjects, levels of high sensitivity CRP are statistically significantly higher in IBS patients ($P < 0.001$) [69]. So literature data supports the presence of low-grade inflammation in IBS since the levels of high-sensitivity CRP, though were still within the normal range, were higher in IBS than in controls [69].

A similar situation is for calprotectin, which is used mainly for differential diagnosis of inflammatory bowel diseases [73], but there are also studies that showed increased levels of calprotectin in IBS patients when comparing the values of those of healthy controls [72].

In the search to quantify the levels of inflammation, many authors proposed various biomarkers, and others proposed multiple biomarkers such as a panel or a set of markers [75, 76].

2.5. Genes and inflammation in IBS

Genetic factors have also been suspected as being involved in the inflammation in IBS.

Regarding genes and polymorphism, there are several studies that have assessed gene polymorphism, of which IL-10 and α tumor necrosis factor are some of the ones that are being intensively investigated [77–79].

As for the other studies that addressed IBS, their findings are inconsistent since some of the studies that assessed IL-10 genotypes in IBS patients versus controls showed high-producer genotype for IL-10 had a lower frequency statistically significant in IBS than in controls ($P = 0.003$) [79], and other studies did not find statistically significant difference of IL-10 polymorphism in IBS patients [78]. Schmulson et al. [78] assessed two polymorphisms: IL-10 (-1082G/A) and α tumor necrosis factor (-308G/A) in IBS patients and compared them with controls. There were no statistically significant differences between IBS and controls regarding either of the two polymorphisms.

There are also other studies besides these that assessed single nucleotide polymorphisms and more complex studies such as genome-wide association studies [80].

2.6. New hypotheses

There is a growing interest in applying the latest techniques used in molecular biology also for the study of IBS, such as the study of microRNA—miRNAs [81], small interfering RNA—siRNAs [82] or new approaches such as meta-omics [83].

Recently, new directions have been proposed in the study of the etiopathogenesis of IBS [81, 84]. The role of stem cells has been already intensively researched [85, 86], even in inflammatory bowel diseases [87], but these potent cells have raised interest about their role or potential use in IBS.

Very recent data advances the hypotheses that intestinal stem cells might be involved in the inflammatory paths discussed in IBS [84, 88]. Due to their properties, stem cells not only are able to respond to pathogens but also may modulate the spectrum of answers by their secretory functions [84, 89]. These stem cells might also represent therapeutic targets [84], but future studies to identify a specific target, either structural or functional, of the stem cells are mandatory.

The scientific community is eager to develop and improve current technologies, both for identifying new therapeutic targets and also for new treatment.

3. Anti-inflammatory treatment

Treatment of IBS still represents a challenge for clinicians. Due to the marked heterogeneity of the IBS subtypes, we will address anti-inflammatory agents used or those with potential use in IBS. Considering the multifactorial etiology, there are authors who propose a treatment determined by the main pathological path that led to IBS [4]. Literature data are limited concerning pharmacological anti-inflammatory classes studied in IBS as well as for the number of the members of these pharmacological classes that were investigated. Since we cannot still establish the main cause that led to IBS, an etiopathogenetic treatment is not possible, and some are currently being developed; a main aim in the treatment of IBS still is to alleviate the symptoms [1]. Though there are few studies that assessed anti-inflammatory classes or members of these classes in IBS, there is an intensive research activity into unraveling new targets and new treatments [90]. There are ongoing trials [91] and research programs and networks [92] that bring valuable information for a deeper understanding of IBS.

4. Aminosalicylic acid agents

Since the discovery of 5-aminosalicylic acid agents (5-ASA) by Svartz [93] and afterward with their active properties being described by Azad et al. [94], these agents were intensively researched as well as used in clinical practice [95]. The 5-ASA derivates have been used in several inflammatory conditions such as the inflammatory bowel disorders [95]. There are already consistent data regarding the efficacy of 5-ASA in ulcerative colitis [95] as well as regarding their safety. The rationale for prescribing 5-ASA agents in IBS is represented by their anti-inflammatory properties and is the result of several mechanisms [96].

Article	Type of article	Conclusions
Min et al. [97]	Letter	In selected subgroups of IBS might be efficient
Törnblom et al. [98]	Commentaries	In selected subgroups of IBS might be efficient
Lazaraki et al. [99]	Review	Inconclusive regarding the use of mesalazine in IBS
Camilleri et al. [100]	Review	Inconclusive, though some studies show a positive effect on pain, results were not replicated by others
Xue et al. [101]	Letter	Inconclusive—analyzed impact of mesalazine on gut microbiota
Hanevik et al. [102]	Letter + pilot CT	Inefficient
Farup et al. [103]	Letter	Inconclusive – authors underline that Andrews et al. [108] did not analyze drop out patients in their study

Table 1. Articles reviewing the use of 5-ASA in IBS.

Though there are few original studies, there are also reviews that analyze the use of 5-ASA in IBS (Table 1). Literature data indicate that in certain group of patients such as those with

PI-IBS, especially the IBS with diarrhoea (IBS-D) subtype could benefit, at least for a certain period of the anti-inflammatory effects of this class (see **Tables 1** and **2**). Regarding the length of treatment, dosing, and schemes of treatment, there are few data in the literature, and there is no study to assess all of this. Future studies are required in order to configure an a priori set of features regarding what type of IBS patient is likely to respond to 5-ASA treatment, as well as the regimen and dosing.

Article	Type of article, type of IBS	Dose and time of treatment	Conclusions
Barbara et al. [104]	Placebo-controlled trial (CT), multicentre IBS	800 mg tid, 12 weeks	Mesalazine treatment was not statistically significant or more efficient than placebo ($P = 0.870$). In certain groups of patients, it might be useful.
Lam et al. [105]	CT, IBS-D	2 g/day—2 weeks, if tolerated 2 g bid—11 weeks	In certain groups of selected IBS-D patients, it might be efficient, although there is no clear evidence of it being useful.
Bafutto et al. [106]	Pilot study, IBS-D	Various dosing—in the fourth groups	May be useful in certain groups of patients.
Tuteja et al. [107]	CT, PI-IBS	1.6 g bid, 12 weeks	No statistically significant improvement of symptoms ($P \geq 0.11$) nor QOL ($P \geq 0.16$).
Andrews et al. [108]	Pilot study, IBS-D	1.5 g bid, 4 weeks	Significant improvement of pain.
Bafutto et al. [109]	CT, IBS-D	800 mg tid, 30 days	Significant improvement of total symptom score, inclusive of pain. ($P < 0.0001$)
Dorofeyev et al. [110]	CT, IBS, all subtypes	500 mg qid, 28 days	Statistical improvement of abdominal pain ($P < 0.01$) as well as some histopathological aspects.
Hanevik et al. [102]	Letter + pilot CT	800 mg bid, 6 weeks	Inefficient.
Corinaldesi et al. [111]	CT, IBS	800 mg tid, 8 weeks	Mesalazine significantly improved only general well-being ($P = 0.038$), having no significant statistic effect regarding bloating ($P = 0.177$), abdominal pain ($P = 0.084$), or bowel habits.
Preobrazhenskii [112]*	Study	4–6 g daily, not shown	Efficient.

*Articles in other languages (Russian) or full text could not be retrieved.

Table 2. Studies assessing 5-ASA agents in IBS.

4.1. Acetylsalicylic acid

Regarding the use of acetylsalicylic acid, we have identified just one study that assessed it in relation to IBS, but the purpose of the study was to determine if certain anti-inflammatory drugs could induce constipation [113]. In fact, the study assessed that the use of some anti-inflammatory drugs among acetylsalicylic acid was related to constipation. [113].

4.2. Mast cell stabilizers

Mast cell stabilizers (cromoglycate and ketotifen) have been tested in IBS, but there are very few literature data concerning this class of drugs. Also, the criteria used for diagnosing IBS were different; therefore, there is no uniformity when comparing these studies. Subsequent studies are mandatory in order to have the answer: which IBS patients are suited to a mast cell stabilizer treatment and what is the dosing, or what is a suitable regimen.

4.3. Ketotifen

Klooker et al. [114] investigated ketotifen, suggesting that it can reduce visceral hypersensitivity and improve the quality of life. Though there is just one study to investigate ketotifen in IBS patients, there has already been questions about its safety [115]. For certain other studies, to assess this class for IBS treatment is mandatory in order to grade the levels of evidence. Although there is just one study with positive results, we also consider encouraging these results [33], and we strongly feel that there are more therapeutic options that have not yet been explored.

4.4. Cromoglycate

Regarding cromoglycate, there are several studies that assessed it in IBS patients. Literature data suggest that they could have a beneficial role in certain groups of patients, especially in those who have also food allergies or intolerances (see **Table 3**). There are methodological issues concerning these studies; so in order to reduce some of the biases, rigorous parallel studies are needed.

Article	Conclusion
Leri et al. [116]	Efficient (in conjunction with dietary exclusions in IBS patients with food intolerance)
Stefanini et al. [117]	Efficient (in IBS patients with food intolerance)
Grazioli et al. [118]	Efficient (in pediatric IBS patients with food intolerance)
Stefanini et al. [119]	Efficient (in IBS patients with food intolerance)
Lunardi et al. [120]	Efficient (in IBS patients with food intolerance)
Paganelli et al. [121]	Inconclusive
Antico et al. [122]*	—
Stefanini et al. [123]	Efficient
Tomecki et al.* [124]	Inefficient

*Article in other languages than English (Polish, Italian) also could not be retrieved.

Table 3. Articles that assessed cromoglycate in IBS.

4.5. Montelukast

There is just one report of the use of montelukast in IBS stating a positive effect [125]. Considering the pathways that are involved in the pathogenesis of IBS, it seems reasonable that the authors proposed and used it. The wonder is that there are so few data regarding it, though there are data regarding IBS and allergies [29]. Montelukast might be an option for the patients who have IBS and allergic conditions, but there is a lack of studies to address this issue. Rigorous trials with such drugs are needed in order to conclude about their use in IBS.

4.6. Corticosteroids

Some authors even proposed corticosteroids as anti-inflammatory agents in IBS [126]. A short course-3 weeks, 30 mg prednisolone/day was administered to PI-IBS patients and compared with placebo. There was no statistically significant difference between the number of enterochromaffin cells between patients treated with prednisolone and those that received placebo ($P = 0.5$). Though for the reduction of the number of T lymphocytes in the lamina propria. Dunlop et al. [126] found a statistically significant difference that favors prednisolone, there was no improvement regarding several symptoms of IBS.

Due to their known side effects, one study investigated the impact of using oral steroids, showing that they do not have a higher risk for inducing IBS symptoms in adults under 40 years [127].

We conducted a search on PubMed search motor between 1–21st July 2016 using multiple strategies as seen in **Table 4**. There is just one study that assessed the corticoid therapy in IBS, though there are several authors who consider corticosteroids as a reasonable treatment option in certain subgroups of IBS patients (**Table 4**).

Strategy	Results	Appropriate	Inappropriate
"Corticosteroids, irritable bowel syndrome"	91	2 [127, 128]	89
"Corticosteroids, IBS"	64	1 [128]	63
"Prednisone, irritable bowel syndrome"	5	0	5
"Prednisolone, irritable bowel syndrome"	12	1 [126]	11
"Prednisolone, IBS"	5	1 [127]	4
"Budesonide, irritable bowel syndrome"	10	1 [128]	9

Table 4. Results retrieved by several search strategies on PubMed search motor.

4.7. Imunglobulin E antibody (Omalizumab)

There is just one study that addresses this issue [28], which presents a case of a patient that had concurrently IBS and asthma. The patient received an IgE antibody with a major improvement of IBS symptoms. These results suggest that in certain subgroups of patients with concurrent diseases as IBS and atopic status, or extra-intestinal symptoms, IgE antibodies might be useful.

5. Conclusions

Inflammation remains an important pathway involved in the pathogenesis of IBS. Despite the high interest in the field of functional gastrointestinal disorders, till now, researchers have not entirely discovered all the pieces of the complex puzzle that is the etiopathogenesis of IBS, or all of the components of the pathways that finally lead to IBS.

Newer techniques allow detection and promote research of mediators that are involved in inflammation, even in low amounts. Also, the new technologies are able to identify new structures, as well as their potential role to be targeted by pharmacotherapeutic agents.

Results suggest that there are potential pharmacological classes, alongside with potential therapeutic targets that deserve to be reassessed for IBS.

Recent data supports further research of the pathways and structures involved, as well as assessment of not only the newer agents that are currently being developed but also of some of the available ones that do not have sufficient evidence. Emerging therapies that target inflammation are under evaluation, in trials. A multidrug or a multidisciplinary approach needs to be considered in cases that fail to respond to current treatment or to a single therapy, heading toward the current trend, of a personalized medicine.

Abbreviations

5-Aminosalicylic acid agents: 5-ASA

Bis in die: bid

C reactive protein: CRP

Irritable bowel syndrome: IBS

IBS with diarrhoea: IBS-D

Immunoglobulin: Ig

Interleukin: IL

Quarter in die: qid

Quality of life: QOL

Placebo-controlled trial: CT

Postinfectious IBS: PI-IBS

Postdysenteric IBS: PD-IBS

Ter in die: tid

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