

## Possible therapeutic role of IgE blockade in irritable bowel syndrome

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**Author contributions:** Magen E and Chikovani T contributed equally to all aspects of this article.

**Conflict-of-interest statement:** The authors declare no conflicts of interest related to this publication.

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**Manuscript source:** Invited manuscript

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**Received:** July 19, 2016  
**Peer-review started:** July 21, 2016  
**First decision:** September 5, 2016  
**Revised:** September 23, 2016  
**Accepted:** October 27, 2016  
**Article in press:** October 27, 2016  
**Published online:** November 21, 2016

### Abstract

Omalizumab is a humanized monoclonal antibody that binds to the high-affinity type-I IgE Fc receptors on mast cells (MCs) and basophils, inhibiting the IgE immune pathway. Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder, and dysregulation of the immune system likely contributes to its etiology and/or symptomatology. Colonic biopsies from patients with IBS demonstrate considerable increase in the number of degranulating MCs releasing histamine in proximity to nerves, and this event may underlie the common IBS symptom of abdominal pain. Pharmacologic control of MC activation and mediator release is a current area of active interest in the field of IBS research. Recently, we and Pearson *et al* described 2 cases of patients with IBS with diarrhea (IBS-D) showing positive clinical response to omalizumab. In both cases, the female patients had severe, long-lasting IBS-D and achieved an almost complete resolution of IBS symptoms. Both patients were also able to discontinue all IBS medications after commencing the anti-IgE therapy. For both patients, the omalizumab treatment showed a relatively rapid onset of action, resembling the efficacy observed in and previously reported for patients with chronic spontaneous urticaria. In this Editorial, we discuss the possible biological mechanisms that may underlie the clinical efficacy of omalizumab in IBS. We suggest that there is a need for a well-designed prospective study to investigate the therapeutic effects of anti-IgE in IBS.

**Key words:** IgE; Omalizumab; Irritable bowel syndrome; Anti-inflammatory; Irritable bowel syndrome with diarrhea

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**Core tip:** Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder diagnosed. A growing body of research suggests that mast cells (MCs) releasing histamine in the colonic mucosa might contribute to the etiology and/or symptomatology of IBS. Blockade of the high-affinity type- I IgE Fc receptors on MCs by omalizumab has been observed as an effective therapy in 2 patients with IBS. We suggest that anti-IgE antibody therapy might be an attractive therapeutic option for functional bowel disorders.

Magen E, Chikovani T. Possible therapeutic role of IgE blockade in irritable bowel syndrome. *World J Gastroenterol* 2016; 22(43): 9451-9456 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i43/9451.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i43.9451>

## INTRODUCTION

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder, diagnosed in up to 15% of the worldwide population; yet, the underlying pathophysiology remains poorly understood<sup>[1]</sup>. According to the Rome III criteria, IBS is generally subtyped in relation to the domination of bowel habits, and includes IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS with both constipation and diarrhea, and IBS without constipation or diarrhea<sup>[1]</sup>. The etiology of IBS appears to be multifactorial, and no single therapeutic option has yet provided a satisfactory efficacy; consequently, IBS patients commonly express a high level of dissatisfaction with their current therapies<sup>[2]</sup>.

Stress in early life is now considered an important etiologic factor of IBS, as it has been suggested to promote higher visceral hypersensitivity and anxiety-like behaviors<sup>[3]</sup>. Early-life stress has also been demonstrated to be related to neuroendocrine-immune alterations in childhood, suggesting its ability to trigger inflammatory immune processes and place a child at risk for developing inflammatory diseases<sup>[3]</sup>. Moreover, stressful events have been shown to exacerbate symptoms of IBS in adults, thereby decreasing visceral pain thresholds and mucosal barrier function<sup>[4]</sup>.

One current hypothesis of the IBS pathophysiology is that IBS represents a disruption of the "brain-gut axis", in which early-life stress and psychiatric comorbidity stimulate low-grade inflammation and mast cell (MC) infiltration into the bowel<sup>[5]</sup>. The low-grade inflammation in IBS can further activate the hypothalamic-pituitary-adrenal axis<sup>[6]</sup> and may trigger elevations in the inflammatory cytokines [such as interleukin (IL)-6 and IL-1 $\beta$ , as well as tumor necrosis factor- $\alpha$  (TNF $\alpha$ )], despite the absence of visible signs of inflammation-triggering conditions, such as infection or wounds (*i.e.*, ulceration) in the gut<sup>[7]</sup>.

Another hypothesis is that immune response to food antigens may be responsible for development of the low-grade inflammation associated with IBS<sup>[8]</sup>. However, reports have indicated that most cases of IBS test negative for type 1 IgE-mediated food allergy-related serum-specific IgE (measured by skin prick and radioallergosorbent test)<sup>[9,10]</sup>; nevertheless, the studies yielding these findings have been based on questionnaires that otherwise indicated an increased prevalence of several forms of food intolerance and atopic diseases amongst the IBS patients investigated.

## IBS as an inflammatory disease involving MCs

Histological as well as serological studies of patients with IBS have demonstrated that low-grade inflammation is a common presentation, along with increased numbers of MCs and increased activation of MCs in the luminal mucosa<sup>[5,11-15]</sup>. Other studies have shown a correlation between the density of MCs in the luminal mucosa and the severity of abdominal pain in IBS<sup>[14,16]</sup>. Therefore, it is generally accepted that infiltration of colonic MCs and their release of inflammatory mediators in proximity to the mucosal innervation could contribute to the perception of abdominal pain in IBS<sup>[14]</sup>.

In patients with IBS-D, activation of MCs in the colonic mucosa has been shown to lead to raised levels of gut hormones, vasoactive intestinal peptide and substance P, ultimately causing the diarrheal condition<sup>[17]</sup>. Since histamine-mediated activation of its cognate H1, H2, H3 and H4 receptors can activate immune-neural signaling in the gut, these receptors represent promising drug targets for treatment of functional gut disorders<sup>[18]</sup>. In a prospective randomized study of IBS patients, the H1 antagonist ketotifen was found to significantly decrease abdominal pain and other IBS symptoms<sup>[19]</sup>. In addition, "intention to treat" pilot studies using other MC stabilizing drugs have provided encouraging clinical results<sup>[20]</sup>.

Degranulated MCs release several immune mediators, such as histamine, tryptase and prostaglandins, all of which influence enteric afferents through proteinase-activated receptors<sup>[21]</sup>. Thus, several pharmacological agents are under development to target MC development, maturation, homing and activation, and some have already shown encouraging results in IBS patients<sup>[22-25]</sup>.

## IBS and food hypersensitivity

While patients with IBS often relate their symptoms to food, a much smaller portion have been diagnosed with food hypersensitivity and have shown improvement on a food-elimination diet<sup>[26]</sup>. Foods frequently reported to provoke IBS symptoms include wheat/grains, milk products, spicy foods, coffee, vegetables, fatty foods and alcohol<sup>[27,28]</sup>. Nevertheless, no direct evidence has been reported in the publicly available literature to advocate that IgE-mediated type I allergic

reactions to food antigens play a *bona fide* role in the pathophysiology of IBS<sup>[29]</sup>.

Comparative studies of patients with IBS and healthy controls have found no differences in results of skin prick tests and immuno-detection of serum-specific IgE antibodies to food antigens<sup>[30]</sup>. Studies to determine the role, if any, of IgG/IgG4-mediated hypersensitivity in IBS have also been inconclusive<sup>[26,31]</sup>. However, colonoscopic allergen provocation test disclosed positive reactions to specific food antigens in most of patients with IBS who were tested<sup>[32]</sup>. It is generally accepted, however, that foods can evoke symptom-onset in IBS patients *via* immune activation or/and altered neuro-endocrine responses<sup>[31]</sup>.

Patients with self-reported food hypersensitivity have been found to have a high prevalence of IBS and atopic disease, along with elevated counts of IgE-positive cells in the duodenal mucosa<sup>[33]</sup>. The pattern of delayed immune reaction to several different foods has been described previously in patients with food intolerance<sup>[34]</sup>. It is possible, for this reason, that serum total and food allergen-specific IgE antibodies assays have a low diagnostic sensitivity in patients with IBS and IBS-like symptoms<sup>[35]</sup>.

Dietary interventions as a treatment strategy for IBS include dietary restriction of fermentable oligo-, di- and monosaccharides and polyols (FODMAPs) which are incompletely absorbed in the small intestine and later fermented in the colon. Although low-FODMAP diets have shown clinical efficacy in achieving symptom reduction for some IBS patients<sup>[36]</sup>, several trials have also shown that these diets are associated with marked reduction in beneficial microbiota (*i.e.*, gut flora with prebiotic properties)<sup>[37]</sup>. Moreover, several meta-analyses of food elimination-based clinical interventions have been unable to detect beneficial effects<sup>[38]</sup>, and dietary therapy of IBS remains a controversial area.

### **Prevalence of asthma and urticaria in patients with IBS**

Several epidemiological studies have demonstrated associations of atopy and asthma with functional gastrointestinal disorders<sup>[9,39-42]</sup>. Thus, it has been theorized that the shared pathophysiology between IBS and asthma may underlie the association between these two disorders, and a causal relationship may not exist.

There is limited data regarding the prevalence of urticaria in IBS. Recently, we found a strong association between IBS and chronic urticaria in a cross-sectional study of a large cohort (11271 patients; manuscript in press), although the pathophysiologic aspects of this association remain largely unknown.

### **Omalizumab**

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that binds to the IgE CH3 domain that lies near the binding site for the high-affinity type- I IgE Fc receptors. This binding neutralizes free

IgE and inhibits the IgE immune pathway on MCs and basophils, without causing sensitization of these cells<sup>[43]</sup>. This biologic has been licensed for use in severe allergic asthma and in severe antihistamine-resistant chronic spontaneous urticaria, and numerous clinical trials have shown encouraging results suggesting its clinical efficacy in several other allergic and autoimmune diseases<sup>[44]</sup>. The evidence indicating MC involvement in IBS pathogenesis suggests the therapeutic potential of anti-IgE antibodies in this disease in particular.

### **Clinical evidence of anti-IgE therapeutic efficacy in IBS**

There is a lacuna in the literature of studies examining a direct link between IgE and IBS. No clinical studies have been reported that investigate the potential efficacy of anti-IgE therapy in IBS. However, we<sup>[45]</sup> and Pearson *et al*<sup>[46]</sup> recently reported on two cases of positive clinical response to omalizumab in patients with IBS-D and concomitant chronic spontaneous urticaria and asthma, respectively. In both cases, female patients with severe, long-lasting IBS-D experienced an almost complete resolution of IBS symptoms and were able to discontinue all IBS medications after commencing the anti-IgE therapy. In both of these patients, the omalizumab therapy induced a relatively rapid onset of action that resembled the efficacy reported for it previously in patients with chronic spontaneous urticaria<sup>[47]</sup>. This finding, however, is very different from the onset of action reported for asthmatic patients, in whom the optimal benefit of omalizumab (with respect to symptoms) takes 12-16 wk<sup>[48]</sup>.

Based on these two case reports, we suggest that the role of IgE and anti-IgE therapy in IBS is worthy of further consideration. However - despite the impressive clinical success of omalizumab therapy that was achieved in the 2 patients with IBS-D cited above - it is very hard to make a generalized conclusion about the overall efficacy of anti-IgE therapy in IBS. To evaluate the role of an anti-IgE biologic-based approach for the treatment of refractory IBS, experimental prospective studies are needed on large numbers of patients with different clinical forms of IBS.

### **Potential mechanisms of anti-IgE therapy in IBS**

Along with the consideration of anti-IgE therapy for IBS, the consideration of how it would exert beneficial effects on such patients is necessary. The mechanisms whereby omalizumab could improve IBS symptoms are currently uncertain. IgE production occurs predominantly at mucosal surfaces<sup>[49]</sup>. IgE activation of mucosal MCs may regulate both the mucosal barrier and the composition of the luminal microbiota<sup>[50]</sup>. Generally, MC-derived proteases contribute to the immune deviation towards Th2 polarization, through the expression of Th2 cytokines<sup>[51]</sup>. Food allergens likewise induce a shift toward Th2 immunity and

sensitize the MCs by binding to their FcεRI receptors<sup>[52]</sup>. Monomeric IgE can enhance MC activity and mediator release<sup>[53]</sup>. Sensitization of MCs with monoclonal IgE stimulates up-regulation of genes encoding the inflammatory cytokines, chemokines, cytokine and chemokine receptors, adhesion molecules, anti-apoptosis proteins and cytoskeletal elements<sup>[52]</sup>. Moreover, it has been shown that a human monoclonal IgE can stimulate MCs to produce histamine-releasing factor<sup>[54]</sup>. Omalizumab, itself, has been shown to sequester monomeric IgE, thereby reducing its priming effect on MCs<sup>[53]</sup>.

Humanized anti-IgE monoclonal antibodies represent a new class of MC stabilizing agents, down-regulating FcεRI density on MCs and preventing their activation by IgE and subsequent mediator release. As MC activation and subsequent mediator release cause major IBS symptoms, pharmacological targeting of MCs by anti-IgE agents may provide an additional tool for the management of IBS.

## CONCLUSION

IBS is the most common functional gastrointestinal disorder diagnosed worldwide, and dysregulation of the immune system most likely contributes to its etiology and/or symptomatology. In elegant experiments employing colonic biopsy samples from patients with IBS, Barbara *et al.*<sup>[14,16]</sup> observed a substantial increase in the number of degranulating MCs releasing histamine in proximity to nerves that are correlated with abdominal pain in IBS. The role of therapeutic MC blockade, and in particular of the subsequent histamine release, in IBS is now an area of active research. While at present only one anti-IgE biological (omalizumab) is licensed, there is an expectation that more anti-IgE medications will enter the market soon. However, these medications are incredibly costly, partially due to their infancy in the overall pharmaceutical market and clinical care settings. Yet, these medications have shown promising initial results in a subset of IBS patients; although, as of yet, we do not understand the underlying pathophysiology. Unfortunately, anti-IgE therapy is not yet a *bona fide* treatment option, and it remains unknown whether it will eventually prove feasible in all patients with IBS. Those patients with atopy (and elevated serum IgE levels) may derive the most benefit from these medications. On the basis of the assessment provided herein, we suggest that further studies are needed to investigate effects of anti-IgE therapy in IBS.

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