Immunoglobulin E in irritable bowel syndrome: another target for treatment? A case report and literature review

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***Abstract*:** Irritable bowel syndrome (IBS) is notoriously difficult to treat and this situation is unlikely to change until the pathophysiology is better understood. There is no doubt that IBS is a multifactorial condition but it is likely that the relative contribution of the various factors involved varies from patient to patient. Consequently, in some individuals one mechanism may have such a strong effect that its elimination may lead to a substantial improvement in symptoms. This paper describes a patient with severe asthma and IBS where the administration of an anti-Immunoglobulin E (IgE) monoclonal antibody not only improved her asthma but also resulted in an almost complete resolution of her IBS symptoms. This observation suggests that some form of allergic process, which may be mediated by IgE, might be driving IBS in some patients and there is evidence from the literature that atopy is more common in this condition. Therefore, in patients with IBS and atopy where the response to standard treatment is poor, it may be worth considering targeting the allergic diathesis. Possible approaches include skin testing with food antigens followed by an appropriate exclusion diet or pharmacological mast cell stabilization.

Keywords: atopy, irritable bowel syndrome, omalizumab, Xolair

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Introduction

Irritable bowel syndrome (IBS) affects up to one in five people over their lifetime and is one of the most common gastrointestinal disorders encountered in primary and secondary care. It is a heterogeneous condition stratified according to the predominant bowel habit leading to three subtypes: IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D) and IBS with a bowel habit alternating between the two (IBS-A). In addition to abdominal bloating and pain, patients frequently complain of a variety of noncolonic symptoms such as low back pain, lethargy, nausea, bladder symptoms and chest pain, which is often referred to as noncardiac chest pain. The pathophysiology of IBS is still poorly understood but it is most likely mediated by a combination of mechanisms including inflammation, autonomic dysfunction, dietary and psychological factors. There have also been reports that atopy may sometimes be associated with IBS [Tobin *et al.* 2008].

Asthma is a chronic respiratory tract disease characterized by wheezing, shortness of breath and cough attributed to inflammatory-mediated bronchial hyperresponsiveness. Asthma is also a multifactorial disease with a variety of underlying phenotypes and pathophysiological mechanisms, with an immunoglobulin E (IgE)-mediated allergic response, being a well established factor in up to 70% of cases. Elevated IgE may dictate treatment options, though alone is not a marker of disease severity [Bousquet *et al.* 2005].

Case report

A 27-year-old woman was referred to the neurogastroenterology unit for an opinion on her progressively deteriorating abdominal symptoms over the previous 5 years. Bowel habit was characterized by diarrhoea alternating with constipation, and on occasions, she also suffered from episodes of faecal incontinence. She also experienced

colicky abdominal pain on a daily basis which was accompanied by abdominal distension requiring the regular loosening of clothing. She also suffered from lethargy, low back pain, nausea and bladder symptoms consistent with a diagnosis of irritable bladder. Previous investigations had revealed no significant abnormalities. She was treated with dietary manipulation, antispasmodics, antidepressants, analgesics and hypnotherapy but her condition failed to respond to any of these modalities. Her symptoms became so severe that she had to give up work.

Her only other comorbidities were severe asthma and allergic rhinitis, which she had had since childhood. More recently, her asthma had become progressively more severe requiring frequent hospital admissions and the use of oral corticosteroids. In addition, she had to abandon competitive athletics. Furthermore, she failed to respond to traditional measures for her asthma, including bronchodilators, inhaled as well as systemic steroids and leukotriene receptor antagonists. In view of the findings of significantly raised IgE levels between 570 and 800 KIU/liter (normal $<$ 200 KIU/liter) and her failure to make progress, she was offered treatment with omalizumab which is an IgE monoclonal antibody.

Omalizumab resulted in a considerable improvement in her asthma and to date she has required no further hospital admissions and an almost complete cessation of oral steroids.

Subsequently, at her last gastroenterology outpatient appointment, she reported that she had experienced an almost complete resolution of her IBS symptoms, was able to discontinue all IBS medications and remains well to date, 4 years after commencing the monoclonal antibody.

Discussion

This observation suggests that in a proportion of patients with IBS, IgE might be a contributory factor.

The role of atopy in IBS

The term atopy was first used in 1923 by Coca and Cooke and there is some evidence that this diathesis might be more common in patients with IBS and other functional gastrointestinal disorders [Coca and Cooke, 1923; Stefanini *et al.* 1992, 1995; Huerta *et al.* 2002; Cole *et al.* 2007; Powell *et al.* 2007; Jones *et al.* 2014]. A more recent survey of 30,000 UK primary care records, over a minimum period of 5 years, confirmed an excess of atopic conditions in all functional gastrointestinal disorders examined, with a prevalence of 44.8% in IBS compared with controls (32.7%) [Jones *et al.* 2014].

Previous literature has suggested that the higher prevalence of atopy in IBS is largely confined to the diarrhoea form of the condition [Dunlop *et al.* 2006]. However, in a survey of 519 consecutive patients with IBS attending our outpatient clinic, we also found an increased prevalence of atopy of 43.5%, but did not observe that this was necessarily confined to IBS-D. Of those with atopy, 27% had IBS-D, 34.5% had IBS-C and the remaining 38.5% had IBS-A.

Mast cells secrete a variety of biological amines which can have effects on both the gastrointestinal and respiratory tracts. It is, therefore, noteworthy that the role of mast cells in IBS is the focus of a considerable amount of recent research and that their degranulation can be precipitated by IgE [Barbara *et al.* 2002, 2004, 2007].

The role of IgE in IBS

IgE is known to play a central role in the pathophysiology of type I hypersensitivity reactions. Following initial contact with an allergen, dendritic cells present the allergen to antigen-specific T cells. In certain people, the T cells respond by releasing a variety of cytokines, stimulating the development of B cells which have the potential to produce IgE. The circulating IgE binds to receptors on the surfaces of both mast cells and basophils. Subsequent exposure to the allergen leads to the cross linking of IgE molecules on mast cells and their degranulation.

There is a paucity of literature examining a direct link between IgE and IBS, which is somewhat surprising considering how many patients claim to have a dietary allergy. There have been no recent studies examining serum IgE levels, skin prick and radioallergosorbent testing (RAST) in IBS patients and those that have been undertaken have produced conflicting results. However, it should be noted that these studies included very small numbers of patients who were poorly defined and therefore it is impossible to draw any firm conclusions [Petitpierre *et al.* 1985; Zwetchkenbaum and Burakoff, 1988; Barau and Dupont, 1990].

It has been suggested that increased intestinal permeability may have a role in the pathogenesis of IBS. Lillestol and colleagues have demonstrated an increase in small intestinal permeability in patients with atopic IBS compared with controls without atopic IBS, although there appeared to be no differences in gastrointestinal symptoms between the two groups. In addition to changes in duodenal permeability, they found significantly increased numbers of duodenal IgE-positive cells as well as raised serum IgE levels in the patients with IBS compared with controls [Lillestol *et al.* 2010]. These observations suggest that in some patients with food hypersensitivity and atopy, there might be an underlining IgE or mast cell mediated component to their symptoms. The role of mast cells in the pathophysiology of IBS has been more extensively investigated.

The role of mast cells in IBS

Mast cells have had an established role in allergic disease and are increasingly being implicated in the pathophysiology of IBS [Cole *et al.* 2007; Tobin *et al.* 2008]. The surface receptors present on mast cells enable the binding of IgE. Antigen binding mediates mast cell degranulation leading to the sequential release of inflammatory mediators. These include histamine, serotonin, proinflammatory cytokines and ultimately eosinophil recruitment in patients with asthma. Release of these mediators induces the hyperresponsiveness which results in the clinical manifestations associated with atopy. Mast cells are also known to release mediators which may affect enteric nerve and smooth muscle function, potentially offering a mechanism for some of the physiological manifestations found in IBS [Stefanini *et al.* 1992; Bousquet *et al.* 2005; Tobin *et al.* 2008; Lee *et al.* 2013]. There have been numerous studies reporting an increased number of mast cells throughout the gastrointestinal tract at various anatomical locations in all IBS subtypes [Libel *et al.* 1993; Guilarte *et al.* 2007; Laukoetter *et al.* 2008; Lee *et al.* 2008; Macsharry *et al.* 2008]. Mast cells have been implicated in intestinal mucosal barrier changes and increased mucosal permeability has recently been demonstrated to be associated with increased mast cell numbers specifically in patients with IBS-D [Lee *et al.* 2013].

Visceral hypersensitivity has long been implicated in the pathophysiology of IBS, although the precise mechanisms involved in this abnormality are not fully understood. There is growing evidence that mast cells may have an important role in visceral hypersensitivity and a positive correlation between mast cell numbers and abdominal pain severity has been shown in patients with IBS [Barbara *et al.* 2004]. Administration of a mast cell stabilizer, ketotifen, has been shown to reduce visceral sensation in patients with IBS compared with placebo [Klooker *et al.* 2010]. More recently, the mechanism by which mast cells might be involved in the pathogenesis of IBS has been further explored by Braak and colleagues. In a study assessing microscopic mucosal inflammation, visceral sensitivity and the stress response in patients with IBS and controls, they failed to show an increase in mast cell numbers in patients with hypersensitive IBS. They concluded that rather than mast cell numbers being important, their activation status and interaction with nerves might be a more significant mechanism [Braak *et al.* 2012]. This adds to the increasing body of evidence that mast cells have an important role in IBS and has the potential to be exploited pharmacologically.

The role of basophils in atopic disease is less well characterized and there is little literature on their role specifically in IBS. However, a recent study looking at the use of omalizumab in patients with a peanut allergy found that the clinical effects were associated with basophil rather than mast cell suppression, which is suggestive that basophils may have a role in food allergy [Savage *et al.* 2012].

Eosinophilic disease in the gastrointestinal tract

There is considerable interest in a condition called eosinophilic oesophagitis which is characterized by the symptoms of chest pain and dysphagia and remains notoriously difficult to treat. More recently, it appears that this tendency to eosinophilic infiltration may not necessarily be confined to the oesophagus. Eosinophilic disease has been reported in other anatomical locations throughout the gastrointestinal tract, including eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis and eosinophilic colitis [Khan and Orenstein, 2008; Alfadda *et al.* 2011; Llado *et al.* 2013; Ko *et al.* 2014].

Initial management involved dietary manipulation, although there is much uncertainty about which foods should be eliminated and for how long [Furuta *et al.* 2007; Castellano Mdel *et al.* 2010]. Furthermore, there is also debate about whether treatment should be empirical or directed by some form of allergy testing. With respect to

pharmacological approaches, there has been one open study of sodium cromoglycate which did not result in any benefit in the paediatric setting [Liacouras *et al.* 2005].

Topical corticosteroids, have been shown to reduce symptoms but symptom improvement does not always correlate with a reduction in eosinophilic infiltration [Teitelbaum *et al.* 2002; Arora *et al.* 2003; Noel *et al.* 2004; Remedios *et al.* 2006]. Furthermore, oesophageal candidiasis can be a problem in some patients receiving this form of treatment.

Omalizumab

Omalizumab is a monoclonal antibody which binds with high affinity to IgE and has been developed for the treatment of patients with an allergic asthma phenotype where symptoms remain uncontrolled with inhaled corticosteroids and long-acting β2 antagonists [British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014]. Two systematic reviews have shown the efficacy of omalizumab in the treatment of moderate to severe asthma, with omalizumab leading to a reduction in the number of exacerbations of their asthma and a high proportion of subjects able to reduce and discontinue inhaled or systemic corticosteroid therapy [Walker *et al.* 2006; Rodrigo *et al.* 2011].

More recently, omalizumab has been used in conditions other than asthma, including rhinitis, atopic dermatitis, urticaria, idiopathic anaphylaxis and eosinophilic oesophagitis [Casale *et al.* 2001; Lane *et al.* 2006; Maurer *et al.* 2013; Clayton *et al.* 2014].

Omalizumab for the management of food allergy has reportedly shown an improvement in gastrointestinal symptoms following an oral intake of the suspected allergen in case reports [Riffelmann, 2008]. One study evaluated the effect of omalizumab on food intolerance symptoms in patients receiving this medication for their asthma. It was noted that all patients reported an improvement in their gastrointestinal symptoms during the treatment period [Rafi *et al.* 2010]. Unfortunately, in the majority of published data reporting on the use of omalizumab in food allergy, participants are taking the medication primarily for respiratory conditions and consequently, the gastrointestinal effects are assessed as a secondary response to treatment.

Omalizumab in food allergy

Omalizumab has attracted a substantial amount of interest in the treatment of food allergy. One study was designed to assess the threshold to peanut allergy in patients with asthma, with known peanut allergy, being treated with omalizumab. Despite the study being concluded early due to the severity of two anaphylactic reactions, the small number of patients completing the protocol showed encouraging results, suggesting that anti-IgE therapy might have a role in peanut allergy [Leung *et al.* 2003]. Other pilot studies have shown encouraging results with omalizumab, facilitating desensitization, with particular interest focusing on peanut allergy [Sampson *et al.* 2007; Schneider *et al.* 2013].

A recent trial described the potential use of omalizumab in food allergy [Begin *et al.* 2014]. It was concluded that this monoclonal antibody might have utility in facilitating more rapid desensitization of patients to multiple food allergens. The authors concluded that these encouraging results indicated that further trials are needed to determine the efficacy of this approach in larger numbers. Consequently, omalizumab may have a role in the management of severe forms of food allergy and deserves further exploration.

The use of omalizumab in urticaria

Urticaria is characterized by itchy hives occurring for at least the previous 6 weeks, with or without angioedema and no apparent environmental trigger. The mainstay of treatment are H_1 antihistamines; however, symptoms may remain despite incrementing the dosage and when this is the case guidelines suggest third-line treatment regimens of immunomodulatory compounds [Zuberbier *et al.* 2014].

There is an increasing body of evidence showing that omalizumab may be an effective treatment modality in urticaria. It has now been approved by the US Food and Drug Administration for use in urticaria based on the results of a series of phase III trials. These have shown the efficacy in urticaria which fails to respond to traditional measures [Kaplan *et al.* 2013; Maurer *et al.* 2013, Saini *et al.* 2013] such as H_1 antihistamine therapy.

Omalizumab in mastocytosis

A further potential use of omalizumab is in the treatment of mastocytosis. Mastocytosis is the

term for a 'heterogeneous group of disorders which is characterised by abnormal growth and accumulation of mast cells in one or more organ systems' [Valent *et al.* 2001: 603–623]. It most commonly affects the integument, skeletal, haematopoietic, cardiopulmonary, central nervous and gastrointestinal systems. Patients often experience gastrointestinal symptoms, including abdominal pain, nausea and diarrhoea. There have been a small number of case reports which indicate that omalizumab may be effective in the treatment of mastocytosis in either standalone therapy or when combined with traditional therapy. However, due to the small numbers of patients reported on in these case reports, further research is required in order to elucidate any potential benefit for omalizumab in the treatment of mastocytosis [Molderings *et al.* 2011; Bell and Jackson, 2012].

Omalizumab in eosinophilic oesophagitis

A potentially exciting application of omalizumab in the gastrointestinal tract is in the management of eosinophilic oesophagitis. However, few studies have been performed looking at the relationship between omalizumab and this condition. The majority of studies performed have had small numbers of participants or have been case series [Foroughi *et al.* 2007; Fang *et al.* 2011; Rocha *et al.* 2011]. More recently, a randomized, placebo-controlled, double-blind trial of omalizumab has been conducted in patients with eosinophilic oesophagitis diagnosed histologically. Following treatment, the participants treated with omalizumab were found to have no significant differences compared with the placebo group, in both eosinophil count and symptom resolution. Subsequently, the authors performed an immunostaining technique on tissue samples from a different cohort of participants with eosinophilic oesophagitis, where a significantly higher amount of IgG4 was found compared with controls. These results suggest that eosinophilic oesophagitis may be of an IgG4 rather than an IgE aetiology, as previously thought [Clayton *et al.* 2014].

Conclusion

The observation that the administration of a monoclonal antibody against IgE resulted in almost complete resolution of this patient's IBS symptoms suggests that this immunoglobulin plays a part in the pathogenesis of IBS, in at least a subset of patients. Consequently, in patients with atopy and IBS, targeting this abnormality might have therapeutic potential, particularly in those individuals not responding to conventional IBS therapies. There is some evidence that sodium cromoglycate has an effect in patients with atopic IBS, especially in those who have positive skin prick tests to food antigens [Stefanini *et al.* 1992, 1995]. Therefore, skin prick or RAST testing patients with IBS and atopy and offering them dietary exclusion based on the results or sodium cromoglycate seems to be worthy of reconsideration. Our observations, in conjunction with the findings that ketotifen improves symptoms in IBS, lends further support to the concept that mast cell stabilization is a potential future therapeutic target in IBS.

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JSP, JM, SA declare no competing interests. RMN has received lecture fees, advisory board fees and support for attending international educational conferences from Astra-Zeneca, Boehringer Ingelheim, Boston Scientific, Chiesi, GSK, Novartis and Vectura. PJW has acted as a consultant for, or received research grant support from the following pharmaceutical companies: Almirall Pharma, Boehringer–Ingelheim, Chr Hansen, Abbott, Danone Research, Ironwood Pharmaceuticals, Norgine, Proctor and Gamble, Shire UK and Sucampo Pharmaceuticals.

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