ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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Overlap Between Irritable Bowel Syndrome and Inflammatory Bowel Disease

Alexander C. Ford, MBChB, MD, FRCP
Professor of Gastroenterology
Honorary Consultant Gastroenterologist
Leeds Institute of Biomedical and Clinical Sciences, University of Leeds
Leeds Gastroenterology Institute, Leeds Teaching Hospitals Trust
Leeds, England, United Kingdom

G&H What features do irritable bowel syndrome and inflammatory bowel disease have in common?

AF It is important to note that bowel symptoms are not specific to any one condition. The gastrointestinal tract has a limited repertoire of symptoms; therefore, different conditions can present with the same, or similar, symptoms. It follows that the symptoms of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) can overlap. Patients with IBS and IBD may experience a change in their bowel habits, usually involving diarrhea, as well as pain, bloating, and mucus per rectum. IBS and IBD also tend to be more common among younger people.

The brain-gut axis is a debated topic. The enteric nervous system supplies the gut, and it has a well-accepted role in functional disorders (such as IBS) that have been retermed disorders of gut-brain interaction. The enteric nervous system may have a role in IBD as well, but the evidence is less convincing. Research suggests that people with IBD, similar to people with IBS, are more likely to have mood disorders and experience anxiety and depression, and that mood disorders may impact the prognosis of either condition adversely. Thus, bidirectional effects of the brain-gut axis may be applicable to both IBS and IBD.

G&H What are the main differences between the 2 conditions?

AF When a patient presents with the symptoms discussed previously, the challenge from a clinical perspective is determining whether the patient has IBS or IBD. The hallmark indicator of IBD is an actual visible mucosal inflammation seen at colonoscopy or cross-sectional imaging. IBD also has well-accepted biomarkers, including fecal calprotectin, whereas IBS is a functional disorder with no accepted biomarker or structural explanation seen at colonoscopy for the symptoms. The colonic mucosa of people with IBS appears normal macroscopically, and although there are reports of microscopic inflammation in people with IBS, these reports tend to be from highly selected groups of patients in experimental studies, rather than from patients seen in routine practice. IBS is much more common than IBD, with a prevalence between 5% and 10%. Research suggests that the prevalence of IBD, at least in the United Kingdom, is approaching 1%.

G&H How should IBD patients who have symptoms of IBS be classified?

AF One of the requirements to be diagnosed with IBS is to have no structural cause of, or any other gastrointestinal explanation for, symptoms, such as celiac disease or IBD. Therefore, if a patient has symptoms similar to those of IBS but has Crohn's disease or ulcerative colitis, he or she technically does not have IBS. I tend to use the phrases IBS-type symptoms or symptoms compatible with IBS to

describe such patients. Another way of classifying these patients is by saying they have ongoing symptoms in the absence of inflammation, which covers the fact that they are experiencing pain, diarrhea, and bloating, but have quiescent disease after investigations such as a colonoscopy, cross-sectional imaging, or a stool sample for a fecal calprotectin measurement.

G&H What is the prevalence of IBS-type symptoms in patients with ulcerative colitis and Crohn's disease?

AF In 2012, Dr Stephen J. Halpin and I conducted a systematic review and meta-analysis of studies of patients with IBD who had answered validated symptom questionnaires for IBS. We found that approximately 35% to 40% of patients with IBD reported IBS-type symptoms. Moreover, we observed that patients with active IBD were almost 5 times as likely to have symptoms compatible with IBS as compared with healthy controls. The prevalence of IBS-type symptoms was high even among patients with IBD that was in remission; we found that patients in this setting were approximately 4 times more likely to report IBS-type symptoms than healthy controls. The prevalence was slightly higher in patients with Crohn's disease than in those with ulcerative colitis, with an odds ratio of 1.62.

There have been other studies since the publication of our meta-analysis that have used more rigorous definitions of remission, such as a fecal calprotectin of less than 250 µg/g. Data from the IBSEN study were published in the *Journal of Crohn's and Colitis* in 2018. The study evaluated patients with ulcerative colitis who had a colonoscopy and who were confirmed to have histologic remission on biopsies taken during the procedure. The authors reported that even among patients with ulcerative colitis with histologic remission, approximately 28% had symptoms that were compatible with IBS.

G&H What is the role of the microbiome in IBS and IBD? Is there a relationship between the microbiome profile and IBS-type symptoms in patients with IBD?

AF I am not aware of many studies that have looked at the role of the microbiome in this setting. However, my colleagues and I conducted a cross-sectional survey of approximately 800 people with IBD to whom we administered IBS questionnaires. Approximately 50% of patients provided a stool sample for fecal calprotectin. After we measured the levels of fecal calprotectin, we compared the microbiome of the people who had endorsed IBS-type symptoms to those who had not. We were not able to show any differences in the microbiome between the 2 groups.

G&H What is the significance of fecal calprotectin and other biomarkers in managing or diagnosing patients with symptom overlap?

AF Fecal calprotectin is important for defining the proportion of patients with inactive disease who still have IBS-type symptoms. Fecal calprotectin assays vary, so cutoff values are not necessarily uniform from one center to another. In general, the recommendation provided by the European Crohn's and Colitis Organisation is that a fecal calprotectin of less than 250 µg/g in patients with IBD should be considered to rule out active disease. My center regards a fecal calprotectin of less than 100 µg/g as completely normal. Thus, if a patient had diarrhea and the clinician suspected IBD, a fecal calprotectin of less than 100 µg/g would not warrant a colonoscopy. However, if it were 100 µg/g or more, the patient should undergo further testing to rule out IBD. In a patient with a documented diagnosis of IBD, a fecal calprotectin of less than 250 µg/g would likely be taken as indicative of quiescent disease. My colleagues and I have found that up to 30% of patients with a fecal calprotectin of less than 250 µg/g will exhibit IBS-type symptoms.

Fecal calprotectin is also important for determining optimal treatment. If a patient has IBD and ongoing symptoms but a fecal calprotectin of less than 250 µg/g, it is unlikely that a clinician would escalate therapy or switch from an immunomodulator to a biologic agent.

G&H How should patients with symptom overlap be managed?

AF There is currently no evidence on which to base treatment decisions for patients who have ongoing symptoms but no sign of mucosal inflammation. Such patients tend to have normal C-reactive protein or fecal calprotectin levels and are therefore excluded from clinical trials of new drugs in IBD, as they are less likely to respond to a drug that treats inflammation. Additionally, there are no clinical trials of the typical treatments used for IBS (eg, antispasmodics, peppermint oil, or tricyclic antidepressants) for patients with symptom overlap.

Dr Selina R. Cox and colleagues recently published results of their trial on the effects of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in patients with quiescent IBD and IBS-type symptoms. A total of 52 patients were randomized to either the low-FODMAP diet or a sham diet for 4 weeks. The authors found that there was a greater proportion of patients whose symptom scores

improved and who had adequate relief of their IBS-type symptoms with the low-FODMAP diet than with the sham diet.

The MODULATE trial, a multiarm, multistage trial funded by the National Institute for Health Research, and for which I am the principal investigator, is due to start recruiting in the next several months in the United Kingdom. Patients with ulcerative colitis who have ongoing troublesome diarrhea in the absence of any evidence of moderate or severe disease activity and a fecal calprotectin of less than 250 µg/g will be enrolled. The trial will compare 4 different active interventions—low-FODMAP diet, low-dose (10-30 mg daily) amitriptyline, ondansetron (often used in diarrhea-predominant IBS), and loperamide (an antidiarrheal drug)—with a control intervention (the standard first-line dietary advice that would usually be given to someone with IBS). The endpoints evaluated will be the effect of these interventions on both diarrhea and quality of life via the Inflammatory Bowel Disease Questionnaire.

G&H What has research shown regarding a possible bidirectional relationship between the 2 conditions?

AF There is evidence that any inflammatory insult to the bowel, such as a bout of diverticulitis or an acute food poisoning–type illness (eg, *Campylobacter* or salmonella), leading to postinfection IBS can cause neuromuscular remodeling. Similarly, a particularly bad bout of inflammation from IBD may lead to IBS-type symptoms. There is debate whether IBS and IBD represent part of a spectrum of the same disease process. While it is not likely that IBS is a mild subset of IBD, there does seem to be a trend for people with IBS to be subsequently diagnosed with Crohn's disease or ulcerative colitis compared to people without IBS-type symptoms. However, this is likely due to initial misdiagnosis as, going back to what I said previously, gastrointestinal symptoms are not particularly specific to a given condition. In other words, patients likely had ulcerative colitis or Crohn's disease at the time they first presented, but were mislabeled as having IBS.

G&H What are the priorities of research?

AF One of the main priorities is gaining a better understanding of why people with quiescent IBD develop IBS-type symptoms. If the microbiome is not involved, then similar mechanisms to those seen in IBS may be implicated. In this case, functional magnetic resonance imaging studies should be conducted to evaluate brain activation for evidence of abnormalities in central pain processing. Additionally, studies are needed to determine whether visceral sensitivity and abnormal motility are involved. Another priority is to identify effective management strategies for patients with IBS-type symptoms in the absence of active disease. It is probably not appropriate to escalate therapy in people whose disease is quiescent or stable because certain treatments, such as azathioprine and biologic agents, have side effects, some of which can be serious. Hopefully, the MODULATE trial will be able to shed some light on which of the 4 active treatments studied will be of benefit in this patient group.

Dr Ford has no relevant conflicts of interest to disclose.

Suggested Reading

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