Editorial

Eluxadoline: a promising therapy that raises many questions

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Introduction

In the United States (US) there are three medications currently approved for the treatment of irritable bowel syndrome (IBS)-D. The most recent additions, rifaximin and eluxadoline, were approved by the US Food and Drug Administration (FDA) on the same day in May, 2015, and were the first therapies approved by the FDA since the approval of alosetron in 2000. Rifaximin, approved for more than a decade for traveler's diarrhea and since 2010 for the prevention of recurrent hepatic encephalopathy, is well recognized by clinicians and has been used extensively as an off-label treatment for IBS and bloating, as well as for small intestinal bacterial overgrowth. Eluxadoline, however, represents a unique addition to the IBS-D therapeutic milieu and clinicians are just gaining experience with it since it became available in January of 2016. Eluxadoline is an orally administered, minimally absorbed mixed opioid receptor modulator, acting as a mu (μOR) and kappa opioid receptor agonist and delta opioid receptor (δOR) antagonist (1). It is thought that the μOR agonist component of eluxadoline reduces propulsive gastrointestinal motility and chloride secretion while the δOR antagonist component reduces both abdominal pain and opposes μOR activation, tending to 'normalize' bowel function rather than constipate (2). The significance of the kappa OR agonism of eluxadoline remains unknown.

Lembo and colleagues recently reported the results of the phase 3 registration trials (IBS-3001 and IBS-3002) that supported FDA approval of eluxadoline in the January 21, 2016 issue of the *New England Journal of Medicine* (3). These two trials included 2,428 patients with IBS-D, defined in accordance with the Rome III criteria, who were randomized to receive 75 or 100 mg eluxadoline or placebo, all twice daily. Both trials evaluated efficacy during 26 weeks of double-blind treatment, following which the IBS-3001 trial continued for an additional 26 weeks of double-blind treatment in order to evaluate long-term safety, and the IBS-3002 trial concluded with a 4-week placebo withdrawal period to assess the effects of treatment cessation. The FDA composite endpoint of simultaneous daily improvement of both worst abdominal pain (≥30% improvement from baseline) and stool consistency (<50% of days with stool type 5 on the Bristol Stool Form Scale) over 1–12 weeks (FDA primary endpoint), and 1–26 weeks [European Medicines Agency (EMA) endpoint] was the primary endpoint of both trials. Pooled data from both trials showed that the primary FDA and EMA endpoints were met by significantly more patients treated with 100 mg eluxadoline than with placebo (25.1% *vs.* 17.1%, P<0.001 in IBS-3001 and 29.6% *vs.* 16.2%, P<0.001 in IBS-3002). For the FDA and EMA primary endpoints, patients treated with 100 mg eluxadoline experienced significantly higher responder rates for stool consistency, but not significantly higher responder rates for improvement in abdominal pain compared with placebo. Similar efficacy was seen in men and women and improvements in the secondary endpoints of stool frequency and bowel movement urgency, IBS global symptom scores, and IBS-quality of life scores were significantly greater with eluxadoline compared with placebo.

The evaluable pooled safety data from the two phase 3 trials showed that the most frequent adverse events (AEs) were constipation, nausea, abdominal pain, vomiting, abdominal distention, and gastroenteritis. Serious adverse events (SAEs) occurred in 4.2%, 4.8%, and 3.0% in the 75 mg, 100 mg, and placebo groups, respectively. Two types of adjudicated SAEs were reported in the pooled treatment groups: eight cases of hepatobiliary events were attributed to sphincter of Oddi spasm (all eight patients had absent

gallbladders and the majority of cases occurred with the 100 mg dose) and five cases of mild pancreatitis. Notably, three of the five patients who developed pancreatitis also had a history of chronic alcohol abuse. These adjudicated SAE cases resolved rapidly with no sequelae, but prompted the FDA to enforce labeling restrictions mandating the use of the 75 mg dose in IBS-D patients without gallbladders and prohibiting use in patients who admit to more than three alcoholic beverages per day.

IBS is a common and important gastrointestinal condition with a worldwide prevalence of between 10% and 15% (4). In general terms, IBS is characterized by abdominal pain or discomfort in association with altered bowel habits over at least three months in the absence of identifiable structural or metabolic abnormalities (5). Starting with the Rome III criteria for IBS, and continued with the recently published Rome IV update, patients can be described as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and mixed (IBS-M), in which stool patterns vary between diarrhea and constipation (6,7).

IBS is a costly condition. Patients with IBS are more likely to seek medical care for depression, anxiety, and somatization disorder, and frequently experience serious negative effects on their social and workplace lives compared to non-IBS controls (8-10). The direct and indirect costs of IBS in the US exceed $30 billion per year and the condition is associated with approximately 3.6 million annual physician visits (9,10). The diagnosis of IBS, particularly in primary care, is widely viewed as a diagnosis of exclusion established by negative testing for organic gastrointestinal or systemic diseases, consequently leading to dramatically higher health care costs related to diagnostic testing (11,12).

The pathogenesis of IBS is unclear, but the condition is generally believed to reflect the complex interactions between visceral hypersensitivity, environmental factors, stress, and the effects of altered serotonergic tone on gut motility (13). It is abundantly clear that there is not a single cause of IBS symptoms and the condition should be thought of as a syndrome of symptoms, rather than as a traditional disease state. Additional etiologies that have been proposed for IBS underscore the wide range of possible causes and include (I) altered gut microbiota; (II) altered immune function; (III) inflammation; (IV) food intolerances; (V) post-infectious sequelae; (VI) impaired gas handling and (VII) altered motility due to volatile bacterial fermentation products (13-17). Historically, IBS therapies have tended to target single IBS symptoms, e.g., laxatives to treat constipation, anti-diarrheals to treat diarrhea, and anti-spasmodics to treat abdominal pain (13), all of which often fail to provide satisfactory relief of global IBS symptoms. Medications with multiple potential targets, designed to positively affect both gastrointestinal motility and abdominal pain, could be expected to have broader treatment effects than these symptom-directed therapies.

For clinicians and patients who deal with IBS-D on a daily basis, recent developments in targeted pharmacologic therapies such as rifaximin and eluxadoline offer hope for additional options and improved outcomes compared to traditional symptom-based therapies. Both rifaximin and eluxadoline, like their competitor alosetron, have demonstrated statistically significant improvement in numerous IBS-D endpoints compared to placebo. As with all new products, enthusiasm for the newer medications should be tempered with consideration of the methodology and results of their clinical development programs, an awareness of FDA endpoints and how they may or may not reflect the routine clinical practice experience, medication costs and availability, patient comorbidities, and potential treatment emergent AEs.

Direct comparison of the primary endpoint results of the pivotal trials of alosetron, rifaximin, and eluxadoline is not possible due to inherent differences in the individual study populations and methodologies. We recently published an analysis based on data included in clinical trial reports for each of these medications in an effort to arrive at a general estimate of the efficacy of the three drugs and concluded that while clear superiority of one agent over another cannot be determined, it is clear that all three produced statistically significant rates of adequate relief of IBS symptoms compared to placebo (18). How, then, should clinicians integrate eluxadoline into their IBS-D therapeutic hierarchy? The politically correct and safe answer is that eluxadoline should be used in a complementary fashion to other therapies, considering individual patient symptoms, disease characteristics, coexisting illnesses, and medication cost, availability, managed care coverage, and safety profile. Because IBS-D is such a heterogeneous disorder, both in terms of etiology and severity, there is no single best therapy, but in keeping with the concept of "first do no harm", it remains appropriate to confine initial interventions to lifestyle and dietary modifications and anti-diarrheal agents for patients with IBS-D. Experience shows that many patients, especially those with more severe symptoms, will fail these initial therapies and will therefore be appropriate candidates for prescription therapies.

The current report by Lembo and colleagues highlights the two eluxadoline registration trials as some of the most compelling IBS-D clinical trials thus far. Both trials are methodologically sound with appropriate regulatory primary endpoints and numerous clinically relevant secondary endpoints. Based on the results of these studies, eluxadoline holds promise to benefit patients with IBS-D who fail to adequately respond to the initial conservative therapeutic approach to IBS-D described above. In fact, the response to eluxadoline in patients who had previously used loperamide without adequate satisfaction was evaluated in the current report by Lembo *et al*. and found to be greater than the response in patients who had not tried loperamide (3). However, the safety profile of eluxadoline does merit caution and adherence to appropriate patient selection and dosing recommendations should be emphasized, as should continued monitoring after initiation of this medication. Analysis of the long-term post-marketing experience with eluxadoline will be critically important given its possible association with clinical syndromes attributable to sphincter of Oddi spasm. A repeat of the AE experiences with alosetron and tegaserod in the US that resulted in their withdrawal or institution of onerous prescribing restrictions would likely have significant negative effects on both patient and clinician confidence and comfort in pharmaceutical therapies for IBS-D and deprive some patients the opportunity for meaningful clinical improvement. It is also important to note that the effect of eluxadoline on the symptom of pain appears, based on the clinical trial results, to be less impressive than the effect on stool consistency. However, Lembo *et al*. present an alternative pain analysis in the supplementary material of their report that shows that eluxadoline delivers consistently greater degrees of abdominal pain than placebo at a variety of pain thresholds above the 30% level specified in the FDA composite endpoint.

Important questions remain regarding eluxadoline that will only be answered with time and additional analyses. When should this medication be used relative to the other prescription agents available for IBS-D? Can it be used for on-demand treatment? Can it be eventually discontinued with durable response after a certain period of time? What are the effects of co-administration with other agents and what are the clinical effects of the kappa OR agonism of eluxadoline? Can it be effectively used for chronic diarrhea that does not qualify as IBS-D or in patients with other conditions such as microscopic colitis, inflammatory bowel disease in remission with persistent IBS features, or perhaps even fecal incontinence. Time and experience will dictate the role of eluxadoline in the clinical management of IBS-D, but the clinical trial results reported by Lembo *et al*. suggest that this agent has the potential to be an important addition for the care of this common and costly condition.

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Footnote

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