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Novel Therapies in IBS-D Treatment

*Judy Nee**
Mohammed Zakari
Anthony J. Lembo

Address
*Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
Email: jnee@bidmc.harvard.edu

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Opinion statement

Irritable bowel syndrome (IBS) is a common gastrointestinal disease characterized by abdominal pain and change in bowel habits. IBS diarrhea predominant (IBS-D), which is arguably the most common subset of IBS, is also associated with rectal urgency, increased frequency, abdominal bloating, and loose to watery stools. Current treatments for diarrhea include mu-opioid agonists (i.e., loperamide, lomotil) and bile acid sequestrants (i.e., cholestyramine) while treatments for abdominal pain include antispasmodics (i.e., hyoscyamine, dicyclomine) and tricyclic antidepressants (i.e., amitriptyline). There are currently 3 FDA-approved treatments for IBS-D, which have been shown to improve both abdominal pain and diarrhea. Alosetron was initially approved by FDA 2000; however, its use is now limited to women with severe IBS-D symptoms refractory to other treatment. Eluxadoline, a mixed mu-opioid agonist, and rifaximin, a broad spectrum gut specific antibiotic, were both FDA approved in 2015. Eluxadoline has been shown to relieve abdominal pain and stool consistency in appropriate candidates. While large trials already showed the efficacy of rifaximin in treating non-constipated IBS for bloating, stool consistency, and abdominal pain, the recent TARGET 3 trial demonstrates that retreatment is also effective. While these new treatments significantly expand options for patients suffering from IBS-D, there is likely to remain a need for additional safe and effective therapies.

Introduction

Irritable bowel syndrome (IBS) is the most common diagnosis in GI clinics and reason for referral to gastroenterology. IBS is characterized by abdominal pain and discomfort associated with a change in bowel habits. The subset of diarrhea predominant IBS (IBS-D) comprises nearly 33 % of IBS [1] and is frequently associated with rectal urgency, increased stool frequency, loose/watery stools, and abdominal bloating.

IBS incurs a heavy economic and social burden on the individual as well as society. Individuals with IBS in the USA incur greater health care costs compared to the general population with estimates ranging from $742 to 7547 per patient per year [2]. Patients with IBS-D report greater impact on daily activities and have lower overall quality of life compared to patients with other subtypes of IBS (i.e., IBS-constipation and IBS-mixed) [3, 4].

IBS-D is caused by multiple pathophysiologic mechanisms and notably varies from one patient to another: there is thought to be a change in the microbiome, altered motility, and hypersensitivity [5–7]. Genetics may also play a role, as IBS appears to cluster in families and is more likely to be present in monozygotic compared to dizygotic twins [8].

Given the number of complex pathways involved in IBS-D, multiple treatment options are needed. While most older treatments target individual symptoms (i.e., diarrhea or abdominal pain), newer agents target multiple symptoms. This review summarizes current treatments for IBS-D with emphasis on the newly FDA-approved medications, eluxadoline, and rifaximin.

Diagnosis

The diagnosis of IBS should be considered in a patient whose symptoms fulfill the Rome III criteria [9]: recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following: (1) improvement with defecation, (2) onset associated with a change in frequency of stool, (3) onset associated with a change in form (appearance) of stool. Symptoms should be present for more than 6 months prior to diagnosis. The IBS-D subtype requires the presence of loose stools in more than 25 % of bowel movements and hard or lumpy stool in less than 25 % of bowel movements.

Alarm features such as weight loss, nighttime awakening, onset after 50 years old, unexplained rectal bleeding, anemia, and weight loss may suggest an organic disease and, therefore, additional testing may be warranted. In the absence of alarm features, a positive diagnosis of IBS can usually be made with limited diagnostic testing. Celiac antibody testing, such as tissue transglutaminase antibody (anti-tTG), is recommended by the ACG Task Force [9] for patients with IBS-D though a recent study from the USA failed to find a higher rate of celiac disease in a large cohort of IBS-D patients [10]. In a 2002 systematic review of 20,000 patients presenting with symptoms of IBS, the presence of abdominal pain decreased the likelihood of a diagnosis of colon cancer and the absence of abdominal pain increased the likelihood [11, 12].

Current therapy in IBS-D treatment

Traditional treatments for diarrhea in IBS-D

Colonic transit is frequently accelerated in IBS-D [13], and therefore, medications aimed at slowing colonic transit may improve diarrhea in some patients.

Loperamide is a synthetic mu-opioid receptor agonist that does not pass through the blood–brain barrier. Loperamide is relatively inexpensive, generally well tolerated, and widely available (i.e., over the counter (OTC)). It is generally effective in decreasing colonic peristalsis and increasing fluid absorption [13, 14]. However, loperamide's efficacy in IBS-D has only been examined in two small studies [15, 16], both with significant methodological limitations. While not conclusive, these studies suggest that loperamide improves stool

consistency but not abdominal pain. Patients should be encouraged to take loperamide prophylactically, starting at 2 mg daily and then titrating up to a maximum of 16 mg daily.

Despite normal ileal structure and histology, up to 50 % of IBS-D patients [17] have bile acid malabsorption (BAM), which leads to increased colonic mucosal permeability, motility, and mucous secretion [18–22]. Bile acid sequestrants such as cholestyramine, colestipol, and colesevelam improve stool consistency and decrease frequency by slowing colonic transit [23–25] and therefore may be useful in IBS-D. Unfortunately, diagnostic tests for BAM are not currently available in the USA and, therefore, a symptomatic trial with a bile acid sequestrant is necessary.

Cholestyramine, the most commonly used bile acid sequestrant, is limited by multiple issues: it has poor taste; interferes with the absorption of other medications; and can lead to common side effects of bloating, nausea, flatulence, and abdominal pain. Long-term compliance can be very poor.

Those who fail cholestyramine may benefit from a trial of colesevelam. In a retrospective review of 92 patients with BAM, 45 % of patients were given colesevelam in dosages ranging from 1.25 to 3.75 mg per day after a cholestyramine "failure." Of all patients who received colesevelam, 47 % of patients reported a successful response [25].

Traditional medications for abdominal pain in IBS-D

Antispasmodics are a heterogeneous group of medications that share a common mechanism of relaxing smooth muscle contractions or reducing excitatory neurotransmission. Currently, dicyclomine and hyoscyamine are the only two non-combination antispasmodics available in the USA by prescription. Both are anticholinergic and therefore may reduce diarrhea and urgency; however, dedicated studies in IBS-D have yet to be performed.

Peppermint oil relaxes gastrointestinal smooth muscle by reducing calcium influx. In a systematic review and meta-analysis, peppermint oil use was associated with significantly greater improvement in global symptoms (392 patients, relative risk 2.23) and abdominal pain (357 patients, relative risk 2.14) [26] in patients with IBS. The number needed to treat was three. In a more recent study using a novel formulation of peppermint designed to provide sustained release in the small bowel, 72 patients with non-constipated IBS defined by the Rome III criteria treated with peppermint oil 180 mg three times a day had a reduced total IBS Symptom Score as well as reduction in individual symptoms such as abdominal pain, bloating, bowel movement urgency compared to placebo over 4 weeks [27]. Notably, there was no significant change in diarrhea, feeling of incomplete evacuation, or gas.

Tricyclic antidepressants (TCAs) have shown to be effective in the global symptoms in IBS, independent of its antidepressant effect. In IBS-D, TCAs may have an added benefit of prolonging orocecal transit time through anticholinergic effects [28]. Only one study has examined the use of the commonly used TCA, amitriptyline, in the IBS-D population. In this study, 50 IBS-D patients were randomized to low dose amitriptyline (10 mg qhs) or placebo for 8 weeks. Patients receiving low dose amitriptyline demonstrated complete response (defined as loss of all symptoms) compared with those receiving placebo (68 vs. 28 %, $P=0.01$) at the end of the second month [29•]. At this, dose amitriptyline was well tolerated with few side effects reported.

The use of selective serotonin uptake inhibitors (SSRIs) is even less studied in IBS-D. Recently, a non-inferiority trial randomized 228 subjects to the SSRI tianeptine 37.5 mg or TCA amitriptyline 10 mg daily for 4 weeks. At 4 weeks, non-inferiority of tianeptine was seen. Eighty-eight percent in the tianeptine compared to 66 % in the amitriptyline group reported relief of global symptoms of IBS. Further, side effects of dry mouth and drowsiness were fewer in the tianeptine group compared to amitriptyline [30].

FDA approved medications for use in IBS-D

Alosetron

Alosetron was the first drug approved by the FDA for usage in IBS-D. Alosetron is a 5HT3 antagonist that slows colonic transit time [31], increases fluid resorption, and decreases visceral hypersensitivity, possibly due to diminished blood flow to specific emotional centers in the brain [32].

In multiple large multicenter randomized controlled studies, alosetron has been shown to improve abdominal pain, decrease stool frequency, and increase stool consistency in IBS-D patients [33–39]. For example, in a trial of 377 women with IBS-D, 27 % more women randomized to alosetron 1 mg BID vs. placebo reported adequate relief of symptoms in 6 out of 12 weeks. Compared to placebo, those who received alosetron experienced decreased percentage days with urgency, more hardened stool consistency, and decreased stool frequency [36]. This affect was seen within a week of initiating treatment and continued throughout the study. Three meta-analyses evaluating a total of 8 trials of alosetron (including 2 trials exclusively in IBS-D patients) found that symptoms persisted in 1576 (49 %) of 3214 patients who received alosetron compared with 1127 (64 %) of 1773 patients allocated to placebo (RR of symptoms persisting=0.79; 95 % CI: 0.69–0.90) [40].

Additionally, alosetron has been shown to lead to improved quality of life scores [41, 42]. Those on alosetron were more likely to report satisfaction with their treatment, less absenteeism from work, and less restriction in their daily activities due to IBS symptoms.

After its initial FDA approval in 2000, alosetron was removed from the market due to complications associated with ischemic colitis and constipation. It was reintroduced in 2002 under new indication restrictions—women with severe IBS-D who have failed conventional therapies. Enrollment is also now required under the Risk Management Program (RMP). To reduce the risk of constipation, the initial starting dose is now 0.5 mg twice a day and may be uptitrated to 1 mg twice a day after a month of therapy if adequate relief of IBS symptoms is not achieved [43•]. Since the initiation of the RMP, the incidence of ischemic colitis, and complications from constipation have been rare at approximately 1 per 1000 patient-years and 0.60 per 1000 patient-years, respectively.

Eluxadoline

Eluxadoline, a mixed mu-opioid agonist and delta opioid antagonist, is one of the two drugs approved by the FDA in 2015 for the treatment of IBS-D. Whereas agents such as loperamide act mainly on the mu-opioid receptor and slow GI motility, the addition of the delta opioid antagonist found in eluxadoline may

also potentiate visceral analgesia [44, 45].

In two large double-blind placebo-controlled phase 3 trials, 2428 patients with IBS-D were randomized to eluxadoline 75 mg, 100 mg, or placebo twice daily for 6 months. During weeks 1–12, 26 % of the eluxadoline 75 mg group compared to 27 % in the eluxadoline 100 mg dosage and 17 % in the placebo group met the composite endpoint of improvement in the worst abdominal pain (30 % reduction from baseline) and an improvement in stool consistency) for at least 50 % of the weeks. During weeks 1–26, composite responders were seen in 27 % in eluxadoline 75 mg, 31 % in eluxadoline 100 mg, compared to 17 % in the placebo group for at least 50 % of the weeks. Differences between eluxadoline and placebo were seen within the first week and sustained throughout the study.

Eluxadoline significantly improved stool consistency, urgency, and stool frequency compared to placebo. There was no significant improvement in the percentage of patients reporting >30 % reduction in worst abdominal pain compared to placebo. However, a small but statistically significant improvement was seen in the eluxadoline 100 mg group who reported greater than 40 or 50 % reduction in worst abdominal pain compared to placebo. Notably, bloating was also improved in the eluxadoline 100 mg group compared to placebo.

The most common side effects were constipation and nausea in those taking the eluxadoline 100 mg dose, but this did not lead to a significant discontinuation of the drug compared to placebo. Significant adverse events (SAE) did occur: five patients (0.3 %) (2 in the eluxadoline 75 mg, 3 in the eluxadoline 100 mg) experienced acute pancreatitis, and eight patients (0.5 %) experienced abdominal pain with elevated hepatic enzymes. Increased consumption of alcohol or the absence of a gallbladder (i.e., prior cholecystectomy) appears to be a risk factor for developing these complications. The most frequent AEs among those who had a cholecystectomy were nausea (10.5 %), constipation (8.5 %), and bronchitis (6.7 %). Therefore, eluxadoline should not be administered to patients with a history of bile duct obstruction, sphincter of Oddi dysfunction, pancreatitis, and alcoholism or alcohol abuse (>3 alcoholic beverages per day) [46•].

Rifaximin

Rifaximin is a gut specific antibiotic previously FDA approved for the treatment of traveler's diarrhea caused by *Escherichia coli* and preventing the recurrence of hepatic encephalopathy. Rifaximin was recently FDA approved for the treatment of IBS-D at a dose of 550 mg three times a day for 14 days. Patients who experience a recurrence of symptoms can be retreated with rifaximin up to two times.

In the initial phase III trials with rifaximin (TARGET 1 and TARGET 2), 1260 non-constipated IBS patients were randomized to rifaximin 550 mg three times a day or placebo for 2 weeks. During the 10-week follow-up period, patients were assessed for weekly global IBS symptoms, weekly IBS related bloating, daily IBS symptoms, and monthly quality of life assessments. 40.2 % of patients receiving rifaximin compared to 30.3 % receiving placebo reported adequate relief in global IBS symptoms for at least 2 of the 4 weeks following treatment. Patients receiving rifaximin were also more likely to have adequate relief of bloating compared to placebo (40.2 vs. 30.3 %, $P<0.001$, in the two studies

combined). Analysis of secondary endpoints of daily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency were also significantly improved in patients receiving rifaximin compared to those receiving placebo [47•].

Due to questions regarding the safety and efficacy of repeated treatment, TARGET 3 was performed. In this trial, 2579 patients with IBS-D were treated with open-label rifaximin 550 mg three times a day for 2 weeks. Response was defined as a 30 % decrease in abdominal pain from baseline as well as a reduction of at least 50 % in the number of days per week with loose or watery bowel movements during at least 2 of 4 weeks immediately following treatment. In total, 42 % (1074/2579) of patients were responders to open-label rifaximin. Of these responders, 64 % (692/1074) experienced symptom recurrence during the 18-week follow-up period.

Those subjects whose symptoms recurred during the 18 week follow-up were the randomized to receive two courses of rifaximin 550 mg TID for 14 days or two courses of placebo three times a day for 14 days, separated by 10 weeks. After the first retreatment, IBS-D patients randomized to repeated treatment with rifaximin were more likely to be responders compared to those randomized to placebo (n=308; 32.6 vs. 25.0 %, P=0.0232). Similarly, after the second retreatment course, 36 % of those randomized to rifaximin were responders compared to 29.3 % randomized to the placebo [48•].

Stool urgency, bloating, abdominal pain, and stool consistency after the first retreatment were statistically significantly improved in those who received rifaximin compared to placebo with a treatment difference of 8.1 to 9.2 %. Upon the second course of retreatment, urgency and bloating continued to be superior in the rifaximin group compared to placebo, with a treatment difference of 7.6 to 12.1 %, whereas abdominal pain, stool consistency were not significant.

Constipation was only reported in 1 (0.3 %) patient in the rifaximin group and 3 (1.0 %) patients in the placebo group. Only one patient in each treatment group discontinued the medication. One case of C. Diff occurred in a patient who had been off of rifaximin for several weeks and had been receiving a concomitant systemic antibiotic.

Taken together, these trials show that a 2-week course of rifaximin may improve symptoms associated with IBS-D and in the case of recurrence of symptoms, retreatment may improve abdominal pain and stool consistency with possible improvements in bloating, stool urgency in some patients. While patients were retreated within an 18-week period of follow-up in the study, it is still unclear as to when and how often treatment should be given. Additionally, identifying patients most likely to respond to rifaximin remains an important area of future research.

Conclusion

Despite the lack of large multicenter trials, traditional therapies continue to play a significant role in the primary management of IBS-D. Since these agents specifically target individual symptoms, more than one of these medications may be needed to target the multiple symptoms associated with IBS-D including abdominal pain, diarrhea, and bloating. The two new FDA-approved drugs,

eluxadoline and rifaximin, target multiple symptoms and provide additional treatment options for patients suffering from IBS-D.

Rifaximin has the potential to provide relatively durable improvement in global symptoms in a subset of patients with IBS-D. It is promising that 36 % of these patients initially treated did not develop recurrence of symptoms. On the other hand, it is not surprising that a large majority of patients either did not respond to the initial or second course of rifaximin given the heterogeneity of IBS-D. Nonetheless, a finite 2-week course of treatment, even if repeated, is attractive in IBS-D patients who may have to remain on medications indefinitely otherwise.

Eluxadoline, likewise, targets multiple symptoms in IBS-D. Notably, eluxadoline significantly improved composite and global endpoints; however, it appears to be more effective at improving bowel function than abdominal pain. Due to its potential for pancreatitis and sphincter of Oddi dysfunction, eluxadoline should be avoided in patients with previous bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation as well as daily alcohol consumption, and caution is warranted in patients without a gallbladder.

The two newly approved medications significantly broaden the potential treatment available for patients with IBS-D.

Compliance with Ethics Guidelines

Conflict of Interest

Judy Nee declares that she has no conflict of interest.
Mohammed Zakari declares that he has no conflict of interest.
Anthony J. Lembo declares previous consultantships with Actavis, Salix, and Prometheus.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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