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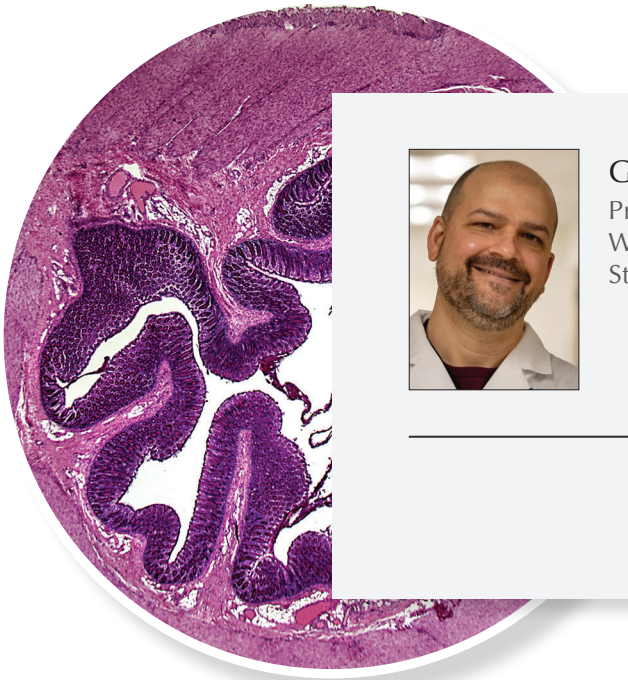
Raising the Bar in the Management of IBS-C



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Raising the Bar in the Management of IBS-C

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Patient Case

A 47-year-old woman presents with complaints of occasional constipation during the past several years (**Table 1**). She states that she has experienced increasing abdominal pain coupled with straining to have a bowel movement on most days during the past 3 years. Occasionally she has experienced small amounts of stool leakage. She estimates that she typically experiences 2 to 3 bowel movements per week, and she describes the stool as either tiny pellets or large and hard. She reports that her pain does improve after defecation, but she rarely feels completely evacuated.

Her medical history is positive for fibromyalgia and anxiety. She describes herself as having a "nervous stomach." She was determined to be perimenopausal at her gynecologic examination earlier in the year. She has no family history of gastrointestinal (GI) diseases or cancer. She has experienced no significant weight loss during the prior few years. She denies noticing blood in her stool or nocturnal symptoms. A systematic review of systems (ROS) is positive for 20 out of 36 symptoms. A colonoscopy performed 2 years earlier was positive for diverticulosis but otherwise unremarkable.

Her current medications include citalopram for anxiety and omeprazole for heartburn. She also takes aspirin and a multivitamin daily, along with a nonsteroidal anti-inflammatory drug approximately 2 to 3 times weekly for back pain. She has tried multiple over-the-counter remedies for her constipation, including fiber, polyethylene glycol, magnesium, docusate sodium, and senna, with only modest relief. A prior physician had prescribed dicyclomine, which she stopped after 2 weeks owing to side effects (dry mouth, dizziness, and sedation) and an overall lack of symptom response.

During her physical examination, moderate lower abdominal tenderness to deep palpation was noted. Her bowel sounds were normal, and no masses were found, but fullness was noted in her lower left quadrant. Laboratory blood tests were normal. During the evaluation, the patient discussed the effect that her symptoms were having on her daily life. As a schoolteacher, her symptoms often caused her to miss work or leave early, given her inability to use the restroom during class. These concerns were mounting, and she became very worried about losing her job and health insurance because of the number of sick days her symptoms have consumed.

The patient was subsequently prescribed linaclotide at 145 µg daily for "chronic constipation". However, she took it only 3 to 4 days per week because she experienced diarrhea and bowel urgency with daily use. At a follow-up appointment 1 month later, she appeared somewhat relieved, stating that her constipation had improved overall (improved bowel frequency and stool consistency). However, during the office discussion she revealed that she continued to experience consistent abdominal pain that she described as a 7 out of 10 in severity. The decision was made to continue treatment but increase her dosage to 290 µg daily.

On the Cover
Light micrograph of a cross section of a colon.

Credit: Alvin Telser / Science Source

Table 1. Key Points of the Patient Case

Patient History	A 47-year-old woman occasional constipation during the past several years • **Abdominal symptoms:** increasing abdominal pain; straining to have a bowel movement on most days during the past 3 years • **Bowel-related symptoms:** small amounts of occasional stool leakage; 2 to 3 bowel movements per week (either tiny pellets or large and hard stools); pain improves after defecation, but rarely feels completely evacuated • **Patient report:** no significant weight loss; no nocturnal symptoms; no blood in stool • **Previous medical history:** fibromyalgia, anxiety, "nervous stomach", perimenopausal, diverticulosis (2 years earlier) • **Family history:** no cancer or GI diseases • **Past medications:** over-the-counter remedies for constipation (fiber, polyethylene glycol, magnesium, docusate sodium, and senna) with only modest relief; dicyclomine, which she stopped after 2 weeks owing to side effects (dry mouth, dizziness, and sedation) and an overall lack of symptom response • **Current medications:** citalopram (10 mg/day), omeprazole (20 mg/day), aspirin (325 mg/day), daily multivitamin, NSAID (2–3 times/week) • **Impact on health-related quality of life (HRQoL):** often misses work or leaves early because of her symptoms and her inability to use the restroom during class; very worried about losing her job and health insurance because of the number of sick days her symptoms have consumed
Initial Clinical Presentation	• Moderate lower abdominal tenderness • Normal bowel sounds • No abdominal masses • Abdominal fullness in left lower quadrant • Laboratory blood tests: normal
GI Provider Recommendation	Initiate treatment with linaclotide (145 μg daily); but the patient took it only 3–4 days/week owing to side effects [diarrhea, bowel urgency])
Response (1 month later)	• Improved bowel frequency and stool consistency • Abdominal pain remains (7/10)
GI Provider Recommendation	Increase linaclotide dosage to 290 μg daily
GI Provider Inquiry (2 months later)	**GI Provider: "Are you feeling better?"** Patient response: "Better than before." **GI Provider: "How much better would you say?"** Patient response: • Abdominal pain improved (50%) but remains bothersome • Still missing work due to abdominal pain, although less than before treatment • **Not satisfied with symptom control**
Patient Inquiry	• **"What treatment options are available to me at this point?"**
As a GI provider, what would you do at this point?	• **"Raise the bar" with respect to expectations for treatment response.** • **Inform the patient that achieving satisfaction with symptom control is the aim of therapy.** • **Educate the patient about the treatment options available.**

At a follow-up appointment 2 months later, her GI provider inquired into symptom improvement, and she responded that she was "better than before." When asked to quantify that improvement, the patient estimated her abdominal pain to be approximately 50% better but stressed that her abdominal pain remained quite bothersome. She was still missing work, although less than before, and she was still not satisfied with her symptom control. The patient inquired if anything could be done to improve her symptoms, including available treatment options.

As a GI provider, what is your diagnosis in this case? What would you do therapeutically at this point? What should both you and the patient expect as an acceptable treatment response? How do you define "satisfaction" with symptom control, which is also the aim of therapy? What are the treatment options available?

Overview of IBS-C

According to the Rome IV criteria, irritable bowel syndrome (IBS) is defined as a disorder of brain-gut interactions in which abdominal pain recurs on average at least 1 day per week along with two or more of the following criteria: related to defecation; associated with a change in the frequency of stool; or associated with a change in the form (appearance) of stool.[1] For a diagnosis of IBS, these criteria must have been met for the previous 3 months and with an onset of symptoms at least 6 months before the diagnosis. IBS is classified as one of 4 different subtypes: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed or alternating bowel habits (IBS-M), and IBS without a significant pattern of abnormal stool (IBS-U).[2] The Rome IV criteria in conjunction with the Bristol Stool Form Scale (BSFS) can establish a patient's IBS subtype (**Table 2**).[3]

Abdominal pain and constipation are hallmark symptoms of IBS-C, and indeed the overlap of these 2 symptoms is requisite in establishing an IBS diagnosis.[4] IBS-C diagnosis relies on a careful medical history, including the timeline of presenting symptoms, evaluation of potential triggers, and identification of alarm signs, or "red flags" (new symptoms in patients over age 50, unintended weight loss, hematochezia, symptoms that awaken the patient at night, fever, acute or rapidly progressing symptoms, and/or a family history of colorectal cancer or inflammatory bowel disease). Other factors such as the patient's diet and current medications must also be reviewed. The physical examination is another important component of the IBS diagnostic evaluation, with a focus on systemic and local conditions that might contribute to constipation, as well as an assessment of the anorectum and pelvic floor muscles. Although the patient's symptoms alone may not be specific to IBS,[5] an assessment for additional elements within the patient's history and associated examination—namely, a high level of somatization, overlapping mood disorder (depression and/or anxiety), normal hemoglobin and C-reactive protein, and a lack of nocturnal stools or blood in the stool—can be very useful in increasing the clinical confidence in an IBS diagnosis while helping to exclude other diagnoses such as inflammatory bowel disease (Crohn's disease, ulcerative colitis), or malignancy.[6]

Chronic constipation conditions, including IBS-C, often occur with overlapping pelvic floor issues such as straining to defecate, stool leakage, and pelvic organ prolapse.[7] Pelvic floor symptom–related distress, such as measured by the Pelvic Floor Distress Inventory (PFDI), is frequently observed in patients with IBS-C. In a study of patients with either IBS-C (n=43) or functional constipation (n=64), pelvic floor distress classified as moderate (PFDI >100 and ≤200) or severe (PFDI >200) was more likely in patients with IBS-C than in patients with functional constipation (57.1% vs 26.5% and 5.7% vs 2.0%, respectively).[7] The subscores of the PFDI were repeatedly and statistically significantly higher in patients with IBS-C than in patients with functional constipation (pelvic organ prolapse: 38.2 vs 25.0; *P*=0.004; colorectal anal: 46.5 vs 37.7; *P*=0.04; and urinary: 33.7 vs 19.5; *P*=0.01), as was the overall PFDI score (118 vs 79.2; *P*=0.001).

Several mechanisms are thought to contribute to the underlying pathophysiology of IBS-C.[8,9] These factors may include alterations in gut motility leading to decreased colonic contraction/peristalsis and water imbalance (diminished fluid secretion/retention) as well as changes in intestinal permeability resulting from widening of the tight junctions between the intestinal epithelial cells and leading to an inflammatory response.[10-13] Importantly, IBS patients may also experience visceral hypersensitivity resulting in increased abdominal symptoms (pain, discomfort) as a consequence of enhanced sensitization of the afferent nerve pathways.[12,14] The pathophysiology of IBS-C has also been traced to alterations of the gut

Table 2. Diagnostic Criteria for IBS-C[1-4]

IBS	Rome IV Diagnostic Criteria Disorder of brain-gut interactions in which abdominal pain recursion average at least 1 d/wk PLUS ≥2 of the following*: • Related to defecation • Associated with a change in the frequency of stool • Associated with a change in the form (appearance) of stool
IBS-C	• BSFS type 1 or 2: >25% of bowel movements • BSFS type 6 or 7: <25% of bowel movements • Hallmark symptoms: abdominal pain and constipation • Medical history and physical examination including evaluation of gastrointestinal symptoms to identify alarm signs: – New symptoms and age older than 50 years – Unintended weight loss – Hematochezia – Symptoms that awaken the patient at night – Fever – Acute or rapidly progressing symptoms – Family history of colorectal cancer or inflammatory bowel disease

*Criteria met for the previous 3 months with onset of symptoms at least 6 months before the diagnosis. BSFS, Bristol Stool Form Scale.

microbiota and other triggers of gut inflammation and immune activation.

The Burden of IBS-C

IBS is associated with a significant burden on patients and a negative impact on their health-related quality of life (HRQoL). An international survey of 1966 patients with IBS reported that patients experienced a restriction of activity for an average of 73.2 days annually (approximately 20% of the year).[15] In a separate online survey of 1667 individuals with IBS-C, 89% of respondents reported their GI symptoms to be "extremely or somewhat bothersome" and more than one-half (53%) scored them as "extremely bothersome".[16] In this same survey, 34% of individuals with IBS-C reported that their symptoms interfered with their participation in personal activities for at least 10 days per month, and 66% stated that their symptoms prevented them from enjoying daily activities. Respondents with IBS-C also reported missing an average of 1.7 days of work or school per month. About two-thirds of survey respondents with IBS-C stated that their symptoms caused them to feel self-conscious. Another study of 789 individuals with IBS-C found 7.59% reported absenteeism and 21.17% reported presenteeism.[17]

The BURDEN IBS-C study reported the results of an online questionnaire administered to 1311 individuals with IBS-C.[18] Patients reported a high degree (63%–66%) of dissatisfaction with therapies, including both over-the-counter and prescription medications. Side effects, most commonly diarrhea, were the primary cause for dissatisfaction. Feelings of frustration (43%) and stress (28%) occurred at a high frequency among individuals with IBS-C. Health care providers believed their patients experienced these sentiments as well, estimating 76% of patients with IBS-C were frustrated and 65% were stressed. Respondents with IBS-C reported that their symptoms impacted productivity on an average of 4 days per month, and affected personal activity on an average of 3 days per month.

Individuals with IBS have been shown to express poorer HRQoL using established instruments, including lower 36-Item Short Form Survey domain scores compared with both the general population and patients with other chronic diseases such as asthma, migraine, and gastroesophageal reflux disease.[19] A substantial burden of depression and anxiety befalls patients with IBS-C.[20] In a study, 25.7% of patients with IBS were found to have borderline or clinically significant depression.[21] Further, some patients have reported contemplating suicide because of their symptoms.[22]

IBS also imposes a significant cost burden on patients as well as society. In one of the few studies focused on IBS-C-related outcomes, a total annual health care charge of $6192 per patient was reported (compared with $1319 for the comparator group).[23] In a group of 789 patients with IBS-C, there were significantly more visits to traditional health care providers as well as the emergency department in the prior 6 months compared with matched comparators.[17]

Pharmacologic Management of IBS-C

The currently available pharmacologic agents with US Food and Drug Administration (FDA)-approved indications for IBS-C include tenapanor, linaclotide, plecanatide, and lubiprostone (**Table 3**).[24] IBS-C pharmacotherapy during the past decade has relied heavily on the guanylate cyclase-C agonists (also known as "secretagogues"), plecanatide and linaclotide. However, the most recently available IBS-C therapy, tenapanor (launched in the US in 2022), works differently than the secretagogues by inhibiting the sodium/hydrogen exchanger isoform 3 (NHE3). NHE3 inhibition by tenapanor leads to 3 important physiologic effects: (1) decreased absorption of dietary sodium, such that luminal water content is retained, intestinal transit time is accelerated, and stool is softened; and based on animal physiologic studies, (2) decreases in intestinal permeability by narrowing the tight junctions between intestinal epithelial cells, and (3) reduction in visceral hypersensitivity, a common finding in patients with IBS-C.[12,13,25] In contrast, the secretagogues (linaclotide, plecanatide, and lubiprostone) all work by promoting colonic fluid secretion. In the United States, the use of these agents is guided by evidence-based recommendations for the management of IBS from the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA).[2,26]

Tenapanor

Tenapanor is an NHE3 inhibitor indicated for treatment of IBS-C in adults.[27,28] It is locally acting with minimal systemic absorption. The efficacy and safety of tenapanor in IBS-C were shown in the placebo-controlled, randomized, phase 3 studies T3MPO-1 and T3MPO-2.[29,30] In both studies, patients with IBS-C (Rome III) were treated with either tenapanor (50 mg twice daily) or placebo. The duration of treatment was 12 weeks followed by a randomized withdrawal period that was 4 weeks in T3MPO-1 (n=606) and 26 weeks in T3MPO-2 (n=593). At baseline, patients reported an average weekly stool frequency of 5 or fewer spontaneous bowel movements (SBMs) and 3 or fewer complete spontaneous bowel movements (CSBMs), patient-reported average weekly stool consistency of BSFS types 1 through 3, and an average weekly abdominal pain score of 3 or higher (on a scale of 0 to 10). The primary

Table 3. Currently Available FDA-approved Pharmacologic Treatments for IBS-C[24]

Drug	FDA approval	What is it?
Lubiprostone	2006	Chloride channel type 2 agonist
Linaclotide	2012	GC-C agonist
Plecanatide	2017	
Tenapanor	2019 (Initial FDA approval) 2022 (US launch)	NHE3 inhibitor

GC-C, guanylate cyclase-C

NHE3, sodium/hydrogen exchanger isoform 3

endpoint was a combined response for at least 6 of 12 weeks of the treatment period, defined as a reduction in average weekly worst abdominal pain of 30.0% or greater from baseline and an increase of at least 1 CSBM per week from baseline, both in the same week.

In T3MPO-1, significantly more patients in the tenapanor group than the placebo group achieved the primary endpoint (27.0% vs 18.7%; Cochran–Mantel–Haenszel [CMH] P=0.020) and abdominal pain response (44.0% vs 33.1%; CMH P=0.008), and the rates of CSBM response were similar between the 2 arms (33.9% vs 29.4%; CMH P=0.270).[29] Tenapanor also was associated with significant improvements in a number of abdominal symptoms compared with placebo for at least 9 of 12 weeks: abdominal discomfort responders (29.0% vs 17.1%; CMH P<0.001), rate of abdominal bloating response (27.0% vs 16.1%; CMH P=0.001), abdominal cramping responders (30.6% vs 23.1%; CMH P=0.044), or abdominal fullness responders (27.4% vs 14.4%; CMH P<0.001). Tenapanor-treated patients experienced significantly greater improvements in global IBS treatment measures (including stool consistency, IBS severity, constipation severity, degree of relief from IBS, and adequate relief from IBS) compared with placebo-treated patients.

Similar results were achieved in T3MPO-2.[30] Significantly more patients in the tenapanor group than the placebo group achieved the primary endpoint (36.5% vs 23.7%; CMH P<0.001), abdominal pain response (49.8% vs 38.3%; CMH P=0.004), and CSBM responses (47.4% vs 33.3%; CMH P<0.001) (**Figure 1**). Over the 26-week treatment period, the tenapanor-treated patients experienced 3.3 CSBMs per week, considered within the healthy range for adults. In the tenapanor arm, improved abdominal pain was reported as early as 1 week after the start of treatment, and abdominal pain decreased by 54% from baseline to week 26. Severe abdominal pain was reduced by 78% from baseline (55%) to week 26 (12%). Tenapanor reduced other abdominal symptoms (including bloating, fullness, discomfort, and cramping) as early as 1 week following treatment initiation.

In T3MPO-2, durable response rates (achieved when patients met the response criteria for at least 3 of the final 4 weeks of the first 12 weeks of the treatment period) were significantly higher in the tenapanor arm compared with the placebo arm—durable abdominal pain response rate (34.8% vs 26.7%; CMH P=0.028), durable CSBM response rate (21.2% vs 5.7%; CMH P<0.001), and combined durable responses (18.1% vs 5.0%; CMH P<0.001).[30] Tenapanor was associated with greater improvements in overall HRQoL from baseline at week 26 compared with placebo (least squares means of 21.5 and 17.3, respectively; least squares mean difference of 4.2; 95% CI, 0.95–7.39; P=0.011).

In both studies, diarrhea was the most frequently reported adverse event and occurred at a higher incidence with tenapanor than with placebo (14.6% vs 1.7% in T3MPO-1 and 16.0% vs 3.7% in T3MPO-2).[29,30] Diarrhea onset typically occurred within the first week of treatment, was generally transient, and was mild to moderate in severity. T3MPO-3, an open-label safety study, reported that tenapanor was well tolerated when taken consecutively for 55 weeks, with no new safety signals and 2.1% overall rate of discontinuation due to adverse events (1.7% attributable to diarrhea).[31]

Lubiprostone

The chloride channel activator lubiprostone is indicated for the treatment of IBS-C in women 18 years of age and older; lubiprostone also carries an FDA-approved indication in chronic idiopathic constipation.[28,32] Efficacy and safety data for lubiprostone in IBS-C were reported in a combined analysis of 2 phase 3 trials that randomized patients to treatment with lubiprostone (8 µg twice daily) or placebo, each administered for 12 weeks to 769 and 385 patients, respectively.[33] The primary efficacy endpoint of the studies and the combined analysis was the overall responder status in the lubiprostone and placebo groups, calculated from the weekly assessments of symptom relief. Monthly responders were defined as patients who rated their IBS symptoms as at least moderately relieved for all 4 weeks of the month or significantly relieved for at least 2 weeks of the month, with no ratings of moderately or severely worse. A patient was considered an overall responder (primary efficacy endpoint) if they were monthly responders for at least 2 of the 3 months of the study.

The combined analysis reported that the total number of overall responders in the lubiprostone group was significantly higher than in the placebo group (17.9% vs

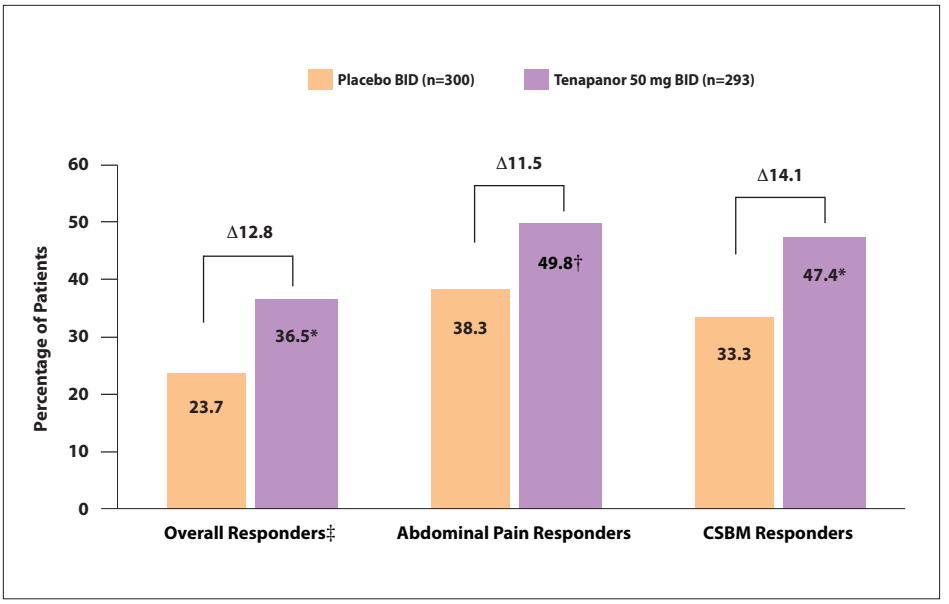

Figure 1. Responder endpoints in T3MPO-2 (26-week trial) with tenapanor[30]

Primary efficacy endpoint: percentage of overall responders for at least 6 of the first 12 weeks of treatment.

*P <0.001

†P =0.004

‡Overall responder defined as patient with a decrease in average weekly worst abdominal pain of ≥30.0% from baseline AND an increase of at least 1 CSBM from baseline, both in the same week, for at least 6 of the first 12 weeks of treatment.

BID, twice daily; CSBM, complete spontaneous bowel movement.

10.1%; P=0.001).[33] Overall responders also reported a greater degree of relief of symptoms including abdominal discomfort or pain, bloating, constipation severity, stool consistency, and straining (P<0.001 for all symptoms reported in overall responders vs nonresponders). The degree of overall response increased over time in the combined analysis with lubiprostone compared with placebo (10.8% vs 7.5%, 18.3% vs 11.4%, and 22.0% vs 14.5% in months 1, 2, and 3, respectively).

An overall analysis of IBS Quality of Life demonstrated a trend toward greater improvement with lubiprostone at week 12 (P=0.066).[33] Clinically meaningful changes (>14 points) were reported with lubiprostone in the IBS Quality of Life domains of social reaction, food avoidance, health worry, body image, and dysphoria. The most frequently reported adverse events involved the GI system (nausea, diarrhea, and abdominal distension) and occurred with similar incidence in the lubiprostone and placebo arms. Across the 2 studies, 4.7% to 5.1% of patients in the lubiprostone arms discontinued owing to adverse events, compared with 4.6% to 7.7% of patients in the placebo arms.

Linaclotide

Linaclotide is a guanylate cyclase-C agonist that is indicated for the treatment of IBS-C in adults; it carries additional FDA-approved indications in chronic idiopathic constipation in adults and functional constipation in pediatric patients.[28,34] The efficacy and safety of linaclotide (290 µg once daily) in IBS-C was established in 2 phase 3 trials.

The first study was a 26-week, randomized, double-blind, placebo-controlled trial of 804 patients.[35] Multiple primary endpoints were evaluated, including the FDA's endpoint for IBS-C response (defined in a patient who reported an improvement of ≥30% from baseline in average daily worst abdominal pain score and an increase of ≥1 CSBM from baseline, both in the same week for 6 or more of 12 weeks). Three other primary endpoints were also measured, based on improvements in abdominal pain and CSBMs for 9 out of 12 weeks. A significantly greater proportion of patients in the linaclotide arm compared with the placebo arm achieved the FDA combined endpoint (33.7% vs 13.9%; P<0.0001), the pain responder criterion (48.9% vs 34.5%), and the CSBM responder criterion (47.6% vs 22.6%). The other primary endpoints were also significantly improved in the linaclotide arm (P<0.0001) as were all secondary endpoints (P<0.001), including abdominal pain, abdominal bloating, and bowel symptoms. Diarrhea occurred more frequently with linaclotide than with placebo (19.7% vs 2.5%; P<0.0001). In the linaclotide arm, onset of diarrhea was within the first week (48.1%) or within the first 4 weeks (75.9%) of initiating therapy. More linaclotide-treated patients discontinued treatment owing to a treatment-emergent adverse event than placebo-treated patients (10.2% vs 2.5%, respectively). Diarrhea was the primary cause of discontinuations attributed to an adverse event.

The second study was a phase 3, double-blind, parallel-group, placebo-controlled trial that randomized 800 patients with IBS-C to receive linaclotide (290 µg once daily) or placebo.[36] Treatments were administered over 12 weeks, followed by a 4-week randomized withdrawal period. The same FDA combined endpoint was one of the primary endpoints in this study, and was achieved by

33.6% of patients in the linaclotide arm compared with 21.0% of patients in the placebo arm (P<0.0001). Additionally, more patients in the linaclotide arm reported the following individual outcomes during at least 6 of the 12 treatment weeks: a reduction of 30% or greater in abdominal pain (50.1% vs 37.5%, P=0.0003), and an increase of at least 1 CSBM from baseline (48.6% vs 29.6%, P<0.0001). During the withdrawal period, patients remaining on linaclotide continued to demonstrate sustained improvement. In contrast, patients rerandomized from linaclotide to placebo showed a return of symptoms but did not worsen relative to baseline. The most common adverse event reported was diarrhea, which resulted in treatment discontinuation among 5.7% of linaclotide-treated patients (compared with 0.3% of placebo-treated patients).

Plecanatide

A second guanylate cyclase-C agonist, plecanatide, is also FDA approved for the treatment of IBS-C in adults and is additionally indicated in chronic idiopathic constipation.[28,37] The efficacy and safety of plecanatide in the treatment of IBS-C was established in 2 identically designed phase 3 clinical trials. Overall, 2189 patients were included in both studies and randomized (1:1:1) to placebo or plecanatide (3 or 6 mg) for 12 weeks.[38] Because only the 3 mg dose of plecenatide is available, the discussion of results is restricted to data pertaining to the 3 mg dose. The same FDA primary endpoint of overall response was used in these studies.

More patients achieved the primary endpoint with plecanatide compared with placebo in both studies (30.2% vs 17.8%; P<0.001 in Study 1, and 21.5% vs 14.2%; P=0.009 in Study 2).[38] All secondary endpoints, including stool frequency/consistency, straining, and abdominal symptoms, were significantly improved with plecanatide compared with placebo. Diarrhea was the most common adverse event (4.3% in the plecanatide group vs 1.0% in the placebo group), with discontinuation owing to diarrhea being infrequent (1.2% with plecanatide and 0 with placebo).

Strategies to Improve Patient Outcomes

Often patients with IBS-C endeavor to self-manage their symptoms, only presenting to a physician when they determine that over-the-counter remedies have failed.[39] With an absence of head-to-head trials, there is no evidence base to define the optimal sequence in which FDA-approved pharmacologic agents should be offered. According to the AGA's clinical decision support tool for IBS treatment, the selection of pharmacologic agent should be based on clinical features and needs of the patient, with the 4 medications discussed in this supplement listed as treatment options for patients with IBS-C after osmotic laxatives and antispasmodics have failed.[26]

Patient expectations regarding treatment and desired outcomes are an essential part of the conversation when initiating treatment.[39] Each patient has their own set of expectations for what therapy can and should bring to them and these expectations are partly framed by the patient's own experience with prior treatments (both prescription and over-the-counter) as well as their knowledge of treatments that are currently available.

Many patients are apprehensive when initiating a prescription medication for treatment of IBS-C and may benefit from a discussion of the risks of adverse events (particularly diarrhea, nausea, abdominal discomfort, and headaches). Clinicians may recommend a new treatment be initiated when patients anticipate spending more time at home (such as on the weekend), in the event that an adverse effect such as diarrhea does occur.

Another important discussion point with patients is the timing of symptom responses to treatment, which may be variable.[39] For example, improvements in bowel frequency may be quite rapid and within days, yet weeks to months may be required to achieve maximal improvements in pain, discomfort, and bloating. If a patient requires management with a combination of therapies, agents with different mechanisms of action should be chosen. Treatment strategies can include rescue therapy (enema, suppository, or stimulant laxative), with direction to be used if satisfactory defecation has not been achieved with the primary treatment regimen.

Once treatment is initiated, it is critical for clinicians to not only ask patients if they are feeling better with treatment, but also understand how much better they are feeling. Quantifying the patient's sense of improvement will help guide clinicians to truly raise the bar for what both clinicians and patients should and can expect as response from treatment, as satisfactory symptom control should also be the aim of therapy.

Returning to the patient case, the GI provider was correct to inquire further about symptom response when the patient's bowel consistency and stool frequency improved. The provider asked about patient's abdominal pain and tried to address it by increasing the dose and frequency of linaclotide to 290 µg daily. Two months later the patient reported that her abdominal pain was "better than before", this was further quantified to be only a 50% improvement compared to her baseline. The abdominal pain remained bothersome and the patient was still missing work because of it and was clearly not satisfied with symptom control. The decision was made, in collaboration with the patient, to transition to tenapanor, a novel NHE3 inhibitor. She also underwent anorectal manometry and balloon expulsion

testing, suggesting evidence of dyssynergic defecation. She was thus referred for biofeedback and pelvic floor therapy, resulting in improved, more complete bowel movements.

Fortunately, clinicians now have more options than ever available to help optimize management of IBS-C symptoms; accordingly, this prompts providers to strive for higher levels of symptom control and treatment satisfaction. For example, in addition to relief of abdominal pain and stool consistency, considerations such as a patient's productivity, engagement in daily activities, and whether they are spending less time preoccupied about their symptoms are all very important treatment outcomes for the patient. Accordingly, these outcomes should be of utmost importance to GI providers and an essential component of the assessment of patient response to IBS-C therapies.

Disclosures

Dr. Sayuk is on the advisory committees/review panels of AbbVie, Ironwood, and Salix; is a speaker and consultant for AbbVie, Ironwood, Salix, Sanofi, Regeneron, and Rome Foundation; and a speaker for GI Health Foundation.

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