ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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GLP-1 RAs and Their Potential to Aggravate or Ameliorate Gastrointestinal Symptoms in IBS

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G&H What are the effects of glucagon-like peptide-1 receptor agonists in the gastrointestinal tract?

MC Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) affect the motor function and the sensory function. From a motor standpoint, the most common problem, or effect, is that the GLP-1 RAs delay gastric emptying. This delay may cause patients given these medications to have nausea or vomiting, especially during the dose escalation, in accordance with US Food and Drug Administration (FDA) guidance. Nevertheless, some patients may have nausea and vomiting. Some patients also may develop constipation or diarrhea. These bowel dysfunction symptoms have been reported to occur in approximately 10% to 20% of patients in different clinical trials, whereas nausea and vomiting at any one time may occur in up to 40% of patients. How this might be relevant in the context of irritable bowel syndrome (IBS) is self-evident: If the patient has diarrhea-predominant IBS, and the GLP-1 RA happens to accelerate colonic transit in that patient, then the diarrhea may become worse. However, in general, GLP-1 RAs tend to slow down motility and inhibit contractile activity, like the migrating motor complex, which is the housekeeper of the intestine that pushes residue down to the colon. If the patient has constipation-predominant IBS, then reducing the motility of the colon could also aggravate the constipation. On the other hand, if the patient happens to have diarrhea-predominant IBS, and the GLP-1 RA slows colonic transit, it could be a benefit to that patient. At the present time, it is very difficult to predict which agent is going to have which effect, but there is published evidence for these effects on altered bowel function and colonic transit.

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G&H Are any of the GLP-1 RAs more or less gut friendly?

MC From the adverse event profiles, no GLP-1 RA appears to be more or less gut friendly. This is because the prevalence of adverse effects with the 3 main classes of medications used mostly in clinical practice—liraglutide (Victoza and Saxenda, Novo Nordisk), semaglutide (Ozempic and Wegovy, Novo Nordisk), and tirzepatide (Zepbound and Mounjaro, Lilly)—have similar proportions of patients with symptoms of nausea, vomiting, diarrhea, and constipation. The gastroenterologist often cannot tell which is the good actor or the bad actor until after trial and error of the treatment in the individual patient.

G&H Could you discuss the evidence on how the effects of GLP-1 RAs vary by the type of IBS and changes in colonic transit?

MC There is evidence predominantly from physiologic studies for an analog of GLP-1 called ROSE-010, which was first tested in IBS in 2008 (although never marketed anywhere in the world). ROSE-010 inhibits the migrating motor complex, which is usually what propels content through the small intestine down towards the colon. ROSE-010 was also associated with slowing of gastric emptying. In a study my colleagues and I conducted at Mayo Clinic in patients with constipation-predominant IBS, paradoxically, ROSE-010 accelerated colonic transit. On the other hand, liraglutide given to patients with ileal pouch–anal anastomosis and prior colectomy reduced the number of bowel movements. In a study done with a wireless motility capsule, there was evidence that GLP-1 RAs slow colonic transit. There was a study using scintigraphy from Mayo Clinic in Arizona, which showed no significant effect on colonic transit measured at 24 hours. However, to demonstrate slowing of colonic transit, it is important to study the patient for 48 or 72 hours, not just 24 hours. In summary, there is evidence of slowing of transit in patients via the wireless motility capsule and in patients with ileal pouch–anal anastomosis.

Conversely, there are also rat studies, for example, that show acceleration of colonic transit, as well as a study in humans with type 1 diabetes mellitus and polyneuropathy showing acceleration of colonic transit.

There is still an incomplete understanding of the effects of GLP-1 RAs on the motor function of the gastrointestinal (GI) tract. One might wonder: What about sensory function? Indeed, there is increasing interest in the fact that the GLP-1 receptor is not only expressed on the vagus nerve, impacting appetite in the upper GI tract, but also on the first of the 3 nerves that take messages of pain and other symptoms from the GI tract to the spinal cord and brain. Thus, the dorsal root ganglion cell body also has a GLP-1 receptor. Conceivably, stimulating the GLP-1 receptor on that first nerve may change the ability to take the message of pain from the gut to the brain. The human evidence for that concept comes from a few studies of the GLP-1 analog ROSE-010 published in 2009 and 2022. The 2022 study showed that medication had a dose-related effect, particularly in females who were more likely to experience relief of their pain. In summary, there is evidence that there could be some benefit in patients with IBS in terms of the reduction of the pain sensation.

G&H What are the key factors to consider in patients with IBS on GLP-1 RAs?

MC The first important factor to consider is what is happening to their bowel dysfunction. Depending on how the bowel dysfunction either ameliorates or deteriorates, it is going to impact the dose selection and whether or not to continue this medication. The second is that many patients with IBS also have upper GI symptoms or functional dyspepsia. Because GLP-1 RAs in general can increase nausea and induce vomiting, and now that there is good evidence of delayed gastric emptying especially of solid food, it is possible that the GLP-1 RAs may aggravate symptoms, particularly in patients who have overlap of functional dyspepsia and IBS. I ask patients how their upper GI symptoms are faring now that they are on a GLP-1 RA.

G&H How should clinical recommendations for managing GI adverse effects of GLP-1 RAs be tailored to IBS patients?

MC In some respects, the same two concepts apply. One needs to assess the impact on the bowel dysfunction and the potential development of functional dyspepsia in these patients, especially if they have already had a history of the symptoms. However, there is a third very important point to add which is to take precautions for the patient on a GLP-1 RA who is about to undergo an endoscopy. There are many guidelines by many societies; some have the patient discontinue the GLP-1 RA 4 weeks ahead if they are on a weekly medication, or a week ahead if on a daily medication, to remove the medicine from the system. Another recommendation from anesthesiology societies is that the patient should have a point-of-care gastric ultrasound before the endoscopy to check to see whether their stomach is full. Not many endoscopy facilities actually have such point-of-care ultrasound capabilities. There are two very practical approaches I take in my practice to prevent putting patients at risk for aspiration. The first is to ask the patient on a GLP-1 RA to take a completely liquid, watery diet for the 24 hours before the procedure. The second is to ask patients whether they have symptoms like nausea, postprandial fullness, or vomiting. In other words, are they in that group of patients that already has delayed stomach emptying?

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To put this in perspective, both clinical trials and database studies have shown that the risk of aspiration

is not significantly greater in patients on GLP-1 RAs than, for example, in patients with diabetes who are on sodium-glucose cotransporter 2 inhibitors or some other therapy, or in the general population of patients having endoscopy. One could quote that literature to say the actual risk of pulmonary aspiration during upper GI endoscopy is extremely low. We also know that for people who are going to have colonoscopy, the risk of aspiration or retention of gastric food identified at upper GI endoscopy is extremely low, probably because they have emptied their bowel with the bowel preparation, and they are usually on a liquid diet the day before the procedure. In summary, it is important to think about the bowel dysfunction and functional dyspepsia and watch out for possible complications in endoscopy.

G&H What else can be done to help mitigate the GI adverse effects of GLP-1 RAs in patients with IBS?

MC One point to emphasize is that very often the symptoms or adverse effects occur during the dose escalation stage. One of the lessons we learned in our clinical trials with GLP-1 RAs is that not every patient can escalate at the same rate. We are very conscious when meeting with patients and changing their dose levels to ask them about their symptoms. Similarly with IBS patients, if they are having significant nausea and vomiting, it is important to not escalate to the next level but go slower. Likewise for a patient with diarrhea-predominant IBS who has worsening diarrhea on the GLP-1 RA, that medication is probably not good for them or a lower dose level may be required, and that may not achieve the desired objectives (weight loss or control of type 2 diabetes mellitus).

G&H Can the effects of GLP-1 RAs in the GI tract be leveraged to the benefit of IBS patients?

MC Absolutely yes, and I will defend the hypothesis based on what I discussed earlier. If the patient has rapid transit IBS with diarrhea, and the GLP-1 RA is going to slow colonic transit, that could benefit the patient. Conversely, if the patient has constipation-predominant IBS, and the GLP-1 RA accelerates colonic transit, as happened in our Mayo Clinic study in IBS with constipation, then that patient could benefit from being on a GLP-1 RA. The third effect still being investigated and researched is the possibility that the GLP-1 RA will reduce pain sensation and other sensations such as bloating and distension experienced by patients with IBS. The theory is that the GLP-1 RA in some way suppresses the function of the first-order neuron taking the sensory message from the GI tract to the spinal cord. Again, those 3 potential benefits depend on the transit profile and the impact on pain sensation.

G&H What further research is needed?

MC In my opinion, as a person who does almost exclusively human research, there is a need for both mechanistic trials and more formal clinical trials with validated patient response outcomes in accordance with FDA guidance regarding the approval of medications for the treatment of IBS. For instance, well-constructed studies are needed to evaluate GI and colonic transit for a full 48 or 72 hours, not stopping at 24 hours. Also, rectal sensation during distension needs to be evaluated to see whether GLP-1 RAs will reduce pain, sensation of gas, and sensation of bloating that comes from distension of a balloon in the rectum. These pharmacodynamic endpoints, transit and sensation, are very helpful from a pathophysiologic standpoint. It is especially important that more clinical trials are conducted to assess patient response outcomes, for example, the frequency and consistency of bowel movements, and average or worst pain daily recorded in the context of a 4- or 12-week trial. The effects of GLP-1 RAs are very significant in so many parts of the body, including the GI tract, and there is an opportunity to enhance the lives of patients with IBS and at least not make them any worse.

Disclosures

Dr Camilleri has served as an advisor to Lilly, with remuneration to his employer the Mayo Clinic, not to him personally.

Suggested Reading

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