Dr. Juan José Gorgojo Martínez
Endocrinology and Nutrition Department
Hospital Universitario Fundación Alcorcón (Madrid, Spain)

How to Improve Gastrointestinal Tolerance in Treatment with GLP-1 Receptor Agonists

1. INTRODUCTION

The development of GLP-1 receptor agonists (GLP-1 RAs) represents a historic milestone in the treatment of highly prevalent conditions such as type 2 diabetes (T2DM) and obesity (1). This therapeutic class enhances glycemic control in T2DM by stimulating insulin secretion and reducing glucagon secretion through a glucose-dependent mechanism, thereby lowering the risk of hypoglycemia. Additionally, GLP-1 RAs act on areas of the central nervous system involved in energy intake, such as the hypotha- »

» lamus and the mesolimbic reward circuit. This action induces appetite reduction, early satiety, and changes in food preferences toward lower-calorie options. These effects result in clinically significant weight loss, predominantly from fat mass, including both subcutaneous and visceral fat. Visceral fat accumulation around and within organs such as the liver, heart, and kidneys is a causal factor in T2DM and cardiovascular (CV) disease (1).

The antihyperglycemic and weight-loss efficacy observed in clinical trials with GLP-1 RAs surpasses that of other approved therapeutic classes for T2DM, excluding dual agonists of GLP-1/GIP receptors, whose first marketed representative is tirzepatide (2,3). This molecule shows even greater efficacy in glycemic control and weight loss than potent GLP-1 RAs like semaglutide, likely due to additional effects on the GIP receptor in the pancreas, central nervous system, and adipose tissue, which are still under investigation (1,3).

GLP-1 RAs exhibit direct benefits on the myocardium and atherosclerotic plaque in vascular walls, as well as indirect benefits on other CV risk factors, such as blood pressure, lipids, albuminuria, and low-grade inflammation[1]. Additionally, clinical benefits have been observed in other conditions, such as chronic kidney disease, sleep apnea, metabolic-associated steatohepatitis, and knee osteoarthritis[1]. A meta-analysis of clinical trials focused on CV safety of GLP-1 RAs in T2DM found significant reductions in a composite outcome of CV morbidity and mortality (MACE-3: CV death, non-fatal myocardial infarction, and non-fatal stroke), hospitalization for heart failure, and progression of chronic kidney disease[4]. Recently, semaglutide, a weekly administered GLP-1 RA, demonstrated a 20% reduction in CV morbidity and mortality in patients with obesity and established CV disease without DM[5], as well as clinical improvement of heart failure in patients with heart failure with preserved ejection fraction, both with and without T2DM[1].

The GLP-1 RAs currently marketed in our country for T2DM are subcutaneous liraglutide (1.2–1.8 mg/day), subcutaneous dulaglutide (0.75–1.5 mg/week), subcutaneous semaglutide (0.5–1.0 mg/week), and oral semaglutide (7–14 mg/day). Subcutaneous tirzepatide is the only dual GLP-1/GIP agonist approved for T2DM treatment (5–10 mg/week). Higher doses of these drugs are available in other countries but not in Spain (e.g., 2.0 mg weekly sc semaglutide, 3.0 and 4.5 mg weekly sc dulaglutide, 15 mg weekly sc tirzepatide). All these drugs, except dulaglutide, require an initial dose titration phase. The observation that these drugs achieved significant weight loss in patients with T2DM led to clinical trials for their approval in patients with obesity, using higher doses than those used in T2DM. Currently, the GLP-1 RAs approved for obesity treatment are subcutaneous liraglutide (3.0 mg/day) and subcutaneous semaglutide (2.4 mg/week). The only dual GLP-1/GIP agonist approved for obesity is tirzepatide, at the same doses authorized for T2DM (5–15 mg/week), although in our country, only the 5 and 10 mg doses are currently available.

2. GLP-1 RAS-RELATED ADVERSE EFFECTS

Numerous clinical trials and real-world observational studies show that the most common adverse effects (AEs) associated with GLP-1 RAs and dual agonists are gastrointestinal (GI) in nature, such as nausea, vomiting, diarrhea, and constipation. Their frequency in clinical trials ranges from 40% to 70% of treated patients (6). ***Table 1*** provides a summary of their frequency in phase III clinical »

GLP-1 RA	PROGRAM	INDICATION	DOSE	ADMINISTRATION	NAUSEA	VOMITING	DIARRHEA	CONSTIPATION
Semaglutide	SUSTAIN	T2DM	1.0 mg	SC weekly	15-24	7-15	7-19	4-7
Semaglutide	STEP	Obesity	2.4 mg	SC weekly	14-58	22-27	10-36	12-37
Semaglutide	PIONEER	T2DM	14 mg	Oral daily	8-23	6-12	5-15	7-12
Liraglutide	LEAD	T2DM	1.8 mg	SC daily	10-40	4-17	8-19	11
Liraglutide	SCALE	Obesity	3.0 mg	SC daily	27-48	7-23	16-26	12-30
Dulaglutide	AWARD	T2DM	1.5 mg	SC weekly	15-29	7-17	11-17	NR
Tirzepatide	SURPASS	T2DM	5-15 mg	SC weekly	12-18	5-9	12-16	6-7
Tirzepatide	SURMOUNT	Obesity	5-15 mg	SC weekly	22-28	8-13	17-22	11-17

TABLE 1. Frequency (% of affected patients) of GI AEs in clinical trials with currently marketed GLP-1 RAs or GLP-1/GIP dual agonists in Spain for people with T2DM or obesity

GLP-1 RAS EXHIBIT DIRECT BENEFITS ON THE MYOCARDIUM AND ATHEROSCLEROTIC PLAQUE IN VASCULAR WALLS, AS WELL AS INDIRECT BENEFITS ON OTHER CV RISK FACTORS, SUCH AS BLOOD PRESSURE, LIPIDS, ALBUMINURIA, AND LOW-GRADE INFLAMMATION

» trials for T2DM and obesity (6,7). GI AEs occur regardless of the half-life (short-/long-acting) or administration route (subcutaneous/oral) of the chosen GLP-1 RA. They are usually transient, typically arising during the dose-escalation phase, generally resolving shortly after reaching the maintenance dose. In most cases, they are mild to moderate in severity and do not lead to drug discontinuation. Real-world clinical experience with these drugs mirrors these observations.

Among the most common GI AEs, nausea consistently emerges as the most frequent event across all clinical trials. This is likely related to the transient delay in gastric emptying during the dose-titration phase and a direct effect on areas of the central nervous system associated with aversive responses and reduced GI tract motility[1]. The prevalence of other GI AEs is lower. In general, the occurrence of GI AEs is higher in trials designed to assess the safety and efficacy profile of these drugs in individuals with obesity. This may be attributed to the fact that doses are higher than those used in trials for people with T2DM. Long-acting drugs have been associated with less nausea and vomiting but more diarrhea, potentially due to a more sustained effect of these compounds on GLP-1 receptors in the intestines (6).

GLP-1 RAs slow gallbladder emptying stimulated by cholecystokinin and increase bile lithogenicity by inducing rapid weight loss and reducing fat intake, similar to what is observed in patients undergoing bariatric surgery. An increased number of gallbladder-related AEs, including cholelithiasis, cholecystitis, and biliary obstruction, has been reported in individuals with T2DM and obesity treated with this therapeutic class, although their incidence is very low, generally below 3% (1,6). Despite the information in the drug fact sheets, multiple clinical trials and meta-analyses have not demonstrated a causal association between GLP-1 RAs and the risk of acute pancreatitis (6).

GI AEs may lead to temporary or permanent discontinuation of GLP-1 RA treatment. While permanent discontinuations range from 3% to 10% of treated patients in clinical trials, according to the drug fact sheets of marketed medications in our country, real-world clinical practice shows that long-term treatment persistence with GLP-1 RAs is low, falling below 36% for some drugs after 1 year[8]. This phenomenon was observed even before the global supply issues with these drugs. Treatment persistence appears to be longer with weekly GLP-1 RAs vs those requiring daily injections.

Discontinuation of GLP-1 RA treatment can have significant clinical implications (9). For example, in clinical trials with semaglutide for obesity, two-thirds of the weight lost during treatment was regained within months after stopping the drug, accompanied by a deterioration in cardiometabolic and inflammatory parameters such as glucose levels, blood pressure, cholesterol, or C-reactive protein. Observational studies suggest an increased CV risk following GLP-1 RA discontinuation, similar to what occurs with other drugs such as statins or SGLT-2 inhibitors (9). Moreover, temporary interruptions can induce cyclical weight changes that result in muscle mass loss and an increased risk of sarcopenia.

Proper management of GI AEs can improve patient experience during treatment with GLP-1 RAs or dual agonists, preventing temporary or permanent discontinuation (6). This undoubtedly has a positive impact on treatment adherence, efficacy, CV and renal benefits, and quality of life for patients treated with these drugs. Therefore, it is essential that patients and healthcare professionals understand the correct procedures to prevent the occurrence of GI AEs or, if they occur, to mitigate their effects and improve adherence to treatment.

3. GENERAL GUIDELINES FOR PREVENTING AND MANAGING GI AES

Table 2 outlines general recommendations for patients to avoid the occurrence of GI AEs and reduce their intensity if they develop. It is worth dedicating a few minutes to explaining these recommendations to patients before initiating treatment. In rare cases of particularly intense and/or persistent GI AEs, healthcare professionals can implement the following additional measures (6):

- Follow the dose-escalation schedule outlined in the drug fact sheets to help patients gradually desensitize (tachyphylaxis) to excessive gastric emptying delays during treatment.
- If GI AEs arise during the dose-escalation phase, modify the planned schedule by implementing one or more of the following:
  - Ensure the patient understands and adheres to dietary recommendations.
  - Avoid dose increases while GI AEs persist.
  - If a GI AE occurs when transitioning to a higher dose, revert to the lower dose and maintain it for 2–4 weeks before gradually increasing again.

»

- For persistent tolerability issues, establish a maintenance dose lower than the maximum recommended in the drug fact sheet.
- In severe cases, temporarily discontinue treatment until the GI AEs resolve, then resume at a lower dose or restart dose escalation from the beginning.
- Conduct a differential diagnosis to rule out underlying conditions causing or exacerbating the symptoms (e.g., gastroenteritis or undiagnosed gastroesophageal pathology).
- Initiate symptomatic treatment tailored to the specific GI AE.
- Consider switching to another GLP-1 RA/dual agonist or changing the administration route, starting the new drug at its lowest dose.

4. SPECIFIC TREATMENT FOR GI AES

4.1 Nausea

Nausea is most common within the first 4–5 weeks of treatment, with symptoms typically resolving after an average of 8 days. The following measures are recommended to alleviate symptoms.6

- Review dietary and food composition recommendations with the patient.
- Consider antiemetic and/or prokinetic medications. Domperidone (10 mg three times daily) is preferred over metoclopramide, particularly for older patients, to minimize extrapyramidal side effects. For oral semaglutide, maintain a 30-minute gap between administering both medications. If antiemetic medication is required for over a month at the maintenance dose, consider reducing the GLP-1 RA dose to enable tolerance without pharmacological support.

4.2 Vomiting

Frequency and duration: Vomiting occurs less frequently than nausea but follows a similar temporal pattern. The initial measures do not differ substantially from those previously reviewed. In cases of abnormally prolonged persistence or unexpected severity,

GENERAL RECOMMENDATIONS
Follow the instructions in the product information leaflet regarding dosage and method of administration.
Improve eating habits.. • Eat slowly. • Eat only when very hungry. • Eat smaller portions. • Avoid lying down after eating. • Stop eating when feeling full. • Increase the frequency of meals. • Avoid drinking through a straw. • Eat without distractions and savor the food. • Try not to be too active after eating. • Avoid eating close to bedtime.
Adapt the composition of the diet to individual needs. • Choose easily digestible and chewable foods, avoid fatty or sugary foods. • Use simple cooking methods like baking, grilling, steaming, or boiling. • Increase fluid intake, especially water and calorie-free drinks (in small sips), drink liquids 1 hour before or after meals during the dose titration phase. • Consume foods high in water content (soups, liquid yogurts, jellies).
Regular physical exercise, preferably outdoors.
Keep a food diary, as it may be helpful to identify foods or meal times that worsen symptoms.
Additional recommendations for patients with nausea:
Consume foods that can relieve nausea symptoms, such as crackers, apples, mint, or ginger-based drinks.
Avoid spicy foods, foods with strong smells, alcohol, and carbonated drinks.
Additional recommendations for patients with vomiting:
Ensure proper hydration.
Eat smaller amounts of food in more frequent meals.
Additional recommendations for patients with diarrhea:
Ensure abundant hydration, e.g., with water, lemon, and a teaspoon of baking soda.
Avoid sports isotonic drinks (spare them for the practice of sports only).
Avoid dairy products, juices, laxative foods, coffee, alcoholic drinks, sodas, very cold or hot foods, products containing sweeteners ending in "ol" (sorbitol, mannitol, xylitol, maltitol), including candies and chewing gum.
Temporarily reduce intake of fiber-rich foods like whole grains, nuts, vegetables, and legumes such as artichokes, asparagus, beans, cauliflower, garlic, mushrooms, onions, peas, lentils, fruits with skins, apricots, blackberries, cherries, mangoes, nectarines, pears, and plums. They should be resumed later because they are heart-healthy.
Consume chicken broth, rice, carrots, ripe fruit without skin, baked fruit.
Additional recommendations for patients with constipation:
Ensure an adequate amount of fiber in the diet.
Increase physical activity.
Ensure the diet is healthy and balanced.
Drink generous amounts of water (or other sugar-free liquids).

TABLE 2. Recommendations to minimize the appearance/severity of GI AEs when starting treatment with GLP-1 RAs. Reference 6.

» additional actions may be implemented6.

- Ensure adequate hydration to prevent complications such as volume depletion or acute renal failure, especially in older patients.
- Consume small amounts of food in more frequent meals.
- Prescribe antiemetic and/or prokinetic drugs, with domperidone as the drug of choice.
- For severe dehydration or oral intolerance, assess the patient in an emergency setting to rule out other conditions and initiate IV hydration and antiemetic therapy. Temporarily discontinue or reduce the drug dose, with close patient monitoring.

4.3 Diarrhea

Diarrhea begins during the first four weeks of treatment, after which its incidence decreases significantly. Symptoms are reported to last an average of three days. The following measures can help resolve or reduce the severity of diarrhea6.

- Review dietary recommendations with patients to mitigate diarrhea.
- If symptoms persist, consider probiotic supplements and/or antidiarrheal agents like loperamide. For patients on metformin and omeprazole, reduce the metformin dose if GLP-1 RAs exacerbate pre-existing diarrhea. In these cases, down titrating metformin can be considered.
- If all else fails, reduce the drug dose, change the administration route, or switch to a different drug at the lowest dose.

4.4 Constipation

Constipation occurs more frequently in patients with obesity than in those with T2DM. It may begin within the first 16 weeks of treatment, particularly during the initial 28 days, and tends to last longer than other GI AEs, with an average duration of 47 days. It is recommended to review the following points with the patient to alleviate constipation symptoms.6 »

- Encourage increased water intake, as GLP-1 RAs reduce fluid consumption.
- Promote bowel habit reeducation.
- Increase dietary fiber intake.
- Consider stool-softening laxatives.
- In severe cases, reduce the drug dose, change the administration route, or switch to another molecule at the lowest dose.

4.5 Gallbladder-related AEs

This is an uncommon AE, but its likelihood of occurrence is higher in patients with a history of pancreatitis or gallbladder disease. Therefore, caution should be exercised in patients with such a medical history.

- Avoid excessive dietary fat restriction; instead, provide adequate amounts of heart-healthy fats rich in oleic acid and omega-3 to prevent gallbladder hypomotility.
- Although no clinical trials have been published, ursodeoxycholic acid (500 mg/day for six months) may be administered prophylactically to patients with a history of cholelithiasis or those experiencing rapid weight loss, as is done for bariatric surgery patients (10).
- For pancreatobiliary complications, manage according to institutional protocols (e.g., cholecystectomy or gallstone removal). Temporarily suspend GLP-1 RA treatment until the underlying cause is resolved. D

CONCLUSIONS

GLP-1 RAs and dual GLP-1/GIP agonists are highly effective drugs with favorable safety profiles for the treatment of T2DM and obesity. Patients should be informed before starting treatment about the potential for GI AEs, which are likely to be mild to moderate and transient, provided the dose-escalation schedule in the drug fact sheet is followed. Educating patients on dietary guidelines can help prevent or mitigate these AEs. Healthcare professionals should flexibly adapt dose-escalation schedules and provide symptomatic treatment for severe and/or persistent AEs. The ultimate goal is to ensure patients maintain the long-term cardiometabolic, renal, and quality-of-life benefits provided by this therapeutic class.

REFERENCES

1. Drucker DJ. Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity. Diabetes Care. 2024 Nov 1;47(11):1873-1888.
2. Karagiannis T, Avgerinos I, Liakos A, Del Prato S, Matthews DR, Tsapas A, Bekiari E. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. Diabetologia. 2022 Aug;65(8):1251-1261.
3. de Mesquita YLL, Pera Calvi I, Reis Marques I, Almeida Cruz S, Padrao EMH, Carvalho PEP, da Silva CHA, Cardoso R, Moura FA, Rafalskiy VV. Efficacy and safety of the dual GIP and GLP-1 receptor agonist tirzepatide for weight loss: a meta-analysis of randomized controlled trials. Int J Obes (Lond). 2023 Oct;47(10):883-892
4. Sattar, N.; Lee, M.; Kristensen, S.L.; Branch, K.; Del Prato, S.; Khurmi, N.S.; Lam, C.; Lopes, R.D.; McMurray, J.; Pratley, R.E.; et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021, 9, 653-662.
5. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I, Oral TK, Michelsen MM, Plutzky J, Tornøe CW, Ryan DH; SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023 Dec 14;389(24):2221-2232.
6. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, Castro A, Cebrián-Cuenca A, de Torres-Sánchez A, García-de-Lucas MD, Núñez J, Obaya JC, Soler MJ, Górriz JL, Rubio-Herrera MÁ. Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with Glp-1 Receptor Agonists: A Multidisciplinary Expert Consensus. J Clin Med. 2022 Dec 24;12(1):145.
7. Ficha técnica Mounjaro EMA 2024. https://cima.aemps.es/cima/dochtml/ft/1221685014/FT_1221685014.html. Consultado el 24 noviembre 2024.
8. Gasoyan H, Pfoh ER, Schulte R, Le P, Butsch WS, Rothberg MB. One-Year Weight Reduction With Semaglutide or Liraglutide in Clinical Practice. JAMA Netw Open. 2024 Sep 3;7(9):e2433326
9. Khan SS, Ndumele CE, Kazi DS. Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists. JAMA. 2024 Nov 13. doi: 10.1001/jama.2024.22284. Epub ahead of print. PMID: 3953574.
10. Al-Huniti M, Alsardia Y, Odeh A, Bdour B, Hassanat R, Aloun A, Sha'ban BW, Nseirat SM. Ursodeoxycholic Acid Prophylaxis and the Reduction of Gallstone Formation After Bariatric Surgery: An Updated Meta-Analysis of Randomized Controlled Trials. Cureus. 2023 Dec 17;15(12):e50.