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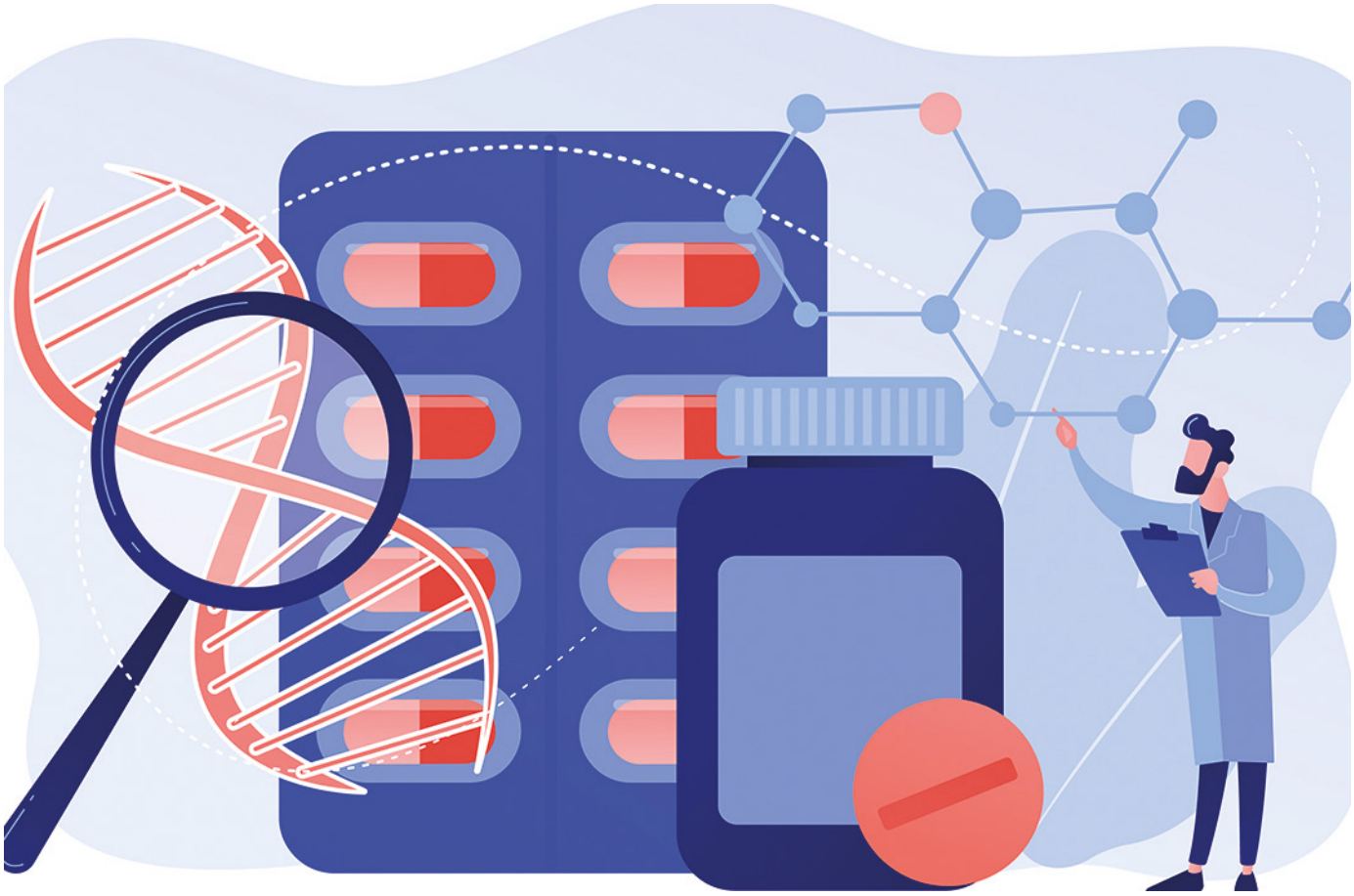


Real-Life Experience with a GLP-1 Receptor Agonist: Oral Semaglutide

Type 2 diabetes mellitus (T2DM) is a disease that affects millions of people worldwide. In Europe, the number of adults with T2D is expected to reach 67 million by 2030 and 69 million by 2045. In Spain, around 386,000 new cases of T2D are diagnosed annually in the adult population.

As the prevalence of T2DM increases, so does the incidence of cardiovascular diseases (CVD) and chronic kidney disease (CKD), so that even at the level of primary care, most people living with type 2 diabetes (PLT2DM) are at a high/very high risk of fatal cardiovascular (CV) events. Consequently, there is a critical need for effective treatments that provide better glycemic control, promote relevant weight loss, and deliver favorable benefits on cardiovascular and renal outcomes, while also reducing the risk of severe complications.

ORAL SEMAGLUTIDE

In the quest for treatments that address the disease in a comprehensive and holistic way, the therapeutic family of glucagon-like peptide-1 receptor agonists (GLP-1RAs) has developed significantly. These drugs are analogs of the incretin peptide GLP-1, a natural hormone produced in the small intestine in response to food intake, whose main mechanism of action includes glucose-dependent insulin release from the pancreas, reducing glucose production by the liver, and slowing gastric emptying, among others, to improve glycemic control and promote satiety. It has been shown that these GLP-1RAs improve glycemic control with a very low risk of hypoglycemia, significantly reduce body weight, and some of them even offer benefits in cardiovascular (CVD) and renal diseases. All this justifies why the main evidence-based clinical practice guidelines advocate for starting a GLP-1RA with demonstrated CV benefit as first-line therapy in PLT2DM with high CVD risk or established atherosclerotic CVD, regardless of HbA1c levels or other concomitant antihyperglycemic treatments. Similarly, there is strong support for the supplementary use of GLP-1RAs in PLT2DM with CKD.

Currently, semaglutide is considered the most effective GLP-1RA, given its powerful effects on glucose reduction and weight loss. A feature of this family is that, traditionally, administration had to be parenteral or injectable. However, relatively recently, we have an important innovation: the development of oral semaglutide in pill form, being the first of its kind. This could be a very interesting option in circumstances where traditional injectable formulations are not available, in countries or regions where accessibility poses a challenge, and when the proper storage of the medication cannot be ensured, beyond the individual's own preference for managing diabetes mellitus. Currently, there is a shortage of injectable treatments, and since November 2022, oral semaglutide has become an alternative that has prevented the discontinuation of these therapies for thousands of people in Spain.

EVIDENCE IN ROUTINE CLINICAL PRACTICE

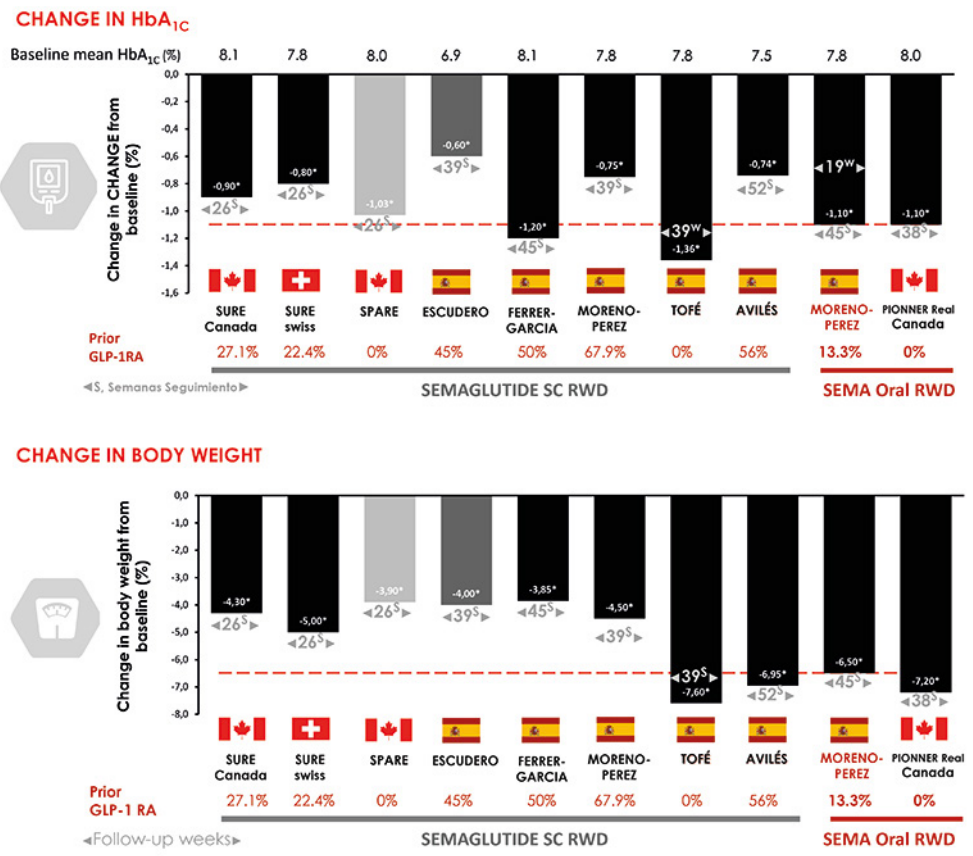
Although randomized clinical trials (RCTs) are the gold standard for assessing the safety and efficacy profile of new therapeutic agents, the strict criteria for including PLT2DM in these studies, which often exclude elderly individuals or those with many associated complications, often result in a low ability to extrapolate the results obtained from these trials to other PLT2DM treated in routine clinical practice. Therefore, as with any therapy, **studies on the real-world** use of oral semaglutide are essential to provide evidence of the effectiveness and safety of this treatment in the routine clinical practice. Real-world studies with oral semaglutide were primarily based on population databases, not designed for research, with short follow-ups, a significant lack of relevant data, or studies with a very small number of PLT2DM studied. Since the available real-world evidence on oral semaglutide was scarce and of limited quality, a Spanish group of researchers, representing the Diabetes Area of the Spanish Society of Endocrinology and Nutrition, conducted a study called ENDO2S-RWD *(ENDOcrinology Oral Sema Real-World Data)* with the aim of exploring the real-world safety and efficacy of oral semaglutide in unselected PLT2DM in a national clinical setting. Below, we will briefly present the characteristics of this clinically significant study, as it represents the largest population on oral semaglutide evaluated worldwide and because it allows an approach to the factors associated with medium-term therapy maintenance, as well as to identify groups of PLT2DM who will benefit most from the initiation of this treatment.

THE ENDO2S-RWD TRIAL

The ENDO2S-RWD trial is a retrospective observational multicenter real-world study with more than 1000 PLT2DM who started treatment with oral semaglutide between November 2021 and November 2022 in 12 departments of the Spanish National Health System. **The study demonstrated that the use of oral semaglutide was safe and effective. Overall, the composite endpoint of ≥ 5% weight loss plus ≥1% HbA1c reduction was achieved in more than a third of patients in the mid-term, and** »

CURRENTLY, SEMAGLUTIDE IS CONSIDERED THE MOST EFFECTIVE GLP-1RA (GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS) DUE TO ITS POWERFUL EFFECTS ON GLUCOSE REDUCTION AND WEIGHT LOSS

FIGURE 1. Comparison of clinical outcomes in routine clinical practice with subcutaneous or orally administered semaglutide.



p < 0.05. Data corresponds to 6-12 months post-initiation. GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; RWD; real-world data.
SURE Canada, Diabetes Canada/CSEM Professional Conference. October 28–30, 2020, Virtual event. Poster 64; SURE Switzerland, G. Rudofsky et al. Presented (online) at the Swiss conference Schweizerischen Gesellschaft für Endokrinologie und Diabetologie on November 13th, Poster 86; SPARE, Brown et al. Diabetes Obes Metab 2020; doi: 10.1111/dom.14117; Ferrer-Garcia et al. 80th Virtual Scientific Sessions of the ADA, 12–16 June 2020. Poster 947-P; Moreno-Perez O. Congreso SEEN, October 2020; Tofé S, et al. Endocrine and Metabolic Science, 2021, 100082., Avilés et al. Clin Kidney J. 2022 Apr 11; 15(8):1593-1600, Moreno-Perez O. et al. Diabetes Obes Metab. 2024;1-5. doi:10.1111/dom.1543. Jain AB, et al. Diabetes Obes Metab. 2024 Mar 11. doi: 10.1111/dom.15493.

ORAL SEMAGLUTIDE IS A HIGHLY SAFE AND EFFECTIVE THERAPEUTIC OPTION FOR MANAGING T2DM IN THE ROUTINE CLINICAL PRACTICE, SERVING AS AN ALTERNATIVE THERAPY IN LIGHT OF THE SHORTAGE OF SUBCUTANEOUS GLP-1RA

» **around 50% of patients with worse metabolic control or higher body mass index (BMI). Additionally, weight loss was > 10% in a third of cases, and more than 2 out of 3 patients achieved HbA1c levels < 7%.** Of note that a third of PLT2DM were not on the 14 mg dose, the highest potency available with oral semaglutide. The rate of serious adverse events was very low, reported by only 0.2% of patients, with a safety profile similar to that of the GLP-1RA family. The most common side effects were related to GI tolerance, and treatment discontinuation was mainly due to lack of continuity in medical care and GI intolerance.

In terms of associated factors of response and continuity of drug use, after adjusting for confounding factors, a higher HbA1c (poorer metabolic control) and BMI (greater degree of obesity) turned out to be predictors of a greater response, while the previous use of GLP-1RA when initiating oral semaglutide reduced its effectiveness. Finally, a higher weight and initial prescription of the drug by an endocrinologist were associated with the maintenance of oral semaglutide treatment over time. If looking for explanations, it could be speculated that more severe obesity might justify greater adherence and a greater initial acceptance of GI effects, »

» while the role of endocrinological prescription as a protective factor in the mid-term could be due to the familiarity with known side effects in this therapeutic group, providing detailed guidance to patients on how to manage them and establishing strategies to minimize them and ensure therapeutic adherence. In this sense, **doctor-patient communication is crucial to meet therapeutic objectives, set realistic expectations, and optimize outcomes in the treatment of this chronic disease.** Greater continuity of care and direct communication with primary care from endocrinology could also be key factors in these findings.

Although it has some limitations inherent to its retrospective design, the results of the ENDO2S-RWD study are comparable and consistent with previous research that has evaluated the safety and efficacy profile of oral semaglutide in PLT2DM, such as the IGNITE and PIONEER REAL CANADA studies, which showed similar results in terms of HbA1c reduction and weight loss with the use of oral semaglutide in real-world settings. Additionally, it supports the results obtained in the PIONEER clinical trial program, the clinical development program for oral semaglutide.

While the homogeneity of the results with oral semaglutide supports the safety and efficacy of this drug in unselected populations, from a practical standpoint, seeking a clinical translation of the results, it is very relevant to compare these results with those obtained in real life with the same molecule but in its subcutaneous formulation. Assuming the inherent limitations of the differences in the studied populations, we can summarize that the percentage of patients with HbA1c < 7% or weight losses ≥ 10% with oral semaglutide, which is similar to that of other studies with real-world data using subcutaneous semaglutide, such as the study by Marzullo et al., the SPARE trial, and the post-hoc pooled analysis of SURE. The ENDO2S-RWD safety profile was, also, consistent with interruption rates with oral semaglutide, which is similar to the rates from retrospective studies on subcutaneous semaglutide and higher than the rates from the SURE pooled prospective studies (Figure 1).

SUMMARY AND FUTURE PERSPECTIVES

In summary, all these findings support the idea that **oral semaglutide is a very safe and effective therapeutic option for managing PLT2DM in daily clinical practice, being an alternative treatment option given the shortage of subcutaneous GLP-1RA administration.** The ENDO2S-RWD trial, as the largest published multicenter study to date, adds robustness to the available real-world evidence on the use of oral semaglutide in more than 1000 unselected PLT2D, with a third of patients experiencing >10% weight loss and approximately two-thirds achieving HbA1c < 7%. The ENDO2S-RWD results may be useful to support clinical decision-making and position GLP-1RAs as key players in the holistic approach to PLT2DM, a chronic disease based on adiposity and the cardio-renal-metabolic syndrome. Furthermore, ENDO2S-RWD outlines 2 key elements to maximize adherence and therefore the benefits derived from the use of oral semaglutide (metabolic, weight, cardiovascular, and renal), and ensure therapeutic success:

1. The importance of a person-centered approach, focusing on detailed information about potential benefits and side effects, along with specific preventive strategies, as well as the consensus of different treatment goals.

2. The crucial importance of continuity of care and the interrelationship between the different specialties involved in the care of people with diabetes, including family and community medicine. D

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