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ORIGINAL RESEARCH

Gastrointestinal disorders potentially associated with Semaglutide: an analysis from the Eudravigilance Database

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ABSTRACT

Background: Semaglutide is a Glucagon-like peptide-1 receptor agonist used in the second-line treatment of poorly controlled type 2 diabetes and can be used in monotherapy or associated with other oral antidiabetics or even insulin, increasing the effectiveness of the treatment. This work aims to analyze the profile of adverse drug reactions reported for semaglutide in Eudravigilance.

Research design and methods: Data on Individual Cases Safety Reports were obtained from the database of the centralized European spontaneous reporting system Eudravigilance by accessing www.adrreports.eu. (1 December 2021).

Results: It is possible to observe a high prevalence of gastrointestinal disorders (N = 3502, 53.2%). The most severe reported cases were primarily gastrointestinal disorders, metabolic, and nutritional disorders, eye disorders, renal and urinary disorders and cardiac disorders, with an evident higher prevalence of adverse gastrointestinal events both in oral and injectable dosage form (N = 133, 50.0% vs N = 588, 47.2%, respectively). Through a comparative analysis, semaglutide had a greater number of reported gastrointestinal adverse events compared to sitagliptin and empaglifozin ($p < 0.00001$).

Conclusions: Semaglutide has a good safety profile, however the definition of subgroups within the type 2 diabetes population who are particularly prone to develop serious adverse event when treated with GLP-1 RAs is crucial.

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Semaglutide; adverse drug reactions; Eudravigilance Database; Glucagon-like peptide-1; type 2 diabetes

1. Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that acts by increasing endogenous insulin levels and decreasing glucagon secretion as a function of glucose levels [1].

GLP-1 receptor agonists (GLP-1 RAs) are used in the second-line treatment of poorly controlled type 2 diabetes (DM2) and can be used in monotherapy or associated with other oral antidiabetics or even insulin, increasing the effectiveness of the treatment [2,3]. They are approved for the treatment of DM2 and obesity, allowing for better glycemic control, weight loss, in addition to being associated with a cardioprotective effect [4]. Currently, semaglutide is being studied within the scope of clinical trials, as it may influence metabolic and histological aspects of nonalcoholic steatohepatitis and, therefore, it is considered a strong candidate for the treatment of this pathology, both in the improvement of liver histology and fibrosis stage [5].

Semaglutide is a recent GLP-1 RA that is available as an injectable dosage form for weekly administration as well as in oral dosage form for daily administration, simplifying the therapeutic regimen and facilitating patient adherence [6–8]. Compared to liraglutide, which is given once daily, semaglutide has a considerably longer half-life, allowing for once-weekly administration [9]. GLP-1RAs decrease blood glucose levels by stimulating glucose-dependent insulin secretion, so hypoglycemia is an infrequent problem and inhibition of glucagon secretion does not occur under hypoglycemic conditions [10].

In patients with or without established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), for whom it is critical to promote body weight reduction, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend drugs GLP-1RA and sodium-glucose cotransporter inhibitors (SGLT2i) as the preferred second-line treatment option for patients with poor glycemic control despite the use of metformin [11,12]. The American Association of Clinical Endocrinologists/American College of Endocrinology consensus also recommends a GLP-1RA or SGLT2i as the preferred treatment option (second-line treatment after metformin) as an alternative to other therapeutic options such as a dipeptidyl peptidase-4 inhibitor (iDPP-4), a thiazolidinedione (TZD), or a sulphonylurea (SU), for patients with DM2 and ASCVD, stage 3 CKD or insufficiency heart disease with reduced ejection fraction [13].

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Semaglutide is used not only in DM2 treatment but also obesity (was approved by the US Food and Drug Administration for chronic weight management) [14]. Its efficacy and safety have been demonstrated when administered subcutaneously at a dose of 2.4 mg once a week in obese patients, with or without diabetes or any other type of associated complication [15,16].

The most frequent adverse events described for the GLP-1RA class, in general, are gastrointestinal (GI) adverse events, such as nausea, vomiting, diarrhea, dyspepsia, and constipation, in addition to an increased risk of worsening diabetic retinopathy [17–21]. By the way, it has been hypothesized that retinophaty worsening is transient and is due to the rapid effect of reducing glycosylated hemoglobin by semaglutide. Over 40 weeks, the SUSTAIN-FORTE study showed the increased potential benefit of semaglutide in this domain [21,22].

This work aims to analyze the profile of adverse drug reactions (ADRs) reported for semaglutide in Eudravigilance (EV), which is a system for managing and analyzing information on suspected adverse reactions to medicines that have been authorized or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network.

2. Materials and methods

In the European Union, all drugs have a risk management plan (RMP) (DIRECTIVE 2010/84/EU) in order to guarantee their therapeutic efficacy and the monitoring of their safety profile [23]. According to the RMP, more data on efficacy and safety are routinely collected through post-marketing studies and reports, which will be regularly reviewed by the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance and Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) [24,25].

2.1. Data source

Data on Individual Cases Safety Reports (ICSRs) were obtained from the database of the centralized European spontaneous reporting system EV by accessing www.adrreports.eu (1 December 2021). The EV, funded by the EMA, is a system for managing and analyzing ICSRs of suspected ADR [25–27].

3. Individual Cases Safety Reports Selection and Descriptive Analysis

- We selected all ICSRs with semaglutide as a suspected drug reported in EV since the approval of its use by the EMA on 8 February 2020 (oral dosage form) or 3 April 2018 (injectable dosage form) until 1 December 2021. Information was collected on sex, age group, primary source, outcome by reaction group and seriousness.
- Qualitative and quantitative analysis for the main outcomes of ICSRs, with more serious ADRs, was carried out from January 1 to 1 December 2021.
- A comparison was made between reported ICSRs, classified as serious, for semaglutide, sitagliptin (iDPP4), and empagliflozin (SGLT2) (whose ICSRs were also extracted and analyzed). This comparative analysis was included as sitagliptin and empagliflozin fall within the same therapeutic approach as semaglutide (second-line treatment for poorly controlled type 2 diabetes), although with different mechanisms of action [28–30].
- A more detailed analysis was also carried out by selecting all ICSRs with semaglutide as a suspected drug reported in EV from 1 October to 1 December 2021 (oral and injectable form). Information was collected on sex, age group, outcome, number of GI events per ICSR, the overall number of suspected ADRs and concomitant medications reported.
- Statistical Analysis – For the statistical analysis IBM SPSS statistics 28 (IBM, Armonk, NY, USA) was used. Categorical variables were described through their respective absolute and relative frequencies (percentages). Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

Each ICSR may include one or more suspected ADR.

Data collection and analysis follow the MedDRA (Medical Dictionary for Regulatory Activities) organizational and hierarchical structure regarding the clinical manifestations (ADRs) included in each ICSR, which are grouped according to System Organ Classes (SOC).

4. Results

4.1. Demographic characteristics of ICSRs

Since the date of marketing authorization in the European Union (8 February 2018 and 3 April 2020 for the injectable and oral dosage forms, respectively), 6584 ICSRs have been reported based on suspicion of drug use. Of those, 550 were related to the oral dosage form and 6034 were related to the injectable dosage form. No statistically significant difference was found between sex and the dosage form used ($p = 0.20437$): 2942 (44.7%) were reported for male patients and 3491 for female (53.0%), with 151 (2.3%) not specifying sex. Most cases refer to the adult population, with 2544 (38.6%) of the cases in the age group 18–64 years, 1593 (24.2%) cases for the age group 65–85 years and 2404 (36.5%) with no specified age group. 4455 (67.7%) of the ICSRs were reported by health professionals and the majority occurred in the European Economic Area (N = 3715, 56.4%) versus Non-European Economic Area (N = 2869, 43.6%). Concerning the individual cases reported by SOCs it is possible to observe a high prevalence of gastrointestinal disorders (N = 3502, 53.2%) (Table 1).

Regarding the seriousness of reported ADRs (serious v nonserious), a statistically significant difference was found

Table 1. Demographic characteristics of ICSRs involving semaglutide reported in the EudraVigilance spontaneous reporting system from 8 February 2018 (injectable form) or 3 April 2020 (oral form) to 1 December 2021.

	Individual Case Safety Reports 6584 (%)		
	Oral dosage forms N = 550	Injectable dosage forms N = 6034	Total N = 6584
Sexb			
Male	246 (44.7)	2696 (44.7)	2942 (44.7)
Female	262 (47.6)	3229 (53.5)	3491 (53.0)
Not specified	42 (7.6)	109 (1.8)	151 (2.3)
Age group			
Pediatrics (<18 Years)	0	6 (0)	6 (0.1)
Adult (18–64 Years)	171 (31.1)	2373 (39.3)	2544 (38.6)
Elderly (65–85 Years)	123 (22.4)	1470 (24.4)	1593 (24.2)
Very Elderly (>85 Years)	6 (1.1)	31 (0.5)	37 (0.6)
Not Specified	250 (45.5)	2154 (35.7)	2404 (36.5)
Type of reporter			
Health Care Professional	398 (72.4)	4057 (67.2)	4455 (67.7)
Non-Health Care Professional	152 (27.6)	1977 (32.8)	2129 (32.3)
Region			
European Economic Area	193 (35.1)	3522 (58.4)	3715 (56.4)
Non-European Economic Area	357 (64.9)	2512 (41.6)	2869 (43.6)
Individual cases reported by system organ classes [a]			
Total adverse events	1029	11,967	12,996
Gastrointestinal disorders	294 (53.5)	3208 (53.2)	3502 (53.2)
Nervous system disorders	85 (15.5)	817 (13.5)	902 (13.7)
Metabolism and nutrition disorders	82 (14.9)	926 (15.3)	1008 (15.3)
Cardiac disorders	41 (7.45)	251 (4.2)	292 (4.4)
Eye disorders	29 (5.3)	424 (7.0)	453 (6.9)
Infections and infestations	22 (4.0)	303 (5.0)	325 (4.9)
Muskoloskeletal and connective tissue disorders	24 (4.4)	267 (4.4)	291 (4.4)
Renal and urinary disorders	30 (5.5)	292 (4.8)	322 (4.9)
Psychiatric disorders	28 (5.1)	244 (4.0)	272 (4.1)
Skin and subcutaneous disorders	32 (5.8)	380 (6.3)	412 (6.3)
Number of individual cases			
Serious	369 (67.1)	3112 (51.6)	3481 (52.9)
Non serious	181 (32.9)	2922 (48.4)	3103 (47.1)

[a]10 most reported ADRs were considered (percentages presented by reported cases).
bPearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

($p < 0.00001$) between oral dosage form (N = 369,67.1% N = 181, vs 32.9%) and injectable dosage form (N = 3112,51.6% vs N = 2922, 48.4%) (Table 1).

4.2. Main reported SOCs

No statistically significant differences were found between the two dosage forms regarding the main SOCs reported (Table 2).

The most serious reported cases from 1 January to 1 December 2021, were primarily GI disorders, metabolic, and nutritional disorders, eye disorders, renal and urinary disorders, and cardiac disorders, with an evident higher prevalence of adverse GI events both in oral dosage form (N = 133, 50.0%) and injectable dosage form (N = 588, 47.2%). The main symptoms reported were vomiting, pancreatitis, nausea, diarrhea, and constipation (Table 2).

4.3. Comparative analysis between semaglutide, sitagliptin, and empagliflozin

For the same period (1 January to 1 December 2021), the most serious adverse events reported for semaglutide, sitagliptin, and empagliflozin were compared, with a higher percentage of GI ADRs reported for semaglutide (47.7%) compared to sitagliptin (34.7%) and empagliflozin (9.8%) ($p < 0.00001$). A higher number of cases of eye disorders were also reported concerning semaglutide (7.9%) compared to sitagliptin (4.2%) and empagliflozin (0.8%), (**$p < 0.00001$**) (Figure 1).

*Pearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

4.4. Characteristics of ICSRs which include Gastrointestinal disorders

Through a detailed analysis of the ICSRs reported with semaglutide as suspected of causing ADR, in a more restricted period (2 months), 164 ICSRs were collected with at least one reported GI disorder. The sex difference was 42.1% vs. 56.7% (male vs. female). However, only 3 ICSRs (1.8%) reported a fatal outcome. Nevertheless, there is a significant percentage of ICSRs that do not refer to the outcome of reported ADRs (43.9%). Most ICSRs reported only one GI adverse event (51.8%), with 745 overall (GI and non-GI) adverse events reported (Table 3).

5. Discussion

Semaglutide is a relatively recent antidiabetic drug on the European market and has shown great efficacy in the

Table 2. Main reported SOCs for oral and injectable semaglutide dosage forms from 1 January to 1 December 2021.

SOC		Individual Case Safety Reports (%)				p-valuea
		Oral form Total (N = 266)		Injectable form Total (N = 1246)		
Gastrointestinal disorders	Vomiting	133	40 (30.1)	588	153 (26.0)	0.40534
	Pancreatitis	(50.0)	35 (26.3)	(47.2)	126 (21.4)	
	Nausea		31 (23.3)		161 (27.4)	
	Diarrhea		20 (15.0)		134 (22.8)	
Metabolism and nutrition disorders	Diabetes inadequate control	40	6 (15.0)	236	6 (2.5)	0.13467
	Dehydratation	(15.0)	10 (25.0)	(18.9)	75 (31.8)	
	Decreased appetite		15 (37.5)		75 (31.8)	
	Diabetic Ketoacidosis		6 (15.0)		21 (8.9)	
Eye disorders	Visual impairment	20	5 (25.0)	99	18 (18.2)	0.81453
	Blindness	(7.5)	2 (10.0)	(7.9)	2 (2.0)	
	Diabetic retinophaty		2 (10.0)		11 (11.1)	
	Vision blurred		2 (10.0)		9 (9.1)	
Renal and urinary disorders	Acute kidney injury	21	12 (57.1)	113	40 (35.4)	0.54072
	Renal failure	(7.9)	0	(9.1)	16 (14.2)	
	Nephropaty		0		3 (2.7)	
	Chronic kidney disease		3 (14.3)		11 (9.7)	
Cardiac disorders	Angina pectoris	27	0	88	6 (6.8)	0.08461
	Atrial fibrillation	(10.2)	7 (25.9)	(7.1)	10 (11.4)	
	Tachycardia		2 (7.4)		6 (6.8)	
	Myocardial infarction		8 (29.6)		15 (17.0)	

aPearson's Chi-Square test was used to verify a possible relationship between these variables with a statistical significance level of 5% ($p < 0.05$).

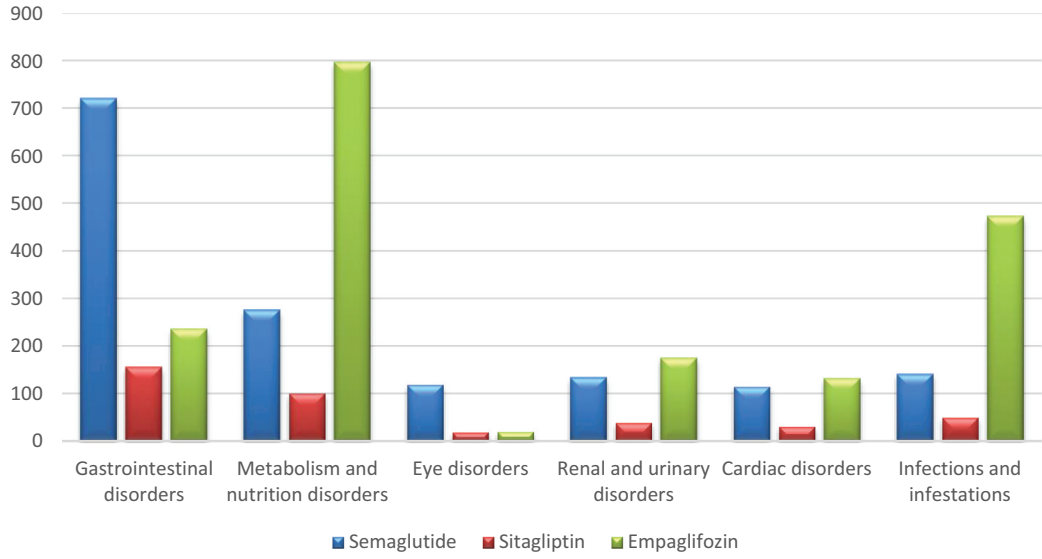

Figure 1. Comparative analysis for the main reported system organ classes (SOCs) adverse events for semaglutide, satagliptin and empagliflozin from 1 January to 1 December 2021.

treatment of DM2 contributing to a significant reduction in Hb1Ac and weight loss, with a low incidence of adverse drug events [9,31]. It can be used in a wide spectrum of DM2 patients, both in primary and secondary prevention, as monotherapy associated with a healthy lifestyle when metformin is contraindicated or combined with other oral antidiabetics and insulin [32,33]. The choice between the oral or injectable dosage form must be made based on the characteristics of each patient, meeting their need [34,35]. The injectable dosage form allows for weekly administration, making the treatment more convenient for the patient and contributing to better adhesion to therapy [36–38]. The benefits of semaglutide in terms of reducing the risk of cardiovascular disease in DM2 patients are in line with the remaining GLP-1 RAs [39,40] .

Spontaneous reports of semaglutide-related ADRs were investigated by analyzing data obtained from EV, to achieve a global view of suspected ADRs, with a focus on gastrointestinal disorders.

Out of a total of 6584 ICSRs reported (mostly by healthcare professionals) from the dates of issue of the marketing authorizations valid throughout the European Union for the oral and injectable forms of semaglutide, it was found that the number of reports was slightly higher for female patients. Some risk factors may justify the higher incidence of adverse events in females, such as higher consumption of medications among women, pharmacokinetic, pharmacodynamic, immunological, and hormonal specificities associated with gender, lower lean body mass index, or differences in terms of the activity of cytochrome P450 enzymes compared to men [41,42].

Table 3. Characteristics of individual cases reported for patients treated with semaglutide (oral and injectable forms) which include gastrointestinal disorders, along 2 months (from 1 October to 1 December 2021).

Gastrointestinal disorders ICSR (N = 164)	
Sex (%)	
Male	69 (42.1)
Female	93 (56.7)
Unknown	2 (1.2)
Age group (%)	
18–64 Years	69 (42.1)
65–85 Years	50 (30.5)
>85 Years	6 (3.7)
Not Specified	39 (23.8)
Outcome (%)	
Fatal	3 (1.8)
Not Recovered/Not Resolved	29 (17.7)
Recovered/Resolved	52 (31.7)
Recovering/Resolving	8 (4.9)
Unknown	72 (43.9)
Number of gastrointestinal disorders per ICSR (%)	
1	85 (51.8)
2	35 (21.3)
3	21 (12.8)
4	15 (9.1)
5 or more	8 (4.9)
Overall of suspected ADRs reported	
Total number	745
Median per ICSR	3
Other drugs	
Total number	379
Median per ICSR	4
Other drugs used chronically to treat gastrointestinal disorders	
Yes	14 cases reported (18 drugs mentioned)

A total of 12,996 suspected ADRs were reported in the ICSRs analyzed, with 53.2% of the patients showing GI disorders, the most representative category in this domain, 15.3% metabolism and nutrition disorders, and 13.7% of nervous system disorders. These results are in line with what has already been described by some authors [43,44].

Regarding the typology of reported ADRs, in more serious cases, it was possible to observe that vomiting, diarrhea, and nausea were the most frequent gastrointestinal clinical manifestations. From the point of view of metabolic and nutritional disorders, there was a considerable report of dehydration and loss of appetite. Urinary and kidney disorders were mainly represented by acute kidney injury and kidney failure. Atrial fibrillation and myocardial infarction were the most represented clinical manifestations in terms of cardiac disorders [9,16]. These results are in line with the information contained in the summary of product characteristics, according to which the most frequent ADR for semalgutide are gastrointestinal disorders (nausea, diarrhea, vomiting, abdominal pain, abdominal distension, among others); hypoglycemia (especially when associated with other antidiabetic drugs); reduced appetite; fatigue; lipase and amylase elevation; or even weight loss [45,46]. For both dosage forms, higher doses are often associated with more frequent GI disorders, as such, a dose-escalation schedule is recommended, starting with a low dose (3 mg) [47–49].

After comparing the ICSRs reported for more serious adverse events for semaglutide, sitagliptin and empagliflozin, over the same period, it was possible to observe that there is a higher percentage of reported GI disorders with semaglutide (47.7%) compared to sitagliptin (34.7%) and empagliflozin (9.8%), meeting the results presented by some researchers [50,51]. In a pharmacoeconomic perspective, semaglutide is cost-effective compared with empagliflozin and sitagliptin for patients with DM2 inadequately controlled on oral glucose-lowering drugs [52].

When analyzing the characteristics of those ICSRs who showed GI disorders in a more restricted period of time (2 months), it was possible to observe that most of them referred to adults and females. Although there is missing information in the outcomes section (31.7% recovered/resolved vs 43.9% unknown), only 1.8% of outcomes were classified as fatal. In addition, GI side effects with GLP-1 Receptor Agonists that tend to diminish over time. A total of 754 overall adverse events (median = 3) and 379 drugs (median per ICSR = 4) used concomitantly by the reported patients were described. Only 14 cases were recorded in which therapy was previously used for the treatment of GI disorders, especially proton pump inhibitors. Some strategies are recommended to minimize the occurrence of GI events associated with semaglutide, namely dietary modifications (by eating smaller amounts at each meal and slowly, avoiding eating when not hungry, avoiding high-fat or spicy food and moderating alcohol intake); dose-escalation schedule, mainly for patients reporting challenges with GI symptoms in the first few weeks of treatment; the use of anti-emetics drugs in acute situations or, as a last resort, switch to an alternative GLP-1RA [9,53].

Nevertheless, semaglutide maintains HbA1c levels within the normal range, with additional reduction in body weight, and is generally well-tolerated [54]. Moreover, GLP-1 RAs can

be combined with all classes of antihyperglycemic agents except DPP-4 inhibitors, which adds flexibility to their use in more complex cases [55–57]

Pharmacovigilance is extremely important at this level, not only for the early detection of potential ADRs but also to contribute to safer drug use, ensuring a better quality of life for patients and minimizing the impact on healthcare systems. Moreover, the definition of subgroups within the type 2 diabetes population who are particularly prone to develop serious adverse event when treated with GLP-1 RAs is crucial [6,58,59].

6. Conclusions

Spontaneous reports of semaglutide-related ADRs published at EV database are mostly GI effects, suggesting the need of interventions to minimize these adverse effects of semaglutide no on the GI tract.

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Author contributions statement

F Roque, M Morgado and MT Herdeiro were involved in the conception and design, all authors were involved in the analysis and interpretation of the data; AC Lopes wrote the first draft of the paper and all authors revised it critically for intellectual content and approved the final version to be published; all authors agree to be accountable for all aspects of the work.

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