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Ozempic (semaglutide) - review of pharmacological properties, mechanism of action and clinical applications

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ABSTRACT:
Introduction: Ozempic is a new generation antihyperglycemic drug used to treat type 2 diabetes in adults whose underlying disease is not sufficiently controlled with physical activity and diet, as well as for long-term weight control in people with excess body weight and comorbidities. The aim of this study is to explore and integrate the latest literature on the analysis of the pharmacology, mechanism of action and clinical applications of Ozempic.
Material and Methods of Research: A literature review focused on keywords related to the topic was performed using databases such as PubMed and Google Scholar.
Results: Ozempic effectively lowers blood glucose levels and supports weight loss in patients with type 2 diabetes and obesity. Clinical trials have demonstrated its superiority over other antidiabetic medications, with significant reductions in HbA1c and body weight. Patients receiving Ozempic experienced improved glycemic control and cardiovascular outcomes, with manageable side effects. Ongoing research suggests additional benefits in cardiovascular prevention and obesity management.
Conclusion: Ozempic (semaglutide) is a potent GLP-1 receptor agonist that effectively improves glycemic control and aids in weight reduction for patients with type 2 diabetes and obesity. Its practical administration, patient education, and regular monitoring are essential for optimal outcomes. Ongoing research and technological advancements, including the development of oral forms, promise to expand its applications and improve patient adherence, making Ozempic a versatile and valuable therapeutic option.

Keywords: ozempic, semaglutide, GLP-1, DM2, obesity

1. Introduction

Ozempic is a medicine used to treat type 2 diabetes in adults whose underlying disease is not adequately controlled with physical activity and diet. Ozempic is also used in patients for whom the use of metformin is contraindicated, as well as as an adjunct in polypharmacy

therapy of type 2 diabetes [1]. The active substance of Ozempic is semaglutide. Semaglutide is a long-acting agonist of the glucagon-like peptide 1 (GLP-1) receptor, similar in structure to glucagon. GLP-1 is an incretin hormone obtained from the intestine, which has a strong effect on stimulating insulin production and at the same time inhibiting glucagon, resulting in a reduction in blood glucose levels. It also increases postprandial satiety and has a negative impact on the desire to eat high-fat products [2, 3].

Semaglutide in increased doses is used in long-term weight control in adults suffering from obesity (BMI ≥ 30 kg/m2) or overweight (BMI ≥ 27 kg/m2) and at least one comorbid condition induced by excessive body weight (including diabetes type II, hypertension, lipid disorders, ischemic heart disease, obstructive sleep apnea) [4].

Type 2 diabetes is a disease that affects millions of people around the world and is caused by progressive impairment of insulin secretion. In this type of disease, environmental factors are definitely the most important: obesity (especially abdominal obesity), little or no physical activity, smoking [5]. The aim of DM II treatment is to maintain optimal blood glucose levels; in the initial stage of the disease, this is possible by lifestyle modification. If left untreated, DM II is a chronic and progressive disease affecting many organ systems in human body.

2. Purpose of the study

The aim of this study is to review and synthesize current literature on review of pharmacological properties, mechanism of action and clinical applications By doing so, it seeks to provide a detailed and comprehensive understanding of their therapeutic potential, clinical benefits, and associated risks.

Materials and methodology

The literature was gathered through searches on PubMed and Google Scholar, supplemented by references from the initially retrieved articles.

Ozempic - the dosage form and composition of the drug (EMA)

Ozempic is produced in 4 solutions (0.25 mg, 0.5 mg, 1 mg and 2 mg solution) for injection in pre-filled pen. Filling materials of the drug include: disodium phosphate dihydrate, propylene glycol phenol, hydrochloric acid (for pH), sodium hydroxide (for pH), water [6].

Ozempic's development history and regulatory approvals (FDA)

In the 1970s, Jens Juul Holst and Joel Habener isolated and studied the hormone GLP-1 in order to fight duodenal ulcer disease. They discovered the significant potency of this incretin by examining animal pancreases. In 1993, Michael Nauck, continuing the research of his predecessors, administered the GLP-1 hormone to patients with type 2 diabetes for the first time [7]. As a result, a significant increase in insulin stimulation was noted in the blood of people in the research sample, the production of glucagon was inhibited, and the glucose level decreased significantly. Unfortunately, many side effects of the therapy were observed, which is why attempts were still made to improve the form of the drug [8].

In 1998, scientists at Novo Nordisk developed the drug, liraglutide, a peptide 1 receptor agonist. In June 2008, they entered phase two clinical trials using semaglutide, which was administered once a week, to evaluate whether it could be a long-acting alternative to

liraglutide. This drug was called Ozempic. On December 5, 2017, Novo Nordisk got FDA approval for Ozempic (semaglutide) pen to treat patients with DM II [9].

3. Semaglutide as a GLP-1 analogue, effect on insulin and glucagon secretion

Glucagon-like peptide 1 (GLP-1) is a hormone found in the human intestine, composed of 29 amino acid residues. GLP-1 is secreted after food intake from intestinal L cells, especially after high-carbohydrate and high-fat meals. It is released in two phases, the early phase occurs 10–15 minutes after a meal, the second, extended phase occurs 30–60 minutes after food consumption. GLP-1 binds to the GLP-1 receptor (GLP-1 R) on pancreatic β-cells, then stimulates insulin release depending on glucose levels [10].
Semaglutide is an analogue of glucagon-like peptide-1 (GLP-1), which is a human incretin hormone that is 94% homologous to GLP-1. Semaglutide selectively binds to the GLP-1 receptor, causing its activation. In the human body, GLP-1 receptors are found in cells of the pancreas, heart muscle, brain, veins, arteries, kidneys and immune cells [11]. Ozempic, a long-acting semaglutide, can be administered to patients once a week, this is achieved by binding of the drug molecules to albumin, causing a decrease in the renal clearance of Ozempic, which in turn protects it from being metabolized and broken down by enzymes. Semaglutide significantly reduces fasting and postprandial glucose levels [11]. Additionally, it stimulates insulin synthesis, ensuring the replenishment of insulin stores in pancreatic beta cells, and has a positive proinsulin to insulin ratio, which indicates an improvement in the efficiency of β-cell functioning and an increase in insulin production. Semaglutide also inhibits secretion in a glucose-dependent manner [12]. During hypoglycemia, Ozempic does not affect the body's natural response by increasing glucagon levels and does not negatively affect C-peptide levels in patients with DM II. Ozempic slows down gastric emptying after a meal, which causes a prolonged feeling of satiety and increases the sensitivity of tissues to insulin [13].

Effect on appetite and body weight

Ozempic inhibits the rate of gastric emptying after a meal, and its use causes a delay in the early phase of gastric emptying. As a consequence, glucose later appears in the patient's blood after eating food. Ozempic administered subcutaneously once a week has a beneficial effect on weight loss (with a simultaneous use of a reduced-calorie diet and regular physical activity) [14]. This drug suppresses appetite and has a positive effect on patients' self-control and appetite. Additionally, it has properties that reduce patients' willingness to eat high-fat foods. Ozempic is an effective drug in the treatment of patients suffering from obesity, especially abdominal obesity. Clinical trials have proven an average weight loss of 10-15% of patients after 68 weeks of using the drug [15].

Extra-pancreatic effects

During clinical trials of Ozempic, it was proven that semaglutide has a beneficial effect on lowering plasma lipid levels, lowers systolic blood pressure and reduces inflammation. In animal studies, semaglutide slowed the progression of atherosclerosis by inhibiting the growth

and inflammation of atherosclerotic plaques. Fasting and postprandial lipid levels were monitored during drug therapy. Semaglutide significantly reduced triglyceride and LDL cholesterol levels by 12% [16].
GLP-1 analogues have a beneficial effect on reducing inflammation (reducing CRP values) and lowering blood pressure (they have a positive effect on the function of vascular endothelium, have a vasodilatory effect and stimulate natriuresis, which consequently reduces the afterload of the heart [17]. During clinical trials conducted among patients with heart failure with preserved ejection fraction and obesity, the use of Ozempic had a beneficial effect on the health and well-being of patients. The use of the drug significantly reduced physical symptoms, improved the patients' physical performance and also had a beneficial effect on weight loss [18].

4. Pharmacological properties of Ozempic

Ozempic is administered subcutaneously in the upper arm, abdomen, or thigh, reaching a maximum concentration in 1 to 3 days, with similar exposure in the above-mentioned anatomical regions. After 4 to 5 weeks of once-weekly administration [19], semaglutide reaches steady-state exposure. The concentration around which the Ozempic stays is 16 nmol/l and 30 nmol/l, for 0,5mg and 1 mg dosage per week accordingly (in patients with T2DM). Clinical tests comparing the steady-state concentration of 1 mg and 2 mg subcutaneous administration of semaglutide showed that the concentrations were 27 nmol/l and 54 nmol/l [20]. With increasing dosage, the exposure to the drug rises proportionally. The absolute bioavailability of Ozempic is around 89% and is almost entirely bound to plasma albumin (over 99%). It is metabolized by destroying the peptide backbone by proteolytic enzymes and following beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) may also be involved. Semagultide is eliminated mainly via urine but also through faeces, with approximately 3% of the excreted drug still intact. Semaglutide has an elimination half-life around seven days, which indicates that the drug will be present in circulation for about five weeks after the last dose administration [21]. Phase 3a studies have shown that age, gender, race, ethnicity, and hepatic or renal impairment do not cause a relevant change to the pharmacokinetics of the Ozempic [22], but also displayed the impact of patient’s higher body weight in the semaglutide exposure, which can be much lower in this case.

Pharmacotherapy using a subcutaneous form of semaglutide starts with 0,25 mg injection once weekly for four weeks. It is an initiation of the treatment and is ineffective in glycemic control. After that, the dose can be increased to 0,5 mg per week. If blood glucose monitoring is still inefficient after another four weeks, the dosage can be increased to 1 mg once weekly, and then 2 mg once weekly, which is the maximum recommended dosage. Ozempic should be administered on the same day each week, with or without a meal, and if there is a necessity to change the day of drug administration, the time between two injections should be at least 72 hours (>3 days) [20].

In case of overdosing on Ozempic, treatment should be initiated according to the patient's clinical symptoms and physical examination. A prolonged observation and therapy might be necessary because of the semaglutide half-life, which is approximately seven days. During clinical trials of Ozempic, the overdose of up to 4 mg in one dose and 4 mg per week was reported. The main adverse reaction was nausea, and they recovered without complications [20].

Ozempic delays gastric emptying, which directly impacts the absorption of oral-administered medications. It should be used cautiously in subjects requiring rapid absorption of oral medicaments. The in vitro studies of semaglutide revealed a very low potential to inhibit or induce CYP enzymes and to inhibit drug transporters [20, 21]. Based on clinical trials of reactions between co-administered drugs such as paracetamol, metformin, digoxin, atorvastatin, and oral contraceptive drugs (levonorgestrel/ethinylestradiol) and Ozempic, no relevant interaction was observed. Therefore, no adjustment of the dose of oral medicaments mentioned above is needed. Semaglutide does not change overall exposure and affects the pharmacodynamics of warfarin and other coumarin derivatives, so there is no need for dosage modification. Still, there were reported cases of decreased INR in therapy using semaglutide and acenocoumarol. Hence, it is recommended that INR be controlled frequently in subjects starting treatment and during therapy [20].

5. Clinical particulars of Ozempic

Ozempic is recommended for chronic weight management (weight loss and maintenance) alongside increased physical activity and reduced calorie diet in patients with obesity and overweight with one weight-related comorbidity (such as type 2 diabetes, high blood pressure, or hypercholesterolemia). It is also indicated to improve glycemic control in subjects diagnosed with T2DM, which is insufficiently controlled. It can be used in monotherapy due to metformin intolerance or contraindications and in addition to other diabetic medicaments. Semaglutide is not used in T1DM therapy (it stimulates insulin secretion and lowers glucagon secretion) or diabetic ketoacidosis treatment [20]. Ozempic reduces the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in the group of patients diagnosed with cardiovascular disease alongside obesity or overweight.

The STEP (Semaglutide Treatment Effect in People with Obesity) program investigates body weight changes following the Ozempic therapy with different doses of subcutaneous semaglutide injections and placebo groups. The trials revealed that once-weekly 2,4 mg of semaglutide, as an addition to lifestyle modification in patients without T2D, led to ~15%-17% reduction of body weight in over 68 weeks, with minor weight loss in patients with T2D (around 9,6%). Also, more significant progress was noticed in the group administrated 2,4 mg of semaglutide than in the subjects treated with 1 mg injections or placebo group [30].

Multiple trials in the SUSTAIN program investigate differences between once-weekly injectable semaglutide and other antidiabetic medicines in patients with type 2 diabetes. The studies showed the superiority of the 0,5mg and 1 mg doses of semaglutide to 0,75 mg and

1,5 mg dulaglutide, respectively, in body weight and HbA1c reduction. Ozempic, in comparison to medications such as sitagliptin, exenatide ER (both with metformin or metformin and sulfonylurea), basal insulin, insulin glargine (with 1-2 oral antidiabetic medicaments) insulin aspart, proved significant greater weight loss and glycemic control. In SUSTAIN 4 (semaglutide vs. Insulin glargine) and SUSTAIN 11 (semaglutide vs. Insulin aspart as an add-on to insulin glargine and metformin), the increased mean baseline body weight was observed in groups of patients using insulins. SUSTAIN 6 trials analyzed the impact of semaglutide therapy on subjects with cardiovascular diseases and with higher risks of MACE (major adverse cardiovascular event). It resulted in a 26% risk reduction in the primary composite outcome, mainly in the rates of non-fatal stroke and non-fatal myocardial infarction [20].

6. Safety and long-term risks of Ozempic

There are few adverse effects of semaglutide. Most common are gastrointestinal disturbances, including nausea, vomiting, and diarrhea. Studies have shown in phase 3 trials that patients receiving Ozempic more often presented ailments from the digestive system than patients with administrated placebo [23]. In the group of subjects with coexisting conditions, the occurrence of GI disturbances was higher [24]. The frequency of GI complaints is also associated with higher doses of semaglutide, which is why the therapy is escalated in time, starting with small doses. Because of that, symptoms occur in the first eight to twelve weeks of treatment. The adverse effects are mild to moderate in severity, usually self-limiting [24], and to prevent them, it is recommended to consume slowly reduced portions of a meal, avoid high-fat products, and stop eating when satiety appears.

Hypoglycemia is another unwanted result of using Ozempic, but it is also infrequent. It occurred in a similar percentage between placebo and patients with ongoing semaglutide therapy, with a higher risk of manifesting in subjects treated (besides semaglutide) with insulin or sulfonylurea. In this case it is advised to reduce doses of oral antidiabetics, and low- and short-acting insulin analogues [25].

Pancreatitis or pancreatic cancer is relatively rare (based on the SUSTAIN and PIONEER trials) and must be taken into consideration regarding overall higher risk in patients with DM, obesity, and co-medication. Although GLP-1 receptor agonists may cause pancreatic inflammation, cellular proliferation, and also intra-epithelial neoplasia, it was pointed out in the preclinical studies that semiglutide has no unfavorable effect on pancreatic tissue [24, 26]. In the case of the conditions mentioned above, Ozempic should be discontinued and should not be restarted if ailments are confirmed [20].

Semaglutide, like all GLP-1 RAs, may also increase heart rate. Clinical trials showed an increase of heart rate up to 1-6 beats per minute from the baseline of 72-76 bmp [20] without cardiac events associated with it.

Furthermore, Ozempic in a long-term therapy reduces the risk of nephropathy and renal impairment, but dehydration induced by GI disturbances, and also decreased fluid intake and medications such as ACEI, ARB, or diuretics might lead to acute kidney failure.

In the group of subjects with diabetic retinopathy treated with semaglutide, trials revealed an early worsening of this condition due to rapid improvement in glycemic control, especially in patients also using insulin therapy. Recent studies showed that GLP-1RAs had no effect on angiogenesis and no direct association between severe diabetic retinopathy progression and semaglutide exposure (except lowering blood glucose) [24, 27].

Box warning for thyroid C-cell tumors, which Ozempic received, was based on data from rodent studies, where thyroid C-cells (which secret calcitonin) have high expression of GLP-1 receptor. Its stimulation may lead to an increased risk of medullary carcinomas and adenomas (by upregulation of the calcitonin gene expression and following C-cell hyperplasia) [24, 28]. Further studies found an insignificant amount of GLP-1 receptors expressed in human and non-human primates thyroids [28] (following observation with much higher doses of different GLP-1RA liraglutide, without developing any abnormalities) [24]. Although the European Medicines Agency's Pharmacovigilance Risk Assessment Committee found no association between GLP-1RAs (including semaglutide) and thyroid cancer, the overall risk of thyroid carcinogenesis and general thyroid disorders is much higher in the group of patients qualified for treatment using semaglutide (obesity factor) [29]. Ozempic is contraindicated in subjects with a family or personal history of medullary thyroid cancer or MEN2. All patients, regardless of medical history, must be informed about potential symptoms of thyroid tumors, such as dysphagia, dyspnea, mass in the neck, or persistent hoarseness [21]. Significantly increased serum calcitonin value (usually over 50ng/L) might suggest MTC, and the subject must be further evaluated. The presence of the thyroid nodules also should be further examined [21].

7. Practical aspects of using Ozempic

Dosage Regimens and Method of Administration

Ozempic, a brand name for semaglutide, is a glucagon-like peptide-1 (GLP-1) receptor agonist primarily used to improve glycemic control in adults with type 2 diabetes. The recommended initial dose of Ozempic is 0.25 mg once weekly, administered subcutaneously. After four weeks, the dose should be increased to 0.5 mg once weekly. If additional glycemic control is necessary, the dose can be further increased to 1 mg once weekly after another four weeks [31]. The administration site can be the abdomen, thigh, or upper arm, and it is important to rotate the injection site each week [32].

Recommendations for Patient Monitoring

Patients starting Ozempic therapy should be monitored regularly for changes in blood glucose levels, particularly within the initial weeks of treatment. Regular monitoring of HbA1c levels is recommended to assess long-term glycemic control. Additionally, monitoring

for potential adverse effects such as gastrointestinal issues (e.g., nausea, vomiting, and diarrhea) is essential [33]. It is also important to monitor renal function periodically, especially in patients with pre-existing kidney conditions [34].

Patient Education and Support in Therapy

Effective patient education is crucial for the successful use of Ozempic. Patients should be instructed on proper injection techniques and the importance of adhering to the dosing schedule. Educating patients about potential side effects and how to manage them can enhance adherence and improve outcomes. Providing support through regular follow-ups and creating an open line of communication for any concerns or questions can significantly enhance patient confidence and compliance [35].

8. Current Research and Future Development Directions

Research on new indications

Recent studies have shown promising results for the use of Ozempic in treating obesity. Clinical trials indicate that semaglutide can significantly reduce body weight in obese patients, making it a potential therapy for weight management [36]. Furthermore, there is ongoing research into its role in cardiovascular prevention, with evidence suggesting that it may reduce major adverse cardiovascular events in patients with type 2 diabetes [37].

Development of Oral Forms and Other Technological Innovations

A significant development in the field of GLP-1 receptor agonists is the advent of oral semaglutide. This form offers an alternative for patients who are averse to injections, potentially improving adherence and convenience [38]. Additionally, advancements in drug delivery technologies are being explored to enhance the stability and efficacy of oral semaglutide [39].

Potential Future Changes in Clinical Guidelines

As research progresses, it is anticipated that clinical guidelines will evolve to incorporate new findings. The potential approval of Ozempic for additional indications such as obesity and cardiovascular prevention could lead to broader use of the medication. Furthermore, the availability of an oral form may influence treatment algorithms and patient preferences, potentially making Ozempic a more versatile option in managing type 2 diabetes and related conditions [40].

9. Conclusion

Ozempic (semaglutide) represents a significant advancement in the management of type 2 diabetes and obesity, offering a potent and long-acting GLP-1 receptor agonist that effectively improves glycemic control and aids in weight reduction. Its pharmacological properties, including delayed gastric emptying, enhanced insulin secretion, and reduced glucagon levels, contribute to its efficacy in lowering blood glucose levels and promoting weight loss. Clinical trials and studies have demonstrated its superior performance compared to other antidiabetic agents, making it a valuable addition to the therapeutic arsenal for managing type 2 diabetes.

The practical aspects of Ozempic use, such as its dosing regimen, method of administration, and patient education, are crucial for optimizing treatment outcomes. Regular patient monitoring and education on injection techniques, potential side effects, and adherence to dosing schedules are essential components of effective therapy. Ensuring patient support through continuous follow-ups and communication can further enhance compliance and confidence in using Ozempic.

Current research is expanding the potential indications for Ozempic, including its use in obesity management and cardiovascular prevention. The development of oral forms of semaglutide and other technological innovations promise to improve patient adherence and convenience, potentially transforming the treatment landscape. As new evidence emerges, clinical guidelines are expected to evolve, incorporating these advancements and broadening the scope of Ozempic's applications.

In summary, Ozempic offers substantial benefits for patients with type 2 diabetes and obesity, with ongoing research and technological developments poised to further enhance its clinical utility. As a result, it stands out as a versatile and effective therapeutic option, promising improved outcomes for a wide range of patients.

DISCLOSURE

Author’s contribution

Anna Maria Koman: Conceptualization, writing rough preparation,
Katarzyna Gadżała: Writing rough preparation, formal analysis,
Marzena Pliszka: supervision,
Karolina Alicja Palacz: visualization, data curation
Klaudia Brygida Kułak: Methodology, software,
Katarzyna Chamera-Cyrek, Izabela Janik: check,

Sabina Przygodzka: writing and editing,

Martyna Kuśmierska: project administration

Izabela Sztybór: resources, investigation,

Project administration: Katarzyna Gadżała

All authors have read and agreed with the published version of the manuscript.

Conflict of interest

The authors deny any conflict of interest

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