FRAŃCZUK, Agata, SZPULAK, Angelika, KOPCZYŃSKA, Ewelina, MAKŁOWICZ, Aleksandra, KULETA, Katarzyna, GŁOSKOWSKA, Julia, GRZELKA, Michalina, SŁYCHAN, Katarzyna, GŁUSZCZYK, Agnieszka and PLIZGA, Jakub. Danuglipron – an innovate GLP agonist - literature short review. Quality in Sport. 2024;19:53802. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.19.53802
https://apcz.umk.pl/QS/article/view/53802

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

Received: 24.07.2024. Revised: 08.08.2024. Accepted: 14.08.2024. Published: 18.08.2024.

Short review

Danuglipron- nowatorski agonista receptorów GLP - przegląd literatury

Danuglipron –an innovate GLP agonist - literature short review

1. Agata Frańczuk, MD
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0008-7840-5282; franczuk.agata@gmail.com

2. Angelika Szpulak, MD
Brzeg Medical Centrum, ul. Mossora 1, 49-300 Brzeg
https://orcid.org/0009-0000-2660-7538; angelika@brzeg.net

3. Ewelina Kopczyńska, MD
Gromkowski Regional Specialist Hospital, ul. Koszarowa 5, 51-149 Wrocław,
https://orcid.org/0009-0006-5665-6043; ewekop13@gmail.com

4. Aleksandra Makłowicz, MD
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0007-7667-836X; ola.maklowicz@gmail.com

5. Katarzyna Kuleta, MD
10. Military Clinical Hospital Powstańców Warszawy 5, 85-681 Bydgoszcz
https://orcid.org/0009-0007-3491-7721; kuletka8@gmail.com

6. Julia Głoskowska, MD
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland
https://orcid.org/0009-0004-2634-006X; juliagloskowska@icloud.com

7. Michalina Grzelka, MD
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland
https://orcid.org/0009-0000-1515-5564; michalinagrzelka1@gmail.com

8. Katarzyna Słychan, MD
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland
https://orcid.org/0000-0003-3772-737X; kateslychan@gmail.com

9. Agnieszka Głuszczyk, MD
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland
https://orcid.org/0009-0003-5552-4186; gluszczyk.agnieszka@gmail.com

10. Jakub Plizga, MD
4. Military Clinical Hospital SP ZOZ, Rudolfa Weigla 5, 53-114 Wrocław, Poland
https://orcid.org/0009-0001-1172-9919; jakubplizga7@gmail.com

Corresponding author: Agata Frańczuk, MD, franczuk.agata@gmail.com

Abstract:

Obesity and type 2 diabetes mellitus (T2DM) are global health problems with increasing prevalence, associated with numerous metabolic, cardiovascular and renal complications.(1,2) Current treatments include GLP-1 receptor agonists (GLP-1RAs), which have shown benefits in weight reduction and glycaemic control. Danuglipron, a novel, oral, small-molecule GLP-1RA, is being investigated for its efficacy in treating these conditions. The novel oral method of administration may contribute to an increase in its regularity of use among patients who find systematic use of injections difficult. The aim of our study is to describe this new drug, its' mechanism of action and discuss possible benefits versus adverse effects.

Obesity and type 2 diabetes mellitus (T2DM) represent significant global health challenges with a rising prevalence, linked to a multitude of metabolic, cardiovascular, and renal complications. Current therapeutic approaches encompass GLP-1 receptor agonists (GLP-1RAs), which have exhibited favorable outcomes in weight management and glycemic regulation. Danuglipron, an innovative oral small-molecule GLP-1RA, is undergoing investigation for its effectiveness in addressing these conditions. The unique oral delivery method could potentially enhance its adherence among patients encountering difficulties with routine injections. Our study aims to delineate this novel medication, elucidate its mechanism of action, and deliberate on the prospective benefits versus drawbacks.

Keywords: danuglipron; weight loss; obesity; diabetes: GLP agonist

Introduction

As a global health problem, diabetes causes an upsetting number of deaths each year. During the period 2000- 2019, the age-specific diabetes mortality rate increased by 3% (3). Projections for the future are influenced by negative scenarios including a continued escalation in the number of patients with an outstanding popularity of type 2 diabetes (4). The meaning of diabetes has enlarged impressively worldwide, with the number of new cases increasing twofold from around 11.3 million in 1990 to 22.9 million in 2017 (5). This growth is seen across all regions and socio-economic groups, but is specially visible in low- and middle-income countries (6).

Obesity is a medical condition strictly lined to type 2 diabetes. It is a global health problem with severe repercussions for individuals and societies. Its commonness has rised drastically in recent decades, spreading over both developed and developing countries. In the USA, more than 40 per cent of adults are obese, and in some ethnic minorities, such as African-Americans, the rate can reach even 50 per cent (5,7). Obesity remarkably increases the probability of many chronic diseases, such as heart disease, hypertension, and some cancers. Moreover obese people have a sevenfold higher risk of diabetes compared to people of normal weight(5).

The increase in the number of patients suffering from type 2 diabetes and obesity has resulted in intensive development of pharmacology, so that euglycemia and weight loss can now be achieved by various groups of drugs. One of these is the GLP-1 receptor agonists (GLP-1RAs). Stimulation of the GLP-1 receptor (GLP-1R) allows to trigger insulin release and reduct glucagon secretion in response to glucose levels. Additional functions include suppressing appetite and promoting weight loss, as well as slowing gastric emptying(8,9). Through their positive effects on patients' cardiovascular and renal complaints and by taking into account their comorbidities and glycemic needs, these drugs appear to be one of the more preferable therapeutic alternatives (10,11). The leading drug in this group is semaglutide, which is administered by subcutaneous injections, which may hinder regular and systematic use of the substance in patients who prefer easier methods of drug administration (12).

A way to meet such patients may be the newly developed, potent, low-molecular-weight, orally administered GLP-1RAs - danuglipron (PF-06882961). It appears that the combination

of such pharmacotherapy with appropriate diet and exercise aimed at weight reduction and glycaemic control may have a positive impact on the health of both patients with and without previously diagnosed type 2 diabetes (13). Studies in a humanised mouse model showed that the substance inhibits food intake and stimulates glucose- dependent insulin secretion to a similar extent as injectable GLP-1R agonists. During a phase 1 study, the drug reduced both body weight and glycaemic indices, revealing its highly acceptable pharmacokinetics and safety profiles in adults with type 2 diabetes taking metformin (4). This work aims to collect and compare the available scientific articles on danugliprone considering its efficacy and safety of the therapy used.

Methodology:

An electronic search was completed in PubMed database. Recommendations were extracted from the identified articles and collated as themes. However, the available literature is notably limited due to the fact that the reviewed medication is still in clinical trials.

Discusson:

Danuglipron, as a small-molecule glucagon-like peptide 1 receptor (GLP-1R) agonist, is involved not only in blood glucose regulation but also appetite suppression, which makes it a promising candidate for the treatment of both obesity and diabetes. The method of functioning of danuglipron relates to promoting insulin secretion in response to food and inhibition of glucagon release. Therefore it plays part in improved glycaemic control (14,15). Although danuglipron is administered twice a day, Pfizer, the company conducting research on the molecule, anticipates the possibility of a single daily dose in the future(16). Furthermore, the drug can be used with or without a meal (8).

In clinical trials, danuglipron has demonstrated the ability to significantly reduce body weight in obese patients. In a phase 2b study, patients receiving danuglipron experienced a weight reduction of between 6.9% and 11.7% after 32 weeks of treatment, compared to a slight increase in weight in the placebo group (14). In addition, another study demonstrated that significantly notable weight reduction was also present in both T2DM and obese patients

compared to the control group (mean difference (MD) = -3.26 kg; 95% CI = [-4.79, -1.72]; P < 0.001 and MD = -7.52 kg; 95% confidence interval (CI) = [-14.63, -0.41]; P = 0.038; P for difference between subgroups = 0.25) (16) These results let us believe that danuglipron may be a potent tool in the fight against obesity, contributing to outstanding weight loss.

Danuglipron also gives hope in the treatment of type 2 diabetes. In the phase 2b study, patients received either placebo or danuglipron at doses of 2.5 mg, 10 mg, 40 mg, 80 mg or 120 mg, all administered orally twice a day with food for 16 weeks. Participants reported a significant reduction in levels of glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) in each group. However, in patients receiving 120 mg danuglipron twice a day, the mean change in HbA1c was -1.16% and the change in fasting plasma glucose (FPG) was -33.24 mg/dL after 16 weeks of treatment (17). Another study also showed a significant reduction in HbA1c levels in patients with type 2 diabetes mellitus (T2DM) compared to MD controls = -1.03%; 95% confidence interval (CI) = [-1.29, -0.77]; P < 0.001) (16). These effects shed a bright light on the further use of the drug.

The pharmacokinetics of danuglipron have been well studied and the drug shows a favorable pharmacokinetic profile. This includes rapid absorption and reaching peak plasma concentrations, which enables effective glycemic and weight management (16). In addition, danuglipron is administered orally, which is a significant advantage over other GLP-1 agonists that require subcutaneous administration. Unfortunately, despite its obvious benefits, like most drugs in this class, danuglipron is also associated with some side effects, mainly on the gastrointestinal side, such as nausea, vomiting and diarrhoea, the frequency of which was investigated for both the 80mg and 120mg dose. Surprisingly the higher dose less frequently caused diarrhoea.(4). Nevertheless further research might be required.

Summary

Ultimately, taking in consideration significant inconvenience correlated with regular injectable medication in obese and diabetic patients, and the usefulness of danuglipron in both minimizing glycated hemoglobin, fasting glucose and body mass levels, danuglipron has the potential to be a revolutionary discovery in medicine. With predictable side effects, that are

quite similar to the entire group of GLP-1 agonists and the opportunity to take it orally, danuglipron could prove to be a fairly safe tool, that helps diabetic patients in controlling their glycemic parameters and obese people in losing weight. Despite the positive results, further long-term studies are vital to exhaustively understand the effectiveness, safety and tolerability of danuglipron and its potential advantages related to cardiovascular and renal systems. Although the drug is currently during the testing phase it seems to be the alternative for diabetes and obesity epidemics.

In the realm of diabetes and obesity research, the focus on innovative pharmacological treatments continues to expand. Beyond the realm of GLP-1 receptor agonists, there is a growing interest in exploring novel therapeutic approaches that can address the complexities of these interconnected health challenges. One promising avenue of investigation lies in the realm of personalized medicine, where treatments can be tailored to individual genetic and metabolic profiles to optimize outcomes.

The role of lifestyle interventions cannot be understated in managing diabetes and obesity. Integrating dietary modifications, regular physical activity, and behavioral changes can significantly impact disease progression and overall health outcomes. Encouraging patients to adopt sustainable lifestyle habits is essential in complementing pharmacological interventions and promoting long-term well-being.

As we navigate the evolving landscape of diabetes and obesity management, interdisciplinary collaboration between healthcare providers, researchers, and policymakers is crucial. By fostering a holistic approach that considers the multifaceted nature of these conditions, we can strive towards more effective prevention strategies and treatment modalities. Embracing a comprehensive view of health that encompasses both medical and lifestyle factors is key to addressing the complex challenges posed by diabetes and obesity in our society today.

Disclosures

Author's contribution:

Conceptualisation Methodology: AM, AF, KS Software: not applicable; Check: AS, EK, KK, AM, JP Formal analysis: JG, MG, AF, KS Investigation: AM, AF, AG, KK Resources: not applicable; Data curation: Writing - rough preparation: AG, AF, JP, MG, KS, JG, KK Writing - review and editing: AS, EK, Visualisation: AG, JP, JG, MG Supervision: AS, EK, AF Project administration: AF

Receiving Funding: not applicable

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

Funding Statement: This Research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

Conflicts of Interests: The authors declare no conflict of interest.

Bibliography:

1.Tomic D, The burden and risks of emerging complications of diabetes mellitus. 2022 doi:10.1038/s41574-022-00690-7

2.World Health Organization. Accelerating action to stop obesity, 2023.

3.World Health Organisation. Diabetes; 2023.

4.Saxena AR, Danuglipron (PF-06882961) in type 2 diabetes: a randomized, placebo-controlled, multiple ascending-dose phase 1 trial. 2023 doi:10.1038/s41591-021-01391-w

5.Congdon P, The obesity epidemic: Causes, context, prevention. 2022 doi: 10.3389/fpubh.2022.1030180

6.Jacqueline A. Seiglie, Diabetes Prevalence and Its Relationship With Education, Wealth, and BMI in 29 Low- and Middle-Income Countries. 2020 doi: 10.2337/dc19-1782

7.Hecker, J., Burden of disease study of overweight and obesity; the societal impact in terms of cost-of- illness and health-related quality of life. 2022 doi: https://doi.org/10.1186/s12889-021-12449-2

8.Griffith DA, A small-molecule oral ago-nist of the human glucagon-like peptide-1 receptor. 2022 doi: https://doi.org/10.1021/acs.jmedchem.1c01856

9.Gary E. Aspnes, 6-Azaspiro[2.5]acetates as small molecule agonists of the human glucagon- like peptide-1 receptor doi: https://doi.org/10.1016/j.bmcl.2023.129454
10.W. Timothy Garvey, American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines For Medical Care of Patients with Obesity doi: https://doi.org/10.4158/EP161365.GL
11.Søren L Kristensen, Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials, 2019, DOI: 10.1016/S2213-8587(19)30249-9
12.Igarashi A, Preference for oral andinjectable GLP-1 RA therapy profiles in Japanese patients with type 2diabetes: a discrete choice experiment. 2021, DOI: 10.1007/s12325-020-01561-1
13.M.V. Sikirica Reasons for discontinuation of GLP1 receptor agonists: data from a real-world cross- sectional survey of physicians and their patients with type 2 diabetes, 2017, doi:10.2147/DMSO.S141235
14.Saxena AR, Efficacy and Safety of Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist Danuglipron for Glycemic Control Among Patients With Type 2 Diabetes: A Randomized Clinical Trial. 2023 doi:10.1001/jamanetworkopen.2023.14493
15.Bækdal TA, Effect of various dosing conditions on the pharmacokinetics of oral semaglutide, a human glucagon-like peptide-1 analogue in a tablet formulation. 2021, doi:10.1007/s13300-021- 01078
16.Ono R, A phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of danuglipron (PF-06882961), an oral small-molecule glucagon-like peptide-1 receptor agonist, in Japanese adults with type 2 diabetes mellitus. Diabetes Obes Metab. 2023 doi: 10.1111/dom.14928.
17.Fatima H, Evaluating Glycemic Control Efficacy and Safety of the Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist Danuglipron in Type 2 Diabetes Patients: A Systemic Review and Meta- Analysis. 2023 Nov, doi: 10.2147/DMSO.S439587.