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Cotadutide as an Innovative Approach to Glycemic Control and Weight Reduction in Patients with Type 2 Diabetes – A Contemporary Review

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ABSTRACT

Background. Type 2 diabetes is a chronic metabolic disorder associated with impaired insulin secretion and insulin resistance, leading to persistent hyperglycemia and multiple complications. Despite advances in pharmacotherapy, many patients fail to achieve optimal metabolic control, highlighting the need for novel therapeutic approaches.

Aim. The aim of this study was to present the current state of knowledge regarding cotadutide as a potential therapeutic option in the treatment of type 2 diabetes, with particular emphasis on its mechanism of action, clinical efficacy, and safety profile.

Materials and methods. A narrative review of available literature was conducted, including clinical trials, meta-analyses, and preclinical studies evaluating the efficacy and safety of cotadutide in patients with type 2 diabetes and related metabolic disorders.

Results. Cotadutide is a dual GLP-1 and glucagon agonist, that demonstrates a significant improvement regarding glycemia, body weight reduction and positive influence on metabolic parameters, in comparison to placebo. Clinical trials showed decrease in HbA1c, body weight and albuminuria, as well as potential benefits in liver and kidney function. The most common adverse effects involve the gastrointestinal tract.

Conclusions. Cotadutide is a promising factor in diabetes type 2 treatment. It shows a broad spectrum of positive effects on metabolic parameters. However, further analysis and large-scale, long-term studies are required to establish its efficacy and safety.

Keywords: type 2 diabetes, cotadutide, GLP-1 receptor agonist, glycemic control, weight reduction

1. Introduction

Type 2 diabetes is a chronic metabolic disease characterized by hyperglycemia resulting from impaired insulin secretion by pancreatic β-cells and decreased sensitivity of peripheral tissues to the action of insulin [1]. The pathogenesis of this disease is multifactorial and includes genetic predisposition; however, environmental factors such as obesity - especially abdominal obesity - and low physical activity also play a significant role [1,2]. Excess free fatty acids released by visceral adipose tissue increase fat oxidation in muscles, which results in inhibition of glycolysis, while in the liver this contributes to increased gluconeogenesis [2]. These phenomena enhance compensatory insulin secretion by β-cells and may lead to disruption of glucose metabolism, ultimately resulting in the development of diabetes [1].

Chronic hyperglycemia characteristic of diabetes leads to the development of numerous microvascular and macrovascular complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular diseases, which constitute the main cause of increased morbidity and

mortality among patients with diabetes [1,3]. In recent years, an increase in the incidence of type 2 diabetes has been observed worldwide. Approximately hundreds of millions of people globally live with diabetes, and more than 90% of cases are type 2 diabetes [4]. Projections indicate that the number of people with diabetes may rise to approximately 853 million by 2050 [4]. Diabetes represents a significant burden for both healthcare systems and the global economy and is responsible for millions of deaths each year [4].

Therapeutic management of type 2 diabetes includes both non-pharmacological interventions, such as weight reduction, dietary modification, and increased physical activity, as well as pharmacotherapy [1]. The main groups of antidiabetic drugs include metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin [3]. Despite significant progress in diabetes pharmacotherapy, a substantial proportion of patients fail to achieve sustained, optimal metabolic control, and some available therapies are associated with adverse effects such as hypoglycemia, weight gain, or limited long-term effectiveness [3].

Therefore, there is growing interest in the development of new therapeutic strategies that enable a multidirectional approach targeting the pathophysiological mechanisms of type 2 diabetes. Particular attention is being paid to therapies capable of simultaneously modulating several metabolic pathways. One of the promising research directions involves dual incretin receptor agonists, including cotadutide (MEDI0382) - a synthetic peptide that acts as a dual agonist of the receptors for glucagon-like peptide-1 (GLP-1) and glucagon [5]. The aim of this paper is to present the current state of knowledge regarding cotadutide as a potential new therapeutic option in the treatment of type 2 diabetes, with particular emphasis on its mechanism of action, clinical efficacy, safety of use, and comparison with other GLP-1 receptor agonists.

2. What is cotadutide

Cotadutide is a dual GLP-1 and glucagon receptor agonist, with a GLP-1 to glucagon receptor agonistic activity ratio of 5:1. The combination of GLP-1 and glucagon receptor agonism is thought to have better clinical effects than GLP-1 receptor agonism alone due to the complementary effects of glucagon in suppressing appetite, oxidizing lipids in the liver, and increasing energy expenditure [6].

The main actions of GLP-1 are stimulation of insulin secretion (i.e., acting as an incretin hormone). It also inhibits gastrointestinal motility and secretion. GLP-1 also appears to physiologically regulate appetite and food intake. Because of these actions, GLP-1 or GLP-1

receptor agonists are now recommended for the treatment of type 2 diabetes. Reduced GLP-1 secretion may contribute to the development of obesity, and excessive secretion may cause reactive postprandial hypoglycemia [7].

In addition, glucagon receptors are strongly expressed in the kidneys, particularly in the thick ascending limb of Henle's loop and distal tubules. Hence, its use in patients with diabetic kidney disease is postulated [8]. In a phase 2 clinical trial involving nearly 20 patients with type 2 diabetes and elevated albuminuria, cotadutide reduced albuminuria by 51% compared to placebo after approximately 30 days of therapy [9].

Cotadutide is currently being developed for the treatment of type 2 diabetes, obesity, and non-alcoholic steatohepatitis. Clinical and preclinical studies in type 2 diabetes have shown that cotadutide improves glycemic control and promotes weight loss. In animal models, the beneficial effects of glucagon include reduced hepatic lipogenesis, inflammation, and fibrosis, along with improved hepatic mitochondrial function. The significant improvement in NASH and fibrosis outcomes in preclinical mouse models after treatment with cotadutide was significantly greater than after treatment with the GLP-1 monoagonist liraglutide. In humans, the glucagon receptor is highly expressed in liver and kidney tissue, suggesting that glucagon plays a role in liver and kidney physiology [10].

3. Clinical studies

Researchers evaluated the difference in effectiveness of treatment between cotadutide and liraglutide, in patients with BMI ≥25 kg/m2 and type 2 diabetes (HbA1c 7,0%-10.5% [53-91 mmol/mol]), treated with metformin. In randomized, double- blind study patients were assigned to groups receiving: 100 μg (n = 100), 200 μg (n = 256), or 300 μg (n = 256); placebo (n = 110); or open-label liraglutide 1.8 mg (n = 110)-all administered subcutaneously.

Researchers used HbA1c and weight differences after 14 and 54 weeks to compare treatment effects. The results showed that cotadutide led to significant reductions in HbA1c and body weight compared with placebo (all $P < 0.001$). Liver parameters (AST, ALT, propeptide of type III collagen, fibrosis-4 index, and nonalcoholic fatty liver disease fibrosis score) also improved compared with placebo; however, no significant advantage was observed when these parameters were compared with liraglutide. Regarding body weight, cotadutide at 200 μg produced a reduction comparable to liraglutide, whereas at 300 μg, the weight loss was greater than that seen with liraglutide [10].

In another study, the researchers assessed the efficacy, safety, and tolerability of cotadutide in patients with type 2 diabetes and chronic kidney disease. Patients were assigned

to receive cotadutide (50–300 μg; n = 21) or placebo (n = 20). The study demonstrated improved postprandial glucose tolerance (−26.71% vs. +3.68%, $p < 0.001$) and weight loss (−3.41 kg vs. −0.13 kg, $p < 0.001$) compared with placebo. Additionally, albumin-to-creatinine ratio (ACR) decreased by 51% after one month of therapy ($p = 0.0504$) in patients with micro- and macroalbuminuria (n = 18). Glomerular filtration rate did not change significantly [9].

A meta-analysis reviewed 663 scientific articles regarding the safety and efficacy of cotadutide in treating patients with type 2 diabetes. Cotadutide was superior to placebo in reducing body weight (mean difference [MD] = 3.31 kg, $p < 0.00001$), glycated hemoglobin (HbA1c) (MD = 0.68%, $p < 0.00001$), glucose area under the plasma concentration curve (AUC [0–4 h]) (MD = 30.15, $p < 0.00001$), and fasting plasma glucose over time (MD = 31.31 mg/dL, $p < 0.00001$). Overall, cotadutide was shown to be safe and effective in reducing plasma glucose, HbA1c, and body weight in individuals with type 2 diabetes [11].

4. Safety of Cotadutide therapy

Most common adverse effects

Cotadutide, a dual glucagon-like peptide-1 (GLP-1) and glucagon receptor agonist, has been evaluated in several clinical trials assessing its efficacy and safety in patients with metabolic disorders such as type 2 diabetes mellitus, obesity, and non-alkoholic steatohepatitis (NASH). Overall, the available evidence suggests that cotadutide is generally well tolerated, although treatment is associated with a relatively high incidence of mild to moderate adverse events, particularly gastrointestinal symptoms. The most frequently reported adverse events during cotadutide therapy include nausea, vomiting, and decreased appetite. These symptoms are consistent with the known pharmacological effects of incretin-based therapies and are similar to those observed with GLP-1 receptor agonists. In a clinical study assessing the pharmacokinetics, safety, and efficacy of cotadutide in overweight or obese individuals with or without type 2 diabetes, gastrointestinal adverse events were the most common treatment-related events. Nausea and vomiting were reported more frequently in participants receiving cotadutide compared with placebo, although most events were mild or moderate in severity and tended to occur during the dose-escalation phase of therapy. Importantly, no unexpected safety signals were identified in this study [12].

Similar findings were reported in a randomized clinical trial evaluating cotadutide in patients with type 2 diabetes and chronic kidney disease. In this study, adverse events occurred in a greater proportion of participants receiving cotadutide compared with those receiving placebo. However, the majority of these events were mild to moderate and primarily

gastrointestinal in nature. The most commonly reported symptoms included nausea, vomiting, diarrhoea, and dyspepsia. Despite the higher incidence of adverse events, discontinuation rates due to adverse effects were relatively low [9].

More recent clinical data obtained in patients with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis also demonstrated a high frequency of adverse events among participants treated with cotadutide. In this study, adverse events were reported in over 90% of patients receiving the higher dose of cotadutide and in approximately 77% of those receiving the lower dose, compared with about 38% in the placebo group. Nevertheless, most adverse events were mild to moderate and primarily involved gastrointestinal symptoms, which were consistent with the established safety profile of incretin-based therapies [13].

In addition to gastrointestinal symptoms, other reported adverse events include a modest increase in heart rate. These effects have also been observed with other agents acting on incretin pathways. Overall, available clinical data suggest that cotadutide demonstrates a predictable safety profile largely consistent with its mechanism of action [12].

Risk of hypoglycemia

One important aspect of the safety profile of antidiabetic therapies is the potential risk of hypoglycemia. Available evidence suggests that cotadutide is associated with a relatively low risk of hypoglycemic events when used without agents that independently increase the risk of hypoglycemia [12].

The mechanism of action of cotadutide partly explains this favorable safety characteristic. Similar to GLP-1 receptor agonists, cotadutide enhances glucose-dependent insulin secretion, meaning that insulin release is stimulated primarily in the presence of elevated blood glucose levels. As a result, the risk of hypoglycemia is limited when the drug is administered without agents such as insulin [12].

Clinical studies support this observation. In a pharmacokinetic and safety study conducted in individuals with varying degrees of renal impairment, episodes of hypoglycemia were infrequent and generally mild. Importantly, no clinically significant increase in hypoglycemic events was observed across different levels of renal function, suggesting that cotadutide may be used safely in this patient population with appropriate monitoring [14].
Similarly, in clinical trials conducted in patients with type 2 diabetes, hypoglycemic episodes were rare and generally mild. These findings indicate that cotadutide itself does not appear to substantially increase the risk of hypoglycemia, which is an important advantage compared with some traditional glucose-lowering therapies [12].

Limitations and considerations in therapy

Despite its promising metabolic effects and generally favorable safety profile, cotadutide therapy has several limitations that should be considered. One of the main challenges is the relatively high frequency of gastrointestinal adverse events, which may affect treatment adherence in some patients [15]. Although these symptoms are usually transient and mild, they may require gradual dose escalation and careful patient monitoring.

Another limitation is the still limited amount of long-term safety data. Most available clinical studies evaluating cotadutide have been conducted in phase 1 or phase 2 trials with relatively small sample sizes and short treatment durations [12,15]. Therefore, additional large-scale and long-term studies are necessary to fully assess the safety and tolerability of this drug in broader patient populations.

Furthermore, the safety profile may vary depending on patient characteristics such as the presence of comorbid conditions, including chronic kidney disease or liver disease. Although preliminary data suggest that cotadutide can be safely used in patients with renal impairment without significant pharmacokinetic alterations, careful evaluation is still required in specific patient groups [14]

5. Cotadutide in comparison to other GLP-1 agonists

Several studies and meta-analyses have been conducted to compare the efficacy of cotadutide and other GLP-1 analogs. Most significant reduction in FBG (fasting blood glucose) and HbA1c levels was observed in patients treated with tirzepatide (dual GIP and GLP-1 receptor agonist), followed closely by semaglutide (mono GLP-1 agonist) and retatrutide (triple receptor agonist targeting GLP-1, GIP, and glucagon receptors). However, cotadutide was also reported to contribute notably to FBG reduction, especially compared to liraglutide (mono GLP-1 agonist), which administration did not result in significant decline in FBG levels [16].

It must be noted, that in another meta-analysis, conducted by Kamrul-Hasan, Abul Bashar Mohammad et al., it was indicated that cotadutide is as effective as the first-generation GLP-1 receptor agonists such as lixisenatide and exenatide, though the efficacy is lower than the newer generation GLP-1 agonists like liraglutide, dulaglutide, and semaglutide [17]. In said analysis it was also suggested that the weight loss potential of cotadutide surpasses that of GLP-1RA drugs such as lixisenatide, exenatide, liraglutide, and dulaglutide [15].

The varying conclusions of cited meta-analyses may be results of the fact that the analysed studies had a short duration and involved few participants, therefore further research is crucial for objective assessment of cotadutide’s full clinical potential.

The risk of adverse effects (AEs) in cotadutide therapy was statistically significantly increased compared to placebo with gastrointestinal side effects similar to those common in patients treated with glp-1 agonists (e.g. nausea, vomiting, constipation, decreased appetite). Despite possible risk of AEs occurring more frequently in patients treated with cotadutide compared to other GLP-1 agonists - due to its agonism towards glucagon receptor, therefore potentially delaying gastric emptying - said risk was not increased when compared to mono GLP-1 agonists liraglutide and semaglutide [15] nor other glucagon receptor agonists [18].

It was noted that specific receptor targeting and varying receptor affinities can improve clinical efficacy in treatment with GLP-1 agonists. This tailored approach enables the therapy to be matched to the patient's individual profile, although further research is required [16]. A possible advantage of cotadutide against mono GLP-1 agonists was suggested due to its unique agonistic effect towards glucagon receptors. Since said receptors are highly expressed in liver and kidney tissue, cotadutide therapy could potentially influence hepatic and renal physiology [19]. Potential beneficial effect on kidney function was suggested by Parker et al. in a study conducted on patients with both type 2 diabetes and chronic kidney disease, with reductions in urinary albumin-to-creatinine ratios in patients receiving cotadutide treatment vs placebo[12]. Additionally, in studies on rodents, cotadutide administration led to a reduction in hepatic glycogen content, improved hepatic mitochondrial function, reduced inflammation, as well as reduced steatosis and liver fibrosis [20]. In studies on humans, improvements in lipid profile, AST and ALT levels, propeptide of type III collagen level, fibrosis-4 index, and nonalcoholic fatty liver disease fibrosis score were observed with cotadutide 300 μg versus placebo, but not with liraglutide [10]. In a study conducted by Parker et al., it was shown that cotadutide promotes greater reductions in liver glycogen and fat compared with placebo and liraglutide [21]. Altogether, to fully define cotadutide’s place among other GLP-1 agonists, further research is needed.

6. Future perspectives

The study findings [21] indicate that simultaneous activation of GLP-1 and glucagon receptors leads to beneficial effects on liver metabolism, overall metabolic status, and body weight reduction. These results highlight the therapeutic potential of dual-agonist peptides in the treatment of metabolic disorders.

NASH remains a significant unmet medical need, and effective therapies should target key disease features such as steatosis, inflammation, hepatocyte injury, and liver fibrosis. Cotadutide reduces liver steatosis, inflammation, and fibrosis in mouse models of NASH, while

also promoting weight loss and improving glucose metabolism. Although the GLP-1 monoagonist liraglutide produced similar weight loss, cotadutide demonstrated greater benefits for liver health, likely due to additional glucagon receptor activation. Cotadutide also inhibited hepatic lipogenesis and enhanced mitochondrial oxidative capacity, suggesting improved hepatic energy metabolism. Together with clinical evidence showing reduced liver fat in patients with type 2 diabetes, these findings indicate that cotadutide may represent a promising therapeutic option for NAFLD/NASH. [5]

Preclinical studies in diet-induced NASH mouse models demonstrated that cotadutide significantly lowered both the NAFLD activity score and liver fibrosis. [20]

Another study suggests that cotadutide may provide therapeutic benefits for patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Treatment with cotadutide was associated with improvements in albuminuria, glycemic control, blood pressure, and body weight, as well as a reduction in insulin requirements compared with placebo. The observed decreases in HbA1c, systolic blood pressure, and body weight are clinically meaningful and may contribute to long-term renal and cardiovascular protection, as these metabolic risk factors are closely linked to the progression of kidney dysfunction and cardiovascular complications. These findings support and extend previous evidence on the benefits of GLP-1 receptor agonists in patients with diabetic kidney disease [22,23] Overall, the results suggest that dual GLP-1 and glucagon receptor agonism may provide additional kidney-related benefits, although larger and longer-term studies are needed to confirm these effects on renal outcomes. [6]

7. Conclusions

Cotadutide is a dual GLP-1 and glucagon agonist that promises a modern therapeutic strategy in type 2 diabetes treatment. Due to its multidirectional mechanism it influences not only glycemic control, but also body weight reduction and improves metabolic parameters, in comparison to placebo. Current studies indicate potential liver and kidney protective effect, as well as comparable safety profile compared to other incretin therapies. The most commonly observed adverse effects are gastrointestinal tract reactions similar to those common in patients treated with glp-1 agonists (e.g. nausea, vomiting, constipation, decreased appetite).

Despite promising clinical results, further analysis and long-term studies including large-scale patient groups are required to establish its efficacy and safety.

Disclosure

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