Endokrynologia Polska
DOI: 10.5603/EP.a2021.0022
Volume/Tom 72; Number/Numer 2/2021
ISSN 0423–104X, e-ISSN 2299–8306

Adjuvant therapy in type 1 diabetes mellitus — choice or necessity in the COVID-19 pandemic?

Edyta Cichocka

Department of Internal Medicine, Diabetology, and Nephrology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

The COVID-19 pandemic has had a significant impact on the daily functioning of hospital and outpatient specialist centres. The restrictions we have been under since the spring 2020 have translated into difficulties in access to diagnostic and treatment procedures. As a result, telemedicine consultations have frequently become the only form of contact between a patient and a medical specialist. Further restrictions on the use of sports facilities, confinement at home, and remote working have translated into excessive food intake, lower physical activity and, consequently, weight gain, and deterioration of diabetes control. When conducting telemedicine diabetes consultations of frequently obese patients with uncontrolled glycaemia, a diabetologist is faced with the difficult task of modification of diabetes treatment in the case of a significant reduction in their physical activity and difficulties with the maintenance of a diet.

While next to insulin, new hypoglycaemic drugs are available for patients with type 2 diabetes (T2DM), intensive insulin therapy still remains the gold standard for type 1 diabetes treatment (T1DM).

A paper on the use of adjuvant therapy in type 1 diabetes was published in the previous issue of *Endokrynologia Polska* [1]. The search for new therapeutic options in patients with type 1 diabetes is the result of the increasing incidence of metabolic disorders in this group of patients, including obesity and, paradoxically, insulin resistance, which is particularly evident during the COVID-19 pandemic.

The aim of such treatment is to support exogenous insulin therapy to achieve the therapeutic goal and at the same time to reduce the risk of hypoglycaemia and to have a beneficial effect on body weight. Potential therapeutic options include metformin (which has been used for many years) and new hypoglycaemic drugs, such as SGLT2 inhibitors and GLP-1 analogues.

Metformin is the first-line drug in the therapy of T2DM, the main effect of which is to inhibit liver gluconeogenesis and reduce insulin resistance. It has been shown that the addition of metformin to insulin therapy in type 1 diabetic patients results in improved glycaemic control, reduces the need for insulin and the incidence of metabolic syndrome, and promotes the reduction and maintenance of normal body weight (1.4–6.0 kg, on average) [2, 3]. The use of metformin is not associated with an increased frequency of hypoglycaemic episodes or the risk of lactic acidosis, and the main adverse effects include gastrointestinal disorders typical of this group of drugs [2–3]. Metformin is particularly important in the treatment of patients with T1DM and polycystic ovary syndrome (PCOS), in whom insulin resistance is often associated with obesity [4, 5]. In women with PCOS, metformin has a beneficial effect not only on carbohydrate metabolism, but also on lipid and hormone metabolism. It increases the secretion of oestrogen and sex hormone-binding globulin (SHBG). It also reduces the production of ovarian and adrenal androgens [6]. Metformin has not been approved by the FDA for T1DM. However, both the American Diabetes Association and many European societies recognize the potential benefits of metformin as an adjuvant for insulin therapy, particularly in overweight and obese patients [7]. As a result, metformin is the most commonly prescribed drug to supplement insulin therapy in patients with T1DM and is used in about 8% of patients [7].

Sodium–glucose cotransporter 2 inhibitors (SGLT2) lower glycaemia independently of insulin. Inhibition of SGLT2 results in a number of beneficial effects, including loss of excess calories in urine (and consequently reduction in insulin requirements), weight loss, increase in insulin sensitivity, reduction in blood pressure, slowing the progression of albuminuria and diabetic nephropathy. Empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin are approved for the treatment of T2DM, and some of them have also shown beneficial effects on the cardiovascular system and kidney function [8–10]. Sotagliflozin, approved also for the treatment of T1DM, is a dual SGLT1 and SGLT2 inhibitor. Additionally, it inhibits intestinal glucose reabsorption, thus reducing postprandial hyperglycaemia.

Edyta Cichocka MD, PhD, Department of Internal Medicine, Diabetology, and Nephrology in Zabrze, ul. 3 Maja 13/15, 41–800 Zabrze, Poland, tel: (+48) 530 032 206; e-mail: ecichocka@sum.edu.pl

Adding an SGLT-2 inhibitor to the therapy of T1DM has been shown to be associated with a significant reduction in HbA1c concentrations, a decrease in body weight and glycaemic variability, and an increase in time-in-range (TIR). The systolic blood pressure and daily insulin requirements are also reduced [11]. The possible adverse effects of adjuvant therapy with SGLT2 inhibitors in T1DM should also be considered (e.g. clinically significant urogenital infections and euglycaemic ketoacidosis). These adverse effects not only hinder the treatment process, but also require careful selection of patients undergoing such treatment [12]. In 2019, The European Medicines Agency (EMA) approved dapagliflozin 5 mg to be an adjuvant drug for the treatment of T1DM in patients with BMI no less than 27 kg/m^2 in whom insulin therapy alone does not result in optimal metabolic control. However, the American Food and Drug Administration (FDA) has not approved this treatment. Dapagliflozin (5 mg) is also used in Poland. Sotagliflozin has been approved by the EMA for T1DM. However, the FDA has not approved it [12].

GLP-1 analogues are effective and safe in patients with T1DM, as indicated by clinical trials. Liraglutide is a member of this class of drugs. GLP-1 analogues mimic the action of endogenous glucagon-like peptide-1 (GLP-1), which is an intestinal hormone released in response to food intake, thus regulating blood glucose levels. It acts by increasing insulin secretion by β cells of the pancreas in a glucose-dependent mechanism. It inhibits glucagon secretion, slows gastric emptying, and inhibits appetite. In addition to achieving improvement in glycaemic control and reduction in HbA_{1c} concentrations, liraglutide has been shown to lower arterial pressure, and reduce body weight and insulin requirements. Additionally, it has a positive effect on the quality of life. A significant weight loss (of 2.5 to 6.5 kg) was demonstrated in patients with T1DM who received liraglutide 1.8 mg [13, 14]. Data on the influence of other GLP-1 analogues on T1DM are limited.

In conclusion, in addition to insulin, more therapeutic options are available for patients with type 1 diabetes, particularly for those with obesity and metabolic syndrome.

When establishing a treatment regimen, the following must be considered: indications included in the summary of product characteristics and the related limitations (off-label therapy), the lack of indications for reimbursement, which results in high costs of treatment and the possibility of adverse effects, which requires careful selection of patients and their thorough education.

Conflict of interest

None declared.

References

1. Cichocka E, Maj-Podsiadło A, Gumprecht J. Adjuvant therapy in type 1 diabetes mellitus. Endokrynol Pol. 2021; Ahead of Print, doi: 10.5603/EP.a2021.0003.
2. Al Khalifah RA, Alnhdi A, Alghar H, et al. The effect of adding metformin to insulin therapy for type 1 diabetes mellitus children: A systematic review and meta-analysis. Pediatr Diabetes. 2017; 18(7): 664–673, doi: 10.1111/pedi.12493, indexed in Pubmed: 28145083.
3. Libman IM, Miller KM, DiMeglio LA, et al. T1D Exchange Clinic Network Metformin RCT Study Group. Effect of Metformin Added to Insulin on Glycemic Control Among Overweight/Obese Adolescents With Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2015; 314(21): 2241–2250, doi: 10.1001/jama.2015.16174, indexed in Pubmed: 26624824.
4. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997; 18(6): 774–800, doi: 10.1210/edrv.18.6.0318, indexed in Pubmed: 9408743.
5. Escobar-Morreale HF, Roldán-Martín MB, Escobar-Morreale HF, et al. Type 1 Diabetes and Polycystic Ovary Syndrome: Systematic Review and Meta-analysis. Diabetes Care. 2016; 39(4): 639–648, doi: 10.2337/dc15-2577, indexed in Pubmed: 27208367.
6. Milewicz A, Kudła M, Spaczyński RZ, et al. The polycystic ovary syndrome: a position statement from the Polish Society of Endocrinology, the Polish Society of Gynaecologists and Obstetricians, and the Polish Society of Gynaecological Endocrinology. Endokrynol Pol. 2018; 69(4), doi: 10.5603/EP.2018.0046, indexed in Pubmed: 30209800.
7. Casu A, Bilal A, Pratley RE, et al. Advancing Care for Type 1 Diabetes, Obesity Network (ACT1ON). Pharmacological therapies to address obesity in type 1 diabetes. Curr Opin Endocrinol Diabetes Obes. 2020; 27(4): 194–206, doi: 10.1097/MED.0000000000000555, indexed in Pubmed: 32618631.
8. Maj-Podsiadło A, Cichocka E, Gumprecht J, et al. SGLT-2 inhibitors as adjunctive to insulin therapy in type 1 diabetes. Clin Diab. 2020; 9(3): 189–192, doi: 10.5603/dk.2020.0013.
9. Huang Y, Jiang Z, Wei Y, et al. Short- and medium-term efficacy of sodium glucose cotransporter 2 (SGLT-2) inhibitors for the treatment of type 1 diabetes: systematic review and meta-analysis. Endokrynol Pol. 2020; 71(4): 325–333, doi: 10.5603/EP.a2020.0034, indexed in Pubmed: 32901912.
10. Yamada T, Shojima N, Noma H, et al. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: Systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2018; 20(7): 1755–1761, doi: 10.1111/dom.13260, indexed in Pubmed: 29451721.
11. Danne T, Cariou B, Buse JB, et al. Improved Time in Range and Glycemic Variability With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: A Pooled Analysis of 24-Week Continuous Glucose Monitoring Data From the inTandem Program. Diabetes Care. 2019; 42(5): 919–930, doi: 10.2337/dc18-2149, indexed in Pubmed: 30833371.
12. Danne T, Garg S, Peters AL, et al. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care. 2019; 42(6): 1147–1154, doi: 10.2337/dc18-2316, indexed in Pubmed: 30728224.
13. Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2016; 4(3): 221–232, doi: 10.1016/S2213-8587(15)00436-2, indexed in Pubmed: 26656289.
14. Mathieu C, Zinman B, Hemmingsson JU, et al. ADJUNCT ONE Investigators. Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial. Diabetes Care. 2016; 39(10): 1702–1710, doi: 10.2337/dc16-0691, indexed in Pubmed: 27506222.