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Sotagliflozin, an inhibitor of sodium-glucose cotransporters 1 and 2 (SGLT1 / 2), as a new therapeutic approach for patients with type 1 diabetes mellitus

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Sotaglifosine, a complex inhibitor of SGLT1 / 2 cotransporters, as a new therapeutic option for patients with type 1 diabetes

Sotagliflozin, an inhibitor of sodium-glucose cotransporters 1 and 2 (SGLT1 / 2), as a new therapeutic approach for patients with type 1 diabetes mellitus

Summary

Sotagliflozin (SOTA) is a dual inhibitor of SGLT1 and SGLT2 used in adults with type 1 diabetes. The mechanism of action, based on the inhibition of both the SGLT1 and SGLT2 cotransporters, allows simultaneous increase of glucose excretion and slowing down the absorption of glucose in the intestine. Recently, test results have been published showing a beneficial effect of sotagliflozin on type 1 diabetes control [1,2,3].

Sotagliflozin use leads to a significant reduction in glycosylated haemoglobin (HbA1c) [1,2,3] , postprandial glucose reduction [1,2,3], weight loss [1,2,3], systolic blood pressure reduction [1,2,3] and reducing the risk of hypoglycaemia during the treatment [1,2,3].

Treatment of type 1 diabetes is based on a model of intensive, functional insulin therapy with the use of human insulin preparations or analogues of this insulin [10]. The therapy is carried out by multiple, subcutaneous injections of insulin doses or in the form of continuous insulin infusion with a personal insulin pump [10].

According to the recommendations of the Polish Diabetes Association (PTD) for patients with type 1 diabetes in terms of glycemic control, the primary goal is to maintain HbA1C 7% (53mmol / mol) and when the goal is not associated with the risk of hypoglycaemia, the target value is 6.5%. The use of proper treatment and sustaining HbA1C at the level recommended by PTD allows to prevent acute and chronic complications of the disease and at the same time allows patients to live actively and, consequently, improves their life quality [10].

According to recently published studies, preparations from SGLT-1 and SGLT-2 inhibitor groups may be helpful in obtaining and sustaining the treatment objective recommended by PTD.

Keywords :

SGLT-1 and SGLT-2 inhibitor, sotaglifosin, type 1 HbA1C diabetes, hypoglycaemia

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Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from the defect of insulin secretion and/or insulin action. Type 1 diabetes is a multifactorial disease that consists of immunological, genetic and environmental factors [10].

Type 1 diabetes is characterized by an early onset: age of onset below 30 years old (LADA exception), often very early in the first years of life. The highest peak of incidence is recorded at the age of 10-12 (it occurs earlier in girls), slightly smaller at the age of 16-19.

Early onset of type 1 diabetes in children and adolescents is the result of the depletion of the secretory pancreatic β cells. The onset of the disease is usually sudden, and the disease itself is unstable. This course of disease is associated with a high risk of complications, both acute - in the form of ketoacidosis or hypoglycaemic coma, as well as long-term - in the form of micro- and macrovascular complications.

The course of type 1 diabetes diagnosed above 30 years of age (LADA) is not as dynamic. The onset is usually not as severe as in children, and the symptoms build up over time, usually over a period of a few months. Its slow onset can cause that hyperglycaemia growing in the latent period initiates the development of chronic complications from the micro- and macrovascular group. Due to the late diagnosis of LADA as well as clinical symptoms and diagnostic difficulties, this diabetes subtype affects 5-10% of people who were initially diagnosed with type 2 diabetes. This usually causes poorly applied therapy in this group of patients, which further exposes patients to the emergence of chronic complications.

Optimal therapy aims to reduce the risk of acute and chronic complications. Chronic hyperglycaemia and large daily fluctuations in blood glucose levels are associated with damage or dysfunction and failure of various organs, especially eyes, kidneys, nerves, heart and blood vessels [6, 7, 8, 10, 11].

In the case of type 1 diabetes, rapid diagnosis and proper pharmacotherapy are particularly important.

In the long duration of the disease, it is extremely important to achieve all the goals recommended by PTD, because only in this case the risk of late diabetic complications is effectively minimized.

Treatment of type 1 diabetes [10]

In type 1 diabetes, the Polish Diabetes Association recommends achieving the complex treatment goals set out in Table 1:

Table 1. Criteria for levelling type 1 diabetes according to the Polish Diabetes Association [10]

HbA1c	7% / 6.5%
On empty stomach and before meal	80-110 mg/dl (4.4-6.1 mmol/l)
2 hours after the start of the meal	140 mg/dl (7.8 mmol /l)
LDL cholesterol, in people with very high cardiovascular risk	<70 mg/dl
LDL-C concentration in people at high cardiovascular risk	<100 mg/dl
LDL-C concentration in people with moderate and low cardiovascular risk	<115 mg/dl
Concentration of "non-HDL" cholesterol in people with diabetes with very high cardiovascular risk	<100 mg/dl
Concentration of "non-HDL" cholesterol in people with high-risk diabetes	<130 mg/dl
Concentration of "non-HDL" cholesterol in people under 40 years old with type 1 diabetes mellitus, without vascular complications and other cardiovascular risk factors	<145 mg /dl
Concentration of triglycerides	<150 mg/dl
Blood pressure	systolic: <140 mm Hg diastolic: <90 mm Hg

Due to the aetiology of type 1 diabetes, resulting from the destruction of pancreatic beta cells, the only form of treatment is intensive, functional insulin therapy. Until now, oral medications have not been recommended in type 1 diabetes.
However, recently there have been studies on the use of a new group of oral drugs in patients with type 1 diabetes - selective sodium potassium cotransporter inhibitors (SGLT1 / SGLT2), in particular studies on sotagliflozin as a dual inhibitor of both SGLT1 and SGLT2 [1,2 , 3.4] .
Selective inhibitors of sodium-glucose cotransporter, such as canagliflozin or dapagliflozin, appeared on the market as alternative preparations to previously used oral medications or as a supplement to them in type 2 diabetes. Administration of these substances proved to be an effective solution due to their high effectiveness in lowering blood glucose levels. Currently, they are increasingly used in type 2 diabetes, according to their current registration.

Mechanism of action of SGLT1 / SGLT2 inhibitors

SGLT belongs to a large family of transmembrane proteins transporting glucose, amino acids, vitamins, osmolytes and some ions in the small intestine and kidney canal. Among the six described isoforms of Na + / glucose cotransporters, SGLT1 and SGLT2 seem to be the most important for glucose transport [36]. Due to the above, these two transporters were tested for their use in the treatment of diabetes.
SGLT1 is a membrane protein transporting glucose and Na + ions in a 1:2 ratio.
It is the main transporter of glucose in the small intestine [26-27]. Inhibition of SGLT1 activity slows down intestinal glucose absorption [13, 35], independent of insulin [13] and renal

function [28], leading to lower postprandial glucose levels [15,27] and increased levels of glucagon-like peptide-1 and YY peptide [30.31].
SGLT2 is a transporter with a lower affinity but higher bandwidth for glucose compared to SGLT1 and the ratio of glucose transport to Na+ ions is 1:1.
SGLT2 is expressed primarily in the kidney, where it absorbs again 90% of filtered glucose [19]. Inhibition of SGLT2 increases the excretion of glucose in the urine [16,23,24], which improves glycemic control [26-29] independently of insulin[24], with additional clinical benefits in the form of reduced body mass [1,2,3,26 , 27] and lowering of systolic blood pressure [1,2,3,27,28].

Sotagliflozin (SOTA) is a dual inhibitor of SGLT1 and SGLT2. The mechanism of action based on the combination of inhibition of both SGLT1 and SGLT2 cotransporter allows simultaneous increase of glucose excretion in the urine and slowing down the absorption of glucose in the intestine [1-10].
Due to the mechanism of action of SGLT1/2 inhibitors, these substances, originally tested for use in the treatment of type 2 diabetes, have recently also been subjected to observation for use in type 1 diabetes as supplementary insulin therapy.
International studies (inTandem 1, inTandem 2, inTandem 3) carried out in 2017 and 2018, present the results of a 24-week observation of the appropriateness of adding sotagliflozin - SGLT1/2 inhibitor to insulin therapy in type 1 diabetes[1,2,3,4] .

Study review

In the inTandem 1, inTandem 2 and inTandem 3 studies, the sotagliflozin preparation, which was an inhibitor of both SGLT1 and SGLT2 cotransporters, was subjected to observation [1,2,3].
In all of the studies conducted, treatment with sotagliflozin was associated with intensive insulin therapy.
The aim of the study was to find an answer to the question whether there are benefits from the use of a new group of drugs in patients with type 1 diabetes.

InTandem 3 study

In 2017 in the New England Journal of Medicine published work on the efficacy of sotagliflozin in combination with insulin in patients with type 1 diabetes [2].
The inTandem3 study was conducted in 133 centres and included a total of 1402 patients. The study group included patients over 18 years of age with type 1 diabetes, with HbA1C between 7% and 11% and Body Mass Index at least 18.5 [1].
Patients were assigned to two groups. For the first group (699 patients), sotagliflozin 400 mg was added to insulin in the form of two tablets taken once a day before the first meal. In the second observation group (703 patients), placebo was added to insulinotherapy in the form of two tablets identical in the form of sotagliflozin, given in the same scheme [1].
In this study, a composite primary endpoint was identified, consisting of a reduction in HbA1C below 7% with no severe hypoglycaemia and episodes of ketoacidosis after 24 weeks of study duration [1].

The results of the inTandem3 study according to the end points determined in the study are presented in Table 2 [1].

Table 2. Endpoints of the inTandem3 study

Test endpoints	Insulin + sotagliflozin 400 mg n=699	Insulin + placebo n=703
Primary endpoint: HbA1C 7% No episodes of hypoglycaemia No episodes of ketoacidosis (DKA)	200 (28.6%)	107 (15.2%)
Secondary end points:		
HbA1C 7%	206 (29.6%)	111 (15.8%)
Severe hypoglycaemia 1 episode	21 (3%)	17 (2.4%)
Night hypoglycaemia 1 episode	2 (0.3%)	5 (0.7%)
Ketoacidosis 1 episode	21 (3.0%)	4 (0.6%)
Documented hypoglycaemia	673 (96,3%)	670 (95.3%)
Documented nocturnal hypoglycaemia	521 (74.5%)	553 (78.7%)
Hypoglycaemia 70 mg / dl	69.8 patients/year	77.9 patients/year
Hypoglycaemia 55 mg / dl	11.8 patients/year	15,4 patients/year
Complex secondary endpoints:		
HbA1C 7% No weight gain or weight loss> 5%	171 (24.5%)	51 (7.3%)

The primary endpoint was evaluated in patients using multiple-injection regimens and in patients treated with a personal insulin pump.

Comparison of groups of patients treated with multiple injections compared to patients treated with insulin pumps - results obtained in the inTandem 3 study, presented in table 3 [1].

Table 3. Primary endpoint obtained in the inTandem3 study in patients treated with multiple injections of insulin vs. treated with a personal insulin pump.

Primary endpoint HbA1 7% No severe episodes of hypoglycaemia No episodes of ketoacidosis (DKA)	Insulin + sotagliflozin n=699	Insulin + placebo n=703
All patients	200/699 (28.6%)	107/703 (15.2%)
Patients with insulin pumps	88/275 (32.0%)	45/280 (16.1%)
Patients treated with multiple injections	112/424 (26.4%)	62/423 (14.7%)

The primary endpoint in inTandem3 study was significantly higher in the sotagliflozin group compared to the placebo group, regardless of the insulin regimen (multiple injections vs. personal insulin pump) [1].

The secondary endpoint was defined as: the incidence of hypoglycaemia and episodes of ketoacidosis, change in HbA1C level compared to baseline after 24 weeks of treatment, change in body weight, change in daily insulin dose and change in blood pressure in patients with initial 130 mmHg and various combinations of the above.

Analysis of the study in terms of achieving secondary endpoints showed:

1. A similar incidence of hypoglycaemia below 70 mg/dl in both groups [1],

Hypoglycaems below 55 mg/dl were significantly less frequent in the sotagliflozin group [1],

2. Significantly higher number of patients in the sotagliflozin group who achieved HbA1C below 7% in relation to the placebo group [1],
3. Significantly higher number of patients who achieved HbA1C below 7%, with no increase in body weight in the study group, compared to the control group [1],
4. Significantly higher in the group with sotagliflozin reduction of body weight compared to the baseline, observed after 24 weeks. On average, it was 3 kg [1],
5. Reduction of insulin dose in the sotagliflozin group [1],
6. Lowering the blood pressure in patients enrolled in the study with a pressure above 130 mmHg (after 16 weeks of the study) in the study group by an average of 3.5 mmHg [1],
7. Significantly more frequent episodes of ketoacidosis in patients with sotagliflozin [1].

In the conclusions of this study, the authors draw attention to the benefits of adding a new group of SGLT1/2 inhibitors to insulin therapy, while stressing more frequent episodes of ketoacidosis [1].

In 2018, inTandem1, 2 studies [2,3] were published in Diabetes Care.

InTandem 1 study.

A randomized, 3-phase study in which patients with type 1 diabetes in North America were under observation. Due to the oral preparation added to insulin, patients were divided into 3 groups: placebo group n=268, group with sotaglifosine - 200mg dose n=263, group with sotaglifosin 400mg dose n=262. Allocations to a specific group occurred after a 6-week dose optimization of the previously taken insulin.
The study included men and women over 18 years of age suffering from type 1 diabetes. The condition for recruitment for the study was also HbA1C level between 7% and 11%. Patients were randomly assigned 1:1:1 to sotagliflozin 200 mg: 400 mg: placebo groups.
The oral medications added to insulin therapy were given to the first meal once a day, while the insulin dose was reduced by 30%.
The duration of the study was set at 24 weeks, with a follow-up of up to 52 weeks.
The study determined the primary endpoint, which was HbA1C change from the baseline after 24 weeks of study duration [3].
The results of the inTandem1 study are presented in Table 4 [3].

Table 4. Results of the inTandem 1 study according to the end points determined in the study.

Endpoints	insulin + sotagliflozin 200mg n=263	insulin + sotagliflozin 400mg n=262	insulin + placebo n=268
Primary endpoint			
HbA1c change from baseline after 24 weeks	-0.36%	-0.41%	-
Secondary end points			
1. Secondary composite endpoint: HbA1C 7% No severe episodes of hypoglycaemia No episodes of ketoacidosis (DKA)	33.46% *	43.51% *	21.64% *

2. Secondary endpoint Number of patients who obtained HbA1C 7%	27.2% * 27.7% #	40.3% * 35.4% #	15.7% * 18.4% #
3. A secondary composite endpoint: HbA1C 7% No weight gain	30.42%	43.51%	8.58%
4 Secondary composite endpoint: HbA1C 7% No severe episodes of hypoglycaemia No episodes of ketoacidosis (DKA) No weight gain	27.76%	40.84%	7.84%
Hypoglycaemia 55 mg / dl	6.5% #	6.5% #	9.7% #
Episodes of ketoacidosis (DKA)	3.4% #	4.2% #	0.4% #

* -24 week of study
# -52 week of study

The first secondary point was determined as a composite point and it determined the number of patients who achieved HbA1C 7% and with no hypoglycaemic and ketoacidosis episodes observed during the course of the study. The other secondary points were related to the change in body weight compared to baseline, changes in insulin doses and to the level of fasting blood glucose lowering. Other observations also concerned the level of blood pressure reduction in patients with a base pressure of 130 mmHg [3].

The primary endpoint was achieved by significantly more patients who initially had HbA1C 7% and during the course of the study achieved a reduction in this parameter below 7% after 24 weeks compared to the placebo group. This result was maintained after a follow-up extended to 52 weeks [3].

With respect to insulin doses, a fall in the pradial insulin dose of 5.7% was observed in the 200 mg sotagliflozin group, whereas in the 400 mg group it was 12.67% after 24 weeks. The basal insulin doses in the placebo group increased, whereas in the SGLT1 / 2 group the doses were lowered after 52 weeks by 5.53% for 200 mg dose and 15.63% for 400 mg dose [3].

The assessment of the risk of severe hypoglycaemia in the placebo group compared to sotagliflozin is more favourable for the second group. After 52 weeks of the study, the frequency of documented severe hypoglycaemia below 70mg/dl was demonstrated, for 17 (6.5%) patients with sotagliflozin and 26 patients (9.7%) with placebo. The incidence of hypoglycaemia was similar for both doses of sotagliflozin.

The weight reduction for 200 mg of sotagliflozin was 2.35 kg after 24 weeks and 3.14 kg after 52 weeks. For 400 mg dose, the weight loss was 3.45 kg after 24 weeks and 4.32 kg after 52 weeks.

The composite endpoints of the inTandem1 study were defined as:

1. The reduction of HbA1C 7% without hypoglycaemic episodes, ketoacidosis and without weight gain after 24 weeks,
2. Reduction in HbA1C 7% in the absence of weight gain after 24 weeks.

Both endpoints were achieved much more frequently in the sotagliflozin group, with the percentage of patients who achieved these points was higher for 400 mg dose [3].

During the study, ketoacidosis occurred significantly more often in patients taking sotagliflozin 200 mg - 9 patients (3.4%), 400mg - 11 patients (4.2%), while in the placebo group only in 1 patient (0.4%). During the follow-up, a total of 82 patients reported episodes of ketoacidosis, however, due to this reason only 4 patients in each of 200 mg and 400 mg groups resigned from sotagliflozin treatment [3].

Summing up the 52-week study, it can be concluded that in the group with sotagliflozin compared to the placebo group, the reduction was significantly more frequent: HbA1C ≤ 7%, body weight, insulin dose, the incidence of hypoglycaemic episodes. However, there was an increase in the frequency of episodes of ketoacidosis in this group of patients [3].

InTandem 2 study

In 2018, Diabetes Care published the inTandem 2 study. It aimed to investigate the appropriateness of using selective SGLT1/2 inhibitors in combination with insulin, in relation to the combination of insulin and placebo, in patients with type 1 diabetes in Europe. The paper considers the aspects of efficacy and safety of the combination therapy with the use of sotagliflozin.

It was an international 3 phase study, designed as a double-blind trial lasting 52 weeks. Overall, 782 patients participated in the study. Patients were qualified for the follow-up according to the following criteria: men and women over 18 years of age with type 1 diabetes who had HbA1C above 7% and below 11%. They were assigned to three study groups: n=258 to the placebo group, n=261 to the sotagliflozin group at a dose of 200 mg and n=263 to a dose of 400 mg. Patients were assigned to these groups after prior optimization of the insulin dose. Sotagliflozin doses were given to patients in scheme 1 once a day.
The dose of pradial insulin in the patients was reduced by 30% after the first dose of the studied drugs.

Table 5. Results of the inTandem2 study according to the endpoints determined in the study [2].

Endpoints	Insulin + Sotagliflozin 200 mg n=261	Insulin + Sotagliflozin 400 mg n=263	insulin + placebo n=258
Primary endpoint			
HbA1C change from baseline after 24 weeks	-0.37%	-0.35%	
The number of patients who obtained HbA1C ≤ 7%	33.3% *	33.8% *	15.1% *
	27.2% #	27.8% #	15.5% #
1. A secondary composite endpoint: HbA1C ≤ 7% No severe episodes of hypoglycaemia No episodes of ketoacidosis (DKA)	31.42% *	32.32% *	15.12% *
2. Secondary composite endpoint: Drop of HbA1C 0.5% No severe episodes of hypoglycaemia	-	44.87% * 37.26% #	17.44% * 19.38% #

No episodes of ketoacidosis (DKA)			
3. Secondary composite endpoint: HbA1C ≤ 7% No weight gain	 25.67% * 19.92% #	 29.66% * 22.81% #	 6.98% * 8.53% #
4. Secondary composite endpoint: HbA1C ≤ 7% No severe episodes of hypoglycaemia No episodes of ketoacidosis (DKA) No weight gain	 24.14% * 18.39% #	 28.14% * 21.67% #	 6.98% * 7.75% #
Hypoglycaemia 55 mg / dl	16.7% *	15.4% *	28.9% *
Documented severe hypoglycaemia	5.0% #	2.3% #	5.0% #
Episodes of ketoacidosis	0.8% * 2.3% #	1.5% * 3.4% #	0% * 0% #

* -24 week of study
# -52 week of study

The primary endpoint of the inTandem 2 study was a reduction in HbA1C level relative to baseline after 24 weeks of the follow-up.
The first secondary endpoint of the study was a composite point and consisted of a reduction in HbA1C below 7%, in the absence of severe hypoglycaemic episodes and ketoacidosis, and was verified after 24 weeks.
Additional secondary endpoints are: change in body weight relative to baseline, change in insulin dose, fasting blood glucose levels and blood pressure lowering in patients who entered the study at a rate above 130 mmHg. The study looked at episodes of ketoacidosis and hypoglycaemia.

The primary endpoint after 24 weeks reached significantly more patients in the sotagfliflozin group, in both doses, and this result was maintained in the extended 52-week follow-up [2].
In the initial group, HbA1C lower than 7% was observed in 13 out of 214 patients in the placebo group, 52 out of 211 patients with sotagliflozin 200 mg and 57 out of 217 patients with 400 mg dose [2].

The daily insulin doses were reduced after 24 weeks in the sotagliflozin group with respect to the placebo group by 5.82% and 4.67%, respectively at doses of 200 and 400mg [2].

The decrease in body weight observed during the study concerned the group in which sotagliflozin was added to the insulin therapy. At 200 mg dose, it was 1.98 kg after 24 weeks and 2.18 kg after 52 weeks, while 400 mg dose gave a weight loss of 2.58 kg after 24 weeks and 2.92 kg after 52 weeks [2].
The composite endpoint determined by achieving HbA1C levels below 7%, without hypoglycaemic episodes and ketoacidosis, achieved significantly more patients from the sotagliflozin group at both 200 mg and 400 mg doses after 24 weeks[2].

After 24 and 52 weeks, 44.87% and 37.26% of patients taking sotaglifosine 400 mg received a reduction in HbA1C 0.5%, without episodes of hypoglycaemia and ketoacidosis, compared to the placebo group, where the result was respectively 17.44% and 19.38% of patients [2].

Another endpoint, determined by lowering HbA1C below 7% with no weight gain determined after 24 weeks reached 25.67% for 200 mg dose, 29.66% for 400 mg dose, compared to the placebo group with 6.98 %. After 52 weeks these proportions were respectively at the level of 19.92%, 22.81% and 8.53%, [2].

The study observed that after 24 weeks more patients who achieved HbA1C below 7% with a simultaneous 5% weight loss belonged to the group taking sotagliflozin in a dose of 200mg - 6.12% and 400mg 8.34% [2].

Another composite point, in which a simultaneous occurrence of 7% HbA1C reduction, no gain or decrease in body weight and absence of hypoglycaemic episodes, nor ketoacidosis was observed, after 24 weeks reached 24.14% for sotagliflozin 200 mg and 28.14% for 400 doses mg, compared to the placebo group 6.98%. After 52 weeks these values were 18.39%, 21.67% and 7.75%, respectively [2].

The inTandem2 study also looked at the incidence of hypoglycaemia in patients in individual study groups.

Severe hypoglycaemic episodes, defined in the study as a reduction in the level of glycaemia 55 mg/dl, were significantly less frequent in the group receiving combination therapy with sotaglifosin in both doses of 200 mg and 400 mg. After 24 weeks, they occurred respectively in 16.7% and 15.45%, compared to placebo in 28.9% [2].

Observation of patients with regard to the incidence of episodes of ketoacidosis showed that after 52 weeks 15 of 782 subjects experienced them. In the placebo group, no episodes of ketoacidosis were observed, whereas for a dose of 200 mg sotaglifosine in 6 out of 261 patients and for a dose of 400 mg, 9 of 263 reported the occurrence of ketoacidosis. During the 52-week study period, 4 patients discontinued treatment with 400 mg of sotaglifosine due to episodes of ketoacidosis [2].

Summing up the 52-week inTandem2 study, the most important seems to be the significantly higher reduction of HbA1C in the sotagliflozin group achieved for both doses (200 and 400 mg). It is especially valuable because it does not affect the safety of therapy, as demonstrated by complex endpoints. Lowering HbA1C is not associated with weight gain and increased frequency of hypoglycaemic episodes. Only worrying are more frequent episodes of ketoacidosis appearing in the group with sotagliflozin added to insulin therapy.

In the inTandem 1 and inTandem 2 studies, the same primary endpoints were determined, defined as the HbA1C change from baseline after 24 weeks of study duration, the results in Table 6. The initial value to evaluate the change in this parameter was the HbA1C level obtained by patients after 6 weeks of insulin treatment optimization.

Table 6. Comparison of primary end points in inTandem1 and 2 [2,3]

	inTandem 1			inTandem 2		
	placebo	SOTA 200 mg	SOTA 400 mg	placebo	SOTA 200 mg	SOTA 400 mg
Primary HbA1C	8.21%	8.26%	8.20%	8.42%	8.35%	8.38%
HbA1C output	7.54%	7.61%	7.56%	7.79%	7.74%	7.71%
HbA1C after 24 weeks	7.50%	7.17%	7.08%	7.79%	7.36%	7.35%
Difference	-0.07	-0.43	-0.48	-0.02	-0.39	-0.37
Number of patients who have reached the primary endpoint	246	245	242	239	239	241

InTandem4 study

In 2017, the results of the inTandem 4 survey were presented at the European Association for the Study of Diabetes.
In this study, a dose of 75 mg sotagliflozin appeared for the first time alongside 200 and 400 doses. The observation in this study lasted 12 weeks of a double-blind, after an earlier 2-week screening.
The study included 141 patients who received sotagliflozin at doses of 75, 200, 400 mg and placebo added to the stabilized insulin dose. Patients were assigned to 4 study groups: 36 patients to the placebo group and 3 groups with sotaglifosine successively n=35 for 75 mg, n=35 for 200 mg and n=35 for 400 mg.
The HbA1C change achieved after week 12 of the study was determined as the primary endpoint.
Secondary end points were determined as a change from baseline achieved by patients during 12 weeks, in the range of:

1. glucose level determined in urine,
2. glucose level 2 hours after a meal (standardized meal),
3. body weight,
4. fasting blood glucose levels.

In the inTandem4 study, it was found that the primary endpoint was significantly more commonly achieved in the group with insulin added to the sotaglifosine group compared to the placebo group [4].
A comparison of the 3 groups studied shows that 200 mg dose is significantly more effective in reducing HbA1C [4].
Both 200 and 400 mg doses significantly reduced the level of glycaemia measured 2 hours after a meal. The 400 mg dose was the most effective in this case, lowering the blood glucose level by 2.76 mmol/L, compared to the 200 mg dose - 1.54 mmol/L, 75 mg - 1.15 mmol/L and placebo - 0.03 mmol/L [4].
Regarding the change in body weight observed after 12 weeks of the study, similar weight losses of -1.25 kg and -1.48 kg were recorded at a dose of 200 mg and 400 mg. In the placebo group there was a slight increase in body weight, an average of 1.13 kg [4].
Another secondary endpoint was the reduction in blood pressure in patients who initially had this parameter greater than 130mmHg. In this case, a decrease in blood pressure was observed in the sotagliflozin group - regardless of the dose, with the highest decrease at 400 mg compared to placebo and it was -15.8 mmHg [4].
Regarding the safety aspects, this study showed that the risk of hypoglycaemia is similar in all groups, including the placebo group.
Episodes of ketoacidosis were significantly more common in the sotagliflozin 400 mg group [4].
InTandem4 study was conducted on a smaller group of patients, compared to inTandem studies 1, 2 and 3 and within much shorter observation period. Despite this, it confirmed the promising efficacy of sotagliflozin, with high safety in the group of patients with type 1 diabetes.

Summary

1. The studies showed that patients who received sotagliflozin for insulin therapy regardless of the dose used had a benefit in the form of HbA1C reduction compared to patients with a placebo, the results are presented in Table 7 [1,2,3].

Table 7. The number of patients with HbA1C 7% after 24 weeks of the study for SGLT1 / 2 in a dose of 400mg [1,2,3].

Number of patients with HbA1C ⁰ 7%	inTandem3		inTandem2		inTandem1	
	SOTA 400	placebo	SOTA 400	placebo	SOTA 400	placebo
	29.6%	15.8%	33.8%	15.1%	40.3%	15.7%

2. Through the secondary composite endpoint, it was shown that the decrease in HbA1C was achieved without compromising the safety of the therapy.

The secondary, composite endpoint, defined as a decrease in HbA1C 7% with no episodes of hypoglycaemia and episodes of diabetic ketoacidosis (DKA), was assessed in inTandem1 and 2 studies, Table 8. At the same time, the primary endpoint was determined in the inTandem study 3. In this way, a specific endpoint was achieved in individual studies after 24 weeks of their duration by the following group of patients [1,2,3].

Table 8. Decrease in HbA1C with no episodes of hypoglycaemia and DKA, as determined in percent by InTandem1,2,3 studies

	inTandem1	inTandem2	inTandem3
Placebo	21.64%	15.1%	15.2%
SOTA 200mg	33.46%	33.3%	-
SOTA 400mg	43.51%	33.8%	28.6%

3. In the studies, the need to correct the dose of insulin was found.

For the sotagliflozin group of patients, regardless of the dose, significant reduction in insulin doses compared to placebo groups was demonstrated, as shown in Table 9.

Table 9. Combined data showing the reduction of insulin doses in inTandem1 and 2 studies after 52 weeks [1,2,3].

	Daily insulin dose			Basal insulin			Pradial insulin		
	placebo	SOTA 200	SOTA 400	placebo	SOTA 200	SOTA 400	Placebo	SOTA 200	SOTA 400
IU/day	0.18	-3.51	-5.86	1.58	-0.64	-1.72	-1.45	3.08	4.28

In the inTandem 3 study, insulin dose reduction after 24 weeks of study duration in a group of patients with 400 mg sotagliflozin added, Table 10.

Table 10. Reduction of insulin doses in the inTandem3 study

	Daily insulin dose	Basal insulin	Pradial insulin
	SOTA 400	SOTA 400	SOTA 400
IU/day	-5.3	-2.6	-2.8

4. Additional end points:

Weight loss during the test, results in table 11 and 12 [1,2,3]

Table 11. Summary of weight loss after 24 weeks of study duration

inTandem3	inTandem2	inTandem 1
400 mg	200/400 mg	200/400 mg
-2.98 (kg)	-1.98 / -2.58 (kg)	2.35 / 3.45

Table 12. Summary of weight loss after 52 weeks of study duration

inTandem3	inTandem2	inTandem 1
400mg	200/400 mg	200/400 mg
*	-2.18 / -2.92 (kg)	-3.14 / -4,32kg

Changes in LDL level observed in inTandem1,2,3 studies, collected in Table 13.

Table 13. Change of LDL level during the study [1,2,3]

inTandem3	inTandem2	inTandem1
400 mg	200/400 / placebo	200/400/placebo
-	+ 0.13/0.14 / 0.05 (mmol/L)	+ 0.1/ 0.1/ 0.2(mmol/L)

Studies have shown a weight loss in patients who received sotagliflozin for insulin therapy, compared to the placebo group, where there was a slight increase in body weight. With respect to changes in LDL level, in patients studied, however, the increase for sotagliflozin and placebo groups was comparable [1,2,3].

Adverse reactions reported in the studies were mostly related to episodes of diabetic ketoacidosis (DKA). They appeared significantly more often in the group with sotagliflozin, the results are contained in Table 14.

Table 14. Episodes of ketoacidosis (DKA) [1,2,3]

	inTandem1			inTandem2			inTandem3	
DKA	placebo	SOTA 200	SOTA 400	placebo	SOTA 200	SOTA 400	placebo	SOTA 400
	0.4%	3.8%	4.2%	0%	2.3%	3.4%	0.6%	3.0%

6. Among the most frequent adverse reactions in the study were:

Table 15. Adverse reactions observed in inTandem1,2,3

Adverse reaction	inTandem1			inTandem2			inTandem3	
	placebo	SOTA 200	SOTA 400	placebo	SOTA 200	SOTA 400	placebo	SOTA 4 400
Diarrhoea	6.7%	8.4%	10.3%	3.5%	4.6%	7.2%	2.3%	4.1%
Urinary tract infections	7.1%	9.9%	4.2%	5.0%	4.2%	6.8%	3.8%	3.6%
Genital system Infections	3.4%	9.1%	13.0%	2.3%	9.2%	11.0%	2.1%	6.4%

Adverse reactions such as: episodes of ketoacidosis, diarrhoea and genitourinary tract infections were significantly more frequent in the group of patients receiving combination therapy with sotagliflozin. Usually, in the case of side effects such as diarrhoea, genitourinary tract infections, they have been moderate or mild in severity. These symptoms were not in most cases the reason for giving up participation in the study [1,2,3].

In all studies, the primary endpoint was achieved in the much larger group receiving SGLT1/SGLT2 inhibitors compared to the control group, where placebo was added to insulin. This was accompanied by much more frequent episodes of ketoacidosis compared to the placebo group [1,2,3].
Comparison of the 200 and 400 mg doses used in the inTandem studies 1 and 2 shows that 400 mg dose reduced HbA1C more effectively than 200 mg dose [2,3]. It was also shown that 40.3% of patients achieved HbA1C below 7% using an oral dose of 400mg (inTandem 1) [3]. In the inTandem2 study, the composite endpoint reached 1 in 5 patients treated with Insulin and sotagliflozin, compared to the placebo group, in which this point reached 1 in 13 patients [2].
In all studies, the better results achieved with 400 mg dose were associated with more frequent undesirable episodes of acidosis - 3-4% for 400 mg compared to 2-3% for 200 mg dose [1,2,3,4].
The frequency of appearance of hypoglycaemic episodes and the stability of blood glucose levels throughout the day were also controlled. The inTandem1 and 2 studies showed that hypoglycaemic episodes in the sotaglifosin-treated groups were significantly less frequently compared to placebo, regardless of the dose administered [1,2,3,4].
Slightly different results were obtained by the authors of the 2017 study, where the hypoglycaemia frequency below 70mg/dl was similar in both groups compared to placebo and was about 90%, while the frequency of severe hypoglycaemia below 55mg/dl was significantly lower in the sotagliflozin group compared to placebo group and was defined at about 11-15 patients/year [1].
All of the studies showed high stability of glycemic levels, while lowering the daily amount of insulin administered.
In addition, fluctuations in body weight, blood pressure and cholesterol were evaluated.
In the sotagliflozin group, weight loss was observed after week 24 of the study compared to the placebo group. This effect not only lasted until week 52, but further weight loss was observed in this group. On average, weight loss ranged from 2 to 3 kg, depending on the dose of sotagliflozin (200 or 400 mg).
The beneficial effect of combination therapy on blood pressure has also been demonstrated. In patients of this group there was a reduction of pressure on average by 3-4 mmHg .
A disturbing element of the therapy combined with Flozynes are episodes of ketoacidosis appearing during its course. Their prevalence is around 3-4%, which is a much higher percentage compared to the placebo group, where the result was 0.4-0.6% [1,2,3,4].

Conclusions :

The combination of insulin therapy and SGLT1 / SGLT2 inhibitor in the treatment of type 1 diabetes seems justified, although it undoubtedly requires observational studies.
Decreased HbA1C in a larger number of patients in the combination group compared to the placebo group supports the combination.
Due to the long duration of the disease and the need to protect the patient against late complications, it is necessary to maintain the appropriate glycemic levels, with the least amount of side effects, especially hypoglycaemia.
After analyzing the studies, it seems that almost all of the tested criteria compare favourably in the group in which SGLT1/SGLT2 inhibitors were added to insulin.
In this group, the HbA1C level and the level of fasting blood glucose and postprandial glucose are reduced to the range included in the recommendations of the PTD. It is extremely

important that the patient achieves an improvement in the level of these parameters without the risk of hypoglycaemia.

It seems also beneficial to lower the daily insulin requirement.

The incidence of episodes of ketoacidosis is the parameter that is disadvantageous in all analyzed studies. These episodes occurred significantly more frequently in the sotagliflozin group [1,2,3,4]. This aspect of the study requires further analysis.

Despite the interesting results of the studies and the benefits of combined therapy in patients with type 1 diabetes, this is still experimental therapy. SGLT1/2 inhibitors are not registered in Poland for the treatment of type 1 diabetes, and their use is difficult due to high costs.

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