

Empagliflozin in type 1 diabetes

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Abstract: There is a clear unmet need in people living with type 1 diabetes (T1D). Although the quality of life of people with T1D has improved, issues like hypoglycemia, weight gain and variability in glucose profiles remain. In this review, the clinical efficacy and safety of empagliflozin, a sodium-glucose cotransporter type 2 (SGLT2) inhibitor in T1D, is described based on a review of phase 2 and 3 studies to date. Empagliflozin and SGLT2 inhibitors, in general, are effective glucose-lowering drugs, which also work in people with T1D. Recent phase II and III studies, including the EASE trials for empagliflozin, showed a clear beneficial effect on HbA1c, body weight, glucose variability and total daily insulin use in people with T1D. No increase in hypoglycemia risk, in particular severe hypoglycemia, was observed, but genital infections were more prevalent. The use of SGLT2 inhibitors comes with a decrease in insulin doses, making individuals more prone to diabetic ketoacidosis (DKA). The uniqueness of the EASE program is that here, a very low dose of empagliflozin was used, with less, but still present, effects on metabolic outcomes, but interestingly a lower risk of DKA. Importantly, even in the higher doses of empagliflozin, it is clear that the overall risk for DKA remains low, most likely by educating patients and caretakers intensively on this subject. In conclusion, evidence is building on the potential of using empagliflozin, like other SGLT2 inhibitors, in T1D. However, to date, the use of empagliflozin is not approved in people with T1D. Clinicians will have to weigh the potential short- and long-term benefits of these adjunct therapies versus the potential acute side effects, in particular, the small but real risk of DKA in the individual T1D patient.

Keywords: type 1 diabetes, SGLT2 inhibitor, empagliflozin, EASE trials

Introduction

Treatment of people living with type 1 diabetes (T1D) has come a long way since the first time insulin was administered to a child with T1D. Better insulin preparations, in particular novel insulin analogs, insulin pens, insulin pumps, but also the advent of glucose monitoring, first as capillary measured glucose and more recently flash or continuous glucose monitoring, have revolutionized therapy. Living with T1D is completely different in this century than in the last. But, besides the fact that this disease continues to demand major efforts by the person living with T1D as well as by the health-care teams accompanying him or her, people with T1D continue to show increased morbidity and mortality.¹ Excess life years lost remain, with chronic complications like cardiovascular and renal disease at older age and diabetic ketoacidosis (DKA) and hypoglycemia at younger age as prime causes. In day-to-day life, people with T1D not only are confronted with frustrating fluctuations in glucose levels but also see their weight increasing over time, with overweight present in 42% and obesity in 23.8% of people with T1D.²

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These unmet needs have led to the search for better adjunct therapies, in particular, more stable glucose control, with less risk of hypoglycemia and less weight gain. Only one adjunct therapy to insulin is approved by the FDA and none in Europe for use in T1D, namely pramlintide. Even in the USA pramlintide use is not widespread, due to the fact that it needs to be injected several times a day at mealtimes and in particular due to its side effects of nausea and vomiting. A meta-analysis of the studies performed with pramlintide indicates moreover that although HbA1c lowering is achieved; side effects like nausea and vomiting are real, but moreover hypoglycemic events are more frequent.³

Clinicians have added metformin to insulin therapy in many people with T1D off label, but studies and longer-term real-world observations show only weak to modest improvements in glycemic control and body weight.⁴ Great expectations came with GLP1 receptor agonists after initial short-term studies. The ADJUNCT program confirmed the beneficial effects on weight, but also demonstrated that glucose lowering, although robust, was transient and accompanied by an increase in (severe) hypoglycemic events and increased risk of ketosis.^{5,6}

SLGT inhibition as adjunct therapies in T1D

There are high hopes for the sodium glucose transporter (SGLT) inhibitors. These agents block the transporters for sodium and glucose in kidney (SGLT 1 and 2) and gut (SGLT1), and SGLT2 inhibitors have been introduced in the treatment of people with type 2 diabetes (T2D). SGLT2 inhibition induces glucosuria through inhibition of reabsorption of glomerular-filtered glucose in the proximal tubule of the kidney, thus lowering glucose, inducing weight loss and lowering systolic blood pressure. Of importance, these agents do not need the beta-cell for their glucose-lowering effect and can thus be used in individuals at all stages of type 2 diabetes, even in combination with insulin. Their appealing profile, with glucose lowering without weight gain and even modest weight loss as well as the fact that by themselves they do not cause hypoglycemia, has earned them preferred places in decision algorithms proposed by scientific organizations like ADA and EASD.⁷

Their position as glucose-lowering agents has become even stronger in recent years, with the growing evidence of the impact of these agents on hard outcomes in T2D, beyond glucose control, in particular, cardiovascular and renal protection. Landmark studies like EMPAREG (empagliflozin),

CANVAS (canagliflozin) and DECLARE (dapagliflozin) have shown a dramatic impact of these agents on prevention of hospitalization for heart failure in people with T2D both with and without established cardiovascular disease.^{8–10} These studies also showed dramatic effects on renal endpoints, with composite renal endpoints (significant drop in eGFR, end-stage renal disease, and renal death) being almost halved in those taking the SGLT2 inhibitor.

From the early days, it was obvious that these agents would also lower glycemia in people with other types of diabetes, in particular, T1D. Short-term studies indicated robust lowering in HbA1c, lowering insulin needs for glucose control, no increase in severe hypoglycemia and also the expected lowering of body weight.¹¹

Empagliflozin in T1DM

The FDA and EMA have approved three drugs of the SGLT2 class for use in people with T2D: canagliflozin, dapagliflozin, and empagliflozin. Recently, a fourth SGLT2 inhibitor was approved by the FDA, ertugliflozin. In this report, we will focus on empagliflozin and its potential for use in T1D.

Empagliflozin is a selective SGLT 2 inhibitor, lowering both fasting and postprandial plasma glucose in a non-insulin-dependent manner by increasing 24 h-urinary glucose excretion. Empagliflozin is rapidly absorbed and reaches peak plasma concentrations after approximately 1.33–3.0 h. The mean half-life ranged from 5.6 to 13.1 h in single rising-dose studies, and from 10.3 to 18.8 h in multiple-dose studies.¹²

Empagliflozin is on the European and US market under the trade name Jardiance[®] (Boehringer Ingelheim, Ingelheim, Germany).

In an 8-week single-arm pilot study in patients with T1D, empagliflozin as adjunct to insulin led to a significant reduction in HbA1c¹³ followed by a whole development program called EASE (Empagliflozin as Adjunct to inSulin thErapy).

First, the EASE 1 trial was designed to investigate the pharmacodynamics, efficacy, and safety of empagliflozin as adjunct to insulin in patients with T1D.¹⁴ Seventy-five patients were included in this double-blind placebo-controlled phase II study. Patients had a poor glycemic control with a mean HbA1c $\geq 7.5\%$ to $\leq 10.5\%$. Patients received once-daily empagliflozin 2.5 mg; empagliflozin 10 mg, empagliflozin 25 mg or placebo for 28 days adjunct to a basal-bolus insulin regimen. For the first seven days, the insulin dose was kept as stable as possible. Afterward, medical teams could adapt the insulin dose to achieve optimal glycemic control. Empagliflozin

significantly increased 24 h urinary glucose excretion at 7 and 28 days. This resulted in HbA1c reductions at day 28 from -0.35 to -0.49% ; weight reductions at day 28 from -1.5 kg to -1.9 kg and total daily insulin dose reductions at day 28 from -0.07 to -0.09 U/kg. Over the entire study, rates of hypoglycemic events were lower with empagliflozin than with placebo. No genital infection occurred and only one urine tract infection was observed in a female patient on empagliflozin 25 mg. Although this study showed promising results in terms of efficacy and safety of empagliflozin as adjunct to insulin in patients with T1D, the power of this study was limited by its short duration and small sample size.

This small pilot study was followed by two large double-blind, placebo-controlled phase III trials: EASE-2 with empagliflozin 10 mg ($n=243$), 25 mg ($n=244$), and placebo ($n=243$), 52-week treatment; and EASE-3 with empagliflozin 2.5 mg ($n=241$), 10 mg ($n=248$), 25 mg ($n=245$), and placebo ($n=241$), 26-week treatment.¹⁵ The objective of the EASE program was again to evaluate the safety and efficacy of empagliflozin of 10 and 25 mg doses plus a unique lower dose (2.5 mg) as an adjunct to intensified insulin in patients with T1D. Baseline characteristics were balanced among all treatment groups (respectively, EASE 2–3: 45–43 years, diabetes duration 22.5–21 years, HbA1c 8.1–8.2%, mean total insulin dose 0.7 units/kg, and BMI 29.1–28.2 kg/m²).

In EASE-2 and 3, all empagliflozin doses led to statistically significant HbA1c reductions after 26 weeks. Placebo-adjusted HbA1c reductions were greatest with the empagliflozin 10 mg (-0.45 to -0.54%) and 25 mg (-0.52 to -0.53%) doses, but also the low dose of empagliflozin 2.5 mg reduced HbA1c (-0.28%) in a significant way. The effect on HbA1c was sustained at week 52 in the EASE-2 study. In addition, treatment with empagliflozin resulted in a placebo-corrected reduction in body weight (up to -3.4 kg), systolic blood pressure (up to -3.9 mmHg) and diastolic blood pressure (up to -2.3 mmHg) with overall comparable results for 10 mg and 25 mg across studies after 26 weeks. In EASE-3, the low dose of empagliflozin 2.5 mg followed the same beneficial trend, but to a lesser extent than the two higher doses: weight reduction (-1.8 kg) and lower systolic blood pressure (-2.1 mmHg) (Table 1).

Comparison with other SGLT inhibitors

An initial report on canagliflozin (100 mg or 300 mg adjunct to insulin versus placebo plus insulin) showed promising results in terms of HbA1c, body weight, and

insulin dose reduction. Henry et al showed that 36.9%, 41.4% and 14.5% of patients attained the primary objective ($>0.4\%$ reduction of HbA1c with no weight gain) for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively.¹⁶

The Tandem program on sotagliflozin, a dual SGLT1/2 inhibitor, demonstrated adequate clinical efficacy with a mean HbA1c reduction compared with placebo of -0.46% , and a change in weight of -3 kg in patients treated with 400 mg sotagliflozin versus placebo for 24 weeks (inTandem-3 study).¹⁷ Results were confirmed in both the Tandem 1 and 2 studies, respectively conducted in the USA/Canada and Europe for 52 weeks. Of interest, sotagliflozin increased the time in range with more than 3 h, without increasing the time in hypoglycemia.^{18,19}

The DEPICT program reported on the use of dapagliflozin in T1D. Two pivotal studies (DEPICT-1 and 2) both reported very similar results. Although the study design was similar, there are some differences between the two studies, namely different geographic distribution of patients (more Asian people) and fewer site visits in DEPICT2. In the DEPICT 1 study, T1D patients with poorly controlled diabetes were randomly assigned to once-daily administration of dapagliflozin 5 mg, dapagliflozin 10 mg or placebo. After 24 weeks of therapy, HbA1c was reduced -0.42% and -0.45% by dapagliflozin 5 mg and 10 mg, respectively, compared to -0.03% in the placebo-treated patients. Compared to placebo, patients treated with dapagliflozin 5 mg or 10 mg lost -2.96 kg and -3.72 kg.¹¹ The DEPICT-2 study showed similar results: mean change in HbA1c compared with placebo is -0.37% and -0.42% by dapagliflozin 5 mg and 10 mg respectively. Mean reduction in weight compared with placebo was -3.2 kg and -3.7 kg.²⁰ Effects on HbA1c, weight, and insulin dose reduction were largely maintained until 52 weeks.¹¹ Also for the DEPICT program, the SGLT2 inhibitor was reported to increase the time in range, without increasing the time in hypoglycemia, a feature of great importance for people living with T1D.

Safety and tolerability of empagliflozin in T1DM Hypoglycemia

SGLT2 inhibitors do not cause hypoglycemia by themselves, as their mechanism of action is insulin-independent. But combining SGLT2 inhibitors with insulin could potentially

Table 1 EASE 2 and EASE 3 trial

Study	Dose	Study duration	Participants (N)	Age (years)	BMI (kg/m ²)	HbA1c at change vs placebo (%) 26 w	HbA1c change vs placebo (%) 26 w	Weight change vs placebo (kg) 26 w	SBP/DBP change vs placebo (mmHg) 26 w
EASE 2		52		45	29.1	8.1			
	Placebo		243						
	10 mg		243				-0.54	-2.7	-2.1/-1.3
	25 mg		244				-0.53	-3.3	-3.7/-2.3
EASE 3		26		43	28.2	8.2			
	Placebo		241						
	2.5 mg		241				-0.28	-1.8	-2.1/-0.3
	10 mg		248				-0.45	-3	-3.9/-1.7
	25 mg		245				-0.52	-3.4	-3.7/-1.4

Abbreviation: EASE, Empagliflozin as Adjunctive to inSulin thErapy.

increase the risk of hypoglycemia. Rosenstock et al showed a similar overall risk of symptomatic hypoglycemia for empagliflozin 10 and 25 versus placebo, up to week 52.¹⁵ Empagliflozin 2.5 mg showed the same trend up to week 26. Also, no increase in severe hypoglycemia was documented: respectively, 1.2%, 4.1%, 2.7% and 3.1% for empagliflozin 2.5 mg, 10 mg, 25 mg versus placebo. These results are in line with what was observed in the programs of the other SGLT inhibitors.

Urogenital infections

One could expect more urogenital infections on SGLT2 inhibitors, as urinary glucose may cause additional growth of commensal urogenital microorganisms. Studies in T2D demonstrated that indeed the risk of genital infections, but not urinary infections is increased with this class of agents. Also in the EASE studies with empagliflozin in T1D, genital infections were more frequent with empagliflozin than placebo. Respectively, 12.8% and 14.3% of the patients reported genital infections for empagliflozin 10 mg and 25 mg versus only 4.3% of the patients on placebo. In EASE-3, patients on empagliflozin 2.5 mg faced double the risk of getting a genital infection than patients on placebo. Nevertheless, the infections observed were in most cases mild to moderate and easily treatable with standard therapy. On the contrary, urinary tract infections occurred with similar frequency. Again, these observations are in line with the other SGLT inhibitors.¹⁵

Diabetic ketoacidosis

The use of SGLT inhibitors lowers blood glucose levels in a non-insulin dependent manner. As a consequence, insulin dose can often be reduced. Actually, the introduction of SGLT inhibitors leads to a decrease in insulin dose in most patients, in order to avoid hypoglycemia. However, when insulin is decreased too dramatically, a critical level can be reached where levels of insulin are not high enough to suppress lipolysis in peripheral fat tissues, ensuing in ketone body formation and eventually leading to DKA. All programs studying SGLT2 or SGLT1/2 inhibitors in T1D have taken into account this risk, and have trained medical teams and patients to test ketone levels and have instructed them with tips on how to avoid progression to DKA. Still, all programs have reported an imbalance in DKA events, with 2–4 times more events reported in SGLT treated patients. Also in the EASE program, the rate for confirmed adjudicated DKA on the 10 and 25 mg empagliflozin dose was higher than on placebo, respectively, 4.3%, 3.3% and 1.2% (results of EASE 2 and 3 were pooled). DKA severity was dose-dependent. In the group of 25 mg one patient died. DKA was more frequent in female patients and in patients on insulin pumps. In all cases of DKA, patients had at least one precipitating factor (eg, illness or material failure). Of great interest, no increase in DKA was observed by 26 weeks in the group on empagliflozin 2.5 mg compared to placebo (0.8% versus 1.2%).¹⁵

General safety

Hepatic events, acute renal impairment, and bone fractures occurred in similar frequency in all groups on empagliflozin compared to placebo.¹⁵

Discussion

There is a clear unmet need in people living with T1D. Although quality of life of people with T1D has improved, issues like hypoglycemia, weight gain and variability in glucose profiles remain. Empagliflozin and SGLT inhibitors, in general, are effective glucose-lowering drugs, that also work in people with T1D. Recent phase II and III studies, including the EASE trials for empagliflozin, showed a clear beneficial effect on HbA1c, body weight, glucose variability and total daily insulin use in T1DM patients. However, to date, the use of empagliflozin is not indicated in people with T1D.

The uniqueness of the EASE program is that here, a very low dose of the agent was used, with less, but still present, effects on metabolic outcomes, but interestingly a lower risk of DKA. This is an important issue, as clinicians, patients and in particular regulators are very nervous about the increase in DKA risk. When looking in detail however at the DKA risk in the higher doses of empagliflozin, and by extension at those observed with dapagliflozin, sotagliflozin, and canagliflozin, it is clear that overall risk for DKA was low. When comparing the risk of DKA in the SGLT studies in placebo-treated patients, this risk was lower than what was observed in the real world. This is clear proof that intensive education and rescue plans for patients on what to do when ketones are present can avoid DKA in many cases. Still, however, an imbalance remains. The worrisome point with the DKA in people with T1D on SGLT inhibitors is that glycemic levels are not as high as clinicians and patients are used to when not taking SGLT inhibitors, due to the glucosuria. Glycemic levels in DKA cases in SGLT inhibitor-treated individuals are often below the 250 mg/dL threshold used by the American Diabetes Association in its definition of DKA, thus called “euglycemic DKA”. This holds a danger when patients are presenting to unexperienced medical teams. Details on the DKA episode of the person who died in the empagliflozin 25 mg arm will help in understanding the most dangerous situations, but already now, profiling of the people who progressed to overt DKA shows that people on insulin pumps had an increased risk. Also, often,

a precipitating event, like an infection or omitted insulin doses, was present. The most interesting point in the EASE program with empagliflozin is that fact that here a very low dose of empagliflozin, below the full potential of glucosuria-induction, was used: 2.5 mg. In this arm, no imbalance in DKA was observed versus placebo, opening great perspectives of finding a “sweet spot” for use of these agents. Great caution on overenthusiasm, however, is warranted, as this is only one study, with a 26-week observation duration. Similar observations were initially also made in the DEPICT program, where the 24-week analysis of the DEPICT-1 study also showed no imbalance of DKA,²¹ with an imbalance present in the DEPICT-2 study and also appearing at 52 weeks in the DEPICT-1 study.²⁰ In any case, when considering using SGLT inhibitors in people with T1D, this should happen only in well-selected patients. Patients should be well educated on the risk of not having enough insulin on board (material failure), they should be informed about the symptoms of DKA (eg, nausea, vomiting, and abdominal pain), they need to be instructed to measure ketone bodies when not feeling well (also at normal glucose levels, as ketoacidosis can manifest at much lower glycaemia) and to seek medical attention when ketone bodies are positive.²² Further, clinicians should reduce insulin therapy with consideration (probably no more than 20%) and stop the administration of SGLT2 inhibitors when patients feel sick or undergo surgery. Finally, not all T1DM patients are good candidates for adjunct therapy. Patients with high HbA1c values are already under-dosed in insulin and should not receive a therapy that will further decrease insulin doses.

A final important argument for using SGLT inhibitors, and in particular empagliflozin in people with T1D, is based on the exciting observations in people with T2D on cardiovascular and renal protection. Also, people with T1D have a high cardiovascular and renal risk. The EMPAREG-OUTCOME trial showed a clear benefit in cardiovascular disease and in arresting the progression of renal disease in T2D patients with pre-existing cardiovascular disease. This was confirmed in later programs for SGLT2 inhibitors (canagliflozin CANVAS, dapagliflozin DECLARE) and even extended to beneficial cardiovascular effects, in particular, heart failure, and renal protection in those without pre-existing cardiovascular disease.^{8–10} It is at present unknown whether the same protective effect will occur in people with T1D, but there are many reasons to believe it will exist.

The cardiovascular effect is definitely the result of multiple beneficial effects of SGLT2 inhibitors happening at the same time, including lower blood pressure, enhanced diuresis (with reduced pre- and afterload), weight loss, and increased hematocrit. Recently interesting metabolic hypotheses have been put forward, suggesting that the small increase in ketone levels may offer a better energy substrate to the heart.²³

Empagliflozin has shown to reduce intraglomerular pressure and improve hyperfiltration in people with T1D.²⁴ In a small study, Cherney et al administered 25 mg empagliflozin for 8 weeks to patients with and without renal hyperfiltration. In the group with hyperfiltration, GFR was significantly decreased by 33 mL/min/1.73 m², suggesting that the observations in T2D patients on renal protection may well happen also in people with T1D. Of interest, the study dedicated to renal endpoints, EMPA-KIDNEY,²⁵ will be the only dedicated renal study with SGLT inhibitors specifically including people with T1D.

In conclusion, evidence is building on the potential of using empagliflozin, like other SGLT inhibitors, in T1D. However, clinicians, patients, and regulators will have to weigh the potential short- and long-term benefits of these adjunct therapies in people with T1D versus the potential acute side effects, in particular the small, but real risk of DKA.

Disclosure

CM serves or has served on the advisory panel for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Dianax and UCB. Katholieke Universiteit Leuven has received research support for CM from Medtronic, Novo Nordisk, Sanofi, Merck Sharp, Dohme Ltd, Eli Lilly and Company, Roche, Abbott, ActoBio Therapeutics and Novartis; CM serves or has served on the speakers bureau for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly and Company, Boehringer Ingelheim, Astra Zeneca©, and Novartis. Financial compensation for these activities has been received by Katholieke Universiteit Leuven. CM reports grants from Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd, Eli Lilly, Novartis, Boehringer Ingelheim, Roche Diagnostics, Medtronic, Intrexon, Abbott, Bristol Myers Squibb, AstraZeneca, Hanmi Pharmaceuticals, and UCB outside the submitted work. The authors report no other conflicts of interest in this work.

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