Adjunctive Oral Therapy With SGLT Inhibitors for Treatment of Type 1 Diabetes

BACKGROUND

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease characterized by hyperglycemia resulting from loss of pancreatic islet β-cells and subsequent insulin deficiency.[1] Although the introduction of insulin therapy in 1922 dramatically changed the fatal prognosis for those with T1D,[1] the disease continues to cause increased morbidity and mortality from long-term complications.[2,3]

Chronic complications of T1D are categorized as either microvascular or macrovascular. Diabetes-specific microvascular complications include retinopathy, nephropathy, and neuropathy and result in blindness, kidney failure, and amputations.[2] Macrovascular complications are less specific to–but highly associated with–diabetes, and include cardiovascular disease, cerebrovascular accidents, and peripheral vascular disease.[1]

The landmark Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, showed that reducing hyperglycemia and achieving near-normal glucose levels through intensive insulin therapy reduces these chronic complications.[2] Intensive therapy can include multiple daily injection therapy or continuous subcutaneous insulin infusion with external pumps, guided by self-monitoring of blood glucose and clinician-assisted measurement of glycated hemoglobin (HbA_{1C}) levels.[2]

However, peripheral insulin delivery and lack of feedback inhibition are limitations to this approach[4,5] and contribute to body weight increase in individuals undergoing intensive insulin therapy.[2] An estimated two-thirds of individuals with T1D are overweight or obese.[6] Moreover, the beneficial effects of intensive insulin therapy on cardiovascular disease diminishes with excessive weight gain.[7] Cardiovascular disease remains the primary cause of death among diabetic individuals treated with insulin.[8]

Intensive insulin therapy also leads to higher incidences of hypoglycemia.[2] Moderate hypoglycemia induces both autonomic and neuroglycopenic symptoms, and leads to severe hypoglycemia if not corrected.[9] During severe hypoglycemia, which requires assistance for recovery, individuals can experience reversible and permanent abnormalities of cardiovascular, neurological, and cognitive function, including coma, convulsions, stroke, arrhythmias, myocardial ischemia, and cardiac failure.[9,10] Individuals that repeatedly experience severe hypoglycemia can develop impaired awareness of hypoglycemia, which affects approximately 20% of people with T1D.[9] Individuals with T1D experience severe hypoglycemia at a rate of about 1 event per patient per year.[6] Whereas non-severe, self-treated hypoglycemia occurs at an average of twice a week.[6]

Despite these limitations, intensive insulin therapy remains the standard of care for T1D.[10] To support T1D management through intensive insulin therapy, substantial technological advances have been made available in recent years. Data from the T1D Exchange registry showed that both insulin pump use and continuous glucose monitoring has increased in the last 8 years.[11]

Although using this technology was associated with lower HbA_{1C} levels, 79% of adults with T1D failed to achieve the glycemic control goal recommended by the American Diabetes Association (HbA_{1C} < 7.0%).[10,11]

A recent survey among adults with T1D revealed that, in addition to lowering and maintaining HbA_{1C} levels, increasing time-in-range and simplifying treatment are important unmet needs in the management of T1D. Furthermore, a preference for oral adjunct therapies to address these unmet needs was apparent.[12] Adjunct therapies that improve glycemic control without increasing the risk for hypoglycemia or weight gain are of great patient interest.[13] Consequently, non-insulin adjunct therapies have been proposed as a means to improve glycemic control in T1D.[4]

Most non-insulin adjunct therapies approved for type 2 diabetes (T2D) are not effective in T1D. The only FDA-approved adjunct therapy for T1D is pramlintide, an injected amylin analog drug that is rarely used clinically due to its limited efficacy and unfavorable side effects, such as severe hypoglycemia.[13–15] Other antihyperglycemic drugs have failed to show benefit in randomized trials.[15]

Sodium-glucose cotransporter (SGLT) inhibitors are a new class of insulin-independent oral medications. When used as an adjunct therapy to insulin in individuals with T1D, SGLT inhibitors effectively reduce HbA_{1C} levels, glycemic variability, blood pressure, and body weight without causing hypoglycemia.[13] SGLT2 inhibitors block the SGLT2 transporter in the proximal tubule of the kidney, resulting in glucosuria and natriuresis.[13] In contrast, SGLT2/1 inhibitors also block SGLT1 in the gastrointestinal tract, delaying the absorption of glucose and consequently reducing postprandial glucose.[16]

The FDA has approved 4 SGLT2 inhibitors for the treatment of T2D: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.[17] Several phase 3 trials have been performed to test their efficacy and safety as adjunctive insulin therapy in adults with T1D. Currently, dapagliflozin, as well as the SGLT2/1 inhibitor sotagliflozin, are under regulatory review by the FDA as an adjunct therapy in T1D,[18,19] and both drugs were recently approved in Europe for treatment of adults with T1D.[20,21]

Thomas Danne, Professor of Pediatrics, Children's Hospital *Auf der Bult*, Hannover, Germany, commented that "Millions of people across Europe who live with type 1 diabetes struggle to control their blood sugar, even with optimal insulin therapy," and the approval offers "a new treatment option physicians can now consider in combination with insulin therapy for appropriate patients."[21]

However, SGLT inhibitors are associated with increased rates of diabetic ketoacidosis (DKA), particularly when used as adjunctive insulin therapy for the treatment of T1D.[22] It has been proposed that the lower blood glucose associated with SGLT2 inhibitors prompts a decrease in insulin dose. The decreased dose may enhance lipolysis, leading to increased release of free fatty acids from adipose tissue, which are then used for ketogenesis by the liver.[22] SGLT inhibitors are also associated with an increase in glucagon, and it is the balance of glucagon and insulin that regulate these metabolic pathways.[13] SGLT inhibition also increases urinary glucose loss, which may contribute to the development of ketosis, particularly in the context of dehydration, physiological stress, robust physical activity, and low-carbohydrate diets.[13] Ketosis may advance to metabolic acidosis; for DKA to be diagnosed, both ketosis and acidosis must be present.[23]

Many study participants and patients using these medications off-label have presented with euglycemic DKA.[24] Prior to use of SGLT inhibitors in the T1D community, education and support are necessary for both patients and medical providers to prevent and treat euglycemic DKA in this context.[25] Furthermore, preventative strategies must be established for individuals using these drugs to avoid DKA, and physicians should consider and assess patient adherence to these strategies when selecting the ideal candidates for treatment.[13]

Clinicians may be unfamiliar with these new therapies and would benefit from education on the treatment options that may soon be available for T1D. Furthermore, the use of SGLT inhibitors in routine T1D care will require specific education for both patients and health care providers to ensure patient safety and minimize the risk of DKA.[4]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of recent clinical trial data for SGLT inhibitor adjunctive therapy in T1D

Learning Objective #1: Describe the recent clinical data on SGLT inhibitor therapy for treatment of T1D

Recently, several phase 3 trials tested the efficacy and safety of various SGLT inhibitors as adjunctive insulin therapy in adults with T1D.

Dapagliflozin is an SLGT2 inhibitor approved for the treatment of T2D. DEPICT-1 (Efficacy and Safety of Dapagliflozin in Patients with Inadequately Controlled Type 1 Diabetes) is a double-blind, phase 3 trial that evaluated the efficacy and safety of dapagliflozin as an adjunct therapy to insulin in patients with inadequately controlled T1D.[26] The primary efficacy outcome was the change from baseline in Hb_{A1C} levels after 24 weeks of treatment. Secondary efficacy outcomes included a change in total daily insulin dose, change in body weight, as well as changes in glucose readings obtained from continuous glucose monitoring.[26]

Following 8 weeks of diabetes management optimization, 788 patients were randomly assigned to receive 5 mg of dapagliflozin, 10 mg of dapagliflozin, or placebo. The mean baseline HbA_{1C} was 8.53%. Both doses of dapagliflozin significantly reduced HbA_{1C} from baseline at week 24. For the 5- and 10-mg doses, mean reductions in HbA_{1C} compared with placebo were 0.42% ($P < .0001$) and 0.45% ($P < .0001$), respectively. Dapagliflozin also decreased body weight, total insulin dose, and glycemic variability. The benefits of dapagliflozin treatment were achieved with no increase in hypoglycemia as compared with the placebo treatment.[26]

Adverse events included DKA, which occurred in 4 patients in the 5-mg dapagliflozin group, 5 patients in the 10-mg dapagliflozin group, and 3 patients in the placebo group. Genital infections occurred more often in the dapagliflozin groups compared with the placebo groups, and were also more common amongst women.[26]

DEPICT-2 is a second study evaluating the efficacy and safety of dapagliflozin, with the same study design as DEPICT-1 but differing in the number of site visits and the geographical footprint.[27] Consistent results were observed in the two studies; however, in the DEPICT-2 study, more DKA events were detected in the dapagliflozin groups as compared with placebo. The study authors attributed this inter-study difference to the small number of events. Results from the ongoing 28-week extension phase for the DEPICT studies may better assess the DKA risk associated with the use of dapagliflozin.[27]

Similar results were observed for the highly selective SGLT2 inhibitor, empagliflozin, in the double-blind, phase 3 EASE (Empagliflozin as Adjunctive to Insulin Therapy) trials.[28] In these studies, the efficacy and safety of 2.5-, 10-, and 25-mg doses of empagliflozin were evaluated as add-on therapy to intensified insulin in patients with T1D. EASE-2 evaluated the two higher doses of empagliflozin over 26 weeks and included 733 patients, while EASE-3 also evaluated the low 2.5-mg dose of empagliflozin over 26 weeks and included 977 patients. The primary endpoint of these studies was the change in HbA1c at week 26. Secondary endpoints included analyses of hypoglycemia, weight, glucose time-in-range, insulin dose, and blood pressure.[28]

A 6-week investigator-guided insulin intensification period resulted in an average baseline HbA_{1C} of 8.1% to 8.2%. After 26 weeks of treatment, mean HbA_{1C} reduction was dose-dependent; 2.5-, 10-, and 25-mg doses reduced HbA_{1C} 0.28% ($P < .0001$), 0.54% ($P < .0001$), and 0.53% ($P < .0001$), respectively. Furthermore, all empagliflozin doses reduced mean weight, increased time-in-range, lowered total daily insulin, and decreased systolic blood pressure. Drug benefits were not accompanied by an increase in hypoglycemia relative to placebo.[28]

Empagliflozin drug-related adverse events were similar to those observed with dapagliflozin and included an increased occurrence of genital infections as well as an increased rate of DKA. Although the rate of DKA was similar in the 2.5-mg dose group (0.8%) and the placebo group (1.2%), rates of DKA in the 10-mg (4.3%) and 25-mg (3.3%) dose groups were higher.[28]

The study authors suggested that the use of lower SGLT2 inhibitor doses for treatment of T1D could achieve the optimal balance between safety and efficacy.[28] "Given the risk of DKA for people with type 1 diabetes, the 2.5 mg-empagliflozin dose warrants consideration, as it balances glycemic and metabolic improvements that are relevant to patients without increasing their risk of DKA or other serious adverse

events," commented Bernard Zinman, MD, Professor in the Department of Medicine, University of Toronto and Senior Scientist at the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada.[29]

Efficacy and safety of the dual SGLT1/SGLT2 inhibitor sotagliflozin in combination with optimized insulin in T1D was evaluated in the inTandem studies.[30] These phase 3, double-blind trials encompassed the 24-week, global inTandem3 study,[31] as well as the 52-week North American inTandem1[15] and European inTandem2 studies.[32] Together, the studies represent the largest-ever conducted phase 3 trial among T1D patients with the longest treatment duration.[33]

In the inTandem3 study, 1402 patients with T1D who were on insulin therapy were randomly assigned to receive a daily dose of 400 mg of sotagliflozin or placebo for 24 weeks.[31] The primary endpoint was an HbA_{1C} level of less than 7.0% at week 24, with no episodes of severe hypoglycemia or DKA after randomization. Secondary endpoints assessed weight, systolic blood pressure, and mean daily bolus of insulin.[31]

The primary endpoint was reached by a significantly greater proportion of patients in the sotagliflozin group than in the placebo group (28.6% vs. 15.2%, $P < .001$). Further, significant reductions were observed for weight, systolic blood pressure, and mean daily bolus of insulin in the sotagliflozin group versus the placebo group ($P < .002$). As observed for the SGLT2 inhibitors, the rate of DKA was higher in the sotagliflozin group (3.0%) than in the placebo group (0.6%).[31]

The inTandem1 and inTandem2 studies differed from inTandem3 in that they were carried out over 52-weeks and insulin doses were optimized for 6 weeks before baseline.[15,32] The two studies had a primary endpoint of HbA_{1C} change from baseline at 24 weeks. Secondary endpoints for both studies included a composite of the proportion of patients with HbA_{1C} less than 7.0%, no episode of severe hypoglycemia, and no episode of DKA at week 24. HbA1c, weight, fasting glucose, insulin dose, and patient-assessed satisfaction and distress were other secondary endpoints.[15,32]

Placebo-adjusted changes in HbA_{1C} levels from baseline (7.8%) were -0.36% for the 200-mg sotagliflozin group and -0.41% for the 400-mg group ($P < .001$ for both) at 24 weeks in the inTandem1 study.[15] Similar placebo-adjusted changes in HbA_{1C} from baseline (7.57%) were observed at 24 weeks in the inTandem2 study with reductions of 0.37% and 0.35% with sotagliflozin 200 and 400 mg, respectively ($P < .001$ for both).[32] In both studies, greater proportions of sotagliflozin-treated patients met the composite endpoint at 52 weeks. Further, weight loss, lower insulin dose, and improved patient-reported outcomes were observed.[15,32]

As observed with other SGLT inhibitors, there were increased incidences of DKA that occurred in a dose-dependent manner. In the inTandem1 trial, DKA occurred in 3.4% of the participants taking 200 mg of sotagliflozin and 4.2% receiving the 400-mg dose, but only in 0.4% receiving placebo.[15] Similar observations were made in the inTandem2 trial; there were no incidences of DKA in the placebo group, but it occurred in 2.3% and 3.4% of patients receiving the 200- and 400-mg sotagliflozin dose, respectively.[32]

Study authors concluded that although SGLT inhibition is associated with DKA, the risk is manageable with proper education and mitigation plans, and this risk is outweighed by the beneficial effects of SGLT inhibitors on HbA_{1C}, glycemic variability, and weight with less hypoglycemia.[15]

"More than 1.25 million adults in the US live with T1D, and more than 75 percent of these people who use insulin alone have blood glucose levels above target. Despite recent advances, the challenges of T1D management, specifically hypoglycemia or fear of hypoglycemia, weight gain, glucose variability and patient burden, prevent many patients from reaching their treatment goals. The profile of sotagliflozin to improve glucose control beyond what can be achieved with intensified insulin alone while addressing these challenges has the potential to improve the lives of people with T1D" explained inTandem1 lead study investigator John Buse, MD, PhD, director of the Diabetes Center, director of the NC Translational

and Clinical Sciences Institute, and executive associate dean for clinical research at the University of North Carolina School of Medicine in Chapel Hill."[34]

Gap #2: Clinicians may be unaware of strategies for mitigating DKA risk in patients with T1D using SGLT inhibitor adjunctive therapy

Learning Objective #2: Identify current DKA risk mitigation strategies for patients with T1D using SGLT inhibitor adjunctive therapy

Clinical trials of SGLT inhibitors as adjuncts to insulin therapy in T1D demonstrate that, despite their pronounced benefits for individuals with T1D, SGLT inhibitors are associated with increased risk of developing DKA.[15,23,26–28,32] This is a class-wide effect that appears to be dose-dependent.[13]

The Advanced Technologies and Treatment for Diabetes Congress convened an international panel of physicians and researchers with expertise in using SGLT inhibitor therapy. The experts developed strategies to mitigate DKA risk in individuals with T1D using this adjunctive therapy.[13]

When selecting appropriate patients for adjunctive SGLT inhibitor therapy, clinicians must first verify that the patient has normal ketone levels (<0.6 mmol/L).[13] Several risk factors must be considered in the context of each patient's lifestyle, behaviors, and ability or willingness to follow prescribed regimens for monitoring ketones and performing strategies to mitigate DKA if elevated ketones are present. SGLT inhibitors should not be prescribed to patients on low-carbohydrate or ketogenic diets.[13] Furthermore, clinicians should recognize that patients who skip meals or drink excessive alcohol are at increased risk of developing DKA if taking SGLT inhibitors.[13] The same is true for patients on an insulin pump, as they are at risk of pump or infusion set malfunction. Individuals with T1D are also at a higher risk if they commonly miss insulin doses and experience prolonged bouts of severe hyperglycemia or have recurrent episodes of DKA.[13] Finally, individuals with T1D who are pregnant or children should not use SGLT inhibitors as there is no data currently available on the use of this adjunctive therapy in these populations.[32]

The panel has established a list of patient criteria for SGLT inhibitor therapy that includes patient adherence, training, access to ketone testing materials, and immediate access to a clinician if ketone levels are elevated.[13] Ketone self-testing can be achieved through a blood ketone meter or urine testing. However, the panel recommends that capillary blood ketone measurement be used over urine testing because it is more accurate. Testing should be performed if patients experience any symptoms consistent with DKA, as well as any changes in diet, activity, or insulin dose. Ketone testing is also necessary if patients get injured or have surgery, or are experiencing infection, dehydration, or stress.[13] It is critical that in any of these situations, patients stop SGLT inhibitor therapy, even in the absence of high ketone levels.[13]

If blood ketone levels are elevated (>0.6 mmol/L), patients should follow the STICH protocol for risk mitigation: stop SGLT inhibitor treatment, insulin administration, carbohydrate consumption, and hydration.[13,23] Blood ketone levels should be monitored, and if they remain high or increase above 1.6 mmol/L, patients should be instructed to seek medical treatment.[13] The panel suggests that all patients receiving SGLT inhibitor therapy be given educational materials, including wallet cards and refrigerator magnets, that provide a "quick reference" for treatment.[13]

Clinicians prescribing SGLT inhibitor therapy must understand how to mitigate DKA risk and be willing to educate their patients as well. Further, prescribing clinicians, as well as emergency department staff, must be aware of how to promptly recognize DKA in T1D patients taking SGLT inhibitors. Like DKA, euglycemic DKA is characterized by anion gap metabolic acidosis and ketonemia. However, in euglycemic DKA, these identifying symptoms can occur with normal or modestly elevated blood glucose levels of <250 mg/dL.[13] Due to the renal action of SGLT inhibition, ketonuria and bicarbonate may not accurately reflect the patients' metabolic state. Therefore, direct measurement of β-hydroxybutyrate and pH is suggested to confirm DKA in patients on SGLT inhibitor therapy.[23] The panel recommends that this

message in be included in all professional educational initiatives as well as a description of the STICH protocol for the treatment of DKA in patients on SGLT inhibitor therapy.[13]

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CONCLUSION

In individuals with T1D, there is an unmet need for adjunctive therapies to insulin that improve glycemic control in the absence of increased rates of hypoglycemia and weight gain.[24] Oral adjunctive SGLT inhibitor therapy has proved effective in reducing HbA_{1C}, glycemic variability, total daily insulin dose, blood pressure, body weight, as well as increasing time-in-range, without increased rates of hypoglycemia. Furthermore, cardiovascular and renal benefits have been observed in T2D SGLT inhibitor trials, which may represent class effects that would also benefit individuals with T1D.[13] The potential health benefits of SGLT inhibitors for individuals with T1D are significant. However, SGLT inhibitor use coincides with a greater risk of DKA amongst those taking them. Therefore, strategies for mitigating DKA risk are crucial for the safe use of SGLT inhibitors. Education is essential to supply clinicians with the knowledge and confidence necessary to provide the best possible care for individuals with T1D seeking adjunctive SGLT inhibitor therapy.

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