



Diabetic Ketoacidosis With Canagliflozin, a Sodium–Glucose Cotransporter 2 Inhibitor, in Patients With Type 1 Diabetes

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OBJECTIVE

To assess the incidence of serious adverse events (AEs) of diabetic ketoacidosis (DKA) with canagliflozin, a sodium–glucose cotransporter 2 inhibitor, as an add-on to insulin in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

In this 18-week, randomized, double-blind, phase 2 study, patients ($N = 351$; HbA_{1c} 7.0–9.0% [53–75 mmol/mol]) on multiple daily insulin injections or continuous subcutaneous insulin infusion received canagliflozin 100 or 300 mg or placebo once daily. The incidence of ketone-related AEs, defined as any event from a prespecified list of preferred terms (i.e., acidosis, blood ketone body increased, blood ketone body present, DKA, diabetic ketoacidotic hyperglycemic coma, ketoacidosis, ketonemia, ketonuria, ketosis, metabolic acidosis, urine ketone body present), including serious AEs of DKA, was assessed based on AE reports.

RESULTS

At week 18, the incidence of any ketone-related AE with canagliflozin 100 and 300 mg was 5.1% ($n = 6$ of 117) and 9.4% ($n = 11$ of 117), respectively; no patients in the placebo group experienced a ketone-related AE. The incidence of serious AEs of DKA was 4.3% ($n = 5$ of 117) with canagliflozin 100 mg and 6.0% ($n = 7$ of 117) with canagliflozin 300 mg; all serious events occurred in the presence of circumstances that are known to potentially precipitate DKA (e.g., infection, insulin pump failure). Among the 12 patients with a serious AE of DKA, blood glucose levels ranged from 9.4 to >44.4 mmol/L (170 to >800 mg/dL). Baseline characteristics were generally similar in patients with and without a ketone-related AE.

CONCLUSIONS

Canagliflozin was associated with an increased incidence of serious AEs of DKA in patients with type 1 diabetes inadequately controlled with insulin. Mitigation strategies are needed for use in future clinical trials to reduce the risk of DKA with canagliflozin treatment in patients with type 1 diabetes.

Diabetic ketoacidosis (DKA) is a serious and potentially life-threatening complication of diabetes that is characterized by hyperglycemia, metabolic acidosis, and an increase in circulating ketones (1,2). DKA results from a combination of reduced insulin levels and increased levels of regulatory hormones, such as glucagon and cortisol (1,2). This decrease in insulin and increase in counterregulatory hormones

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stimulates the release of free fatty acids from adipose tissue, which are then further oxidized into ketone bodies in the liver. The accumulation of ketone bodies, primarily β -hydroxybutyrate and acetoacetate, leads to ketonemia and metabolic acidosis (1,3).

DKA occurs predominantly in patients with type 1 diabetes but can also be a rare complication in those with type 2 diabetes (1). DKA may also affect patients with latent autoimmune diabetes of adulthood and those with ketosis-prone diabetes (i.e., patients without the typical presentation of autoimmune type 1 diabetes) (4,5). Most cases of DKA are associated with precipitating factors, such as infection, intercurrent illness, surgical stress, and poor compliance with insulin therapy (1,6). Infection is the most common precipitating factor, occurring in 30–50% of cases of DKA (6).

Both the U.S. Food and Drug Administration and European Medicines Agency have issued statements warning that treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors may be associated with an increased risk of DKA (7,8). SGLT2 inhibition lowers blood glucose through an insulin-independent mechanism of action by lowering the renal threshold for glucose and increasing urinary glucose excretion (UGE), which results in mild osmotic diuresis and net caloric loss (9–11). SGLT2 inhibitors are approved to treat type 2 diabetes, yet initial studies indicate that they may improve glycemic control in patients with type 1 diabetes as an adjunct to insulin therapy (12–17). Rare, but serious, cases of DKA have been reported in patients with either type 1 or type 2 diabetes treated with SGLT2 inhibitors in clinical practice (18). In some of these cases, the presentation of DKA was atypical because blood glucose levels were only moderately elevated. Patients treated with SGLT2 inhibitors may be at a greater risk for DKA because increased UGE (ranging from 50 to 100 g/day) can result in lower hyperglycemia than might be expected in the setting of DKA (19). Increased UGE lowers plasma glucose levels, which may cause patients with type 1 diabetes on background insulin to lower their insulin doses to avoid hypoglycemia. The reduction in insulin suppresses glucose oxidation and stimulates lipolysis and the mobilization

of free fatty acids that are converted to ketones (19,20). SGLT2 inhibition has also been shown to increase glucagon secretion, potentially through reductions in insulin dose and a possible direct effect of SGLT2 inhibitors on pancreatic α -cells; increases in glucagon further alter the insulin-to-glucagon ratio to stimulate gluconeogenesis and ketone production (19–22). Reductions in the insulin-to-glucagon ratio in patients treated with SGLT2 inhibitors may increase susceptibility to DKA in the presence of risk factors (e.g., pump malfunctions, carbohydrate restriction, increased alcohol consumption) that may not otherwise result in DKA (20). On the basis of an analysis of the U.S. T1D Exchange clinic registry, the frequency of DKA is \sim 5% in patients \geq 26 years of age with type 1 diabetes and is as high as 10% in patients aged 13–26 years (23); therefore, understanding the risk of DKA associated with SGLT2 inhibition is important if these medications are eventually approved for use in patients with type 1 diabetes in clinical practice.

The efficacy and safety of the SGLT2 inhibitor canagliflozin was assessed in a phase 2 study as an add-on to insulin in patients with type 1 diabetes; details of the study have been previously reported (15). Briefly, canagliflozin provided reductions in HbA_{1c}, body weight, and insulin dose, with no increase in hypoglycemia over 18 weeks. This article describes the incidence of serious adverse events (AEs) of DKA with canagliflozin in patients with type 1 diabetes based on data from that study.

RESEARCH DESIGN AND METHODS

Study Design and Patients

This study was a randomized, multicenter, placebo-controlled, double-blind, phase 2 trial that consisted of a 2-week prerandomization period followed by an 18-week double-blind treatment phase and a 2-week follow-up period for all patients. Eligible patients were men and women with type 1 diabetes for \geq 1 year who had an HbA_{1c} of 7.0–9.0% (53–75 mmol/mol) at screening and were on a stable insulin regimen with multiple daily insulin injections or continuous subcutaneous insulin infusion for \geq 8 weeks before screening. Patients were 25–65 years of age with a BMI of 21–35 kg/m² at screening. Key

exclusion criteria were a history of type 2 diabetes; DKA or a severe hypoglycemic event (defined as an event that required assistance from another person or resulted in seizure or loss of consciousness) within 6 months before randomization; myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident \leq 12 weeks before screening; history of New York Heart Association class III–IV cardiac disease; uncontrolled hypertension; estimated glomerular filtration rate $<$ 70 mL/min/1.73 m²; or treatment with an antihyperglycemic agent other than insulin within 12 weeks before screening. Patients were randomly assigned in a 1:1:1 ratio to canagliflozin 100 or 300 mg or placebo once daily taken before the first meal of the day. Further details on randomization and blinding have been previously reported (15).

The study was conducted in accordance with ethical principles that comply with the Declaration of Helsinki and are consistent with good clinical practices and applicable regulatory requirements. The study protocol and amendments were approved by institutional review boards and independent ethics committees at participating institutions. All patients provided written informed consent before participation.

Insulin Therapy

Before randomization, patients with HbA_{1c} \leq 8.0% (\leq 64 mmol/mol) at screening were recommended, at the discretion of the investigator, to reduce their basal insulin dose by 20%, and patients with HbA_{1c} $>$ 8.0% ($>$ 64 mmol/mol) at screening were recommended to reduce their basal insulin dose by 10%. Algorithms for titrating basal and bolus insulin doses to achieve prespecified prebreakfast, prelunch, predinner, and bedtime glucose levels were provided as a general guideline for investigators (15). Compliance with insulin therapy was assessed based on patient records of basal and bolus insulin doses at specified time points.

End Points and Assessments

The primary efficacy end point of the study was the proportion of patients at week 18 with an HbA_{1c} reduction \geq 0.4% (\geq 4.4 mmol/mol) and no increase in body weight relative to baseline (15).

Change from baseline in insulin dosage, after the initial 10–20% downtitration, was assessed at week 18. Overall safety and tolerability were assessed based on AE reports, safety laboratory tests, vital sign measurements, and physical examinations. A ketone-related AE was defined as any event from a prespecified list of preferred terms (i.e., acidosis, blood ketone body increased, blood ketone body present, DKA, diabetic ketoacidotic hyperglycemic coma, ketoacidosis, ketonemia, ketonuria, ketosis, metabolic acidosis, urine ketone body present). Patients were counseled on how to recognize and monitor signs and symptoms of DKA and received instructions on when to contact the study site or seek medical attention per local guidelines. Guidelines for the diagnosis, treatment, and prevention of DKA provided to investigators and patients are included in the Supplementary Data. Patients were instructed to test their urine for ketones if blood glucose was >13.9 mmol/L (>250 mg/dL) or if they felt ill, even if blood glucose levels were normal. Furthermore, patients were advised on how to appropriately manage insulin and diet during illness and how to monitor for glucose and ketones. Supplies for serum ketone measurements were not provided. Interruption of the study drug during an illness was based on the discretion of the investigator or treating physician.

Statistical Analyses

Safety analyses were conducted by using the modified intent-to-treat analysis set (i.e., all patients who were randomized and received one or more doses of double-blind study drug) and included all reported AEs with onset during the treatment phase (i.e., treatment-emergent AEs). Statistical testing of comparisons of canagliflozin versus placebo was not performed (not prespecified) for safety analyses; therefore, *P* values are not reported.

RESULTS

Overall Safety

At week 18, the overall incidence of AEs was higher in the canagliflozin 100 and 300 mg groups (55.6% and 67.5%, respectively) than in the placebo group (54.7%) and were mainly associated with an increased incidence of AEs related to the mechanism of SGLT2

inhibition (i.e., urinary tract infections, AEs related to osmotic diuresis and volume depletion) (15), consistent with the safety profile reported in studies of canagliflozin in patients with type 2 diabetes. The incidence of AEs leading to discontinuation was low across groups (one patient in the canagliflozin 100 mg group, two in the canagliflozin 300 mg group, and none in the placebo group). The incidence of serious AEs was 7.7% and 6.8% with canagliflozin 100 and 300 mg, respectively; no patients treated with placebo experienced a serious AE. This difference was mainly driven by serious AEs of DKA.

Incidence of Ketone-Related AEs and Serious AEs of DKA

The incidence of any ketone-related AE at week 18 with canagliflozin 100 and 300 mg was 5.1% (*n* = 6 of 117) and 9.4% (*n* = 11 of 117), respectively; no patients in the placebo group experienced a ketone-related AE (Table 1). The majority of ketone-related AEs occurred after 1 month of treatment with canagliflozin 100 and 300 mg (Supplementary Fig. 1). The incidence of serious AEs of DKA that required hospitalization was 4.3% (*n* = 5 of 117) with canagliflozin 100 mg and 6.0% (*n* = 7 of 117) with canagliflozin 300 mg. In these 12 patients, blood glucose levels at the time of hospitalization ranged from 9.4 to >44.4 mmol/L (170 to >800 mg/dL); 5 of these patients had blood glucose levels <13.9 mmol/L (250 mg/dL), the typical glucose threshold used to define DKA. Three of the 12 patients had pH values <7.0 at the time of hospitalization. Specific details of the 12 patients with serious AEs of DKA, including laboratory results, are presented in Table 2. The median time to a serious AE of DKA was 116 days (range 27–130 days) with canagliflozin 100 mg and 32 days (range 5–110 days) with canagliflozin 300 mg;

given the wide range and small sample size, it is not possible to make conclusions regarding the time to onset of a serious AE of DKA. One patient with an initial serious AE of DKA and a subsequent nonserious ketone-related AE (i.e., increased urine ketones) discontinued the study. All patients experiencing a serious AE of DKA also had a coexisting condition at the time of the event that may have contributed to the development of DKA, including infection (influenza, pneumonia, infusion-site infection, food poisoning), reduction in insulin dose (insulin pump failure or malfunction, non-compliance with insulin dosing), and reduction in food intake.

Characteristics of Patients With and Without a Ketone-Related AE

Baseline demographic and disease characteristics were generally similar in patients with and without a ketone-related AE (Table 3). The mean baseline HbA_{1c} was 8.0% (64 mmol/mol) and 7.9% (63 mmol/mol) in patients with and without a ketone-related AE, respectively; the mean duration of type 1 diabetes was 22 years in both groups. History of DKA was not a predictor of whether a patient experienced a ketone-related AE in this study. Of the 17 patients with a ketone-related AE, 12 were female. At week 18, reductions from baseline in body weight were similar with canagliflozin 100 and 300 mg in patients with (–2.7% and –5.5%, respectively) and without (–3.2% and –5.1%, respectively) a ketone-related AE. In the 12 patients with a serious AE of DKA, changes from baseline in body weight at the closest study assessment before the event (Table 2) were similar to the observed changes in patients with or without ketone-related AEs at week 18. Most of these patients (*n* = 8) had a weight loss of <5.0%, and the largest body weight reduction observed was

Table 1—Summary of the incidence of ketone-related AEs and serious AEs of DKA

	Placebo (<i>n</i> = 117)	CANA 100 mg (<i>n</i> = 117)	CANA 300 mg (<i>n</i> = 117)
Any ketone-related AE*	0	6 (5.1)	11 (9.4)†
Serious AEs of DKA requiring hospitalization	0	5 (4.3)	7 (6.0)
Nonserious ketone-related AEs‡	0	1 (0.9)	5 (4.3)

Data are *n* of patients (%). CANA, canagliflozin. *Including DKA, ketoacidosis, and urine ketone body present. †One patient had an initial serious DKA event and a subsequent nonserious AE of increased urine ketones. ‡Including ketoacidosis in two patients and the presence of urine ketones in four patients.

Table 2—Summary of patients with serious AEs of DKA

Treatment group	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	
CANA 100 mg	CANA 100 mg	CANA 100 mg	CANA 100 mg	CANA 100 mg	CANA 100 mg	CANA 300 mg	CANA 300 mg	CANA 300 mg	CANA 300 mg	CANA 300 mg	CANA 300 mg	CANA 300 mg	
Sex	M	F	F	F	F	M	M	M	F	F	F	F	
Age (years)	34	28	27	41	41	56	41	44	54	60	28	42	
Diabetes duration (at randomization) (years)	16.5	18.7	10.9	28.5	23.0	45.3	32.4	16.2	14.3	20.0	17.7	34.0	
History of DKA	Yes	Yes	No	No	Yes	No	No	No	No	No	No	No	
Insulin administration method	MDI	CSII	MDI	CSII	CSII	MDI	CSII	CSII	CSII	CSII	MDI	CSII	
Baseline HbA _{1c} (% [mmol/mol])	7.9 (63)	8.2 (66)	8.5 (69)	6.9 (52)	8.6 (70)	7.5 (58)	7.9 (63)	8.3 (67)	7.9 (63)	7.9 (63)	8.5 (69)	8.3 (67)	
Baseline body weight (kg)	88.5	74.1	84.7	92.4	89.0	78.0	95.3	64.9	84.8	65.9	60.7	91.0	
Percentage change in body weight at closest assessment before DKA event	-3.6	-1.8	0.4	-4.8	-7.4	-3.5	0.8	-1.4	-2.6	-0.5	NA†	-2.6	
Onset day relative to first dose	116	77	27	116	130	110	27	28	103	47	5	32	
pH	6.9	7.2	7.3	7.3	6.9	7.1	7.0	NA	NA	6.9	7.2	7.2	
Ketones: 3BOH (blood), AC (blood), and/or urine ketone*	3BOH: 6.3 mmol/L	Blood ketones NOS: 150 mg/dL	Blood ketones NOS: 0.71 (high)	ur ≥80 (high)	NA	3BOH: >5 mmol/L	AC: 320 mg/dL; ur +++	AC: large; ur +++	AC: positive (moderate); ur +++	Blood ketones NOS: >20 (high)	ur +++++	NA	
Anion gap (mmol/L)	>35	22	14.6	19.6	>37	27	NA	31	>28	NA	NA	NA	
Bicarbonate (mmol/L)	NA	11.5	15	12	<5	6.1	7.2	NA	NA	6	5.5	10.1	
Blood glucose (mmol/L) [mg/dL]†	33.2 (598)	10.8 (194)	31.3 (563)	11.0 (199)	44.8 (807)	12.1 (218)	22.3 (401)	19.4 (>350)	27.0 (486)	>36.1 (>650)	13.5 (243)	9.4 (170)	
Precipitating factors	<ul style="list-style-type: none"> ● Pneumonia 	<ul style="list-style-type: none"> ● Failure of the insulin infusion pump set the day before hospitalization, which resulted in hyperglycemia before the pump 	<ul style="list-style-type: none"> ● Noncompliance with insulin therapy, with last dose of basal insulin administered on day 25 	<ul style="list-style-type: none"> ● Insulin pump malfunction 	<ul style="list-style-type: none"> ● Pneumonia 	<ul style="list-style-type: none"> ● Influenza with vomiting and weight loss of 4.5 kg before hospitalization 	<ul style="list-style-type: none"> ● Low-carbohydrate diet with reduction in insulin dose 	<ul style="list-style-type: none"> ● Interruption of insulin infusion by insulin pump for 6 h the day before hospitalization 	<ul style="list-style-type: none"> ● Sepsis secondary to infection at the insulin pump injection site 	<ul style="list-style-type: none"> ● Gastroenteritis/abdominal sepsis 	<ul style="list-style-type: none"> ● Death in family 	<ul style="list-style-type: none"> ● Viral infection 	<ul style="list-style-type: none"> ● Tooth extraction and root canal
		<ul style="list-style-type: none"> ● Excessive consumption of alcohol the day before hospitalization 						<ul style="list-style-type: none"> ● Increased alcohol consumption 				<ul style="list-style-type: none"> ● Uncontrolled diet with noncompliance with insulin therapy and improper monitoring of blood glucose 	

3BOH, 3-β-hydroxybutyrate; AC, acetone; CANA, canagliflozin; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injection; NA, not assessed; NOS, not otherwise specified; ur, urine ketone; +, positive result. *Ketone data are reported using units provided in hospital records. †At the time of hospital admission. ‡The only body weight measurement taken before the DKA event was at baseline.

Table 3—Baseline demographic and disease characteristics of patients with and without a ketone-related AE

	Patients with a ketone-related AE*		Patients without a ketone-related AE		
	CANA 100 mg (n = 6)	CANA 300 mg (n = 11)	Placebo (n = 117)	CANA 100 mg (n = 111)	CANA 300 mg (n = 106)
Sex					
Male	1 (16.7)	4 (36.4)	63 (53.8)	68 (61.3)	61 (57.5)
Female	5 (83.3)	7 (63.6)	54 (46.2)	43 (38.7)	45 (42.5)
Age (years)	32.8 ± 6.9	45.8 ± 11.2	42.0 ± 11.9	42.5 ± 11.6	42.5 ± 10.9
HbA _{1c}					
%	7.9 ± 0.6	8.0 ± 0.3	7.9 ± 0.6	7.9 ± 0.5	8.0 ± 0.5
mmol/mol	63 ± 6.6	64 ± 3.3	63 ± 6.6	63 ± 5.5	64 ± 5.5
Duration of type 1 diabetes (years)	18.8 ± 6.2	23.3 ± 10.4	23.3 ± 11.0	22.2 ± 11.7	21.7 ± 10.7
Prior DKA	3 (50.0)	1 (9.1)	14 (12.0)	10 (9.0)	14 (13.2)

Data are n (%) or mean ± SD. CANA, canagliflozin. *No patients in the placebo group experienced a ketone-related AE.

–7.4% in a patient treated with canagliflozin 100 mg; two patients had small increases (<1.0%) in body weight, and one did not have a body weight measurement postbaseline before the DKA event.

In the overall study population, canagliflozin was associated with reductions in daily insulin dose from baseline at week 18 (15). For the 12 patients with a serious AE of DKA, data on changes in insulin dose at the time of the event were not available. Relative to baseline insulin levels (i.e., after the protocol-specified 10–20% downtitration), mean reductions in total insulin dose at week 18 were greater with canagliflozin 300 mg in patients with a ketone-related AE than in those without a ketone-related AE (Table 4); however, an increase in total insulin dose was seen with canagliflozin 100 mg in patients with a ketone-related AE

compared with a decrease in those without a ketone-related AE. Results were similar when change in insulin dose was determined relative to insulin levels at screening (i.e., before the initial 10–20% downtitration). Whether these changes in insulin dose are meaningful given the small number of patients with a ketone-related AE and the large SDs observed is unclear.

CONCLUSIONS

Treatment with canagliflozin 100 and 300 mg for 18 weeks was associated with an increased incidence of serious AEs of DKA in patients with type 1 diabetes on background insulin therapy. All patients with a serious AE of DKA had precipitating factors that likely contributed to the development of DKA (e.g., infection, decrease in carbohydrate intake, interruption/reduction

of insulin therapy). There were no apparent differences in baseline characteristics in patients with a ketone-related AE compared with those without a ketone-related AE that would predict greater or lesser risk. Most patients did not have a history of DKA, including those who experienced a serious AE of DKA in this study. Although more men than women were enrolled in this study, more women than men experienced a ketone-related AE; however, the incidence of DKA generally is reported to be similar in men and women (1). Insulin dose reductions appeared to be greater over 18 weeks in patients with a ketone-related AE than in those without, but this analysis is of limited value because insulin doses were not recorded at the time of the event. Although DKA typically is characterized by hyperglycemia, blood glucose monitoring was not sufficient to

Table 4—Change in insulin dose in patients with and without a ketone-related AE at week 18

	Patients with a ketone-related AE*		Patients without a ketone-related AE		
	CANA 100 mg (n = 6)	CANA 300 mg (n = 11)	Placebo (n = 117)	CANA 100 mg (n = 111)	CANA 300 mg (n = 106)
Insulin dose at baseline† (IU/day)					
Total insulin	52.0 ± 19.4	52.4 ± 21.6	57.8 ± 29.4	51.8 ± 17.9	52.9 ± 21.5
Change at week 18 (%)	15.0 ± 72.5	–14.9 ± 17.7	5.1 ± 32.6	–5.0 ± 24.3	–6.1 ± 48.3
Basal insulin	27.1 ± 12.6	26.6 ± 13.3	27.6 ± 14.5	26.7 ± 10.5	27.1 ± 13.9
Change at week 18 (%)	–7.3 ± 30.5	–9.7 ± 12.4	15.9 ± 33.2	–3.2 ± 18.0	–6.9 ± 24.4
Bolus insulin	25.3 ± 12.1	26.9 ± 13.5	30.4 ± 20.3	25.5 ± 11.1	27.0 ± 13.0
Change at week 18 (%)	–2.8 ± 70.7	–22.5 ± 36.9	–5.5 ± 35.6	0.3 ± 57.3	–14.3 ± 33.9
Insulin dose at screening‡ (IU/day)					
Total insulin	56.8 ± 20.5	56.4 ± 22.4	62.6 ± 31.0	56.8 ± 19.3	57.0 ± 22.2
Change at week 18 (%)	4.3 ± 55.0	–20.0 ± 15.9	–3.7 ± 28.0	–13.8 ± 21.4	–13.7 ± 42.9
Basal insulin	32.0 ± 13.5	30.6 ± 14.3	32.5 ± 16.5	31.8 ± 12.0	31.2 ± 15.0
Change at week 18 (%)	–18.8 ± 20.3	–20.0 ± 11.0	–2.1 ± 28.9	–19.0 ± 16.1	–19.5 ± 22.5
Bolus insulin	25.3 ± 12.1	26.9 ± 13.5	30.4 ± 20.2	25.5 ± 11.1	27.0 ± 13.0
Change at week 18 (%)	–2.3 ± 63.2	–22.5 ± 36.9	–5.5 ± 35.6	0.3 ± 57.3	–14.1 ± 33.7

Data are mean ± SD. CANA, canagliflozin. *No patients in the placebo group experienced a ketone-related AE. †After the initial protocol-specified 10–20% downtitration. ‡Before the initial protocol-specified 10–20% downtitration.

detect DKA in this study because some serious events occurred with minimal increases in blood glucose. As a result, some patients received a misdiagnosis from their health care providers, thus delaying proper treatment.

DKA has also been reported in pilot studies of the SGLT2 inhibitors sotagliflozin and empagliflozin in patients with type 1 diabetes (13,14). All cases ($n = 2$ of 16 patients treated with sotagliflozin and $n = 2$ of 40 patients treated with empagliflozin) were associated with precipitating causes (i.e., gastroenteritis, insulin pump failure). Similar findings have also been reported in clinical practice. A retrospective study in 27 patients with type 1 diabetes treated with canagliflozin 100 mg reported two cases of DKA that developed due to insulin pump failure and cessation of insulin therapy (16). A recent case series described 13 episodes of DKA in patients with type 1 ($n = 7$) and type 2 ($n = 2$) diabetes treated with SGLT2 inhibitors (18). In all cases, patients had near-normal blood glucose levels and contributing factors (e.g., reduced insulin dose in most patients with type 1 diabetes, surgery in both patients with type 2 diabetes). DKA in patients with type 2 diabetes is rare but may occur in times of acute illness, such as trauma, surgery, or infection (1). A separate analysis of serious AEs of DKA in the canagliflozin type 2 diabetes clinical trial program ($n = 17,596$ patients) demonstrated that DKA occurred at a low frequency ($<0.1\%$) in canagliflozin-treated patients with an overall incidence of 0.5, 0.8, and 0.2 per 1,000 patient-years in the canagliflozin 100 and 300 mg and comparator groups, respectively (24). In that analysis, the majority of canagliflozin-treated patients with a serious AE of DKA were on insulin and had precipitating factors similar to those reported in the current study (e.g., infection, noncompliance with insulin therapy); 6 of the 10 canagliflozin-treated patients showed evidence of autoimmune diabetes (i.e., latent autoimmune diabetes of adulthood, type 1 diabetes, GAD65 antibody positive). The underlying mechanisms of increased DKA incidence in patients treated with SGLT2 inhibitors are not fully understood but may be related to the insulin-independent reduction of blood glucose through increased UGE, which allows for glycemic

control with concomitant reduction in insulin requirement, and the potential increase in glucagon secretion associated with SGLT2 inhibition, which leads to a decrease in the insulin-to-glucagon ratio and promotes ketogenesis.

A limitation of this study was that very little was known about the risk of DKA in patients with type 1 diabetes treated with SGLT2 inhibitors when the study was initiated. Although it was acknowledged that patients may be at an increased risk for developing DKA, no specific monitoring guidelines or mitigation strategies were implemented other than providing instructions on the importance of ketone monitoring and sick-day management. These instructions were not specific to the study but followed standard American Diabetes Association recommendations and were implemented at the beginning of the study. Additionally, patients were provided urine ketone test strips at the beginning of the study, which were replaced if needed. Study investigators were reminded of the importance of ketone monitoring and sick-day management throughout the study and used their judgment regarding participant reinforcement. Investigators were also required to review reported serious AEs throughout the study, including cases of DKA.

Patients were instructed to monitor urine ketones as part of standard sick-day management guidelines (i.e., during an illness or if blood glucose levels were ≥ 13.9 mmol/L [≥ 250 mg/dL]). Although DKA typically is characterized by blood glucose levels >13.9 mmol/L (>250 mg/dL), bicarbonate levels <18 mmol/L, and the presence of ketones (2), physicians did not use strict criteria for diagnosing DKA. However, as described previously, DKA in patients treated with SGLT2 inhibitors can occur with minimal symptoms (18), and patients may not have the characteristic marked increase in blood glucose, thus delaying diagnosis and treatment.

Another limitation of this study is that the protocol did not instruct patients to proactively record details of their treatment regimen that might pertain to DKA, such as changes in insulin doses. As a result, it was not possible to obtain reliable information regarding the exact reduction in insulin dose preceding a DKA event in most cases because patients may have been unable to remember these changes, the pump data were

no longer available, and/or changes were not recorded by the treating physician in hospital records.

Because of the potentially life-threatening nature of DKA in patients with type 1 diabetes, further development of SGLT2 inhibitor therapy as a treatment for type 1 diabetes should proceed with caution. On the basis of the findings from this phase 2 study, potential mitigation strategies for future clinical trials in patients with type 1 diabetes may include routine monitoring of blood and urine ketones throughout the study; use of lower canagliflozin doses; interruption of treatment during any illness or if undergoing major surgical procedures; discontinuation of treatment if ketone levels remain elevated despite increases in insulin dose; and provision of more detailed algorithms for ketone and blood glucose assessments, insulin dose adjustments, carbohydrate intake, and when to contact a physician. In addition, regulatory scrutiny of such trials will be important to ensure patient safety before SGLT2 inhibitor therapy is approved for use in type 1 diabetes.

Additionally, patients, treating physicians, and emergency care providers must be made aware of the potential risks of DKA with SGLT2 inhibitor therapy. Patients taking SGLT2 inhibitors and their physicians should closely monitor serum ketones when patients are ill, have reduced insulin and/or food intake, or experience any circumstance that is known to be associated with an increased risk of DKA (e.g., increased alcohol consumption, unusual strenuous or prolonged physical exercise, intense physical or psychological stress). In these circumstances, serum ketones should be monitored regardless of concomitant blood glucose levels. Should ketone elevation occur, patients should increase insulin and fluid intake and consider interruption of canagliflozin treatment during times of illness and before undergoing surgical procedures. Furthermore, patients should seek medical attention when having symptoms of DKA or elevated ketone levels that cannot be safely self-managed by increasing insulin and/or food intake.

In summary, treatment with canagliflozin for 18 weeks was associated with an increased incidence of ketone-related

AEs, including serious AEs of DKA, in patients with type 1 diabetes. The increased risk of DKA may be related to reductions in insulin dose and/or increases in insulin resistance during times of illness or stress. Mitigation strategies are expected to reduce the risk of DKA in patients with type 1 diabetes in future clinical trials, and mechanistic preclinical studies are currently ongoing to understand the relationship between canagliflozin and development of DKA.

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