Role of Noninsulin Therapies in the Treatment of Type 1 Diabetes

Sara E. Lingow,[1,2] Sandra D. Burke,[3] Amie D. Brooks,[1] and Pat S. Rafferty[1]

Individuals with type 1 diabetes represent only ~6% of all patients with diabetes in the United States and require characteristically complex treatment modalities (1). Autoimmune pancreatic β-cell destruction ultimately results in an absolute insulin deficiency, the presence of autoimmune markers, and little to no residual C-peptide (2,3). Additionally, pancreatic α-cell dysfunction is present, resulting in excess glucagon in both the fasting and postprandial states, and the gastric emptying rate is altered in many patients.

Exogenous insulin serves as the foundation of therapy for type 1 diabetes and is commonly delivered via a multiple-dose regimen or an insulin pump. The two most common adverse effects associated with insulin use are hypoglycemia and weight gain. Recent data suggest that 68% of people with type 1 diabetes are overweight or obese and that severe hypoglycemia occurs at a rate of 9–20% (4). The latter complication is considered a limiting factor to achieving glycemic targets in the type 1 diabetes population. Indeed, the average A1C for adults ≥18 years of age with type 1 diabetes in the United States was 7.9% in 2015, a value well above the target of 7% recommended by the American Diabetes Association for most adult patients. Further complicating matters, diabetic ketoacidosis (DKA) occurs at a rate of 10% per year in some age-groups (4). Overall, these data suggest a need for adjunctive therapies for type 1 diabetes that reduce the risk for hypoglycemia and weight gain.

While β-cell dysfunction is clearly a therapeutic focus for all types of diabetes, multiple other pathways of hyperglycemia present opportunities for alternate treatment modalities that may assist in achieving glycemic targets (5). The ideal pharmacotherapy regimen for a patient with type 1 diabetes would not only target the β-cell dysfunction, but also decrease blood glucose through hyperglycemic pathways independent of β-cell function.

One possible adjuvant therapy is the amylin analog pramlintide, which was approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 1 diabetes in 2005 (6). Pramlintide delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety (7). When 30 or 60 μg pramlintide is administered subcutaneously in addition to insulin three to four times daily, there is a reduction in the total daily dose (TDD) of insulin, a decrease in body weight, and a modest reduction in A1C (8–10). Unfortunately, significant nausea and vomiting, high cost, and the need for multiple daily injections results in relatively uncommon use of pramlintide in this population.

Metformin, dipeptidyl-peptidase-4 inhibitors, and thiazolidinediones have also been studied in type 1 diabetes but have not demonstrated clinically significant beneficial outcomes and therefore have not been approved by the FDA for this

[1]St. Louis College of Pharmacy, St. Louis, MO

[2]St. Louis County Department of Public Health, St. Louis, MO

[3]Goldfarb School of Nursing at Barnes-Jewish College, St. Louis, MO

S.E.L. is currently affiliated with Banner Health, Loveland, CO.

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use (3). The role of two other noninsulin classes of medications, sodium–glucose cotransporter (SGLT) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, have also been studied in type 1 diabetes. This literature review focuses on the use of these agents in patients with type 1 diabetes and provides a critical appraisal of evidence regarding their efficacy and safety for this purpose.

SGLT Inhibitors

Located in the proximal tubule of the nephron, the SGLT2 receptor is responsible for 90% of renal glucose reabsorption. Inhibition of this transporter reduces reabsorption of filtered glucose, thereby increasing glucosuria and reducing plasma glucose concentrations (7). The SGLT1 receptor is located in both the proximal renal tubule and the proximal small intestine. In the proximal renal tubule, it is responsible for reabsorption of the remaining 10% of renal glucose. In the small intestine, it is the primary transporter in glucose and galactose absorption (11,12). Because the mechanism of SGLT inhibitors is independent of β-cell function, this drug class may offer glucose-lowering benefit to patients with type 1 diabetes (3). Known adverse effects of SGLT inhibitors include lipid abnormalities, genital infections, hypotension, and euglycemic DKA (7). A list of available SGLT inhibitors can be found in Table 1.

Early studies of SGLT inhibitors in patients with type 1 diabetes demonstrated modest improvements in glycemic control, weight reduction, and insulin dose reduction but were limited by small sample sizes and short durations. Although these benefits were promising, patients receiving SGLT inhibitors also experienced more episodes of ketoacidosis and genital mycotic infections (11,13–16).

Two large-scale clinical trials evaluating the role of SGLT inhibitors in type 1 diabetes are described in Table 2. The DEPICT-1 trial (17) evaluated the safety and efficacy of dapagliflozin, an SGLT2 inhibitor, added to insulin therapy in 833 patients with type 1 diabetes over 24 weeks. The primary outcome, change in A1C at 24 weeks, statistically favored treatment with dapagliflozin 5 or 10 mg compared to placebo. Severe hypoglycemia occurred in 21 (8%), 19 (6%), and 19 (7%) of the patients in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. Adjudicated definite DKA occurred in four (1%), five (2%), and three (1%) patients in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. This trial excluded patients with a recent history of severe hypoglycemia or DKA.

The inTandem 3 trial (12) evaluated the safety and efficacy of sotagliflozin, an SLGT1 and SLGT2 inhibitor, in 1,402 patients with type 1 diabetes over 24 weeks. The combined safety and efficacy primary outcome was the proportion of patients achieving an A1C <7.0% without hypoglycemia or DKA. Two hundred of the patients in the sotagliflozin group (28.6%) achieved this primary outcome, whereas 107 (15.2%) patients in the placebo group achieved the outcome, resulting in a number needed to treat of eight. Conversely, of patients who failed to meet the target A1C, more patients in the sotagliflozin group had at least one episode of DKA compared to placebo (16 [2.3%] vs. 13 [1.8%], respectively, P <0.003), resulting in a number needed to harm of 50. The rate of DKA events in the sotagliflozin group was higher in patients who used an insulin pump compared to those who did not use an insulin pump. As in the DEPICT-1 study, this trial excluded patients with a recent history of DKA or hypoglycemia.

The data from these two landmark trials further support the benefits of reduction in A1C, weight, and insulin TDD with SGLT inhibitors. Although both trials excluded patients with a recent history of severe hypoglycemia, there is no indication in the literature of an increased risk of hypoglycemia with these agents. There is a risk of ketoacidosis; therefore, these agents should not be used in patients with a history of or who are known to be at increased risk for DKA.

A position statement from the American Association of Clinical Endocrinologists and American College of Endocrinology recommends that future trials of SGLT inhibitors in type 1 diabetes should use lower doses of these agents and that insulin doses should not be routinely reduced on initiation of an SGLT inhibitor (18). Future trials that are longer in duration and specifically designed to evaluate the long-term safety of these medications in patients with type 1 diabetes are essential. Additionally, future studies should evaluate the benefit of this class in the prevention or delay of microvascular and macrovascular complications of diabetes.

GLP-1 Receptor Agonists

Human GLP-1 is a peptide that, in conjunction with glucose-dependent insulinotropic polypeptide, is responsible for >90% of the increased insulin secretion after an oral glucose load. Human GLP-1 levels rise shortly after food ingestion, enhancing insulin secretion, suppressing glucagon secretion, slowing gastric emptying, and reducing food intake by increasing satiety (19). GLP-1 receptor agonists are analogs of human GLP-1 that increase glucose-dependent insulin secretion, delay inappropriate glucagon secretion, delay gastric emptying, and decrease food intake. Animal models and in vitro data have also demonstrated increased β-cell growth and replication. The proposed benefit of GLP-1 receptor agonists in type 1 diabetes is mostly related to the mechanistic avenues independent of β-cell function. However, the potential to improve residual β-cell function and increase glucose-dependent insulin secretion may be beneficial early in the diagnosis of type 1 diabetes.

The most common adverse effects of GLP-1 receptor agonists include

TABLE 1. Available SGLT Inhibitors and GLP-1 Receptor Agonists (7,11–17,21–29,36,37)

	Available Doses	Administration	Average Wholesale Price for 30 Days*	Studies in Type 1 Diabetes
SGLT inhibitors				
Canagliflozin	100 and 300 mg	By mouth once daily	$557.50	Henry et al., 2015 (15)
Dapagliflozin	5 and 10 mg	By mouth once daily	$557.45	Kuhadiya et al., 2016 (16) Dandona et al., 2017 (17)
Empagliflozin	10 and 25 mg	By mouth once daily	$557.94	Perkins et al., 2014 (13) Pieber et al., 2015 (14)
Sotagliflozin†	400 mg	By mouth once daily	—	Sands et al., 2015 (11) Garg et al., 2017 (12)
GLP-1 receptor agonists				
Albiglutide	30 and 50 µg	SQ injection once weekly	$626.41	Not studied
Dulaglutide	0.75 and 1.5 mg	SQ injection once weekly	$876.24	Not studied
Exenatide	5 and 10 µg	SQ injection twice daily	$850.06	Hari Kumar et al., 2013 (23)
Exenatide ER	2 mg	SQ injection once weekly	$792.19	Traina et al., 2014 (24)
Liraglutide	0.6, 1.2, 1.8, and 3.0 mg‡	SQ injection once daily	0.6 and 1.2 mg: $645.34 1.8 mg: $968.00 3.0 mg: $1,440.50‡	Kielgast et al., 2011 (21) Kuhadiya et al., 2013, 2016 (22,27) Frandsen et al., 2015 (25) Dejgaard et al., 2016 (26) Mathieu et al., 2016 (28) Ahrén et al., 2016 (29) Dubé et al., 2018 (36)
Lixisenatide	10 and 20 µg	SQ injection once daily	$707.42	Not studied
Semaglutide	0.25, 0.5, and 1 mg	SQ injection once weekly	$811.20	Not studied

**Average wholesale price per package as of 18 June 2018. †Dual SLGT1 and SGLT2 inhibitor; not approved for use in the United States. ‡3.0 mg dose is approved by the FDA for the treatment of obesity only. SQ, subcutaneous.*

TABLE 2. Landmark Trials of SGLT Inhibitors in Type 1 Diabetes

Trial	Comparison	Baseline A1C, %	Change in A1C Versus Placebo, %	Change in TDD Versus Placebo, %	Change in Weight Versus Placebo, kg
Dandona et al., 2017 "DEPICT-1" (17)	Dapagliflozin 5 and 10 mg + TTT insulin vs. placebo (*n* = 833)	D5: 8.52 D10: 8.50 P: 8.35	D5: –0.42* D10: –0.45*	D5: –8.8* D10: –13.2*	D5: –2.96* D10: –3.72*
Garg et al., 2017 "inTandem 3" (12)	Sotagliflozin 400 mg + TTT insulin vs. placebo (*n* = 1,402)	SOT: 8.26 P: 8.21	–0.46*	–9.9*	–2.98*

**Statistically significant difference. D5, dapagliflozin 5 mg; D10, dapagliflozin 10 mg; P, placebo; SOT, sotagliflozin; TTT, treat-to-target.*

TABLE 3. Landmark Trials of GLP-1 Receptor Agonists in Type 1 Diabetes

Trial	Comparison	Baseline A1C, %	Baseline C-Peptide–Positive, %	Change in A1C Versus Placebo, %	Change in TDD Versus Placebo, %	Change in Weight Versus Placebo, kg
Mathieu et al., 2016 "ADJUNCT-ONE" (28)	Liraglutide 0.6, 1.2, and 1.8 mg + TTT insulin versus placebo	L0.6: 8.18 L1.2: 8.16 L1.8: 8.14 P: 8.15	L0.6: 21.6 L1.2: 16.2 L1.8: 16.9 P: 14.9	L0.6: –0.09 L1.2: –0.15* L1.8: –0.20*	L0.6: 0 L1.2: –2* L1.8: –5*	L0.6: –2.2* L1.2: –3.6* L1.8: –4.9*
Ahrén et al., 2016 "ADJUNCT-TWO" (29)	Liraglutide 0.6, 1.2, and 1.8 mg + capped insulin versus placebo	L0.6: 8.09 L1.2: 8.07 L1.8: 8.04 P: 8.12	L0.6: 17 L1.2: 16 L1.8: 16 P: 11	L0.6: –0.24* L1.2: –0.23* L1.8: –0.35*	L0.6: –5* L1.2: –7* L1.8: –10*	L0.6: –2.5* L1.2: –4.0* L1.8: –5.1*

**Statistically significant difference. L0.6, liraglutide 0.6 mg; L1.2, liraglutide 1.2 mg; L1.8, liraglutide 1.8 mg; P, placebo.*

nausea and vomiting, increased heart rate, and headache. This class should not be used in patients with a personal or family history of thyroid cancer or multiple endocrine neoplasia syndrome (7,20). A list of GLP-1 receptor agents can be found in Table 1.

Preliminary literature evaluating the role of GLP-1 receptor agonists in type 1 diabetes is largely inconclusive. Except for one 56-week trial, most trials had small sample sizes and short durations ranging from 4 to 26 weeks. The results of the trials were variable with regard to A1C reduction (–0.3 to –2.3%), weight loss (–0.5 to –6 kg), and reduction in TDD of insulin up to 20%. Although the benefits demonstrated in these early studies are promising, many of the studies were retrospective, open-label, or observational, limiting their usefulness (21–27).

Two large-scale trials examining the use of GLP-1 receptor agonists in type 1 diabetes are described in Table 3. The ADJUNCT-ONE (28) trial evaluated the safety and efficacy of liraglutide added to treat-to-target insulin with regard to effects on A1C, insulin requirement, and body weight in adults with type 1 diabetes over 52 weeks. A statistically significant decrease in A1C and insulin TDD was seen with liraglutide 1.2 and 1.8 mg doses compared to placebo. All three doses of liraglutide were associated with weight loss.

Although benefits were seen at the higher doses of liraglutide, they were accompanied by an increased rate of symptomatic hypoglycemic events. The rate of symptomatic hypoglycemia events observed was 16.5/patient-year of exposure (PYE) and 16.1 PYE in the liraglutide 1.8 and 1.2 mg groups, respectively, compared to a rate of 12.3/PYE in the placebo group ($P < 0.05$). Additionally, liraglutide 1.8 mg was associated with a higher rate of hyperglycemic episodes with ketosis. There were a total of eight adjudicated events of DKA in all three liraglutide groups combined. In all but one of these events, a clinically relevant

event unrelated to the study drug was deemed to be the trigger of the DKA.

Lastly, gastrointestinal adverse effects, particularly nausea, were notable in all liraglutide groups. The ADJUNCT-ONE authors identified that patients with residual C-peptide levels at baseline had a greater decrease in A1C with liraglutide 1.8 and 1.2 mg compared to those without residual C-peptide at the same doses. Additionally, patients with residual C-peptide experienced fewer episodes of hypoglycemia or hyperglycemia with ketosis.

The ADJUNCT-TWO trial (29) evaluated the efficacy and safety of liraglutide added to a capped insulin dose in patients with type 1 diabetes over 26 weeks. All three doses of liraglutide demonstrated a statistically significant decrease in A1C, insulin TDD, and body weight compared to placebo. The highest rate of symptomatic hypoglycemia was unexpectedly seen in the liraglutide 1.2 mg arm. As in the ADJUNCT-ONE trial, hyperglycemia with ketosis was seen most often in the liraglutide 1.8 mg arm. The subgroup analysis of ADJUNCT-TWO revealed that patients with residual C-peptide at baseline showed a greater reduction in A1C with liraglutide 1.8 mg compared to those without residual C-peptide (29).

ADJUNCT-ONE and ADJUNCT-TWO are the largest trials available to date evaluating liraglutide in type 1 diabetes. Although the results of both trials are promising with regard to A1C reduction, weight loss, and reduction in insulin requirements, the treatment did show an increased risk of dose-dependent hypoglycemia and hyperglycemia with ketosis, as well as gastrointestinal adverse events. Future studies focused on prevention of microvascular or macrovascular outcomes would be beneficial to truly determine the clinical utility of this class in type 1 diabetes.

Comparing SGLT Inhibitors and GLP-1 Receptor Agonists in Type 1 Diabetes

Overall, the benefits of both SGLT inhibitors and GLP-1 receptor agonists in addition to insulin therapy in type 1 diabetes appear to be promising. However, the potential for adverse effects, lack of FDA approval for use in type 1 diabetes, the additional cost of the therapeutic regimen (Table 1), as well as a lack of insurance coverage for drugs in either class for patients with type 1 diabetes limit the practicality of their use at present.

Given these constraints, patients with type 1 diabetes who are overweight or obese and interested in an oral agent may be good candidates for an SGLT inhibitor. Duration of diabetes does not appear to be a factor affecting the efficacy of SGLT inhibitors in type 1 diabetes. Because the trials did not show an increased rate of hypoglycemia in patients with type 1 diabetes, agents from this class might be an option if used with caution in patients who are at risk for hypoglycemia. However, this class should be avoided in patients with a recent history of or who are known to be at increased risk of a DKA episode. Patients on insulin pumps may be at higher risk of DKA due to mechanical pump failures; therefore, extreme caution should be used if recommending an SGLT inhibitor for patients using an insulin pump. Sotagliflozin is the only SGLT inhibitor currently under FDA review for potential approval of use in type 1 diabetes. The FDA is expected to take action on this in March 2019 (30).

A GLP-1 receptor agonist may be a better option in patients with newer-onset type 1 diabetes, residual β-cell function, or residual C-peptide levels, given that the preliminary literature and subgroup analyses show the most benefit in this population. Obese and overweight patients with type 1 diabetes may benefit from the weight loss properties of GLP-1 receptor agonists, but drugs from this class should be used with caution in patients at a higher risk of DKA or hypoglycemic events, as the recent evidence showed a higher incidence of these adverse effects. Similar to pramlintide, GLP-1 receptor agonists would add an undesirable additional injection to the medication regimen in this patient population. However, a GLP-1 receptor agonist is a once-daily or once-weekly injection, whereas pramlintide must be injected before each meal three to four times per day.

Paradigm Shift

Landmark trials such as the Diabetes Control and Complications Trial and its long-term follow-up the Epidemiology of Diabetes Interventions and Complications study have demonstrated that there is a direct, inverse correlation between duration of time within glycemic targets and risk of microvascular and macrovascular complications (31,32). In recent years, the overall approach to medication management in type 2 diabetes has changed from a primary focus on A1C lowering to a broader focus on the reduction of complication risk via nonglycemic pathways. This shift is, in large part, due to results of trials such as LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), CANVAS (Canagliflozin Cardiovascular Assessment Study), and EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), which have shown cardiovascular and renal benefits irrespective of A1C lowering with the use of specific drug classes in patients with type 2 diabetes and elevated cardiovascular risk (33–35). Perhaps there is also more to prevention of complications in patients with type 1 diabetes than merely striving for glycemic goals with the use of insulin. These noninsulin agents may have pleiotropic benefits that extend beyond glycemic control. Future trials evaluating the prevention of microvascular and

macrovascular complications with SGLT inhibitors and GLP-1 receptor agonists in the treatment of type 1 diabetes have the potential to transform current treatment algorithms.

Duality of Interest

S.D.B. serves as an associate editor of *Diabetes Spectrum* but was not involved in reviewing or accepting this article. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

S.E.L. researched literature, wrote the manuscript, contributed to discussion, and reviewed and edited content. S.D.B. contributed to discussion and reviewed and edited the manuscript. A.D.B. researched data, contributed to discussion, and reviewed/edited the manuscript. P.S.R. researched literature, contributed to discussion, and reviewed and edited the content. S.E.L. is the guarantor of this work and, as such, had full access to all the literature reviewed and takes responsibility for the integrity of the literature evaluation and the accuracy of this manuscript.

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