SGLT2 inhibitors in type 1 diabetes: knocked down, but up again?

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Life expectancy is still significantly reduced in type 1 diabetes and quality of life is frequently impacted by eye, kidney, foot and cardiovascular disease. Achieving and sustaining control of blood glucose to reduce the risk of these complications remains a significant challenge for many affected individuals.

One strategy currently under investigation is "re-purposing" agents from other conditions as adjunct therapy.[1] An ideal adjunct agent - added in with insulin therapy - would provide a sustained reduction in blood glucose without increasing hypoglycaemia while preventing insulin-induced weight gain and improving cardiovascular outcome. A number of candidates have emerged from the novel classes of glucose-lowering agents recently introduced for type 2 diabetes.

Dapagliflozin, empagliflozin and canagliflozin are phlorizin derivatives approved for use in type 2 diabetes that inhibit sodium glucose transporter 2 (SGLT2) and thereby reduce renal tubular glucose reabsorption (and hence blood glucose) by promoting urinary glucose excretion. Those agents with less selectivity (e.g. canagliflozin) also inhibit SGLT1 and therefore reduce intestinal glucose absorption.[2] These agents are increasingly used in the treatment of type 2 diabetes, driven initially by a profile associated with weight reduction (due to a negative caloric balance) and BP reduction (associated natriuresis) but more recently by positive results from large cardiovascular outcome trials.[3,4]

Diabetologists quickly recognised the insulin-independent mode of action of SGLT2 inhibitors as having potential in type 1 diabetes. However, initial enthusiasm for "off-label" use was tempered early in 2015 by case reports of ketoacidosis in types 1 and 2 diabetes - in some cases without much elevation of blood glucose ("euglycaemic").[5] For this reason, the FDA has not approved SGLT2 inhibitors for type 1 diabetes and warning labels have been in place in type 2 diabetes since May 2015.[6] In December 2015, a phase 2 clinical trial in 351

patients with type 1 diabetes reported ketoacidosis in 5.1% and 9.4% of those randomized to 100 mg and 300 mg of canagliflozin but none in those randomised to placebo.[7]

Ketoacidosis during SGLT2 inhibitor treatment in type 1 diabetes might be attributable to excessive dose reduction of insulin and/or delay in recognising early signs due to occurrence at glucose levels closer to target. However, physiological studies (mostly with empagliflozin) in type 2 diabetes have increasingly revealed profound effects on fuel substrate metabolism with increased reliance on free fatty acids and ketone bodies rather than glucose and pyruvate.[8] Synthesis of ATP from these substrates is more efficient: for cardiac muscle in particular, ketones can be considered a "superfuel." As *ex vivo* studies have demonstrated that SGLT2 is expressed in human pancreatic α-cells, and that its inhibition by dapagliflozin directly triggers glucagon secretion, a tendency towards ketosis may even be a direct consequence of SGLT2 inhibition.[9] In summary, the mechanisms underlying serendipitous efficacy of SGLT2 inhibition in type 2 diabetes could also be their downfall for safety in type 1 diabetes.

In the present issue of the *Lancet Diabetes and Endocrinology*, Dandona et al report the results of a Phase 3 clinical trial with the SGLT2 inhibitor dapagliflozin (DEPICT-1) as adjunct therapy in adults with type 1 diabetes. In the primary pre-specified analysis, mean HbA1c at 24 weeks in participants randomized to dapagliflozin 10 mg daily who did not discontinue treatment was reduced by 0.45% percentage units (4.9 mmol/mol) from a baseline of 8.5% (70 mmol/moL), while mean weight was reduced by ≅3.1 kg from 82.4 kg (3.7 %) and mean daily insulin dose by ≅5.6 units (9%) from 62 units (adjusted for weight reduction). There was no tendency for increased hypoglycaemia. Formally-adjudicated ketoacidosis occurred in four participants on 5 mg (1.4%) and five participants (1.7%) on 10

mg dapagliflozin and in no cases on placebo; all five participants developing ketoacidosis on the higher dose discontinued in the trial.

DEPICT-1 therefore provides encouraging short term data for the efficacy of adjunct SGLT2 inhibition in type 1 diabetes but may also provide insights into how risk of ketoacidosis can be minimised. The results should be considered in the context of similar recently-presented (but as-yet-unpublished) findings with the dual SGLT2/ SGLT1 inhibitor sotagliflozin (inTandem 1 trial, 24 weeks, n=793)[10] and forthcoming results from other trials including with the selective SGLT2 inhibitor empagliflozin (ClinicalTrials.gov NCT02414958 and NCT02580591).

Participants in DEPICT-1 were provided with a combined home blood glucose and ketone meter and advised to measure glucose four times daily and ketones whenever glucose levels were consistently elevated. Risk of ketoacidosis was reviewed at fortnightly face-to-face visits. During an eight week lead-in phase, HbA1c fell by more than 0.5% (5.5 mmol/mol) in many participants, protecting the trial from overestimating efficacy but also highlighting the independent effect of frequent study visits. Nevertheless, the investigators showed an eye on translating their clinical trial findings to the "real world," by providing a very simple rule that insulin doses should be reduced by no more than 20% when study medication was started and that they should subsequently be titrated back towards the initial dose. This rule appeared to be quite effective in mitigating ketoacidosis, and is feasible to implement in modern clinical practice as meters that measure ketones are increasingly available. It was also effective in avoiding excess hypoglycaemia, a problem which was encountered in adjunct therapy trials of the glucagon-like peptide 1 agonist liraglutide in type 1 diabetes.[11]

A 26 week extension phase of DEPICT-1 is now in progress. Follow-up for longer than one year would be preferable as effects of adjunct therapies on glycaemic control in type 1

diabetes are not always sustained. For example, in the recent REMOVAL trial of metformin in type 1 diabetes, reductions in weight and LDL cholesterol were sustained for three years but improvements in glycated haemoglobin at 3-6 months regressed to baseline by 12-18 months as participants titrated back their insulin, presumably towards their hypoglycaemia "comfort zone."[12]

Regulators are likely to await at least the results of 12 month follow-up as well as data from other ongoing trials before considering an indication for SGLT2 inhibitors in type 1 diabetes. This might be appropriate for individuals who have a good understanding of the early warning signs of ketoacidosis, undertake regular home monitoring (including of blood ketones) and exhibit a high level of self-monitoring and communication with their diabetes team. Larger and longer-term trials assessing broader safety and efficacy should then be conducted with levels of clinical oversight similar to usual care. A cardiovascular outcome trial has never been undertaken in type 1 diabetes, but if ketoacidosis risk can be mitigated as in DEPICT-1, long term use of SGLT2 inhibitors as adjunct therapy could ultimately be shown to impact both microvascular and cardiovascular complications.

(1098 words)

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