SGLT2 inhibitors and renal complications in type 1 diabetes

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Adding in non-insulin agents is one of several promising strategies under investigation to improve glycaemic control in type 1 diabetes. Unlike uptitration of insulin, the ideal "adjunct" agent would not cause increased hypoglycaemia and weight gain.[1] It would also reduce rates of cardiovascular, renal and other adverse outcomes by improving glycaemic control and/or other mechanisms. These still result in an average reduced life expectancy of 11-13 years.[2]

Of several drug classes recently repurposed from type 2 to type 1 diabetes, sodium-glucose co-transporter-2 (SGLT2) inhibitors have made the most progress. The concept is that inhibiting reabsorption of glucose (and sodium) in the proximal renal tubules reduces blood glucose only when it is above the renal threshold, so hypoglycaemia is not increased, while weight is reduced due to urinary loss of glucose equivalent to ≈200 kcal per day. As adverse cardiovascular events are reduced in type 2 diabetes by these agents (EMPAREG, CANVAS, DECLARE-TIMI trials),[3] it is not unreasonable to extrapolate that this might also happen in type 1.

In this issue of *The Lancet Diabetes & Endocrinology*, *Groop et al [Ref4]* examine the effect of the SGLT2 inhibitor dapagliflozin on albuminuria in adults with type 1 diabetes in a *post hoc* subgroup analysis of the DEPICT Phase 3 trial programme.[5] They report that in approximately 15% of DEPICT-1 and DEPICT-2 trial participants with albuminuria at baseline (n = 251), dapagliflozin reduced urinary albumin excretion (albumin: creatinine ratio, ACR) *vs.* placebo. This finding is biologically plausible given compelling recent evidence that dapagliflozin and other SGLT2 inhibitors reduce rates of end-stage kidney disease in chronic kidney disease,[6] whether or not associated with type 2 diabetes.[7] Mechanistically, SGLT2 inhibitors are thought to protect the glomerulus by reflex constriction of the afferent arteriole in response to renal tubular sodium loss rather than by relaxation of the efferent arteriole as with renin-angiotensin system (RAS) blocking agents.

Despite the many beneficial effects of SGLT2 inhibition in several conditions, including heart failure, their promotion of ketosis has been the major barrier to widespread uptake in type 1 diabetes, in which diabetic ketoacidosis (DKA) still accounts for more than a fifth of deaths.[8] It does not seem

likely that this adverse effect can be eliminated, as many of the positive effects, particularly on heart failure outcomes, are thought to be mediated by increased availability of free fatty acids and ketone bodies for metabolism.

Nevertheless, of the SGLT2 inhibitors that entered Phase 3 trials in type 1 diabetes, dapagliflozin (DEPICT programme) and sotagliflozin (inTandem programme) have relatively favourable therapeutic profiles.[8,9] In pooled analyses of the former, dapagliflozin 5 mg/day on average reduced HbA1c by 0.34% *vs.* placebo at 52 weeks in the context of a threefold elevation in adjudicated DKA risk *vs.* placebo (4.62 *vs.* 1.27 events per 100 patient years), falling substantially in those with BMI ≥ 27 kg/m^2 (1.86 *vs*. 1.17 per 100 patient years). Based on such therapeutic profiles, both dapagliflozin and sotagliflozin were granted European and Japanese (but not US) licenses for adjunct therapy in type 1 diabetes in the first half of 2019 for those with BMI ≥ 27 kg/m. The UK National Institute for Healthcare Excellence (NICE, nice.org.uk) subsequently recommended both as cost-effective for use within the NHS for those who additionally had a relatively high insulin requirement (≥ 0.5 units/kg/day) and had completed an evidence-based quality-assured structured education programme. Of note, at the time of writing, dapagliflozin is widely available but sotagliflozin has yet to be launched in many countries.

NICE estimated that around 90,000 of the estimated 370,000 adults living with type 1 diabetes in the UK might be eligible for SGLT2 inhibition. However, one year on from approval, uptake has been low. Although many diabetologists have cared for people with type 1 who have derived great benefit (usually in the context of regular blood ketone monitoring), their enthusiasm has been tempered by small numbers of hospitalised cases of severe treatment-resistant diabetic ketoacidosis attributed to SGLT2 inhibitor therapy, in some cases presenting late due to relative euglycaemia. The strength of this perception was reinforced during the early months of COVID-19 by guidance from the Association of British Clinical Diabetologists that SGLT2 inhibitors should be stopped in all people with diabetes (even those with type 2) admitted to hospital.[10]

Presumably on a principle of *primum non nocer*e, some UK centres went even further and proactively contacted stable patients with type 1 diabetes to advise discontinuation, even those who were able to skip doses on "sick days" as recommended. As SGLT2 inhibitors are restarted can this now be informed by the knowledge that renoprotection is an additional and previously unrecognised benefit?

The analysis by *Groop et al* has some limitations. As it was based on a non-prespecified surrogate measure in small numbers of individuals during relatively short-term follow-up, it could not report on clinical renal outcomes. 27% reduction in ACR observed in those allocated to placebo indicated considerable regression to the mean. In addition, despite evidence suggesting dose-dependence, ACR reduction with the licensed dose of dapagliflozin (5 mg/day) was not statistically significant. This contrasts with significant ACR reduction with the licensed dose of sotagliflozin (200 mg/day) - although in this case ACR reduction was not significant with a higher dose (400 mg/day).[9]

Despite these considerations, when taken in the context of evidence with SGLT2 inhibition in other conditions and recent data with sotagliflozin, the dapagliflozin analysis by Groop et al contributes to proof of concept for renoprotection for this class in type 1 diabetes and helps tip the overall balance towards benefit rather than risk. However, adequately powered trials based on clinical outcomes are clearly still required for the use of these and other adjunct therapies in type 1 diabetes.

(946 words)

Author contributions

The manuscript was conceived and written by JRP

Conflicts of interest

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