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EXPERT OPINION

Luseogliflozin and other sodium-glucose cotransporter 2 inhibitors: no enemy but time?

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Glycosuria is being increasingly recognised as not only a symptom but also as a novel therapeutic approach in the management of type 2 diabetes mellitus (T2DM). This is accomplished through sodium glucose co-transporter 2 (SGLT2) inhibitors. Consequently, the safety and efficacy of these new agents have been thoroughly studied, both in randomised controlled trials and in systematic reviews and meta-analyses. More recently, a review on the mechanism of action, clinical efficacy and safety of luseogliflozin, a new highly selective SGLT2 inhibitor approved and launched in Japan for T2DM, has documented that this drug lowers plasma glucose concentration and body weight, and that it exhibits benefits in other metabolic parameters with a good safety profile. Despite the promising characteristics of this drug, important issues await consideration. These include the question as to when and to whom early use of SGLT2 inhibitors would be most suitable, as well as instructions on reduction of sulfonylurea dosage during add-on treatment. Further important questions are long-term safety concerns and cost-effectiveness of this new therapeutic class. Finally, we need to know more about the potential differences between the various SGLT2 inhibitors, as such differences might prove clinically useful in selection of hypoglycaemic agents.

Keywords: diabetes mellitus, luseogliflozin, oral hypoglycaemic agents, sodium-glucose transport inhibitors, therapy.

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Aretaeus was the first to describe diabetes as a condition, which provoked "melting down of the flesh and limbs into urine" [1]. It was much later, in 1776, that Matthew Dobson described the sweet taste of urine as a distinct characteristic of diabetes, concluding that kidneys excreted sugar that "previously existed in the serum of the blood" [2]. His opinion met with some disapproval in his era [2]. The vital role of kidney in human physiology by helping maintain glucose balance was later described in 1938 by Bergman and colleagues [3]. More recent data confirm that normoglycaemia is accomplished through the balanced actions of glucose absorption in the gastrointestinal tract, glycogenolysis in the liver, glucose reabsorption and glucose excretion in the kidney along with gluconeogenesis in the liver and the kidney [4,5]. Under normal conditions, ~ 180 g of glucose are filtered by the kidney glomerulus per day, and virtually the entire amount is reabsorbed in the proximal tubule [6]. The absorption of glucose in the small intestine and the reabsorption in the kidney occurs passively by glucose transporters (GLUTs) and actively by sodium-glucose cotransporters (SGLTs) [7].

The SGLT2 and GLUT2 are expressed predominantly in cells of the proximal tubule of the kidney on the S1 segment, where the majority of glucose reabsorption (~ 90%) is accomplished [7]. Meanwhile, ~ 10% is reabsorbed in the S3 regimen, where SGLT1 and GLUT1 are located [7]. Glycosuria will appear if the filtered glucose exceeds the glucose threshold of 180 mg/dl or the filtered glucose load exceeds

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375 mg/min or if the renal reabsorptive capacity is reduced [4,5]. More recently, glycosuria can be induced by the SGLT2 inhibitors. These represent a new class of hypoglycaemic agents free from the commonest and dose-limiting untoward effects of antidiabetic treatment, namely hypoglycaemia and weight gain [8]. Glycosuria induced by SGLT2 inhibitors occurs in a fashion similar to familial renal glycosuria, a rare autosomal benign condition characterised by a defect in renal glucose reabsorption due to impaired SGLT2 receptors in the S1 regimen of the proximal tubule [9]. Interestingly, the chronic glycosuria of patients suffering from this condition does not appear to be associated with kidney complications, and patients are mainly asymptomatic, even in the complete absence of glucose re-absorptive capacity [9]. This background knowledge seems to provide a rationale for the therapeutic use of SGLT2 inhibitors in type 2 diabetes mellitus (T2DM).

Indeed, the safety and efficacy of these agents in T2DM have been thoroughly studied, both in randomised controlled trials and in systematic reviews and meta-analyses [7,10-13]. Vasilakou *et al.* [10] have recently demonstrated that the use of canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, tofogliflozin, ertugliflozin and remogliflozin was accompanied by a significant reduction in HbA_{1c} levels compared with placebo as monotherapy (mean difference -0.79%) or as add-on treatment (mean difference -0.61%), or against active comparator as add-on treatment (mean difference -0.16%). However, no difference was found when comparison was made against active comparator as monotherapy (mean difference -0.05%), especially against metformin [10]. Furthermore, compared with placebo, the use of SGLT2 inhibitors was associated with significant reduction in fasting plasma glucose (FPG) (mean reduction -0.70 mmol/l), body weight (mean reduction -0.59 kg), systolic (mean reduction -0.27 mm Hg) and diastolic blood pressure (mean reduction -0.24 mm Hg) from baseline [11]. High-density lipoprotein (HDL) levels were significantly increased from baseline (mean increase + 0.21 mg/dl), whereas there was no change in low-density lipoprotein (LDL) levels [11]. Conversely, both dapagliflozin and canagliflozin were associated with genital tract infections, whereas the former was also associated with urinary tract infections, both infections being more common among female participants [11]. Vasilakou *et al.* [10] also inferred that a minimal increase in the risk of hypoglycaemia was noted in comparison to placebo, but SGLT2 inhibitors were at least as safe as the active comparator [10]. Nonetheless, the number of patients who experienced serious adverse events or discontinued treatment due to adverse events did not differ significantly between SGLT2 inhibitors and placebo-treated patients [11].

In a similar fashion, it has previously been shown that dapagliflozin led to significant reductions in HbA_{1c} and FPG levels and to improvement of metabolic parameters, such as body mass index, blood pressure and serum uric acid compared with placebo [12,13]. However, doses exceeding 10 – 20 mg/d offered no additional benefits [12]. Additionally, dapagliflozin was linked to a dose-related increase in the risk of genital and urinary tract infections and a mild increase in the risk of hypoglycaemia when combined with insulin or sulfonylureas [12].

It would next be relevant to enquire about data on cardiovascular outcomes. Such data have hitherto been rather inconclusive, but the US FDA has already noted a numerical though insignificant increase in non-fatal strokes among patients treated with canagliflozin [10]. As regards dapagliflozin, there has been a numerical though insignificant increase in bladder and breast cancer cases [10]. Last but not least, dapagliflozin and high-dose canagliflozin administration in patients with moderate kidney damage has been shown to increase the risk of renal-related adverse events [10].

More recently, a review on the mechanism of action, clinical efficacy, safety and metabolic effects of luseogliflozin, a new highly selective SGLT2 inhibitor approved and launched in Japan (doses of 2.5 and 5 mg) for T2DM, has been published [14]. The efficacy of this new agent has been confirmed both in monotherapy and in combination with oral hypoglycaemic agents in once-daily administration of 2.5 mg. Moreover, the risk of drug interactions during concomitant use with other drugs appeared low [14]. Importantly, no dose adjustment was necessary in patients with mild-to-moderate renal impairment, liver dysfunction or in elderly patients [14]. Not only did luseogliflozin improve glycaemic control, but it also decreased body weight, waist circumference, blood pressure, uric acid, triglycerides, and it increased HDL and adiponectin levels [14], the latter being suggestive of a reduction in visceral fat [14]. In terms of untoward effects, the risk of hypoglycaemia appeared low in monotherapy and in combination with other oral hypoglycaemic agents except for sulfonylureas. The incidence of urinary and genital tract infections was low, as compared with other drugs of this category, and this would appear reassuring [14]. Still, we should bear in mind that studies with luseogliflozin in Japan may have included a greater proportion of male participants, thereby reducing the risk of such infections [14]. Other than the aforementioned safety issues, luseogliflozin was not associated with major clinical problems regarding bone metabolism, pollakiuria, volume depletion, malignant tumours or kidney/liver function [14]. Finally, there was no change in risk factors for cardiovascular disease [14].

1. Conclusion

Luseogliflozin has recently shown safety and efficacy, both as monotherapy and as add-on treatment [14]. Longitudinal trials are now expected to provide answers on long-term safety issues. Meanwhile, granted the great interest of the scientific community on new antidiabetic agents without important untoward effects, the publication of this review adds to the importance of SGLT2 inhibitors as a class in representing an alternative choice in the therapeutic algorithm for T2DM.

2. Expert opinion

Although the aforementioned findings encourage the use of SGLT2 inhibitors in the management of T2DM, important issues await consideration. First, SGLT2 and GLUT2 expression and transport activity increase due to elevated plasma glucose levels [15]. As a result, hyperglycaemia in diabetes is specifically associated with increased proximal tubular glucose uptake. Generally, the hyperglycaemic milieu is thought to contribute to the development of chronic, including renal, complications. Development of the latter occurs through the activation of hyperglycemia-associated pathways, namely gluconeogenesis, increased flux through the hexoamine pathway, sorbitol accumulation, and, last but not least, formation of advanced glycation end-products [15]. Against this background, correction of hyperglycaemia with SGLT2 inhibitors, by contrast, exerts two major effects: a) downregulation of gene expression for SGLT2/GLUT2 levels, thereby contributing to restoration of normoglycaemia; b) progressive diminution in the efficacy of this drug category with diminishing hyperglycaemia, because the aforementioned efficacy depends, directly, on the amount of glucose filtered in the glomerulus (and so, indirectly, on hyperglycaemia) [15]. Of additional note, this efficacy declines with progression of renal impairment [15]. Therefore, it is important to choose the right time in the natural history of T2DM to administer SGLT2 inhibitors. It seems, indeed, rational to assume that early restoration of normoglycaemia would then have the potential to normalise perturbations of physiology and, thus possibly, ameliorate or retard chronic renal complications.

Second, although the medical community is discussing the place of SGLT2 inhibitors in the therapeutic algorithm for T2DM, it is now the right time to acquire more data on several important issues. One such issue is the potential increase in ketones, which is attributable to increased lipid metabolism and may prove to be relevant in specific patient categories, including underweight patients, with low carbohydrate intake, impaired insulin secretion, long-standing T2DM and/or old age [8,14]. In elderly subjects, there is also the risk of dehydration [8,14]. Thus, suitable candidates appear to be mainly middle-aged patients with metabolic syndrome, good nutritional status and with preserved insulin secretion capacity, renal and cardiovascular function [14]. Another issue is genital and urinary tract infections: meanwhile, patients prone to these should be monitored carefully [8,10,12].

Third, given the increased rate of hypoglycaemias in combination with sulfonylureas and insulin [8,12,14], a protocol of insulin and/or sulfonylurea dose adjustment during add-on treatment with SGLT2 inhibitors would be highly welcome. Naturally, a fourth major issue pertains to long-term safety concerns, especially cardiovascular and cerebrovascular safety, malignancies, potential bone pathology and liver and renal function. Accordingly, large-scale post-marketing surveillance is necessary to provide more reassurance.

In addition, we need to understand better the differences between the various drugs of this new category. Such differences may relate not only to glycaemic efficacy, but also to their effects on body weight, blood pressure, serum lipids (especially LDL), visceral fat, uric acid, etc., and might prove very important in selecting a particular SGLT2 inhibitor in practice. Finally, the cost-effectiveness of SGLT2 inhibitors needs additional evaluation.

In conclusion, luseogliflozin is a useful and promising new SGLT2 inhibitor. The agents of this class are being increasingly appreciated and used in T2DM. However, time will show their long-term value in our therapeutic armamentarium.

Declaration of interest

K Pafili has no conflicts of interest. N Papanas has been an advisory board member of TrigoCare International; has participated in sponsored studies by Novo Nordisk and Novartis; has received honoraria as a speaker for Astra-Zeneca, Eli-Lilly, Novo Nordisk and Pfizer; and attended conferences sponsored by TrigoCare International, Novo Nordisk, Sanofi-Aventis and Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

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• **An important systematic review and meta-analysis of SGLT2 inhibitors, showing that these drugs may improve short-term outcomes in T2DM, but effects on long-term outcomes and safety are unclear.**

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