




COMMENTARY

SGLT1 and SGLT1 Inhibitors: A Role to Be Assessed in the Current Clinical Practice

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Received: October 23, 2017

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ABSTRACT

Diabetes is a complex disease of increasingly common occurrence worldwide. Attaining optimal glycemic control is the main challenge to prevent the development of diabetes-related complications and/or to stop their progression. In recent years, the pharmacologic toolkit for the treatment of diabetes has considerably expanded, thus paving the way to more pathophysiology-oriented therapies. For instance, the sodium-glucose cotransporters SGLT2 and SGLT1 have been in the spotlight because of better knowledge of their physiology and therapeutic potential. At present, whereas the SGLT2 inhibitors are widely applied in current clinical practice as an effective and well-tolerated treatment that increases the urinary excretion of glucose, less is known about the use

of SGLT1 inhibitors. SGLT1s are of primary importance in the small intestine, an organ that does not express SGLT2, while in the kidney they are expressed in the late renal proximal tubules, where it reabsorbs the glucose escaped from the upstream SGLT2. Hence, SGLT1-mediated glucose reabsorption in the kidney is increased when the tubular glucose load overwhelms the capacity of SGLT2 or when the latter is inhibited. The role of SGLT1 in intestinal and renal glucose transport makes the transporter a potential target for antidiabetic therapy. Here, we briefly report the evidence on LX2761, a new inhibitor against SGLT1 and SGLT2 in vitro, which acts in vivo as a selective inhibitor of SGLT1 in the gastrointestinal tract. LX2761 improves glycemic control without the glycosuria-related side effects of SGLT2 inhibitors, particularly genitourinary tract infections. However, whether it represents a valid therapeutic option for all patients with diabetes or is more appropriate for specific phenotypes, e.g., patients with concomitant diabetes and chronic kidney disease, who may benefit less from the renal mechanism of selective SGLT2 inhibitors, remains to be tested in large randomized controlled trials.

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Keywords: Glucose transporters; Glycemic control; SGLT1; SGLT1 inhibitors; SGLT2

COMMENTARY

In recent years, the renal sodium/glucose cotransporters SGLT1 and SGLT2 have gained increasing attention from researchers and clinicians, given their potential role as an effective and generally well-tolerated treatment option for the attainment of a proper glycemic control [1, 2]. However, the renal expression of both SGLT2 and SGLT1 in the proximal tubule of patients with type 2 diabetes (T2D) is still not completely elucidated, and experimental studies from different research groups have reported conflicting results [3–7].

In this regard, Solini et al. [3] recently reported that the renal expression of SGLT1 in patients with T2D was similar to that of their normoglycemic (NG) counterparts, which also showed higher expression of SGLT2. The patients included in the analysis had a mean diabetes duration of about 3 years and were on a glucose-lowering therapy with oral hypoglycemic agents, without SGLT2 inhibitors and/or insulin therapy. These observations have not been reported by previous studies in mouse models of diabetes [4] or in human T2D patients [5–7]. As a potential explanation for their findings, the authors found that clinical factors such as duration of diabetes, different pharmacologic treatments, varying degrees of glycemic control and the extent of renal impairment may limit the comparability of the study findings and may have influenced the expression of each pair of brush border/basolateral transporters SGLT2/GLUT2 and SGLT1/GLUT1 located, respectively, in the S1-S2 and S3 segments of the tubular nephron.

However, Norton et al. [7] observed that in patients with T2D the expression of SGLT1 mRNA was increased more than fourfold in kidney biopsy specimens compared to individuals with normal glucose regulation. In this case, the authors argued that poorer glycemic control, older age and a decreased glomerular filtration rate may explain, at least in part, the increased expression of SGLT1 mRNA in patients with T2D. The authors also observed significant correlations of higher expression of SGLT1 mRNA with increasing levels of fasting plasma glucose

($r = 0.63$, $p < 0.001$), post-prandial glucose ($r = 0.36$, $p < 0.05$) and glycosylated hemoglobin ($r = 0.43$, $p < 0.01$), but not with age ($p = 0.21$) and blood pressure ($p = 0.82$). These results are in accordance with previous evidence on the positive correlation of glycemia and HbA1c with the number of SGLT1 cotransporters [2, 6].

Norton et al. [7] point out that the increased expression of SGLT1 in patients with T2D may develop as a compensatory mechanism to increase glucose reabsorption and could therefore potentially limit the efficacy of SGLT2 inhibitors. Indeed, under physiologic conditions, the SGLT2 accounts for about 95% of filtered glucose reabsorption (160–180 g/day) in the S1 and S2 segments of the proximal tubule, while the pharmacologic treatment with SGLT2-specific inhibitor treatment reduces the glucose reabsorption by 50–70% [8]. Regarding the properties and anatomic distribution of the SGLT1 and SGLT2 cotransporters, it is also worth noting that SGLT2 is primarily expressed in the kidney, while SGLT1 does not solely mediate the glucose reabsorption of the remaining filtered glucose (about 3–5%) in the last S3 segment of the proximal tubule [8], but it is also the main sodium/glucose cotransporter in the small gut. It has been hypothesized that SGLT1 activity could be increased as a compensatory mechanism in case of a massive tubular glucose load overwhelming the reabsorption capacity of the SGLT2 cotransporter as happens during the supra-physiologic glycosuria induced by glucose-lowering therapy with SGLT2 inhibitors [8]. However, SGLT2 selective inhibitors have been reported to be less effective in patients with moderate to severe renal dysfunction [9], which is an issue of considerable relevance considering that it affects 30–40% of all diabetic patients. In this setting, the inhibition of SGLT1 may be a promising option for achieving better glycemic control [10]. In fact, intestinal SGLT1 is responsible for most of the glucose absorption, and its blockade induces an increased glucose load to the distal gut [10]. This article does not contain any new studies with human or animal subjects performed by any of the authors.

SGLT1 mutations in mouse models may offer valid examples of SGLT1 inhibition because these phenotypes show a lack of effect of SGLT1

in the intestinal lumen with severe osmotic diarrhea and metabolic acidosis caused by the non-absorbed excess of glucose [11, 12]. Of note, the administrations of nonselective and selective SGLT1 inhibitors in humans are not accompanied by these serious adverse effects. Indeed, sotagliflozin, also known as LX4211, a nonselective SGLT2/1 inhibitor, was reported to be safe and well tolerated (namely without gastrointestinal side effects) when administered to 36 patients with T2D in a once-daily oral dose of 150 or 300 mg for 28 days [13]. The main reason for its safety was ascribed to the incomplete inhibition of intestinal SGLT1. Similarly, GSK-1614235, a selective SGLT1 inhibitor, has been administered without serious safety issues to 12 healthy subjects in a 20-mg oral dose in a randomized controlled trial [14]. The plasma concentrations of GSK-1614235 indicated very low levels of the active molecule with rapid clearance and a significant 50% glucose reabsorption reduction compared to placebo. In both studies, SGLT1 inhibitor administration obtained satisfactory glycemic control, suggesting that even a low dose of SGLT1 inhibitors may be sufficient to correct hyperglycemia.

According to the potential of enhanced glycemic control through SGLT1 inhibition that also avoids the glycosuria-related side effects of SGLT2 inhibitors, particularly genitourinary tract infections, Goodwin et al. [15] recently reported the discovery of LX2761, a more potent SGLT1 inhibitor restricted to the intestinal lumen that delays intestinal glucose absorption in vivo. The authors disclosed LX2761 after the methyl substitution of the xyloside core of sotagliflozin, which guaranteed a slightly higher potency at SGLT1 and, more importantly, compatibility with synthesis and starting material availability. As expected with the delayed glucose absorption that is the prevalent mechanism of SGLT1 inhibition in the intestine, male C57 mice treated with LX2761 exhibited a significant increase in cecal glucose levels and decrease in cecal pH due to fermentation of glucose to short chain fatty acids in the cecum. LX2761 was designed to remain in the intestine after oral delivery to inhibit SGLT1 locally without affecting the SGLT1/2 mechanism in the kidney. LX2761

resulted as a chemically stable and very potent inhibitor against SGLT1 and SGLT2 in vitro but acted as a selective SGLT1 inhibitor in vivo in the gastrointestinal tract. This new SGLT1 antagonist could represent a valid therapeutic strategy in the future for the treatment of diabetes, particularly in patients with renal impairment who may benefit less from the renal mechanism of selective SGLT2 inhibitors.

CONCLUSION

In conclusion, further randomized controlled trials comparing the effects of selective and nonselective SGLT1 inhibitors in patients with T2D and concomitant chronic kidney disease are warranted to assess the efficacy and the safety of these drugs according to the extant glomerular filtration rate. Indeed, further stratified analyses in other subgroups of patients with T2D are needed to better elucidate whether those presenting with higher expression levels of renal SGLT1 may be exposed to an increased risk of hypoglycemia or other complications, particularly in the context of the polypharmacy that typically characterizes patients with T2D and other comorbid conditions.

ACKNOWLEDGEMENTS

No funding or sponsorship was received for this study or publication of this article. The article processing charges were funded by the authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Disclosures. Leonardo Spatola, Silvia Finazzi, Claudio Angelini, Marco Dauriz and Salvatore Badalamenti have nothing to disclose.

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