New indications of SGLT2-inhibitors

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Inhibitors of the sodium-glucose cotransporter 2 (SGLT2) are dramatically changing the management of heart failure and, especially, chronic kidney disease. Indeed, this class of drugs, which was initially developed to improve glycemia control in Type 2 diabetics, is now widely recommended by global/international guidelines as part of the standard care for both diabetics and non-diabetics presenting with heart failure and/or albuminuric chronic kidney disease. Indeed, large outcome trials have conclusively demonstrated their efficacy and safety, with some undesirable effects that are easily manageable in clinical practice, such as mycotic genital infection. The key challenge for the coming years is to ensure that the broad population of patients susceptible to benefit from SGLT2-i is actually treated by these drugs. In the near future, additional trials may further enlarge the population targeted by this drug class.

Nouvelles indications des inhibiteurs de SGLT2

Les inhibiteurs du cotransporteur sodium-glucose 2 (SGLT2) modifient radicalement la prise en charge de l'insuffisance cardiaque et, surtout, de la maladie rénale chronique. En effet, cette classe de médicaments, qui a été initialement développée pour améliorer le contrôle de la glycémie chez les diabétiques de type 2, est maintenant largement recommandée par les directives mondiales/internationales comme faisant partie des soins standard pour les diabétiques et les non-diabétiques présentant une insuffisance cardiaque et/ou une maladie rénale chronique albuminurique. En effet, de vastes essais cliniques ont démontré de manière concluante leur efficacité et leur sécurité, avec quelques effets indésirables facilement gérables dans la pratique clinique, tels que l'infection génitale mycotique. Le principal défi pour les années à venir est de veiller à ce que la vaste population de patients susceptibles de bénéficier des SGLT2-i soit effectivement traitée par ces médicaments. Dans un avenir proche, des essais supplémentaires pourraient élargir encore la population ciblée par cette classe de médicaments.

MOTS-CLÉS

Inhibiteurs du cotransporteur sodium-glucose 2 (SGLT2-i), maladie rénale chronique, insuffisance cardiaque, étude contrôlée randomisée, néphroprotection, maladie cardiaque, Directives KDIGO, diabète de type 2

INTRODUCTION

In this paper, I briefly review how sodium-glucose cotransporter 2 inhibitors (SGLT2-i) were first developed as drugs for type 2 diabetes. Next, I review the main results of the large outcome trials, demonstrating a benefit of SGLT2-i for the heart and kidneys. As a nephrologist, I emphasize the trials focusing on the kidney. Lastly, I briefly discuss the safety and tolerance of SGLT2-i, before concluding.

KEY WORDS ▶ **SGLT2-inhibitor, chronic kidney disease, heart failure, randomized controlled trial, nephroprotection, cardiovascular disease, KDIGO guidelines, diabetes type 2**

HOW DID WE GET WHERE WE ARE NOW?

The glucosuric properties of phlorizin were identified more than 140 years ago. The inhibition of glucose reabsorption by the proximal tubule was established almost a century later as the causal mechanism of glucosuria. Indeed, the sodium-glucose cotransporter 2 (SGLT2) is highly expressed in the brush border of the early segment of the kidney proximal tubule and accounts for the reabsorption of most of filtered glucose. The role of SGLT2 in glucose homeostasis is further supported by the identification of homozygous or compound heterozygous variants in the SCL5A2 gene, which encodes for SGLT2, as the cause of renal glucosuria, a rare and benign condition characterized by urinary glucose excretion (60–120 g/day) with normal blood glucose levels (1). As a result of this potential drug target and benign phenotype of familial glucosuria, the pharmaceutical industry developed orally active derivatives of phlorizin. This class of drugs proved effective to improve glucose control first in rats, then in humans.

More importantly, because rosiglitazone, another drug able to improve glucose control in type 2 diabetes, was shown in 2008 to sharply increase the risk of heart failure, drug agencies requested from drug companies considering the development of additional drugs for type 2 diabetes, to demonstrate in large trials not only their efficacy (better glucose control) but also cardiovascular and renal safety (2). As a result, multiple trials were performed with SGLT2-inhibitors. They demonstrated that this class of drugs not only is safe and effective but even associated with definite clinical benefits, both for the heart and kidneys.

CARDIOVASCULAR PROTECTION

Recent cardiovascular outcome trials conducted with SGLT2-i demonstrate a consistent reduction of the risk of hospitalization for heart failure. The included patients were both diabetics and non-diabetics, with a mean age ranging from 66 to 72 years. Around 65% of subjects were males. They were at high cardiovascular risk, with a history of heart failure in 22 to 100% (2).

In a very recent meta-analysis, the authors included 5 randomized controlled trials (DELIVER, EMPEROR-Preserved, DAPA-HF, EMPEROR-Reduced and SOLOIST-WHF). The latter trial randomized to the use of sotagliflozin (that inhibits both SGLT1, mostly expressed in the bowel, and SGLT2) versus placebo. The authors of the meta-analysis conclude that SGLT2-i reduced the risk of cardiovascular death and hospitalisation for heart failure in a broad range of patients with heart failure, supporting their role as a foundational therapy for heart failure, irrespective of ejection fraction or care setting (3). Of interest, the benefit associated with SGLT2-inhibition was remarkably similar and consistent in diabetics and non-diabetics.

Not surprisingly, the role of SGLT2-i in the management of heart failure is already recognized by the most recent update of Guidelines, both in Europe and the USA (4,5). The reader interested by an in-depth discussion of the cardiovascular benefits of SGLT2-i may refer to a very recent review by Braunwald in the New England Journal of Medicine (2).

NEPHROPROTECTION

The first signal of a potential benefit on the kidney was obtained when a prespecified secondary analysis of the EMPAREG-Outcome trial was performed in a population of patients with type 2 diabetes at high cardiovascular risk but mostly without severe CKD. The risk of the renal outcome of incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal replacement therapy, or death from renal disease) was reduced by 39% in patients randomized to empagliflozin 10 or 25 mg versus placebo (6).

CREDENCE subsequently was the first randomized controlled trial to assess the efficacy and safety of SGLT-i on a primary kidney outcome. The study included over 4400 patients with type 2 diabetes and CKD (an eGFR of 30–90 ml/min per 1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 300–5000 mg/g). Participants were randomly assigned to receive either canagliflozin 100 mg o.d. or placebo, on top of RAS inhibition, given to >99% of patients. After a median follow-up of 2.6 years, the relative risk of the primary composite outcome of kidney failure (dialysis, transplantation or a sustained eGFR <15 ml/min), a doubling of serum creatinine level, or death from cardiovascular or kidney disease was 30% lower in the canagliflozin group, irrespective of the severity of CKD or the level of albuminuria at inclusion (7). Safety and tolerance were excellent. A post-hoc analysis of CREDENCE showed that the effects of canagliflozin on kidney, cardiovascular, and mortality outcomes were consistent for the subgroup of patients with a baseline eGFR < 30 ml/min/1.73m^2

The DAPA-CKD trial investigated the renal benefit of dapagliflozin (10 mg daily) in over 4300 patients with CKD (eGFR 25–75 ml/min/1.73 m^2 and UACR 200–5000 mg/g) (8). Fifteen percent of the participants had an eGFR <30 ml/min 1.73 m^2), 33% did not have diabetes, and 98% were treated

with RAS inhibitors. The primary outcome was a composite of sustained decline in eGFR of 50% or more, kidney failure (eGFR <15 ml/min, need for dialysis or transplantation) or death from a kidney disease-related or cardiovascular cause. The trial was stopped early after a median of 2.4 years because of the superiority of dapagliflozin compared to placebo. Dapagliflozin reduced by 39% the risk of the primary composite, a benefit independent of the severity of CKD, level of albuminuria and presence of diabetes.

Dapagliflozin also contributed to better preservation of kidney function (loss of eGFR >50%, –44%); reduction in the need for kidney replacement therapy (–34%); and better cardiovascular and survival outcomes (hospitalization for heart failure or death from cardiovascular causes, –29%; death from any cause, –31%). Safety and tolerance were excellent.

Of note, CREDENCE and DAPA-CKD included patients with relatively high levels of albuminuria (UACR ≥300 and ≥200 mg/g, respectively). The EMPA-KIDNEY trial is designed to answer whether progression of CKD can be delayed too in patients with a low eGFR (20-45) and lower levels of albuminuria. The primary results should be presented this fall at the American Society of Nephrology.

Pre-specified analyses of the DAPA-CKD trial demonstrated the effects of dapagliflozin on major adverse kidney events in subgroups of patients with primary glomerular diseases and albuminuria, such as in IgA nephropathy and focal segmental glomerulosclerosis. Interestingly, in DAPA-CKD, dapagliflozin also reduced (rather than increased) quite significantly the risk of acute kidney injury (AKI). It should be mentioned that these outcome trials excluded patients with lupus nephritis, ANCA vasculitis and autosomal dominant polycystic kidney disease, and the potential benefits of SGLT2 inhibitors in these populations have not yet been investigated.

Altogether, CREDENCE and DAPA-CKD provided concordant, solid evidence that SGLT2 inhibitors slow down the progression of kidney disease, irrespective of the presence of diabetes, the severity of CKD and level of proteinuria, on top of standard of care including the use of RAS blockers.

The mechanisms through which SGLT2 inhibitors improve kidney outcomes remain incompletely understood and are almost certainly multifactorial. Renoprotection conferred by gliflozins is not explained by consequences on plasma glucose concentrations, blood pressure, and body weight. Additional potential mechanisms notably include impact on intraglomerular hemodynamics, and the derived impact on albuminuria; podocyte integrity; cell metabolism, hypoxia and erythropoiesis; and inflammation and fibrosis. Their detailed discussion is beyond the scope of this brief contribution.

SAFETY AND TOLERANCE OF SGLT2-i

The most common adverse effect of SGLT2-I is genital mycotic infection, reported in 2–7% of the patients in large outcome trials (1). Patients with immobility, incontinence, intertrigo in the groin region, chronic diarrhea, or inability to maintain genital hygiene are at increased risk and the risk-benefit balance should be carefully weighed before initiating a SGLT2 inhibitor in this population. Prophylactic topical antifungal medication may be considered in selected high-risk patients. Importantly, the use of SGLT2 inhibitors is not associated with an increased risk of urinary tract infection.

A relatively rare but severe adverse effect is euglycemic ketoacidosis. Diagnosis is challenging as glycemia may be normal or only mildly elevated, and symptoms are non-specific. Prevention is important, and patients should be advised to maintain appropriate fluid intake; ensure adequate carbohydrate intake and avoid low-carbohydrate diets; avoid skipping insulin and skipping meals; temporary discontinuation of SGLT2 inhibitors may be wise in situations of acute illness, vomiting, diarrhea, inability to eat or drink, and before an elective surgical or invasive procedure (9). Treatment relies on drug discontinuation, restoration of extracellular fluid volume, and insulin supplementation; alkali therapy might be useful in patients with CKD and in those with severe acidemia.

Mild volume depletion is also frequent at the start of SGLT2-i. This is welcome in most patients but it is important carefully assess fluid balance, consider initially decreasing the dose of diuretics, especially if high, and monitor volume status after treatment initiation, especially in high risk patients such as the elderly, severe heart failure and severe CKD patients (9).

Finally, SGLT2 inhibitors cause a modest decrease in eGFR after initiation, resulting from improved glomerular hemodynamics. Decrease in eGFR is reversible, does not preclude long-term benefits on eGFR, and should not prompt drug discontinuation (9).

A last point deserves a mention here: whereas diuretics, commonly used in the management of heart failure and CKD patients increase uric acid plasma level, SGLT2-i on the contrary decrease the uric acid level. Thus, it should not come as a surprise that a recent large observational study showed that being under an SGLT2-i independently reduced the risk of gout in diabetics in Taiwan (10).

CONCLUSION

SGLT2-i are now widely recommended by global/international guidelines as part of the standard of care of both diabetics and non-diabetics in heart failure and albuminuric chronic kidney disease, because these drugs are safe and effective. The key challenge for the coming years will be to make sure that the broad population of patients susceptible to benefit from SGLT2-i is actually treated. Additional ongoing trials may further broaden in the near future the target populations.

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