A new role of SGLT-2 — treatment of IgA-nephropathy?

Syeda Zeenat Sahar Junaid,[1] Muhammad Muntazir Mehdi Khan,[2] Henna Fatma[3]

Madam, Sodium Glucose co-transporter 2 inhibitors (SGLT2) paved their way into traditional science books less than a decade ago as a new class of drugs treating diabetes. However, the ongoing discovery of their ever-widening array of uses shows that we are still yet to tap into their full potential. SGLT2 inhibitors or the "gliflozins" selectively target SGLT2 co-transporters in proximal tubules of the nephron. The inhibition reduces the renal threshold for glucose reabsorption, resulting in glucosuria and lowering blood glucose levels. They have added benefits in kidney and cardiovascular outcomes in diabetics. These positive reno-protective effects are not just exclusively for diabetic patients- non-diabetic chronic kidney disease (CKD) may benefit from gliflozins.

Ig-A nephropathy (IGAN) is the most common glomerulonephritis worldwide. There is no population-based prevalence in Pakistan, but various centres have reported a prevalence between 2-20.83%.[1] A multitude of drug candidates have been investigated to halt disease progression, including RAAS inhibitors, steroids and immunosuppressants, but have not shown significant utility.

Within this class of drugs, dapagliflozin has emerged as a novel therapeutic option to slow kidney function decline in patients with IgA nephropathy. In a pre-specified analysis of the DAPA-CKD trial, a subset of patients having IgAN was evaluated.[2] Of the 270 patients, 137 were provided dapagliflozin and 133 a placebo and followed for median of 2.1 years. The primary outcome was a steady reduction in eGFR of 50% or more, end-stage kidney disease, or mortality from a kidney disease-related or cardiovascular cause. Primary outcome occurred with 4% participants on dapagliflozin and 15% on placebo. The mean rates of eGFR decline with dapagliflozin were lesser compared to placebo. Adverse events were not particularly high in the group randomized to dapagliflozin compared to placebo and no increase in risk of ketoacidosis or hypoglycaemia in the dapagliflozin group.

Various compelling explanations for this amelioration of the eGFR decline in patients receiving SGLT2 include the reduction in intra-glomerular pressures, natriuresis and improved blood pressure control,[3] direct action on endothelial cells, modulating the effects of adhesion molecules and reducing inflammatory cytokines and reactive oxygen species. Some data suggest anti-inflammatory and antifibrotic effects on renal tubules.[4]

For a long time, there has been a shortage in the armamentarium of drugs that can substantially reduce progression to kidney failure in IgAN. The results from the upcoming EMPA-kidney trial can bring more exciting developments.[5] Pakistan has always been at the forefront in countering IgAN, and it is worth the time and effort to explore SGLT2 inhibitors more proactively.

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[1]Aga Khan University Hospital, Karachi, [2]5th Year MBBS Student, [3]Department of Internal Medicine, Aga Khan University Hospital, Karachi, Pakistan.
Correspondence: Muhammad Muntazir Mehdi Khan.
Email: muntazir.khan@scholar.aku.edu
ORCID ID. 0000-0001-7196-2328
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