SGLT2 Inhibitors for the Management of IgA Nephropathy: A New Therapeutic Paradigm for an Old Entity?

By George Vasquez-Rios

Immunglobulin A nephropathy (IgAN) is the most common glomerular disease worldwide (1). The prevalence varies geographically, and estimates of disease burden depend on the registry data assessed. The pathophysiology of this condition includes circulating and glomerular immune complexes comprised of galactose-deficient IgA1, an IgA autoantigen (directed against the hinge region O-glycan), and C3 (1). Experimental models suggest that environmental factors can trigger aberrant IgA production in highly active sites such as the mucosal-associated lymphoid tissue (MALT) in the gastrointestinal tract, which ultimately leads to immune complex deposition in key compartments of the kidney. Mesangial cells serve not only as a glomerular capillary support network but also as highly reactive elements capable of producing inflammatory mediators after contact with IgA, leading to mesangial expansion, matrix production, and an endothelial influx of inflammatory cells (2).

Whereas the immune-mediated nature of this condition is recognized and a topic of active study, treating patients with IgAN with immunomodulatory therapies has provided inconsistent results. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines reported the first attempt to summarize the results of the literature including the role of steroids for patients with relatively preserved kidney function (estimated glomerular filtration rate [eGFR] > 50 mL/min/1.73 m2) who had persistent proteinuria >1 g/day; despite 3–6 months of maximal renin-angiotensin-aldosterone system (RAAS) blockade (“standard of care”) (3–5). In 2015, the STOP-IgA (Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy) study included 162 participants who were randomly allocated to receive standard of care (n = 80) for 6 months, adequate blood pressure and lipid profile control, as well as diet counseling, whereas 82 participants were administered immunosuppressive therapy with methylprednisolone (n = 55); those with an eGFR > 60 mL/min/1.73 m2 or cyclophosphamide C, followed by azathio- prine plus prednisolone (n = 27); those with an eGFR 30–59 mL/min/1.73 m2 (6). The STOP-IgA trial provided the important finding that adding immunosuppressive therapy to optimal standard of care may not provide substantial kidney-related benefits in patients with high-risk IgAN.

Furthermore, although the addition of immunosuppressive therapy reduced the risk of proteinuria in a subgroup of patients, there was no significant difference between the immunosuppression and the standard-of-care group with regard to reducing renal kidney function decline or kidney events in the pooled analysis. This is in contrast to previous studies that had suggested a potential benefit from immunosuppressive drugs in patients with severe histological lesions, according to the Oxford Classification (MEST-C) (7); rapidly progressive kidney disease; and high proteinuria (7–9).

Subsequently, the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study recruited 262 participants with an eGFR of 20–120 mL/min/1.73 m2 and proteinuria (>1 g/day) who were randomized to receive oral methylprednisolone (0.6–0.8 mg/kg/day) versus placebo before weaning over 4–6 months (10). The study was prematurely terminated due to the high incidence of side effects in the treatment group. Since then, the TESTING Low Dose study (ClinicalTrials.gov: NCT01560052) has been actively recruiting patients with an estimated completion date of June 2023 (methylprednisolone 0.4 mg/kg/day vs. placebo). Need for IgAN progression therapies

Because most of the clinical trials in IgAN have been limited by small sample sizes, short follow-up periods, lack of histologic data, or heterogeneity of immunosuppressive regimens, the decision to treat with immunomodulators should be carefully individualized based on key parameters, including degree of proteinuria, extent of fibrosis vs. active histological lesions (which offer a window of opportunity), as well as the side effect profile of the given drug. Therefore, there is still a need for other therapeutic interventions for patients at high risk of progression.

Recently, a pre-specified analysis from the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial was published. This ascertained the effects of sodium glucose co-transporter 2 (SGLT2) inhibitors on the primary composite endpoint of a sustained eGFR decline of ≥50% (confirmed by a second creatinine measurement after at least 28 days), progression to end stage kidney disease (ESKD); defined as maintenance dialysis for at least 4 weeks, kidney transplantation, or an eGFR < 15 mL/min/1.73 m2, or death from a kidney or cardiovascular cause over a median follow-up period of 2.1 years (11).

The study—a clinical trial with the largest number of IgAN patients to date—included 270 participants with investiga- tor-reported IgAN of whom 254 (94%) had a biopsy-proven diagnosis. The study population was characterized by middle-aged adults, primarily of Caucasian or Asian ethnicity, with a low prevalence of diabetes mellitus, a mean eGFR of 43.8 mL/min/1.73 m2, and a median urinary albumin-to-creatinine ratio (uACR) of 900 mg/g. Participants had been taking either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) for at least 4 weeks before randomization. No data were presented for mineralocorticoid receptor blocker use, although heart failure prevalence was low.

The primary outcome occurred in 6 (4%) participants in the treatment arm and in 20 (15%) in the placebo arm (hazard ratio [HR]: 0.29; 95% confidence interval [CI], 0.12–0.73). Additionally, the least mean squares eGFR slopes from baseline to end of treatment in the dapagliflozin group were −3.9 mL/min/1.73 m2 per year compared to −4.7 mL/min/1.73 m2 per year in the placebo group, resulting in a between-group difference of 1.2 mL/min/1.73 m2 per year (95% CI, −0.12 to 2.51 mL/min/1.73 m2 per year). These findings were consistent when evaluated by prespecified baseline eGFR and uACR categories.

Similar to the results in the entire cohort in patients in CREDENCE and DAPA-CKD trials, patients in the study group exhibited reversible eGFR re- ductions during the first 4 weeks of ther- apy initiation that progressively stabilized. Also, the mean percentage difference in uACR between dapagliflozin and placebo at month 4 was −35% (95% CI, −51 to −18.9, p < 0.001), which seemed to persist throughout the study. In addition, blood pressure recordings were lower in the treat- ment group compared to the placebo group. Adverse events that prompted discontinua- tion of the study drug were comparable in the treatment (6/137) and placebo (7/133) groups. However, serious adverse events were recorded more frequently in the placebo group (12.1% vs. 25.6%).

The implications of these results are striking and confront us with a new para- digm in the treatment approach of IgAN. SGLT2 inhibitors exhibit different mecha- nisms within the kidney and in distant organs. Blocking Na-mediated glucose reabsorption in the proximal segments of the nephron increases the distal delivery of Na+ and Cl− to the macula densa, thereby inducing a tubuloglomerular feedback that results in constriction of the afferent artery. Reduction of the intraglomerular pressure, and consequently albuminuria (12).

Such hemodynamic effects could sig- nificantly alleviate the sheare stress of sensitiv- e structures such as podocytes that have been implicated in the pathophysiology of diabetic kidney disease (DKD) and could arguably play a role in IgAN progression (13). Furthermore, the natriuretic effect of SGLT2 inhibitors along with their effects on weight reduction, which are known risk factors for high intraglomerular pressure and disease progression in IgAN, could help in blood pressure control (14). As compared to previous results in Canagliflo- zin and Renal Events in Diabetes with Estab- lished Nephropathy Clinical Evaluation (CREDENCE) and DAPA-CKD trials, the effects of dapagliflozin on the primary outcome among IgAN patients are very pronounced starting at month 8, suggesting that not only are immediate hemodynamic effects involved, but also presumably cellular and metabolic effects play a significant role.
Plots of effects of SGLT2 inhibitors include modulation of inflammatory and profibrotic mediators and regulation of toxic intracellular compounds (i.e., advanced glycation end products), among others, as demonstrated in models of type 2 diabetes mellitus (15). However, the role of these factors in the pathogenesis of IgAN is less certain. It is accepted that currently employed immunosuppressive strategies lack conclusive efficacy data, as there is a high-risk toxicity profile. Interestingly, it is possible that addressing data, as there is a high-risk toxicity profile. An interesting observation during the course of the DAPA-CKD trial was that patients with kidney disease progression. Research is needed to ascertain how much of the benefits seen in the treatment group could be attributed to weight loss and blood pressure reduction, which are attainable with other less expensive and evidence-supported medications.

Certainly, recommendations on the RAAS blockade in IgAN are supported by small studies that have shown reduction in proteinuria and less kidney function deterioration. Nonetheless, none of the AEs or ARB trials have shown the significant biomarker stabilization and outcome improvements demonstrated by dapagliflozin (16–18). Moreover, the study population in this pre-specified subgroup seemed to exhibit a high risk for kidney disease progression. When observing the cumulative incidence of the primary endpoint among the patients in the placebo group by month 32, approximately 24% had experienced a combination of sustained eGFR reduction ≥50%, progression toward ESKD, or death from a kidney or cardiovascular cause, which suggests that there was a high rate of rapid progression in the latter group.

Therefore, the effectiveness of dapagliflozin as a co-adjutant therapy in high-risk patients should be carefully examined. Important areas of uncertainty include the safety of using SGLT2 inhibitors in patients with IgAN treated with immunosuppression (excluded in DAPA-CKD) and whether this class could be similarly beneficial among patients with lower levels of albuminuria. Although the results remain consistent when stratified by eGFR (≥85 or <85 mL/min/1.73 m²) and uACR (>1000 or <1000 mg/g per day), the effects of SGLT2 inhibitors should be carefully ascertained in both rapid and slow progressors. Moreover, it is necessary that future studies include more heterogeneous populations such as patients of African ancestry, who are documented to have increased risk for kidney progression and who have been largely underrepresented in IgAN studies (3, 19, 20).

Despite the aforementioned caveats, SGLT2 inhibitors continue to serve as an attractive therapeutic option for a vast number of patients with kidney disease. Clinical trials such as DAPA-CKD are changing the way we understand kidney disease and “raising the bar” for other candidate therapies in this field. The investigators deserve recognition for designing DAPA-CKD as the first event-driven trial of an SGLT2 inhibitor that included patients with CKD due to a broad range of etiologies such as IgAN. SGLT2 inhibitors could be considered as an “add-on” therapy when stabilization of clinical parameters is still needed despite optimal standard of care. Alternatively, they could be used in patients who are intolerant to RAAS blockades.

Future studies should evaluate the effects of SGLT2 inhibitors in a larger population of patients whose standard therapy is optional to uncover their true potential and to evaluate their safety profile when immunosuppressive therapy is concomitantly administered. Finally, although The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY; ClinicalTrials.gov: NCT03594110) should reveal the efficacy and tolerability of SGLT2 inhibitors in patients with non-diabetic CKD, dedicated IgAN trials are very much needed to continue advancing our knowledge of this condition and individualized interventions.

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References