SGLT-2 inhibition in IgA nephropathy: the new standard of care?

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Despite supportive measures that slow the rate of progression of chronic kidney disease in IgA nephropathy, many patients still progress to end-stage kidney disease. Currently employed immunosuppressive strategies lack conclusive efficacy data, while there is evidence for treatment-emergent toxicity. A subanalysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease Trial, which encompassed 270 patients with a diagnosis of IgA nephropathy, now provides early evidence that dapagliflozin may be a safe and effective addition to current standard of care in IgA nephropathy.

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The current standard of care for the management of IgA nephropathy (IgAN) is intensive goal-directed supportive care. The Supportive Versus Immunosuppressive Therapy of Progressive IgA nephropathy (STOP) IgAN trial study clearly demonstrated the benefit of rigorous blood pressure control, maximization of renin-angiotensin system inhibitors (RASi) combined with focused lifestyle modification on slowing the rate of progression of chronic kidney disease (CKD) in IgAN.[1] However, the long-term outcomes of STOP-IgAN show us that even with this approach a significant number of patients with IgAN will experience kidney function decline and progress to end-stage kidney disease.[2] There is a desperate need for safe and effective therapies to treat those patients who remain at high risk of progressive CKD despite optimized supportive care.[3] Currently employed immunosuppressive strategies lack conclusive efficacy data, while there is widely accepted evidence for treatment-emergent toxicity (Rovin BH, Adler SG, Barratt J, *et al.* Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases, unpublished data).[1,4] The article by Wheeler *et al.* in this issue[5] provides early evidence that sodium-glucose cotransporter-2 (SGLT2) inhibitors may be a safe and effective addition to current standard of care in IgAN.

The Dapagliflozin and Prevention of Adverse Outcomes in CKD Trial (DAPA-CKD) randomized 4304 patients with CKD, with or without type 2 diabetes, to either dapagliflozin or placebo.[6,7] The trial was prematurely terminated because of efficacy, with the dapagliflozin group experiencing significantly fewer primary outcome events (composite of a sustained decline in the estimated glomerular filtration rate (GFR) of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes) over a median of 2.4 years. There were 270 participants within DAPA-CKD with a diagnosis of IgAN; and as part of a prespecified analysis, this subgroup of patients has been analyzed separately and these data are presented in this issue. Of the 270 patients, 137 were randomized to dapagliflozin and 133 to placebo. As in the overall study, use of dapagliflozin was associated with a significant reduction in the frequency of the primary outcome; and in the IgAN cohort, dapagliflozin use resulted in a slowing of the rate of kidney function decline and a reduction in albuminuria.

So how should we view these new data in the context of current standard-of-care treatment for IgAN? Unlike trials specifically focusing on IgAN, in DAPA-CKD, patients with IgAN did not need to be on optimized stable supportive care for a minimum of 90 days before entry into the study. Although all patients did have to be on a stable RASi dose for at least 4 weeks before enrollment, it is not clear from the data available whether RASi dosage had been proactively maximized. In STOP-IgAN, 1 in 3 patients referred for a trial of immunosuppression because they remained at high risk of progression despite "standard therapy" responded to supportive care optimization, such that their proteinuria fell below the inclusion threshold of 0.75 g/d. It is therefore difficult to know in the DAPA-CKD IgAN cohort how much improvement could have been achieved by optimization of currently available treatments before addition of dapagliflozin. This is important when we consider how SGLT2 inhibitors are postulated to act in the kidney. As Wheeler *et al.* state, clinical studies have consistently shown an early and reversible reduction in estimated GFR on initiation of SGLT2 inhibition, suggesting that their renoprotective and antiproteinuric effect may be mediated by a reduction in intraglomerular pressure. Maximization of RASi, optimal blood pressure control, dietary sodium restriction, and lifestyle

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Table 1 | Predicted outcome of the IgAN cohort in DAPA-CKD based on the International IgAN Risk Prediction Tool

Parameter	Baseline characteristics of DAPA-CKD IgAN cohort
Estimated GFR at biopsy, ml/min per 1.73 m^2	44
Systolic blood pressure at biopsy, mm Hg	127
Diastolic blood pressure at biopsy, mm Hg	79
Proteinuria at biopsy, g/d[a]	1.5
Age at biopsy, yr	51
Race	Assuming all were Chinese (in reality, 58.9% of the population were Asian[b]; 40% were White)
Use of ACE inhibitor or ARB at the time of biopsy	Yes (RAS blockade in 100% of the population)
Immunosuppression use at or before biopsy	No
Fictional MEST score[c]	Scenario A: M1, E1, S1, T1 Scenario B: M0, E0, S1, T2
Predicted risk of a 50% decline in estimated GFR or progression to end-stage renal disease 32 mo after renal biopsy	Scenario A: 6.97% Scenario B: 9.99% Scenario B + all White race: 14.48% Scenario B + prior immunosuppression[d] + Japanese: 17.13%

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease Trial; GFR, glomerular filtration rate; IgAN, IgA nephropathy; MEST score, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T); RAS, renin-angiotensin system.

[a]In DAPA-CKD, only albumin-creatinine ratios were available. The median was 0.9 g/g in the IgAN cohort, which we assumed to roughly correspond to an average proteinuria of 1.5 g/d.

[b]DAPA-CKD study sites (N = 392 total) in Asia included China (N = 32), India (N = 18), Japan (N = 49), Korea (N = 16), Philippines (N = 10), and Vietnam (N = 8).

[c]Given a baseline estimated GFR of 44 ml/min per 1.73 m^2, some glomerular scarring (S1) and tubulointerstitial fibrosis (T1 to T2) is expected, whereas often in such patients the more inflammatory, acute changes are variable (i.e., M and E lesions).

[d]The DAPA-CKD study protocol specified that exclusion criteria included patients receiving immunotherapy for primary or secondary kidney disease within the previous 6 months before trial enrollment.

The International IgAN Risk Prediction Tool is available at www.qxmd.com. The table illustrates the risks of progression in hypothetical scenarios where this combination of data was available for a patient within 6 months of kidney biopsy.

modification similarly reduce intraglomerular pressure and, therefore, how much additional reduction (and renoprotection) would be gained from SGLT2 inhibition in a patient on optimized standard-of-care treatment is unclear.

A key foundation of optimized supportive care in IgAN is rigorous blood pressure control. The relationship between improved blood pressure control, reduction in proteinuria, and renoprotection has long been established. In fact, it has been recognized for decades, that even seemingly small differences in blood pressure of the order of 6–7 mm Hg can determine whether GFR loss in IgAN patients is progressive or negligible.[6] In DAPA-CKD, dapagliflozin treatment was associated with a significant reduction in blood pressure of the order of 3–4 mm Hg during follow-up, and it is unclear how much this difference in blood pressure contributed to the difference in outcomes between the groups. It is not stated whether this difference in blood pressure might have related to SGLT2 inhibitor–induced weight loss, which is another important pillar in the supportive care approach in IgAN. Again, as it is not known whether this cohort of IgAN patients were receiving optimized supportive care, it is difficult to determine whether a similar improvement in blood pressure control, with the consequential fall in proteinuria and renoprotection, could have been achieved by adjustments of standard of care, in particular optimization of RASi.

A notable feature in the DAPA-CKD IgAN cohort is the frequent occurrence of the primary composite end point in the placebo control group. Thus, in the cumulative incidence curves at 32 months, almost 24% of this group exhibited a >50% decline in estimated GFR or had reached end-stage kidney disease (the number of deaths was not specified but likely was low in this group). Using these 2 key outcomes (i.e., 50% loss in estimated GFR or end-stage kidney disease), we have entered the "average DAPA-CKD IgAN patient" into the International IgAN risk prediction tool.[8] As shown in Table 1, the calculated risk for either outcome at 32 months ranges from 7%–10% using the prediction tool (i.e., less than half of that observed in the IgAN patients assigned to placebo in DAPA-CKD). In fact, the outcome in the dapagliflozin group was much closer to what the risk prediction tool would have predicted, except that the prediction tool was derived from clinical data that antedated the advent of SGLT2 inhibitors. Only when you assume that all DAPA-CKD patients with IgAN had been from Japan, a country with the highest risk of progression in IgAN and where immunosuppression is widely used to treat IgAN, and that all had extensive tubulointerstitial fibrosis (i.e., the T2 lesion) did we obtain estimates somewhat closer to those observed in the placebo group. However, this was not the case in the study of Wheeler *et al.*,[5] where only 58.9% of the participants were Asian and only 49 of 133 Asian trial sites were in Japan. Coexistent diabetes in 38 of the 270 IgAN patients in the study is also an unlikely explanation for the high number of events in the placebo group, as the risk reduction was similar with dapagliflozin after excluding the diabetic IgAN patients. We are thus left once again with the

speculation that supportive care may not have been used to its full extent in the population studied.

Safety of dapagliflozin in IgAN patients was reported as excellent, with no cases of major hypoglycemia and in particular no case of ketoacidosis. Even though the authors were unable to specify the frequency of genital mycoses, this is unlikely a major problem, because it is believed to relate to glucosuria supporting candida growth and the extent of glucosuria in nondiabetic IgAN patients will be lower than that of patients with diabetic kidney disease.

In summary, the authors are to be congratulated for performing one of the world's largest randomized controlled trials in IgAN patients. The renal benefits of adding dapagliflozin on top of RASi are remarkable in an otherwise high-risk group for further progression and, even more remarkable, the intervention is easy and safe. So, should we give SGLT2 inhibitors on top of RASi to all high-risk patients with IgAN from now on? Given our concerns that inexpensive standard therapy, in particular established supportive measures, may not have been optimized in the IgAN cohort studied, we currently do not (yet) believe so. Rather, we suggest waiting for the outcome of the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) trial (ClinicalTrials.gov Identifier: NCT03594110) or even better, the outcome of a future, dedicated trial in IgAN where SGLT2 inhibition is given on top of optimized supportive care.

DISCLOSURE

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REFERENCES

1. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med*. 2015;373:2225–2236.
2. Rauen T, Wied S, Fitzner C, et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. *Kidney Int*. 2020;98:1044–1052.
3. Floege J, Barbour SJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;95:268–280.
4. Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING Randomized Clinical Trial. *JAMA*. 2017;318:432–442.
5. Wheeler DC, Toto RD, Stefansson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy [e-pub ahead of print]. *Kidney Int*. https://doi.org/10.1016/j.kint.2021.03.033.
6. Kanno Y, Okada H, Saruta T, et al. Blood pressure reduction associated with preservation of renal function in hypertensive patients with IgA nephropathy: a 3-year follow-up. *Clin Nephrol*. 2000;54:360–365.
7. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446.
8. Barbour SJ, Coppo R, Zhang H, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. *JAMA Intern Med*. 2019;179:942–952.