

Journal of Nephro-pathology

CrossMark
click for updates

Administration of sodium-glucose cotransporter-2 inhibitors in IgA nephropathy; a new strategy in the management?

Anastasia Dieti^{1#}, Yeganeh Ragati Haghi^{2#}, Majid Forootan^{3*}¹Department of Life Sciences, School of Sciences, European University Cyprus, Nicosia 2404, Cyprus²Massachusetts College of Pharmacy and Health Sciences - Worcester Campus: Worcester, MA, USA³Department of Internal Medicine, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran

#Anastasia Dieti and Yeganeh Ragati Haghi contributed equally to this paper.

ARTICLE INFO

Article type:
Min-Review*Article history:*
Received: 12 December 2022
Accepted: 1 February 2023
Published online: 4 February 2023*Keywords:*
Sodium-glucose cotransporter-2 inhibitors, Chronic kidney disease, IgA-nephropathy, Diabetic kidney disease, Acute kidney disease, Albuminuria

ABSTRACT

Some of the several effects of sodium-glucose cotransporter-2 inhibitors (SGLT-2i), including their metabolic, anti-inflammatory and hemodynamic properties, along with other kidney protective values, have directed clinicians to give these drugs in IgA-nephropathy (IgAN). According to recent studies regarding the beneficial effects of SGLT-2i on IgAN, it is clear that clinicians are changing their approach towards kidney transplantation when it comes to aggressive immunosuppression. This mini-review aims towards the evaluation of the protective efficacy of SGLT-2i in IgA-nephropathy.

Implication for health policy/practice/research/medical education:

Sodium-glucose cotransporter-2 inhibitors can provide a new strategy to prevent progression of chronic renal failure in individuals with IgA-nephropathy.

Please cite this paper as: Dieti A, Ragati Haghi Y, Forootan M. Administration of sodium-glucose cotransporter-2 inhibitors in IgA nephropathy; a new strategy in the management? J Nephro-pathol. 2023;12(2):e21429. DOI: 10.34172/jnp.2023.21429.

Introduction

IgA-nephropathy (IgAN) has been identified as the furthest common type of glomerulopathy (1), and is responsible for a noteworthy percentage of the end-stage renal disease burden worldwide (2). It constitutes a well-identified form of progressive chronic renal failure (3); however, the clinical course of the IgAN varies from isolated hematuria, microscopic or macroscopic, none-nephrotic range proteinuria, nephrotic syndrome to rapidly progressive kidney disturbances (4). It appears that various environmental factors can stimulate aberrant immunoglobulin-A (IgA) production in areas such as the mucosal-related lymphoid tissue of the alimentary tract, resulting in immune complex deposition in the glomerular structures of the Kidneys (1-3). Renal biopsy, which is necessary for the definitive diagnosis of IgAN, can result in a range of observations including mild

proliferation to significant extra-capillary proliferation of mesangial cells (4). The disease is caused by the dominant mesangial IgA1-immune complex deposits in the mesangial area of the glomeruli (5). These immune complexes are the result of autoimmune IgG recognizing circulating IgA1 as an auto-antigen, therefore classifying IgAN as an autoimmune disease, which results in the accumulation and deposition of pathogenic circulatory IgA1-immune complexes within glomerular structures (6). Mesangial deposition of immune complexes, results in the activation and proliferation of these cells, and the subsequent secretion of pro-inflammatory cytokines, leading to tissue injury and disease development (6). It is suggested that the progression of immunoglobulin-A nephropathy is conducted through a four-hit processes, which is initiated with aberrant glycosylation of IgA1 and increase circulation of these galactose deficient

*Corresponding author: Majid Forootan,
Email: dr_forootan@yahoo.com

IgA1 (Gd-IgA1), the subsequent generation of auto-antibodies targeted against circulating Gd-IgA1, and the formation of immune complexes, some of which become deposited within the glomerulus structure and initiating tissue damage (1,2). In general, IgAN is most dominant in Asians, also observed in Caucasians, however, it is not as common in Africans (7). In most adult cases of IgAN, disease progresses gradually, its characterised by a considerable initial reduction in glomerular filtration rate, accompanied by persistent microhematuria and hypertension along with mild to moderate proteinuria (1). A higher disease progression risk, which leads to more serious clinical features, is observed in Asian populations (7) with endocapillary or extra-capillary proliferation being further detected in Asian versus European patients (7). Several investigations have demonstrated the effects on control of blood pressure. Full suppression of renin-angiotensin system would slow down the development of chronic renal failure during disease (8). However, results from long-term studies demonstrated that, even with this modality, a substantial group of IgAN cases continue into reduction of renal function and end-stage kidney failure (9). Moreover, treatment with immunosuppressives results in resolving proteinuria in some cases, while, no noteworthy difference is detectable in renal function reduction between the immunosuppressive and conventional treatments. Findings from earlier studies suggest a significant effect from immunosuppressive therapy in cases with profound pathological features (10), as well as in cases with rapidly progressive kidney disease and massive proteinuria (10). Although several studies have shown that aggressive forms of IgAN respond appropriately to immunosuppressive strategies like steroids and other immunosuppressive treatments, which could produce a significant ameliorative impact on the development of disease, the adverse effects of these drugs impose a hesitancy in their continues use as treatment options (3). Since most studies on IgAN have had some limitations such as short follow-up, or small sample sizes, judgement on administration of immunomodulatory drugs should be vigilantly personalized according to the patients' condition, taking into consideration the factors such as the quantity of proteinuria, glomerular filtration rate and/or proportion of fibrosis versus active morphological lesions in biopsy and most importantly, the adverse effects of the administered drug (1-3). Therefore, there is a necessity for new and effective drugs to be used in high-risk cases of IgAN progression. The idea of slowing down the progression of disease in chronic types of IgAN, subsequently leading to chronic kidney disease, has recently attracted clinicians, and most physicians still remain under the impression that aiming the upstream immunopathogenesis of this disease

is the best way of dealing with the disease. Hence, most of the IgAN patients still remain under treatment with immunosuppressive agents (3,11). In a recent randomised clinical trial, involving patients with chronic renal failure, the administration of dapagliflozin compared to placebo, resulted in lowering the risk of renal failure and prolonged the survival of patients with chronic kidney disease (12). Out of the 270 participants (with and without type-2 diabetes) that took part in this study, 94% were also confirmed for IgAN via biopsy. Out of these, 137 were randomized to dapagliflozin and 133 received placebo (median follow up was 2.1 years). The results of this study have shown that dapagliflozin, a sodium-glucose cotransporter 2 inhibitor, reduced the urine to creatine ratio by 26% compared to the control group that received the placebo. Additionally, no significant adverse effects were reported in the test-group that received dapagliflozin. The results of this study clearly show that the use of dapagliflozin as treatment could significantly lessen the risk of renal failure and extend kidney survival in patients with chronic disease (12), rendering the use of the particular drug as a promising therapy in IgAN.

Another recent study addressed the cardiovascular safety of the use of anti-diabetic drugs, by the conduction of a randomized clinical trial where Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) were administered to individuals with type-2 diabetes. Interestingly, SGLT-2i were shown to lower that rate of progression of renal failure at baseline, in patients with and without established chronic kidney disease, while they significantly lowered the rate of hospitalization as well as subsequent deaths due to cardiovascular disease (13-17).

Additionally, the above mentioned studies have also shown that inhibition caused by SGLT-2i is equally effective in diabetic versus non-diabetic chronic renal failure cases with proteinuria, which implies that the management and treatment of chronic renal failure provides a better approach to solely focusing on diabetic kidney disease, and could comprise a main part of IgAN therapy (3). Therefore, a primary focused on the beneficial effects of SGLT2i in chronic renal failure (13) is necessary, particularly for examining the beneficial impact of such agents in IgAN. This mini-review aims to contribute to revealing the evidence supporting the protective efficacy of SGLT-2i in IgAN.

Materials and Methods

For the conduction of this mini-review, relevant data were collected following an extended literature search within Google Scholar, Scopus, PubMed, Embase, EBSCO and Web of Science, and by the use of keywords such as sodium-glucose cotransporter-2 inhibitors, chronic kidney disease, IgA nephropathy, diabetic kidney disease, acute kidney

disease, albuminuria, glomerulopathy, immunoglobulin A nephropathy and mesangial proliferation. The current investigation was conducted through a thorough search of the relevant scientific articles published during the period of 2015 to 2022.

Renal impact of sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter-2 inhibitors, belongs to the anti-diabetes group of drugs. As a hybrid diuretic validity, the inhibition of sodium-glucose cotransporter-2 ameliorates high blood sugar, impeding urinary reabsorption of glucose and resulting in glycosuria (18). Current research findings show that the blood sugar lowering efficacy of SGLT-2i is mediated by the prevention of glucose entrance into the proximal kidney tubular cells, consequently resulting in the triggering of glycosuria (19,20). Following blockage of sodium-mediated glucose reabsorption in the renal proximal segments, the use of SGLT-2i results in an increase of distal release of Na⁺ and Cl⁻ ions to the macula densa and restitution of the tubuloglomerular feedback accordingly (20,21). This phenomenon leads to a decrease in afferent arteriole vasodilation, which results in the reduction of proteinuria, diminution of the glomerular hypertension, subsequently leading to albuminuria in diabetic kidney disease (9, 20). In their review, Ravindran and Munusamy discuss the key mechanisms underlying the action of SGLT-2i (21), one being the restoration of the tubuloglomerular feedback by increasing sodium delivery at macula densa, causing constriction of the afferent arteriole entering the Bowman's capsule, and therefore, leading to a reduction in glomerular hyperfiltration. Additionally, SGLT-2i decrease the triggering of the intra-renal renin-angiotensin-aldosterone system, which contributes to further reduction of glomerular hyperfiltration. This also results in an increased production of ketone bodies (these provide an alternate fuel for the production of ATP in mitochondria), that helps reduce subsequent inflammatory responses, and therefore ensuring protection against hypoxia, induction of oxidative stress, and tissue fibrosis (22,23).

Further studies investigating the renal protective effect of SGLT-2i have demonstrated an inhibitory effect on hepcidin, a hormone that regulates the bioavailability of iron in the body, and inducing an early increase in the levels of erythropoietin and latter erythroferrone (24-27), which limits subsequent podocyte injury. Additionally, SGLT-2i have been also demonstrated to ameliorate increased hypertension during cardiovascular heart disease (24). Van Bommel et al have shown that administration of the SGLT-2i drug dapagliflozin to patients with type-2 diabetic mellitus, resulted in a reduced measured glomerular-filtration rate and filtration fraction without

increasing renal vascular resistance (25). The results of these studies provide evidence that the diminution of glomerular hypertension with the use of dapagliflozin is not mediated by vasoconstriction of the afferent arteriole, but, this is rather due to vasodilation of the efferent arteriole instead (25). The pleiotropic efficacy of SGLT-2i agents also include regulation of profibrotic and inflammatory mediators, as well as alteration of toxic intracellular compounds like advanced glycation end-products (26). However, it should be noted that the role of these factors in the development of IgAN, still remains not so well understood. A high-risk toxicity profile and the absence of decisive efficacy information question the use of immunosuppressive therapy as complementary to the treatment of IgAN. The alternative choice of non-immunosuppressive therapy appears to be more attractive, since this is directed more towards renal protection, and is a safer and more effective strategy without evidence of active morphological lesions as defined by the Oxford IgA classification (8).

Conclusion

Investigations regarding the administration of SGLT-2i in IgAN are scarce; however, current evidence supports treatment of chronic renal disease and renoprotection in chronic and mild cases of IgAN, by dual inhibition of SGLT-2 and renin-angiotensin-aldosterone system, instead of focusing on immunosuppression. The future use of SGLT-2i and their effects merits further investigation, requiring the conduction of larger studies to consider the safety of their use in more depth.

Authors' contribution

Conceptualization: MF.

Validation: MF, YRH.

Resources: YHR.

Data curation: MF, YHR.

Writing—original draft preparation: MF.

Writing—reviewing and editing: MF, AD, YRH.

Visualization: MF.

Supervision: AD, MF.

Project management: MF.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

- Floege J, Rauen T, Tang SCW. Current treatment of IgA nephropathy. *Semin Immunopathol.* 2021;43:717-728. doi: 10.1007/s00281-021-00888-3.
- Floege J, Barratt J. IgA nephropathy: a perspective for 2021. *Semin Immunopathol.* 2021;43:625-626. doi: 10.1007/s00281-021-00890-9.
- Anders HJ, Peired AJ, Romagnani P. SGLT2 inhibition requires reconsideration of fundamental paradigms in chronic kidney disease, 'diabetic nephropathy', IgA nephropathy and podocytopathies with FSGS lesions. *Nephrol Dial Transplant.* 2022;37:1609-15. doi: 10.1093/ndt/gfaa329.
- Li H, Lu W, Li H, Liu X, Zhang X, Xie L, et al. Immune characteristics of IgA nephropathy with minimal change disease. *Front Pharmacol.* 2021;12:793511. doi: 10.3389/fphar.2021.793511.
- Xie X, Liu P, Gao L, Zhang X, Lan P, Bijol V, et al. Renal deposition and clearance of recombinant poly-IgA complexes in a model of IgA nephropathy. *J Pathol.* 2021;254:159-172. doi: 10.1002/path.5658.
- Knoppova B, Reily C, King RG, Julian BA, Novak J, Green TJ. Pathogenesis of IgA Nephropathy: Current Understanding and Implications for Development of Disease-Specific Treatment. *J Clin Med.* 2021;10:4501. doi: 10.3390/jcm10194501.
- Zhang H, Barratt J. Is IgA nephropathy the same disease in different parts of the world? *Semin Immunopathol.* 2021;43:707-715. doi: 10.1007/s00281-021-00884-7.
- Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med.* 2015;373:2225-36. doi:10.1056/NEJMoa1415463.
- Barratt J, Floege J. SGLT-2 inhibition in IgA nephropathy: the new standard of care? *Kidney Int.* 2021;100:24-26. doi: 10.1016/j.kint.2021.04.002. PMID: 33878337.
- Barbour SJ, Espino-Hernandez G, Reich HN, Coppo R, Roberts IS, Feehally J, et al. The MEST score provides earlier risk prediction in IgA nephropathy. *Kidney Int.* 2016;89:167-75. doi: 10.1038/ki.2015.322.
- Fellström BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter JW, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet.* 2017;389:2117-27. doi: 10.1016/S0140-6736(17)30550-0.
- Wheeler DC, Toto RD, Stefánsson BV, Jongs N, Chertow GM, Greene T, 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. *Kidney Int.* 2021;100:215-224. doi: 10.1016/j.kint.2021.03.033.
- Mende CW. Chronic kidney disease and SGLT2 inhibitors: a review of the evolving treatment landscape. *Adv Ther.* 2022;39:148-164. doi: 10.1007/s12325-021-01994-2.
- Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondur N, Shaw W, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol.* 2018;6:691-704. doi: 10.1016/S2213-8587(18)30141-4.
- Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med.* 2016;375:323-34. doi: 10.1056/NEJMoa1515920.
- Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2019;380:347-357. doi: 10.1056/NEJMoa1812389.
- Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol.* 2019;7:606-617. doi: 10.1016/S2213-8587(19)30180-9.
- Puglisi S, Rossini A, Poli R, Dughera F, Pia A, Terzolo M, et al. Effects of SGLT2 Inhibitors and GLP-1 Receptor Agonists on Renin-Angiotensin-Aldosterone System. *Front Endocrinol (Lausanne).* 2021;12:738848. doi: 10.3389/fendo.2021.738848.
- Cheung CK, Rajasekaran A, Barratt J, Rizk DV. An Update on the Current State of Management and Clinical Trials for IgA Nephropathy. *J Clin Med.* 2021;10:2493. doi: 10.3390/jcm10112493.
- Sen T, Heerspink HJL. A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. *Cell Metab.* 2021;33:732-739. doi: 10.1016/j.cmet.2021.02.016.
- Ravindran S, Munusamy S. Renoprotective mechanisms of sodium-glucose co-transporter 2 (SGLT2) inhibitors against the progression of diabetic kidney disease. *J Cell Physiol.* 2022;23:1182-1205. doi: 10.1002/jcp.30621.
- Loutradis C, Papadopoulou E, Angeloudi E, Karagiannis A, Sarafidis P. The Beneficial Hemodynamic Actions of SGLT-2 Inhibitors beyond the Management of Hyperglycemia. *Curr Med Chem.* 2020;27:6682-6702. doi: 10.2174/0929867326666191029111713.
- Sarafidis P, Ferro CJ, Morales E, Ortiz A, Malyszko J, Hojs R, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant.* 2019;34:208-30. doi: 10.1093/ndt/gfy407.
- Granata A, Pesce F, Iacoviello M, Anzaldi M, Amico F, Catalano M, et al. SGLT2 Inhibitors: A Broad Impact Therapeutic Option for the Nephrologist. *Front Nephrol.* 2:867075. doi: 10.3389/fneph.2022.867075.
- Van Bommel EJM, Muskiet MHA, van Baar MJB, Tonneijck L, Smits MM, Emanuel AL, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int.* 2020;97:202-212. doi:

- 10.1016/j.kint.2019.09.013.
26. Vasquez-Rios G, Nadkarni GN. SGLT2 inhibitors: emerging roles in the protection against cardiovascular and kidney disease among diabetic patients. *Int J Nephrol Renovasc Dis.* 2020;13:281-296. doi: 10.2147/IJNRD.S268811.
27. Wagner M, Ashby DR, Kurtz C, Alam A, Busbridge M, Raff U, et al. Hepcidin-25 in diabetic chronic kidney disease is predictive for mortality and progression to end stage renal disease. *PLoS One.* 2015;10:e0123072. doi: 10.1371/journal.pone.0123072.

Copyright © 2023 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.