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Sodium–glucose co-transporter-2 inhibitors - empagliflozin and dapagliflozin as future therapy for Alport Syndrome, literature review

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Abstract
Introduction and purposes:
Alport syndrome (AS) is a common hereditary kidney disorder for which there is currently no curative treatment. The current standard of care for AS involves therapeutic blockade of the renin-angiotensin-aldosterone system (RAAS). This review explores the potential of sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i) as a treatment option that may slow the progression of chronic kidney disease (CKD) and prevent the advancement to end-stage kidney disease (ESKD).
Materials and Methods:
A systematic literature search was conducted using PubMed and Google Scholar, employing the following search terms: 'Alport syndrome,' 'SGLT2' 'inhibitors,' 'sodium-glucose transporter 2 inhibitors', 'proteinuria,' 'albuminuria,' 'empagliflozin,' 'dapagliflozin.' Articles published between 2019 and 2024 were included in the search.
Results:
Recent randomized clinical trials have shown that SGLT2i have nephroprotective effects in CKD. SGLT2i may effectively address the hemodynamic overload in addition to RAAS-blockade in AS patients, potentially delaying end-stage renal failure (ESRF) by several years. Studies indicate that empagliflozin and dapagliflozin are well tolerated and significantly reduce proteinuria in patients with AS. However, they may also cause an initial decrease in estimated glomerular filtration rate (eGFR), raising some safety concerns. This highlights the importance of monitoring and evaluating the treatment course in every AS patient starting SGLT2i therapy.
Conclusion:
Our findings contribute to the growing evidence that SGLT2i reduce proteinuria and may slow disease progression. They could become a future standard of care for patients with glomerular kidney diseases like AS. Future research should investigate the earlier use of SGLT2i in treatment and monitor long-term outcomes in treated patients.

Introduction and purpose

Alport syndrome (AS) is the most prevalent inherited chronic kidney disease (CKD), with three distinct patterns of inheritance: X-linked, autosomal, and digenic. AS is characterized by proteinuria and hematuria, leading to chronic inflammation, fibrosis, and progressive kidney disease, often culminating in end-stage renal failure (ESRF) early in life. The disease accounts for 30-40% of proteinuric CKD in children and over 10% of end-stage kidney disease (ESKD) cases in young adults. [1] In the USA and Europe, more than 10,000 children are currently affected, most of whom face a 100% risk of developing ESRF early in life. Children with classical forms of AS, for instance, are at significant risk, which adversely impacts their quality of life and life expectancy. Numerous patient testimonies highlight the substantial unmet medical need for therapies in children with CKD (see the Alport Syndrome Foundation

homepage, the Voice of Patients Report from the FDA, [2] and a video portrait by the German Ministry of Education and Research with English subtitles). [3]
At present, there is no curative treatment for AS. The disease is caused by mutations in the genes coding for type IV collagen (COL4A3, COL4A4, and COL4A5), resulting in defective α3, α4, or α5 chains of type IV collagen, which are critical components of the glomerular basement membrane (GBM). These genetic variants cause a mechanical deficit in the filtration unit, making the weakened and leaky GBM in AS patients an ideal therapeutic target for sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i). [4] This therapeutic potential has led to the off-label use of SGLT2i in children, despite insufficient evidence, as data from elderly patients cannot be directly applied to children. [4,5] An international panel has agreed that SGLT2i appears to be a promising add-on therapy for AS patients at risk of progression and should be prescribed in addition to angiotensin-converting enzyme (ACE) inhibitors (ACEi) or angiotensin II receptor blockers (ARBs), where regional regulations allow. [1]
This review evaluates the evidence for the use of SGLT2i as a potential treatment for AS, with the aim of slowing CKD progression and preventing patients from reaching ESKD.

Material and methods of research

A systematic literature search was conducted using PubMed and Google Scholar, employing the following search terms: 'Alport syndrome,' 'SGLT2' 'inhibitors,' ‘sodium-glucose transporter 2 inhibitors’, 'proteinuria,' 'albuminuria,' 'empagliflozin,' 'dapagliflozin.' Articles published between 2019 and 2024 were included in the search. Frequently cited publications published earlier were also included. The inclusion criteria comprised published papers, case series, and reports focusing on using SGLT2i, especially empagliflozin and dapagliflozin in patients in AS or experimental studies on mice. Additionally, only publications in English were considered eligible for inclusion.

Description of the state of knowledge

CURRENT TREATMENT

Currently, there is no curative treatment for AS. The therapeutic blockade of the renin-angiotensin-aldosterone system (RAAS) is the standard care to slow progression to ESKD. [6] For AS, international therapy guidelines recommend ACEi, particularly Ramipril, as a specific treatment for oligo-symptomatic small children from the age of 2 years. [7] Observational studies in Europe and Asia demonstrate a clear therapeutic effect, and a recent meta-analysis summarized that a randomized controlled trial also shows safety in small children. [8] ACEi-mediated efferent arteriole vasodilatation and inhibition of the podocyte’s angiotensin system provide a significant nephroprotective effect in children with AS. [9] The earlier ACEi treatment begins, the better the protective effect on the vulnerable GBM and dysfunctional podocytes, potentially delaying ESRF by decades. [10] Although early ACEi treatment has been shown to reduce proteinuria and delay disease progression in both retrospective [11] and prospective studies, [12] there is no specific treatment to prevent renal failure in AS patients. For ESRF, the only treatment options are dialysis and kidney transplantation. [1]

Despite the maximum-tolerated RAAS blockade, disease progression in AS underscores the need for new treatments. Several new therapies could serve as adjunctive agents to reduce proteinuria, consequent tubular protein toxicity, and tubulointerstitial fibrosis. These include antimicroRNA21, which has been shown to prolong kidney survival in Alport mice; [13] the combined angiotensin receptor and endothelin receptor inhibitor sparsentan, which has shown promising proteinuria reduction in focal segmental glomerulosclerosis (FSGS); [14] and kidney lipid-modifying agents. Bardoxolone methyl has also been investigated in AS, showing an increase in GFR but also in proteinuria. [15] For all potential adjunctive therapies, monitoring long-term safety and efficacy will be crucial. Given the genetic basis of AS, future curative gene therapy is under investigation in mice through gene replacement or exon skipping approaches, [16] and these remain active areas of research. [17]

In all cases, promoting a healthy lifestyle is essential—exercise, moderation in meat protein and salt intake, maintaining a body mass index below 25 kg/m^2, strict blood pressure control, and avoiding smoking are recommended. [1]

SGLT2 INHIBITORS

Historically, clinical trials exploring treatments to prevent CKD have shown discouraging results, until recent studies highlighted the positive cardiovascular and renal outcomes of SGLT2i in diabetic patients. Despite being primarily used for Type 2 diabetes, SGLT2i have demonstrated nephroprotective properties, suggesting their potential efficacy in treating other forms of progressive kidney diseases. [4] Initially recognized for their ability to slow diabetic kidney disease (DKD) progression and reduce cardiovascular risks without inducing hypoglycemia in non-diabetic patients, SGLT2i were presumed safe for broader kidney disease applications. [18]

Recent randomized trials have underscored SGLT2i nephroprotective benefits in CKD [19], supported by extensive evidence showing their effectiveness in slowing CKD progression, both in diabetic and non-diabetic contexts. [19,20] This nephroprotective effect is attributed to SGLT2-mediated modulation of dilated afferent arterioles in glomeruli, leading to reduced intraglomerular pressure and decreased albuminuria. [18] It is believed that SGLT2i achieve this robust nephroprotection through a combination of afferent arteriole vasoconstriction via tubuloglomerular feedback (TGF) and efferent arteriole vasodilation by ACEi. [4]

SGLT2i work by reducing sodium and glucose reabsorption in the proximal convoluted tubule, thereby increasing their delivery to the distal nephron, stimulating TGF, and ultimately decreasing glomerular hypertension and hyperfiltration. This mechanism results in significant glucosuria, lowering blood glucose levels and independently offering nephroprotective benefits beyond glycemic control. These effects are thought to be mediated by glucose-induced osmotic diuresis, concomitant natriuresis, and subsequent afferent arteriole vasoconstriction, leading to reduced intraglomerular pressure and albuminuria reduction. [19]

Similarly, a recent case series also demonstrated the impact of SGLT2i in reducing proteinuria among adults with inherited podocytopathies. [10] Like previous research, [18,21] the renal hemodynamic effects of SGLT2i (similar to tolvaptan) and their metabolic effects (resembling caloric restriction) may offer protective benefits in autosomal dominant polycystic kidney disease (ADPKD).

SGLT2i also enhance mitochondrial carbon flux, decrease reactive species production, and inhibit mitochondrial damage and ferroptosis. [22,23] Therefore, it is plausible that the nephroprotective effects of SGLT2i are also mediated by reducing renal lipotoxicity, a factor implicated in experimental AS. [24]

Podocyte injury is a common pathological hallmark in various kidney diseases, leading to proteinuria and ultimately glomerulosclerosis. Diseases associated with podocyte injury include FSGS, MCD, MN, IgA nephropathy, collapsing glomerulopathy, AS, and secondary systemic disorders such as DKD, lupus nephritis, and obesity-related glomerulopathy. [25] Lipotoxic podocyte injury involves lipid droplet formation and abnormal cholesterol efflux in podocytes. [26] Liu et al. noted that cholesterol accumulation exacerbates podocyte injury and promotes the progression of DKD and AS; notably, deficiency in sterol-O-acyltransferase-1 can enhance cholesterol efflux and mitigate podocyte injury. [27]

The observational, multicenter international study (NCT02378805) evaluated 112 patients with AS from nine countries and 21 trial sites, focusing on early stages of CKD following initiation of SGLT2i. The primary endpoint of the study was the change in albuminuria (measured as albumin in milligrams per gram of creatinine) after starting SGLT2i therapy. In contrast to larger randomized trials investigating SGLT2i in CKD, participants in this trial were notably younger (mean age 38 ± 14 years; n = 101), had better eGFR (63 ± 35 ml/min/1.73m²; n = 98), and higher levels of albuminuria (1699 ± 1472 mg/g creatinine; n = 51).

After an average of 6 ± 1 months on SGLT2i therapy, there was a significant decrease in albuminuria (1727 ± 1564 vs. 1203 ± 1165 mg/g creatinine; n = 33; p = 0.01). Compared to baseline, significant reductions (>30%) in albuminuria were observed at the first three follow-up visits following initiation of SGLT2i therapy. After nearly one year of SGLT2i therapy, the mean decrease in eGFR was 9 ± 12 ml/min/1.73m² (n = 35). Serum albumin levels significantly increased from 3.7 ± 0.7 to 4.0 ± 0.4 g/dL after a mean follow-up of 12 ± 2 months on SGLT2i therapy (n = 18; p = 0.019). Throughout 68 patient-years of follow-up, adverse events occurred in 11 out of 85 patients (13%), with two cases of severe adverse events noted (acute necrotizing pancreatitis and Fournier's gangrene).

The study demonstrated that adding SGLT2i to RAAS inhibitors has the potential to reduce albuminuria rates in adult patients with AS. Further investigation in this observational study aims to provide long-term data on the course of CKD under SGLT2i therapy in AS, assessing whether the observed reduction in albuminuria translates into clinically meaningful delays in renal failure. This research forms the basis for the ongoing randomized controlled trial Double Protect Alport, evaluating SGLT2i in children and young adults with AS. [28]

EMPAGLIFLOZIN

Numerous studies have affirmed the renal protective effects of the SGLT2i empagliflozin, highlighting its direct and indirect glucose-lowering effects in diabetes. [29] The mechanisms through which empagliflozin safeguards the kidneys include glucose reduction, attenuation of glomerular hyperfiltration, suppression of inflammation and oxidative stress, and promotion of weight loss. [30] These effects suggest that empagliflozin therapy may contribute to regression of DKD. [31] Supporting this hypothesis, research has shown that empagliflozin

lowers levels of various biochemical markers of renal damage and significantly improves renal histopathological lesions, thus restraining DKD progression. [32]

Notably, treatment with empagliflozin reduces lipid droplet accumulation and apoptosis in podocytes, thereby mitigating lipotoxicity and enhancing kidney function in experimental AS. Previous studies have documented increased apoptosis and lipid droplet accumulation in AS podocytes compared to wildtype (WT) podocytes. [27,33]

To further investigate the potential of SGLT2i to reduce lipotoxicity in podocytes and tubular cells isolated from AS mice, immortalized WT and AS podocytes and tubular cells were treated with empagliflozin or a control vehicle. We observed increased cytotoxicity, though not statistically significant, in AS tubular cells compared to WT tubular cells. However, empagliflozin significantly decreased cytotoxicity in AS tubular cells treated with empagliflozin compared to those treated with vehicle alone. Additionally, empagliflozin inhibited the use of pyruvate as a metabolic substrate in AS podocytes. Interestingly, empagliflozin also prolonged the survival of AS mice.

To explore if empagliflozin could enhance survival in mice with non-diabetic renal disease, which typically succumb to renal failure, AS mice were fed empagliflozin-supplemented chow (70 mg/kg) or a standard diet starting at 4 weeks of age for 6 weeks. AS mice typically develop proteinuria by 4 weeks of age and often die by 8-9 weeks. The study demonstrated that empagliflozin extended the lifespan of AS mice by approximately 22% compared to untreated AS mice. Furthermore, empagliflozin, ramipril, and the combination of empagliflozin with ramipril significantly reduced the albumin-to-creatinine ratio and prevented body weight loss in AS mice. These treatments also significantly lowered blood urea nitrogen and creatinine levels, indicating improved renal function in this AS mouse model. Empagliflozin therefore shows promise in enhancing renal function in a mouse model of AS. [34]

It has been proposed that the nephroprotective effects of the SGLT2i empagliflozin primarily involve its impact on the TGF mechanism. [35,36] The TGF system regulates glomerular blood flow, acting as a physiological counter-regulation that safeguards individual nephrons from hyperfiltration, elevated intraglomerular pressure, and sodium and fluid overload in the tubules. [37] Data from various murine models of non-diabetic hyperfiltration, hypervolemia, and hypertension suggest that empagliflozin's nephroprotection relies on a functional TGF mechanism to mitigate chronic hyperfiltration, thereby protecting against glomerular damage and albuminuria. [38] Reduction of intraglomerular pressure is critical for mitigating chronic kidney function decline.

In essence, SGLT2 inhibition results in reduced sodium and glucose uptake in the proximal tubules via SGLT2, increasing their presence in the macula densa. This leads to heightened adenosine generation, which enhances afferent arteriole tone and potentially reduces efferent arteriole tone, thereby decreasing blood flow through the glomeruli and ultimately lowering intraglomerular pressure. [39,40] Experimental evidence shows that empagliflozin's nephroprotective effects extend beyond diabetic nephropathy, improving the structure and function of non-diabetic nephropathies. These benefits include reduced serum creatinine, decreased proteinuria, increased creatinine clearance, and improvements in renal interstitial inflammation, interstitial fibrosis, perivascular fibrosis, and glomerulosclerosis. Notably, the

nephroprotective effect of empagliflozin appears to be more pronounced at higher doses (15 mg/kg/day), suggesting a dose-dependent relationship. [41]

The study aimed at evaluating the renal protective effects of linagliptin and empagliflozin revealed several metabolic changes in renal cortices of AS mice compared to WT mice. Specifically, levels of metabolites such as adrenic acid and glucose were elevated, while eicosapentaenoic acid levels were reduced in AS mice. Moreover, there was a notable redistribution of adrenic acid from the glomerular compartment in WT mice to the tubulointerstitial compartment in AS mice.

Both linagliptin and empagliflozin treatments demonstrated reductions in albuminuria, extended the survival of AS mice by approximately 10 days, and decreased glomerulosclerosis and tubulointerstitial fibrosis compared to WT mice. Importantly, there were no significant differences in renal phenotype observed between empagliflozin and linagliptin treatments, and the combination of both drugs did not show superior effects over individual treatments. [42]

Further experiments in mice suggested that triple blockade of RAAS, SGLT2, and mineralocorticoid receptor (MR) may substantially improve renal outcomes in AS and potentially other progressive CKD. In this study, 40 male and 40 female mice were treated with ramipril monotherapy (10 mg/kg), ramipril plus empagliflozin (30 mg/kg), or ramipril plus empagliflozin plus finerenone (10 mg/kg). The mean survival was extended to 103.1±20.3 days with the triple combination, compared to 63.7±10.0 days with vehicle, 77.3±5.3 days with ramipril monotherapy, and 80.3±11.0 days with dual therapy (ramipril plus empagliflozin). Histopathology and RNA sequencing analysis supported the potent anti-sclerotic, anti-inflammatory, and anti-fibrotic effects of the triple blockade. Dual blockade of ACE and SGLT2 also prolonged the mean lifespan of Alport mice beyond ramipril monotherapy. Addition of finerenone to the dual RAAS/SGLT2 blockade significantly prolonged the uremia-free lifespan even when treatment was initiated at an advanced stage of Alport nephropathy. These findings suggest that triple RAAS/SGLT2/MR blockade could represent a potent treatment strategy to prolong uremia-free lifespan in patients with CKD related to AS and potentially other progressive kidney disorders. [43]

It's important to note that the AS mouse model used in these studies is highly progressive, suggesting that treatment effects observed in human patients with AS may be even more favorable than those seen in animal models. [5]

DAPAGLIFLOZIN

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial demonstrated that the SGLT2 inhibitor dapagliflozin reduces the risk of kidney failure and cardiovascular events in patients with CKD, whether or not they have diabetes. The study included 4,304 participants, both diabetic and non-diabetic, with six patients having AS. Dapagliflozin was well tolerated and significantly decreased the risk of any component of the composite renal endpoint (such as a ≥50% decline in eGFR, onset of ESKD, or renal or cardiovascular death) by 44%. [19]

Additionally, the antiproteinuric effect of SGLT2i was confirmed in a 2022 pilot study involving pediatric patients with proteinuric CKD, primarily AS and Dent disease. In this pilot study of nine pediatric patients (mean age 10.4 years, mean weight 34.9 kg, mean BMI

17.8 kg/m², and mean eGFR 104.9 ml/min/1.73 m²), dapagliflozin treatment at doses of 5 mg or 10 mg per day, depending on body weight, was well tolerated. The study showed a reduction in baseline proteinuria by 33.3% at week 4 and 22.6% at week 12. [44]

Although there was a slight decrease in eGFR during dapagliflozin treatment in these pediatric patients, previous meta-analyses have indicated that SGLT2 inhibitors do not cause acute kidney injury and may actually reduce its occurrence. Moreover, reviews suggest that SGLT2 inhibitors preserve kidney function despite the initial decline in eGFR, which reflects a reduction in hyperfiltration. Therefore, the modest reduction in eGFR observed in the short term should not discount the potential renoprotective benefits of dapagliflozin specifically in children with proteinuric CKD. [44]

In patients with CKD, including those with conditions like AS, dapagliflozin has demonstrated beneficial effects in reducing the risk of kidney failure, despite a potential initial acute reduction in eGFR upon treatment initiation. A post hoc analysis of the DAPA-CKD trial revealed that patients who experienced a ≥10% acute reduction in eGFR after 2 weeks of dapagliflozin treatment exhibited slower rates of long-term eGFR decline compared to those with a less pronounced decline or an increase in eGFR. Importantly, adverse event rates among patients receiving dapagliflozin were not linked to the acute change in eGFR. These findings suggest that a modest acute reduction in eGFR when starting dapagliflozin should not deter clinicians from continuing this therapy in the majority of patients, as it does not associate with accelerated CKD progression. [47]

In a recent study involving 118 patients treated with dapagliflozin as standard care, albeit with a small subset of 8 patients having AS (6.8%), significant reductions in proteinuria were observed across various types of glomerulonephritis, including IgA nephropathy and AS. The median follow-up period was 12.2 months, during which proteinuria decreased significantly from 1139 to 701 mg/g creatinine ($p < 0.001$). While there was a slight decrease in eGFR levels (54 vs. 52 ml/min/1.73 m²; $p < 0.001$) and an increase in creatinine values (122 vs. 128 μmol/l; $p < 0.001$), dapagliflozin was well tolerated overall. This study underscores the significant role of dapagliflozin in reducing proteinuria among patients with primary glomerulonephritis, including those with AS. [48]

In a cohort study focusing on autosomal recessive AS, the efficacy and safety of dapagliflozin (5 mg) were evaluated in three adult patients over a 4 to 6-month follow-up period. The study found a decreasing trend in proteinuria across all three cases, with 24-hour proteinuria decreasing by 0.17 g/24h (8.9%), 0.61 g/24h (39.9%), and 0.69 g/24h (52.3%) respectively. Urinary albumin-creatinine ratio also decreased significantly, by 374.92 mg/g (26.9%), 561.03 mg/g (44.0%), and 234.33 mg/g (68.7%) respectively. Furthermore, serum albumin levels showed an overall increase. Notably, there were no significant changes in serum creatinine and eGFR, and no patients discontinued dapagliflozin due to safety concerns or experienced clinically adverse effects. This pilot study reported promising efficacy and tolerance of half-dose dapagliflozin in AS patients, especially those with decreased renal function. [49]

In contrast, a single-center, observational, prospective study involving eight adult AS patients without diabetes and with persistent proteinuria despite maximum tolerated doses of RAAS inhibitors prescribed dapagliflozin 10 mg daily. The median follow-up duration was 213.5

days (interquartile range [IQR] 208.3-259). At baseline, the median urinary protein-to-creatinine ratio (Up/cr) was 1.4 (IQR 0.8-2.1), and after dapagliflozin treatment, it was 1.5 (IQR 0.8-2.6), with no significant difference ($p = 0.727$).

The Up/cr ratio improved in three patients but worsened in five. Median eGFR at baseline was 80.3 ml/min (IQR 40.9-109.5), and after dapagliflozin initiation, it was 74.7 ml/min (IQR 40.4-112.0), also showing no significant change ($p = 0.727$). The study did not observe improvement in Up/cr with dapagliflozin treatment, and there was a slight decrease in eGFR, possibly due to the known hemodynamic effects of SGLT2i. Despite these findings, the study concluded that the small cohort size and short study duration should not discourage the use of SGLT2i in AS patients. [50]

COMPARISON OF EMPAGLIFLOZIN AND DAPAGLIFLOZIN

An observational, non-interventional prospective case series was conducted with six male patients diagnosed with AS or FSGS, all of whom received SGLT2i in addition to RAAS blockade. The patients were treated off-label with once-daily 10 mg empagliflozin ($n = 3$) or dapagliflozin ($n = 3$). Among the four older patients with X-linked AS, there was a consistent response to SGLT2 inhibition. For instance, in female patient 3, SGLT2i compensated for the discontinuation of ACEI therapy due to angioedema. Patients 4 and 5, both elderly AS patients, benefited from SGLT2i with a reduction in proteinuria without a significant decline in their eGFR. Patient 6, who had the shortest follow-up, did not show immediate improvement in proteinuria and experienced a downgrade from CKD stage G3aA3 to G3bA3.

Before initiation of SGLT2i, the mean serum creatinine was 1.46 (SD ± 0.42), which increased to 1.58 (SD ± 0.55) afterward. The mean urinary albumin-creatinine ratio decreased from 1827 (SD ± 1560) to 1127 (SD ± 854) mg/g creatinine after SGLT2 inhibitor initiation. Most patients experienced a dip in eGFR after starting SGLT2i, raising initial safety concerns. This underscores the importance of closely monitoring AS patients receiving SGLT2i. Despite the initial eGFR decline, no acute renal failure, hypovolemia, urinary tract infections, or mycotic infections were observed, and none of the patients discontinued SGLT2 inhibitor therapy due to side effects. Overall, combining SGLT2i with RAAS blockade was well tolerated and effective in reducing initial eGFR and lowering albuminuria. [10,51]

Furthermore, current clinical studies suggest that different SGLT2 inhibitor compounds may have varying efficacy profiles, with some indicating that empagliflozin is more effective than dapagliflozin in certain contexts. [52,53]

Summary

AS serves as a paradigm of progressive CKD characterized by proteinuria and fibrosis, mirroring features seen in other more prevalent kidney disorders. Currently, there are no curative therapies available for AS, yet patients are often young and relatively free of other health conditions, making them ideal candidates for clinical trials. Given the substantial affected population, there is a significant opportunity to explore SGLT2i as a promising therapeutic strategy to alleviate the hemodynamic burden on the glomerular filtration barrier in hereditary podocytopathies.

Our findings support existing evidence suggesting that SGLT2i should become standard care for patients with glomerular kidney diseases like AS. Future research should investigate the

potential benefits of initiating SGLT2i earlier in the course of glomerulonephritis, alongside immunosuppressive therapies, and explore their effects on mesangial cells.
Specific randomized clinical trials are crucial to validate these findings in genetically well-defined populations that urgently require more effective, early-stage, and safe nephroprotective treatments.
The safety of SGLT2i in AS patients has yet to be extensively studied beyond case reports. Nevertheless, SGLT2i hold considerable promise in mitigating hemodynamic overload when added to RAAS blockade, potentially delaying end-stage renal failure by several years. AS registries can play a pivotal role in evaluating the efficacy and safety of SGLT2 inhibitor treatments broadly, and in addressing critical questions regarding the optimal timing and patient selection for this therapy. Long-term monitoring of treated patients is essential to understanding sustained outcomes.
Advancements in research exploring innovative therapeutic approaches for AS are encouraging and offer hope to thousands of affected individuals. Given the urgent medical need and the potential impact, any effective drug for AS would likely receive expedited approval as an orphan drug, further underscoring the significance of ongoing research efforts in this field.

Disclosure
Conceptualization, MK, and KC; methodology, MK; software, KK; check, MK, KK and JL; formal analysis, JL; investigation, MK; resources, KK; data curation, JL; writing - rough preparation, MK, JL, KK; writing - review and editing, KC, MK; visualization, MK, KC, MK, KK, JL; supervision, KC; project administration, KC; receiving funding, MK
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