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SGLT2-Inhibition in patients with Alport syndrome

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Running head

SGLT2-inhibition in Alport syndrome

Abstract

Introduction: Large-scale trials showed positive outcomes of sodium–glucose cotransporter-2 inhibitors (SGLT2i) in adults with chronic kidney disease (CKD). Whether the use of SGLT2i is safe and effective in patients with the common hereditary CKD Alport syndrome has not yet been investigated specifically in larger cohorts.

Methods: This observational, multi-center, international study (NCT02378805) assessed 112 patients with Alport syndrome after start of SGLT2i. The study's primary endpoint was change of albuminuria in albumin/gram creatinine from start of therapy.

Results: Compared to randomized trials investigating the effect of SGLT2i in CKD, the adult patients in this study were younger (38±14 years) and had a better estimated glomerular filtration rate, eGFR, (63±35 ml/min/1.73m^2; n=98). Maximum follow up was 32 months. Compared to baseline, at the first three follow-up visits (months 1 to 3, 4 to 8 and 9 to 15) after initiation of SGLT2i-therapy, a significant reduction of albuminuria in milligrams albumin/gram creatinine (>30%) was observed. Mean loss of eGFR was 9±12 ml/min/1.73 m^2 almost one year after initiation of SGLT2i-therapy (n=35). At a total of 71 patient-years at risk, 0.24 adverse events per patient year on SGLT2i were reported.

Conclusion: This study indicates that, additive to RAS-inhibition, SGLT2i have the potential to reduce the amount of albuminuria in patients with Alport syndrome. Future studies are needed to investigate the long-term effects of SGLT2i on CKD progression in patients with Alport syndrome to assess whether the observed reduction in albuminuria translates to a delay in kidney failure.

Key words

SGLT2-inhibition; Dapagliflozin; Empagliflozin; Alport syndrome; Albuminuria; sodium–glucose cotransporter-2 inhibitors, *COL4*, kidney failure

Introduction

Slowing progression of chronic kidney disease (CKD) has highest priority in nephrology. Recent randomized clinical trials (RCTs) demonstrated the nephroprotective effect of sodium–glucose cotransporter-2 inhibitors (SGLT2i) in CKD for adult patients.[1–5] The hereditary type IV collagen disease Alport syndrome (AS), is the most common monogenetic glomerular kidney disease.[6–8] Patients living with AS may develop CKD early in life. The disruption of type IV collagen structure in AS leads to a dysfunction of the basement membrane filtration barrier of the glomeruli with initial micro-hematuria, microalbuminuria and, with disease progression, overt proteinuria, finally progressing to kidney failure (KF), and can be accompanied by hearing loss and ocular lesions.[9–12] The majority of patients with AS have an X-linked (*COL4A5* gene) inheritance, while up to 30% have an autosomal (*COL4A3* or *COL4A4* genes) inheritance.[13–15] If started early, therapy with inhibitors of the renin-angiotensin system (RASi) can delay renal failure by years, however, many patients still reach KF at a relatively young age. Therefore, new therapy options are needed.

SGLT2i have been approved for the treatment in adults with any kind of CKD in many countries, which is why SGLT2i are also prescribed increasingly for patients with AS.[16] In previous RCTs, the nephroprotective effects of SGLT2i were examined primarily in patients with diabetic kidney disease or other more common causes of non-diabetic CKD. Whether the use of SGLT2i is safe and effective in patients with AS (and thus a different pathogenesis than other CKDs) has not yet been investigated specifically in larger cohorts.[17–20] Therefore, this international, multi-center, observational, non-interventional study investigated potential side effects of SGLT2i in patients with AS and possible nephroprotective effects using the change in albuminuria and estimated glomerular filtration rate (eGFR) as surrogate parameter for CKD-progression.[21]

Methods

Study population

This multi-center, observational study included a total of 112 patients with AS, who started therapy with SGLT2i. Patients from nine countries and 21 study sites were recruited from 2021 to 2023. The presentation of this study's design at the International Workshop on Alport Syndrome 2021 led to the recruitment of potential study sites.[22] Some patients were followed retrospectively (n=99) and others prospectively (n=13). The diagnosis of AS was confirmed genetically or by kidney biopsy (patient or affected relative). Patients living with X-linked, autosomal recessive or autosomal dominant AS were included. Patients were not included if they received kidney transplantation, were on dialysis or did not wish to contribute. Data were pseudonymized at the study site or, in the UK, by the National Registry of Rare Kidney Diseases (RaDaR, for which all patients provided written informed consent with ethical approval provided by NHS South West—Central Bristol Research Ethics Committee (14/SW/1088)). The registry and data storage, in conformity with Good Clinical Practice guidelines, were approved by the Ethics Committee of the University Medical Center Göttingen as part of the European Alport Therapy Registry (AZ 10/11/06; renewed version in 2014 and 2020; ClinicalTrials.gov identifier NCT 02378805).

Intervention and outcome measures

This non-interventional study explored the intra-individual treatment effects of SGLT2i (in most patients on top of RASi). A standardized questionnaire was used as Case Report Form (CRF) to obtain data on demographic parameters, medication, blood and urine test results as well as possible side effects. The study protocol and CRF were approved by the local ethics committee and are provided as supplemental material. Exchange of pseudonymized data was

secured by individual contracts (data processing and cooperation agreements) between the participating centers. All investigators, who contributed data, vouch for the completeness and accuracy of the data set and analyses, and for the fidelity of the study to the protocol. The decision to submit the manuscript for publication was made by all the authors.

Baseline was defined as start of therapy with SGLT2i. The study's primary endpoint was change of albuminuria in mg/g creatinine six month after baseline. If albuminuria was not available, proteinuria was analyzed.[23] Considering the different local standards of measurement, percentage changes from baseline were calculated for overall comparison in patients with overt proteinuria. Additional analyses were performed approximately 3 months after baseline, one year after baseline and, if available, at individual's longest follow up (up to 32 month). Additional analysis included demographic parameters, change of body mass index (BMI), blood pressure and renal function [estimated glomerular filtration rate (eGFR)]. Patients younger than 18 years of age (n=10) were analyzed separately. In children, the CKiD U25 formula could not be used as cystatin c was not available, therefore the Schwartz formula was used to calculate eGFR.

Statistical methods

Statistical comparisons were not formally powered or prespecified. Continuous variables were presented as mean and standard deviation (SD) or as median and inter-quartile range (IQR), categorical variables as frequencies (percentages). For intra-individual comparison of continuous outcomes, a paired t-test was used. To study subgroups, comparison of means between groups was conducted with the unpaired Student's t-test. If equal variances were not assumed, the Welch test was used for group comparison. Pearson's correlation was performed to assess correlations. Probability values (p values) below 0.05 were considered statistically

significant. Data analyses were performed with IBM SPSS Statistics (version 28 for MacOS, IBM Corporation, Armonk, NY, USA).

Results

The duration of therapy in this observational study with SGLT2i in 112 patients with AS added up to a total of 82 patient-years on SGLT2i. Mean follow up time was 9±7 month. At baseline, mean age was 36±15 years , mean eGFR was 68±38 ml/min/1.73m² (n=108) and mean albuminuria was 1689±1455 mg/g creatinine (n=53). Most patients were treated with dapagliflozin (107/112; 96%) and 5 patients were treated with empagliflozin (4%).

Adult patients

Baseline characteristics at initiation of SGLT2i therapy

Table 1 shows baseline characteristics from the 102 adult patients with AS. The mean age at baseline was 38±14 years. The majority of patients were Caucasian (80%) and most patients (63/96; 66%) were male. Diagnosis of AS was confirmed by biopsy in 16 patients (17%), by genetic testing in 51 patients (53%) and by both in 29 patients (30%) (n=96). In 6 patients, it was not reported, how diagnosis was secured. The mode of inheritance was reported in 88 patients (86%). In these patients, 58 patients had X-linked AS (66%), 29 patients had autosomal AS (including autosomal dominant and autosomal recessive AS) (33%) and one patient had AS with diegenic heterozygous variants in the *COL4A3* and *COL4A5* genes (1%). Most adult patients (95/102; 93%) were treated with RASi. Of those, 45 patients (47%) were treated with angiotensin-converting enzyme inhibitors (ACEi), 42 patients (44%) were treated with angiotensin receptor blockers (ARB) and eight patients (8%) were treated with both. Hearing loss was reported in 15 patients (16%; n=93). Most frequent comorbidities were hypercholesterolemia (36/89; 40%), high blood pressure (33/88; 38%), hyperuricemia (25/88; 28%) and vitamin D deficiency (17/88; 19%). The mean BMI was 27±6 kg/m² (n=77), 19 patients

were obese (19/77; 25%). Mean eGFR was 63±35 ml/min/1.73 m² (n=98) and mean albuminuria was 1699±1472 mg/g creatinine (n=51).

First follow up after one to three month(s) (V1)

At a mean time on SGLT2i-therapy of 2±1 months, 67 of the 102 patients (66%) had their first follow up after initiation of treatment. Mean age in these patients was 38±16 years (n=66). Albuminuria was measured in 30 patients and significantly decreased from 1797±1600 mg/g creatinine to 1197±978 mg/g creatinine (p=0.002) (Figure 1A). Proteinuria was measured in 17 patients and decreased from 1101±1119 to 766±857 mg/L (p=0.067). Serum creatinine significantly increased from 1.7±0.7 to 1.8±0.8 mg/dl (n=64; p<0.001) and, correspondingly eGFR dropped from 58±32 to 55±32 ml/min/1.73 m² (n=62; p=0.004) (Figure 1B). Systolic blood pressure was lower (126±15 vs 123±20 mmHg; p=0.147), while diastolic blood pressure remained similar (77±10 vs 78±11 mmHg; p=0.438) (n=55).

Second follow up after four to eight months (V2)

At a mean time on SGLT2i-therapy of 6±1 months, 74 of 102 patients (73%) had a follow up (V2): albuminuria decreased significantly (1727±1564 vs. 1203±1165 mg/g creatinine; n=33; p=0.01) (Figure 2A) and proteinuria decreased from 1191±1206 to 749±613 mg/L (n=15; p=0.098). Serum creatinine increased significantly from 1.6±0.7 to 1.7±0.9 mg/dL (n=73; p<0.001), and corresponding eGFR dropped from 63±34 to 59±33 ml/min/1.73 m² (n=72; p<0.001) (Figure 2B). Systolic blood pressure was significantly lower at V2 (128±14 vs. 124±13 mmHg; n=51; p=0.029), while diastolic blood pressure remained similar (79±12 vs. 78±11 mmHg; n=51; p=0.369). BMI also remained similar (27±7 vs. 27±7 kg/m²; n=35; p=0.6).

Median reduction of proteinuria or albuminuria was similar in male (n=34) and female patients (n=17) (26%, IQR:68 vs 34%, IQR:81; p=0.795). A non-significant trend towards a higher median reduction of proteinuria or albuminuria was observed in patients with autosomal AS (41% IQR: 105; n=17) than in patients with X-linked AS (27%, IQR:61; n=29) (p=0.531). Furthermore, a non-significant trend towards a higher reduction of albuminuria was observed in patients receiving ARBs (712±876 mg/g creatinine; n=16) than in patients treated with ACEis (338±833 mg/g creatinine; n=14) (p=0.243).

Third follow up after nine to fifteen month (V3)

At a mean time on SGLT2i-therapy of 12±2 months, 38 of the 102 patients (37%) had a follow-up (V3): albuminuria was still significantly lower compared to baseline (1737±1796 vs. 1189±1158 mg/g creatinine (n=22; p=0.032) (Figure 3A). Serum-creatinine increased significantly from 1.6±0.6 to 2±0.8 mg/dl (n=34; p<0.001), and, correspondingly eGFR dropped from 57±30 to 49±28 ml/min/1.73 m² (n=35; p<0.001) (Figure 3B). Mean loss of eGFR was 9±12 ml/min/1.73 m² almost one year after baseline (n=35) and a significant negative correlation between the amount of albuminuria at baseline and the change in eGFR was observed (r=-0.82, p<0.01; n=20) (Figure 4). BMI (27±6 vs. 27±6 kg/m²; n=22; p=0.62) and blood pressure were almost similar (systolic blood pressure: 127±13 vs. 126±16 mmHg; n=26; p=0.827; diastolic blood pressure: 82±12 vs. 81±11 mmHg; n=26; p=0.705).

Longest follow up about 2 years after initiation of SGLT2i-therapy (V4)

In 13 patients, data on a longer follow-up were available (mean follow-up 24±6 month). Albuminuria was still lower compared to baseline (2127±1666 vs. 1903±1371 mg/g creatinine;

n=7; p=0.524). Serum-creatinine increased significantly from 1.3±0.6 to 1.5±0.7 mg/dl (n=11; p=0.04), and corresponding eGFR dropped from 75±46 to 67±42 ml/min/1.73 m² (n=11; p=0.05).

Serum-Albumin as surrogate marker of loss of urine-proteins

At a mean follow up of 12±2 month after initiation of SGLT2i-therapy, serum-albumin increased significantly from 3.7±0.7 to 4.0±0.4 g/dL (n=18; p=0.019). The change in serum-albumin in patients with hypoalbuminemia at baseline was calculated and a relevant increase was observed: serum-albumin increased from 3.1±0.4 to 3.4±0.3 mg/dL after a mean follow up of 9±7 month after baseline (n=17; p=0.06). Out of 17 patients with hypoalbuminemia at baseline, 8 (47%) recovered to serum-albumin levels within the normal range at follow up.

Course of eGFR

A total of 16 patients had a follow-up at every single predefined visit. In these patients, a similar decrease of eGFR compared to the overall cohort was observed (55.1±22.8 ml/min/1.73 m² to 46.3±19 ml/min/1.73 m²; p=0.02) (Figure 5).

Genotype phenotype correlation

To investigate a possible influence of the genotype, male patients with XLAS were divided in two groups depending on their pathogenic variant causing AS. Out of 28 patients, 17 (61%) had missense variants and 11 (39%) patients had non-missense variants (defining a faster progression of their CKD). At baseline, patients with missense variants were older (35±12 years; n=16 vs. 27±9 years; n=11), had a significant lower eGFR 63±33 (n=16) vs. 92±32 ml/min/1.73 m² (n=11) and a higher median amount of albuminuria of 1865 (IQR: 2442; n=11) vs. 750 (IQR: 763; n=5) mg/g creatinine. Of note, despite the higher amount of albuminuria at

baseline, at V2 after a mean follow up of 6 month, a significantly higher loss of eGFR was observed in patients with non-missense variants (13±9 ml/min/1.73 m²; n=16) than in patients with missense variants (4±9 ml/min/1.73 m²; n=11) (p=0.023). In parallel, median amount of albuminuria decreased in patients with missense variants from 1865 (IQR: 2442) to 775 (IQR: 1615) mg/g creatinine, while median amount of albuminuria increased in patients with non-missense variants to 1086 (IQR: 450) mg/g creatinine.

Children

Table 2 shows the baseline characteristics and follow-up data from the 10 children in this study. All children were treated with an ACEi. Hearing loss was reported in 3 patients (30%). One patient had also hypercholesterolemia and vitamin D deficiency. In one patient hyperglycemia was reported.

At baseline, mean age was 15±3 years (range: 9 – 17 years), mean BMI was 21±4 kg/m². The mean longest follow-up time was 4±5 months. Serum-creatinine increased from 0.8±0.3 to 0.9±0.3 mg/dL and eGFR decreased from 119±32 to 107±34 ml/min (n=10). In most patients, proteinuria was measured in mg/dl (n=8) and increased slightly (114±94 vs 122±110 mg/dL). Interestingly, in the two patients with already overt proteinuria, in which albuminuria was measured, albuminuria decreased from 1426±1247 to 641±190 mg/g creatinine. Blood pressure remained similar (116±13/72±11 vs 117±13/71±13 mmHg; n=8).

Safety

Data on adverse events (AEs) were reported in 89 patients (79%). At a total of 71 patient-years at risk (mean time on therapy was 10±7 months), 0.24 AEs per patient year on SGLT2i were reported. In 72 patients (81%), there were no AEs reported (Figure 6A). The AEs in the

remaining 17 patients (18%) included impairment of kidney function (n=7, in one patient during a severe infection with SARS-CoV-2), headache (n=2), hypovolemia (n=1), one bone-fracture (bike accident), genital infection in one female and one patient reported an unwanted loss of weight. A 33 year-old female was hospitalized because of an acute necrotizing pancreatitis two years after therapy with SGLT2i was started. A 33 year old male with XLAS received a kidney transplantation five month after SGLT2i was started. One 44 years old male with compound heterozygous autosomal AS and an eGFR of 27 ml/min/1.73 m^2, when SGLT2i was started, reached KF nine month later. Ketoacidosis or major hypoglycemic events were not reported. The most severe AE was observed in a male without diabetes, who developed Fournier's gangrene after 23 months of treatment with SGLT2i.[24] In brief, this life-threatening situation developed within hours, requiring emergency wound debridement. During his stay on the intensive care unit, the patient developed an acute on chronic kidney injury AKIN III, however, kidney function recovered to baseline. The patient slowly recovered with sequelae. Data on discontinuation of therapy were available in 106 patients (95%). Therapy was discontinued in 9 patients (8%) (Figure 6B). Mean time to discontinuation of therapy was 10±8 month (Figure 6C). Therapy was discontinued due to increase of creatinine (n=1) or polyuria (n=1). In two patients, SGLT2i was discontinued due to impairment of kidney function and was restarted after infusion therapy. The patient with unwanted weight loss decided to pause therapy for a few months and restarted therapy with SGLT2i. Therapy was stopped permanently in the patient with the Fournier's gangrene and the patient with acute necrotizing pancreatitis. In one patient, the reason for discontinuation was not reported. In the 10 children of our study, there were no AEs observed and the treatment with SGLT2i was not discontinued.

Discussion

This worldwide, observational study investigated a cohort of patients with AS, who started therapy with SGLT2i, including 10 children. The primary endpoint was change of albuminuria after six months on therapy. The primary mechanism by which SGLT2is are considered to be nephroprotective is afferent vasoconstriction and reduction in intraglomerular pressure due the tubuloglomerular feedback via the macula densa.[25,26] A marker of this reduction is a decrease in the amount of albuminuria, which is largely independent of concomitant changes in metabolic parameters or eGFR.[27] Notably, a 25% decrease in albuminuria has been reported to provide confidence that an intervention would result in a clinical benefit.[28] In the adult patients of this study, at the first three follow-up visits after initiation of SGLT2i-therapy, a consistent and significant reduction of albuminuria by >30% was observed. This can be interpreted as promising signal that the reduction of albuminuria in these patients might result in clinical benefit at longer follow-up. Importantly, this study showed a significant correlation between the amount of albuminuria at baseline and the later change of eGFR in patients with AS. Patients with truncating gene-variants causing AS are less responsive to RASi-therapy.[29] This study indicates that AS patients with non-missense variants might also be less responsive to SGLT2i-therapy than patients with missense variants, as a significant higher loss of eGFR was observed in AS patients with non-missense variants in this study. Therefore, future studies investigating SGLT2i in AS should consider stratifying by genotype.

At baseline, a relevant number of patients had a hypoalbuminemia. In agreement with the decrease of albuminuria after start of SGLT2i-therapy, 47% of the patients with hypoalbuminemia at baseline recovered to a normal serum-albumin at follow-up. One can speculate that the positive effect of SGLT2i-therapy on lowering albuminuria contributed to the increase in serum-albumin though regression to the mean over the cause of this study

cannot be ruled out. Therefore, SGLT2i might be considered as an additional treatment option in patients with AS and hypoalbuminemia due to nephrotic range albuminuria.

Approximately one year after baseline, a significantly decrease in the eGFR of -9±12 ml/min/1.73 m² per year was observed. SGLT2i can cause an acute transient decrease in eGFR through a reduction in glomerular pressure.[30] For that reason, the decrease in eGFR observed in this study is thought to be – in parts – triggered by the initiation of SGLT2i-therapy. However, the change in eGFR in this study appears to be higher compared to previously described changes in eGFR in other glomerular diseases: eGFR changed by −3.7 and -3.5 mL/min/1.73 m²/year in patients with focal segmental glomerulosclerosis and IgA nephropathy. [31,32] Due to the observational nature of this study, the change in eGFR is not placebo-controlled. While this limitation should be acknowledged, patients with AS need to be recognized a high-risk group for fast CKD-progression.[33]

SGLT2is are, irrespective of hypertension status, associated with a slight reduction in blood pressure mediated through natriuresis, reduction in arterial stiffness and improvement in endothelial function.[34–37] In this study, systolic blood pressure was significantly lower at V2 (128±14 vs. 124±13 mmHg). However, this difference was not observed after a longer follow-up, possibly due to the small number of patients remaining at that time point. The slight decrease of blood pressure might contribute to the nephroprotective effect of SGLT2is. Reducing glomerular filtration pressure can alleviate proteinuria and subsequent renal tubular and interstitial damage.[6,11,38] Therefore, preventing angiotensin II–mediated constriction of the efferent arteriole by RASi is the cornerstone of antiproteinuric therapy to reduce podocyte injury in AS.[39,40] SGLT2i are expected to have an additive effect on the glomerulus via afferent arteriole constriction. Therefore, combining RASi with SGLT2i in patients with albuminuria due to glomerular disease is anticipated to enhance kidney failure-free timespan.[41] Although

the precise mechanisms underlying preservation of kidney function by SGLT2i are not fully understood, other proposed pathways include inflammation and fibrosis suppression as well as a reduction in renal ischemia.[42,43]

Therapy with SGLT2i was overall well tolerated with a relatively low rate of discontinuation of therapy or reported adverse events. Adverse events related to hypovolemia, which were reported to be more common in patients treated with SGLT2i, was observed in one patient.[44] Ketoacidosis or severe hypoglycemia were not observed, but two severe adverse events (acute necrotizing pancreatitis and Fournier's gangrene) occurred. Due to the relevant loss of eGFR and severe adverse events observed in this study (though a relationship between SGLT2i and these events is uncertain), a cautious approach is currently recommended when administering SGLT2 inhibitors to patients with AS. Furthermore, this underscore the importance of generating further high-level evidence for efficacy and safety when SGLT2i are prescribed in rare disease like AS, at early stages of CKD or in young patients, especially children, as these groups were not well represented in the previous RCTs. Therefore, the multicenter, randomized, double-blind, placebo-controlled, trial DOUBLE PRO-TECT Alport trial (NCT05944016) will assess safety and efficacy of the SGLT2i Dapagliflozin in children and young adults with AS. Eligible patients will be 2:1 randomly assigned to 48 weeks of treatment with Dapagliflozin or placebo. The primary endpoint will be change in UACR and, as key secondary outcome, eGFR change will be analyzed.[45]

This study had limitations that warrant cautious interpretation of the results: Due to the observational nature of this study, the timing of UACR and eGFR assessments after treatment initiation were not standardized and changes in eGFR and UACR were not placebo-controlled. The retrospective design also limits the ability to comprehensively assess the safety profile of SGLT2i in patients with AS. While the lack of a control arm limits the generalizability of the

study findings, including one might have posed challenges in interpretation. Patients in a control arm would likely have a more stable disease course compared to those who opted for a new treatment option. This inherent selection bias would have complicated the analysis of treatment effects. Therefore, the study design focused on intra-individual changes in eGFR and UACR to assess treatment response. Conversely, this approach introduces a potential selection bias of its own, with a possible overrepresentation of patients with a higher risk of CKD progression. Furthermore, only a small number of children and adolescents could be included in the study, the observation period for these patients was relatively short, and due to the unavailability of Cystatin C, the CKiD U25 formula could not be used. Additionally, for six patients, the method used to confirm the diagnosis was not provided.

Despite these limitations, this study provides first evidence for a possible nephroprotective effect of SGLT2i in patients with AS by including a substantial number of patients with AS, considering the rarity of the disease and the recent approval of SGLT2i for CKD, and formed the scientific basis for the current RCT with SGLT2i in children and young adults with AS, *DOUBLE PRO-TECT Alport*.

Conclusions

In conclusion, this study indicates that, additive to RASi, SGLT2i have the potential to reduce the amount of albuminuria in patients with Alport syndrome. This study successfully formed the scientific basis for the current RCT with SGLT2i in children and young adults with AS, *DOUBLE PRO-TECT Alport*. Future studies are needed to investigate the long-term effects of SGLT2i on CKD progression in patients with AS to assess whether the observed reduction in albuminuria translates to a delay in kidney failure.

DISCLOSURE

JB, OG, TF and JS are members of the steering committee of the DOUBLE PRO-TECT Alport trial. OG received advisory fees from AstraZeneca, his employer received advisory fees from Boehringer Ingelheim. MH has received speaker fees from AstraZeneca. The other authors declare no conflicts of interest.

DATA STATEMENT

After de-identification, individual participant data that underlie the results reported in this article will be shared to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. The full study protocol is provided as supplement. Requests should be sent to the corresponding author.

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MC, MS, RUM, PT, BH, MZ, BK and JH contributed to data collection, data interpretation, and discussion of the results and the manuscript. All authors edited and approved the final version of the article.

Supplementary Material:

Supplementary Material

STROBE Checklist

Guard Alport study protocol

Questionnaire

Supplementary information is available at KI Report's website.

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Tables:

Table 1: Demographic and clinical characteristics of the 102 adult patients in GA at baseline.

Values are mean+SD or n(%) as appropriate

ACEi, Angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, Body-Mass-Index; RASi, inhibitiors of the renin-angiotensin system

	N	
Age (years)	102	38±14
Male no. (%)	96	63 (66)
Ethnicity	88	
Caucasian		68 (80)
Asian		16 (19)
Hispanic		1 (1)
Country (%)	102	
Belgium		6 (6)
China		3 (3)
France		6 (6)
Germany		39 (38)
Lithuania		8 (8)
South Korea		9 (9)
Switzerland		2 (2)
UK		22 (22)
USA		7 (7)
Mode of inheritance (%)	88	
X-linked		58 (66)
Autosomal		29 (33)
Digen		1 (1)
RASi	102	95 (93)
ACEi		45 (47)
ARB		42 (44)
ACEi + ARB		8 (8)
BMI (kg/m^2)	77	27±6
Systolic/diastolic blood pressure (mmHg)	82	127±16/78±11
Albumin (g/dL)	69	3.8±0.5
Creatinine (mg/dl)	101	1.6±0.7
eGFR (ml/min/1.73 m^2)	98	63±35
Albuminuria (mg/g creatinine)	51	1699 ±1472
Proteinuria (mg/g creatinine)	36	1805±1326

Table 2: Baseline characteristics and follow up data after a mean follow up of 4±5 month in 10 children. Values are mean+SD or n(%) as appropriate

	N	Baseline	Follow up
Age (years)	10	15±3	
Male no. (%)	5	5 (50)	
Mode of inheritance (%)	10		
X-linked		9 (10)	
Autosomal		1 (10)	
BMI (kg/m^2)	10	21±4	
Systolic/diastolic blood pressure (mmHg)	8	116±13/72±11	117±13/71±13
Creatinine (mg/dl)	10	0.8±0.3	0.9±0.3
eGFR (ml/min/1.73 m^2)	10	119±32	107±36
Proteinuria (mg/dL)	8	114±94	122±110
Albuminuria (mg/g creatinine)	2	1426±1247	641±190

Figures

Figure 1: Albuminuria and eGFR at V1 (months 1-3)

A Albuminuria before initiation of SGLT2i therapy (baseline; blue) and after a mean follow up of 2±1 months (V1; red) of SGLT2i therapy (p=0.002, n=30; geometric mean with 95% CI)

B eGFR before initiation of SGLT2i therapy (baseline; blue) and after mean follow up of 2±1 months (V1, red) (p=0.004, n=62; mean with 95%CI).

Figure 2: Albuminuria and eGFR at V2 (months 4-8)

A Albuminuria before initiation of SGLT2i-therapy (baseline; blue) and after a mean follow up of 6±1 month (V2; red) (p=0.01, n=33, geometric mean with 95% CI);

B eGFR before initiation of SGLT2i-therapy (baseline, blue) and after a mean follow up of 6±1 month (V2; red) (p<0.001, n=72, mean with 95%CI).

Figure 3: Albuminuria and eGFR at V3 (months 9-15)

A Albuminuria before initiation of SGLT2i-therapy (baseline; blue) and after a mean follow up of 12±2 month (V3; dark red) (p=0.032, n=22 , geometric mean with 95% CI);

B eGFR before initiation of SGLT2i-therapy (baseline; blue) and after a mean follow up of 12±2 month (V3; dark red) (p<0.001, n=35 , mean with 95%CI).

Figure 4: Correlation between amount of albuminuria at baseline and the change in eGFR after initiation of SGLT2i

Pearson's correlation between amount of albuminuria at baseline and absolute change in eGFR at a mean follow up of 11±2 month (r=0.821; p=<0.01; n=20)

Figure 5: Change in eGFR over time after initiation of SGLT2i-therapy

eGFR at baseline, V1 (months 1-3), V2 (months 4-8) and V3 (months 9-15) in 16 patients, who completed every visit from V1 to V3;

Figure 6: Frequency of adverse events and discontinuation of SGLT2i-therapy

A Number of patients with observed adverse events (AEs) (white) and patients without observed AEs (dark grey) (n=89);

B Number of patients without (therapy continued; white) and with discontinuation of therapy with SGLT2i (therapy discontinued; dark grey) (n=106).

C Time to discontinuation of SGLT2i-therapy in month. The reason for discontinuation in one patient after seven month was not reported.