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The Role of Matrix Metalloproteinase Inhibitor (Doxycycline) for the Treatment of Primary Focal Segmental Glomerulosclerosis

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ABSTRACT

Background: Nephrotic range proteinuria, segmental obliteration or collapse of glomerular capillary loops in some glomeruli, and increased extracellular matrix are the hallmarks of the podocytopathy known as focal and segmental glomerulosclerosis (FSGS).

Objective: This research set out to determine if the matrix metalloproteinase inhibitor doxycycline (DOX) could be useful in the management of primary focal segmental glomerulosclerosis.

Patients and Methods: This prospective cohort study was conducted on 100 patients with primary FSGS, who were recruited from Nephrology Department at Benha University Hospital. Informed consents were signed after getting approval from the Ethics Committee of Benha University. Inclusion criteria were age >18 years, primary FSGS, diagnosis is confirmed by renal biopsy, patients with overt albuminuria (A/C ratio>30 mg/g and urinary albumin > 30 mg/day). **Results:** The hemoglobin level was significantly higher at follow-up compared to baseline level in group 1 (P=0.026) and was insignificantly different between baseline and at follow-up in group 2. Hemoglobin level at baseline and follow-up was insignificantly different between both groups. C-reactive protein was significantly lower at follow-up compared to baseline level in group 1 and 2 (P<0.001). C-reactive protein was significantly lower at follow-up in group 2 compared to group 1 (P<0.001) and was insignificantly different between both groups at baseline. Platelet count and white blood cells were insignificantly different between baseline and at follow-up in both groups. There was an insignificant difference between both groups regarding platelet count and white blood cells at baseline and at follow-up**. Conclusions:** Patients who received DOX alongside conventional therapy exhibited notable improvements in clinical and biochemical parameters, including reduced proteinuria and enhanced kidney function, compared to those receiving conventional therapy alone. These findings suggest that DOX may hold promise as a supplementary treatment strategy for FS.

Keywords: Matrix Metalloproteinase Inhibitor, Doxycycline, Primary Focal Segmental Glomerulosclerosis.

INTRODUCTION

The podocytopathy described as focal and segmental glomerulosclerosis (FSGS) is characterised by increased extracellular matrix in specific glomeruli, nephrotic-range proteinuria, and segmental obliteration or collapse of glomerular capillary loops. In the United States, focal segmental glomerulosclerosis (FSGS) is the leading cause of kidney failure (ESRD)[1,2].

Idiopathic FSGS is distinguished by a poor renal prognosis, relapses, and non-responsiveness to immunosuppressive medications; it recurs in less than 30-50 percent of patients following kidney transplantation, and renal graft failure is common [1].

Matrix metalloproteinases (MMP) are endopeptidases that contain zinc and have multiple domains. Fibrosis and extracellular matrix remodelling are their respective functions. These entities are found in numerous organs, including the kidney[3]. MMP-2 and MMP-9 were found in mesangial cells and serum from patients with chronic renal disease. Podocytes' expression was upregulated in response to inflammation [4]. Doxycycline, a well-known tetracycline antibiotic, is an intriguingly well-tolerated drug with significant MMP inhibitory activity at subantimicrobial dosage levels. Clinical studies are currently being conducted to determine the efficacy of this function as an MMP inhibitor in the fields of dermatology, cardiovascular medicine, ophthalmology, and dentistry, all of which were identified in the context of periodontitis research[5]. The mechanism by which subantimicrobial dosage doxycycline (DOX) (SDD) inhibits MMPs is a direct inhibition of the active form of MMPs by the binding of calcium and zinc ions, as well as a direct inhibition of the activation of latent pro-MMPs. Patients with diabetic nephropathy (DN) who received DOX for three months saw a reduction in proteinuria.[6].

Doxycycline, an MMP inhibitor, improves glomerulosclerosis (GS), but has negative effects on the glomeruli. However, there is no data on the effect of MMP inhibitors or DOX in FSGS.

The current study sought to investigate doxycycline, a matrix metalloproteinase inhibitor, and its powerful use in focal segmental glomerulosclerosis therapy.

PATIENTS AND METHODS

One hundred patients with primary focal segmental glomerulosclerosis (FSGS) were enrolled from the nephrology clinic at Benha University Hospital in this prospective cohort research.

Ethical approval:

After receiving clearance from the Benha University Ethics Committee, informed consents were signed by the participants. Every participant was given a code number and told the study's rationale. The Helsinki Declaration was followed throughout the study's conduct.

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Patients with overt albuminuria (A/C ratio>30 mg/g and urine albumin > 30 mg/day) and age >18 years were considered for inclusion.

Patients were not allowed to participate if they exhibited any of the following characteristics: hepatic dysfunction (transaminase levels >2xULN), secondary FSGS, hypersensitivity to tetracycline derivatives, systemic long-term antimicrobial therapy within the previous 6 months, serum creatinine levels >1.4 mg/dL, incompatibility of DOX with the patient's concurrent medications.

Two groups of patients were selected at random:

- **Group 1:** Patients (50) with FSGS under conventional therapy as control group.
- **Group 2:** Patients (50) with FSGS under conventional therapy and DOX 100 mg/day for 3 months. Those patients were informed about using DOX in treatment (benefits and side effects).
- **Follow-Up:** Regular follow-up appointments were crucial to assess the response to treatment and to manage any emerging issues. Follow-up visits were scheduled at regular intervals, every 2 weeks or monthly, during the 3-month treatment period. During follow-up visits, laboratory tests, including serum creatinine, blood urea, urine albumin/creatinine ratio, eGFR, fasting blood sugar, lipid profile, liver function, CRP and CBC, were performed to track the response to treatment and ensure patient safety.

Adjustments to medication dosages or treatment plans were made based on the patient's clinical response and any observed adverse effects.

All studied cases were subjected to the following:

In-depth interviewing with a focus on: Personal history: age, sex, Comorbidities: Diabetes mellitus, hypertension, cardiovascular diseases (CVS), anemia, **Drug history:** [(Non-steroidal Anti-inflammatory (NSAID), Aminoglycosides, Erythropoietin stimulating agents (ESA), Angiotensin converting enzymes inhibitors (ACEI)], History of surgical operations.

General examination including mental state, jaundice or pallor and general comment on patient conscious,

Vital signs: rate of breathing and body temperature, blood pressure, pulse, capillary filling time, Assessment of body mass index (BMI). Systemic examination with special stress on: Blood pressure (Systolic and diastolic), temperature by oral route, body mass index (BMI), pulmonary congestion, ascites, lower limb edema.

Cardiovascular System: For detection of any abnormal heart sounds or murmurs.

Abdominal Examination

Laboratory investigations: Random blood sugar (mg/dl), complete blood count (RBCs count, Haematocrit and Hb concentration), Serum creatinine and blood urea (mg/dl), Chronic kidney Disease Epidemiology Collaboration's estimated glomerular filtration rate (eGFR) (CKD-EPI). Liver function tests; serum glutamic-oxaloacetic transaminase (SGOT) (IU/L), SGPT (IU/L) alkaline phosphatase (IU/L), S. bilirubin (mg/dl), S. albumin (g/dl), serum calcium (mg/dl), serum phosphate (mg/dl), lipid profile [S. Cholesterol (mg/dl), S. triglycerides (mg/dl), S. HDL (mg/dl), S.LDL (mg/dl)], C-reactive protein (mg/dl), serum uric acid (mg/dl), urine analysis, urinary 24 protein every 2 weeks, urinary albumin/creatinine ration (mg/g), and virology (HCV Ab, HBsAg, HIV Ab).

Radiological investigations:

Chest-X-ray, Abdominal ultrasonography (with details on kidney site, size, back pressure and corticomedullary different ion), Echocardiography for assessment of EF, LVH, IHD or HT failure, ECG.

Follow up: Proteinuria disappears, Proteinuria of 0.3 g/d or less was used as the cutoff for CR. Proteinuria reductions of 50% or proteinuria levels between 0.3 and 3.5 grammes per day were considered partial remissions. Proteinuria >3.5 g/d after achieving CR, Adverse effects of medicines taken in both groups during relapse of proteinuria remission.

Sample size calculation:

G power version 3.1.9.4 was used to assess the impact of the matrix metalloproteinase inhibitor DOX on renal functions in people with diabetic nephropathy. Using the criteria established by Cohen (1988), the effect size of this study was determined to be 1.04. The significance level was set at 0.05 and the level of power was set at 0.95. With an effect size of this magnitude, a sample size of N = 42 (t-test: difference between two independent groups) was required, with at least 21 patients in each group.

Statistical analysis

SPSS v25 was used for the statistical analysis (IBM Inc., Armonk, IL, USA). Quantitative variables were summarised by means, standard deviations (SDs), and range, and the unpaired Student's t-test was used to draw inferences about differences between groups. Chi-square test was utilised to conduct analyses on frequency and percentage (percent) values for qualitative variables. The means of two populations was compared using a paired sample t-test when there is a correlation between the samples. To be considered statistically significant, the P value had to be less than 0.05 with two tails.

RESULTS

The eligibility of 139 patients was assessed for this trial; 27 did not meet the criteria, while 12 others chose not to take part. The remaining one hundred patients were split into two groups at random (50 patients in each). After the first 100 patients were examined, 90 remained in the study due to attrition (50 patients in group 1 and 40 patients in group 2).

There were no statistically significant variations between the groups in terms of age, sex, weight, height, or body mass index, nor was there any difference in the length of disease [**Table 1].**

Table (1): Comparison of the demographics between the studied groups

		Group 1 (n=50)	Group 2 (n=50)	P value
Age (years)	**Mean ± SD**	51.44 ± 7.95	49.5 ± 7.52	0.213
	Range	36 - 65	36 - 64	
Sex	**Male**	36 (72%)	30 (60%)	0.205
	Female	14 (28%)	20 (40%)	
Duration of disease (years)	**Mean ± SD**	2.0 ± 0.69	2.19 ± 0.84	0.220
	Range	1-3	1-3	

Group 2 had considerably lower levels of triglycerides than group 1. Other lipid profile tests (cholesterol, low density lipoprotein, and high-density lipoprotein) between the two groups did not differ significantly. Group 2 had considerably lower fasting plasma glucose levels than group 1 **[**Error! Not a valid bookmark self-reference.**].**

Table (2): Comparison of lipid profile and fasting blood glucose between the studied groups

		Group 1 (n=50)	Group 2 (n=50)	P value
Cholesterol (mg/dL)	**Mean ± SD**	223.26 ± 48.28	219.52 ± 44.66	0.688
Triglycerides (mg/dL)	**Mean ± SD**	243.74 ± 53.67	213.96 ± 53.15	**0.007***
Low density lipoprotein (mg/dL)	**Mean ± SD**	141.56± 24.91	140.62± 27.09	0.857
High density lipoprotein (mg/dL)	**Mean ± SD**	54.98± 8.74	57.98± 9.47	0.103
Fasting plasma glucose (mg/dL)	**Mean ± SD**	107.08 ± 21.86	97.68± 21.14	**0.031***

*: statistically significant as p value <0.05.

There was no statistically significant difference between the studied groups regarding serum bilirubin, albumin, and alkaline phosphates as well as some minerals, before treatment **[Table 3].**

Table (3): Comparison of serum bilirubin, albumin, and alkaline phosphates as well as some minerals before treatment between the studied groups

		Group 1 (n=50)	Group 2 (n=50)	P value
Serum bilirubin (mg/dL)	**Mean ± SD**	0.79 ± 0.17	0.76 ± 0.17	0.351
Serum albumin (g/dL)	**Mean ± SD**	4.21 ± 0.43	4.26 ± 0.47	0.612
Alkaline phosphatase (IU/L)	**Mean ± SD**	69.62 ± 16.76	69.62± 15.78	1.0
Serum calcium (mg/dL)	**Mean ± SD**	8.53± 0.89	8.3± 0.92	0.193
Serum phosphorus (mg/dL)	**Mean ± SD**	4.33± 0.47	4.26± 0.48	0.426
Serum sodium (mmol/L)	**Mean ± SD**	137.48± 1.64	137.52± 1.71	0.905
Serum potassium (mEq/L)	**Mean ± SD**	4.22± 0.51	4.21± 0.49	0.968

*: statistically significant as p value <0.05

In group 1, the hemoglobin level at follow-up was considerably higher than at baseline, whereas there was no significant difference between baseline and follow-up in group 2. There was insignificant difference in hemoglobin levels between the two groups at either the beginning or end of the study. C-reactive protein was significantly reduced in both groups 1 and 2 after the follow-up period compared to the baseline period. C-reactive protein was significantly lower in group 2 compared to group 1 at follow-up, despite there was no difference between the groups at baseline. There was no significant change in either group's white blood cell or platelet count between the two time points. Platelet and white blood cell counts did not significantly differ between the two groups at either time points studied **[Table 4].**

Table (4): Comparison of complete blood count and C-reactive protein between the studied groups

		Group 1 (n=50)	**Group 2 (n=50)**	**P2**
Hemoglobin (g/dL)	**Baseline**	10.52 ± 1.33	10.53 ± 1.28	0.976
		Group 1 (n=50)	**Group 2 (n=40)**	
	Follow-up	11.0 ± 0.82	10.84± 0.91	0.364
P1		**0.026***	0.163	
		Group 1 (n=50)	**Group 2 (n=50)**	
Platelet (*10^9/L)	**Baseline**	275.02± 15.12	272.26 ± 15.07	0.363
		Group 1 (n=50)	**Group 2 (n=40)**	
	Follow-up	275.44 ± 13.98	275.98 ± 14.37	0.859
P1		0.882	0.232	
		Group 1 (n=50)	**Group 2 (n=50)**	
White blood cells (*10^9/L)	**Baseline**	8.83 ± 1.53	8.88 ± 1.48	0.650
		Group 1 (n=50)	**Group 2 (n=40)**	
	Follow-up	8.84 ± 1.31	8.99 ± 1.51	0.622
P1		0.972	0.550	
		Group 1 (n=50)	**Group 2 (n=50)**	
C-reactive protein (mg/dL)	**Baseline**	82.94 ± 13.98	76.54 ± 18.56	0.201
		Group 1 (n=50)	**Group 2 (n=40)**	
	Follow-up	56.12 ± 13.85	33.51 ± 8.21	**<0.001***
P1		**<0.001***	**<0.001***	

Data are presented as mean ± SD and range, P1: p value within groups, P2: p value between groups, *: statistically significant as p value <0.05.

The alanine aminotransferase levels in group 2 were significantly higher at follow-up compared to baseline, while in group 1 there was no significant difference between the two time points. Baseline and follow-up values of alanine aminotransferase showed no significant differences between the two groups. In both groups, there were no significant differences in baseline and follow-up aspartate aminotransferase levels. There was no significant difference in aspartate aminotransferase levels between the two groups at baseline or at follow-up **[Table 5].**

Table (5): Comparison of alanine aminotransferase and aspartate aminotransferase between the studied groups

		Group 1 (n=50)	**Group 2 (n=50)**	**P2**
Alanine aminotransferase (IU/L)	**Baseline**	24.06 ± 6.00	25.46 ± 6.23	0.280
		Group 1 (n=50)	**Group 2 (n=40)**	
	Follow-up	24.58 ± 6.13	30.15 ± 7.28	**<0.001***
P1		0.700	0.086	
		Group 1 (n=50)	**Group 2 (n=50)**	
Aspartate aminotransferase (IU/L)	**Baseline**	26.84 ± 6.64	28.22 ± 6.85	0.333
		Group 1 (n=50)	**Group 2 (n=40)**	
	Follow-up	28.34 ± 7.07	31.85 ± 7.75	0.157
P1		0.239	0.273	

Data are presented as mean ± SD and range, P1: p value within groups, P2: p value between groups, *: statistically significant as p value <0.05.

Regarding the outcomes the study, group 2 improved significantly more than group 1. Significantly fewer patients in group 2 developed end-stage renal disease and required haemodialysis than in group 1 [Error! Reference source not found.**].**

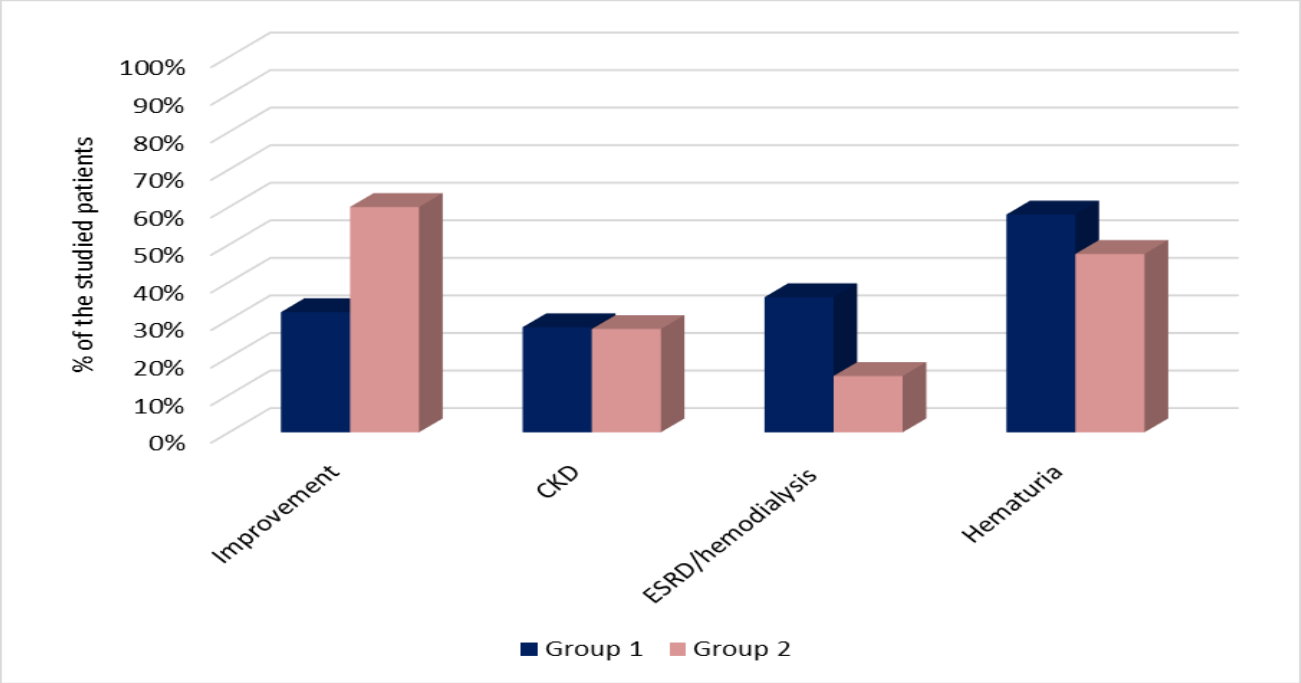

Figure (1): Comparison of the outcome between the studied groups

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DISCUSSION

In comparison to other glomerular disease diagnoses, the prevalence of FSGS appears to be on the rise internationally, and it is a leading cause of end-stage renal disease (ESRD). Due to large global discrepancies in the indications, accessibility, and pathology support for kidney biopsy, it is difficult to determine the true incidence and prevalence of FSGS [7].

A complicated combination of elements, including pathophysiology, histology, and genetics, determines the classification of FSGS. FSGS should be classified as either primary (idiopathic) or secondary. In this category would be familial/genetic forms, virus-associated forms, drug-induced forms, and forms mediated by adaptive structural-functional responses (such as congenital or acquired renal mass/nephron complement depletion) [8].

The turnover of the extracellular matrix is mediated by matrix metalloproteases (MMPs), a class of zinc peptidases. In persistent hypertension, there is evidence that increased MMP activity is involved in the remodelling of resistant arteries. We therefore anticipated that DOX inhibition of MMP activity would reduce vascular remodelling [9].

In this study, the intervention group treated with DOX had significantly lower TG levels than the control group (P=0.007). This conclusion is consistent with the findings of **Chang *et al.*** [10], who evaluated the effect of DOX on LAM-associated cell adhesion, proliferation, and MMP production. This matrix metalloproteinase inhibitor may have a lipid-lowering effect, as this matrix metalloproteinase inhibitor significantly reduced TG levels in individuals treated with DOX compared to the control group.

Other lipid profile variables, including LDL, cholesterol, and HDL, were not significantly different between the two groups. This was in contrast to the findings of **Salminen *et al.*** [11], who did a similar investigation to determine if (SDD) impacts the serum's ability to remove cholesterol from macrophages. For two years, 45 osteopenic postmenopausal women with periodontitis were randomly assigned to receive either fifteen DOX hyclate (20 mg, n = 19) or placebo (n = 26) pills. At baseline, one- and two-year intervals, serum samples were taken. The cholesterol efflux potential of human macrophage culture serum (THP-1) was investigated. They demonstrated significant increases in cholesterol and LDL levels in the DOX-treated group in comparison to the control group. Variations in patient characteristics, duration of treatment, or dose regimens between studies may account for this discrepancy.

In terms of glucose metabolism, the FBG levels of the intervention group treated with DOX were significantly lower than those of the control group (P=0.031). **Chen *et al.*** [12] tested whether the anti-inflammatory properties of DOX at subantimicrobial dosages may improve glycemic control in mice fed a high-fat diet. Mice treated with doxycycline exhibited a substantial decrease in FBG levels, indicating a potential benefit for glycemic management. At 20 g/mL, DOX dramatically increased glucose tolerance and decreased fasting glucose levels. DOX improved insulin resistance, fasting glucose and insulin levels, as well as liver and circulation lipid profiles, according to the findings of **Wang *et al.*** [13].

In group 1, the Hb level at follow-up was significantly greater than at baseline (P=0.026), however in group 2, there was no significant difference between baseline and follow-up. Both baseline and follow-up Hb values were comparable between the two groups. In groups 1 and 2, CRP levels at follow-up were significantly lower than at baseline (P<0.001). At

follow-up, the CRP levels of group 2 were significantly lower than those of group 1 (P<0.001), but there was no difference between the groups at baseline. White blood cell and platelet counts did not differ significantly between baseline and follow-up in either group. Platelet and white blood cell counts were comparable between the two groups at baseline and during follow-up.

Both conventional therapy and DOX treatment contributed to a decrease in CRP levels, with the addition of DOX potentially having a greater anti-inflammatory effect than conventional therapy alone; however, neither conventional therapy nor the addition of DOX had a significant effect on platelet counts.

16 (32 percent) patients in group 1 and 24 (60 percent) patients in group 2 showed improvement. CKD was diagnosed in 14 (28%) patients in group 1 and 11 (27.5%) participants in group 2. 18 (36 percent) patients in group 1 and 6 (15 percent) patients in group 2 developed ESRD/hemodialysis. Hematuria was seen in 29 (58 percent) members of group 1 and 19 (47.5%) members of group 2. Group 2 progressed considerably more than group 1 (P=0.040). In group 2, significantly fewer individuals developed ESRD and required haemodialysis compared to group 1 (P=0.045).

The trial results indicate that the addition of DOX to the standard treatment regimen for patients with primary FSGS resulted in significant improvements in a number of outcome metrics compared to conventional therapy alone. First, a larger proportion of patients in group 2 (60%) improved than in group 1 (40%). This shows that DOX may have a beneficial influence on the clinical outcomes of FSGS, potentially leading to enhanced disease management and symptom reduction [14,15].

Moreover, the prevalence of chronic kidney disease (CKD) was lower in group 2 (27.5%) than in group 1 (35%). This indicates that DOX treatment may have renoprotective effects, delaying the progression of FSGS to more severe stages of kidney disease. Notably, the difference in CKD incidence between the two groups was not statistically significant, suggesting that additional research is required to confirm this trend [16-18].

The lower incidence of ESRD necessitating hemodialysis in group 2 (15%) compared to group 1 (36%) is one of the study's most significant findings. This indicates that the addition of DOX to the treatment regimen may delay or prevent the progression to ESRD, which has substantial consequences for the long-term care and quality of life of patients with FSGS. The statistically significant difference in the incidence of end-stage renal disease (ESRD) between the two groups implies that DOX may aid in preserving renal function [19-20].

Hematuria, the most common symptom of FSGS, was observed in both groups, with a lower prevalence in group 2 (47.5%) than in group 1 (58 percent). Even though the difference between the two groups was not statistically significant, these results suggest that DOX may have some effect in reducing haematuria, a potentially distressing symptom.

CONCLUSIONS

FSGS' patients who received DOX alongside conventional therapy exhibited notable improvements in clinical and biochemical parameters, including reduced proteinuria and enhanced kidney function, compared to those receiving conventional therapy alone. These findings suggest that DOX may hold promise as a supplementary treatment strategy for FSGS.

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Conflict of Interest: Nil

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