In The Name of GOD

ROLE OF CALCINEURIN INHIBITORS IN TREATMENT OF PRIMARY MCD & FSGS

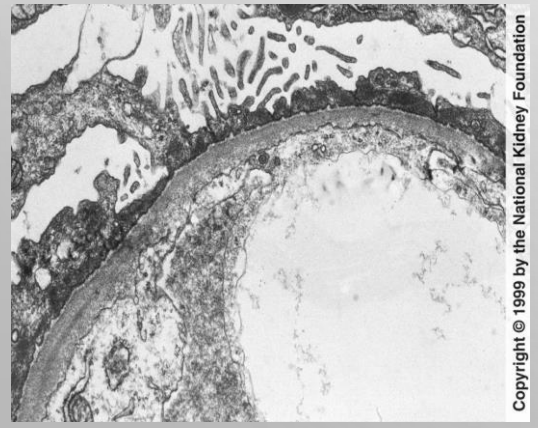
BY: FARNAZ TAVAKOLI

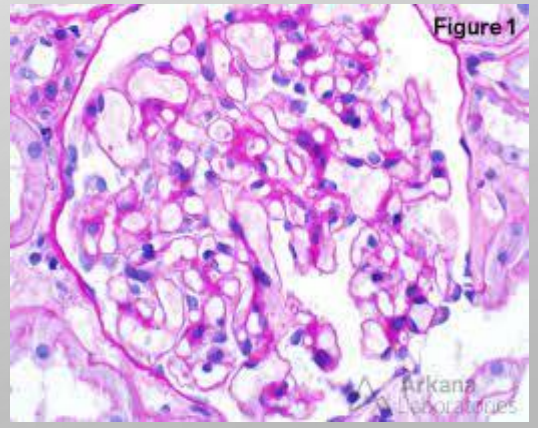
NEPHROLOGY

DR. SHARIATI HOSPITAL

MCD

- **MCD** is a glomerular disease resulting in nephrotic syndrome that is usually **sensitive to steroid treatment.**
- **LM** reveals glomeruli to be normal or minimally altered
- **IF**: without immune deposits on immunofluorescence or electron microscopy.
- **EM**: podocyte foot-process **fusion or effacement**, which are constant and diffuse during active disease and resolve during remission
- Complete remission of proteinuria on corticosteroid treatment, and maintenance of kidney function.



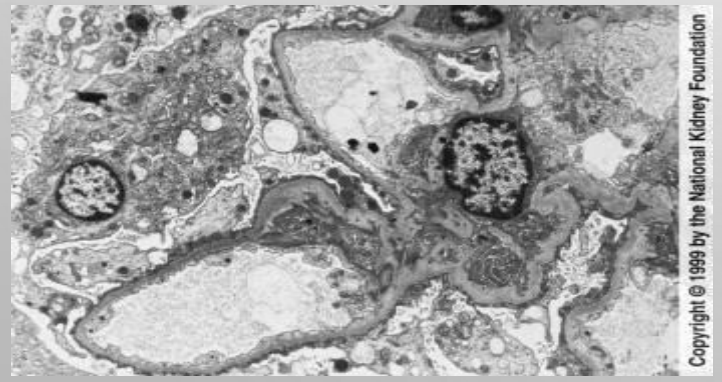


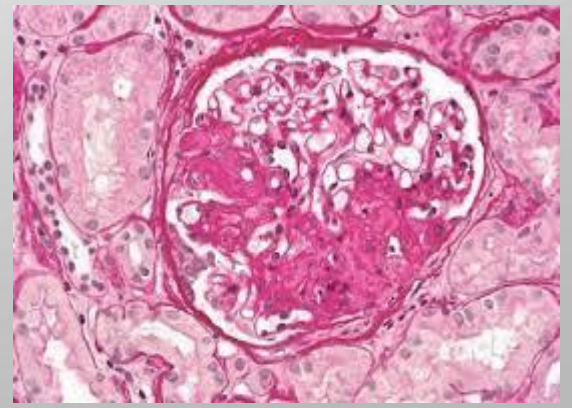
MCD

- There is still debate as to whether MCD is a separate entity or a morphological transition.
- Most agree that MCD is not an evolving disease when drugs revert and stabilize proteinuria.
- In cases with partial drug sensitivity, MCD may instead evolve into focal and segmental glomerulosclerosis.

FSGS

- Is not considered to be a single disease entity but a description of glomerular damage.
- FSGS is a lesion rather than a disease that are related to genetic, immunologic abnormalities and podocyte injury.
- LM: The presence of focal & segmental sclerotic glomerular lesions.
- IF: without immune deposits on immunofluorescence or electron microscopy
- EM: Podocyte foot process effacement
- Higher likelihood of steroid resistance and progression to renal failure

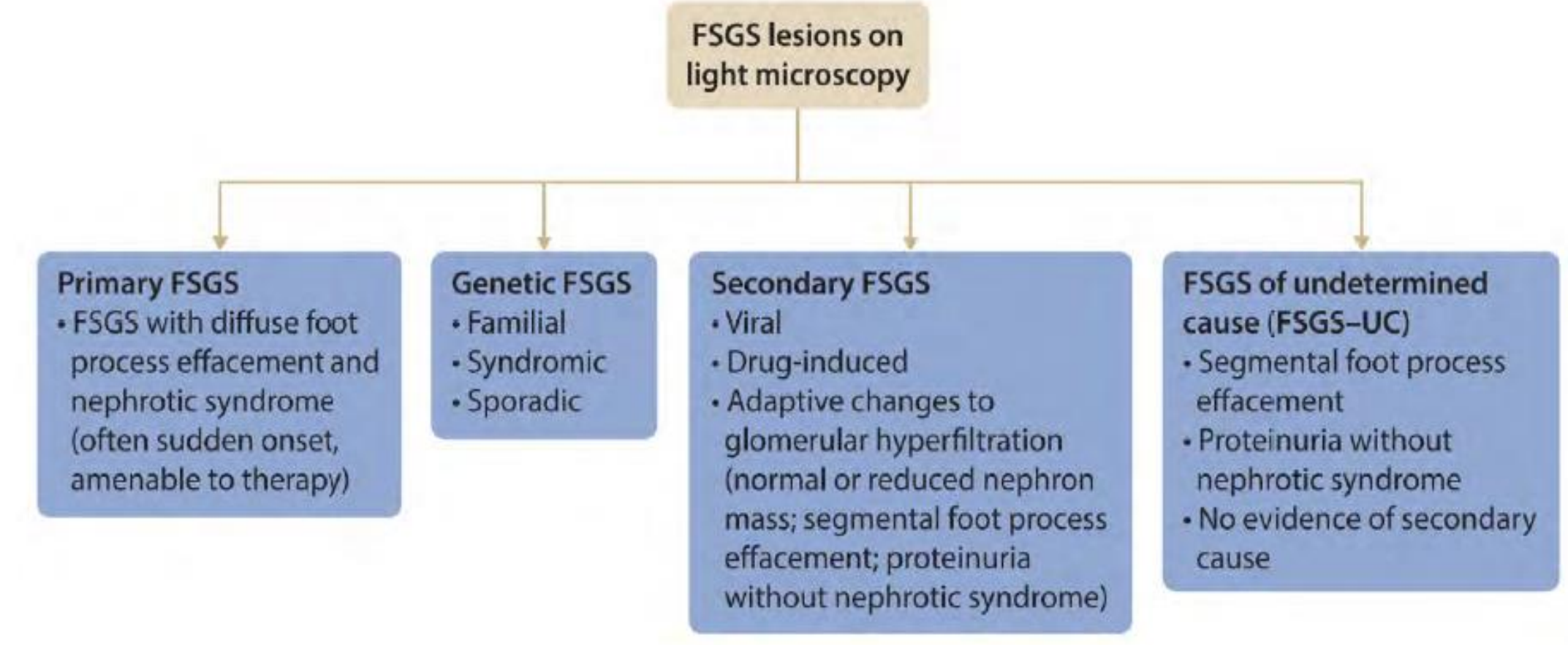




FSGS

- mutations of genes encoding podocyte-specific molecules have been identified as reasons of genetic FSGS including NPHS1, NPHS2, ACTN4, TRPC6 and INF2.
- risk factors for adverse outcomes of FSGS including heavy proteinuria, hypertension, interstitial fibrosis, glomerular sclerosis and reduced renal function.
- Spontaneous remission rate of FSGS is less than 20%
- Overall, FSGS remission rates to immunosuppressive treatments are reported variably between 47% and 66%.
- Effective treatment is difficult in steroid resistant or frequently relapsing patients.

PROPOSED CLASSIFICATION OF FSGS BY KDIGO



ARE MCD/FSGS TWO SEPARATE DISEASES?

OPINION

Minimal change disease and idiopathic FSGS: manifestations of the same disease

Rutger J. Maas[1], Jeroen K. Deegens[1], Bart Smeets[2], Marcus J. Moeller[3] and Jack F. Wetzels[1]

PERSPECTIVES

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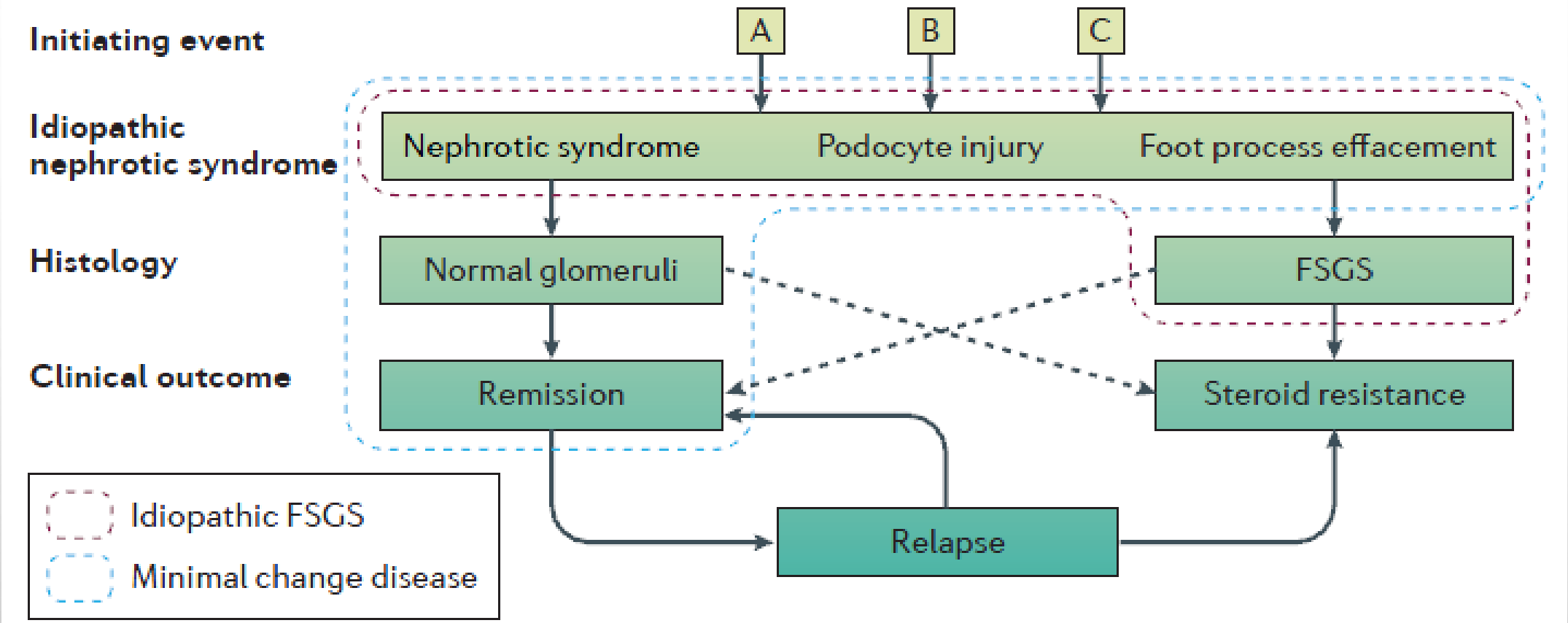
768 | DECEMBER 2016 | VOLUME 12

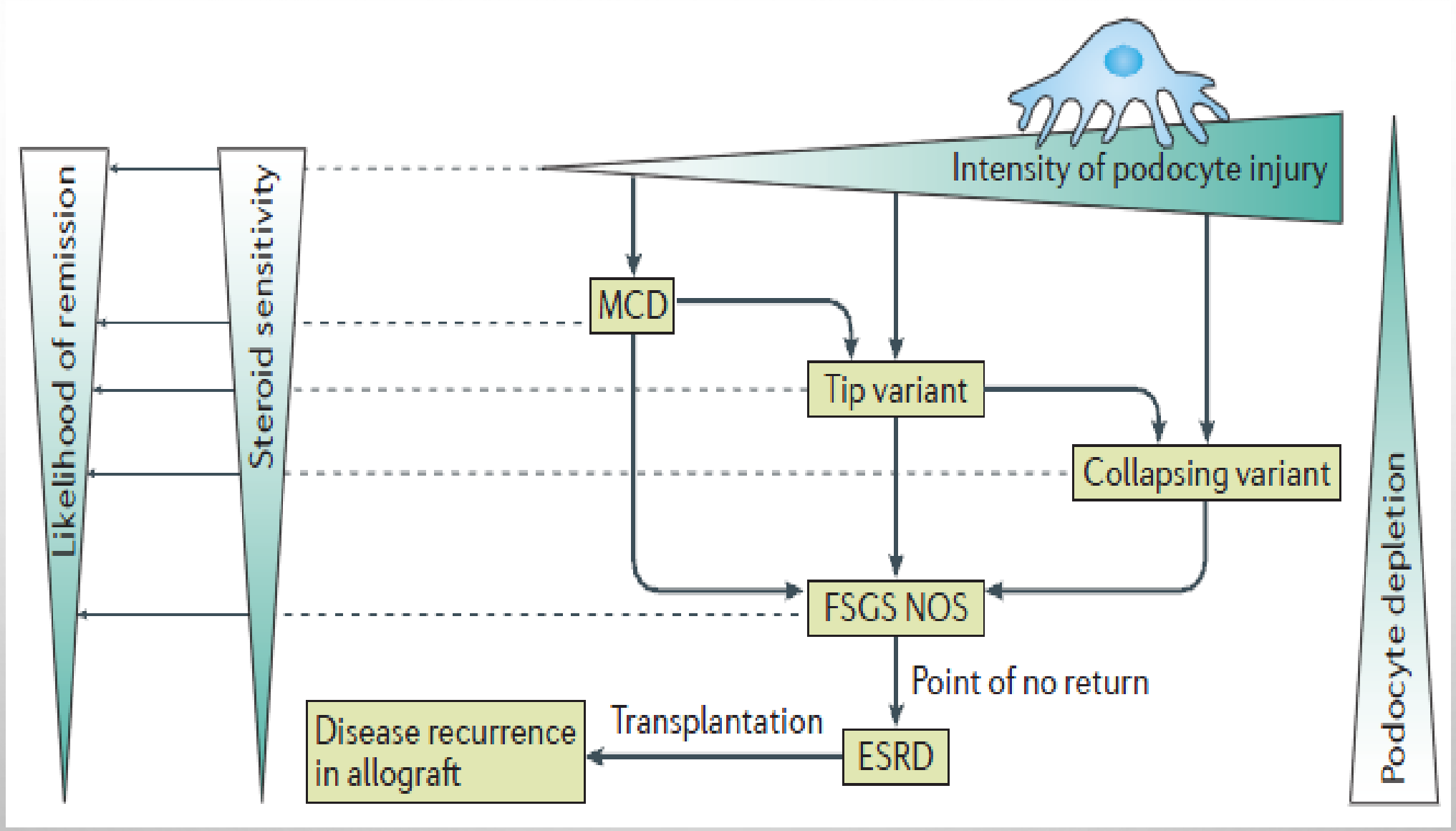
- ***MCD/FSGS*** **are one primary glomerular diseases, and proteinuria is the main clinical manifestation.**
- **The development of proteinuria is due to podocyte injury that damages the integrity of the glomerular filtration barrier.**
- **An early event in podocyte injury results in disorganization of the cytoskeleton and the fusion of foot processes and leads to the development of proteinuria and subsequent kidney damage.**

DOI: 10.1038/nrneph.2016.147



Schematic representation of idiopathic nephrotic syndrome in MCD and FSGS

DOI: 10.1038/nrneph.2016.147



DOI: 10.1038/nrneph.2016.147

Table 1 | Evidence for and against the hypothesis that MCD and idiopathic FSGS are separate entities

	For	Against
Biopsy findings	In steroid-resistant INS with normal appearing glomeruli, FSGS is likely missed owing to sampling error[9,10,7]	Recurrent FSGS is characterized by an initial phase with diffuse podocyte foot process effacement and normal appearing glomeruli on light microscopy, even in biopsy samples with many glomeruli[23,24]
	Later biopsy samples always show FSGS[18,19]	Findings in later biopsy samples are compatible with the concept that FSGS develops over time[18,19]
Animal models	NA	Following an initial phase with only diffuse podocyte foot process effacement, all of the available animal models of persistent proteinuria develop FSGS[33,35–37]; in models of toxic damage to podocytes, FSGS development is dose-dependent[34,37,39]
Circulating factors	FSGS is caused by a circulating permeability factor that is associated with progressive decline in renal function and recurrence of proteinuria after transplantation[56]; MCD is not associated with loss of renal function[118–120]	Circulating factors have been implicated in both MCD and FSGS[55]; they have not been identified but might be identical in MCD and FSGS — this hypothesis is supported by the observation that post-transplantation recurrence of FSGS occurs in patients with initially steroid-sensitive INS who develop secondary steroid resistance[125]
	Serum suPAR concentration is elevated in FSGS compared with MCD; high levels of suPAR were associated with post-transplantation FSGS recurrence[56]	Elevated serum suPAR concentration has not been validated as a biomarker of FSGS; suPAR levels were not elevated in patients with FSGS after correction for renal function[63–66]
	Angptl4 expression was upregulated in the glomeruli of patients with MCD; these patients had a distinctive pattern of Angptl4 oligomers in their urine, which was not seen in patients with FSGS[51]	Glomerular Angptl4 expression was not investigated in patients with FSGS; urinary tests were performed in a small group of patients, and two of the four patients with FSGS were not nephrotic[51]; the results have not yet been validated

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Table 1 | Evidence for and against the hypothesis that MCD and idiopathic FSGS are separate entities

	For	Against
Histological markers	Patients with MCD can be differentiated from those with FSGS by urinary B7-1 excretion[90,91]	Elevated urinary B7-1 excretion in MCD has not been validated; patients with FSGS may also have strong B7-1 expression[93]
	Decreased glomerular α-dystroglycan staining has been documented in MCD; expression of α-dystroglycan was normal in idiopathic FSGS[98,99]	Among patients with INS, dystroglycan staining did not predict proteinuria remission in response to therapy[99]; differential expression of α-dystroglycan between MCD and idiopathic FSGS was not confirmed in a subsequent study[100]
	The ratio of podocin to synaptopodin mRNA expression distinguished patients with MCD from those with early-stage idiopathic FSGS and a steroid-resistant disease course[101]	Differences in the ratio of podocin to synaptopodin mRNA expression in patients with MCD and idiopathic FSGS have not been validated; studies of glomerular mRNA expression profiles in idiopathic FSGS[104,102] and MCD[102] confirm that podocyte stress and parietal epithelial cell activation are involved in the development of FSGS lesions[103,105]
	Many genes are differentially expressed in the glomeruli of patients with MCD versus those with idiopathic FSGS[102,104]	The reported gene profiles are compatible with different stages of disease progression rather than differences in the aetiology of MCD and idiopathic FSGS[102,104]
Immune pathogenesis	Evidence suggests that abnormal T-cell function underlies MCD[68,71]; this mechanism has not been reported in FSGS	T-cell function in MCD and idiopathic FSGS has not been systematically compared; data from a humanized mouse model suggest that $CD34^+$ peripheral blood mononuclear cells are involved in the pathogenesis of both MCD and idiopathic FSGS[74]
Genetic causes	FSGS often has genetic causes[75,77–80]; no genetic causes of MCD have been identified	Genetic FSGS often has clear features of secondary FSGS with a gradual increase in proteinuria and incomplete podocyte foot process effacement[77,79]; no genetic causes of idiopathic steroid-sensitive FSGS have been reported
Steroid responses	MCD is steroid sensitive, whereas FSGS is steroid resistant	Some patients with MCD might have relapsing or secondary steroid-resistant disease resulting in FSGS, whereas some patients with FSGS might have complete remission on corticosteroid treatment[120,122,123]

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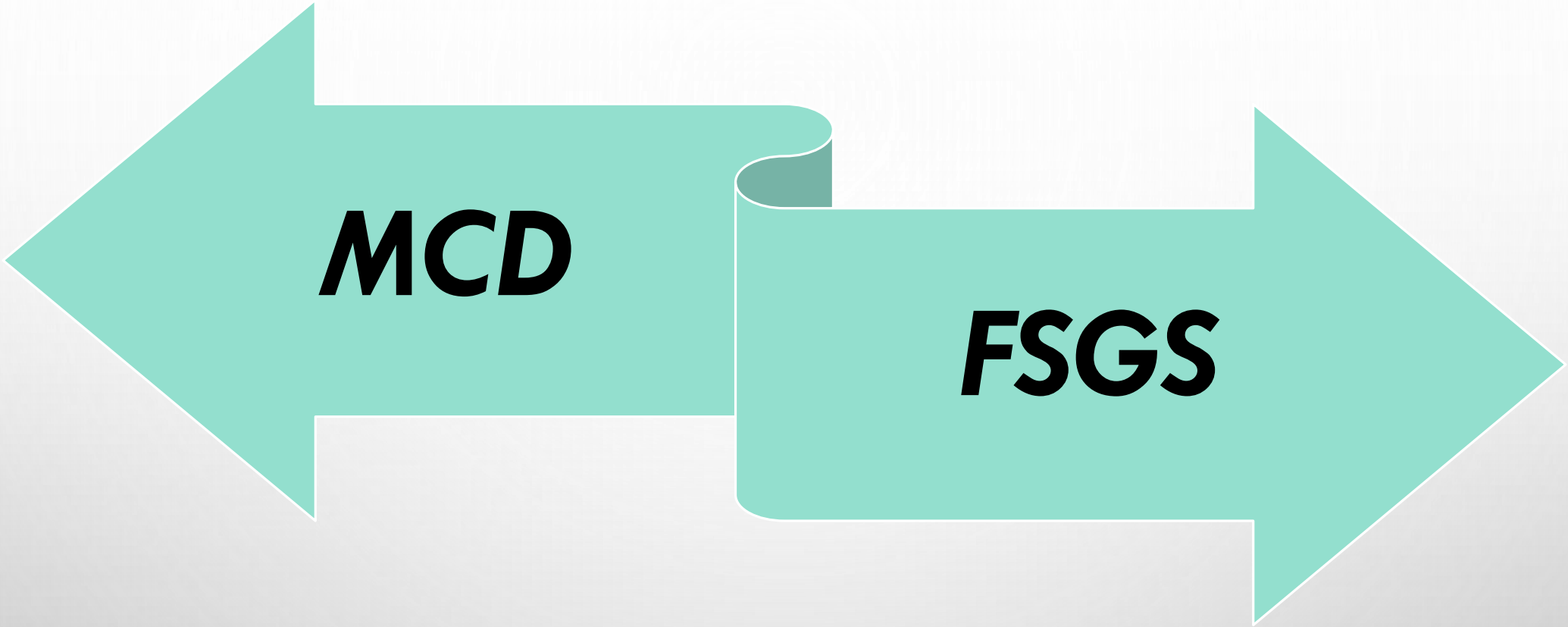


Now, there are a lot of evidence to propose that MCD and idiopathic FSGS are different manifestations of the same progressive disease.

DOI: 10.1038/nrneph.2016.147

INITIAL THERAPY in PRIMARY GN

Non nephrotic

1- ACE/ARB

2- DIURETICS

3- STATIN

Nephrotic

1- Immunosuppressive therapy

2- plus conservative therapy

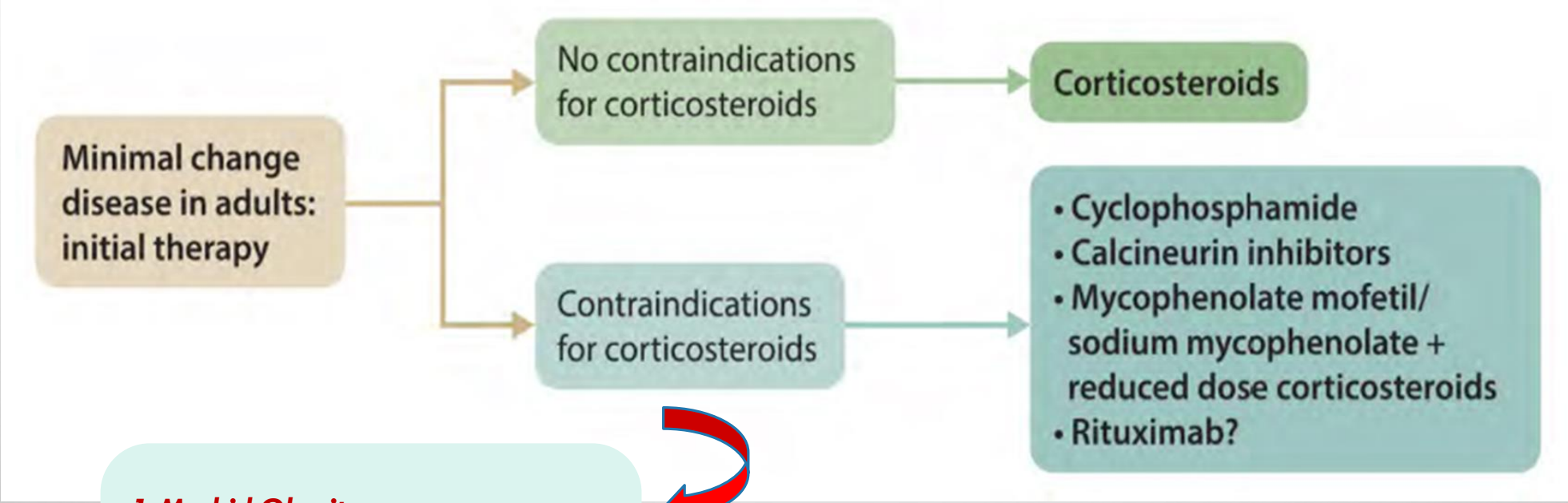
PUBLIC REVIEW DRAFT

JUNE 2020

INITIAL TREATMENT OF PRIMARY MCD

Recommendation 5.3.1. We recommend high-dose oral corticosteroids for initial treatment of MCD *(1C)*.

ALGORITHM FOR THE INITIAL TREATMENT OF MCD IN ADULTS



1-Morbid Obesity
2-Poorly controlled Diabetes
3-Severe Osteoporosis
4-Severe Psychiatric Disturbances
5-Active GIB

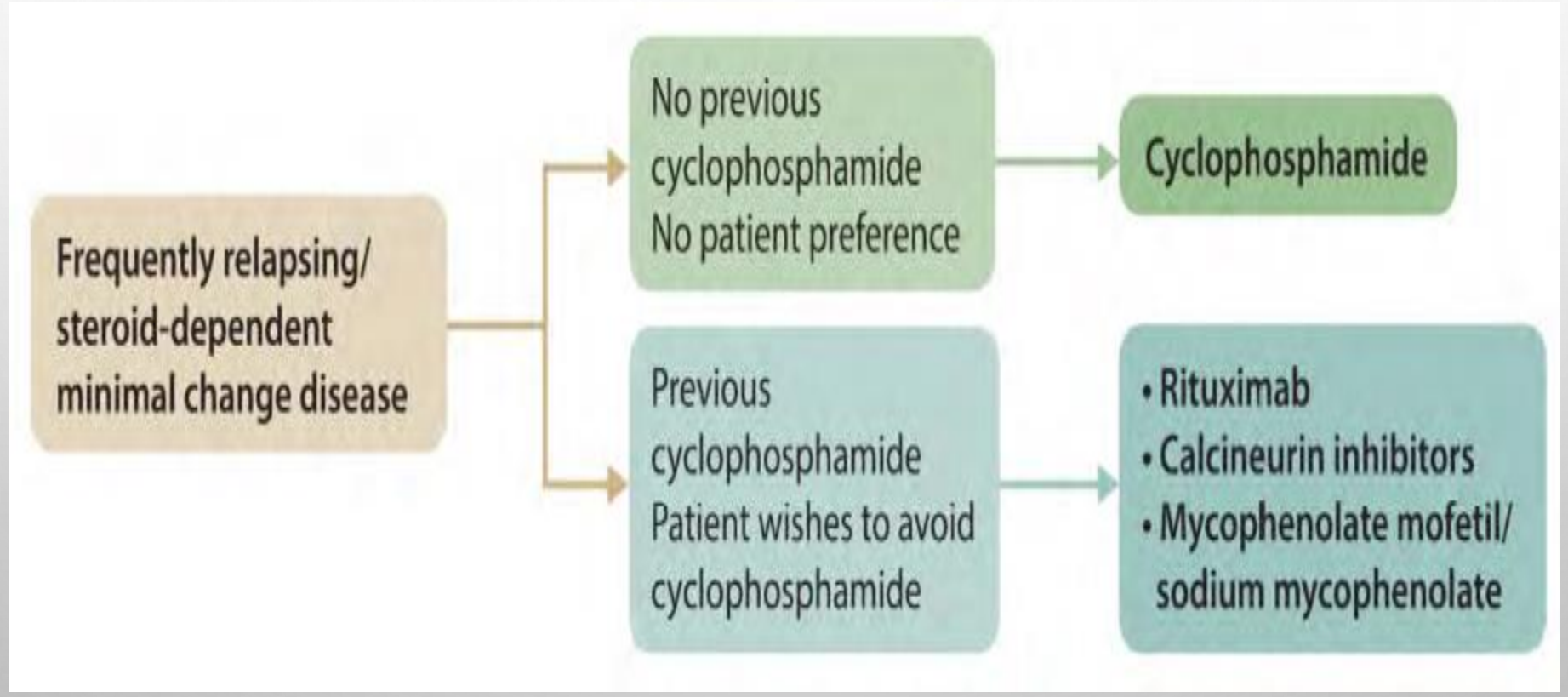
INITIAL TREATMENT OF MCD IN ADULTS

Medication	Regimen	Remission rates (complete and partial)
Initial episode, corticosteroid treatment		
Prednisone or prednisolone	Dose: 1 mg/kg per day (maximum 80 mg/day) or 2 mg/kg every other day (maximum 120 mg every other day), for a minimum of 4 weeks, and a maximum of 16 weeks (as tolerated). After remission, taper over at least 24 weeks	80%–90%
Initial episode with contraindication to corticosteroids		
Oral cyclophosphamide	2–2.5 mg/kg per day for 8 weeks	75%
Cyclosporine	3–5 mg/kg per day in divided doses for 1–2 years	75%
Tacrolimus	0.05–0.1 mg/kg per day in divided doses for 1–2 years	90%*

DEFINITION OF REMISSION, RELAPSE, RESISTANCE, AND DEPENDENCE FOR MCD

Complete remission
Reduction of proteinuria to <0.3 g/day or urine protein:creatinine ratio <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/L)
Partial remissions
Reduction of proteinuria to 0.3–<3.5 g/day or urine PCR 300–<3500 mg/g (or 30–<350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Corticosteroid-resistant MCD
Persistence of proteinuria >3.5 g/day or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/day or 2 mg/kg every other day for >16 weeks
Frequently relapsing MCD
Two or more relapses per 6 months (or four or more relapses per 12 months)
Corticosteroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing corticosteroid therapy

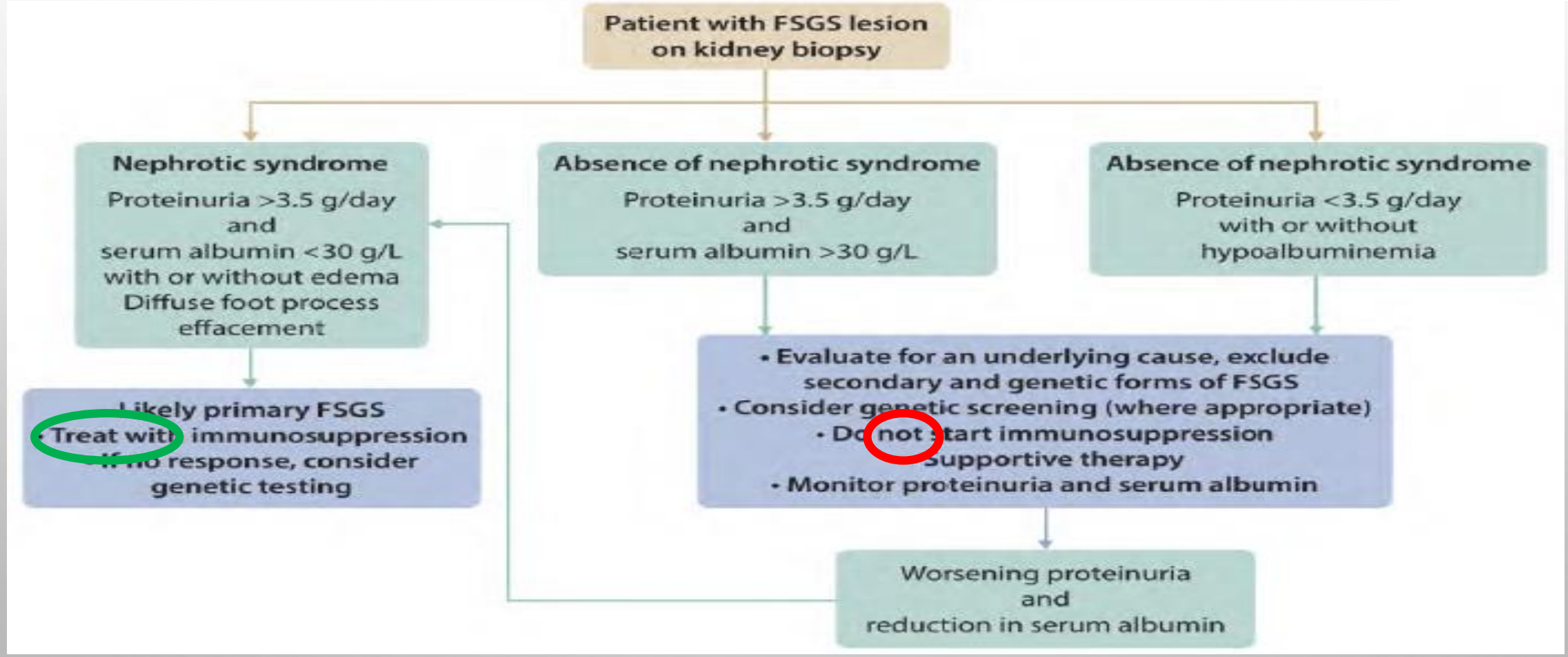
ALGORITHM FOR TREATMENT OF FR/SD MCD IN ADULTS



TREATMENT OF FR/SD MCD IN ADULTS

Frequently relapsing/ steroid-dependent patients		
Oral cyclophosphamide	2–2.5 mg/kg/day, adjusted for white blood counts, for 8–12 weeks. 12 weeks may be associated with less relapse in steroid-dependent MCD	75%
Calcineurin inhibitors • Cyclosporine • Tacrolimus	**Initial dose:** 3–5 mg/kg per day in divided doses for 1–2 years 0.05–0.1 mg/kg per day in divided doses for 1–2 years • If serum levels are being monitored, suggested initial levels: - Cyclosporine: 150–200 ng/ml - Tacrolimus: 4–7 ng/ml • After withdrawal of corticosteroids reduce CNI dose if possible Suggested doses: <3mg/kg/day for cyclosporine and <0.05 mg/kg/day for tacrolimus • Attempt gradual taper and discontinuation of CNI after a minimum of one year of therapy if possible • If CNI-dependent reduce dose to lowest possible to maintain remission with monitoring of kidney function (kidney biopsy if kidney dysfunction) Switch to alternate medication if evidence of CNI toxicity	70–90% 90%
Rituximab	**Induction regimens:** • 375 mg/m² weekly for 4 doses • 375 mg/m² × single dose; repeat after one week if CD19 cells >5/mm³ • 1 g/dose for 2 doses, 2 weeks apart **Relapse after induction:** • 375mg/m² × 1 dose or • 1g i.v. × 1 dose	70% (20% off all immunosuppression, 50% on one other immunosuppressive drug)
Mycophenolic acid analogues • Mycophenolate mofetil • Sodium mycophenolate	**Initial dose:** 1000 mg twice daily 720 mg twice daily • Attempt gradual taper and discontinuation of mycophenolic acid analogues after a minimum of one year of therapy if possible	

Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology



INITIAL TREATMENT OF PRIMARY FSGS

Recommendation 6.2.2.1. We recommend that high-dose oral corticosteroids be used as the first-line immunosuppressive treatment for primary FSGS *(1D)*.

Initial treatment of primary FSGS

Corticosteroids

Starting dose:

- High dose corticosteroid therapy with prednisone at daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg)

High dose corticosteroid treatment duration:

- Continue high dose corticosteroid therapy for at least 4 weeks and until complete remission is achieved, or a maximum of 16 weeks, whichever is earlier
- Patients who are likely to remit will show some degree of proteinuria reduction before 16 weeks of high dose treatment
- It may not be necessary to persist with high-dose corticosteroid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side-effects

Corticosteroid tapering:

- If complete remission is achieved rapidly, continue high dose corticosteroid treatment for at least 4 weeks or for 2 weeks after the disappearance of proteinuria, whichever is longer. Reduce prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months
- If partial remission is achieved within 8 to 12 weeks of high dose corticosteroid treatment, continue until 16 weeks to ascertain whether further reduction of proteinuria and complete remission may occur. Thereafter, reduce the dose of prednisone by 5 mg every 1–2 weeks to complete a total duration of 6 months
- If the patient proves to be corticosteroid-resistant or develops significant toxicities, corticosteroids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered

Calcineurin inhibitors

Starting dose:

- Cyclosporine 3–5 mg/kg/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses
- Target trough levels could be measured to minimize nephrotoxicity
- Cyclosporine target trough level: 100–175 ng/ml
- Tacrolimus target trough level: 5–10 ng/ml

Treatment duration for determining CNI efficacy:

- Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment

Total CNI treatment duration:

- In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses
- The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated

Calcineurin inhibitors as alternative initial therapy

Use CNI with or without low-dose prednisone as initial therapy, in patients who are increased risk for glucocorticoid toxicity :

1- Morbid Obesity

2- Uncontrol Diabetic patients

3- Severe osteoporosis

4- >70 years of age

5- Psychological disorders

6- GIB

Avoid using CNI in patients who have:

1-Significant vascular lesions or glomerulosclerosis

2- Severe Interstitial fibrosis and tubular atrophy on renal biopsy

3- Chronic reduction in kidney function with an eGFR <30 mL/min per 1.73 m2

DEFINITION OF REMISSION, RELAPSE, RESISTANCE, AND DEPENDENCE FOR FSGS

Complete remission
Reduction of proteinuria to <0.3 g/d or urine PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/L)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or urine PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved or an increase in proteinuria by >50% during partial remission

Corticosteroid-resistant FSGS
Persistence of proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for at least 16 weeks
Corticosteroid-dependent FSGS
Relapse occurring during or within 2 weeks of completing corticosteroid therapy
CNI-resistant FSGS
Persistence of proteinuria >3.5 g/d or urine PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite cyclosporine treatment at trough levels of 100–175 ng/ml or tacrolimus treatment at trough levels of 5–10 ng/ml for >6 months
CNI-dependent FSGS
Relapse occurring during or within 2 weeks of completing cyclosporine or tacrolimus therapy for >12 months

Treatment of corticosteroid-resistant primary FSGS

Treatment	Dose and duration
Calcineurin inhibitors	**Starting dose:** • Cyclosporine 3–5 mg/kg/day in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/day in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml • Tacrolimus target trough level: 5–10 ng/ml
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated
Inability to tolerate or contraindication to calcineurin inhibitors	Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

When We Do Not Prescribe Immunosuppressive Drugs?

We Do Not Prescribe Immunosuppressive Drugs, IF:

1- Sustained reduced eGFR<30 ml/min/1.73m2

2- Extensive glomerulosclerosis or vascular lesions on biopsy

3- Evidence of severe interstitial fibrosis and tubular atrophy on biopsy

Role of Calcineurin inhibitor in Primary GN

Nephrol Dial Transplant (2011) 26: 18–24
doi: 10.1093/ndt/gfq617
Advance Access publication 11 October 2010

Editorial Reviews

NDT
Nephrology Dialysis Transplantation

The podocyte as a direct target of immunosuppressive agents

Eva Schönenberger[1], Jochen H. Ehrich[2], Hermann Haller[1] and Mario Schiffer[1]

Podocytes play a key role in maintaining the blood–urine barrier for high-molecular-weight proteins. They are considered to be terminally differentiated, and podocyte loss cannot be compensated by regenerative proliferation. Various diseases leading to podocyte damage and loss result in proteinuria and cause nephrotic syndrome. Therefore, direct therapeutical strategies to protect podocytes in disease situations are a logical concept to prevent disease or to delay disease progression. Acquired podocytopathies like idiopathic focal segmental glomerulosclerosis and minimal change disease are historically considered as immunological diseases. Therefore, immunosuppressive agents such as steroids and calcineurin inhibitors are the commonly used treatment strategies. However, the causative disease mechanisms behind these treatment strategies remain elusive. Recent evidence shows that immunosuppressive agents, in addition to the effect on the immune system, directly influence the unique structure and function of podocytes. In this context, the actin cytoskeleton of the podocyte and cytokines such as vascular endothelial growth factor play a pivotal role. In this review, we summarize the direct effects on podocytes obtained *in vivo* and *in vitro* after treatment with calcineurin inhibitors, mTOR inhibitors and glucocorticoids. These direct effects could play a key role in the treatment concepts of podocytopathies with an important impact on the long-term renal function in patients with pharmacological immunosuppression.

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SCIENTIFIC REPORTS

OPEN

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Calcineurin inhibitors cyclosporin A and tacrolimus protect against podocyte injury induced by puromycin aminonucleoside in rodent models

- Podocyte injury and the appearance of proteinuria are features of minimal-change disease (MCD).
- Cyclosporin A (CsA) and tacrolimus (FK506) has been reported to reduce proteinuria in patients with nephrotic syndrome, but mechanisms remain unknown.
- We, therefore, investigated the protective mechanisms of CsA and FK506 on proteinuria in a rat model of MCD induced by puromycin aminonucleoside (PAN) and in vitro cultured mouse podocytes.

SCIENTIFIC REPORTS | 6:32087 | DOI: 10.1038/srep32087

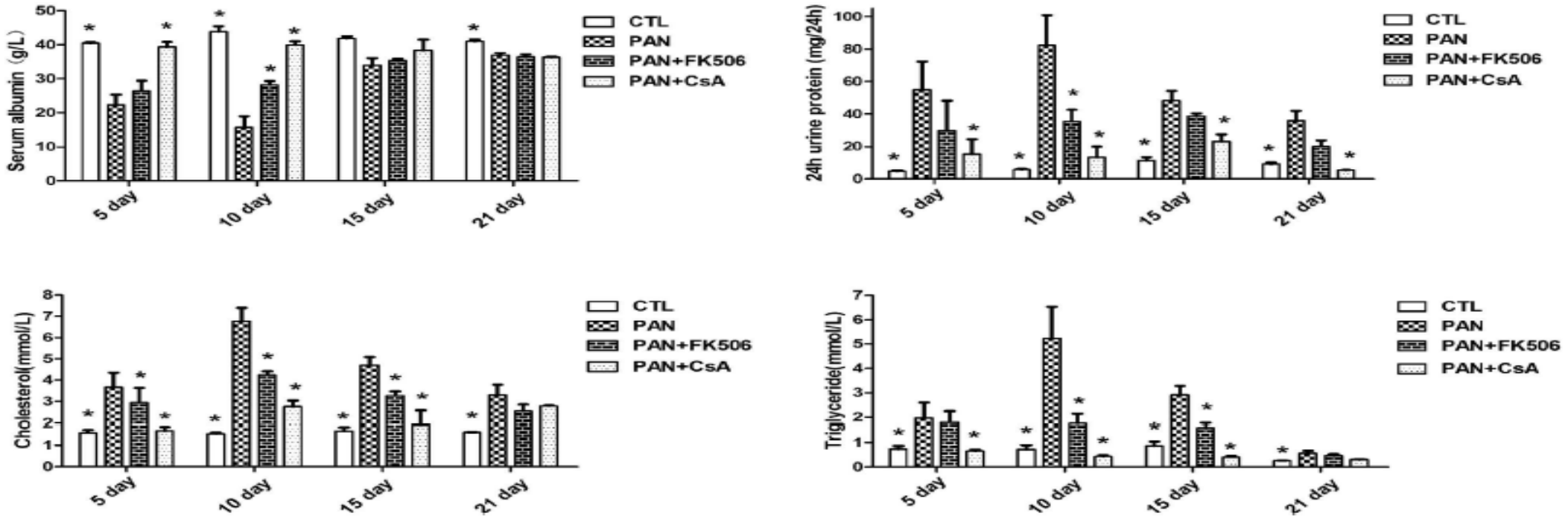
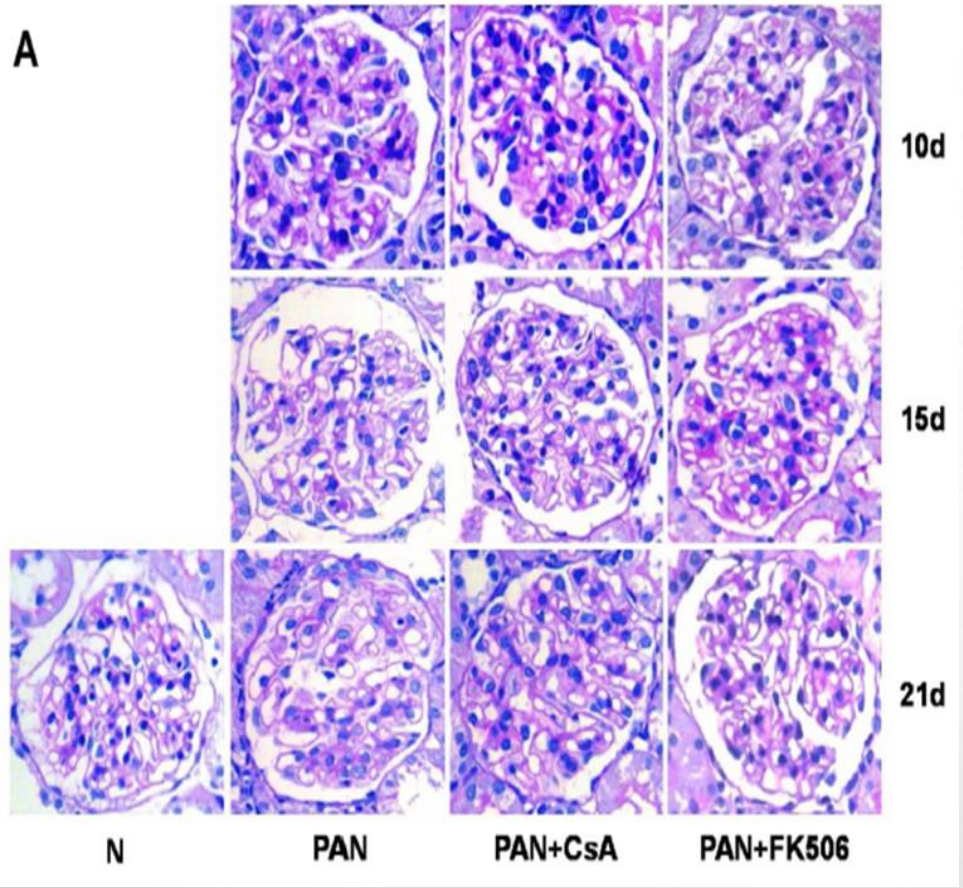
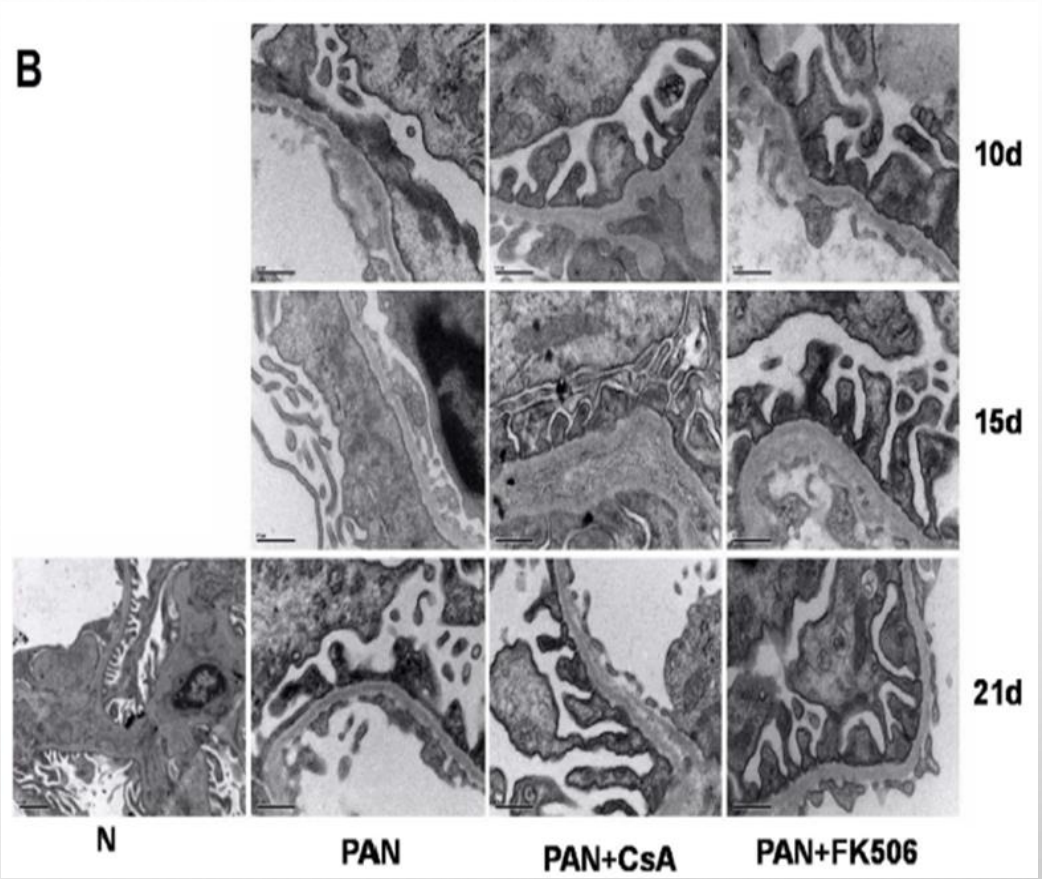


Figure 1. CsA and FK506 ameliorate proteinuria, and serum albumin, triglyceride, and cholesterol abnormalities in SD rats. CsA and FK506 reduced the 24-h urinary protein, decreased the triglyceride and cholesterol levels, and restored the serum albumin level in PAN-treated rats. **CTL**, normal rats; **PAN**, PAN-treated rats; **PAN + FK506**, intragastric administration of FK506 starting at the same time as PAN injection; **PAN + CsA**, intraperitoneal injection of CsA starting at the same time as PAN injection ($n = 5$ per group; $^*P < 0.05$ *vs* PAN group).

SCIENTIFIC REPORTS | 6:32087 | DOI: 10.1038/srep32087





- FIGURE 2. GLOMERULAR MORPHOLOGY AND FOOT PROCESSES IN NORMAL, PAN, PAN + FK506, AND PAN + CSA TREATED SD RATS. ***(A)*** PAS STAINING SHOWED NO DIFFERENCE IN GLOMERULAR MORPHOLOGY BETWEEN GROUPS AT INDICATED STAGES AFTER CSA AND FK506 TREATMENT IN PAN INJURED SD RATS. ***(B)*** TRANSMISSION ELECTRON MICROSCOPY SHOWED EXTENSIVE FOOT-PROCESS EFFACEMENT AT 10 AND 15 DAYS AFTER PAN INJECTION. ***CSA AND FK506 TREATMENT SIGNIFICANTLY DECREASED FOOT-PROCESS WIDTH COMPARED WITH PAN-ONLY RATS.***

SCIENTIFIC REPORTS | 6:32087 | DOI: 10.1038/srep32087

Table 1. Effects of CsA and FK506 on foot-process width in SD rats.

Foot process width (nm)	10 days	15 days	21 days
Normal control	306 ± 225		
PAN model	1273 ± 1014	960 ± 630	744 ± 401
CsA treatment	650 ± 277$^{\Delta\Delta}$	530 ± 234$^{\Delta\Delta}$	477 ± 167$^{\Delta\Delta}$
FK506 treatment	862 ± 394$^{\Delta\Delta}$	395 ± 93$^{\Delta\Delta}$	374 ± 90$^{\Delta\Delta}$

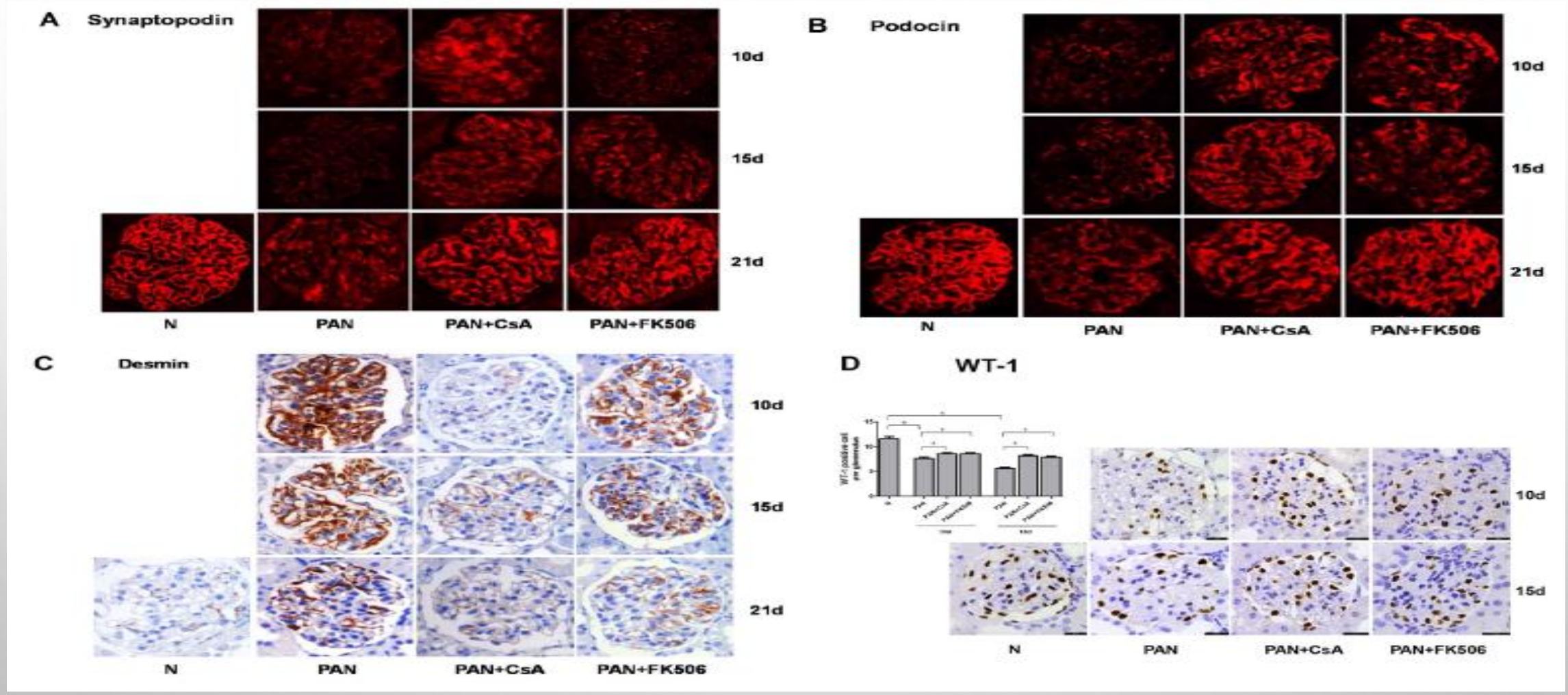


Figure 3. Expression of synaptopodin, podocin, desmin and WT-1 in kidney glomerulus from SD rats subjected to various treatments. Immunofluorescent and immunohistochemical staining for synaptopodin (A), podocin (B), desmin (C) and WT-1(D) showed that CsA treatments rescued the expression of synaptopodin, podocin and WT-1 in PAN-treated SD rats and inhibited PAN induced desmin expression.

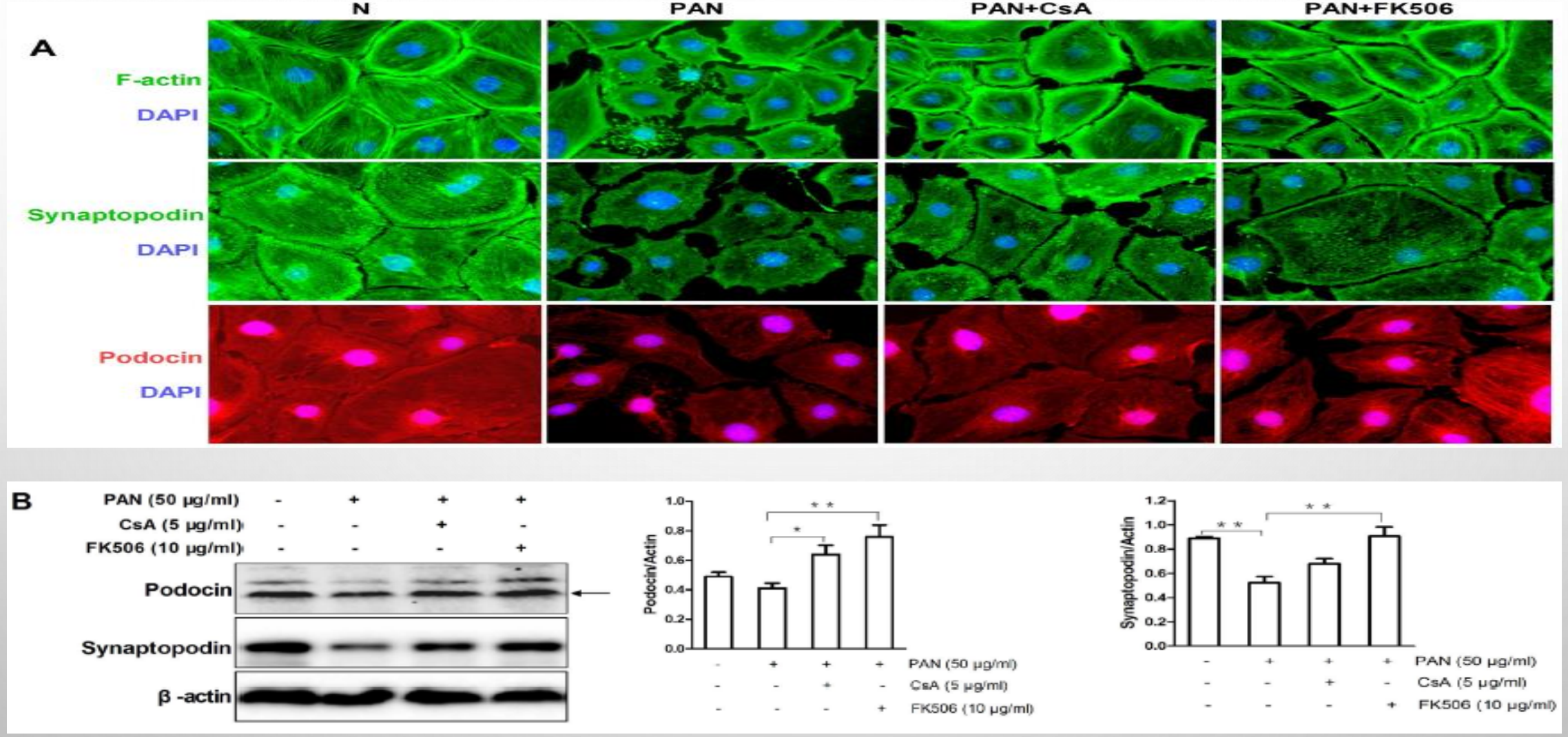


Figure 4. CsA and FK506 pretreatment protect against PAN-induced injury in cultured mouse podocytes *in vitro*. (A) Immunofluorescence of F-actin, synaptopodin and podocin in PAN treated mouse podocytes after CsA and FK506 treatment. Original magnification, X400. (B) Western blot analyses of podocin and synaptopodin in PAN injured mousepodocytes after CsA and FK506 treatment for 24 h (podocin: N

Physiological Reports

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ORIGINAL RESEARCH

Role of calcineurin (CN) in kidney glomerular podocyte: CN inhibitor ameliorated proteinuria by inhibiting the redistribution of CN at the slit diaphragm

Calcineurin Expressed at Slit Diaphragm of Podocyte — A. Wakamatsu *et al.*

- A CNI is assumed to ameliorate proteinuria by preventing the overproduction of T-cell cytokines.
- However, recent reports suggest that CNI has a direct effect on podocyte.
- It is accepted that a slit diaphragm (SD), a unique cell–cell junction of podocytes, is a critical barrier preventing a leak of plasma protein into urine.
- Therefore, we hypothesized that CNI has an effect on the SD. In this study, we analyzed the expression of CN in physiological and in the nephrotic model caused by the antibody against nephrin, a critical component of the SD.

Physiol Rep, 4 (6), 2016, e12679, doi: 10.14814/phy2.12679

Physiological Reports

Open Access

Physiological Reports ISSN 2051-817X

ORIGINAL RESEARCH

Role of calcineurin (CN) in kidney glomerular podocyte: CN inhibitor ameliorated proteinuria by inhibiting the redistribution of CN at the slit diaphragm

Calcineurin Expressed at Slit Diaphragm of Podocyte — A. Wakamatsu *et al.*

- ***We observed that CN is expressed at the SD in normal rat and human kidney sections and has an interaction with nephrin.***
- ***The staining of CN at the SD was reduced in the nephrotic model, while CN activity and redistribution in glomeruli was increased.***
- ***We also observed that the treatment with tacrolimus, a CNI, in this nephrotic model suppressed the redistribution of CN, nephrin, and other SD components and ameliorated proteinuria.***
- ***These observations suggested that the redistribution and the activation of CN may participate in the development of the SD injury.***

Physiol Rep, 4 (6), 2016, e12679, doi: 10.14814/phy2.12679

Canadian Society of Nephrology/ Société canadienne de néphrologie
CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Review

Calcineurin Inhibitors in the Treatment of Primary Focal Segmental Glomerulosclerosis: A Systematic Review and Meta-analysis of the Literature

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SAGE

Louis-Philippe Laurin[1,2], Patrick H. Nachman[3], and Bethany J. Foster[2,4,5]

Abstract

Purpose of review: Primary focal segmental glomerulosclerosis (FSGS) is the most common cause of nephrotic syndrome in adults. Glucocorticoids have been evaluated in the treatment of primary FSGS in numerous retrospective studies. Evidence suggesting a role for including calcineurin inhibitors (CNIs) in early therapy remains limited. The aim of this study was to systematically review the literature examining the efficacy of CNIs in the treatment of primary FSGS both as first-line therapy and as an adjunctive agent in steroid-resistant patients, with respect to remission in proteinuria and renal survival.

Sources of information: PubMed and EMBASE were searched from inception to August 2014 for prospective controlled trials, and case-control and cohort studies.

Findings: After systematically applying our inclusion criteria, a total of 152 titles and abstracts were identified. Six randomized controlled trials and 2 cohort studies were reviewed. Three randomized controlled trials compared CNIs with placebo or supportive therapy. The pooled relative "risk" of proteinuria remission associated with cyclosporine was 7.0 (95% confidence interval, 2.9-16.8) compared with placebo/supportive therapy. There was very low heterogeneity among these studies with an *I*-squared of 0%. Three studies compared CNIs with another immunosuppressive agent. All prospective trials were conducted in patients with primary FSGS deemed steroid-resistant.

Limitations: The relatively small number of included studies and their heterogeneity with respect to treatment protocols, and possible publication bias, limit conclusions drawn from this systematic review.

Implications: The efficacy of CNIs has been evaluated in steroid-resistant primary FSGS patients. There is no evidence supporting their role as first-line therapy. Further studies are needed to determine this role.

RENAL FAILURE, 2016
VOL. 38, NO. 6, 894–898
http://dx.doi.org/10.3109/0886022X.2016.1164063

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CLINICAL STUDY

A prospective study of collapsing focal segmental glomerulosclerosis

Ramachandran Raja[a]*, Ritambhra Nada[b]*, Ashok K. Yadav[a], Ashwani Kumar[b], Ajay Goyal[a], Vivek Kumar[a], Manish Rathi[a], H. S. Kohli[a], K. L. Gupta[a], Vinay Sakhuja[a] and Vivekanand Jha[a,c]

Table 1. Comparison of clinical and pathological parameters of cFSGS and steroid and tacrolimus resistant FSGS.

	cFSGS (*n*–22)	Resistant FSGS (*n*–19)	*p* values
Age (years)	26.9 ± 9.4 (14–55)	28.1 ± 8.6 (18–43)	0.67
Sex (Male/Female)	15/07	15/04	0.49
Proteinuria (gm/day)	4.6 ± 3.0 (1.2–13)	4.5 ± 3.8 (1.2 ± 15.2)	0.93
Serum creatinine (mg/dl)	4.1 ± 3.7 (0.7–12.2)	1.4 ± 0.7 (0.7–1.1)	0.003
Serum albumin (gm/dl)	2.1 ± 0.6 (1.2–3.6)	2.0 ± 0.5 (0.64–4.5)	0.63
Hypertension	17(77.2%)	06(31.5%)	0.004
ESRD/Death	12 (54.5%)	05 (15.7%)	0.11
Progressive CKD	04 (18.1%)	05 (15.7%)	0.70
Percentage collapse (%)	48.0 ± 33.7 (4.5–100)	None	<0.0001
IFTA (≥2+)	8 (36.3%)	None	0.004
Tubulocystic inclusion	09 (40.9%)	None	0.001
TMA	08 (36.3%)	None	0.004
Arteriosclerosis	04 (18.2%)	None	0.11
Ki67	15 (68.1%)	None	<0.0001
WT1	22 (100%)	None	<0.0001
PAX2	13 (59%)	None	<0.0001
Parvo B19	08 (36.3%)	03 (15.7%)	0.17

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Collapsing focal segmental glomerulosclerosis (cFSGS) is characterized by rapid progression to end-stage renal disease (ESRD). We evaluated the clinicopathological spectrum of cFSGS and compared its clinical behavior to steroid and tacrolimus (TAC)-resistant noncollapsing focal segmental glomerulosclerosis (FSGS). All patients (>14 years) diagnosed with cFSGS were enrolled in the study. Staining for differentiated podocyte markers such as WT 1, PAX and KI67 were performed in all patients. The outcome and histological features of cFSGS was compared with a prospectively followed cohort of steroid and TAC-resistant noncollapsing FSGS. The study included 22 cFSGS patients and 19 cases of steroid and TAC-resistant FSGS. Complete remission, partial remission, steroid resistance, progression to ESRD and death were observed in 13.6%, 4.5%, 27.3%, 36.4% and 18.2% patients, respectively. Patients with cFSGS had higher serum creatinine and more advanced tubulointerstitial changes compared to resistant FSGS. Twenty-six percent of therapy resistant noncollapsing FSGS progressed to ESRD after two years of stopping TAC. However, there was no difference in progression to ESRD between cFSGS and therapy-resistant noncollapsing FSGS at the end of two years. Glomerular collapse in the setting of FSGS is poorly responsive to treatment and has a high rate of progression to ESRD. The long-term prognosis of cFSGS and steroid and TAC-resistant FSGS are similar.

original article

http://www.kidney-international.org

see commentary on page 798

Clinical trial of focal segmental glomerulosclerosis in children and young adults

Debbie S. Gipson[1], Howard Trachtman[2], Frederick J. Kaskel[3], Tom H. Greene[4], Milena K. Radeva[5],

- This NIH-funded multicenter randomized study of FSGS treatment compared the efficacy of a 12-month course of cyclosporine to a combination of oral pulse dexamethasone and mycophenolate mofetil in children and adults with steroid-resistant primary FSGS.
- Of the 192 patients enrolled, 138 were randomized to cyclosporine (72) or to mycophenolate/dexamethasone (66).

Kidney International (2011) **80,** 868–878; doi:10.1038/ki.2011.195;

original article

http://www.kidney-international.org

see commentary on page 798

Clinical trial of focal segmental glomerulosclerosis in children and young adults

Debbie S. Gipson[1], Howard Trachtman[2], Frederick J. Kaskel[3], Tom H. Greene[4], Milena K. Radeva[5],

- Partial or complete remission was achieved in 22 (33%) mycophenolate/dexamethasone and 33(45.8%) cyclosporine treated patients at 12 months.
- The main secondary outcome, preservation of remission for 26 weeks following cessation of treatment, was not significantly different between these two therapies.
- Moreover, only a quarter of the patients in the two groups had a sustained response 6 months following discontinuation of immunosuppressive medications.
- Thus, our study did not find a difference in rates of proteinuria remission following 12 months of cyclosporine compared to mycophenolate/dexamethasone in patients with steroid-resistant FSGS.

Kidney International (2011) **80,** 868–878; doi:10.1038/ki.2011.195;

Management of steroid-resistant nephrotic syndrome in children and adolescents

Review

Kjell Tullus, Hazel Webb, Arvind Bagga

- About 10–15% of children with idiopathic nephrotic syndrome who do not show complete remission of proteinuria following 4 weeks' treatment with corticosteroids are considered to have steroid-resistant nephrotic syndrome
- For 30% of patients with steroid-resistant nephrotic syndrome, the condition results from a genetic cause; for the remainder, the disease is probably caused by a circulating factor
- Renal histology shows minimal change disease and focal segmental glomerulosclerosis (FSGS) in most patients.

www.thelancet.com/child-adolescent Published online October 17, 2018 http://dx.doi.org/10.1016/S2352-4642(18)30283-9

Management of steroid-resistant nephrotic syndrome in children and adolescents

Review

Kjell Tullus, Hazel Webb, Arvind Bagga

- Approximately 50–70% of patients with steroid resistance show complete or partial remission following treatment with a calcineurin inhibitor (either ciclosporin or tacrolimus)
- Although additional treatment with mycophenolate mofetil or rituximab is considered in children who are resistant to treatment with steroids and calcineurin inhibitors, their efficacy to induce remission is low
- Patients with a genetic FSGS or those who do not show complete or partial remission following treatment with calcineurin inhibitors have high risk of end-stage renal failure
- Patients with late resistance and absence of a genetic cause show high risk of recurrent FSGS in the renal allograft
- Intensification of treatment with ciclosporin or tacrolimus, and combined treatment with rituximab and plasma exchange might prevent or treat recurrent FSGS effectively.

www.thelancet.com/child-adolescent Published online October 17, 2018 http://dx.doi.org/10.1016/S2352-4642(18)30283-9

Management of steroid-resistant nephrotic syndrome in children and adolescents

Review

Kjell Tullus, Hazel Webb, Arvind Bagga

Panel 2: **Prevention and management of recurrent focal segmental glomerulosclerosis after kidney transplantation**

Prevention of recurrence

- Ensure period of normalised serum albumin before transplantation
- Genetic screening of recipient if living-related donor
- Intravenous rituximab (375 mg/m²; one or two doses) 2 weeks before transplantation
- Plasma exchanges (begin 7–10 days before transplantation)
- Induction with intravenous methylprednisolone and basiliximab; triple immunosuppression
- Post-transplantation proteinuria screen: daily for 1 week; weekly for 4 weeks; every 3 months for first year; and every 6 months thereafter

Treatments for recurrence

- Plasma exchange (8–12 sessions for response; might require long-term for maintenance of remission; 1–1·5 volume exchanges) on alternate days for 7–10 sessions, then taper and continue until proteinuria subsides
- Methylprednisolone (10–15 mg/kg intravenously, three doses daily)
- Switch to high-dose ciclosporin, targeting trough concentrations of 250–300 ng/mL for 2–3 weeks; alternatively, continue tacrolimus at higher dose
- Rituximab (1–6 doses used; early use and normal serum albumin at onset predict response): 375 mg/m², two doses 1 week apart; avoid plasma exchange for 36 h following treatment; monitor CD19 depletion
- Other treatments (considered for refractory patients; variable efficacy): low-density lipoprotein apheresis, and oral cyclophosphamide (8–12 weeks) to replace mycophenolate mofetil.

www.thelancet.com/child-adolescent Published online October 17, 2018 http://dx.doi.org/10.1016/S2352-4642(18)30283-9

Advanced Therapeutics in FSGS

NEPHROLOGY

Nephrology **23,** Suppl. 4 (2018) 57–61

Review Article

Advanced therapeutics in focal and segmental glomerulosclerosis

YUNZI LIU, YIFAN SHI, RONG REN, JINGYUAN XIE, WEIMING WANG and NAN CHEN

Department of Nephrology, Ruijin Hospital, Institute of Nephrology, Shanghai Jiao Tong University School of Medicine, Shanghai, China

- ✓ **Corticosteroid: FSGS patients with proteinuria 1.0–3.5 g/day, the remission rate was significantly high.**
- ✓ **CNI: is recommended for patients with FSGS who fail to respond to corticosteroids alone. CNI showed good efficacy, and the remission rate was reported as 57.1%–77.8%. There was a significant increased complete or partial remission rate in FSGS patients with CSA plus low dose prednisone versus prednisone alone.**
- ✓ **MMF: is not more effective than cyclosporine or CTX in preserving kidney function.**
- ✓ **CTX: Due to the side effects and uncertain efficacy, CTX is gradually being faded out as the first-line treatment. CTX is still an appropriate choice for some refractory cases, and may be considered as first-line immunosuppressive.**

doi: 10.1111/nep.13463

NEPHROLOGY

Nephrology **23,** Suppl. 4 (2018) 57–61

Review Article

Advanced therapeutics in focal and segmental glomerulosclerosis

YUNZI LIU, YIFAN SHI, RONG REN, JINGYUAN XIE, WEIMING WANG and NAN CHEN

Department of Nephrology, Ruijin Hospital, Institute of Nephrology, Shanghai Jiao Tong University School of Medicine, Shanghai, China

- ✓ **Rituximab:** has a good efficacy on the three types of FSGS patients (SDNS, SRNS and FRNS), especially SDNS. Complete or partial remission rate increased, and relapse rate decreased.
- ✓ **Adalimumab:** is effective not only in FSGS patients who are resistant to traditional immunosuppressive agents, but also in FSGS patients who have long-term use of rituximab and develop into drug resistance. those patients who are allergic to rituximab and unable to continue to use it, they have a good tolerance to adalimumab.
- ✓ Researchers applied adalimumab to five immunosuppressive agent resistant patients. After 6 months treatment, all patients' urine protein levels returned to normal and creatinine remained stable.

doi: 10.1111/nep.13463

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Abatacept in B7-1–Positive Proteinuric Kidney Disease

- ✓ **Abatacept**: Recent studies have shown that the co-stimulation of B7-1 molecules involved in T cells in podocytes is related to the occurrence and development of NS.
- ✓ One study first verified in vitro podocyte experiments that the expression of B7-1 in podocytes rises with external factors stimulation.
- ✓ Abatacept, as an intervention, can significantly inhibit its expression. In subsequent clinical applications, the investigators selected five patients with FSGS (steroid resistance FSGS or frequently relapsing FSGS). At the same time, immunofluorescence of renal biopsies in these patients all showed significant expression of B7-1.
- ✓ After the treatment of Abatacept, all patients achieved clinical remission.

N Engl J Med 2013;369:2416-23.
DOI: 10.1056/NEJMoa1304572

Novel treatment (new drug/intervention; established drug/procedure in new situation)

CASE REPORT

Low-dose ofatumumab for rituximab-resistant nephrotic syndrome

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Accepted 31 August 2015

Drug resistant idiopathic nephrotic syndrome (DRNS) remains a therapeutic dilemma. In this pilot study, the efficacy of the new fully humanised, anti-CD20 monoclonal antibody ofatumumab was tested in 4 children with persistence of proteinuria for at least 12 months in spite of a full drug approach (including rituximab). We used a low-dose 2-infusion ofatumumab model (300+700 mg/1.73 m^2 2 weeks apart) using specified premedication. Transient normalisation of proteinuria (persisting for 2 months) was achieved in 1 child while another presented stable remission after 12 months; both had normal renal function. The outcome was not modified in the remaining 2 children presenting an impaired renal function. These results demonstrate that low-dose ofatumumab may induce remittance of proteinuria in children with a long story of DRNS and normal renal function. Further studies are needed to test whether higher doses of ofatumumab can also modify proteinuria in patients with impaired renal function.

Bonanni A, *et al*. *BMJ Case Rep* 2015. doi:10.1136/bcr-2015-210208

Thank you