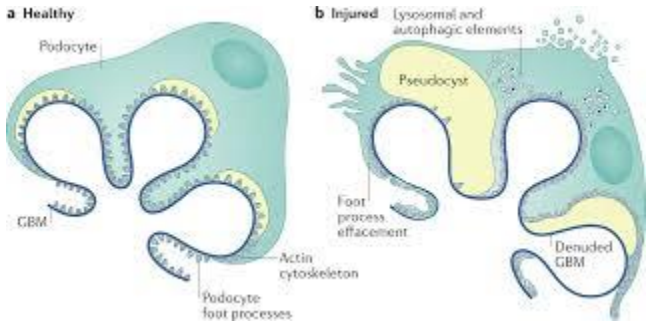
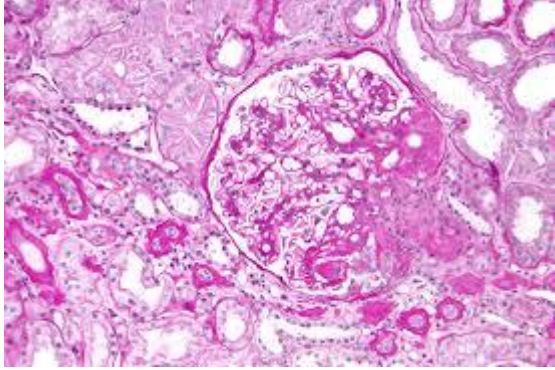
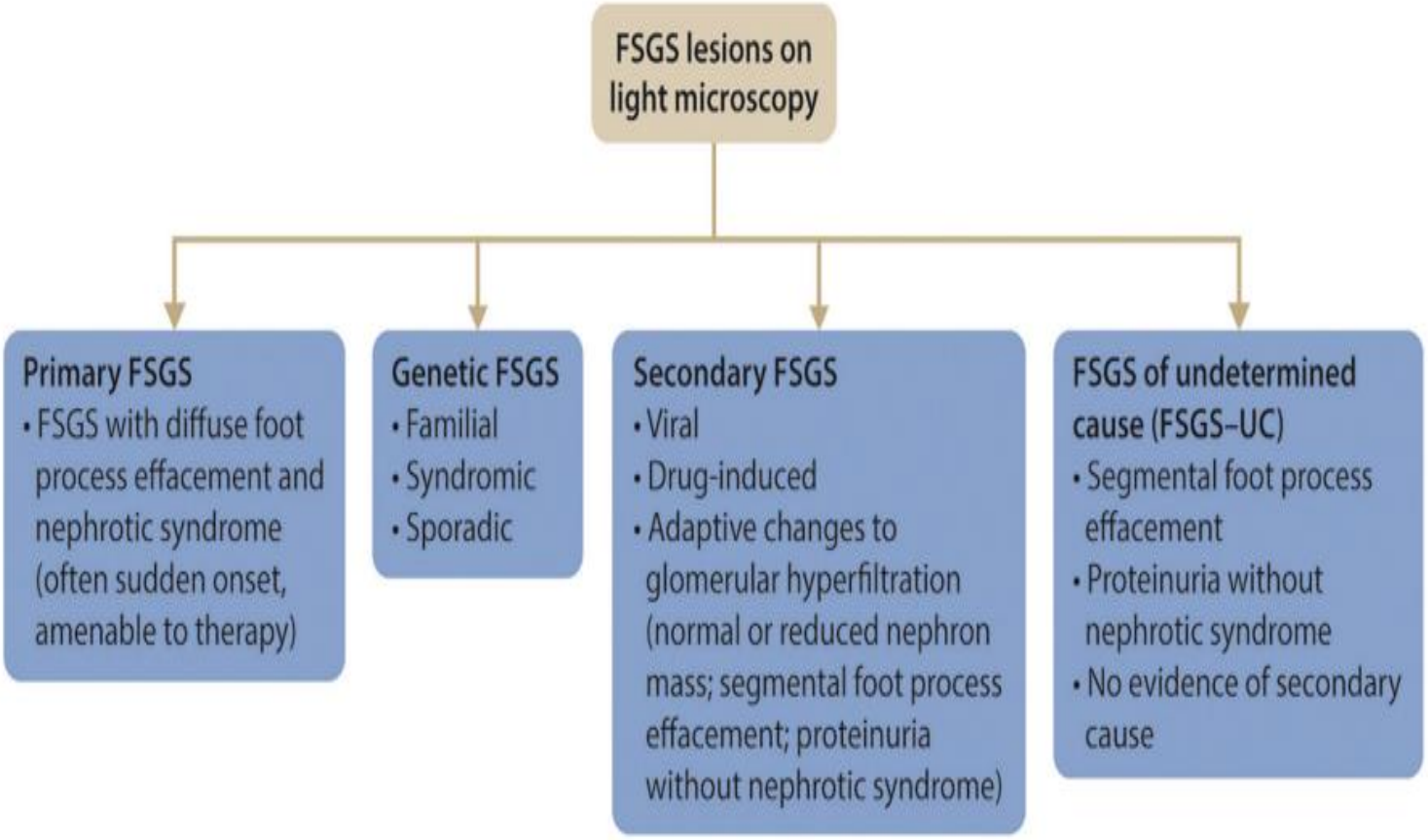




Focal segmental glomerulosclerosis (FSGS) Treatment and prognosis

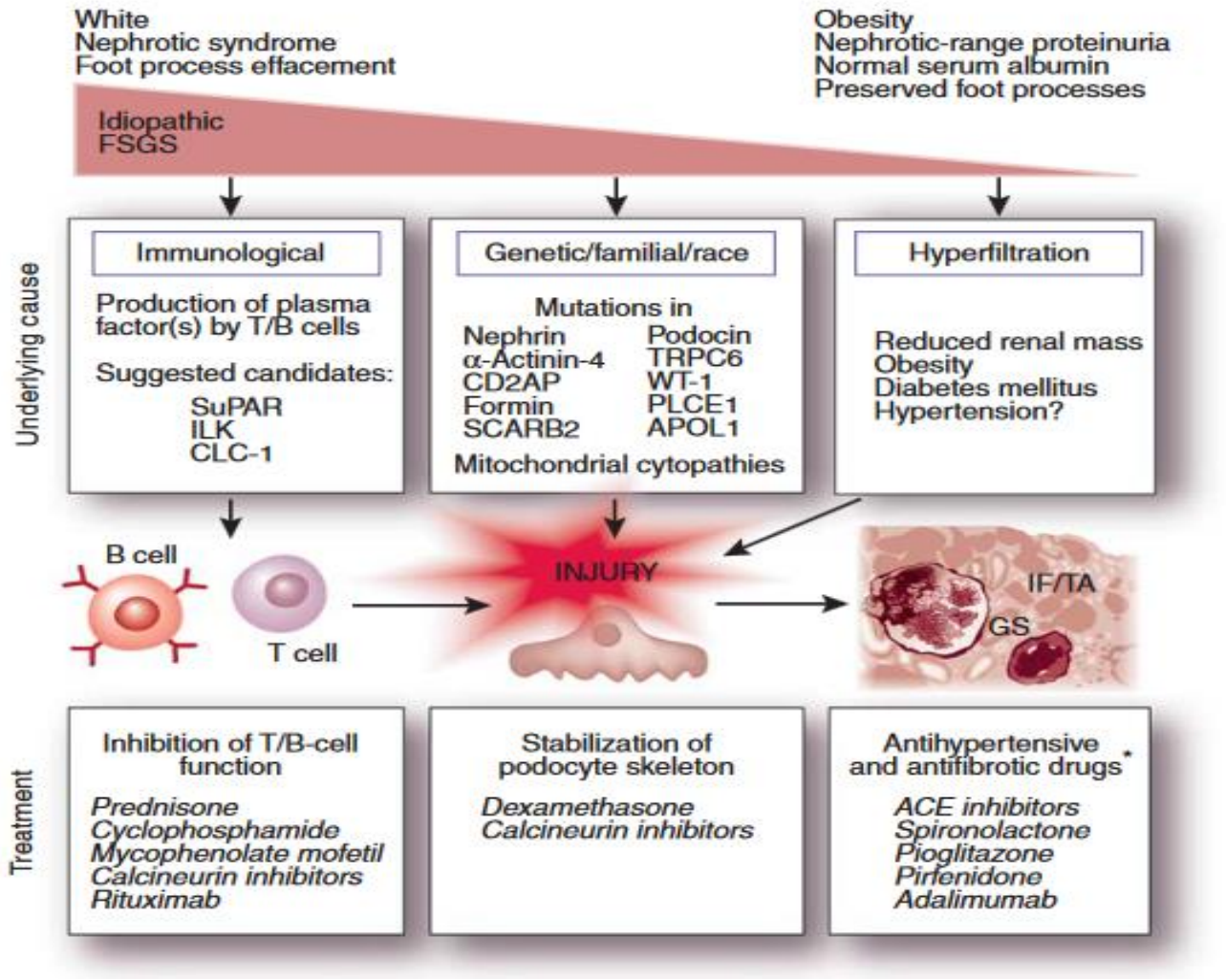
Dr. F. Ahmadi
Professor Of nephrology
Tehran University Medical Sciences(TUMS)

Proposed classification of FSGS. FSGS, focal segmental glomerulosclerosis



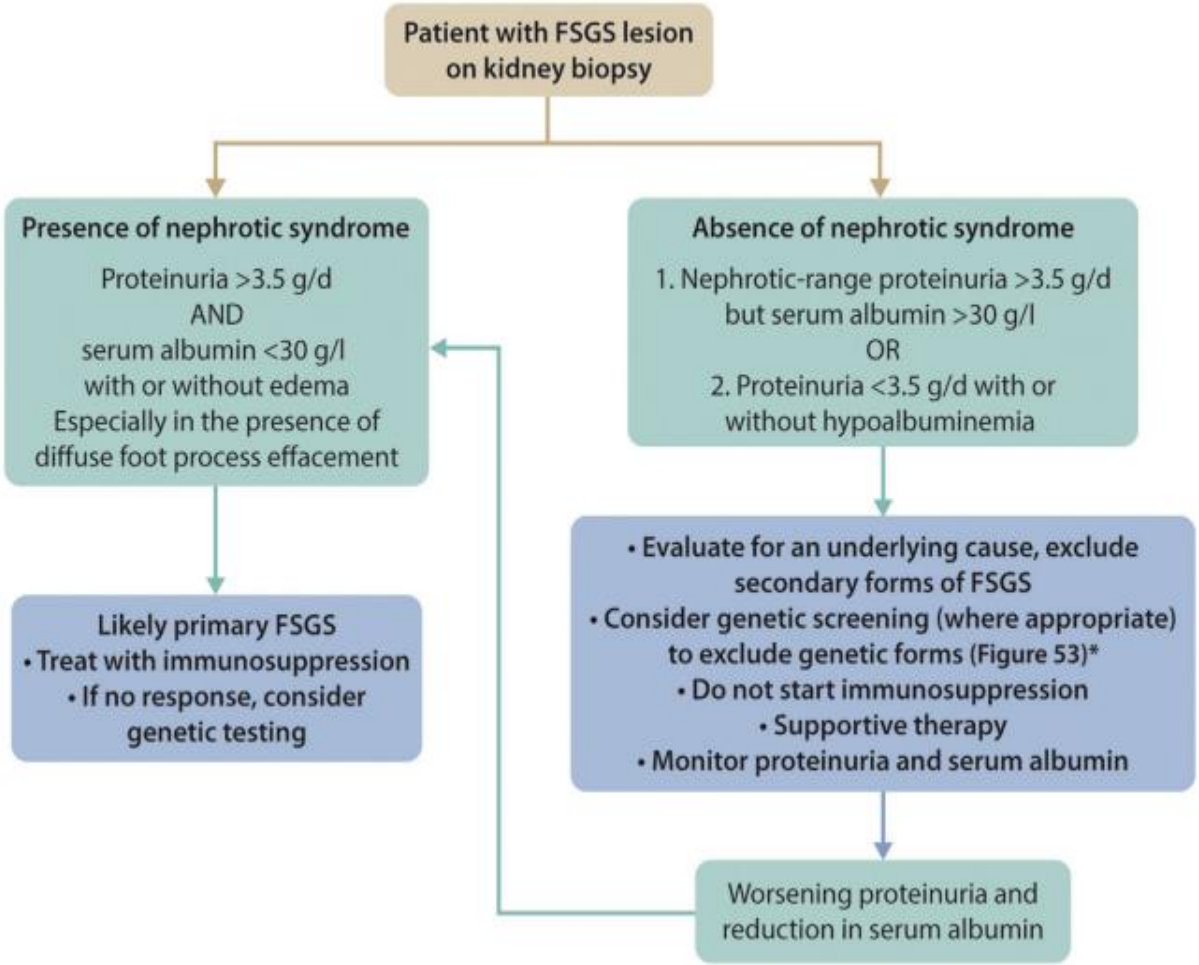
Kidney International (2021) 100, 753–779

The heterogeneity of focal segmental glomerulosclerosis



Kidney International (2011) 80

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



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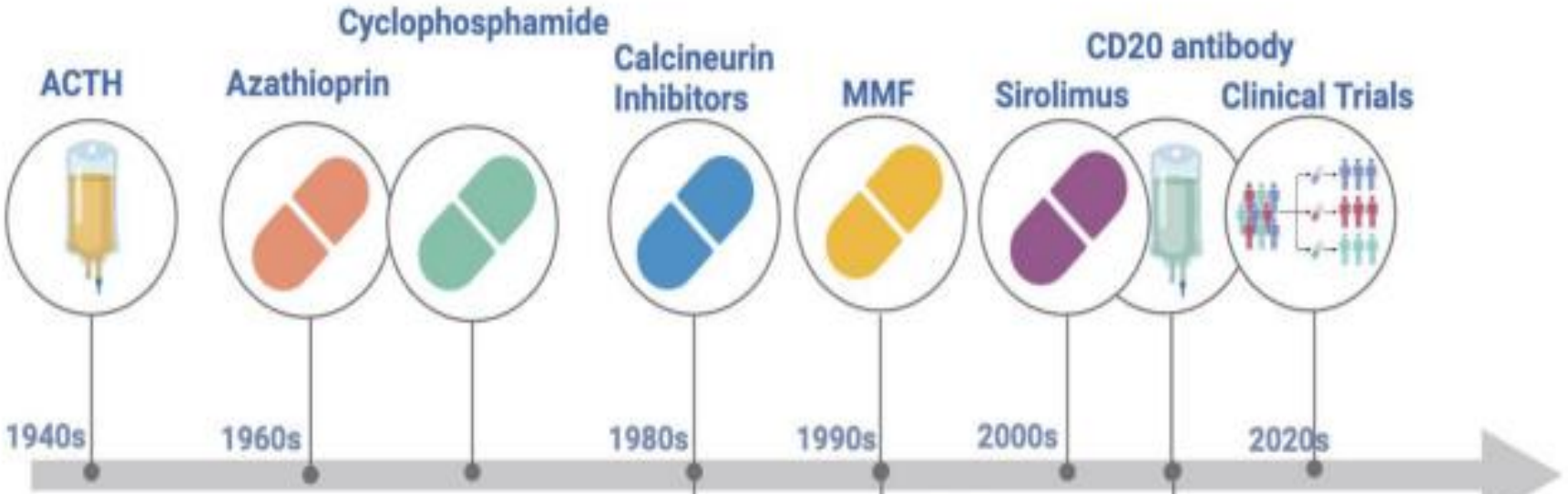
Timeline of treatment in FSGS



ACTH:
Has showed benefits in proteinuria reduction in adults.
Has showed no effects in children.

Azathioprin:
May reduce proteinuria but no evidence in adults.

Has no evidence of being superior compared to corticosteroid in children.

Cyclophosphamide:
Is infective in adults and children.

Calcineurin inhibitors:
Have shown widespread use and effectiveness. Discerning superiority between CNI remains elusive from historical data.

MMF:
Demonstrates proteinuria reduction in adults.
Promise data in children by sparing corticosteroid use.

Sirolimus:
No efficacy in FSGS

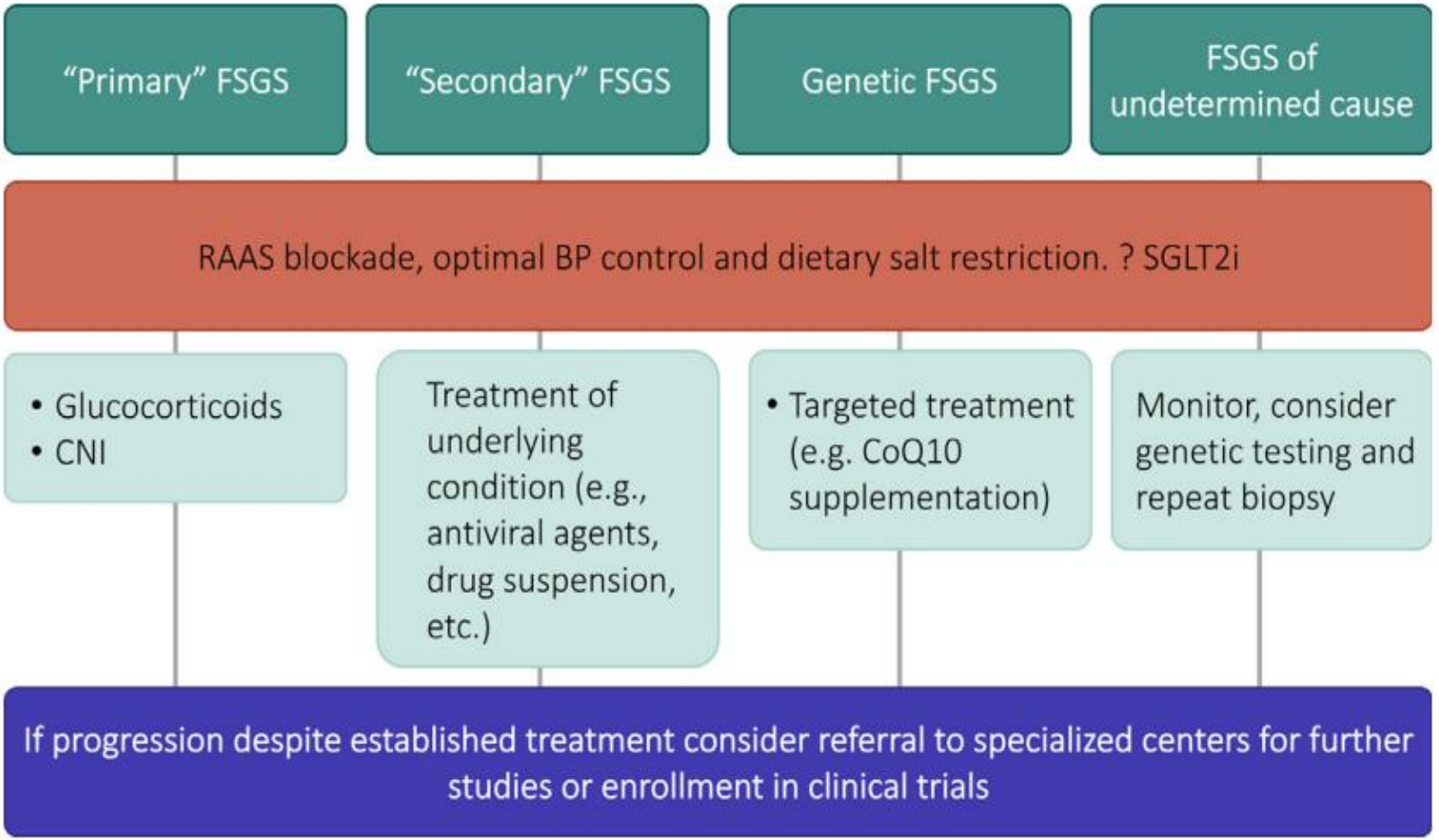
Rituximab:
Has limited evidence

Clinical Trials
Sparsentan, Atrasentan, TRPC5 channel modulators, SLIT2 antagonists, APOL1 inhibitors, and other promising interventions.

MATCH
Novel approach by providing participants with results of biomarker analyses

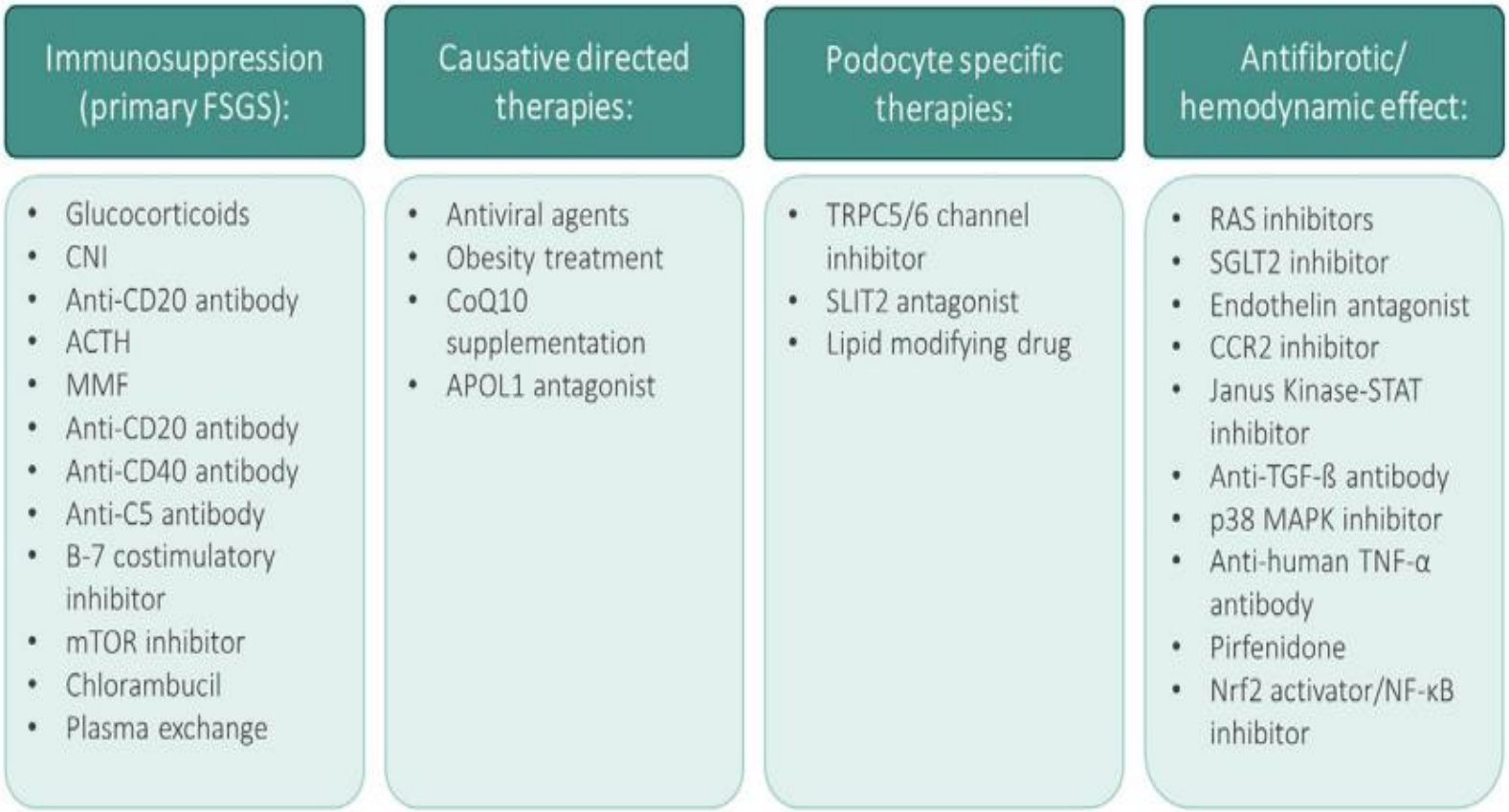
Kidney Med Vol 6 | Iss 6 | June 2024 | 100844

Current treatment of FSGS based on KDIGO practice guideline recommendations



Kidney International Reports (2023) 8, 30–35

Treatment of FSGS organized by class, including both established and emerging therapeutic options.



Kidney International Reports (2023) 8, 30–35

Treatment protocols for FSGS

Treatment	Dose and duration
Glucocorticoids	**Starting dose:** • High-dose glucocorticoid 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 glucocorticoid treatment duration: • Continue high-dose glucocorticoid 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 glucocorticoid therapy until 16 weeks if the proteinuria is persistent and unremitting, especially in patients who are experiencing side effects
	Glucocorticoid tapering: • If complete remission is achieved rapidly, continue high-dose glucocorticoid treatment for 2 weeks or 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 glucocorticoid 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 steroid-resistant or develops significant toxicities, glucocorticoids should be rapidly tapered as tolerated and treatment with alternative immunosuppression like a CNI should be considered

Kidney International (2021) 100, 753–779

Later Response to Corticosteroids in Adults with Primary FSGS is Associated with Favorable Outcomes

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Retrospective cohort study

Patients with pFSGS (1995 – 2014) n = 51

No complete remission after 8 weeks of high dose corticosteroids (CS)

47 years Median age

7.1 years Median follow-up

At 8 weeks

10 patients were in partial remission

Remission after high-dose CS monotherapy (median 17 weeks, IQR 11-21)

9 patients (18%) Complete

18 patients (35%) Partial

Additional immunosuppression for persistent nephrotic range proteinuria (n = 22 out of 24)

3 patients Complete remission

11 patients Partial remission

≥20% decrease in proteinuria

predicts response to immunosuppression

8 patients

were primary non-responders

1.2g (0.4-3.0g/ 24h)

proteinuria at end of follow-up

Renal survival

3 y	92%
5 y	87%
10 y	64%

KI REPORTS
Kidney International Reports

Rood et al, 2022
Visual abstract by:
Michelle Lim, MBChB MRCP

@whatsthegfr

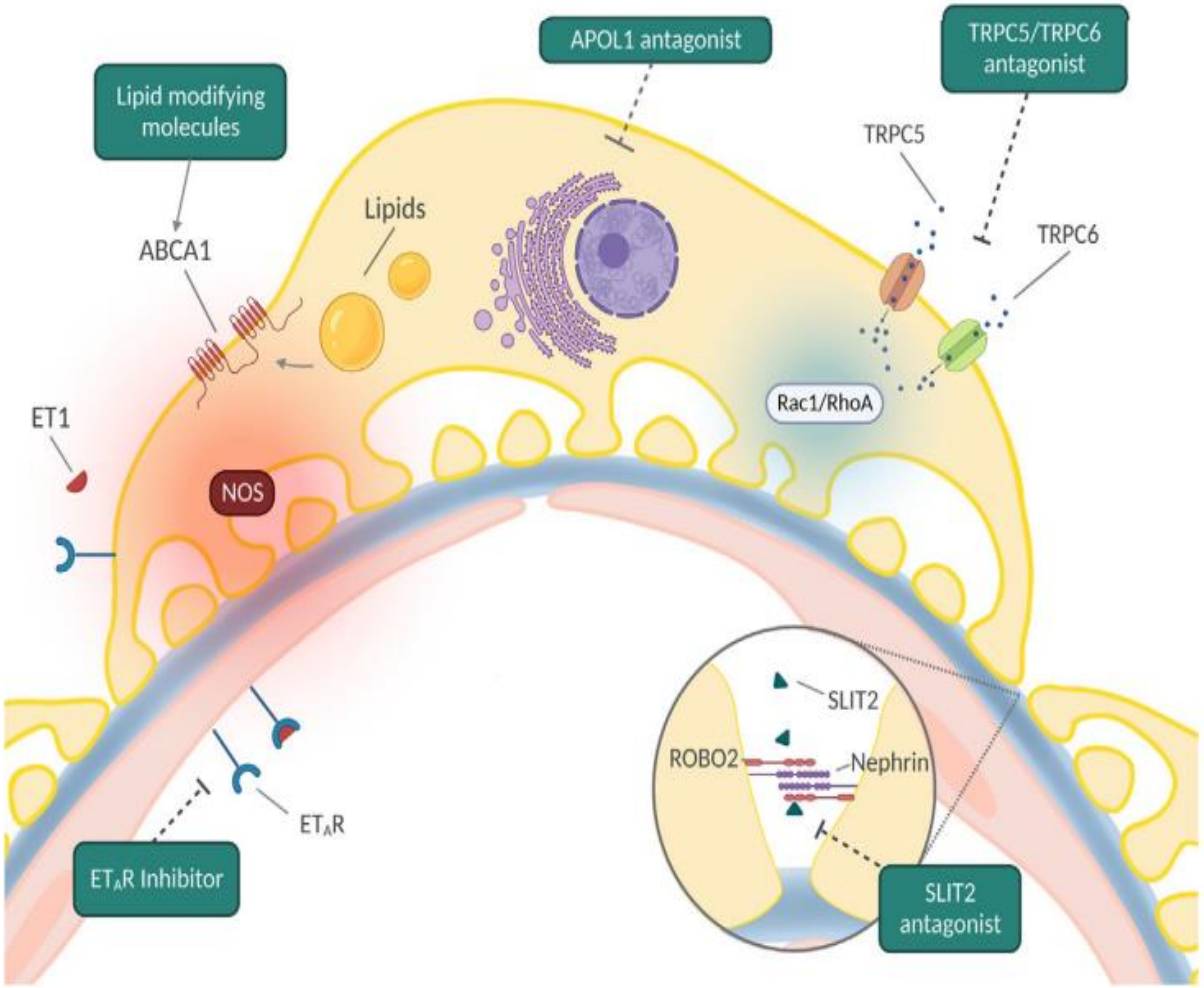
Conclusion Patients with presumed pFSGS often respond late to immunosuppressive therapy. A decrease of proteinuria >20% after 8 weeks of therapy is a promising predictor of responsiveness. Better biomarkers are needed to predict response and outcome.

Treatment protocols for FSGS

Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 4–6 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

Kidney International (2021) 100, 753–779

Promising emerging therapeutic targets and their mechanism of action in the treatment of focal segmental glomerulosclerosis



Kidney International Reports (2023) 8, 30–35

Some recent and ongoing clinical trials in focal segmental glomerulosclerosis

NCT number	Drug	Mechanism of action	Status	Phase	Completion
NCT01613118	Sparsentan	Dual ETA receptor/AT1 receptor antagonist	Active, not recruiting	Phase 2	February 2026
NCT03493685				Phase 3	
NCT05003986			Peds: Recruiting	Phase 2	June 2025
NCT04573920	Atrasentan	Dual ETA receptor/AT1 receptor antagonist	Recruiting	Phase 2	February 2026
NCT03970122	GFB-887	*TRPC5* channel inhibitor	Completed	Phase 1	April 2020
NCT04387448			Recruiting	Phase 2	August 2022
NCT04950114				Phase 2	September 2025
NCT03448692	PF-067301512	*SLIT2* antagonist	Recruiting	Phase 2	August 2025
NCT04340362	VX-147	*APOL1* antagonist	Completed	Phase 2	December 2021
NCT05312879			Recruiting	Phase 2/3	June 2026
NCT05267262	R3R01	Lipid-modifying drug	Not yet recruiting	Phase 2	December 2023
NCT05213624	BI764198	*TRPC6* inhibitor	Recruiting	Phase 2	August 2023
NCT05183646	DMX-200 (repagermanium)	*CCR2* inhibitor	Recruiting	Phase 3	June 2026
NCT05314231	ALXN1720	Anti-C5 mini-body	Not yet recruiting	Phase 1	March 2023
NCT05237388	Baricitinib	Janus kinase-*STAT* inhibitor	Not yet recruiting	Phase 2	March 2026
NCT00814255	Adalimumab	Antihuman TNF-α antibody	Completed	Phase 2	February 2014
NCT04009668			+TR-MCD: Recruiting	Phase 2	July 2024
NCT05441826	VB119	Anti-CD19 antibody	Recruiting	Phase 2	February 2024
NCT04983888	Obinutuzumab	Anti-CD20 antibody	Recruiting	Phase 2	September 2024

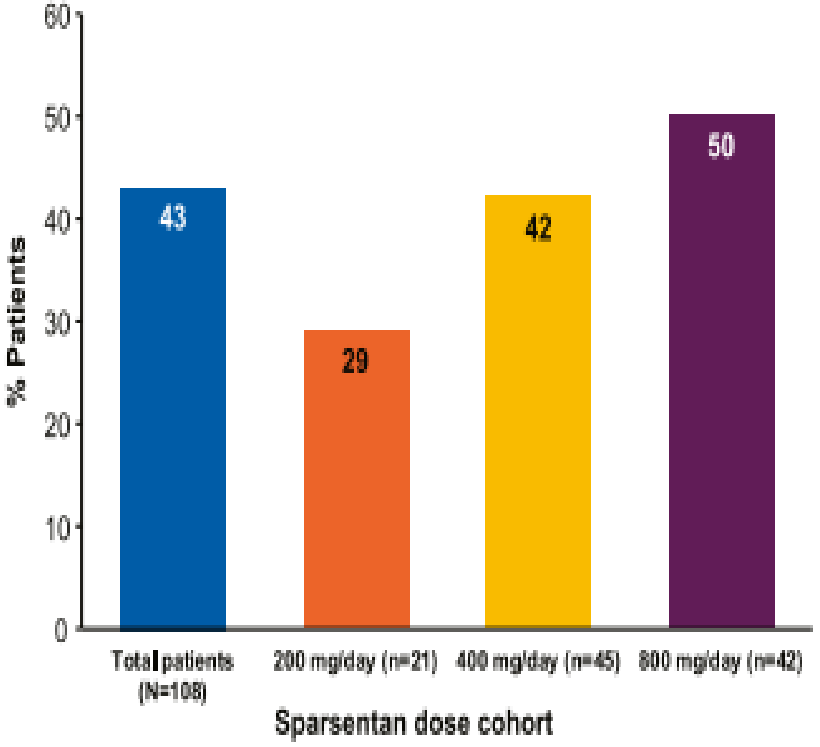
Kidney International Reports (2023) 8, 30–35

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Implications of Complete Proteinuria Remission at any Time in Focal Segmental Glomerulosclerosis: Sparsentan DUET Trial

Howard Trachtman[1], Ulysses Diva[2], Edward Murphy[2], Kaijun Wang[2], Jula Inrig[3] and Radko Komers[3]

- We conclude that sparsentan can be safely administered for extended periods and exerts a sustained antiproteinuric effect
- Achievement of CR at any time during follow-up, even if it is not sustained, may be an indicator of a favorable response to treatment and a predictor of improved kidney function outcomes.



Implications of Complete Proteinuria Remission at Any Time in Focal Segmental Glomerulosclerosis: Sparsentan DUET Trial

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

COHORT AND METHODS

Post hoc analysis of patients enrolled in DUET trial of Sparsentan in FSGS.

108 patients who received ≥ 1 Sparsentan dose were included.

BP, edema, proteinuria and kidney function evaluated every 12 weeks.

RESULTS

Median follow up of 47 months.

Complete remission (CR) was ≤ 0.3g/g.

46 patients (43%) had ≥ 1 CR.

61% of CR occured in 1yr of starting Sparsentan.

Increased likelihood of CR with high Sparsentan dose or baseline sub nephrotic proteinuria.

≥ 1 CR associated with slower eGFR decline vs non-CR patients. P<0.05

Immunosuppression more frequent in patients who achieved CR.

Anti proteinuric effect of Sparsentan was additive to concomitant immunosuppression.

KI REPORTS
Kidney International Reports

Trachtman H et al, 2023

Visual abstract by:
Krishnam Raju Penmatsa. MD,DM,DNB.
@krishnadoctor1

Conclusion Sparsentan can be safely administered for extended periods and exerts a sustained anti proteinuric effect. Achievement of CR at any tim during follow up, even if it is not sustained, may be a favourable response to treatment and a predictor of improved kidney function outcomes.

Clinical Kidney Journal, 2023, vol. 16, no. 8, 1199–1205

https://doi.org/10.1093/ckj/sfad122
Advance Access Publication Date: 24 May 2023
Editorial Comment

EDITORIAL COMMENT

Rituximab in the treatment of primary FSGS: time for its use in routine clinical practice?

Adam D. Morris, Lauren Floyd, Alexander Woywodt and Ajay Dhaygude

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Correspondence to: Adam D. Morris; E-mail: adam.morris@lthtr.nhs.uk

Summary of the studies that demonstrate the use of rituximab in the treatment of FSGS

Study title	Author	Date	Summary	Limitations
Focal segmental glomerular sclerosis can be effectively treated using an intensive B cell depletion therapy [4]	Roccatello *et al.*	2023	Seven patients with FSGS managed with combination therapy including 6 doses of RTX. Five patients had partial response at 12 months and one remained in complete remission at 36 months	Small case series. Three patients were identified as having a genetic mutation, one of whom had a mutation for *IFN2* gene
The role of rituximab in primary focal segmental glomerular sclerosis of the adult [34]	Tedesco *et al.*	2022	Thirty-one patients were treated with RTX. Response rates at 3, 6 and 12 months was 39%, 52% and 42%, respectively. 80% of responders at 12 months maintained a sustained response with ongoing treatment	Patients included had a long disease course prior to RTX treatment. No genetic analysis was undertaken and there was variation in the RTX and standard glucocorticoid dosing
Rituximab therapy for focal segmental glomerular sclerosis and minimal change disease disease in adults: a systematic review and meta-analysis [44]	Hansrivijit *et al.*	2020	Sixteen studies included with a total of 221 patients (23.1% with FSGS). Over half (53.6%) of FSGS patients achieved remission with RTX but there was a significant relapse rate	The majority of patients had MCD rather than FSGS. Only observational studies were included without any control cohorts
High-dose rituximab ineffective for focal segmental glomerulosclerosis: a long-term observation study [31]	Roccatello *et al.*	2017	Eight patients were treated with high-dose RTX (8 weekly doses of 375 mg/m^2). Seven out of eight patients failed to improve and remained	Small case series. Patients included all had major risk factor precluding standardized glucocorticoid treatment

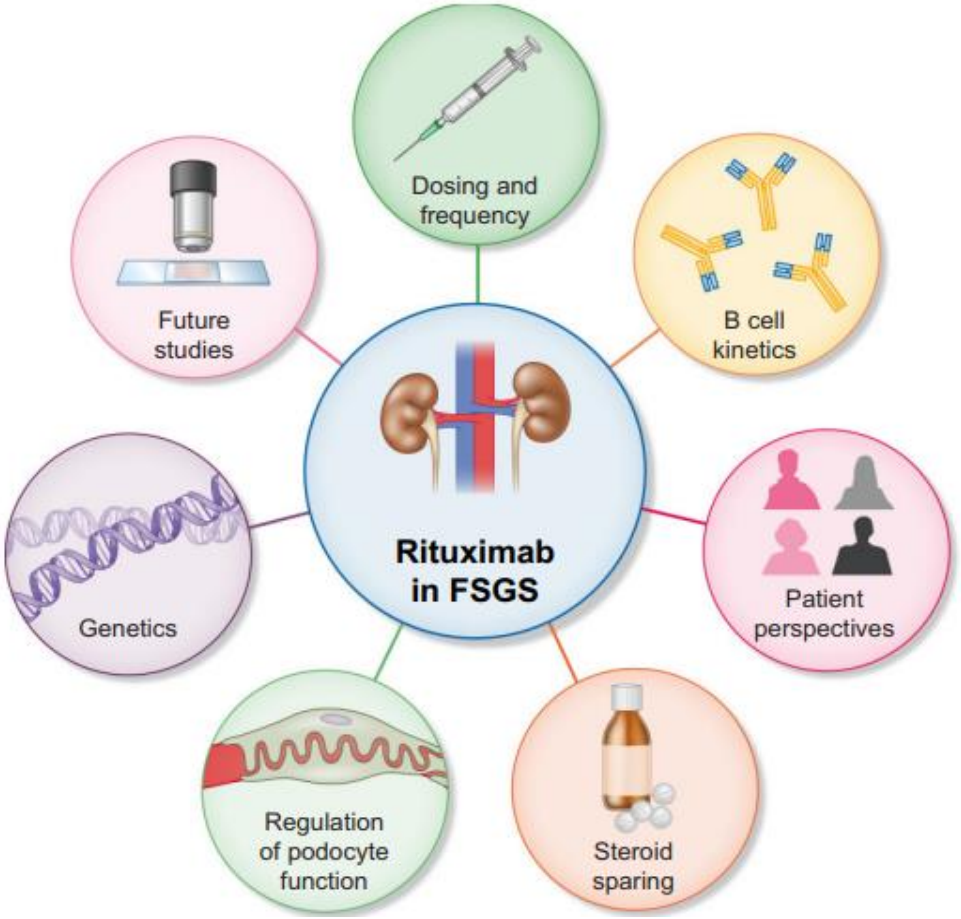
Clinical Kidney Journal, 2023, vol. 16, no. 8, 1199–1205

Summary of the studies that demonstrate the use of rituximab in the treatment of FSGS

T lymphocyte activation markers as predictors of responsiveness to rituximab among patients with FSGS [29]	Chan *et al.*	2016	Twenty-two paediatric patients treated with RTX following a lack of sustained remission treatment with either calcineurin inhibitors, mycophenolate or cyclophosphamide. Twelve responded to therapy with reduced T-cell activation compared with non-responder on immunological profiling	Small retrospective observational study. No genetic analysis was undertaken, with limited response rate and biomarker findings remain unvalidated
Rituximab in adult patients with multi-relapsing/steroid-dependent minimal change disease and focal segmental glomerulosclerosis: a report of 5 cases [32]	Kronbichler *et al.*	2013	Five patients were treated with RTX and achieved complete remission even when other immunosuppressive treatment was withdrawn. One patient relapsed after 23 months but was treated successfully with further RTX	Small case series with only three FSGS patients included
Rituximab treatment for adult patients with focal segmental glomerulosclerosis [33]	Ochi *et al.*	2012	Four patients: two were steroid resistant and two were steroid dependent. The two patients with steroid-dependent FSGS achieved complete remission in contrast to those who had steroid-resistant disease	Small study size and only a single dose of RTX was given. Those with steroid resistant disease had a longer duration of disease and worse renal function by comparison
Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis [28]	Fornoni *et al.*	2011	Forty-one transplant patients at high risk of recurrent FSGS. Twenty-seven received RTX and demonstrated lower incidence of post-transplant proteinuria and renal impairment	Although there has a trend to higher graft survival in the RTX treated patients at 6 and 12 months, this was not statistically significant

Clinical Kidney Journal, 2023, vol. 16, no. 8, 1199–1205

The scientific questions and unknowns that exist in clinical practice when using rituximab as treatment for primary FSGS



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EDITORIAL COMMENT

Rituximab in the treatment of primary FSGS: time for its use in routine clinical practice?

Adam D. Morris, Lauren Floyd, Alexander Woywodt and Ajay Dhaygude

- The evidence to suggest that rituximab may become routine treatment for many patients with FSGS is thin but tangible. Following exclusion of an underlying genetic mutation and other secondary causes, we propose that rituximab can be considered in those with high risk of glucocorticoid toxicity, CNI nephrotoxicity or failed initial treatment following exclusion of other causes, and that repeated dosing may be required to achieve therapeutic effect.

Efficacy of Rituximab in Treatment Resistant Focal Segmental Glomerulosclerosis with Elevated SuPAR with Activation of Podocyte β3 Integrin

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods

Open label pilot study

Primary FSGS (N=9)
1. Treatment resistant
2. SuPAR >3500 pg/mL^{-1}
3. B3 integrin activation

Serologic tests
24-hr urine protein
suPAR levels
B3 integrin activity

Dec 2016 – Jan 2019

Intervention

Rituximab 1000 mg at days 1 and 15

Baseline Characteristics

37±16 years
Mean age

67±38 ml/min
Mean eGFR

7.7±4.61 g/day
24 hr proteinuria

Prior exposure to immunosuppression for all patients

Outcomes

6 months

1 Partial response
1 Complete remission

GFR declined (60±38 ml/min)
1 patient progressed to ESRD

No significant change in urine protein at 12 months
(7.27±7.30 g/day)

3 serious adverse events
1 infusion-related reaction
1 leukopenia

SuPAR – soluble urokinase-type plasminogen activator receptor

KI REPORTS
Kidney International Reports

Hladunewich et al, 2022

Visual abstract by:
Carlo Trinidad, MD
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Conclusion Rituximab was ineffective when administered to adult patients with treatment resistant primary FSGS with a high suPAR and evidence of podocyte activation.

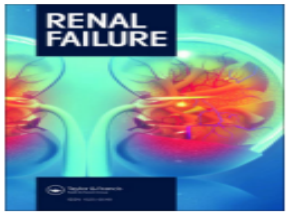
Renal Failure

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/irnf20

Efficacy of extracorporeal plasma therapy for adult native kidney patients with Primary FSGS: a Systematic review

Table 4. Summary of renal outcomes following different EPT in primary FSGS.

Patients (*n*)	Responders, n/total (%)	CR, n/total (%)	PR, n/total (%)	Follow up duration
PE (31)	20/31 (65) Long-term 15/31 (48)[a]			• 14.4 ± 6.8 months in 5 case report studies [22,23,25,28,29] • 29 ± 4 months in a case series study [18] • 27.5 ± 6.3 months in a case series study [17] • 17 months (IQR 15, 20) in a case series study [31]
Non-HD (30)	19/30 (63)	8/30 (27)	11/30 (37)	
HD (1)	1/1 (100)			
LDL-A (61)	33/61 (54) Long-term 12/28 (43)			• 3 weeks, 3 months and 4 months in 3 case report studies, respectively [21,26,27] • 2 week, 4 weeks and 2 years in 3 case series studies, respectively [30,34,35]
Non-HD (59)	31/59 (53)	12/29 (41)[b]	1/29 (3)[b]	
HD (2)	2/2 (100)			
IA (10)[c]	4/10 (40) Long-term ¼ (25)	0/10 (0)	4/10 (40)	• 25 weeks and 6 months in 2 patients, respectively [32] • NA in 7 patients
LCAP (2)[c]	1/2 (50) Long-term 1/2 (50)	1/2 (50)		• 47 and 40 months, respectively [36]



Renal Failure

Taylor & Francis

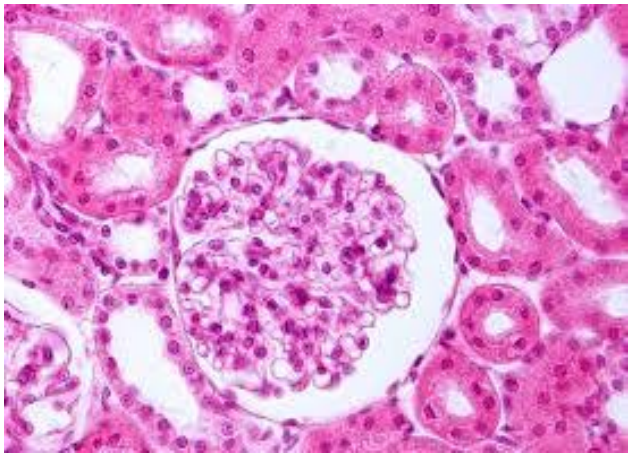
ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/irnf20

Efficacy of extracorporeal plasma therapy for adult native kidney patients with Primary FSGS: a Systematic review

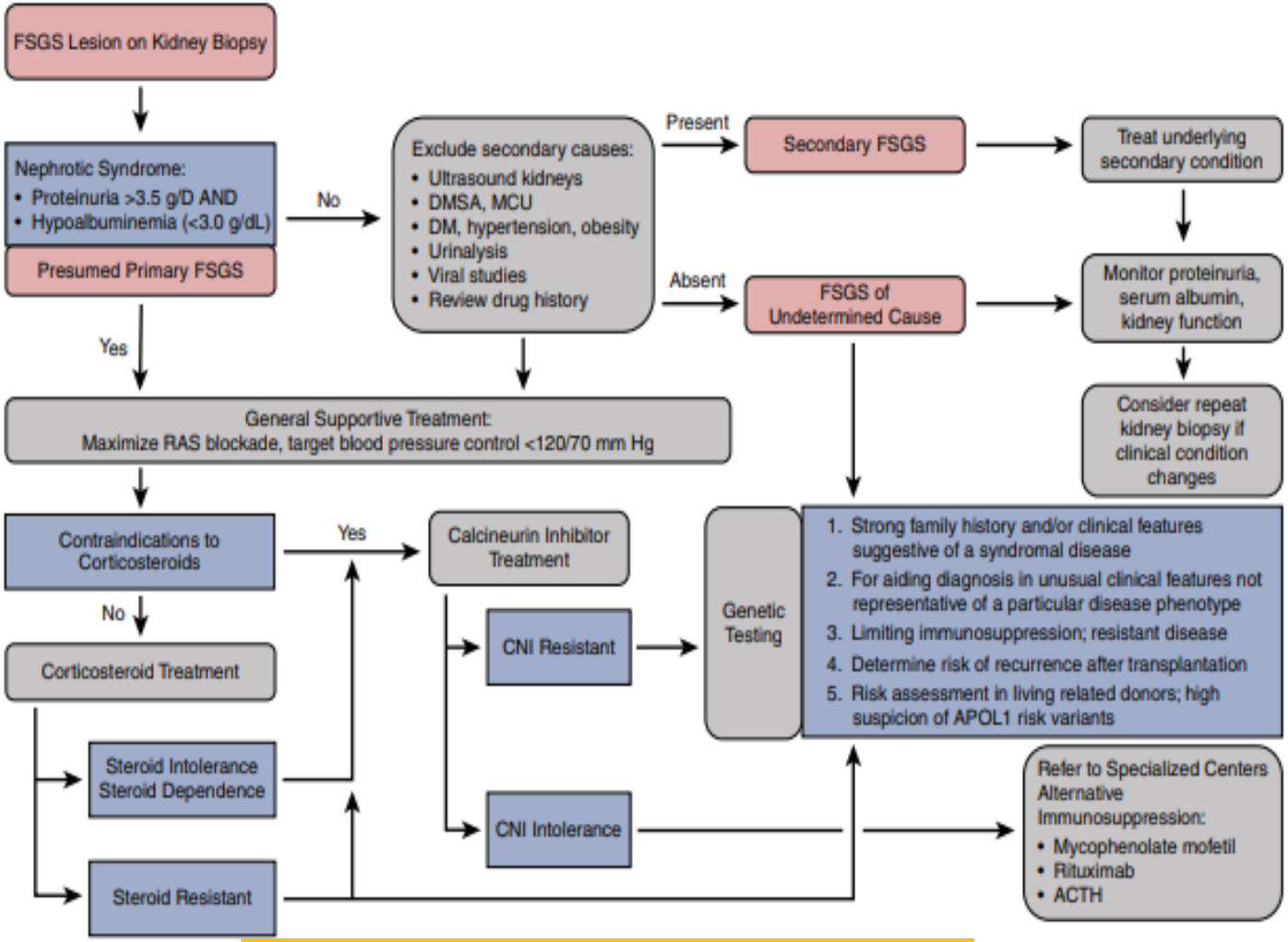
- EPT utilized concomitantly with immunosuppressive therapy showed benefit in some patients with refractory primary FSGS. PE appeared to have a higher overall response rate than LDL-A and IA

Prognosis in FSGS

- Massive proteinuria>14g/d
- Cr >1.3 mg/dl
- Interstitial fibrosis>20%
- Cellular lesion >1%
- APOL1



Approach to a patient with an FSGS lesion on the kidney biopsy



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