Proteinuria in FSGS and IgA Nephropathy & The Dual Role of ET-1 and Ang II

Spotlight on IgA nephropathy – clinical significance of proteinuria

Loreto Gesualdo, Italy

The talk was framed by a case study of a 28-year-old Caucasian male with typical characteristics for IgA nephropathy:

- MEST* score(s): M1, E1, S1, T1
- Estimated glomerular filtration rate (eGFR): 67 mL/min/1.73 m2
- Blood pressure: 140/86 mmHg
- Proteinuria: 1.5 g/d
- ACEi/ARBs*?: Yes; 3 months
- Immunosuppressive therapy (IST)?: No

**MEST, mesangial hypercellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.*

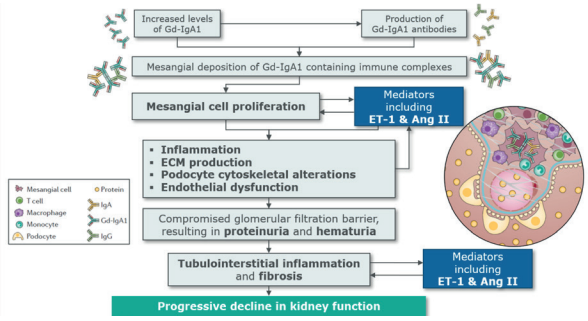


Figure 1.
IgA nephropathy is an immune complex-mediated glomerular disease. Chart based on data from Lai K, et al. Nat Rev Dis Primers 2016; 2:16001; Wyatt RJ & Julian BA. N Engl J Med 2013; 368:2402–2414; Suzuki H, et al. J Am Soc Nephrol 2011; 22:1795–1803; Kohan DE & Barton M. Kidney Int 2014; 86:896–904; Komers R & Plotkin H. Am J Physiol Regul Integr Comp Physiol 2016; 310:R877–R884; Raina R, et al. Kidney Dis 2020; 6:22–34.

IgA nephropathy is the most prevalent primary glomerulonephritis worldwide, with a global incidence of approximately 2.5 per 100,000 persons per year.[1] Patients with IgA nephropathy were found to have a 53% increased risk of all-cause mortality and 6-year reduction in life expectancy compared with matched controls.[2]

IgA nephropathy profoundly impacts patients' lives. IgA nephropathy is associated with depression and anxiety, often centered on fear of uncertainty and complications with therapy,[3] as well as reduced physical functioning, and ability to perform daily routines.[4]

IgA nephropathy is an immune complex-mediated glomerular disease (see fig 1).

Sustained proteinuria > 1 g/d has been shown to be the strongest predictor of the rate of progression of IgA nephropathy, with each incremental g/d over 1g associated with a 10- to 25-fold more rapid rate of decline in kidney function and similar differences in kidney survival. However, reduction in proteinuria can predict delay in time to kidney failure conferred by treatment effect.[5] A study presented at last year's ERA Congress showed that a 30% reduction in proteinuria at 9 months was associated with an increase in the median time to kidney failure of 10.7 years.[6] Since it plays such an important role in determining the clinical outcome, proteinuria is incorporated in risk stratification for patients with IgA nephropathy. The International IgAN Prediction Tool, recommended by the KDIGO Guidelines, incorporates clinical and histologic data to provide a prognosis at the time of biopsy to help identify patients who are at a high risk of rapid disease progression and require urgent care to protect kidney function.[7,8]

Like a substantial number of patients, the individual in the case study remained at high risk of disease progression despite first-line treatment approaches (see Fig 2), with a risk of a 50% decline in eGFR and 19.77% risk of progression to end-stage renal disease five years after renal biopsy.

Current treatment recommendations center on management of blood pressure and proteinuria. For example, the KDIGO Clinical Practice Guidelines for Glomerular Diseases state, "The goal of therapy in IgA nephropathy, is to preserve kidney function through management of blood pressure (systolic blood pressure <120 mmHg) and proteinuria (<1 g/24 hrs), which is pivotal for slowing progressive kidney disease."[8]

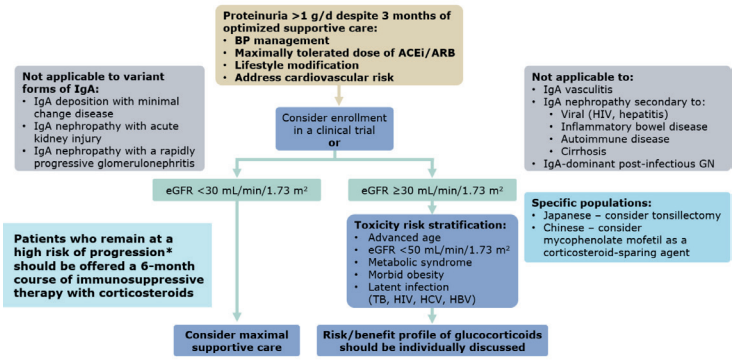
Questions[17]	Case study results
Estimated eGFR at biopsy (ml/min/1.73m^2)	67 ml/min/1.73m^2
Systolic blood pressure at biopsy (mm Hg)	140 mm Hg
Diastolic blood pressure at biopsy (mm Hg)	86 mm Hg
Proteinuria at biopsy (g/day)	1.5 g/day

Figure 2.
Application of the international IgA nephropathy prediction tool for the individual in the case study

Race (Caucasian, Chinese, Japanese, Other)	Caucasian
Use of an ACE inhibitor or ARB at the time of biopsy (yes/no)	Yes
MEST M-score (0 or 1)	1
MEST E-score (0 or 1)	1
MEST S-score (0 or 1)	1
MEST T-score (0, 1 or 2)	1
Immunosuppression use at or prior to biopsy (yes/no)	No
At how many months after renal biopsy would you like to determine risk of progression?	60 months

Looking at the management flow chart from KDIGO[8] (see fig 3) for patients with IgA nephropathy who remain at high risk of progression (defined as proteinuria >0.75–1 g/d despite 3 months of optimized supportive care), it is clear to see the next steps for the individual in the case study. As he has proteinuria > 1g/d, despite 3 month of optimized supportive care, and poorly controlled blood pressure, the first step is to increase the renin-angiotensin-system (RAS) inhibition to the maximum tolerated dose. Lifestyle modification and other steps to address cardiovascular risk must also be part of the management plan. This is a patient who might be considered either for enrollment in a clinical trial or, after stratifying the toxicity risk, for treatment with glucocorticoids.

Figure 3.
Management of patients with IgA nephropathy who remain at high risk of progression
Adapted from KDIGO 2021 Clinical practice guideline for the management of glomerular diseases. Kidney Int 2021; 100(4S):S1–S276.



There remains a high unmet clinical need in IgA nephropathy therapy:

- Approximately half of patients remain above the target proteinuria level of >0.75–1 g/d, and are at a high risk of disease progression[8]
- The use of RAS blockade with ACEis/ARBs and immunosuppression versus RAS blockade alone is still debated.[9] The ongoing low-dose TESTING Study should be very helpful to address this issue
- Corticosteroid therapy should be avoided in certain patients, and carries a significant risk of toxicity[8]

Looking to the horizon, there are a number of phase 3 trials investigating novel therapeutic approaches for the treatment of IgA nephropathy:

Trial	ClinicalTrials.gov Identifier
NEFIGARD	NCT03643965
PROTECT	NCT03762850
ARTEMIS-IgAN	NCT03608033
APPLAUSE-IgAN	NCT04578834
ALIGN	NCT04573478

Spotlight on FSGS – clinical significance of proteinuria

Sian Griffin, UK

The talk was framed by a case study of a 32-year-old Caucasian female with primary focal segmental glomerulosclerosis (FSGS):

- eGFR: 58 mL/min/1.73 m^2
- Blood pressure: 142/86 mmHg
- Proteinuria: 3.7 g/d (baseline: 8.2 g/d and nephrotic syndrome)
- ACEi/ARBs*?: Yes; 4 months
- IST?: Yes; glucocorticoids for 12 weeks

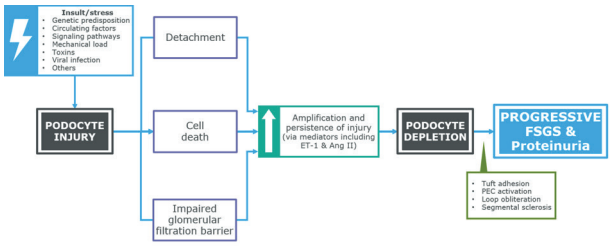


Figure 4.
FSGS is caused by sustained injury to podocytes, leading to elevated and persistent proteinuria. Chart based on data from: Abbate M, et al. Am J Pathol 2002; 161:2179–2193; Abbate M, et al. J Am Soc Nephrol 2006; 17:2974–2984; De Vriese AS, et al. J Am Soc Nephrol 2018; 29:759–774; Jefferson JA & Shankland SJ. Adv Chronic Kidney Dis 2014; 21:408–416; Kohan DE & Barton M. Kidney Int 2014; 86:896–904; Komers R & Plotkin H. Am J Physiol Regul Integr Comp Physiol 2016; 310:R877–R884.

FSGS is uncommon but is a leading glomerular cause of kidney failure. The global incidence is estimated as 0.1/100,000/year in children and 0.8/100,000/year in adults.[1] Based on analyses conducted from the Idiopathic Nephrotic Syndrome Rare Diseases Group (RaDaR-INS) in the UK, kidney failure occurs in up to 45% of adult and pediatric patients in 10 years, and is associated with an increase in mortality.[10]

FSGS is caused by sustained injury to podocytes, leading to elevated and persistent proteinuria (see fig 4), which can come from a number of different mechanisms.

The classical presentation of immune-related FSGS seems to be associated with a circulating factor, as evidenced by the potential for rapid recurrence after kidney transplantation. A number of toxins and drugs can affect the podocytes – notably bisphosphonates, MTOR inhibitors and anabolic steroids – as well as viral infections, and that which is best characterized is associated with HIV. These factors converge to cause podocyte injury.

The podocyte is a very resilient cell because it is exposed to fluctuating mechanical stress during day-to-day variations in blood pressure in response to meals, but its response to sustained injury may include detachment from the underlying glomerular basement membrane, death of

the podocyte and impairment of the glomerular filtration barrier.

There seems to be a critical threshold of podocyte loss. In early stages there can be some extension of the podocytes to cover the denuded glomerular basement membrane, but amplification and persistence of injury in the glomerular tuft, mediated by inflammatory and profibrotic mediators including endothelin-1 (ET-1) and angiotensin II (Ang II).

The podocyte is a terminally differentiated cell, so large-scale depletion of the podocytes results in large areas of bare glomerular basement membrane which then forms synechial connections to the overlying parietal epithelial cells, which can become activated. There is ongoing inflammation with obliteration of the capillary loop and segmental sclerosis. Histologically we see progressive FSGS which manifests clinically as proteinuria.

The KDIGO Guidelines were updated in 2021 to classify FSGS based on proteinuria, etiology, and histologic presentation on biopsy:[8]

- Primary FSGS: FSGS lesions, extensive foot process effacement, and nephrotic syndrome (defined as proteinuria >3.5 g/d and hypoalbuminemia (<30 g/L), often accompanied by dyslipidemia and edema). It disproportionately affects children and young adults, with a significant and often lifelong impact
- Secondary FSGS: FSGS lesions, accompanying a pathophysiologic process known to cause FSGS
- Genetic FSGS: FSGS lesions in patients who have mutations in podocyte or glomerular basement membrane proteins
- FSGS of undetermined cause: FSGS lesions with no identifiable cause and an absence of nephrotic syndrome

FSGS profoundly impacts patients' lives. Patients frequently report physical symptoms including severe edema, fatigue, and shortness of breath and often experience mental symptoms such as anxiety, depression, negative effects on sleep, and a reduced ability to socialize.[11] Pregnancy carries significant risks to both the patient and the fetus, as well as to the underlying disease.[8] This can be particularly devastating for young women and is an important issue to cover when counselling patients.

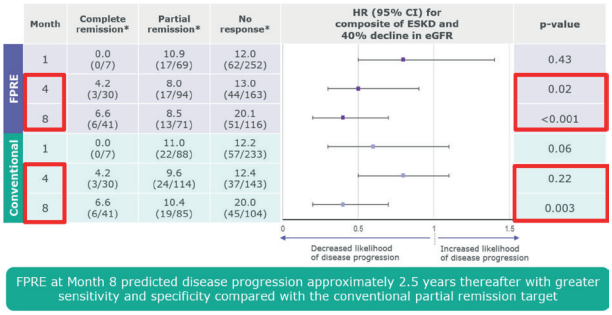


Figure 5.
FPRE for Proteinuria Predicts Kidney Survival Earlier than the Conventional Target. Adapted from Troost JP, et al. Clin J Am Soc Nephrol 2018; 13:414–421.

Persistent proteinuria in FSGS is a risk factor for progressive kidney failure and more severe proteinuria is associated with a faster time to kidney failure.[12] Less than 15% of patients with non-nephrotic proteinuria progress to kidney failure in 10 years, but 50% or more of patients with nephrotic proteinuria (>3 g/d) progress to kidney failure in 5–10 years.[12] For patients with massive proteinuria (>10–14 g/d), the average time to kidney failure is 2–3 years.[12]

Achieving partial or complete remission of proteinuria greatly improves kidney survival. An analysis of 338 adult patients with biopsy-proven FSGS (97% receiving RASi) using data from the US Department of Defense healthcare network found that complete and partial remission occurred in 26% and 25% of patients, respectively, where complete remission was defined as a reduction in proteinuria to <0.3 g/d with <25% reduction in eGFR from baseline at biopsy diagnosis. Kidney survival was significantly better with complete and partial remission than no remission at 5, 10, and 15 years.[13]

An analysis of 281 nephrotic FSGS patients from the Toronto Glomerulonephritis Registry found that relapse from partial remission was significantly associated with worse kidney outcomes in FSGS. 52% (61/117) of patients who achieved partial remission (defined as >50% reduction in peak proteinuria and to subnephrotic levels [<3.5 g/d]) relapsed after a median time of 7 months, compared to 36% (20/55) of patients from a complete remission (proteinuria value <0.3g/d) after a median time of 20 months. Relapse in the partial remission group was significantly associated with worsening kidney function (p=0.03) and a higher risk of kidney failure compared with patients who achieved

partial remission with no relapse (HR=2.90; 95% CI=1.09–7.72; p=0.03).[14]

Further stratifying those patients who have undergone a partial remission to predict those who will have either a good, or an inferior, long-term survival. Data on 466 well-characterized patients with FSGS and proteinuria were analyzed to refine proteinuria definitions. The conventional definition of partial remission is a 50% reduction in proteinuria to <3.5 g/g. The more robust FSGS data-derived partial remission endpoint (FPRE), with ≥40% reduction in proteinuria to the range 0.3-1.5 g/g, was found to be associated with better long-term outcomes and became significant as a predictor of improved long-term outcome earlier than the conventional partial remission target (see fig 5).[15] This is helpful both as an endpoint in clinical trials and when advising patients in the clinic of their likely progress.

There is significant unmet need for better treatments for these patients with a favorable safety profile. ACEis and ARBs are considered standard of care, and guidelines recommend high-dose oral glucocorticoids or Calcineurin inhibitors (CNIs), despite the lack of evidence from RCTs, as first-line IST for primary FSGS.[8] However:

- Long periods of IST are required[12]
- IST is associated with significant risk of toxicity[8]
- Relapse is common with all current therapeutic options[8]
- A substantial number of FSGS patients do not achieve proteinuria remission and remain at a high risk of progressive kidney disease[14]

There are two phase 3 trials investigating novel therapies in FSGS on the horizon:

Trial	ClinicalTrials.gov Identifier
DUPLEX	NCT03493685
ACTION3	NCT05183646

Evidence for the dual role of ET-1 and Ang II in proteinuria and CKD progression in IgA nephropathy and FSGS

Pierre-Louis Tharaux, France

ET-1 and Ang II in CKD

ET-1 and Ang II act in tandem to promote CKD progression via multiple mechanisms, including promoting inflammation, vascular dysfunction, glomerular dysfunction and tubulointerstitial injury; however, they have opposing actions on sodium homeostasis. [16–18]

ET-1 and Ang II in IgA nephropathy

Several further studies suggest a role for ET-1 in IgA nephropathy:

- Elevated ET-1 in kidney biopsies from patients with IgA nephropathy correlates with proteinuria and 1-year progression[19,20]
- Specific ETAR antagonism in a murine model of IgA nephropathy reduced proteinuria and downregulated pro-inflammatory, pro-fibrotic, and pro-sclerotic pathways[21]

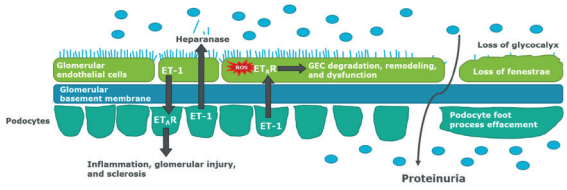


Figure 6.
Podocyte-endothelial cell interaction. Adapted from: Ebefors K, et al. Kidney Int 2019; 96:957–970; Garsen M, et al. J Am Soc Nephrol 2016; 27:3545–3551; Kohan DE & Barton M. Kidney Int 2014; 86:896–904; Mahtal N, et al. Front Med (Lausanne) 2021; 8:659013. GEC, glomerular endothelial cell; ROS, reactive oxygen species.

ET-1 and Ang II in FSGS

Expression of both ET-1 and ETAR is elevated in patients with primary FSGS. This was demonstrated by studies showing increased urinary output of ET-1 in patients with FSGS compared to healthy volunteers,[22] and increased levels of ETAR-positive glomerular endothelial cells in kidney biopsies of patients with FSGS versus controls.[23]

Experimental evidence indicates that, when stimulated by ET-1, the functional cytoskeletal dynamics of the podocyte are altered, promoting cell detachment and loss of the foot processes. When activated by ET-1, the podocyte can also produce heparanase, an enzyme that will cleave off the endothelial glycocalyx – the first layer of the glomerular filtration barrier that ensures selectivity against proteinuria in the glomerulus. The endothelial cells also react to exaggerated ET-1 signaling by triggering reactive oxygen species (ROS), opening the endothelial junctions leading to degradation of glomerular endothelial cells. This means that all layers of the glomerular filtration barrier are impaired with exaggerated ET-1 signaling (see fig 6).[16,24,25]

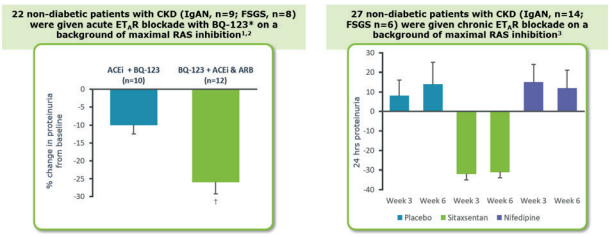


Figure 7.
Combined RAS blockade and ETAR inhibition has demonstrated a substantial anti-proteinuric effect in studies including patients with IgA nephropathy and FSGS. * BQ-123 is a selective ETAR antagonist; † p<0.01. 1. Dhaun N, et al. Hypertension 2009; 54:113–119; 2. Dhaun N, et al. Hypertension 2009; 54:e19–e20; 3. Dhaun N, et al. Hypertension 2011; 57:772–779.

Clinical evidence for dual antagonism

The RADAR study in 211 patients with diabetic nephropathy and proteinuria showed that selective ETAR antagonism with atrasentan (0.75mg or 1.25mg) on a background of stable RAS inhibition achieved a significant reduction in proteinuria.[26]

In the SONAR study, 2,684 patients with Type 2 diabetes and proteinuria were given ETAR blockade with atrasentan on a background of maximal RAS inhibition for ≥4 weeks. Atrasentan was shown to have a beneficial effect on progression of CKD, measured by a primary composite renal outcome (doubling of serum creatinine or ESKD [chronic dialysis for >90 days, kidney transplantation, eGFR <15 mL/min/1.73 m^2, or death from kidney failure]).[27]

Combined RAS blockade and ETAR inhibition has demonstrated a substantial anti-proteinuric effect in studies including patients with IgA nephropathy and FSGS (see fig 7).

Dual endothelin angiotensin receptor antagonists (DEARAs)

DEARAs such as sparsentan have regions with affinity for both ETAR and AT1R and can bind individually to either receptor to inhibit intracellular signaling.[17] Both receptors are associated with potent vasoconstrictive, proliferative, pro-inflammatory, and pro-fibrotic effects.In two separate phase 3 trials in patients with IgA nephropathy and FSGS, a dual endothelin and angiotensin receptor antagonist has been shown to be able to reduce proteinuria to a greater extent than angiotensin receptor blockade alone, with a comparable safety profile to the active comparator.[28,29]

Further readings

1. McGrogan A, *et al. Nephrol Dial Transplant* 2011; **26**:414–430
2. Jarrick S, *et al. J Am Soc Nephrol* 2019; **30**:866–876
3. Lai KN, *et al. Nat Rev Dis Primers* 2016; **2**:16001
4. Cleary J & Drennan J. *J Adv Nurs* 2005; **51**:577–586
5. Reich HN, *et al. J Am Soc Nephrol* 2007; **18**:3177–3183
6. Carroll KJ, et al. ERA-EDTA Congress 2021 (oral presentation MO246)
7. QxMD. International IgAN Prediction Tool. Available at: https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool (accessed May 2022)
8. KDIGO 2021 Glomerular Disease Guidelines *Kidney Int* 2021; **100**(4S):S1–S276.
9. Campbell KN, *Kidney360* 2021; **29**:1084-1086
10. Saleem MA, et al. ASN Congress 2021. Abstract PO1529 (Poster)
11. Mathias SD, *et al. Am J Kidney Dis* 2017: **70**:532–540
12. Korbet SM. *J Am Soc Nephrol* 2012; **23**:1769–1776
13. Forster B, *et al. KIDNEY360* 2020; **2**:105–113

14. Troyanov S, *et al. J Am Soc Nephrol* 2005; **16**:1061–1068
15. Troost JP, *et al. Clin J Am Soc Nephrol* 2018; **13**:414–421
16. Kohan DE & Barton M. *Kidney Int* 2014; **86**:896–904
17. Komers R & Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016; **310**:R877–R884Pergola PE, *et al. Adv Chronic Kidney Dis.* 2019;26(4):272-291
18. Raina R, *et al. Kidney Dis* 2020; **6**:22–34.
19. Lehrke I, *et al. J Am Soc Nephrol* 2001; **12**:2321–2329
20. Tycová I, *et al. Physiol Res* 2018; **67**:93–105
21. King A, *et al.* WCN 2021; poster presentation (POS-378)
22. Chen HC, *et al. J Clin Lab Anal* 2001; **15**:59–63
23. van de Lest N, *et al. KI Reports* 2021; **6**:1939–1948
24. Ebefors K, *et al. Kidney Int* 2019; **96**:957–970
25. Garsen M, *et al. J Am Soc Nephrol* 2016; **27**:3545–3551;
26. de Zeeuw D, *et al. J Am Soc Nephrol* 2014; **25**:1083–1093
27. Heerspink HJ, *et al. Lancet* 2019; **393**:1937–1947
28. Travere Therapeutics press release. Available at: https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-positive-topline-interim-results (accessed May 2022)
29. Travere Therapeutics press release. Available at: https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-achievement-interim-proteinuria (Accessed May 2022)