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REVIEW

Advances in primary glomerulonephritis

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Abstract

Primary glomerulonephritis comprises several renal-limited diseases that can cause haematoproteinuria, chronic kidney disease, nephrosis and end stage kidney disease. The most common of these are IgA nephropathy (IgAN), primary membranous nephropathy (PMN), Focal Segmental Glomerulosclerosis (FSGS) and Minimal Change Disease (MCD). Although rare, these diseases cause a significant burden to health care systems, given the high cost of treating End Stage Kidney Disease (ESKD) with dialysis or transplantation. Until recently, the pathogenesis of primary gloerulonephritis has remained obscure. However, recent advances in understanding of how these diseases evolve has led to the introduction of novel therapeutic agents. Trials are underway or have recently completed that have huge implications for the standard of care for the primary glomerulonephritidies, and should dramatically reduce the number of patients who progress onto end stage kidney disease. This article reviews the international Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the treatment of IgAN, PMN, FSGS and MCD, as well as recent research on pathogenesis and treatment.

Key words: Focal segmental glomerulosclerosis; IgA nephropathy; Membranous glomerulonephritis; Minimal change disease

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Introduction

Primary glomerulonephritis comprises several renal limited diseases that present in a number of ways, including nephritic syndrome, nephrotic syndrome, asymptomatic haemoproteinuria and chronic kidney disease, sometimes at end stage requiring renal replacement therapy. They include IgA nephropathy (IgAN), primary membranous nephropathy (PMN), Focal Segmental Glomerulosclerosis (FSGS) and Minimal Change Disease (MCD). The last two decades have seen enormous advances in understanding of the pathogenesis of these diseases and with that, the development of more targeted and effective therapies. Proteinuria is a marker of early disease, and predicts prognosis – reducing proteinuria is now recognised as a surrogate for slowly eventual progression to End Stage Kidney Disease (ESKD). Treatment strategies therefore focus on both generic approaches to reduce proteinuria and slow rate of change of estimated glomerular filtration rate (eGFR), and targeting the underlying disease process, using proteinuria as a marker of efficacy. Here, we review the latest advances in the three most common primary glomerulonephritidies – IgAN, PMN and FSGS and MCD.

IgA nephropathy

Epidemiology

IgA nephropathy is the most common cause of primary glomerulonephritis worldwide and a leading cause of chronic kidney disease (CKD) (Yeo et al, 2019). 25–30% of patients will progress to ESKD within 20–25 years of diagnosis (Barret and Feehally, 2006). IgAN has an incidence of at least 2.5 per 100,000 population per year, peaking in the second and third decade. The prevalence of IgAN varies across globally – it causes 40% of primary glomerulonephritis in Japan compared with 25% in Europe. Sex incidence also varies geographically, with an affected male to female ratio of 3:1 in Europe but 1:1 in East Asia (Yeo et al, 2019). Genomewide association studies have confirmed different genetic risk factors predispose to IgAN in East Asian compared to Western populations (Yeo et al, 2019).

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Pathogenesis

IgAN is a highly heterogenous condition that can present with a wide spectrum of clinical phenotype, from isolated haematuria to ESKD. IgA is the predominant immunoglobulin at mucosal surfaces and activation of the mucosal immune system can trigger IgAN, with 30–40% of patients developing macroscopic haematuria within 72 hours of an upper respiratory tract or gastrointestinal infection (Barret and Feehally, 2006). The development of IgAN requires a sequence of events where immune tolerance is broken, known as the 'four-hit hypothesis' (Figure 1).

Diagnosis

Diagnosis of IgAN requires a renal biopsy. The histological hallmark is IgA deposition in glomerular mesangium with associated mesangial expansion and/or hypercellularity. The Oxford Classification is used to score the histology according to the degree of mesangial, endocapillary, segmental and tubule-interstitial involvement, as well as the presence of glomerular crescents (MEST-C score), and this in turn can be used in the International IgAN Prediction Tool to quantify risk of progression to ESKD (Barbour et al, 2019).

Management of primary IgA nephropathy

Currently, the internationally recognised Kidney Disease Improving Global Outcomes (KDIGO) Guidelines for Glomerulonephritis advocate management should focus on best supportive care, reducing proteinuria with renal angiotensin aldosterone system inhibition (RAASi) and optimising blood pressure control (Barret and Feehally, 2006). However, immunosuppression is suggested in some patients, and newer agents under investigation now are likely to be widely used in the near future.

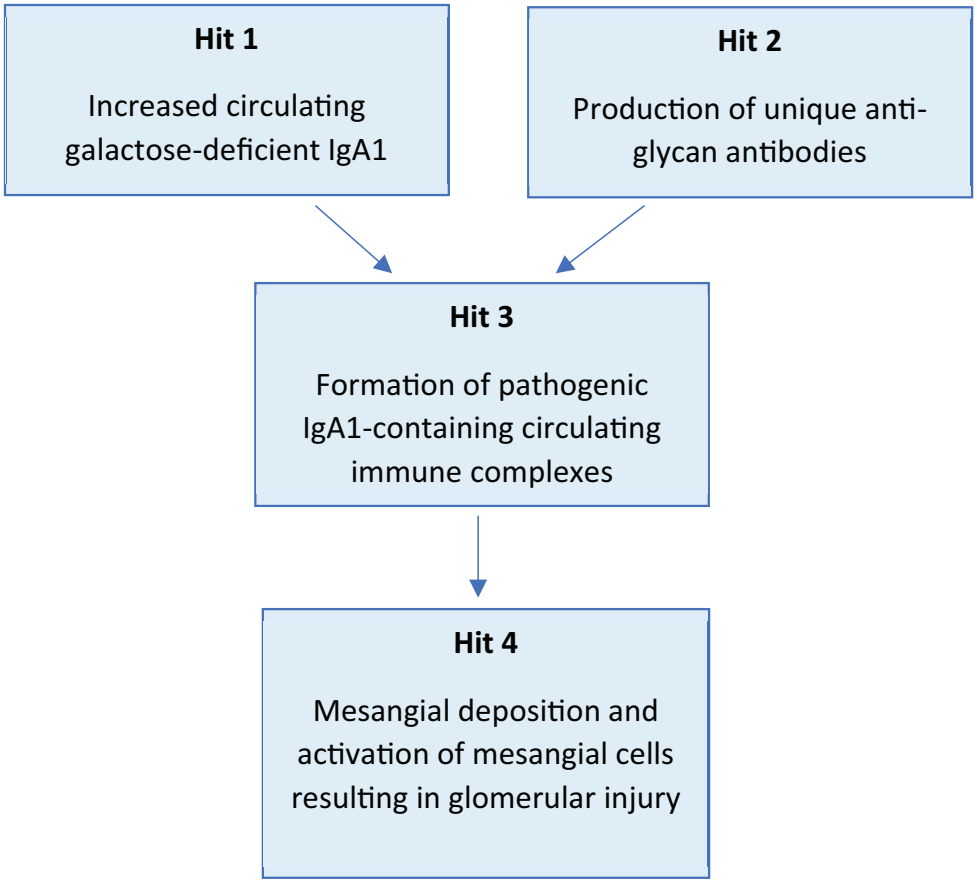

Figure 1. Pathogenesis of IgA nephropathy (IgAN), four-hit hypothesis.

Supportive care

Proteinuria is strongly associated with disease progression. All IgAN patients with proteinuria > 0.5g/day should receive RAASi, uptitrated to maximum tolerated dose (KDIGO Executive Committee, 2021).

Recent data from large randomized control trials (RCTs) supports the use of sodium/glucose cotransporter 2 inhibitors (SGLT2i) as part of supportive care. DAPA-CKD and EMPA-Kidney collectively recruited 987 proteinuric IgAN patients. A meta-analysis of these two RCTs assessed the composite primary outcome of: ESKD, sustained decline in eGFR to < 10 mL/min/1.73 m^2, sustained decline of ≥ 40% in eGFR from the time of randomisation or death due to renal causes. Participants treated with SGLT2i had a relative risk of kidney disease progression of 0.49 [95% CI, 0.32–0.74] compared to placebo (The EMPA-KIDNEY Collaborative Group, 2023). Based on these data, SGLT2i should be started if there is persistent proteinuria of > 0.5 g/day despite maximum tolerated RAASi.

Sparsentan is a dual endothelin type A and angiotensin II type 1 receptor antagonist. The phase 3 PROTECT study randomised 404 patients to receive sparsentan or irbesartan. At two years of follow up, patients in the sparsentan group had a slower rate of estimated glomerular filtration rate (eGFR) decline than those in the irbesartan group: eGFR chronic 2-year slope (weeks 6–110) was −2.7 mL/min per 1.73 m^2 per year vs −3.8 mL/min per 1.73 m^2 per year (p=0.037), with the sparsentan group demonstrating a significant reduction in proteinuria at 36 weeks that was maintained till study end. Adverse events were similar between the 2 groups (Rovin et al, 2023). On the basis of these data, sparsentan use has been given accelerated Food and Drug Administration approval for patients at risk of progression of IgAN.

Glucocorticoids

For patients who are at high risk of disease progression (proteinuria > 1 g/day despite 3–6 months of optimised supportive care), KDIGO recommends considering glucocorticoid therapy– but emphasises the need to consider and discuss the important risk of treatment-emergent toxicity, particularly those with an eGFR < 50 mL/min per 1.73 m^2 (KDIGO Executive Committee, 2021). In the TESTING trial, IgAN patients with proteinuria > 1 g/day were randomised to oral methylprednisolone or placebo. TESTING was halted after recruiting 262 of the planned 750 participants due to increased number of serious adverse events (SAEs) in the glucocorticoid group vs placebo (22 vs 4). The primary outcome was a composite measure of 40% reduction in eGFR, kidney failure, kidney associated death. At time of analysis there were fewer outcomes in the glucocorticoid group suggesting efficacy. The trial then restarted with a reduced glucocorticoid regimen and antibiotic prophylaxis. Both full and reduced dose glucocorticoid regimens significantly reduced progression to the primary endpoint when compared to placebo, with no significant difference between the 2 regimens. There were only 6 SAEs in the reduced dose glucocorticoid group (including 1 infection-related death) compared to 3 in the placebo group (Jicheng et al, 2022), thus the reduced glucocorticoid approach for IgAN patients may reduce progression in those at greatest risk without an unacceptably high infection risk.

Glucocorticoids suppress production of galactose deficient IgA1(Gd-IgA1) by gut associated lymphoid tissue (GALT). Using a non-absorbed form of glucocorticoid to target GALT may therefore reduce the systemic side effects and infection risk. The NefIgArd Phase 3 clinical trial compared placebo with a 9-month treatment course of ileal targeted budesonide, Nefecon, in 364 patients with IgAN and > 1g/day proteinuria, followed by a 15 month follow up. After 9 months, the budesonide group had a 27% reduction in urine protein creatinine ratio (uPCR) vs placebo and stabilisation of eGFR, compared to a deterioration with placebo. The infection rate was similar between the two groups and no patients were hospitalised. After 15 months follow up, eGFR decline for Nefecon treated patients was half that in the placebo group. Given the improvements in renal function and proteinuria, the drug has been given accelerated FDA approval for IgAN (Lafayette et al, 2023a).

Targeting B cells

The cytokines B Lymphocyte Stimulator (BLyS) and A Proliferation-inducing Ligand (APRIL) cause naive mucosal B cells to class-switch into IgA secreting plasma cells

that produce Gd-IgA1. Atacicept is a fusion protein which inhibits BLyS and APRIL and therefore might reduce the formation and deposition of pathogenic Gd-IgA1 in glomeruli (Lafayette et al, 2023b). In the phase 2b, dose ranging trial ORIGIN, 116 patients with IgAN and proteinuria > 0.75 g/day were randomised to or placebo weekly for 36 weeks. The 150 mg group (n=33) had a 33% reduction in uPCR from baseline after 24 weeks compared to 7% with placebo, and no increased infection.

Sibeprenlimab is a monoclonal antibody that binds to and neutralises APRIL-results from a Phase 2 trial in IgAN showed a significant reduction in proteinuria compared to placebo (Mathur et al, 2023). Phase 3 RCTs using Sibeprenlimab and Atacicept in IgAN are awaited, but BlyS/APRIL inhibition seems a promising approach to treat IgAN.

Targeting complement

Iptacopan is an alternative complement pathway inhibitor (Factor B inhibitor). A phase 2 trial showed three months treatment with iptacopan significantly reduced proteinuria with no treatment emergent SAEs (Zhang et al, 2023). The phase 3 clinical trial APPLAUSE-IgAN has randomised 450 IgAN patients to either iptacopan or placebo for 24 months with the primary outcome being reduction in urine protein creatinine ratio (uPCR) and rate of eGFR decline over the 24 months. An interim analysis at 9 months reportedly showed a statistically significant reduction in uPCR in the iptacopan group, although peer-reviewed data are currently unpublished (Novartis, unpublished observations, 2023).

Many other therapies are also being considered for the treatment of IgAN – 28 Clinical Trial of an Investigational Medicinal Products (CTIMPs) are listed on ClinicalTrials.gov as recruiting or in set up. Although treatment options are limited for patients currently, over the next decade it is likely that many more therapies will become available, and the challenge for nephrologists will be to decide which patients will benefit from which drugs or combinations of drugs.

Primary membranous nephropathy

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in the non-diabetic adult population. 80% of cases are idiopathic and classed as PMN, while the remaining 20% have an identifiable trigger such as malignancy, infection or drugs and together comprise secondary membranous nephropathy (SMN). PMN is an autoimmune condition characterised by autoantibodies targeting human podocyte antigens. These result in the formation of immune complexes deposited in the glomerular basement membrane, leading to podocyte dysfunction with proteinuria and reduced glomerular filtration (Couser, 2017).

The global incidence of PMN is 8–10/million and typically impacts individuals aged > 40, peaking between 50 to 60 years. It is more common in men, and affected women have a better prognosis. Approximately 40 to 50% of patients develop ESKD after 10 years (Couser, 2017).

Aetiology

Understanding of the pathogenesis of PMN has progressed markedly in the last 15 years, starting with the landmark discovery in 2009 that phospholipase A-2 Receptor (PLA2R) was the major target antigen of PMN, present in 70–80% of patients. Anti-PLA2R antibody levels correlate with disease activity, progression and therapy response (Beck et al, 2009). The antibody such a high specificity to PMN that it can be used in diagnosis for patients where renal biopsy is too high risk.

Since 2009, further autoantibodies have been identified in anti-PLA2R negative cases – some solely implicated in PMN and others in both primary and secondary disease. These affect only a minority of patients compared with anti-PLA2R and include autoantibodies to Thrombospondin type-1 domain-containing 7A (THSD7), affecting 3% of patients with membranous nephropathy (Tomas et al, 2014). Antibodies to Exostin 1 and 2 have been described in PMN and SMN, including class V lupus nephritis. Nerve epidermal growth factor-like 1 (NELL-1) has also been identified as the responsible antigen in some patients: compared to anti-PLA2R antibody positive patients, a higher proportion of NELL-1 positive patients have a malignancy (33%) (Caza et al, 2021).

Clinical presentation

PMN manifests as nephrotic syndrome, characterised by low serum albumin, proteinuria exceeding 3 g per day, and oedema. Patients are often hypertensive and have an increased thrombotic risk due to urinary loss of antithrombin 3, hence anticoagulation is indicated with a serum albumin less than 25 g/dL. At presentation, renal function may be normal or already impaired.

Identifying the autoantigen is useful in predicting the risk of an associated malignancy (Table 1) (Puri, 2022).

Treatment

The modified Ponticelli regimen, which combines high doses of glucocorticoids with cyclophosphamide for a 6 month treatment period, has long been used to treat PMN and still has highest remission rates. However, it is associated with significant side effects, and several approaches have been used to try to limit treatment associated morbidity. Patients are categorised as low, medium, high and very high risk based on several criteria *(*Table 2*)* (KDIGO Executive Committee, 2021). Treatment is given in accordance with risk level *(*Figure 2*)* (KDIGO Executive Committee, 2021).

Immunosuppressive therapy is not recommended in low risk patients as they are more likely to remit spontaneously 45% within 6 months (KDIGO Executive Committee, 2021). RAASi is effective in the management of proteinuria and hypertension in these patients. sGLT2i may also be helpful, but the evidence here is not as strong as in IgAN.

For patients at a moderate risk of progression the calcineurin inhibitor (CNI) tacrolimus and ciclosporin are effective in inducing remission but with high relapse rates when they discontinued. Rituximab or RAASi only with regular monitoring is an alternate management strategy.

GEMRITUX randomised patients to receive the anti-CD 20 monoclonal antibody rituximab or standard of care with RAASi. Although there was no difference in the primary end-point of complete or partial remission at 6 months, remission rate doubled by 17 months after treatment in the rituximab group, consistent with previous uncontrolled studies where time to proteinuria nadir after rituximab was up to 36 months. Interestingly, phospholipase A-2 receptor (PLA2R) levels were significantly lower as early as 3 months in the rituximab arm (Dahan et al, 2017).

Table 1. Membranous nephropathy (MN) autoantigen in malignancy

MN autoantigen in malignancy		
Names and targets	**Prevalence in autoantigen associated MN**	**Association of malignancy and autoantigens**
• PLA2-R	• 70–80% with idiopathic MN • M > F	• No clear temporal association with malignancy and PLA2R (+) MN • 9–33% of PLA2R (+) patients may develop early malignancy (within 2 years of diagnosis)
• THSD7A	• 1–3% of all membranous • Upto 10% of patients negative for PLA2R	• Up to 6–25% of THSD7A (+) MN cases found to be temporally associated with malignancy • Commonly gastrointestinal and genitourinary system
• NELL-1	• Found in 4–16% of PLA2R/ THSD7 negative patients with MN • M > F	• Up to 33% of patients with NELL-1 (+) MN may have associated malignancy • Most commonly genitourinary and breast

Adapted from infographic membranous Nephropathy, GlomCon Aug, 2022 (Puri, 2022). PLA2-R, phospholipase A-2 Receptor; THSD7, Thrombospondin type-1 domain-containing 7A; NELL-1, Nerve epidermal growth factor-like 1.

Table 2. Treatment approach in primary membranous nephropathy (PMN). Adapted from KDIGO (KDIGO Executive Committee, 2021)

Low risk	Moderate risk	High risk	Very high risk
Normal eGFR, proteinuria < 3.5 d/d and albumin > 30 g/L OR	Normal eGFR, proteinuria > 3.5 g/d and no drop > 50% after 6 months of RAASi AND	eGFR < 60 mL/min/1.73 m^2 and/or proteinuria > 8 g/d for > 6 months OR	Life threatening nephrotic syndrome OR
Normal eGFR, proteinuria < 3.5 g/d or a drop > 50% after months of RAASi	Not fulfilling high risk criteria	Normal eGFR, proteinuria > 3.5 g/d and no drop > 50% after 6 months of RAASi AND At least one of the following Serum albumin < 25 g/L PLA2Rab > 50 RU/mL Urinary alpha1 microglobulin > 250 mg/d Selectivity index > 0.20	Rapid deterioration of kidney function not otherwise explained

KDIGO, Kidney Disease Improving Global Outcomes; eGFR, estimated glomerular filtration rate.

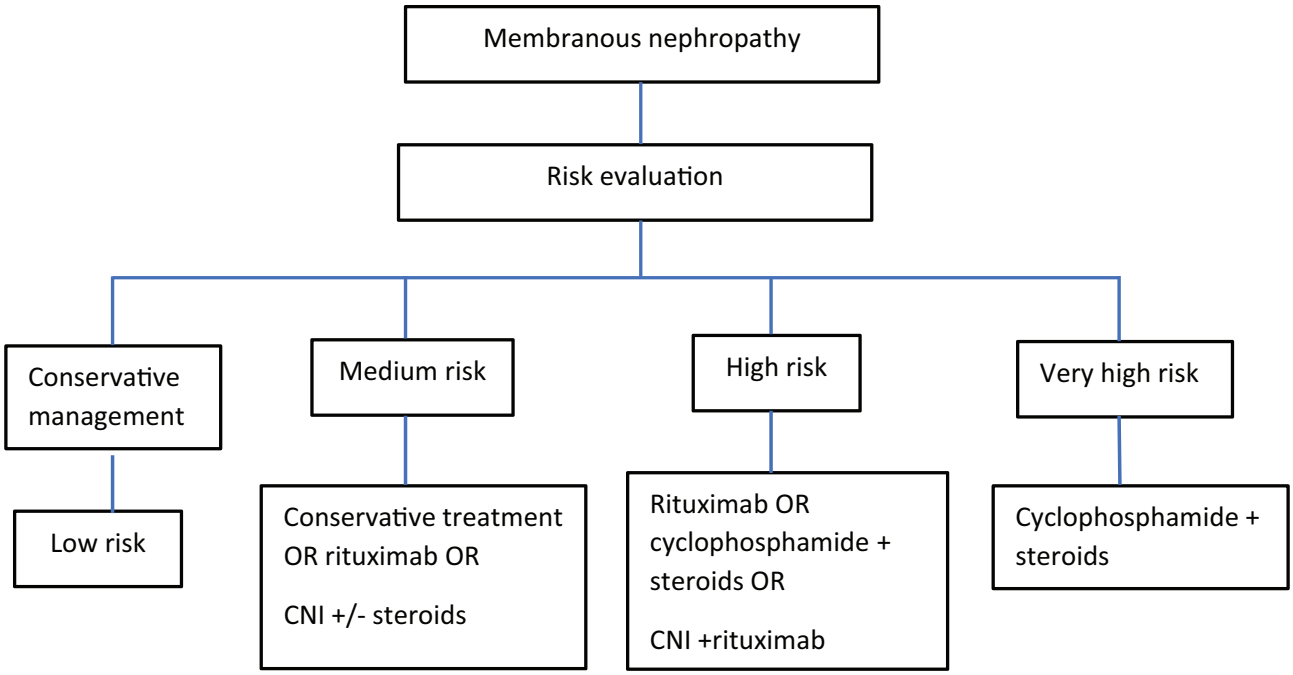

Figure 2. Treatment approach in primary membranous nephropathy. Adapted from KDIGO (KDIGO Executive Committee, 2021). CNI, calcineurin inhibitor.

The MENTOR Trial randomised PMN patients with a high risk of progression to rituximab or ciclosporin monotherapy. Rituximab 1 g was given at Day 1 and 15 with an additional 6 month dose if proteinuria had dropped > 25%. The ciclosporin group were treated for 12 months if proteinuria fell > 25% at 6 months (with treatment stopped at 6 months if complete remission was achieved). At 24 months, more patients in the rituximab group were in complete remission, and this group also had greater improvement in proteinuria.

Ciclosporin caused a faster decline in proteinuria than rituximab initially– but this effect was not sustained when treatment was withdrawn, with high relapse rates (Fervenza et al, 2019).

The STARMEN trial compared the modified Ponticelli regimen to a combination of rituximab and tacrolimus for high risk PMN. In the cyclophosphamide-steroid arm, 83.7% patients achieved complete/partial remission with 60% achieving full remission, compared to only 26% in the rituximab and tacrolimus arm. However, total rituximab doses were lower than in MENTOR, as all except 2 patients were only given 1g, compared with 4g rituximab in MENTOR (Fernández-Juárez et al, 2021).

KDIGO recommends the modified Ponticelli regimen for those patients with very high risk PMN and where other treatments have failed, which occurs at about a third of patients (KDIGO Executive Committee, 2021). Given the toxicity of the modified Ponticelli, better treatments are needed. There are a number of RCTs underway in PMN, using the anti-BlyS monoclonal antibody belimumab in combination with rituximab compared to rituximab alone (REBOOT), and the newer anti-CD 20 antibody obinutuzimab compared to the modified Ponticelli (REMIT).

Minimal change disease and focal segmental glomerulosclerosis

Primary minimal change disease and focal segmental glomerulosclerosis

Primary MCD and FSGS are rare, affecting about 10/million population/year. Together they cause 50% of adult idiopathic nephrotic syndrome presentations. When nephrotic, patients require frequent hospital admissions; infections and venous thrombo-embolism are common and can be fatal. With treatment, patients with MCD usually have preserved renal function, however, those with FSGS frequently progress to ESKD. Patients with FSGS and nephrotic syndrome have five year renal survival rates of 60–90% and ten year renal survival rates of 30–50% (Rydel et al, 1995). 10 year survival improves to 80% if remission from proteinuria is achieved (Stirling et al, 2005).

Primary MCD and FSGS are historically described as two separate disease entities but are more likely to be part of a disease continuum (Maas et al, 2016). Both conditions are characterised by electron-microscopic evidence within the glomerulus of diffuse effacement of podocyte foot processes, resulting in a severe functional defect in selective permeability. In FSGS, there is additional focal (i.e., in some areas of the kidney cortex) and segmental (segments of the glomerulus are affected) fibrosis and occlusion of the glomerular capillaries, while glomeruli not displaying segmental lesions demonstrate the classical features of MCD at electron microscopy.

Pathogenesis

The aetiology of primary MCD and FSGS has not been completely delineated. However, there is strong evidence of a circulating factor – nephrotic syndrome recurs following kidney transplantation in 20–30% of patients with FSGS (Ponticelli, 2010). This may be auto-antibody: in a recent study, 29% patients with MCD had anti-nephrin antibodies in the serum at the time of nephrosis, and on renal biopsy, IgG co-localised with nephrin (Watts et al, 2022). The same group have also demonstrated anti-nephrin antibodies in patients with FSGS (Avillach et al, 2023).

Treatment

Primary MCD and FSGS respond to immunosuppression with glucocorticoids in the majority of patients, with MCD typically responding faster than FSGS. Response rates may be higher in MCD at 90%, compared to 40–80% in FSGS. In steroid responsive patients with both diseases, recurrent relapses occur in approximately 75% when the steroid dose is reduced or withdrawn. These frequently relapsing (FR) or steroid dependent (SD) patients accrue a high steroid exposure over time, with weight gain, diabetes, infection and osteoporosis, hence steroid sparing agents are regularly used in MCD/FSGS. Cyclophosphamide is effective at maintaining remission in SD/FR MCD/FSGS, but the severe cumulative toxicity

precludes long term use. CNIs are also effective at maintaining remission, however, relapse rates are high on stopping therapy, so repeated prolonged courses are often required – and CNIs themselves are nephrotoxic (Figure 3) (KDIGO Executive Committee, 2021).

The recent description of the autoantibodies to nephrin as a possible cause of MCD/FSGS fits with evidence that B cell depletion may be an effective treatment. Rituximab is effective in children with FR nephrotic syndrome due to MCD. In one RCT, children treated with rituximab demonstrated a > 50% increase in the median time to relapse compared to the placebo-treated group (p=0.0001) (Iijima et al, 2014). No RCTs have assessed efficacy in adults – but the TURING trial is ongoing in the UK to test the hypothesis that rituximab prolongs remission in adults with relapsing MCD/FSGS.

Secondary focal segmental glomerulosclerosis

FSGS often presents as a secondary form, characterised by non-nephrotic range proteinuria and progression to ESKD. 5 main causes of secondary FSGS are described:

1. Adaptive FSGS. Here, there is a mismatch between glomerular load and the filtration capacity of the glomeruli, creating an excessive pressure in the glomeruli that causing damage to the podocytes and scarring within the glomeruli. This can occur in obesity, or where there has previously been renal damage, e.g., post nephrectomy or previous renal damage by a process such as reflux nephropathy.
2. Viruses including CMV and HIV.
3. Medications including interferon, lithium, bisphosphonates.
4. Genetic FSGS. Variants in at least 38 genes have been associated with FSGS, both genetic risk loci and high-penetrance mutations that manifest either Mendelian inheritance (for nuclear genes) or maternal inheritance (for genes encoded by mitochondrial DNA).
5. Apolipoprotein L1 (APOL1) associated FSGS. APOL1-associated FSGS is an important cause of FSGS in individuals of sub-Saharan African descent (Genovese et al, 2010). The effect is largely recessive, requiring two risk alleles. In the United States, approximately 40% of ESKD attributed to FSGS occurs in blacks, and of this, 72% is associated with APOL1 genetic variants, thus, approximately one third of FSGS in the United States is associated with APOL1 variants. Individuals homozygous for the APOL1 risk variant have a faster progression to ESKD than those with FSGS without the variant.

Treatment of secondary focal segmental glomerulosclerosis

The mainstay of treatment is proteinuria reduction. The recent KDIGO guidelines suggest supportive therapy with RAASi (Figure 3) (KDIGO Executive Committee, 2021).

DUPLEX, a Phase 3 RCT comparing sparsentan to irbesartan in 371 FSGS patients, showed a significant reduction in proteinuria at 36 weeks, maintained throughout the 24 month study period, but no significant difference in rate of change of eGFR (Rheault et al, 2023).

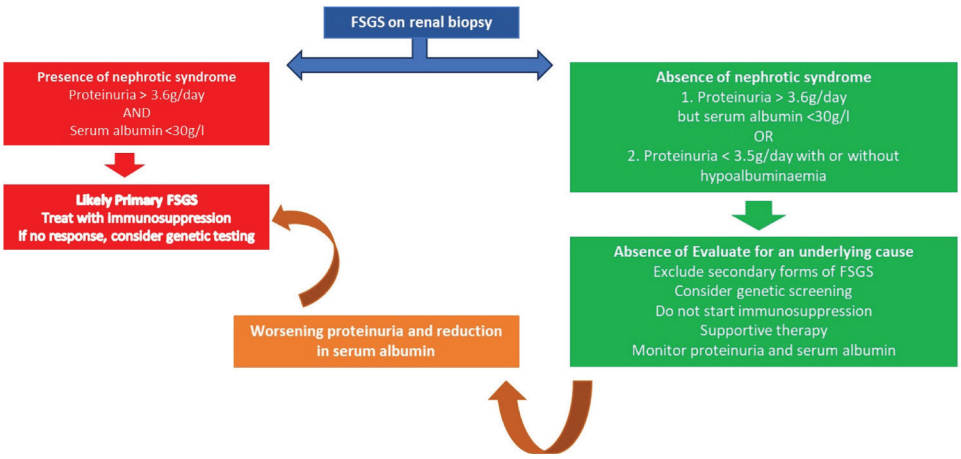

Figure 3. Treatment approach for focal segmental glomerulosclerosis. Based on KDIGO guidelines (KDIGO Executive Committee, 2021). FSGS, Focal Segmental Glomerulosclerosis.

Treating APOL1-related focal segmental glomerulosclerosis

Understanding the role of the gain of function varient of APOL1 in driving FSGS has led to the development of inaxaplin, a small molecule that inhibits APOL1 channel function. In a Phase 2b RCT, patients with two APOL1 variants and biopsy proven FSGS had a 48% reduction in proteinuria after 13 weeks of treatment (Egbuna et al, 2023).

Conclusion

After decades of slow progress in understanding and treatment of primary glomerulonephritis, this century has seen rapid developments in this area of nephrology, which seem poised to continue in future years, and treatment guidelines will require regular review and update.

Key points

- Primary glomerulonephritis are kidney-limited diseases, characterised by proteinuria, that without treatment progress to ESKD. The most common types are IgAN, PMN, MCD and FSGS.
- Recent evidence has defined the role of auto-antibodies in the pathogenesis of IgAN, PMN, FSGS and MCD.
- These diseases often respond to immunosuppression – but the best approach to immunosuppression is unclear and is the subject of many ongoing clinical trials.

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Availability of data and materials

All the data of this study are included in this article.

Author contributions

BE, RC and LW contributed to the conception of the work, analysis and interpretation of the data. All authors contributed to the manuscript's drafting, revisions, and important editorial changes. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agree to be accountable for all aspects.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

References

Avillach C, Wang QY, Watts AJ, Weins A. Anti-nephrin antibody as a potential etiology in primary focal segmental sclerosis (FSGS). J Am Soc Nephrol. 2023;34(11S):7. https://doi.org/10.1681/ASN.20233411S17b

Barbour SJ, Coppo R, Zhang H et al. Evaluating a new international risk-prediction tool in IgA nephropathy. JAMA Intern Med. 2019;179(7):942–952. https://doi.org/10.1001/jamainternmed.2019.0600

Barret J, Feehally J. Treatment of IgA nephropathy. Kidney Int. 2006;69(11):1934–1938. https://doi.org/10.1038/sj.ki.5000419

Beck LH Jr, Bonegio RGB, Lambeau G et al. M-type phospholipase A_2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):11–21. https://doi.org/10.1056/NEJMoa0810457

Caza TN, Hassen SI, Dvanajscak Z et al. NELL-1 is a target antigen in malignancy-associated membranous nephropathy. Kidney Int. 2021;99(4):967–976. https://doi.org/10.1016/j.kint.2020.07.039

Couser WG. Primary membranous nephropathy. Clin J Am Soc Nephrol. 2017;12(6):983–997. https://doi.org/10.2215/CJN.11761116

Dahan K, Debiec H, Plaisier E et al. Rituximab for severe membranous nephropathy – 6 month extended follow up. J Am Soc Nephrol. 2017;28(1):348–358. https://doi.org/10.1681/ASN.2016040449

Egbuna O, Zimmerman B, Manos G et al. Inaxaplin for proteinuric kidney disease in persons with two APOL1 variants. N Engl J Med. 2023;388(11):969–979. https://doi.org/10.1056/NEJMoa2202396

Fernández-Juárez G, Rojas-Rivera J, Logt AV et al. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. Kidney Int. 2021;99(4):986–998. https://doi.org/10.1016/j.kint.2020.10.014

Fervenza FC, Appel GB, Barbour SJ et al. Rituximab or ciclosporin in the treatment of membranous nephropathy. N Engl J Med. 2019;381(1):36–46. https://doi.org/10.1056/NEJMoa1814427

Genovese G, Friedman DJ, Ross MD et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841–845. https://doi.org/10.1126/science.1193032

Iijima K, Sako M, Nozu K et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2014;384(9950):1273–1281. https://doi.org/10.1016/S0140-6736(14)60541-9

Jicheng LV, Wong MG, Hladunewich MA et al. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA Nephropathy: the TESTING Randomised Clinical Trial. JAMA. 2022;327(19):1888–1898. https://doi.org/10.1001/jama.2022.5368

KDIGO Executive Committee. KDIGO clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4S):88–127. https://doi.org/10.1016/j.kint.2021.05.021

Lafayette R, Kristensen J, Stone A et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. Lancet. 2023a;402(10405):859–870. https://doi.org/10.1016/S0140-6736(23)01554-4

Lafayette R, Maes B, Lin C et al. #3848 Origin trial: 24-wk primary analysis of a randomised double-blind, placebo-controlled PH2B study of Atacicept in patients with IGAN. Nephrol Dialy Transplant. 2023b;38(Supplement_1). https://doi.org/10.1093/ndt/gfad063a_3848

Maas RJ, Deegens JK, Smeets B et al. Minimal change disease and idiopathic FSGS: manifestations of the same disease. Nat Rev Nephrol. 2016;12(12):768–776. https://doi.org/10.1038/nrneph.2016.147

Mathur M, Barratt J, Chacko B et al. A phase 2 trial of Sibeprenlimab in patients with IgA Nephropathy. N Engl J Med. 2023;390(1):20–31. https://doi.org/10.1056/NEJMoa2305635

Ponticelli C. Recurrence of focal segmental glomerular sclerosis (FSGS) after renal transplantation. Nephrol Dial Transplant. 2010;25(1):25–31. https://doi.org/10.1093/ndt/gfp538

Puri P. Membranous Nephropathy Autoantigens in Malignancy Infographic. 2022. https://pubs.glomcon.org/membranous-nephropathy-autoantigens-in-malignancy/ (accessed 04 August 2022)

Rheault MN, Alpers CE, Barratt J et al. Sparsentan versus irbesartan in focal segmental glomerulosclerosis. N Engl J Med. 2023;389(26):2436–2445. https://doi.org/10.1056/NEJMoa2308550

Rovin BH, Barratt J, Heerspink HJL et al. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active controlled, phase 3 trial. Lancet. 2023;402(10417):2077–2090. https://doi.org/10.1016/S0140-6736(23)02302-4

Rydel JJ, Korbet SM, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. Am J Kidney Dis. 1995;25(4):534–542. https://doi.org/10.1016/0272-6386(95)90120-5

Stirling CM, Mathieson P, Boulton-Jones JM et al. Treatment and outcome of adult patients with primary focal segmental glomerulosclerosis in five UK renal units. QJM. 2005;98(6):443–449. https://doi.org/10.1093/qjmed/hci072

The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–127. https://doi.org/10.1056/NEJMoa2204233

Tomas NM, Beck LH Jr, Meyer-Schwesinger C et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371(24):2277–2287. https://doi.org/10.1056/NEJMoa1409354

Watts AJB, Keller KH, Lerner G et al. Discovery of autoantibodies targeting nephrin in minimal change disease supports a novel autoimmune etiology. J Am Soc Nephrol. 2022;33(1):238–252. https://doi.org/10.1681/ASN.2021060794

Yeo SC, Goh SM, Barratt J. Is immunoglobulin A nephropathy different in different ethnic populations? Nephrology. 2019;24(9):885–895. https://doi.org/10.1111/nep.13592

Zhang H, Rizk DV, Perkovic V et al. Results of a randomised double-blind placebo-controlled phase 2 study propose Iptacopan as an alternative complement pathway inhibitor for IgA nephropathy. Kidney Int. 2024;105(1):189–199. https://doi.org/10.1016/j.kint.2023.09.027