CURRENT APPROACHES IN GLOMERULAR DISEASES

Editor:
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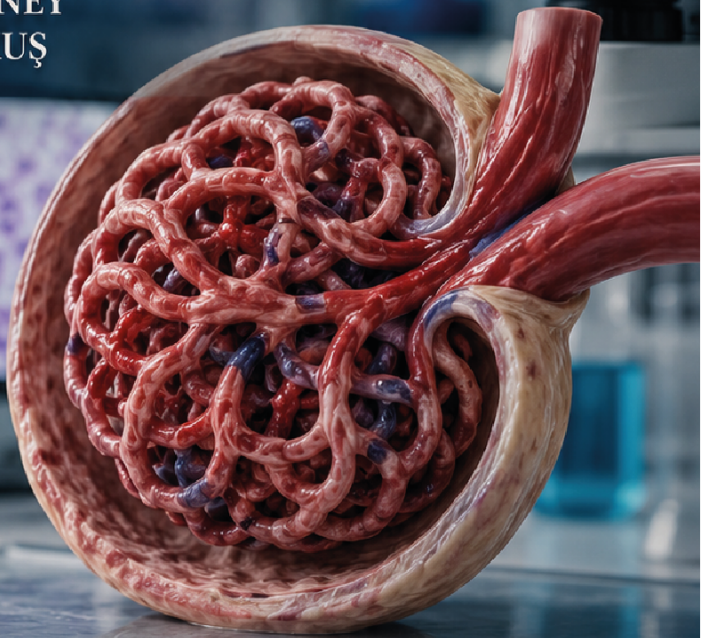

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İÇİNDEKİLER

BÖLÜM 1

MEMBRANOUS NEPHROPATHY

FATİH ERGÜL[1]

Introduction

Definition

Membranous nephropathy (MN) is an immune complex-mediated glomerulopathy characterized by the deposition of immunoglobulin G (IgG) and complement components in the subepithelial region of the glomerular capillary wall, particularly beneath the podocytes. These immune deposits lead to podocyte injury, resulting in increased permeability of the glomerular filtration barrier and ultimately causing proteinuria and nephrotic syndrome (Ayalon & Beck Jr, 2015). Primary MN is an organ-specific autoimmune disease in which autoantibodies directed against an intrinsic podocyte antigen play a central role in pathogenesis, accounting for approximately 75–80% of all MN cases. The disease typically develops in the absence of an identifiable triggering factor (Barbour et al., 2012).

Pathogenesis

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The pathogenesis of MN is primarily driven by an immune response involving circulating antibodies directed against intrinsic podocyte antigens. This mechanism was first demonstrated in cases of antenatal MN resulting from the transplacental transfer of maternal alloantibodies against neutral endopeptidase (NEP) expressed on the podocyte surface (Bobart et al., 2019). The most important target antigen identified in primary MN is the M-type phospholipase A2 receptor (PLA2R), which is expressed on podocytes.

Serum anti-PLA2R antibodies can be detected in approximately 75–80% of patients with primary MN, whereas these antibodies are only rarely observed in secondary MN (Burbelo et al., 2020). Anti-PLA2R antibodies predominantly belong to the IgG4 subclass, and both the antigen and the corresponding antibodies co-localize within glomerular immune deposits characteristic of primary MN (Cattran et al., 1995). Disease activity is closely associated with the presence and persistence of circulating autoantibodies. A spontaneous decline in autoantibody levels or their reduction following immunosuppressive therapy may lead to the development of immunological remission.

If immunological remission occurs before extensive podocyte loss and significant remodelling of the glomerular basement membrane have developed, complete recovery may be achievable. Nevertheless, proteinuria may persist clinically for several months despite immunological remission. In patients with advanced podocyte depletion, proteinuria may continue despite immunological remission, and progressive glomerulosclerosis, tubular atrophy, and interstitial fibrosis may subsequently develop.

Clinical Manifestations

Approximately 70–80% of patients with membranous nephropathy (MN) present with nephrotic syndrome. In the remaining patients, diagnosis is preceded by months or even years of persistent, generally nonselective, sub nephrotic-range proteinuria (<3.5 g/day) (De Vriese et al., 2022). Microscopic hematuria is observed in approximately 30–40% of cases; however, erythrocyte casts are uncommon. The presence of erythrocyte casts should raise suspicion for a concomitant proliferative glomerular disease.

Anti-PLA2R antibodies are positive in approximately 75–80% of patients with primary MN. Serum complement levels are typically within the normal range, and other autoimmune markers, including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor, are usually negative.

At the time of diagnosis, hypertension is present in approximately 10–20% of patients. Renal function is preserved in the majority of cases, and fewer than 10% of patients present with kidney failure. Hypertension and a reduced glomerular filtration rate (GFR) are more commonly observed in older individuals and are frequently associated with tubulointerstitial and vascular changes identified on kidney biopsy (Debiec et al., 2002).

Complications of nephrotic syndrome, including dyslipidaemia, infections, thromboembolic events, and cardiovascular complications, may occur early in the course of the disease and can significantly influence prognosis. Therefore, the evaluation of patients with MN should encompass not only proteinuria and kidney function but also the systemic consequences of nephrotic syndrome, which require careful monitoring.

Pathology

In the early stages of membranous nephropathy (MN), the glomeruli and interstitial may appear normal on light microscopy; therefore, the diagnosis is often established by immunofluorescence

and electron microscopy. As the disease progresses, diffuse thickening of the glomerular capillary walls develops. In advanced stages, resorption of immune deposits may result in the formation of lucent areas and crater-like structures within the glomerular basement membrane (GBM).

On immunofluorescence microscopy, granular IgG deposition along the glomerular capillary walls is the characteristic finding. In primary MN, the predominant immunoglobulin subclass is typically IgG4. In contrast, prominent mesangial deposition of IgA or IgM should raise suspicion for systemic lupus erythematosus or other causes of secondary MN (East & Isacke, 2002).

Electron microscopy demonstrates characteristic subepithelial electron-dense immune deposits. In primary MN, these deposits are predominantly located in the subepithelial region, whereas subendothelial deposits are absent and mesangial deposits are uncommon. The disease is classically classified into four pathological stages:

- **Stage I:** Homogeneous subepithelial immune deposits accompanied by effacement of podocyte foot processes.
- **Stage II:** Formation of characteristic “spikes” due to extension of basement membrane material between adjacent immune deposits.
- **Stage III:** Encasement of immune deposits by newly formed basement membrane material.
- **Stage IV:** Marked GBM thickening, lucency of immune deposits secondary to resorption, and attenuation of the spike appearance (Francis et al., 2016).

Diagnosis and Differential Diagnosis

In patients with membranous nephropathy (MN) presenting with nephrotic syndrome, the differential diagnosis includes minimal change disease, focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis, C3 glomerulopathies, amyloidosis, light-chain deposition disease, lupus nephritis, and diabetic nephropathy. In cases presenting with asymptomatic non-nephrotic proteinuria, the differential diagnosis is considerably broader.

Although a definitive diagnosis is established by kidney biopsy in most cases, a diagnosis of primary MN can be made without biopsy in patients with proteinuria who have positive anti-PLA2R antibodies, an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2, and negative screening results for autoimmune diseases, infections, and malignancies (Hoxha et al., 2017).

Negative anti-PLA2R and anti-THSD7A serological tests do not exclude primary MN. In some patients, particularly during the early stages of disease or during remission, serological testing may be negative despite positive staining for the corresponding antigens within glomerular tissue. Secondary MN accounts for approximately 20–30% of all cases. The most common causes include systemic lupus erythematosus, hepatitis B virus infection, malignancies, and drug-induced disease (Jha et al., 2007).

Treatment

Non-Immunosuppressive Therapy

Conservative management of membranous nephropathy (MN) aims to control oedema, hypertension, proteinuria, and dyslipidaemia. In patients with proteinuria exceeding 1 g/day, the target blood pressure is <125/75 mmHg, provided there are no contraindications. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce proteinuria and slow the progression of kidney disease, with

therapeutic effects typically becoming evident within the first three months of treatment.

ACEI or ARB therapy is recommended even in patients at low risk of disease progression (proteinuria <4 g/day). To maximize treatment efficacy, a low-sodium diet containing approximately 1.5–2 g of sodium per day should be implemented. In patients with persistent nephrotic-range proteinuria, statin therapy may be considered to reduce cardiovascular risk, with a target low-density lipoprotein (LDL) cholesterol level of <100 mg/dL (Kanigicherla et al., 2013).

Persistent nephrotic syndrome, particularly in MN, is associated with an increased risk of both venous and arterial thromboembolic events. One of the most important determinants of thrombotic risk is hypoalbuminemia. The risk of venous thromboembolism rises substantially when the serum albumin level falls below 2.5 g/dL. In patients with a low or moderate bleeding risk and a serum albumin concentration <2–2.5 g/dL, the benefits of prophylactic anticoagulation are generally considered to outweigh the associated risks (Lee et al., 2016).

Immunosuppressive Therapy

Immunosuppressive therapy should be considered in patients with nephrotic-range proteinuria (>4 g/day) that persists for at least six months despite optimal supportive treatment and has not decreased by more than 50% from baseline. In addition, the presence of severe nephrotic syndrome–related symptoms or an increase in serum creatinine of more than 30% within 12 months identifies patients at high risk of disease progression who may require earlier initiation of immunosuppressive therapy (Nikolopoulou et al., 2019).

Corticosteroids

Corticosteroid monotherapy has not been shown to provide significant long-term benefits in reducing proteinuria, preserving kidney function, or improving renal survival in membranous nephropathy. Therefore, the use of oral corticosteroids as monotherapy is not recommended for the treatment of MN (Qin et al., 2011).

Cytotoxic Agents Combined with Corticosteroids

In patients with moderate-risk primary membranous nephropathy, alternating corticosteroid and cyclophosphamide therapy has been shown to increase remission rates and improve renal survival. Approximately 80% of patients treated with this regimen achieve either complete or partial remission, while disease progression is significantly reduced compared with supportive therapy alone. However, the potential long-term toxicities of cyclophosphamide, including infertility, infections, and malignancies, should be carefully considered when selecting treatment (Rovin et al., 2021).

Calcineurin Inhibitors

Both cyclosporine and tacrolimus reduce proteinuria through their immunosuppressive effects as well as direct stabilization of podocytes. Clinical studies have demonstrated complete or partial remission in approximately 70–75% of treated patients. Nevertheless, relapse rates following treatment discontinuation are high and may reach 40–50% in some series. Consequently, prolonged low-dose maintenance therapy may be required in selected patients receiving calcineurin inhibitors (Ruggenenti et al., 2012).

Mycophenolate Mofetil

Studies evaluating the efficacy of mycophenolate mofetil (MMF) have produced inconsistent results. Although initial

remission rates may be favorable, relapses are common, and long-term outcomes have not been shown to be superior to those achieved with calcineurin inhibitors or other immunosuppressive regimens. Furthermore, the addition of MMF to calcineurin inhibitor therapy has not demonstrated significant additional benefit (Sethi et al., 2020).

Rituximab

Rituximab is currently regarded as one of the most effective and safest treatment options for primary MN. Clinical studies have reported complete or partial remission in approximately 60–70% of patients, accompanied by an early and marked reduction in anti-PLA2R antibody levels. In the MENTOR trial, the largest randomized controlled study conducted in this field, remission was achieved in 60% of patients receiving rituximab at month 24, compared with 20% of those treated with cyclosporine. Additionally, renal function was better preserved in the rituximab group (Shiiki et al., 2004).

Considering the long-term adverse effects associated with cytotoxic agents, such as infertility and malignancy, together with the high efficacy and low relapse rates observed with rituximab, current treatment strategies increasingly favour rituximab as a first-line immunosuppressive therapy for many patients with primary membranous nephropathy (20–21).

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BÖLÜM 2

CURRENT APROACHES IN THE MANAGEMENT OF IGA NEPHROPATHY

MUSTAFA YILUZAR[1]

Introduction, Definition, Epidemiology, and Pathogenesis

IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide, with a global incidence estimated at approximately 2.5 per 100,000 individuals (Rajasekaran et al., 2021; Pattrapornpisut et al., 2021). The disease predominantly affects young and middle-aged adults and can culminate in end-stage renal disease (ESRD) secondary to progressive renal dysfunction, with notably 25% to 50% of patients progressing to ESRD within 20 years of diagnosis. Furthermore, the prevalence and clinical course vary significantly depending on ethnicity, race, geography, and genetic predisposition, with Asian populations exhibiting higher incidence rates and a more severe disease phenotype (Tota et al., 2023; Chang & Li, 2020).

The pathophysiology of the disease is widely conceptualized as a multi-hit mechanism comprising four distinct stages. Initially, a

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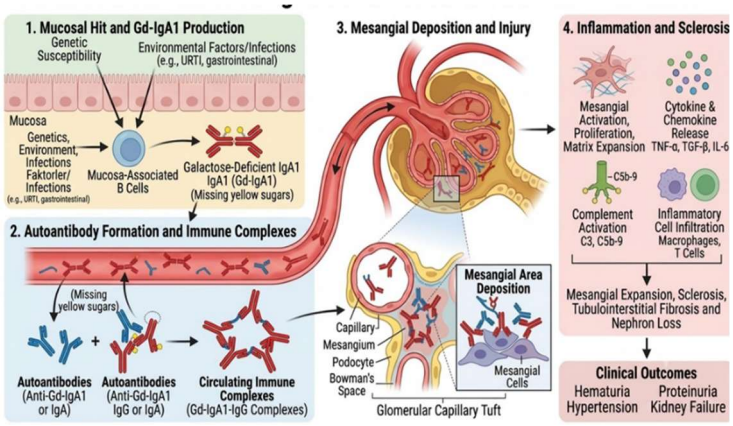
defect occurs in the galactosylation of IgA1 antibodies within the gut mucosal immune system, representing Hit 1. This defect leads to elevated circulating levels of galactose-deficient IgA1 (Gd-IgA1) antibodies, which subsequently trigger the production of autoantibodies, specifically IgG antibodies, constituting Hit 2. Following this immune response, circulating IgG and Gd-IgA1 immune complexes are formed as Hit 3. These immune complexes eventually deposit in the glomerular mesangium, initiating a local inflammatory cascade, and this sustained inflammation ultimately leads to progressive renal injury and a subsequent decline in glomerular function, which marks Hit 4 (Lim et al., 2024). The visual overview of this four-hit cascade and the targeted therapeutic sites is proposed in the literature (see Figure 1).

Figure 1.The Multi-Step Model of IgA Nephropathy Pathogenesis.



Reference: Mustafa YILUZAR

Clinical Presentation

The clinical manifestations of IgA nephropathy at initial presentation can be highly variable, encompassing macroscopic haematuria, asymptomatic haematuria accompanied by or without proteinuria, acute kidney injury (AKI), nephrotic syndrome, and chronic kidney disease (CKD). Despite this diverse clinical

spectrum, the definitive diagnosis of IgAN relies exclusively on a renal biopsy. Patients presenting with a proteinuria level of 500 mg/day or higher should be evaluated for a renal biopsy to facilitate early diagnosis and therapeutic intervention. Once the diagnosis is confirmed, patients must undergo a thorough prognostic evaluation.

Prognostic Evaluation

The prognostic assessment in IgAN utilizes histopathological findings, the degree of proteinuria, and the estimated glomerular filtration rate (eGFR) at the time of diagnosis to predict long-term outcomes and guide clinical management (Stamellou et al., 2025).

To standardize the classification of pathological findings, the Oxford Classification defined in 2009 is employed (Cattran et al., 2009; Trimarchi et al., 2017). This classification encompasses five distinct pathological features, collectively known as the MEST-C score:

- Mesangial hypercellularity (M)
- Endocapillary hypercellularity (E)
- Segmental glomerulosclerosis (S)
- Tubular atrophy/interstitial fibrosis (T)

Crescent formation (C), which was incorporated in the 2016 update (Cattran et al., 2009; Trimarchi et al., 2017).

Proteinuria is another critical prognostic indicator, with its magnitude being the strongest predictor of disease progression. Patients with sustained proteinuria levels exceeding 1 g/day carry a significantly high risk of CKD progression (KDIGO, 2021).

While the 2021 KDIGO guidelines recommended reducing proteinuria to below 1 g/day, recent evidence has reshaped this threshold. Recent studies have demonstrated that approximately

30% of patients with a mean proteinuria level between 0.4 and 0.8 g/g progress to kidney failure within 10 years (Reich et al., 2007).

Consequently, the updated 2025 KDIGO guidelines recommend targeting a reduction in proteinuria to less than 0.5 g/day, with an ideal target of less than 0.3 g/day (Stamellou et al., 2025).

Furthermore, persistent macrohematuria is strongly associated with IgAN progression. The resolution of haematuria exerts a favourable effect on long-term renal outcomes, making it a key therapeutic target in novel immunomodulatory treatment strategies (Sevillano et al., 2017; Zand et al., 2023).

Indications for Renal Biopsy

A renal biopsy is required for the definitive diagnosis of IgA nephropathy. Biopsy is indicated for patients with daily proteinuria exceeding 500 mg or those experiencing a decline in glomerular filtration rate. Conversely, a renal biopsy is not indicated for patients presenting with isolated macrohematuria, daily proteinuria under 500 mg, and a normal eGFR (Rovin et al., 2021).

For patients who do not undergo a biopsy, management should initiate with renin-angiotensin system (RAS) blockade and sodium-glucose cotransporter-2 inhibitors (SGLT2-i), coupled with rigorous and close monitoring of proteinuria levels and eGFR (Szeto et al., 2001).

Therapeutic Management of IgA Nephropathy

Therapeutic strategies in IgA nephropathy (IgAN) are primarily directed toward the following objectives.

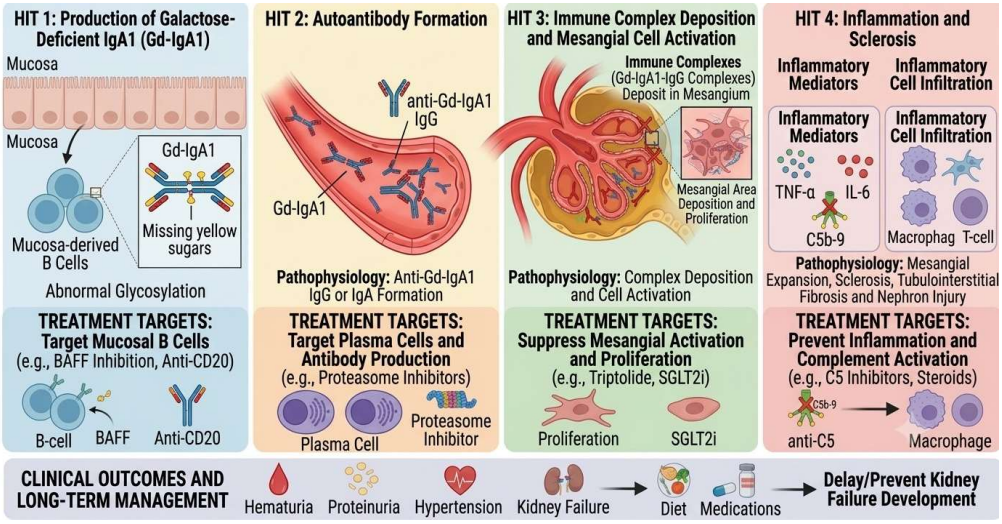
Inhibiting the production or reducing the circulating levels of galactose-deficient IgA1 (Gd-IgA1) and its corresponding IgG/IgA autoantibodies.

Preventing or minimizing the formation of IgA-containing immune complexes, thereby mitigating immune complex-mediated glomerular injury (the optimal duration of therapy remains to be fully elucidated).

Implementing nephroprotective strategies to minimize subsequent nephron loss following histological injury (Floege et al., 2025; Teng et al., 2025).

Post-treatment therapeutic targets should aim to reduce proteinuria to less than 0.5 g/day, with an ideal target of less than 0.3 g/day (Floege et al., 2025). The comprehensive therapeutic algorithm including supportive and targeted interventions is illustrated in Figure 2.

Fig. 2. The Four-Hit Hypothesis and Targeted Therapeutic Approaches in the Pathogenesis of IgA Nephropathy.



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Nephroprotective Therapies

Optimal Supportive Care

Optimal supportive care serves as the foundational management strategy. It encompasses a sodium-restricted diet, lipid optimization, smoking cessation, weight management, stringent blood pressure control, and pharmacological interventions ("KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases," 2021).

Renin-Angiotensin System (RAS) Inhibition

RAS inhibition represents the cornerstone of nephroprotective supportive therapy (Li et al., 2006; Stamellou et al., 2025). The 2021 KDIGO guidelines recommend targeting a systolic blood pressure of less than 120 mmHg in these patients ("KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases," 2021).

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-i)

SGLT2 inhibitors are strongly recommended for IgAN patients presenting with persistent proteinuria. Their therapeutic efficacy is derived from promoting natriuresis, which subsequently leads to a reduction in both intraglomerular hydrostatic pressure and systemic blood pressure (Heerspink et al., 2020).

Endothelin Receptor Antagonists (ERA)

Endothelin-1 induces potent vasoconstriction by activating endothelin A (ET-A) receptors, which can subsequently promote podocyte injury, localized inflammation, and progressive fibrosis, thereby driving chronic kidney disease (CKD) progression (De Miguel et al., 2016). Ongoing clinical trials evaluating dual endothelin/angiotensin receptor antagonists or selective endothelin-1 antagonists (e.g., sparsentan, atrasentan) have demonstrated

significant and clinically meaningful reductions in proteinuria (Heerspink et al., 2023)(Heerspink et al., 2023; Kohan et al., 2013).

Mineralocorticoid Receptor Antagonists (MRA)

Blockade of mineralocorticoid receptors, which are expressed on podocytes, endothelial cells, and mesangial cells, has been shown to attenuate glomerular and tubulointerstitial fibrosis (Cosimato et al., 2021). Traditional MRAs, such as spironolactone and eplerenone, can achieve significant reductions in proteinuria when combined with RAS blockers; however, this combination is associated with an increased risk of hyperkalaemia (Bolignano et al., 2014).

Conversely, finerenone—a novel non-steroidal, selective MRA—has been demonstrated to delay CKD progression and reduce cardiovascular risk in patients with CKD (Bakris et al., 2020).

Anti-inflammatory and Immunomodulatory Therapies

Corticosteroids

The updated 2025 KDIGO guidelines highlight two primary therapeutic targets for anti-inflammatory intervention: depleting pathogenic IgA production and suppressing local renal inflammation (Stamellou et al., 2025). Although systemic corticosteroids exert potent anti-inflammatory effects, their direct impact on pathogenic IgA synthesis remains fully to be clarified, though several studies in the literature suggest they may lower circulating Gd-IgA1 levels (Zan et al., 2025).

The 2021 KDIGO guidelines recommended systemic corticosteroid therapy for patients who maintained a proteinuria level of equal to or greater than 1 g/day despite receiving at least 3 to 6 months of maximally tolerated supportive care.. ("KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases," 2021).

In contrast, the 2025 KDIGO guidelines recommend targeted-release formulation (TRF) budesonide (Nefecon) as a first-line targeted therapy, administered as a 9-month course (Floege et al., 2025). In clinical settings where TRF-budesonide is unavailable, a 6-month course of low-dose (0.4 mg/kg) systemic corticosteroids may be considered for carefully selected, high-risk patients (Floege et al., 2025).

Given that systemic corticosteroid regimens are frequently limited by severe systemic adverse effects and poor patient tolerability, their use should be restricted to a highly select patient population for a strict 6-month duration ("KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases," 2021) (McGuire, 2023).

Furthermore, the 2025 KDIGO guidelines recommend that patients undergoing corticosteroid therapy receive antimicrobial prophylaxis, including coverage for Pneumocystis jirovecii pneumonia (PJP) (Stamellou et al., 2025).

Abnormal mucosal IgA1 production plays a pivotal role in increasing the risk of IgAN development (Yeo et al., 2018).

Mucosa-associated lymphoid tissue (MALT), particularly Peyer's patches concentrated in the distal ileum, is a primary site for aberrant Gd-IgA1 synthesis. TRF-budesonide is designed to deliver the active drug directly to the distal ileum, thereby suppressing Gd-IgA1 production at its source (Lim et al., 2024; Wimbury et al., 2024). Due to its high first-pass hepatic metabolism and minimal systemic absorption, TRF-budesonide exhibits a significantly more favourable systemic side-effect profile compared to conventional systemic corticosteroids (Lim et al., 2024).

Complement Inhibitors

Immunohistopathological analyses of renal biopsies from IgAN patients have revealed extensive glomerular deposition of complement proteins, including C3, C4d, properdin, mannan-binding lectin (MBL), and the terminal complement complex (C5b-9). These findings strongly implicate the complement system—specifically the alternative and lectin pathways—in the pathogenesis of IgAN (Floege, 2024; Roos et al., 2006).

Consequently, numerous clinical trials evaluating complement inhibitors in IgAN are currently underway. Preliminary data demonstrate that complement inhibition yields significant reductions in proteinuria and effectively slows the rate of eGFR decline. Prominent therapeutic candidates currently under investigation include:

Narsoplimab: A monoclonal antibody targeting MASP-2, a key enzyme in the activation of the lectin pathway.

Iptacopan: An oral, small-molecule inhibitor of Factor B, a critical component of the alternative pathway.

Pegcetacoplan: A targeted C3 inhibitor.

Avacopan: An oral C5a receptor antagonist.

Ravulizumab: A long-acting monoclonal antibody directed against C5 (Lafayette et al., 2020; McCoy et al., 1974).

B-Cell Targeted Therapies

Therapeutic B-cell depletion via CD20 inhibition with rituximab has failed to demonstrate efficacy in reducing proteinuria, preserving renal function, or lowering circulating Gd-IgA1 levels in IgAN patients (Lafayette et al., 2017).

B-cell activation and proliferation can be stimulated independently of T-cells by two key ligands: B-cell activating factor (BAFF) and A Proliferation-Inducing Ligand (APRIL). These

mediators play a critical role in driving Gd-IgA1 synthesis within mucosal surfaces (Moldoveanu et al., 2007; Rovin et al., 2023; Zhao et al., 2012). In murine models, overproduction of BAFF has been shown to induce an IgA-like nephritis. Furthermore, patients with IgAN exhibit elevated serum levels of APRIL, which correlate directly with higher circulating concentrations of Gd-IgA1 (Zhai et al., 2016).

Novel therapeutic agents targeting these cytokines are currently being evaluated in clinical trials. These include sibeprenlimab and zigakibart (monoclonal antibodies selectively inhibiting APRIL) and atacicept (a dual BAFF/APRIL inhibitor). Phase 1 and 2 trial results for these agents have demonstrated that dual or selective inhibition of these ligands achieves significant and substantial reductions in proteinuria (Heerspink et al., 2025; Mathur et al., 2024; Perkovic et al., 2026). Additionally, clinical evaluation is ongoing for felzartamab, a monoclonal antibody targeting CD38 expressed on long-lived plasma cells (Maixnerova et al., 2022).

Regarding antimetabolite therapies, mycophenolate mofetil (MMF), which inhibits B- and T-lymphocyte proliferation, has yielded conflicting results. Clinical trials conducted in Caucasian cohorts failed to demonstrate significant benefits regarding proteinuria reduction or renal function preservation; however, trials performed in Chinese patient populations showed significant efficacy in reducing proteinuria (Frisch et al., 2005; Tang et al., 2005).

Conclusion

IgA nephropathy remains the most frequently diagnosed primary glomerular disease globally and carries a substantial risk of progressive renal injury and subsequent kidney failure. Accordingly, contemporary management emphasizes early disease control, prevention of structural renal damage, and the preservation of

functional nephrons. To achieve these targets, novel mechanism-driven therapeutic options have successfully entered clinical practice, and a robust pipeline of targeted agents continues to expand within ongoing clinical trials.

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BÖLÜM 3

CURRENT APPROACHES IN THE MANAGEMENT OF ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

BEYZA DOĞAN[1]

Introduction

Definition

Anti-glomerular basement membrane (anti-GBM) disease is a rare autoimmune disorder in which the target antigen is localized within the non-collagenous domain of the alpha chain of type IV collagen. Circulating anti-GBM antibodies accumulate within the kidneys and/or lungs, potentially culminating in rapidly progressive glomerulonephritis (RPGN) and pulmonary haemorrhage. Due to the shared basement membrane antigens between alveoli and glomeruli, the kidneys and lungs constitute the primary target organs(Jennette et al., 2013). Historically, "Goodpasture syndrome" and "Goodpasture disease" are older terms often used synonymously to refer to anti-GBM antibody-mediated disease; however, they also denote the clinical constellation of glomerulonephritis and

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pulmonary haemorrhage, regardless of the underlying pathogenesis(McAdoo & Pusey, 2017).While anti-GBM disease can present as an isolated renal pathology without pulmonary involvement, Goodpasture's disease or syndrome invariably features pulmonary manifestation. Although some clinicians colloquially define any concurrent renal and pulmonary involvement as "Goodpasture's syndrome," the term fundamentally implies the presence of anti-GBM antibodies. Approximately 40% to 60% of cases are associated with alveolar haemorrhage, whereas isolated pulmonary involvement accounts for less than 10% of anti-GBM disease presentations(Rout & DeVrieze, 2026).

Epidemiology

Goodpasture's syndrome (anti-glomerular basement membrane disease) is a rare autoimmune disorder eponymously named after Ernest Goodpasture, who first described the condition in 1919(Peto & Salama, 2011). Characterized by IgG autoantibodies targeting the non-collagenous domain of the alpha3 chain of type IV collagen, the disease has a remarkably low incidence, affecting approximately 0.5 to 1.0 individuals per million annually. Epidemically, the disease exhibits a bimodal age distribution, with peaks occurring predominantly in the third and sixth decades of life.

Notably, the clinical presentation varies substantially by age; younger patients demonstrate a significantly higher propensity for severe pulmonary involvement (diffuse alveolar haemorrhage), whereas elderly patients are more likely to present with a less severe, renal-limited manifestation of the disease(Y.-R. Liu et al., 2025).

Pathogenesis

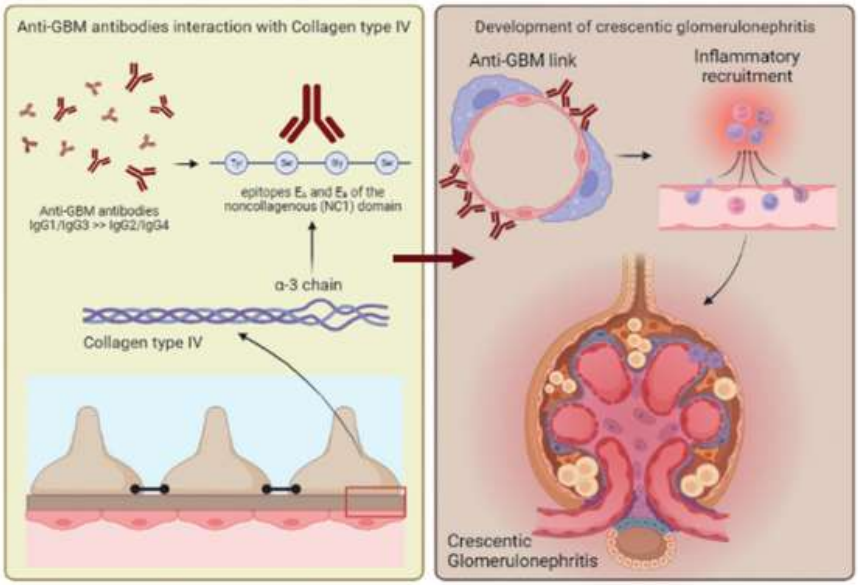
Goodpasture syndrome is a rare but devastating autoimmune disorder driven by a complex interplay between genetic susceptibility and environmental triggers, culminating in rapidly progressive glomerulonephritis (RPGN) and alveolar haemorrhage.

The primary immunopathogenesis involves circulating polyclonal IgG autoantibodies (predominantly IgG1 and IgG3 subclasses) directed against the EA and EB cryptic epitopes within the no collagenous (NC1) domain of the alpha3(IV) chain of type IV collagen. Antibodies may also target the alpha4(IV) and alpha5(IV) chains, as well as peroxidasin(Fouka et al., 2024). While laminin-521 (LM521)—the major isoform in mature glomerular and alveolar basement membranes—has emerged as a novel antigenic target in recent case reports, its precise immunopathogenesis remains incompletely understood. Under physiological conditions, these pathogenic epitopes remain hidden; however, they can undergo conformational shifts and become exposed due to various predisposing factors, including smoking, adventitious infections (such as SARS-CoV-2), long-term hydrocarbon or heavy metal exposure, and hair dye use. On a genetic level, major histocompatibility complex (MHC) class II alleles strongly dictate susceptibility and outcomes; HLA-DR2 and specifically HLA-DRB1*1501 and HLA-DRB1*1502 are associated with increased vulnerability and a worse prognosis, whereas HLA-DRB1*01 and HLA-DRB1*07 exert protective effects.

The cellular arm of immunity, particularly CD4+ T helper cells (Th1 and Th17), plays an essential role by driving B-cell activation, antibody production, and direct tissue injury, a process further exacerbated by the dysregulation of regulatory T cells (CD4+ CD25+). Notably, 21% to 47% of patients exhibit dual positivity for anti-neutrophil cytoplasmic antibodies (ANCAs, primarily anti-MPO), which often precede anti-GBM antibodies and unmask the cryptic epitopes, leading to a more severe clinical phenotype. Once the anti-GBM antibodies bind to the basement membranes, they trigger robust inflammation and localized complement activation predominantly via the classical (CP) and alternative pathways (AP), while the lectin pathway (LP) remains largely inactive except in rare

IgG4-dominant cases that interact directly with mannose-binding lectin (MBL). This cascade is characterized by widespread linear or granular deposition of C3 activation fragments along the GBM in 41% to 69.2% of patients—often fuelled by local C3 synthesis by resident renal cells which acts independently of circulating complement, serves as a predictor of poor renal survival, and promotes autoreactive T-cell expansion—whereas upstream C1q deposition remains rare (3% to 16.7%) due to low antibody titters and lack of covalent binding. Downstream AP amplification is evidenced by substantial glomerular deposition of factor B, properdin, C3d, C4d, and the membrane attack complex (C5b-9), which are significantly enhanced in areas of crescent formation. This profound inflammatory milieu, further marked by systemically elevated plasma and urinary levels of anaphylatoxin C5a and soluble C5b-9 (SC5b-9) that directly correlate with baseline serum creatinine and cellular crescents, induces mechanical rupture and gap formation within the basement membranes(Zhang et al., 2025).This inflammatory milieu causes mechanical disruption and gap formation in the basement membranes; in the lungs, this leads to the extravasation of erythrocytes into the alveoli, manifesting as diffuse alveolar haemorrhage. In the kidneys, the disruption causes protein leakage into the Bowman's space, recruitment of lymphocytes and macrophages, and the proliferation of parietal cells, resulting in vascular necrosis and crescentic glomerulonephritis (Figure 1)(Reggiani et al., 2023).

Fig. 1. Schematic representation of the pathogenesis of anti-GBM glomerulonephritis



Reference:(Reggiani et al., 2023)

Classification

Within the histopathological and clinical taxonomy of RPGN, cases are stratified based on their underlying immunopathogenic mechanisms. Under this framework, classical anti-glomerular basement membrane disease is classified as Type I RPGN, driven by the linear deposition of pathogenic autoantibodies along the glomerular capillary wall. Furthermore, according to the revised International Chapel Hill Consensus Conference nomenclature on vasculitis, anti-GBM disease is formally categorized as an immune complex small vessel vasculitis(Jennette et al., 2013).Anti-GBM disease exhibits diverse clinical variants, with the prominent subtypes detailed below.

Anti-GBM disease associated with membranous nephropathy (MN); Coexistence with MN defines a milder clinical phenotype characterized by lower baseline creatinine, absence of oliguria, and superior one-year kidney survival (62% vs. 13%),

likely driven by lower antibody titters against the specific E_B conformational epitope of alpha3(IV) NC1 and undetectable anti-PLA2R antibodies(Bu et al., 2023).

Anti-GBM disease without detectable circulating antibodies ("Atypical" anti-GBM); Accounting for approximately 12% of cases, this variant presents with mild renal impairment and bright linear IgG deposition *without* crescentic GN or circulating antibodies on standard ELISAs, frequently demonstrating monoclonality and a slow progression with high one-year survival. This seronegative discrepancy is driven by the shorter half-life of circulating versus tissue-bound antibodies, restricted target reactivity to non-standard epitopes (e.g., isolated anti-laminin 521), or IgG4 subclass restriction, which is characteristically observed in young female smokers presenting with severe pulmonary involvement(Chauveau et al., 2024).

Post-Transplant Recurrence of Anti-GBM Disease; Clinically evident recurrence in the allograft presents from months to years' post-transplantation with haematuria, proteinuria, and rising creatinine, typically associated with positive circulating anti-GBM antibodies and a high risk of subsequent graft loss despite therapy. Conversely, the post-transplant recurrence of the rare atypical variant exhibits a distinct clinical presentation, notably characterized by the absence of detectable circulating anti-GBM autoantibodies(Coche et al., 2021).

Clinical Manifestations

Goodpasture disease is a rare cause of end-stage kidney disease (ESKD), its onset typically precipitates a sharp and catastrophic deterioration of renal function. While concurrent lung and renal involvement occur in approximately 40% to 60% of cases—classically designated as Goodpasture syndrome—some patients present with isolated renal or pulmonary manifestations.

Strikingly, 55% of patients are immediately dialysis-dependent upon presentation, and renal function is successfully restored in only 3% of these dialysis-dependent individuals, highlighting the aggressive nature of the disease. Typical presentation is characterized by rapidly progressive glomerulonephritis (RPGN) in 80% to 90% of cases—marked by active urinary sediment, sub nephrotic proteinuria, and oliguria—where microscopic haematuria is nearly universal and gross haematuria occurs in less than 25% of patients (Y. R. Liu et al., 2025).

Pulmonary involvement manifests as alveolar haemorrhage in 25% to 30% of patients—predominantly in young males with a history of smoking or hydrocarbon exposure—frequently leading to hypoxemia (58%) and acute respiratory failure requiring intubation (50%). Other systemic features like arthritis, rash, or myalgia are uncommon and strongly suggest concurrent ANCA-associated vasculitis (AAV), which co-exists in up to 30% of patients, while cerebral vasculitis remains exceedingly rare(Clerte et al., 2022). Diagnostically, typical disease relies on detecting serum or tissue-bound anti-GBM antibodies; however, "atypical" variants present a distinct challenge, characterized by mild renal impairment, proteinuria, haematuria, and bright, linear IgG or IgG4 deposition along the GBM without crescentic glomerulonephritis or detectable circulating antibodies on conventional commercial immunoassays. These atypical cases, often featuring monoclonality or isolated severe lung disease in young females, are driven by autoantibodies targeting different non-standard epitopes or possessing a diminished capacity to recruit inflammatory cells(Bharati et al., 2024; Reggiani et al., 2023).

Treatment

Given the rapidly progressive and life-threatening nature of anti-glomerular basement membrane (anti-GBM) disease, swift

initiation of empiric therapy—including glucocorticoids and/or plasma exchange—is strictly indicated upon high clinical suspicion, even prior to definitive serological confirmation. Current therapeutic algorithms focus on the immediate eradication of pathogenic autoantibodies and the suppression of further antibody synthesis(McAdoo & Pusey, 2025)(Figure 2).

The gold-standard first-line induction regimen comprises Therapeutic Plasma Exchange (PEX), Glucocorticoids (Prednisone), and Cyclophosphamide(Bose et al., 2025).

Absolute Indications for Treatment:

All patients presenting with diffuse alveolar haemorrhage (haemoptysis), irrespective of the presence or severity of concurrent renal impairment.

All patients presenting with renal involvement who remain dialysis-independent at presentation.

Management of Dialysis-Dependent Patients: In patients presenting with advanced renal failure requiring immediate renal replacement therapy (RRT) without concomitant alveolar haemorrhage—particularly those demonstrating 100% crescentic formation on renal biopsy—immunosuppressive therapy is frequently withheld due to a negligible probability of renal recovery(Bose et al., 2025). However, a brief 2-to-3-week therapeutic trial remains rational in specific sub-populations, including:

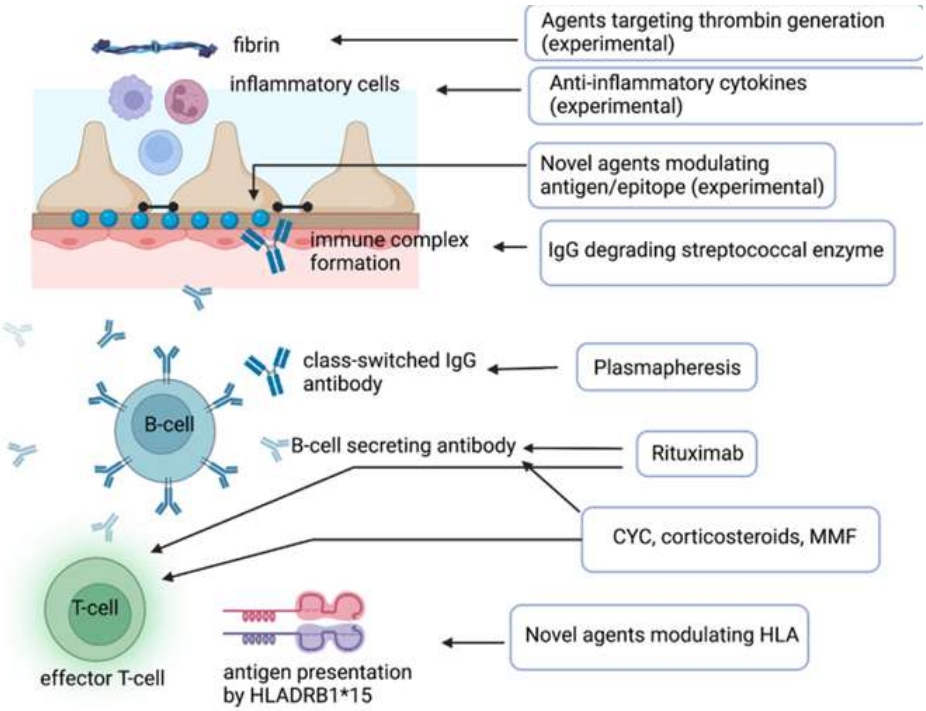
Hyperacute presentations where irreversible chronic injury cannot be definitively predicted.

Younger individuals with high physiological tolerance for aggressive immunosuppression.

Biopsies showing focal crescentic glomerular damage with prominent acute tubular injury rather than diffuse sclerosis.

Double-positive patients concurrent for both anti-GBM and antineutrophil cytoplasmic autoantibodies (ANCA), who exhibit features of systemic vasculitis.

Figure 2. Pathogenesis and therapeutic targets in anti-GBM disease.



Reference:(Bharati et al., 2024)

Apheresis Modalities: PEX vs. Immunoadsorption

Therapeutic Plasma Exchange (PEX); PEX represents a cornerstone of therapy. Robust, large-scale multi-centre cohort data (from French, Chinese, and Japanese registries) demonstrate that the early addition of PEX to standard immunosuppression achieves rapid autoantibody clearance, resolves pulmonary haemorrhage, and dramatically improves 1-year and 5-year patient survival. Notably, national registry data confirm a significant reduction in in-hospital

mortality even among severe, dialysis-dependent cohorts. Current international guidelines (KDIGO and ASFA) recommend a regimen of 5 to 10 sessions (with an average of 8 sessions predicting optimal risk reduction).

Immunoadsorption (IA); IA serves as a highly efficient alternative to PEX regarding the kinetics of pathogenic IgG clearance and overall clinical efficacy. Large observational data indicate that IA yields comparable patient and renal survival rates to PEX, while offering a superior safety profile. By selectively filtering IgG and preserving essential plasma components, IA significantly mitigates the risk of extra-pulmonary bleeding and minimizes blood transfusion requirements, rendering it a highly favourable alternative where available.

Cytotoxic Immunosuppression: Cyclophosphamide

First-line induction therapy for anti-GBM disease primarily relies on daily oral cyclophosphamide (typically 2–3 mg/kg/day, up to a maximum of 200 mg, or reduced to 50–100 mg/day in elderly or dialysis-dependent patients), a strategy fully aligned with current KDIGO guidelines(de Groot et al., 2009). Because the parent drug is water-soluble with a low molecular weight, daily oral administration achieves more consistent drug exposure than pulsed intravenous regimens in patients undergoing concomitant extracorporeal therapies like plasmapheresis (PEX). Furthermore, given that anti-GBM disease exhibits a low relapse rate and usually requires only a 3-month course of cytotoxic therapy, concerns regarding cumulative cyclophosphamide toxicity are less pronounced than in ANCA-associated vasculitis (AAV). Concurrently, glucocorticoid therapy is initiated via oral prednisolone at 1 mg/kg/day (maximum 60 mg/day), tapered weekly to 20 mg by week 6, and completely discontinued within 6 months; notably, high-dose intravenous pulses or reduced-dose regimens lack

established efficacy data in this specific population and are generally avoided if PEX and cyclophosphamide are promptly initiated(Bose et al., 2025).

Mycophenolate Mofetil & Cyclosporine

The clinical deployment of other traditional alternative immunosuppressive agents, specifically mycophenolate mofetil (MMF) and cyclosporine, is exceptionally poorly described in the literature, with data limited to isolated case reports or small series. Due to this distinct lack of robust clinical evidence, neither agent can be recommended for first-line utility or induction therapy in anti-GBM disease. These maintenance components may, however, harbour a secondary role in delivering extended immunosuppressive treatment for rare, atypical cases characterized by persistent anti-GBM antibody positivity well after the standard three-month course of cyclophosphamide therapy has been successfully completed(Kiykim et al., 2010).

Current therapeutics:

Rituximab; Although rituximab effectively depletes circulating CD20+ B cells, it does not target other pathogenetically involved cell types—such as T cells, neutrophils, or monocytes/macrophages—unlike cyclophosphamide. Consequently, existing clinical evidence remains insufficient to recommend rituximab as a first-line induction agent in anti-GBM disease. Its utility is strictly restricted to cases with compelling contraindications to cyclophosphamide, refractory or severe disease as an adjunctive treatment, or as a strategy to lower antibody titters prior to kidney transplantation. Furthermore, because rituximab is highly susceptible to premature clearance by PEX, its administration must be carefully timed, necessitating a 24-to-48-hour delay in

apheresis procedures post-infusion or the consideration of additional doses after PEX cycles are completed(Ivković et al., 2025).

Avacopan; Novel steroid-sparing therapies, most notably Avacopan, currently lack established efficacy data and remain unproven in isolated anti-GBM disease; therefore, reduced-dose glucocorticoid regimens cannot be safely assumed to be effective. However, the clinical application of Avacopan may be selectively considered as an adjunctive strategy alongside standard glucocorticoid treatment in a specific subset of patients. Specifically, this approach is reserved for individuals presenting with double-positive ANCA and anti-GBM serology, where the therapeutic principles of ANCA-associated vasculitis (AAV) management can be partially extrapolated(Sayed et al., 2025).

İmflidase: Derived from Streptococcus pyogenes, imlifidase (IdeS) is an innovative endopeptidase that rapidly cleaves all human IgG subclasses at the hinge region into Fab and Fc fragments. Distinct from PEX, it possesses the unique capacity to clear not only circulating antibodies but also tissue-bound antibodies already fixed to the glomerular basement membrane(Soveri et al., 2019).

As one of the current therapeutic modalities for anti-GBM disease evaluated within the scope of the GOOD-IDES clinical trials, imlifidase specifically targets and cleaves the pathogenic IgG-type autoantibodies responsible for triggering complement activation in the disease pathogenesis, thereby effectively mitigating the inflammatory function of the classical pathway and subsequent tissue injury (Tyrberg et al., 2026).

Conclusion

In conclusion, Anti-GBM disease is a critical component of pulmonorenal syndromes that can manifest as RPGN, potentially culminating in ESKD. While emerging therapeutic agents are currently under investigation alongside conventional treatment

modalities, renal transplantation remains the definitive therapeutic strategy for patients requiring long-term renal replacement therapy. Consistent with established clinical guidelines (KDIGO), kidney transplantation in this specific cohort mandates strict adherence to immunological remission.

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BÖLÜM 4

MEMBRANOPROLİFERATİVE GLOMERULONEPHRİTİS

MİKAİL DAĞ[1]

Introduction

Membranoproliferative glomerulonephritis (MPGN) is not so much a specific disease as it is a histological pattern of damage characterized by thickening of the glomerular basement membrane, mesangial cell proliferation, and the formation of a “double contour” in the capillary wall (Andrew S Bomback, Vivek Charu, & Fadi Fakhouri, 2025; Yu, Deoliveira, Chung, & Lafayette, 2024). Historically classified as Type I, Type II, and Type III based on electron microscopy (EM) findings (Yu et al., 2024), is currently divided into two main groups based on immunofluorescence (IF) microscopy findings, which more accurately reflect the underlying pathogenesis: immune complex-mediated MPGN (IC-MPGN) and complement-mediated MPGN (C3 glomerulopathy [C3G]) (Bomback & Appel, 2012; Sethi & Fervenza, 2012; Sethi, Nester, & Smith, 2012). IC-MPGN typically develops due to activation of the

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classical complement pathway associated with secondary causes such as infections, autoimmune diseases, or monoclonal gammopathies (Alexander & Sethi, 2019; Rovin et al., 2021); C3G (C3 glomerulonephritis and “dense deposit” disease) arises from dysregulation of the alternative complement pathway due to genetic mutations or autoantibodies (Heiderscheit, Hauer, & Smith, 2022; Sethi, De Vriese, & Fervenza, 2023; Stea, D'Ettorre, Mitrotti, & Gesualdo, 2024).

The clinical spectrum of the disease ranges from asymptomatic hematuria and proteinuria to nephrotic syndrome and rapidly progressive glomerulonephritis (RPGN) (Sethi & Fervenza, 2012; Wendt, Sobhani, Diefenhardt, Trappe, & Völker, 2024). Renal biopsy is the gold standard for diagnosis, and ruling out secondary causes is essential. Treatment management includes targeting secondary etiologies (e.g., antiviral therapy, targeted therapy), supportive care (RAAS inhibition), and, when necessary, the use of immunosuppressive agents such as mycophenolate mofetil (MMF) and corticosteroids (Bomback, Smith, et al., 2012; Licht et al., 2006; Marina Vivarelli et al., 2024; Wendt et al., 2024). In this group of diseases, which generally has a poor prognosis, approximately half of the patients progress to end-stage renal failure within 10 years, and high relapse rates are observed following kidney transplantation(Kavanagh, Ariceta, et al., 2025; Schmitt, Bohle, Reineke, Mayer-Eichberger, & Vogl, 1990). In recent years, proximal complement inhibitors targeting the alternative complement pathway (iptacopan, pegcetacoplan) have emerged as promising new strategies for the treatment of these devastating diseases (M. Vivarelli et al., 2024).

General Information

Membranoproliferative glomerulonephritis (MPGN) is not a single, specific disease but rather a specific pattern of glomerular

damage identified by light microscopy in renal biopsies (Cook & Pickering, 2015). This pattern is characterized by increased cellularity and matrix in the mesangial area, endocapillary proliferation, and thickening of the glomerular basement membrane (GBM) along the capillary wall, resulting in a “double contour” (tram-track) appearance (Bomback & Appel, 2012; Cook & Pickering, 2015; Yu et al., 2024). These structural changes often result in the glomerular tuft taking on a lobular appearance (Cameron et al., 1983; Zhou, 2007). Advancing pathophysiological understanding has shown that MPGN serves as a starting point requiring elucidation of underlying immunological or complement-mediated mechanisms rather than merely a morphological diagnosis (Yu et al., 2024).

Historical Development and Classification

Historically, MPGN has been classified into three types based on the localization of deposits observed in electron microscopy (EM) findings (Bomback & Appel, 2012; Sethi & Fervenza, 2012; Sethi et al., 2012):

1. Type I MPGN: It is characterized by subendothelial and mesangial electron-dense deposits.
2. Type II MPGN (Dense Deposit Disease—DDD): Characterized by the presence of ribbon-like deposits of high osmotic density that extend along the glomerular basement membrane.
3. Type III MPGN: This is a form in which subepithelial deposits are observed in addition to subendothelial and mesangial deposits.

However, this EM-based classification has proven inadequate for clinical management because different pathogenic processes (such as both immune-complex-mediated and

complement-mediated diseases) can produce the same EM findings (Sethi et al., 2012).

Current Immunofluorescence (IF) Classification

In the 2010s, a new classification system based on the pathogenesis of the disease was proposed (Bomback, Canetta, et al., 2012; Hou et al., 2014). In this system, MPGN is divided into two main groups based on immunofluorescence microscopy findings:

1. Immune Complex-Mediated MPGN (IC-MPGN): Immunofluorescent examination reveals distinct deposits of immunoglobulin (Ig) and complement (C3, C1q, etc.) in combination.
2. Complement-mediated MPGN (C3 glomerulopathy—C3G): Immunofluorescence examination reveals only C3 deposition, or the intensity of C3 staining is at least twice that of any other immunoreactant. There is no Ig deposition, or only trace amounts are present. C3G is further divided into two subtypes based on electron microscopic findings (Xiao, Pickering, & Smith, 2014):
    - C3 Glomerulonephritis (C3GN): Amorphous, electron-dense deposits are observed in the subendothelial, mesangial, and/or subepithelial spaces.
    - Dense Deposit Disease (DDD): Sausage- or ribbon-like, highly dense (osmophilic) intramembranous deposits are observed within the lamina densa.

Pathogenesis of IC-MPGN

In this group, the underlying mechanism is the accumulation of circulating immune complexes in the kidneys resulting from chronic antigenemia and their activation of the classical complement

pathway (Alexander & Sethi, 2019). The migration of inflammatory cells (neutrophils, macrophages) to the glomerulus triggers endothelial and mesangial proliferation, resulting in the characteristic pattern of damage (Alchi & Jayne, 2010). Underlying secondary causes include chronic viral (HCV, HBV), bacterial, or parasitic infections; autoimmune diseases (Systemic Lupus Erythematosus [SLE], Sjögren's Syndrome, Rheumatoid Arthritis); and monoclonal gammopathies (Alchi & Jayne, 2010). If no underlying cause can be identified despite advanced diagnostic tests, the condition is referred to as "idiopathic IC-MPGN" (A. S. Bomback, V. Charu, & F. Fakhouri, 2025).

Pathogenesis of C3 Glomerulopathy

At the core of C3G lies the uncontrolled activation (dysregulation) of the alternative complement pathway (AP) (Noris & Remuzzi, 2024; Wendt et al., 2024). AP is normally present in the circulation at a consistently low level and is tightly regulated by regulatory proteins (Factor H, Factor I, etc.). In C3G, this regulation is disrupted by two main mechanisms:

- Genetic Mutations: Pathogenic mutations are observed in genes responsible for complement regulation (C3, CFB, CFH, CFI, and CFHR1-5) in approximately 20–25% of cases (Wendt et al., 2024).
- Acquired Autoantibodies: Detected in 50–80% of cases (M. C. Pickering et al., 2013). The most common is C3 Nephritic Factor (C3NeF), which stabilizes the C3 convertase enzyme (C3bBb) and prolongs its half-life (Caravaca-Fontán, Lucientes, Cavero, & Praga, 2020; M. C. Pickering et al., 2013). In addition, antibodies against C5NeF, anti-Factor H, or anti-Factor B—which stabilize the C5 convertase—also contribute to AP dysregulation

(Marinozzi et al., 2017; Ohi, Watanabe, Fujita, Seki, & Hatano, 1990). In some cases, monoclonal immunoglobulins can disrupt AP control by acting as autoantibodies themselves (Filippone & Farber, 2026).

Epidemiology, Clinical Findings, and Diagnosis Epidemiology

MPGN and C3G are rare diseases. The incidence of C3G worldwide is estimated to be 1–3 cases per million people (A. S. Bomback et al., 2025). Although MPGN can occur at any age, C3G spectrum and idiopathic forms predominantly occur in children and young adults, whereas IC-MPGN and forms associated with monoclonal gammopathy are more commonly observed in older adults (Levy, Gubler, & Habib, 1979; Nakagawa et al., 2018; Walker, Ferrario, Joh, & Bonsib, 2007).

Clinical and Laboratory Findings

Patients may present with a wide range of clinical presentations, ranging from isolated asymptomatic microscopic hematuria and proteinuria to full-blown nephrotic syndrome, chronic nephritic syndrome, and even rapidly progressive crescentic glomerulonephritis (Wendt et al., 2024). While nephrotic syndrome is more common in adults, acute nephritic presentation is more common in children (Filippone & Farber, 2026). Hypocomplementemia is detected in the majority of patients (Wendt et al., 2024). In cases of IC-MPGN, both C3 and C4 levels may be low due to classical pathway activation; in C3G cases, C3 levels are typically low, while C4 levels are within the normal range (Iatropoulos et al., 2018; Iatropoulos et al., 2016).

Diagnostic Approach

In every patient with an MPGN pattern, an integrated evaluation of LM, IF, and EM in the kidney biopsy is essential for

establishing a specific diagnosis (Sethi & Fervenza, 2012). Once the diagnosis has been made, underlying secondary factors must be ruled out:

- For IC-MPGN: Hepatitis B/C, HIV, autoimmune serology (ANA, anti-dsDNA), cryoglobulinemia, serum/urine protein electrophoresis, and free light chain analysis (for monoclonal gammopathies) (Wendt et al., 2024).
- For C3G: Advanced complement tests should be performed. These include serum MAC (sC5b-9) levels, AP functional tests (AH50), a complement genetic mutation panel, and autoantibody screenings (C3NeF, C5NeF, anti-FH) (Matthew C Pickering et al., 2013). In addition, when C3G is detected in patients over 50 years of age, monoclonal gammopathies (MGRS) must be ruled out (Marinozzi et al., 2017).

Histopathological Features and Differential Diagnosis
Histopathology

Under a light microscope, glomeruli acquire a characteristic "lobular" structure due to an increase in mesangial cells and matrix that narrows the capillary lumens (Saha, Pendergraft, Jennette, & Falk, 2020). The classic double-contour appearance (tram-track) results from mesangial cell interposition and the synthesis of new basement membranes in response to immune deposits (Alchi & Jayne, 2010). Depending on the severity of the disease, crescent formation, neutrophil infiltration, and, in the chronic phase, glomerulosclerosis and tubulointerstitial fibrosis may be observed (MADIAS, 1995; Saha et al., 2020). To avoid missing masked monoclonal deposits in routine IF staining, particularly in older patients and cases of suspected MGRS (Monoclonal Gammopathy

of Renal Significance), performing IF on paraffin sections following pronase digestion significantly improves diagnostic accuracy (Larsen et al., 2015).

Differential Diagnosis

Other lesion patterns that could account for the MPGN pattern must be carefully ruled out.

- Thrombotic microangiopathy (TMA): In conditions such as atypical HUS (aHUS), antiphospholipid antibody syndrome, or radiation nephritis, the chronic healing process associated with endothelial damage mimics the MPGN pattern. However, in these cases, immunofluorescence microscopy shows no deposition of Ig or complement (Fernando C Fervenza & Sethi, 2020; Ponticelli, Calatroni, & Moroni, 2023).
- Post-infectious glomerulonephritis (PIGN): In the acute phase, it may present with a crescentic or exudative pattern, may show C3-dominant staining, and may be confused with C3G. However, PIGN typically resolves spontaneously within weeks of the infection, both clinically and in laboratory findings (low C3 levels), and features characteristic giant subepithelial “hump”-like deposits on EM. (De Silva, Jayasinghe, & Amarathunga, 2021; Sethi, Sullivan, & Smith, 2014; Suga et al., 2010).

Treatment Approaches

According to the guidelines, supportive therapy (blood pressure control, salt restriction, and RAAS inhibitors and SGLT2 inhibitors to reduce proteinuria) should be initiated as standard practice for all patients with MPGN and C3G (Wendt et al., 2024).

Treatment of Secondary IC-MPGN

The cornerstone of treatment is controlling the underlying disease. In HCV-associated cases, antiviral therapy is administered; in conditions such as SLE, disease-specific immunosuppression is used. In MPGN developing on a MGRS background (e.g., PGNMID), specific chemotherapeutic agents targeting plasma cell or B-cell clones (Bortezomib, anti-CD20 agents) are used (Geara, Bhoj, & Hogan, 2021; Wendt et al., 2024).

Treatment of Primary/Idiopathic IC-MPGN and C3G

Treatment for this group is tailored to the severity of the disease. In stable patients with only mild proteinuria, supportive care may be sufficient (Fernando C. Fervenza & Sethi, 2026). However, in cases of moderate-to-severe disease (proteinuria >1.5 g/day, nephritic flare, or impaired renal function), a combination of mycophenolate mofetil (MMF) and oral corticosteroids is recommended as first-line immunosuppressive therapy (Fernando C. Fervenza & Sethi, 2026). In cases of RPGN (rapidly progressive crescentic glomerulonephritis), high-dose intravenous methylprednisolone and cyclophosphamide induction therapy may be administered (Le Quintrec et al., 2018; Yu et al., 2024). In refractory cases or in patients with high levels of soluble C5b-9 indicating terminal pathway activation, the C5 inhibitor eculizumab has been used off-label and has been reported to yield beneficial results, particularly in crescentic flares (Le Quintrec et al., 2018; Wendt et al., 2024).

Prognosis

The natural course of the disease is far from encouraging. In both IC-MPGN and C3G cases, approximately 30% to 50% of patients progress to end-stage renal disease (ESRD) within 10 years of diagnosis (Masoud et al., 2025; Nasr et al., 2011; Schaefer et al., 2024). The primary prognostic factors that negatively affect renal

survival are: a low estimated glomerular filtration rate (eGFR) at baseline, nephrotic-level proteinuria, the presence of cellular/fibro cellular crescents on biopsy, and the tubulo-interstitial fibrosis/tubular atrophy (IFTA) score (Lomax-Browne et al., 2022).

Recurrence After Kidney Transplant

Post-transplant disease recurrence is a common and serious problem that leads to graft loss (Caravaca-Fontán et al., 2023). According to historical data, the recurrence rate in cases of Type II MPGN (DDD) reaches 80–90%, whereas in IC-MPGN it is around 20–30% (Braun et al., 2005). According to modern definitions, it has been shown that relapse rates exceed 60% in the IC-MPGN and C3G forms, particularly in cases of dysproteinaemia, and that this is one of the leading causes of graft loss (Cosio & Cattran, 2017; Servais et al., 2012).

Future Treatment Goals

Because current immunosuppressive therapies suppress general inflammation rather than targeting the disease pathogenesis and have high rates of side effects, recent research has focused on drugs that specifically target the complement cascade (proximal complement inhibitors) (Kavanagh, Ariceta, et al., 2025).

- Iptacopan: An oral agent that inhibits Factor B in the alternative complement pathway (Marina Vivarelli et al., 2024). Phase 3 studies have shown that it reduces proteinuria by inhibiting AP activation and prevents C3 accumulation in patients with C3G (Kavanagh, Bomback, et al., 2025). It recently received FDA approval for the treatment of C3G in adults.
- Pegcetacoplan: A subcutaneous agent that directly targets C3 and C3b. In the Phase 3 VALIANT trial, it achieved significant success by substantially

reducing proteinuria in patients with both primary and post-transplant relapsed C3G and IC-MPGN. (Nester et al., 2024). These targeted therapies are expected to replace conventional immunosuppression and bring about a paradigm shift in the management of primary MPGN and C3G (Kavanagh, Ariceta, et al., 2025).

Result

Membranoproliferative glomerulonephritis has evolved from being merely a morphological finding into a dynamic group of diseases categorized according to pathophysiological mechanisms (particularly complement dysregulation). A thorough etiological workup following a biopsy-confirmed diagnosis plays a critical role in selecting the appropriate, patient-specific treatment. The limited efficacy of traditional agents such as MMF has begun to be overcome with the development of specific proximal inhibitors targeting the complement system (iptacopan, pegcetacoplan), opening the door to a new era in improving the prognosis of this challenging disease.

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BÖLÜM 5

CLINICAL MANAGEMENT OF ANCA-ASSOCIATED GLOMERULONEPHRITIS

MERT ÜNAL[1]

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a heterogeneous group of systemic inflammatory diseases that primarily affect small blood vessels. They comprise three major clinical syndromes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (Hellmich et al., 2024). AAV is classified as a pauci-immune necrotizing vasculitis, characterized by little or no immune complex deposition within affected tissues (KDIGO ANCA Vasculitis Work Group, 2024).

Pathogenesis and ANCA Serotypes

Pathogenesis

The pathogenesis of the disease is mainly driven by autoantibodies directed against myeloperoxidase (MPO) and

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proteinase 3 (PR3), which are located within the primary granules of neutrophils. These circulating antibodies bind to ANCA antigens expressed on the surface of neutrophils that have been previously primed by pro-inflammatory cytokines, lipopolysaccharides, or complement factors, leading to neutrophil activation. Activated neutrophils release reactive oxygen species (ROS), lytic proteases, and neutrophil extracellular traps, all of which contribute directly to vascular endothelial injury (Geetha & Jefferson, 2020). Recent studies have also demonstrated that the alternative complement pathway, particularly C5a, plays an important role in amplifying inflammation by recruiting neutrophils and enhancing ANCA-mediated neutrophil activation (Kettritz, 2017).

Renal Presentation and Diagnostic Approach

Although AAV is a systemic disease, kidney involvement is one of its most frequent and serious manifestations. Renal involvement occurs in up to 90% of patients with MPA and up to 80% of patients with GPA, whereas it is observed in approximately 45% of patients with EGPA (Jennette & Falk, 1997).

Clinically, ANCA-associated glomerulonephritis most commonly presents as rapidly progressive glomerulonephritis (RPGN), characterized by a rapid decline in glomerular filtration rate over days to weeks. Urinalysis typically demonstrates dysmorphic erythrocytes of glomerular origin, cellular casts, proteinuria, and occasionally pyuria in the absence of infection. In the past, the disease was often fatal. However, with the introduction of immunosuppressive agents such as cyclophosphamide, it has become a chronic relapsing disease rather than a uniformly fatal condition. Despite these advances, morbidity and mortality related to treatment-associated adverse effects and chronic organ dysfunction remain important clinical challenges.

Types of ANCA

Two major ANCA types are the most frequently encountered, best characterized, and most closely linked to disease pathogenesis. PR3-ANCA develops against the proteinase 3 enzyme located in the primary granules of neutrophils. It is strongly associated with GPA and is detected in the majority of GPA cases. In indirect immunofluorescence assays, it typically demonstrates a cytoplasmic staining pattern (c-ANCA) (Jennette et al., 1998). MPO-ANCA develops against the myeloperoxidase enzyme found in neutrophil granules. It is more commonly associated with MPA and EGPA. In indirect immunofluorescence assays, it usually exhibits a perinuclear staining pattern (p-ANCA) (Jennette et al., 1998).

In addition to these two major antigens, ANCAs may also develop against less common targets such as lysosome-associated membrane protein 2 (LAMP2), complementary PR3 (cPR3) peptides, moesin, plasminogen, and peroxidasin (Bautz et al., 2008; Kain et al., 2008; Suzuki et al., 2014).

Risk Factors

The development of ANCA-associated vasculitis results from a complex interaction between genetic susceptibility and environmental factors that lead to loss of immune tolerance.

Large genetic studies have shown that genetic associations correlate more closely with ANCA serotypes than with clinical disease phenotypes. PR3-ANCA positivity is strongly associated with polymorphisms in HLA-DP, PRTN3, and SERPINA1 genes. In contrast, MPO-ANCA positivity is mainly associated with HLA-DQ variants (Lyons et al., 2012).

Among environmental triggers, respiratory tract infections and chronic nasal carriage of *Staphylococcus aureus* are particularly important. Chronic *S. aureus* carriage has been associated with both disease initiation and an increased risk of relapse (Popa & Tervaert, 2003). In addition, occupational exposure to silica dust,

hydrocarbons, and pesticides, as well as the use of certain medications such as propylthiouracil and hydralazine, have been identified as important environmental risk factors that may contribute to disease development (Gómez-Puerta et al., 2013; Pendergraft & Niles, 2014).

ANCA Serology and the Diagnostic Role of Kidney Biopsy

In the diagnosis of AAV, PR3-ANCA and MPO-ANCA testing should be performed using antigen-specific immunoassays, such as ELISA, rather than indirect immunofluorescence because of their higher diagnostic accuracy. Although ANCA positivity strongly supports the diagnosis, antibody tests may be negative in approximately 10% of patients, particularly in cases limited to the kidney or respiratory tract (Jennette & Falk, 1997).

Kidney biopsy remains the gold standard for the diagnosis of AAV. The diagnosis is confirmed by demonstrating pauci-immune focal segmental necrotizing and crescentic glomerulonephritis with little or no immune complex deposition. In addition to confirming the diagnosis, biopsy provides important prognostic information by distinguishing active and potentially reversible inflammatory lesions, such as crescents and necrosis, from chronic and irreversible damage, including glomerulosclerosis and tubulointerstitial fibrosis. This distinction is critical for predicting long-term renal outcome. Kidney biopsy is also essential for identifying and excluding conditions that require different treatment approaches, such as double-positive disease associated with anti-GBM antibodies (Levy et al., 2004).

Despite its diagnostic value, the most important principle in clinical practice is that kidney biopsy should not delay life-saving treatment. In patients with a clinical presentation consistent with small-vessel vasculitis and positive MPO-ANCA or PR3-ANCA serology, immunosuppressive induction therapy should be started

promptly to prevent organ damage if biopsy cannot be performed immediately or if results are not readily available (Hellmich et al., 2024).

Baseline Assessment Before Immunosuppression

Before initiating remission-induction therapy, patients should undergo rapid assessment of renal severity, extrarenal organ involvement, infection risk, and treatment-related vulnerabilities. Serum creatinine, eGFR, urinalysis, proteinuria, dialysis requirement, and the presence of pulmonary haemorrhage should be evaluated. Anti-GBM antibodies should be tested, and kidney biopsy should be performed whenever feasible without delaying urgent treatment. Screening for hepatitis B, hepatitis C, HIV, and tuberculosis, baseline immunoglobulin levels, vaccination status, fertility considerations, and possible drug-induced AAV should also be reviewed before rituximab or cyclophosphamide is administered (KDIGO ANCA Vasculitis Work Group, 2024).

Risk Stratification Before Induction Therapy

Before selecting an induction regimen, patients should be stratified according to renal disease severity and the presence of life-threatening manifestations.

Treatment consists of two main phases: remission induction and remission maintenance. Remission induction usually covers the first 3–6 months and aims to control active glomerular inflammation and achieve clinical remission. Remission maintenance is used to prevent relapses, reduce further loss of kidney function, and replace more toxic induction agents with a safer long-term immunosuppressive strategy (KDIGO ANCA Vasculitis Work Group, 2024).

Remission Induction

The main treatment options for remission induction are rituximab or cyclophosphamide combined with a glucocorticoid-reduction protocol. Kidney involvement should be considered organ-threatening disease; however, treatment intensity should be determined according to the degree of renal risk. In patients without severe kidney involvement, rapid creatinine increase, or dialysis requirement, induction regimens based on rituximab or cyclophosphamide may be used. In contrast, patients with markedly elevated serum creatinine, rapidly rising creatinine levels, dialysis dependence at presentation, or extensive necrotizing and crescentic glomerulonephritis may be better treated with cyclophosphamide-based therapy or a combination of rituximab and cyclophosphamide (KDIGO ANCA Vasculitis Work Group, 2024; Jones et al., 2010; Stone et al., 2010).

Rituximab

Rituximab is an effective induction agent in newly diagnosed or relapsing ANCA-associated glomerulonephritis. It may be preferred particularly in patients with PR3-ANCA positivity, a history of relapse, young patients in whom fertility preservation is important, patients in whom cyclophosphamide toxicity should be avoided, frail older adults, and situations where a glucocorticoid-sparing strategy is desired. Standard induction regimens include 375 mg/m² once weekly for four doses or 1 g on days 1 and 15. The RAVE trial showed that rituximab was non-inferior to cyclophosphamide in the overall population of patients with severe ANCA-associated vasculitis (AAV). However, since only a limited number of patients with advanced renal dysfunction were enrolled, evidence for rituximab monotherapy in patients with serum creatinine levels >4 mg/dL, markedly reduced eGFR, or dialysis dependence remains limited (Stone et al., 2010). Likewise, the RITUXVAS trial demonstrated that a rituximab-based regimen combined with limited cyclophosphamide exposure achieved

remission rates comparable to those of standard intravenous cyclophosphamide in patients with ANCA-associated vasculitis and significant renal involvement (Jones et al., 2010).

Cyclophosphamide

Cyclophosphamide remains one of the main induction agents, particularly in ANCA-associated glomerulonephritis with severe kidney involvement. It may be administered orally or as intravenous pulse therapy. Intravenous pulse cyclophosphamide is generally given at a dose of 15 mg/kg at weeks 0, 2, 4, 7, 10, and 13, with dose adjustments according to age, kidney function, and leukocyte count. Oral cyclophosphamide usually starts at 2 mg/kg/day and is used for approximately 3 months in most patients. The duration may be extended if disease activity persists, but the shortest effective treatment period should be targeted because of cumulative toxicity. In the CYCLOPS trial, intravenous pulse cyclophosphamide and daily oral cyclophosphamide showed similar efficacy for remission induction in ANCA-associated disease with renal involvement. The pulse regimen was associated with a lower cumulative cyclophosphamide dose and less leukopenia (de Groot et al., 2009).

Glucocorticoid Reduction

Glucocorticoids are a traditional component of induction therapy. However, high-dose and prolonged steroid use is associated with infection, hyperglycaemia, osteoporosis, myopathy, weight gain, psychiatric adverse effects, and cardiovascular complications. Therefore, reducing glucocorticoid exposure is one of the main goals of current treatment strategies. Intravenous methylprednisolone pulses may be used initially in severe or rapidly progressive disease, followed by oral prednisone or prednisolone with gradual tapering according to a reduced-dose protocol. The PEXIVAS trial showed that a reduced-dose glucocorticoid regimen was noninferior to a

standard-dose regimen with respect to death or end-stage kidney disease and was associated with a lower risk of serious infection (Walsh et al., 2020).

Avacopan

Avacopan, a complement C5a receptor inhibitor, may be used as a glucocorticoid-sparing option in the treatment of ANCA-associated glomerulonephritis. It is added to induction therapy based on rituximab or cyclophosphamide and is generally administered at a dose of 30 mg orally twice daily. Patients at high risk for glucocorticoid toxicity, including those with diabetes, osteoporosis, frailty, or an increased risk of infection, may be suitable candidates for Avacopan. In the ADVOCATE trial, Avacopan was noninferior to a prednisone tapering regimen for remission at week 26 and superior for sustained remission at week 52. However, because of cost, accessibility, the need for liver function monitoring, and limited long-term safety data, its use may be more appropriate in selected patients (Jayne et al., 2021). The KDIGO recommendations recognize Avacopan not only as an adjunctive glucocorticoid-sparing therapy but also as a potential alternative to conventional oral glucocorticoid regimens in selected patients. Current evidence suggests that it may provide benefits in reducing cumulative glucocorticoid exposure and improving sustained remission and recovery of kidney function; however, clinical experience in patients with very advanced renal impairment remains relatively limited (Jayne et al., 2021; KDIGO ANCA Vasculitis Work Group, 2024).

Plasma Exchange

Plasma exchange should not be used routinely in ANCA-associated glomerulonephritis but may be considered in selected patients with severe disease. It may be evaluated on an individual basis in patients with serum creatinine levels above 3.4 mg/dL, dialysis dependence at presentation, rapidly rising creatinine, or

diffuse alveolar haemorrhage with hypoxemia. In the PEXIVAS trial, plasma exchange did not significantly reduce the composite outcome of death or end-stage kidney disease in the overall study population. Therefore, plasma exchange should not be considered standard therapy for all patients but may be selectively used in cases with severe renal risk, hypoxemic alveolar haemorrhage, or anti-GBM overlap (KDIGO ANCA Vasculitis Work Group, 2024; Walsh et al., 2020). Potential benefits should be weighed against the increased risk of serious infections and procedure-related complications when plasma exchange is considered.

Plasma exchange has a stronger role in patients with both ANCA and anti-GBM antibodies. These patients may have a renal prognosis similar to anti-GBM disease, and the aim is to remove pathogenic antibodies circulating. However, because of the ANCA-associated component of the disease, there is also a risk of relapse, and an appropriate maintenance immunosuppressive strategy should be planned after acute treatment (KDIGO ANCA Vasculitis Work Group, 2024).

Remission Maintenance

After remission is achieved, patients enter the maintenance phase of treatment. The goals of maintenance therapy are to prevent renal and systemic relapses, reduce further loss of kidney function, and replace more toxic induction therapies with safer long-term strategies. Maintenance treatment is usually continued for 18–48 months, and its duration should be individualized according to relapse risk, ANCA subtype, previous relapses, kidney function, treatment toxicity, and patient preference (KDIGO ANCA Vasculitis Work Group, 2024).

The CYCAZAREM, MAINRITSAN, and RITAZAREM trials are among the landmark studies investigating maintenance therapy. These studies established azathioprine- and rituximab-based

regimens as the principal maintenance treatment strategies in ANCA-associated vasculitis (Jayne et al., 2003; Guillevin et al., 2014; Smith et al., 2023).

Rituximab and azathioprine are the main options for maintenance therapy. Azathioprine is the traditional maintenance agent following cyclophosphamide induction and is generally used at a dose of 1.5–2 mg/kg/day. The CYCAZAREM trial showed that switching to azathioprine after remission induced with cyclophosphamide is an effective maintenance strategy that reduces cyclophosphamide exposure. Rituximab maintenance may be preferred particularly in patients with PR3-ANCA positivity, a history of relapse, previous induction with rituximab, intolerance to azathioprine, or situations where steroid reduction is a priority (Guillevin et al., 2014; Jayne et al., 2003; KDIGO ANCA Vasculitis Work Group, 2024).

Mycophenolate mofetil may be considered as an alternative in patients who cannot tolerate azathioprine, although it is not superior for relapse prevention. Methotrexate may also be an alternative in selected patients, but it should only be used in those with preserved kidney function and an eGFR above 60 mL/min/1.73 m^2. It is not suitable for patients with impaired kidney function because of the risk of toxicity (Hiemstra et al., 2010; KDIGO ANCA Vasculitis Work Group, 2024; Pagnoux et al., 2008).

Relapse Management

Management of relapses should be based on relapse severity. New or worsening hematuria, active urinary sediment, rising serum creatinine, increasing proteinuria, or systemic manifestations should raise suspicion for renal relapse. Changes in ANCA titters alone should not determine treatment decisions and should be interpreted together with the clinical picture and kidney findings. Organ- or life-threatening relapses require re-induction therapy, and rituximab is

preferred in most patients. In patients previously treated with cyclophosphamide, cumulative dose, infertility risk, malignancy risk, and infection risk should be considered (KDIGO ANCA Vasculitis Work Group, 2024; Stone et al., 2010).

Dialysis-Dependent Presentation and Kidney Recovery

In patients who present with dialysis dependence, induction therapy is often initiated because kidney function may recover during the early phase of treatment. However, if the patient remains dialysis-dependent after three months and there is no active extrarenal disease, the benefit of continued immunosuppression may decrease. In such cases, discontinuation of immunosuppressive therapy may be considered after weighing the risks of infection and treatment toxicity. In contrast, treatment should be continued if active disease persists in the lungs, skin, nervous system, or other organs (KDIGO ANCA Vasculitis Work Group, 2024).

Kidney Transplantation

Kidney transplantation is an appropriate option for patients who develop end-stage kidney disease secondary to ANCA-associated glomerulonephritis. Transplantation is generally planned after at least six months of complete clinical remission. ANCA positivity alone is not considered a reason to delay transplantation. However, there should be no active clinical disease, and patients should be closely monitored for relapses (KDIGO ANCA Vasculitis Work Group, 2024).

Supportive Care and Monitoring

Supportive therapy is an essential part of the management of ANCA-associated glomerulonephritis. Prophylaxis against *Pneumocystis jirovecii* pneumonia should be considered in patients receiving intensive immunosuppressive therapy. Screening for hepatitis B, hepatitis C, HIV, and tuberculosis should be performed

before treatment with rituximab or cyclophosphamide, and vaccination status should be reviewed. In patients receiving cyclophosphamide, complete blood counts, neutropenia, infections, hematuria, and bladder toxicity should be monitored. In patients receiving rituximab, immunoglobulin levels, recurrent infections, and the risk of hepatitis B reactivation should be followed. Osteoporosis prophylaxis, blood pressure and glycaemic control, gastrointestinal protection, and monitoring for infection should not be neglected in patients receiving glucocorticoids (de Groot et al., 2009; KDIGO ANCA Vasculitis Work Group, 2024).

Prognosis

The prognosis of ANCA-associated glomerulonephritis has improved substantially over the past decades because of advances in immunosuppressive therapy and supportive care. However, chronic kidney disease, end-stage kidney disease, treatment-related complications, infections, cardiovascular disease, and disease relapses continue to contribute significantly to morbidity and mortality.

Several factors influence renal prognosis. Histopathological classifications such as the Berden classification (focal, crescentic, mixed, and sclerotic classes) and renal risk prediction models have improved prognostic stratification in ANCA-associated glomerulonephritis. These include baseline kidney function, the extent of chronic damage observed on kidney biopsy, the proportion of normal glomeruli, the degree of glomerulosclerosis, and the severity of tubulointerstitial fibrosis. Early diagnosis and prompt initiation of treatment remain the most important factors associated with preservation of kidney function and improved long-term outcomes (Geetha & Jefferson, 2020; KDIGO ANCA Vasculitis Work Group, 2024).

Conclusion

In conclusion, treatment of ANCA-associated glomerulonephritis should be tailored according to the severity of renal involvement. Rituximab and cyclophosphamide are the main agents used for induction therapy. In severe kidney involvement, cyclophosphamide-based therapy or a combination of rituximab and cyclophosphamide may be preferred. Glucocorticoid exposure should be minimized whenever possible, and Avacopan may be considered as a steroid-sparing option in selected patients. Plasma exchange is not a routine treatment but may be considered in patients with severe kidney failure, dialysis dependence, rapidly rising creatinine, hypoxemic alveolar haemorrhage, or anti-GBM overlap. Following remission, maintenance therapy with rituximab or azathioprine should be planned, and treatment duration should be individualized after balancing relapse risk and treatment toxicity (de Groot et al., 2009; Jayne et al., 2021; KDIGO ANCA Vasculitis Work Group, 2024; Stone et al., 2010; Walsh et al., 2020).

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BÖLÜM 6

CURRENT APPROACHES AND FUTURE PERSPECTİVES İN THE MANAGEMENT OF MONOCLONAL GAMMOPATHY OF RENAL SİGNİFİCANCE

DUYGU ARSLAN[1]

Introduction

Monoclonal proteins (M-proteins) are frequently encountered findings in the elderly population, detected in approximately 3% of individuals over the age of 50 and 5% of those over 70. Although the presence of a monoclonal protein is mostly associated with an asymptomatic condition defined as MGUS (Monoclonal Gammopathy of Undetermined Significance), severe organ damage can develop in some patients despite a low tumor burden. While these cases do not meet the criteria for haematological malignancy, the monoclonal immunoglobulins produced induce renal injury through either direct nephrotoxic effects or complement-mediated mechanisms. Consequently, the concept of MGRS (Monoclonal Gammopathy of Renal Significance) was introduced by the IKMG (International Kidney and Monoclonal Gammopathy

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Working Group) in 2012, grouping kidney diseases caused by nephrotoxic monoclonal proteins under this single entity. Today, MGRS is recognized as a broad clinicopathological spectrum encompassing renal lesions associated with MGUS, smouldering multiple myeloma, smouldering Waldenström macroglobulinemia, monoclonal B-cell lymphocytosis, and certain low-grade B-cell lymphoproliferative disorders (Leung et al., 2019).

Epidemiology

The prevalence of MGRS among individuals diagnosed with MGUS in the United States is reported to be 6% (Amaador et al., 2019). Notably, MGRS-associated diseases are present in 40–45% of monoclonal gammopathy patients who undergo a kidney biopsy (Leung et al., 2021). The prevalence scales markedly with age, standing at approximately 3% in adults aged 50 and older, 5% in those over 70, and reaching up to 8% in individuals beyond the age of 80 (Leung et al., 2019a). Although the exact male-to-female ratio remains poorly defined, a higher predisposition is likely in males. Regarding ethnic variations, the prevalence of MGUS is two- to three-fold higher in African Americans compared to Caucasians (Leung et al., 2019a). No specific geographical predisposition has been identified to date.

In 100% of cases, MGRS is associated with an underlying indolent or overt B-cell or plasma cell clonal disorder that does not meet the current criteria for immediate systemic treatment, yet drives symptomatic renal disease (Leung et al., 2019a; Leung et al., 2021).

Pathogenesis

The fundamental mechanism of renal injury in monoclonal gammopathy of renal significance (MGRS) involves the deposition of monoclonal immunoglobulins or immunoglobulin subunits within kidney tissue, alongside their direct or indirect nephrotoxic effects. Kidney diseases associated with MGRS exhibit a highly

heterogeneous spectrum regarding clinical manifestations, histopathological features, extrarenal involvement patterns, and prognosis. This heterogeneity is believed to be largely dictated by the physicochemical properties of the pathogenic monoclonal immunoglobulin, its production rate, and its interaction with the renal microenvironment (Rajkumar et al., 2006).

The most frequent pathological mechanism encountered in MGRS is the deposition of monoclonal light chains in renal tissue. Less commonly, the intact immunoglobulin molecule or heavy chains alone may form deposits. Although monoclonal immunoglobulin depositions can occur across all compartments of the kidney—including the glomeruli, tubulointerstitial space, and renal vasculature—they are most frequently detected within the glomerular capillary walls and the mesangial region (Kapoulas et al., 2015; Al-Hussain et al., 2015; Bridoux et al., 2015).

The nephrotoxic effects of monoclonal immunoglobulins are not confined solely to tissue deposition. Certain monoclonal proteins exhibit autoantibody-like properties that activate the complement system, thereby precipitating renal damage without forming direct deposits. This mechanism plays a critical role particularly in the pathogenesis of MGRS subtypes such as C3 glomerulopathy and thrombotic microangiopathy (Bridoux et al., 2015; Hogan et al., 2019).

Renal Metabolism of Free Light Chains

The kidneys play a central role in the metabolism of free light chains (FLCs). Serum FLC levels are determined by the equilibrium between the quantity produced by plasma cells and their elimination via the kidneys. Due to their low molecular weight, approximately 90% of circulating FLCs pass through the glomerular filtration barrier into Bowman’s space and are subsequently reabsorbed by the proximal tubules (Hogan et al., 2019).

The reabsorption of FLCs is mediated by the megalin-cubilin receptor complex located on the apical surface of proximal tubular epithelial cells. Following intracellular uptake via endocytosis, light chains are degraded and metabolised by lysosomal enzymes. This mechanism constitutes the primary physiological pathway for clearing circulating free light chains (Leung et al., 2021).

Nephrotoxic Effects of Monoclonal Free Light Chains

The specific pattern of kidney injury induced by monoclonal light chains is largely governed by the amino acid sequence within their variable regions and their distinct physicochemical properties. Distinct patterns of renal injury arise from the interaction of light chains with cellular receptors, extracellular matrix components, growth factors, and uromodulin present within the glomerular and tubular microenvironments. Consequently, entirely disparate histopathological profiles can develop even among patients producing similar quantities of monoclonal protein (Kapoulas et al., 2015; Hogan et al., 2019).

When monoclonal light chain production accelerates, the reabsorptive capacity of the proximal tubules becomes overwhelmed, allowing excess light chains to reach the distal segments of the nephron. In the distal tubules and the thick ascending limb of the loop of Henle, these light chains interact with uromodulin (Tamm–Horsfall protein), precipitating the formation of tubular casts, which represents the core pathogenetic mechanism of cast nephropathy (Leung et al., 2021).

Furthermore, an excessive light chain burden induces lysosomal dysfunction and cellular stress responses within proximal tubular cells. Overloading the lysosomal system can lead to acute tubular injury, characterised by vacuolation, cellular fragmentation, and desquamation of tubular epithelial cells. Certain light chains also crystallise intracellularly, giving rise to unique clinicopathological

entities such as light chain proximal tubulopathy and Fanconi syndrome (Hogan et al., 2019; Leung et al., 2021).

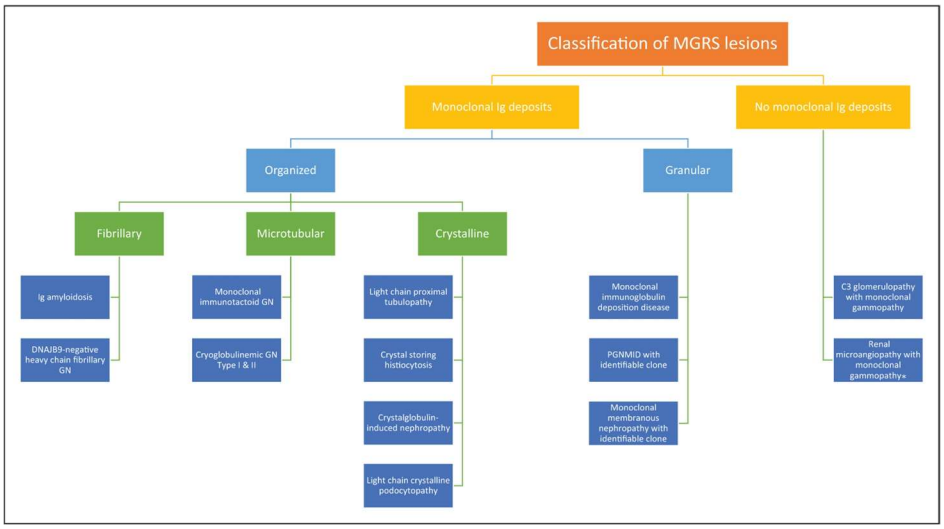
Classification

Under pathological conditions, the renal metabolism of FLCs and the resulting injuries are categorised into two primary patterns based on the affected nephron segment: glomerulopathic and tubulopathy light chain-associated diseases (Leung et al., 2021).

The primary target of the glomerulopathic pattern is the mesangial region. The deposition of monoclonal light chains here drives the development of various glomerular lesions depending on the ultrastructural characteristics of the deposits. Histopathological, these lesions are divided into two categories: glomerulopathies with organised deposits and glomerulopathies with non-organised deposits. Glomerulopathies characterised by organised deposits include AL amyloidosis, Type 1 and Type 2 cryoglobulinaemic glomerulonephritis, and immunotactoid glomerulopathy. Conversely, glomerulopathies characterised by non-organised deposits encompass monoclonal immunoglobulin deposition disease (MIDD), proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID), and monoclonal gammopathy-associated C3 glomerulopathy (Bridoux et al., 2015; Leung et al., 2021).

Monoclonal gammopathies can induce injury not only within glomerular structures but also within the tubulointerstitial compartment. The most prominent lesions in this category are light chain proximal tubulopathy (LCPT)—which may present with or independently of Fanconi syndrome—and light chain cast nephropathy (LCCN). In these conditions, the accumulation of light chains within proximal or distal tubular structures can lead to tubular dysfunction, interstitial inflammation, and progressive loss of renal function (Bridoux et al., 2015; Leung et al., 2021).

Figure 1. Classification of MGRS



Reference:: (Bu & Nasr, 2026)

Light Chain (AL), Heavy Chain (AH), and Light and Heavy Chain (AHL) Amyloidosis

Renal amyloidosis is characterised by the extracellular deposition of amyloid fibrils within glomeruli, tubules, and/or vascular walls. Most monoclonal protein-associated cases originate from immunoglobulin light chains (predominantly isotype); intact immunoglobulins or heavy chains are rare (Dember, 2006). On light microscopy, amyloid appears as pale eosinophilic, PAS-negative or weakly positive, trichrome blue-grey, and silver-negative acellular deposits. Amyloidosis is uniquely Congo red-positive among MGRS lesions, displaying characteristic apple-green birefringence under polarised light.

Immunofluorescence reveals monotypic light or heavy chain staining. Electron microscopy (EM) shows non-branching, randomly arranged fibrils (7–14 nm diameter) in the mesangium, basement membranes, interstitial, and vessel walls. These are systemic conditions, with most patients presenting with multi-organ

involvement at diagnosis (Bridoux et al., 2015; Wechalekar et al., 2016).

Monoclonal Immunoglobulin Deposition Disease (MIDD)

MIDD is a rare MGRS subtype categorised into light chain (LCDD, predominantly), light and heavy chain (LHCDD), and heavy chain (HCDD) deposition diseases. Renal involvement is universal, though cardiac, hepatic, and pulmonary extrarenal manifestations occur. Light microscopy typically reveals nodular glomerulosclerosis, mesangial expansion, and basement membrane thickening, alongside variable tubular atrophy and interstitial fibrosis. Linear monotypic deposits are detected along membranes via immunofluorescence. EM confirms non-fibrillar, electron-dense granular accumulations in subendothelial, mesangial, and tubular basement membrane regions, distinguishing MIDD from other entities (Bridoux et al., 2015; Komatsuda et al., 2013; Rane et al., 2012).

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID)

PGNMID is a rare MGRS glomerulopathy driven by glomerular monoclonal immunoglobulin deposits, predominantly IgG (most commonly IgG3\kappa) and rarely IgA or IgM. Light microscopy typically shows endocapillary proliferative and/or membranoproliferative glomerulonephritis (MPGN) patterns, sometimes with membranous features. Immunofluorescence demonstrates glomeruli-restricted monotypic staining, often accompanied by complement-activating C3 and C1q. EM characteristically identifies non-fibrillar, granular, electron-dense deposits in subendothelial and mesangial zones, confirming diagnosis (Bridoux et al., 2015; Hussain & Sureshkumar, 2017; Sethi et al., 2016; Vignon et al., 2017).

Monoclonal Gammopathy-Associated C3 Glomerulopathy (C3GP)

In C3GP, renal injury is driven by complement dysregulation rather than direct monoclonal deposition. Monoclonal IgGs often act as autoantibodies against alternative complement pathway regulators (e.g., C3 convertase), triggering uncontrolled systemic activation (Lloyd et al., 2016; Zand et al., 2013). Proliferative, MPGN, or endocapillary histopathological patterns predominate. Immunofluorescence characteristically reveals dominant glomerular C3 staining (at least two degrees greater than the sum of immunoglobulins and C1q). EM confirms complement-mediated injury through mesangial and subendothelial electron-dense deposits (Alpers & Kowalewska, 2008).

Immunotactoid Glomerulopathy (ITG)

ITG is a rare glomerular disease defined by organised microtubular deposits (usually IgG with or restriction), frequently presenting as MPGN or diffuse proliferative patterns. Unlike fibrillary glomerulonephritis, these deposits are monoclonal, Congo red-negative, possess hollow centres with distinct lumina, and stain positive for C3. EM shows large parallel microtubular arrays (typically exceeding 30–90 nm in diameter), providing a crucial differentiator from fibrillary patterns (Alpers & Kowalewska, 2008; Bridoux et al., 2015).

Cryoglobulinaemic Glomerulonephritis (CGG)

CGG results from glomerular cryoglobulin deposition, where Type I and Type II forms involve monoclonal immunoglobulins. Type I involves low-temperature precipitation leading to MPGN or vasculitis, characterised by PAS-positive hyaline thrombi and prominent leucocyte infiltration. Immunofluorescence shows co-deposition of C3, C4, and C1q, while EM reveals microtubular, fibrillar, or fingerprint-like organised structures. Type II features

immune complexes formed with polyclonal immunoglobulins, frequently associated with hepatitis C or underlying B-cell disorders (Bridoux et al., 2015; Hiramatsu et al., 2014; Leung et al., 2012; Sethi et al., 2016).

Paraprotein-Associated Fibrillary Glomerulonephritis (FGN)

FGN is primarily polyclonal but can rarely present with monoclonal immunoglobulin deposits, typically showing an MPGN pattern. Deposits are Congo red-negative, distinguishing them from amyloid. Immunofluorescence usually reveals IgG4 (or IgG1) and C3 within the fibrils. EM provides the definitive finding: randomly arranged fibrils measuring 16–24 nm in diameter, which are thicker than amyloid fibrils (Alpers & Kowalewska, 2008; Rosenstock et al., 2003).

Monoclonal Gammopathy-Associated Thrombotic Microangiopathy (TMA)

This rare MGRS variant involves monoclonal immunoglobulin-induced endothelial injury and microvascular thrombosis, supported by a high clinical prevalence of monoclonal gammopathy in TMA patients. Histopathological hallmarks include capillary thrombi, endothelial swelling, mesangiolysis, microaneurysms, and glomerular basement membrane double-contours. Acute tubular injury, interstitial fibrosis, and macrovascular thrombosis may coexist (Ravindran et al., 2017; Vos et al., 2016).

Light Chain Proximal Tubulopathy (LCPT)

LCPT features proximal tubular dysfunction caused by intracellular monoclonal light chain accumulation (predominantly). In the classic variant, these form rod- or rhomboid-shaped, hypereosinophilic, PAS-negative crystalline inclusions within endolysosomes, visible on EM as electron-dense crystals. While the

crystal-forming variant strongly correlates with Fanconi syndrome and severe renal decline, the clinical impact of the non-crystal-forming variant remains less defined (Larsen et al., 2011; Nasr et al., 2006; Stokes et al., 2016).

Crystal-Storing Histiocytosis (CSH)

CSH is a rare deposit disease where monoclonal crystals (mostly) accumulate within the lysosomes of interstitial histiocytes, often accompanied by fibrosis and tubular atrophy. Immunofluorescence demonstrates monoclonal light chains, though immunohistochemistry may be needed. CSH frequently overlaps with LCPT; EM confirms diagnosis by revealing organised crystalline deposits within both histiocytes and tubular epithelium (Bridoux et al., 2015; El Hamel et al., 2010; Marzilli et al., 2000; Nasr et al., 2006).

Diagnosis

MGRS presents variably with progressive renal decline, microscopic haematuria, proteinuria, or proximal tubulopathy (Fanconi syndrome). MGRS must be considered in any unexplained renal disease coinciding with a monoclonal protein (Bridoux et al., 2015; Muchtar et al., 2017; Sethi et al., 2016). Diagnostic screening requires combining serum protein electrophoresis, serum/urine immunofixation, and serum free light chain (sFLC) assays, factoring in renal function adjustments (Campbell et al., 2017; El Hamel et al., 2010; Kyle & Gertz, 1995; Muchtar et al., 2017).

Kidney biopsy is essential, utilizing light microscopy, immunofluorescence, and EM—the latter being indispensable for FGN, ITG, CGG, and LCPT. Mass spectrometry combined with laser microdissection remains the gold standard for amyloid typing (Campbell et al., 2017; Kyle & Gertz, 1995; Sethi et al., 2010; Vrana et al., 2009). Haematological workup (bone marrow biopsy, flow cytometry) must follow to confirm the clonal origin of the deposits

(Dimopoulos et al., 2016; “Guidelines on the Diagnosis and Management of AL Amyloidosis.,” 2004).

Treatment

General Treatment Approach

The primary goal is targeting the underlying B-cell or plasma cell clone to halt nephrotoxic immunoglobulin production and preserve organ function. Deeper haematological responses correlate with superior renal outcomes, necessitating tailored clone-directed regimens based on clone type, renal baseline, and comorbidities (Leung et al., 2012).

Plasma Cell Clone-Directed Therapy

For plasma cell clones, bortezomib forms the cornerstone of treatment, yielding high response rates in AL amyloidosis and MIDD. Autologous stem cell transplantation (ASCT) after high-dose melphalan provides prolonged remissions in eligible patients; otherwise, bortezomib-dexamethasone-cyclophosphamide is preferred. Second-generation proteasome inhibitors (carfilzomib, ixazomib) show promise in plasma cell disorders, though MGRS-specific data remain limited. Ixazomib offers a favourable oral toxicity profile.

The anti-CD38 antibody daratumumab has shown excellent efficacy; adding it to bortezomib-cyclophosphamide-dexamethasone significantly enhances complete response rates in AL amyloidosis. Isatuximab, another anti-CD38 antibody with stronger binding properties, is approved for multiple myeloma and under study for amyloidosis, though prospective data across all MGRS subtypes are still required (Karam et al., 2023; Breitkreutz et al., 2014; Cohen et al., 2015; Dimopoulos et al., 2016; “Guidelines on the Diagnosis and Management of AL Amyloidosis.,” 2004; Kintzel & Dorr, 1995; Scheid et al., 2014).

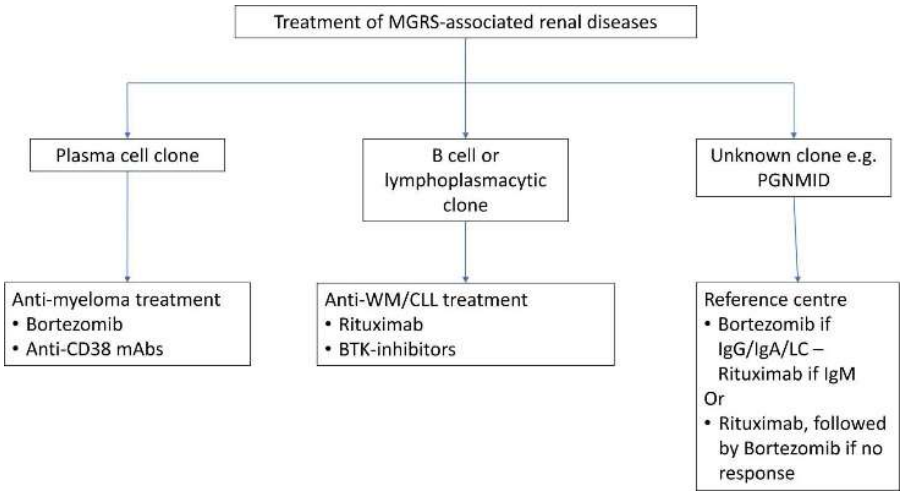
Treatment in IgM-Associated MGRS

For IgM-producing B-cell or lymphoplasmacytic clones, rituximab is the primary therapy, often combined with cyclophosphamide, dexamethasone, or bendamustine, depending on renal tolerance. ASCT remains a selective option (Haubitz et al., 2002; Leung et al., 2019b; Nordstrom et al., 2014; Vieira et al., 2004). The BTK inhibitor ibrutinib is safe in renal impairment and highly effective in related B-cell malignancies, though its exact position in MGRS protocols requires further clinical validation (O'Brien et al., 2018; Dimopoulos et al., 2018; Karam et al., 2023).

Supportive Care

Concurrently, hypertension and proteinuria must be managed using RAAS inhibitors and dietary salt restriction. Diuretics offer additive benefits, though RAAS blockade demands caution in AL amyloidosis due to hypotension risks. Bicarbonate, phosphate, and vitamin D replacements are indicated in Fanconi syndrome to mitigate osteomalacia (Karam et al., 2023).

Fig. 2. Treatment of MGRS-associated renal diseases



Reference: (Karam et al., 2023)

Evaluation of Treatment Response

Monitoring the haematological response holds paramount importance in evaluating treatment efficacy. Serum free light chain (sFLC) analysis constitutes one of the fundamental methods in assessing haematological response. Response is typically categorised as complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR). Achieving a deep haematological response is strongly correlated with superior renal outcomes.

Nevertheless, renal response manifests later than haematological response, and noticeable improvement in renal function may take months or even exceed a year to become apparent. Consequently, long-term, multidisciplinary follow-up of MGRS patients is of crucial importance (Fermand et al., 2013; Hassoun et al., 2008; Leung et al., 2005; Palladini et al., 2012).

Conclusion

Monoclonal gammopathy of renal significance (MGRS) represents a heterogeneous group of disorders with a broad histopathological spectrum, wherein renal injury develops either through the direct deposition of nephrotoxic monoclonal immunoglobulins within the kidney or via complement-mediated mechanisms. Accurate diagnosis requires the detection of the circulating monoclonal protein and the establishment of a causal relationship between this protein and the accompanying renal lesion. To this end, evaluating a kidney biopsy through the combined interpretation of light microscopy, immunofluorescence, immunohistochemical examination, and electron microscopy forms the cornerstone of the diagnostic approach.

Currently, the mainstay of MGRS treatment comprises clone-directed therapies targeting the specific clone responsible for organ damage. Achieving a deep and sustained haematological response is

the primary determinant of both renal and extrarenal organ responses. Given the rarity of the disease, its diverse clinicopathological variants, and the specialised expertise required for its diagnosis and management, it is highly recommended that MGRS patients be evaluated and monitored by multidisciplinary teams comprising nephrologists, haematologists, and nephropathologists. In the future, with the development of more targeted clonal therapies and the widespread adoption of early diagnosis strategies, renal and overall patient survival in MGRS is expected to improve further.

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