Chapter 8: Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury

This chapter replaces the 2012 guideline chapter for idiopathic MPGN. Given the advances in our understanding of underlying etiology and the recognition that MPGN is not a disease but a pattern of glomerular injury, this updated chapter discusses the evaluation and management of the glomerular disease that often have a membranoproliferative pattern of injury, including C3G.[522]

The treatment of MPGN depends upon identification of an underlying cause. In most cases, the MPGN lesion derives from deposition of immunoglobulins and complement as either immune complexes (secondary to an underlying infection/autoimmune process), or monoclonal immunoglobulins, or is due to dysregulation of the alternative complement pathway.

In a few cases of immune complex–mediated MPGN, an identifiable underlying cause cannot be found despite extensive evaluation. This may be seen in children and young adults, but is rarely seen in adults. These patients are considered to have an "idiopathic" immune complex–mediated MPGN or immune complex–mediated MPGN of unknown etiology.

Because previous controlled trials included patients based on the old and now discarded electron-microscopic classification of MPGN, and not on the current classification that uses immunofluorescence microscopy in combination with presumptive disease pathobiology, there is insufficient high-quality evidence to form recommendations for the management of the various diseases that have MPGN histology. Therefore, practice points will be given to assist in clinical decision-making for these patients.

Nomenclature

The membranoproliferative pattern of GN is a light-microscopic pattern of kidney injury, characterized principally by an increased number of intraglomerular cells and diffuse thickening of the glomerular capillary walls. The clinical presentation is not specific, and patients commonly present with proteinuria (frequently associated with the NS), hypertension, glomerular hematuria, and abnormal kidney function. Hypocomplementemia (C3 and/or C4) is often, but not always, present. An MPGN pattern of injury may be found in many unrelated disorders (Figure 68). Identification of the pathogenic mechanisms specific for a disease is critical for appropriate management.

Membranoproliferative lesions were historically classified based on the location of deposits on electron microscopy examination as:

- *Type I MPGN* (MPGN I)—characterized by *subendothelial* and *mesangial* electron-dense deposits consisting of both immunoglobulin and C3
- *Type II MPGN* (MPGN II—Dense deposit disease [DDD])—characterized by electron-dense *intramembranous* deposits, predominantly consisting of complement
- *Type III MPGN* (characterized by *both subepithelial and subendothelial deposits*)

This historical classification was not based on disease pathogenesis, and as a result, different pathogenic processes fell under the collective designation of MPGN.

Advances in our understanding of underlying disease mechanisms leading to the development of a membranoproliferative pattern of kidney injury have resulted in a new pathobiology-based classification. The new classification relies on immunofluorescence examination; deposits are defined as primarily immunoglobulin (monoclonal), polyclonal immunoglobulin and complement, or predominantly complement (Figure 69).[523,524]

On the basis of the immunofluorescence findings, MPGN can be broadly divided into an immunofluorescence-negative subgroup, a complement-dominant subgroup, and an immunoglobulin subgroup, with or without complement. When MPGN is immunoglobulin-positive, regardless of the presence of complement, evaluation for infection, autoimmune disease, and monoclonal gammopathy should be done. Complement-dominant MPGN is further divided into C3/C4 glomerulopathy. A complement-dominant pattern requires evaluation of the alternative pathway of complement. Absence/trace Ig or C3 suggests a TMA.

It should be understood that the presence of an MPGN lesion implies that the pathogenic process has been present for some time and that other patterns of injury, including endocapillary proliferative GN, mesangioproliferative GN, and crescentic GN, may occur as a result of the same process. Thus, the type of lesion initially seen on light microscopy will depend, in part, on the timing of the kidney biopsy in relation to disease chronicity.[525]

Immune complex–mediated GN (ICGN) with an MPGN pattern

ICGN is characterized by the deposition of immune complexes containing both polyclonal immunoglobulins and

Immunoglobulin-/ immune complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C (including HCV-associated mixed cryoglobulinemia), hepatitis B • Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis • Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis **Deposition of immune complexes as a result of an autoimmune disease:** • SLE • Sjögren's syndrome • Rheumatoid arthritis • Mixed connective tissue disease **Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder** **Fibrillary glomerulonephritis** **Idiopathic** • None of the conditions above are present
Complement-mediated	**C3 glomerulonephritis and C3 DDD:** • Mutations in complement regulatory proteins: CFH, CFI, CFHR5 • Mutations in complement factors: C3 • Antibodies to complement factors: C3, C4, and C5 nephritic factors • Antibodies to complement regulatory proteins: CFH, CFI, CFB **C4 glomerulonephritis and C4 DDD**
Membranoproliferative pattern without immune complexes or complement	• Healing phase of HUS/TTP • Antiphospholipid (anticardiolipin) antibody syndrome • POEMS syndrome • Radiation nephritis • Nephropathy associated with bone marrow transplantation • Drug-associated thrombotic microangiopathies • Sickle cell anemia and polycythemia • Dysfibrinogenemia and other pro-thrombotic states • Antitrypsin deficiency

Figure 68 | Causes of a membranoproliferative pattern of injury. CFB, complement factor B; CFH, complement factor H; CFHR5, complement factor H–related protein 5; CFI, complement factor I; DDD, dense deposit disease; HCV, hepatitis C virus; HUS, hemolytic–uremic syndrome; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

complement (excludes IgAN). This lesion classically results from chronic antigenemia with or without circulating immune complexes. ICGN may manifest with the MPGN pattern of injury or other proliferative glomerular lesions.

ICGN is usually due to:

- **Infections:** Hepatitis C and B viral infections are among the most common underlying causes of ICGN, but bacterial and protozoal infections can also cause ICGN.
- **Autoimmunity:** ICGN can be associated with certain autoimmune disorders, such as SLE, Sjögren's syndrome, and rheumatoid arthritis.

GN with monoclonal immunoglobulin deposits

Proliferative patterns of kidney injury secondary to deposition of monoclonal immunoglobulins are observed in patients with monoclonal gammopathies. These disorders are infrequently found in patients with overt hematologic disease, such as multiple myeloma, Waldenström macroglobulinemia, or B cell lymphoma. They most commonly occur in the setting of an indolent clonal, plasma cell, or lymphocytic disorder, and may be classified as a monoclonal gammopathy of renal significance (MGRS).[526] Kidney injury results from direct glomerular deposition of the monoclonal immunoglobulin. Examples include immunotactoid glomerulopathy, type I and type II cryoglobulinemic GN, and proliferative GN with monoclonal Ig deposits (PGNMID). Of note, in approximately 70% of the cases of PGNMID, a clone cannot be detected.[527] Each type can be differentiated by the distribution and ultrastructural appearance of deposits (i.e., amorphous or organized), by electron microscopy.[528] A complete discussion of these entities is beyond the scope of this guideline.

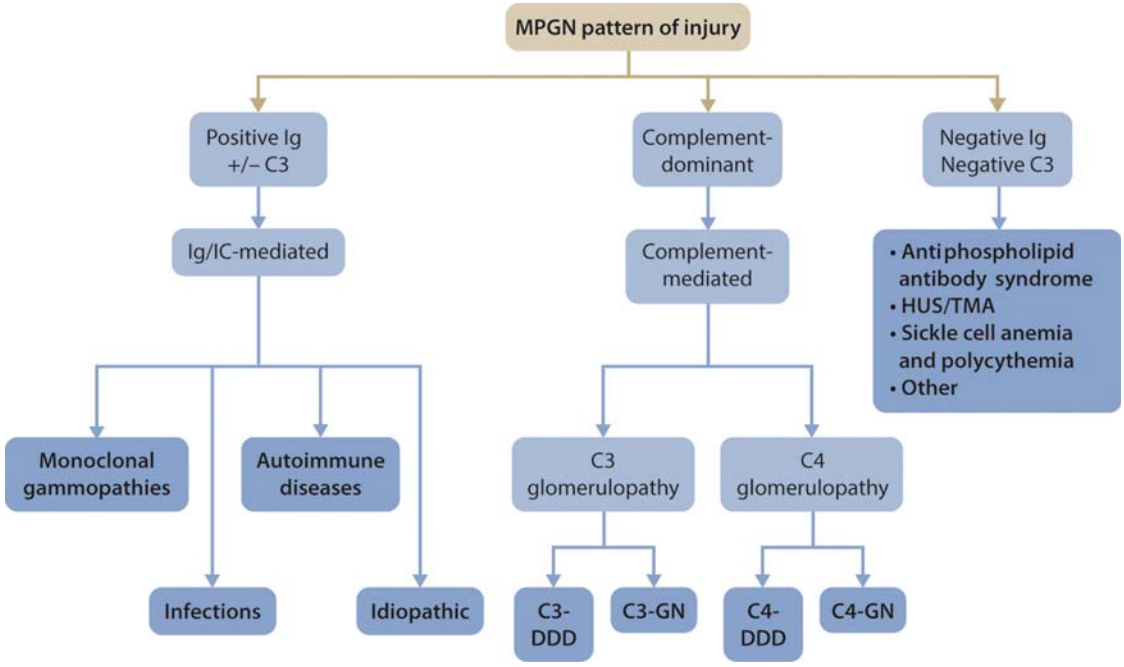

Figure 69 | Pathophysiology of membranoproliferative lesions. DDD, dense deposit disease; GN, glomerulonephritis; HUS, hemolytic–uremic syndrome; IC, immune complex; Ig, immunoglobulin(s); MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

Glomerulonephritis with C3- and C4-dominant deposits

C3G is a rare entity that is defined by *C3-dominant glomerulonephritis* (a proliferative histologic lesion with C3 deposition at least 2 orders of magnitude greater than any other immune reactant) on immunofluorescence.[529] This category includes both DDD and the newer designation of C3 glomerulonephritis (C3GN).[530] Although DDD is defined by highly electron-dense osmophilic, predominantly intramembranous deposits, C3GN is characterized by mesangial and capillary wall deposits of lesser intensity. Other C3-dominant glomerular lesions (e.g., infection-related GN) must be excluded. Masked monoclonal immunoglobulin deposits should be considered in patients with a pattern of C3GN when immunofluorescence shows a small amount of immunoglobulin deposition admixed with C3 deposits. Immunofluorescence studies on paraffin-embedded tissue after pronase digestion may unmask glomerular deposits of monoclonal Ig.[531] An MPGN pattern is inconstantly observed in C3G, and hypocomplementemia is present in only about 50% of cases.[532,533] The underlying disease mechanism of C3G is presumed to result from dysregulation of the alternative complement pathway.[534] A similar entity of complement-mediated GN that is characterized by bright C4d staining but with no or minimal C3 or immunoglobulin deposits on immunofluorescence (C4 glomerulopathy [C4G]) has recently been described.[535] Further studies are required to determine its underlying cause.

8.1 Diagnosis

Practice Point 8.1.1: Evaluate patients with immune complex-mediated GN (ICGN) for underlying disease (Figure 68).

First, consider infection such as HBV and HCV infection, chronic bacterial infection (e.g., endocarditis, shunt nephritis, abscesses), fungal, and particularly in the developing world, parasitic infections (e.g., schistosomiasis, echinococcosis, malaria). Streptococcal serology should be performed in patients with recent history of infection. Second, consider autoimmune disorders such as SLE (particularly in the chronic phase of LN) and, less often, Sjögren's syndrome or rheumatoid arthritis. Besides autoimmunity, an underlying immune abnormality may be a trigger for ICGN. ICGN may be associated with malignancy; therefore, age-appropriate cancer screening may be warranted.

Practice Point 8.1.2: Evaluate patients with GN and monoclonal immunoglobulin deposits for a hematologic malignancy.

Patients with PGNMID, as determined by immunofluorescence, should undergo a complete evaluation for a hematologic malignancy or an indolent plasma cell or lymphocytic disorder, regardless of age, that includes: (i) serum and urine protein electrophoresis; (ii) serum and urine immunofixation; (iii) measurement of serum-free light chain levels; and (iv) hematology consultation to further evaluate for the presence of an underlying B cell/plasma cell clone producing the monoclonal immunoglobulin.[526] Working with a hematologist is important not only to further evaluate these patients (i.e., with a bone marrow biopsy, if indicated) but also because a number of the drugs used to treat these patients are not commonly used by practicing nephrologists.

Practice Point 8.1.3: If no underlying etiology is found for ICGN after extensive workup, evaluate for both

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders‡	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

Figure 70 | Evaluation of abnormalities of the alternative pathway of complement. Adapted from *Kidney International*, volume 89, issue 2, Angioi A, Fervenza FC, Sethi S, et al. Diagnosis of complement alternative pathway disorders, pages 278–288, Copyright © 2016, with permission from the International Society of Nephrology.[539] ‡The presence of a circulating monoclonal gammopathy is less common below the age of 50 years. Ability to detect a monoclonal protein will depend on the sensitivity of the assay used. †Some complement assays may require referral to specialist/research laboratories, and interpretation of complement assays may require expert consultation. AP50, complement alternate pathway activation 50%; Bb, activated factor B; C3d, complement component 3d; C4d, complement component 4d; CFB, complement factor B; CFH, complement factor H; CFHR1-5, complement factor H–related protein 1-5; CFI, complement factor I; CH50, complement hemolytic activity 50%; FB, factor B; FH, factor H; FI, factor I; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MLPA, multiplex ligation-dependent probe amplification; sMAC, soluble membrane attack complex.

complement dysregulation and drivers of complement dysregulation (Figure 70).

Data support a role for complement dysregulation in ICGN.[536,537] In addition, cohort data demonstrate that classic C3G may masquerade as ICGN (i.e., significant immunoglobulin may be present) when an infectious trigger is present at the time of kidney biopsy.[538] Substantiating a role for excess complement activity may inform a treatment approach, over and above supportive measures, and/or standard immunosuppression for active GN. A complete complement workup includes an assessment of overall complement activity, measurement of serum levels of complement proteins, and in select cases, screening for autoantibodies against complement regulatory proteins and genetic studies (Figure 70[539]).

Practice Point 8.1.4: Rule out infection-related GN or postinfectious GN prior to assigning the diagnosis of C3 glomerulopathy (C3G).

Both infection-related GN (i.e., in the presence of active infection) and postinfectious GN (i.e., in patients with a preceding infection that has resolved) are presumed to be nonrecurrent, acute disease processes requiring only a limited workup. Treatment is best focused on resolving the infection while supporting kidney function. Immunosuppression is unlikely to be required except in extreme cases (i.e., rapidly progressive loss of kidney function and/or crescentic glomerular disease) and only after concurrent infection is controlled.

Practice Point 8.1.5: Evaluate for the presence of a monoclonal protein in patients who present for the first time with a C3G diagnosis at ≥50 years of age (Figure 69).

C3G in its classic form is a disease of children and young adults[538,540] related to autoantibody (nephritic factor)-mediated dysregulation of the enzyme complexes of the alternative pathway of complement, or to other key complement pathway proteins, and to a lesser extent to mutations in genes encoding Factor H, Factor I, Complement Factor H–related (CFHR) proteins, or C3.[534] Recently, the association between the production of a monoclonal protein in older adults and the development of C3G has been described.[533,541] In patients over the age of 50 years with C3G, the prevalence of monoclonal gammopathy ranges from 31% to 83% versus approximately 3% in age-matched controls.[533] However, C3G with an associated circulating monoclonal protein has sometimes been reported in patients aged 20–47 years, demonstrating that the disease affects a large age span.[538] The association rests on the epidemiologic findings, as direct evidence demonstrating monoclonal gammopathy as the cause of C3G is lacking in most patients. However, it appears that a number of monoclonal proteins have complement dysregulating features, primarily through direct activation of the complement alternative pathway.[541] The impetus for evaluating a given patient for a clonal B cell disorder stems from the limited data suggesting that a therapeutic strategy that addresses the clone may provide a treatment benefit for a paraprotein-associated C3G.[542] The comprehensive evaluation of a patient suspected of having a monoclonal protein is beyond the scope of this presentation.

8.2 Treatment

8.2.1 ICGN

Prior guidelines supported the use of oral cyclophosphamide or MMF plus low-dose, alternate-day, or daily glucocorticoids

as a therapeutic approach to ICGN, particularly in those with idiopathic disease and NS and/or rapidly progressive diseases. The same advances in our understanding of underlying disease mechanisms that have driven a nomenclature change have also highlighted the confounding heterogeneity of prior disease cohorts. Additionally, idiopathic ICGN is an exceptional condition in adults. Data no longer support the global application of broad-spectrum immunosuppression as in prior recommendations, but rather a more individualized approach. The optimal management of many of the disorders that have an MPGN injury pattern remains to be defined. Unless otherwise indicated, the practice points offered below are based upon very low–quality evidence, clinical experience, and expert opinion. Treatment is often influenced and determined by the severity of proteinuria and kidney dysfunction.

Practice Point 8.2.1.1: When the cause of ICGN is determined, the initial approach to treatment should focus on the underlying pathologic process.

After identification of the underlying trigger for ICGN, the most effective therapy is to treat the primary disease process (Figure 68). In addition, all patients with ICGN are likely to benefit from the usual, routine care considered for patients with other active glomerular disease (Chapter 1).

Practice Point 8.2.1.2: Indolent ICGN, whether idiopathic or linked to a primary disease process, is best managed with supportive care and carefully considered use of immunosuppression.

Patients with indolent disease may present late when active inflammation has subsided. Such patients may have a bland urine sediment with a variable degree of proteinuria and elevation in SCr. Such patients should be treated with RASi alone, unless the kidney biopsy shows signs of active inflammation. Patients who present with advanced kidney disease and severe tubulointerstitial fibrosis on kidney biopsy are less likely to benefit from immunosuppressive therapy even if there is still some active inflammation in the kidneys, so assessment of the extent of chronicity on the kidney biopsy may help in deciding whether or not to treat with immunosuppression.

Practice Point 8.2.1.3: For patients with idiopathic ICGN and proteinuria <3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone.

No evidence exists to support a benefit from immunosuppressive therapy in adults. Given that disease progression can occur, regular monitoring of SCr, proteinuria, and the urinalysis is recommended.

Similarly, there are no data available to inform the threshold for starting immunosuppression for the treatment of ICGN (as defined by the new nomenclature) in children who are not experiencing the NS. The authors recognize that in practice, immunosuppression may be initiated at lower levels of urine protein than may be considered in adults, and MMF is more likely to be utilized as a glucocorticoid-sparing option.

Practice Point 8.2.1.4: For patients with idiopathic ICGN, a nephrotic syndrome, and normal or near-normal SCr, try a limited treatment course of glucocorticoids.

Prednisone (or its equivalent) can be initiated at 1 mg/kg/d (maximum dose of 60–80 mg/d) for 12–16 weeks. If the patient responds, prednisone may be gradually tapered to alternate-day therapy over 6–8 months. If there is <30% reduction in proteinuria after 12–16 weeks, we recommend tapering and discontinuation of prednisone.

Patients with a contraindication to glucocorticoids or unwilling to take glucocorticoids can be treated with a CNI. We do not encourage the extended use of glucocorticoids, where a glucocorticoid-sparing option may be available, particularly in children.

Practice Point 8.2.1.5: For patients with idiopathic ICGN, abnormal kidney function (but without crescentic involvements), active urine sediment, with or without nephrotic-range proteinuria, add glucocorticoids and immunosuppressive therapy to supportive care.

Prednisone (or its equivalent) can be initiated at 1 mg/kg/d (maximum dose 60–80 mg/d) for 12–16 weeks. Patients who respond with stabilization or improvement in kidney function or ≥30% reduction in proteinuria are considered to have a satisfactory response to initial therapy. In such patients, gradually taper and discontinue prednisone.

Patients that experience worsening kidney function and/or <30% reduction in proteinuria after 12–16 weeks are considered to have had an unsatisfactory response. In such patients, reduce the dose of prednisone to 20 mg/d and add MMF. If, after 6–12 months of combined therapy, there is no improvement in kidney function, hematuria, or proteinuria, discontinue therapy, and consider a repeat kidney biopsy. If the kidney biopsy continues to show active GN, consider using cyclophosphamide or rituximab.

Initiate daily oral cyclophosphamide (2 mg/kg/d; maximum 200 mg/d in adults) with prednisone (10 mg/d) for 3–6 months. The cyclophosphamide dose should be reduced by 25% in older adults (age >60 years) and adjusted appropriately for abnormal kidney function.

Alternatively, in adults, initiate rituximab at 1 g followed 14 days later by a second dose of 1 g and repeat this 2 g regimen at 6 months.

In patients with persistent disease activity despite at least 6 months of MMF plus low-dose prednisone or after 3–6 months of daily oral cyclophosphamide plus prednisone or rituximab, discontinue glucocorticoids and immunosuppression and continue supportive therapy.

Practice Point 8.2.1.6: For patients presenting with a rapidly progressive crescentic idiopathic ICGN, treat with high-dose glucocorticoids and cyclophosphamide.

Initiate treatment with i.v. methylprednisolone (1–3 g) followed by oral glucocorticoids and oral cyclophosphamide using a regimen similar to that used for patients with ANCA-associated vasculitis (AAV; Chapter 9).

Practice Point 8.2.1.7: For most patients with idiopathic ICGN presenting with an eGFR <30 ml/min per 1.73 m^2, treat with supportive care alone.

Unless kidney biopsy shows an active necrotizing crescentic glomerulonephritis (NCGN) or other reason that could support use of immunosuppression (i.e., minimal interstitial fibrosis or concomitant acute tubulointerstitial nephritis), these patients should be treated conservatively with referral for kidney transplant evaluation in due course.

Practice Point 8.2.1.8: Patients who fail to respond to the treatment approaches discussed in 8.2.1.4 and 8.2.1.5 should be considered for a clinical trial where available.

8.2.2 C3 glomerulopathy

An optimal treatment strategy for C3G using currently available therapeutics has not been established. Expert opinion has encouraged the usual supportive measures (Chapter 1), as well as the use of immunosuppression in the setting of moderate-to-severe disease, defined as moderate-to-marked proliferation on biopsy and proteinuria (>2 g/d).[543] This opinion is based primarily on 4 retrospective cohorts and on an extrapolation of data from other non-related proliferative glomerulonephritides. Well-controlled data are unavailable.

Practice Point 8.2.2.1: In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe disease should be treated initially with MMF plus glucocorticoids, and if this fails, eculizumab should be considered.

Consider treating patients with C3G who have proteinuria >1 g/d and hematuria or have had declining kidney function for at least 6 months.

The reported effectiveness of immunosuppressive treatment in C3G has been variable. Medjeral-Thomas *et al.* reported 32 patients with C3G who received immunosuppressive treatment (glucocorticoids alone or combined with other drugs). Immunosuppression did not seem to reduce progression to kidney failure as compared to no treatment.[544] Similar results were obtained by Servais *et al.* in a cohort of 85 patients with C3G.[537]

More recent data showed encouraging results with MMF. Rabasco *et al.* reported a relative treatment advantage with MMF in a cohort of 60 patients with C3G.[545] In a mean follow-up of 47 months, the 22 patients who received MMF plus glucocorticoids showed lower rates of ESKD (0% vs. 16.6%) and doubling of SCr (0% vs. 39%) as compared to patients exposed to other immunosuppression. In addition, the rates of remission in the MMF group were significantly higher (19 of 22 patients vs. 9 of 18 patients; $P < 0.05$). The response to immunosuppression seen in this retrospective cohort provided the support for the current expert opinion on treatment approach for C3G.[543]

Similarly, Avasare *et al.* reported the kidney outcomes for 30 patients with C3G after MMF.[546] After a mean follow-up of 3 years, two-thirds had an either stabilized or reduced SCr level and reduced proteinuria. Ravindran *et al.* reported the kidney outcomes on a subcohort of 144 patients with C3G.[533] Of 24 patients given MMF (median follow-up 9.6 months), 3 had improved kidney outcome measures, and 4 had stable disease. Fifteen patients worsened. Finally, Bomback *et al.* reported the results of a subcohort of their 111 patients with C3G.[532] Of the 42 patients exposed to MMF, 19 achieved either a complete or partial remission.

The benefits of terminal complement blockade with the anti-C5 monoclonal antibody eculizumab remain unestablished. A trial involved 3 patients with DDD (including 1 kidney transplant recipient) and 3 patients with C3GN (including 2 kidney transplant recipients), all of whom had proteinuria >1 g/d and/or AKI at enrollment. Complement testing identified pathogenic variants in Complement Factor H (CFH) and CD46 in one patient each and C3 nephritic factors in 3 patients. After 12 months of twice-weekly eculizumab, 3 patients had a renal response (decrease in SCr levels and/or proteinuria), and 1 patient with stable laboratory parameters had histopathologic evidence of improvement. Eculizumab normalized soluble C5b-9 level in all patients with elevated levels of this biomarker of terminal pathway activity at baseline, suggesting it may represent a potentially useful marker of response.

In a recent retrospective study, 26 patients with C3G were treated with eculizumab for a median duration of 14 months. Of these, 6 patients (23%) had a global clinical response, 6 (23%) had a partial clinical response, and 14 (54%) had no response. As compared to those with partial response or no response, responders had lower eGFRs, more rapidly progressive disease, and more extracapillary proliferation on kidney biopsy samples. Age, extent of kidney fibrosis, frequency of NS, and features of alternative pathway activation did not differ. These results are consistent with the fact that eculizumab mainly targets glomerular inflammation and has no effect or limited effect on the complement dysregulation that governs C3G.[547]

In the absence of clear evidence, the use of eculizumab can be considered in patients with progressive disease who fail to respond to other therapies.

Practice Point 8.2.2.2: Patients who fail to respond to the treatment approaches discussed in 8.2.2.1 should be considered for a clinical trial where available.

Research recommendations

- Further define the diagnostic criteria for C3G (utilizing biomarkers and histology characteristics) to allow for the separation of C3G from confounding conditions
- RCTs of immunosuppression in patients with fully characterized idiopathic ICGN and C3G without monoclonal gammopathy
- In-depth study of the role of complement in each of the diseases included in this chapter
- Optimize the evaluation of suspected paraprotein-associated C3G
- RCTs of clone-targeted chemotherapy versus immunosuppression for the treatment of paraprotein-associated glomerular disease