

NEPHROLOGY

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Advances in the Etiology and Management of Immune-mediated Glomerulonephritides

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Immune-mediated inflammatory disease of the glomerulus remains a particular challenge for the nephrologist, whether it is limited to the kidney or a part of a multisystem disease. Studies on animal models and the development of new viral detection assays have led to notable advances in our understanding of disease mechanisms in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immune-complex glomerulonephritis. Off-label use of new antiviral agents and oncologically-active drugs have increased the therapeutic options for managing patients with nephritis. This issue of *Nephrology Rounds* focuses on the management of secondary membranoproliferative nephritis, membranous nephritis, and AAV with glomerulonephritis (GN).

Hepatitis virus-mediated glomerulonephritis

Until recently, many patients with pathological diagnoses of membranoproliferative glomerulonephritis (MPGN) or membranous glomerulonephritis (MGN) were considered to have primary or idiopathic disease and were managed with steroids and immunosuppressive therapy. However, many of these patients were discovered to have currently or previously contracted either hepatitis C virus (HCV) or hepatitis B virus (HBV) infection.¹⁻³ In many cases, patients have no overt liver disease and the primary manifestation is a systemic vasculitis (that includes mixed essential cryoglobulinemia or hypocomplementemic urticarial vasculitis syndrome [HUVS]) or renal limited disease.⁴⁻⁶ With the advent of radioimmuno assays (RIA) and polymerase chain reaction (PCR) for viral DNA and RNA, many patients lacking detectable antibodies were confirmed to have circulating virus and, therefore, active infection. Patients may lack antibodies against the virus because they precipitate out of the serum as immune complexes. Viruses induce kidney disease through a mechanism of polyclonal stimulation of B cells, resulting in production of polyclonal antibodies in an unregulated manner and formation of circulating immune complexes. Alternatively, immunoglobulins (Ig) deposit and then complex in or around the glomerular basement membrane (GBM), where viral antigens may become lodged. In HCV disease, in particular, IgM antibodies with anti-IgG (rheumatoid factor) activity develop, promoting immune-complex formation in the circulation. Several studies have retrieved HCV and HBV proteins from diseased glomeruli, thus supporting the idea that at least some of the immune complexes form locally.^{3,6-8} However, current evidence from mouse models and human studies indicate that immune-complexes and their effects on monocyte and neutrophil activation in the kidney, rather than cellular infection by the virus itself, is the cause of kidney disease.^{9,10} Some patients with MPGN or MGN have a lymphoproliferative disorder or frank lymphoma that can be attributed to chronic HCV infection.^{11,12} Patients with HBV infection are more likely to develop an MGN pattern of disease, while those with HCV are more likely to develop an MPGN pattern.^{13,14} All patients lacking antinuclear antibodies (ANAs) presenting with a renal-limited or systemic syndrome and histological evidence of MPGN or MGN should have a full hepatitis serology screen, as well as quantification of viral load by PCR or RIA for viral DNA or RNA in blood (Figure 1).

Given this new information about the etiology of some "idiopathic GN" patients, a recently addressed question has been whether antiviral therapy can alter the course of kidney disease. Effective antiviral therapies are available for the treatment of HBV and HCV. The treatment goal for HBV is seroconversion into an inactive state and reduced viral replication resulting in less severe liver disease. HBV therapies include interferon (IFN)- α , with immunomodulatory effects resulting in seroconversion, and nucleoside or nucleotide analogues that inhibit viral replication.¹⁵⁻¹⁹ Although there are no randomized controlled trials (RCTs), open-label trials and meta-analyses from Asia support the role of IFN- α and the nucleoside analogue, lamivudine, as effective therapies in inducing remission or preventing progression of MGN and MPGN associated with HBV infection.²⁰⁻²² A meta-analysis of controlled studies revealed complete sustained remission of nephrotic syndrome in >60% of patients treated with IFN- α or lamivudine, correlating closely with clearance of HBV e antigen (HBeAg).²¹

The use of IFN- α or the pegylated version of IFN- α (peg-IFN) is limited in patients with creatinine clearance (CrCl) of <30 mL/min. In such patients, only peg-IFN- α_{2a} is approved by the FDA. Experience with peg-IFN- α_{2b} is limited to small research studies and is not FDA approved for either

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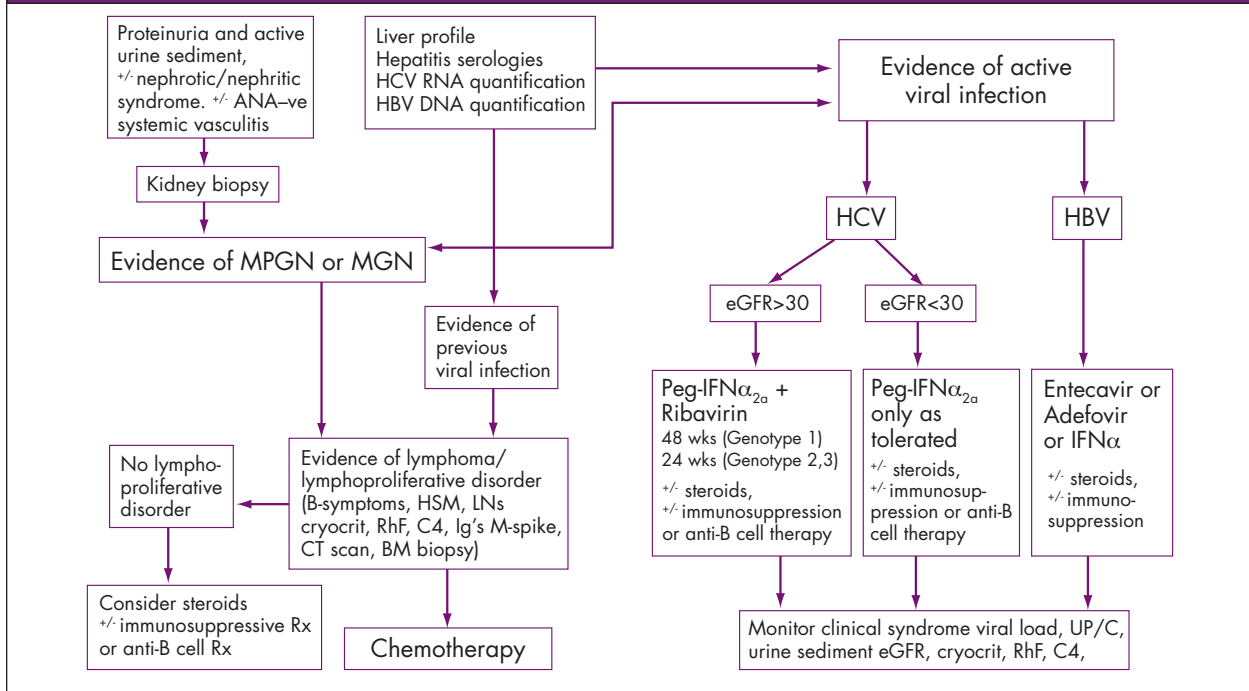
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Figure 1: Algorithm for the management of patients with Hepatitis virus associated Nephritic and Nephrotic syndrome. All patients with antinuclear antibody negative nephritic or nephrotic syndrome should be considered for current or previous hepatitis infection, and be considered for antiviral therapy early in the course of disease.



patients with reduced CrCl or HBV infection with normal renal function. These factors and their frequent side effects limit the use of peg-IFN in the treatment of HBV.

The use of lamivudine is also limited in HBV due to the development of resistance (up to 50% at 4 years).²³ The development of resistance to lamivudine also increases the risk of viral resistance to other antiviral therapies. For this reason, nucleotide analogues like tenofovir and adefovir, and nucleoside analogues like entecavir, are preferred due to a lower incidence of resistance.^{24,25} Although these newer therapies are superior in the management of HBV disease, they have not been shown in controlled studies to affect GN; nevertheless, the clear link between viral clearance and improvement in kidney disease observed in earlier studies has resulted in their acceptance as therapies for GN.

The goal in HBV therapy is to control replication, but the goal in HCV therapy is to eradicate the virus. Therapies directed at HCV are less effective than therapies for HBV. Generally, in patients with HCV and reduced CrCl, peg-IFN α_{2a} alone is considered for treatment as it is the only FDA-approved therapy. Depending on HCV genotype, the duration of therapy varies from 24-48 weeks. A response rate of 15%-25% can be expected, along with a high occurrence of adverse effects. The poor response rate is due to the inability to use ribavirin, which is generally contraindicated in patients with renal insufficiency. A meta-analysis of IFN α therapy in patients with HCV and GN revealed a clear improvement in proteinuria with antiviral therapy, although renal dysfunction was not improved.²⁶ There are case reports of reversal of rapidly progressive glomerulonephritis in patients with HCV-mediated cryoglobulinemic MPGN using combination therapy of peg-IFN α and ribavirin. Single center trials indicate that in patients achieving sustained virological response with this combination, the majority had resolution of cryoglobulinemia and remission of MPGN.²⁷⁻³⁰ These current

antiviral therapies are restricted to patients with glomerular filtration rates (GFRs) of >30 mL/min and they also have significant side effects. Therefore, patients should be identified early in disease evolution and selected for antiviral therapy.

Historically, the mainstay of therapy for patients with idiopathic MPGN or MGN was corticosteroids \pm a chemotherapeutic agent such as cyclophosphamide (CYC) or chlorambucil. Corticosteroids are effective at reducing systemic vasculitis symptoms; however, induction of remission of glomerular diseases with these therapies has been effective in some, but not in others. Chemotherapeutic agents play an important role in reducing plasma cells, B cells, and T cells that drive antibody production and corticosteroids reduce the innate immune response to immune complex deposition. Immunosuppression is associated with worsening of HCV and HBV viral infection in many settings. New humanized antibody therapies with fewer side effects, targeting B cells specifically, have been studied in patients with idiopathic, lymphoproliferative disorder-mediated, and HCV-mediated MPGN. Small single-center studies of HCV-mediated MPGN treated with the anti-B cell therapy, rituximab, report induction of remission in many patients, supporting a role for this new strategy.³¹⁻³³ In addition, these studies reveal no clear evidence of worsening HCV infection.³³ No studies report a role for anti-B-cell therapy in HBV-mediated nephritis, but there are several small studies supporting its role in the treatment of idiopathic MGN³⁴ and other forms of secondary MGN, including those associated with HCV. If patients with HBV are treated with rituximab, they should also receive antiviral therapy to reduce the risk of HBV re-activation and its attendant complications.

Prophylactic therapy with a nucleotide analogue (eg, adefovir) or a nucleoside analogue (eg, entecavir) is recommended in patients with HBV who receive any immunosuppressive therapy. This is generally recommended for patients

with a positive HBV surface antigen (HBsAg) alone, which is suggestive of a chronic infection, or patients with a positive anti-HBs and core antigen (HBcAg), suggestive of previous infection. Both groups are at high risk of reactivation with potent immunosuppressive therapy and stand to benefit from antiviral therapy. There is no role for prophylactic therapy in HCV using either IFN or ribavirin.

The question remains: what is the role of immunosuppressive therapy and/or anti-B cell therapy in the management of patients with hepatitis virus-mediated GN and active virus replication? One strategy is to use immunosuppressive therapy contiguously with antiviral therapy, with a bias toward rituximab because of the reduced risk of worsening HCV infection. This combination therapy would reduce the inflammatory component of disease, while permitting time for antiviral therapy to work. The strategy would also be indicated in patients with HBV and glomerulonephritis to reduce the risk of reactivation. Immunosuppressive therapy with corticosteroids and rituximab is indicated in patients who are ineligible for antiviral therapy or those who have failed antiviral therapy.

Due to the increased risk for developing lymphoproliferative disorders^{35,36} following HBV and particularly HCV infection, it is prudent to consider this diagnosis in all patients with MPGN or MGN who have evidence of previous hepatitis virus infection.

ANCA-associated vasculitis

This group of diseases presents as either renal-limited, rapidly-progressive glomerulonephritis (RPGN); (nephritic syndrome), or as part of a systemic vasculitis. Three patterns of systemic vasculitis are associated with ANCA: Wegener granulomatosis (WG), microscopic polyangiitis, or Churg-Strauss syndrome (CSS). Although the presentation is frequently RPGN, it may present in a more indolent fashion, with mild renal dysfunction and active urine sediment. The severity of proteinuria is frequently mild, but hematuria is almost invariably present. The challenge for the nephrologist is not to miss AAV because early aggressive therapy is very effective in preserving renal function.

Patients with systemic vasculitis frequently have constitutional symptoms, eg, weight loss, fevers, joint pains, and skin rashes. Patients with WG have ear, nose, and throat disease and frequently, lung disease; therefore, they may present with nasal stuffiness, epistaxis, and sinusitis. Patients with CSS frequently have an asthma syndrome with eosinophilia and peripheral nerve involvement (Table 1: cf. supplementary online data). However, renal-limited disease will present with no evidence of systemic disease.

The diagnosis of this complex of diseases requires detection of ANCAs in serum. The autoantibodies are against antigens in the primary granules of neutrophils and lysosomes of monocytes. They are detected by immunofluorescent (IF) serum staining of fixed human neutrophils for specific antibodies against neutrophil cytoplasmic components, at dilutions of <1:20, and also ELISA assay for antibodies against the 2 most common antigens, proteinase-3 (PR3) and myeloperoxidase (MPO). The reason for both IF and ELISA is that neither is very specific and sensitivity is not 100%, however the combination offers improvement (suppl Table 1).^{37,38} A novel ELISA system – Anchor ELISA – is reported to have greater sensitivity/specificity and may replace combined IF and ELISA.³⁹ Furthermore, although the vast majority of ANCAs are against PR3 or MPO antigens, this is not exclusively the case. For example, antibodies against the lysosomal protein LAMP-2 are associated with ANCA-positive pauci-

immune systemic vasculitis⁴⁰ and other ANCAs against elastase, azurocidin, cathepsin G, and lactoferrin are associated with drug-induced vasculitis, HCV-mediated glomerulonephritis, or other autoimmune diseases such as pyoderma gangrenosum.⁴¹ In addition, there are case reports of IgA and IgM ANCAs associated with vasculitis that may be missed on routine screening,^{42,43} although IgA ANCAs are associated with IgA deposition in the kidney.

Several large studies have confirmed that rapid access (<24 hr) to IF and ELISA assays is important in expediting the management of these life-threatening diseases.³⁷ Although these clinical syndromes have ascribed ANCA antigen specificity, large studies indicate that none of the clinical syndromes are exclusively associated with PR3 or MPO antibodies.

A patient with suspected AAV may also require a kidney biopsy, depending on the particular renal circumstances and *a priori* likelihood that there is AAV with kidney involvement. The biopsy characteristically shows a severe inflammatory disease of the glomerulus, characterized by focal and segmental fibrinoid necrosis, extracapillary proliferation, capillary injury, glomerular crescent formation in >40% of glomeruli, and a paucity of Ig deposited in the glomerulus. Ig deposits, predominantly IgM, but also complement components, are believed to represent nonspecific capture of plasma proteins in the diseased glomerular matrix. However, there is evidence from animal models that initial immune-complex deposition in the glomerulus (neutrophil proteins and ANCAs on the endothelial surface) may be a necessary, but transient, component of disease initiation.⁴⁴ Other features of kidney disease may include arteriolar and venular vasculitis, granuloma formation, and varying degrees of tubulointerstitial inflammation and acute tubular necrosis (ATN). Even if the diagnosis is certain from clinical and serological evaluation, a biopsy may provide important information about the anticipated degree of reversibility with immunosuppressive therapy.

A severe complication of AAV is diffuse vasculitis of the lungs, presenting as pulmonary hemorrhage; it may present abruptly or subacutely. It is associated with a significantly higher mortality and all patients should be assessed for pulmonary vasculitis with a focused history and physical and a chest x-ray, possibly followed by a computed tomography (CT) scan or pulmonary function tests. Early treatment for pulmonary hemorrhage may improve outcomes.⁴⁵

Disease mechanisms

Since the discovery of antibodies against neutrophils and monocytes (ANCAs) in the 1980s,⁴⁶⁻⁴⁸ the struggle has been to understand how crescentic glomerulonephritis (CGN) is linked to circulating antibodies, particularly, since part of the pathological definition is a paucity of antibodies in the diseased glomerulus, and neutrophils are not a prominent feature of glomerular disease or the granulomata. Nevertheless, there is abundant evidence of ANCAs binding to neutrophils that have been primed for activation and augmenting or triggering activation (Figure 2: cf. supplementary online data). Neutrophils activated to degranulate will spill cell- and matrix-destructive enzymes and liberate oxygen and nitrogen radicals in and around blood vessels. Poorly controlled release of such mediators can “wreak havoc.” ANCAs are thought to possibly promote activation of neutrophils in small vessels in the presence of another inflammatory stimulus such as an infection, and lead to liberation of inflammatory cytokines. The locally activated neutrophils mediate focal endothelial and capillary basement membrane injury, setting up a secondary inflammatory reaction. *In vitro*

studies indicate that ANCAs bind to the neutrophil surface once the neutrophil is primed by proinflammatory cytokines, which causes redistribution of ANCA antigens to the plasma membrane.⁴⁹ Local immune-complexes form on leukocyte or endothelial surfaces and contribute to cellular activation by FcγR-mediated signaling pathways.⁵⁰ In addition to neutrophils, monocytes and their tissue derivative, the macrophage, also express MPO and other ANCAs. Monocytes and macrophages are prominent inflammatory cells in the crescentic glomeruli of patients with AAV and are implicated as disease mediators in the progression of many models of glomerulonephritis.^{51,52}

Although monocyte activation by ANCAs in this disease group remains less explored, it may be that monocytes and macrophages can become activated in the same way as neutrophils. Despite the findings above, until recently, the role of ANCAs in disease initiation and propagation was unclear. Two mouse models of anti-MPO AAV were developed to help address this question.^{53,54}

In one mouse model, passive transfer of antibodies to normal mice was sufficient to induce crescentic glomerulonephritis (CGN) and vasculitis, confirming the primary role for anti-MPO antibodies in disease initiation.⁵³ However, the same studies indicated that the severity of disease was much more severe if an intact cell-mediated adaptive immunity existed. In humans, the fetus of a pregnant patient with AAV was reported to develop CGN through passive transfer of anti-MPO antibodies across the placental barrier,⁵⁵ seemingly confirming a direct role for ANCAs in disease initiation.

The second mouse model of AAV did not confirm that a simple passive transfer of ANCAs induced disease, rather, a second glomerular injury induced by a subnephritogenic dose of antiglomerular basement antibodies was required to induce CGN with anti-MPO ANCA.⁵⁴ In this second mouse model, disease could also develop in the absence of antibody production, confirming that adaptive cell-mediated immunity against MPO was necessary for disease development.

Human studies point to a TH₁ bias of circulating T cells in AAV patients and evidence for autoimmune CD8⁺ effector T cells exists.⁵⁶ These new insights confirm that circulating antibodies alone can induce vasculitis and CGN in certain circumstances, but suggest that additional local vascular injury is required for disease initiation. The fact that disease can develop in the absence of antibody production in mice confirms a complementary role for cell-mediated immunity in disease initiation, but also in disease propagation. Nevertheless, the central role of antibody production in the pathogenesis of diseases previously thought to be “independent” of humoral responses is reflected in newer approaches to disease therapy. While great advances in the pathogenesis of AAV initiation have been made, there are still many gaps in our knowledge about the mechanisms by which disease propagates.

Although B cells have been primarily thought of as the precursors of plasma cells producing antibodies, recent studies of autoimmunity in the mouse have confirmed that B cells play a pivotal role in early antigen presentation and, therefore, disease initiation.⁵⁷⁻⁵⁹ In elegant studies in the autoimmune mouse model MRL/MRL and MRL/lpr, the absence of B cells completely abrogated the

development of systemic autoimmunity. However, if the B cells are genetically modified to prevent antibody production, systemic autoimmunity progresses at the same tempo, except that autoantibodies are not produced and end-organ damage is by cell-mediated events. These studies suggest that B cells may play a more central role in the development of autoimmune responses than previously thought and that therapies directed at B cells may be highly effective regardless of the relative importance of antibody production in pathogenesis.

Therapies

Over the last 30 years, prednisone and CYC have evolved to become established first-line treatment that may be supplemented by pulsed high-dose methylprednisolone (MP) at initiation of therapy. The CYC may be given intravenously (IV), although there is evidence that oral CYC may be superior in this group of diseases (Figure 3: cf. supplementary online data).⁶⁰⁻⁶³ There are no RCTs, only single-center experiences, often with historical controls.⁶⁴⁻⁶⁶ Nevertheless, nearly all cases of untreated pauci-immune CGN progress to endstage renal disease.⁶³ Similar to studies of lupus nephritis, corticosteroid therapy with prednisone, methylprednisolone, or dexamethasone is the first-line treatment. CYC appears most effective at limiting relapse and may permit more rapid lowering of prednisone doses. Accepted practice a decade ago left the clinician with many uncertainties when making management decisions. Nephrologists have struggled to complete RCTs in patients with glomerulonephritis. Several RCTs completed in patients with AAV and kidney disease were done in collaboration with rheumatologists and have helped guide best practice.

The first study concerned the use of pulsed MP or plasmapheresis (PE) in the induction of remission. Both therapies have associated risks (eg, infection, avascular necrosis, transmission of viruses etc.) European patients (150) presenting with AAV, RPGN, and severe renal impairment (Cr>5) were treated with standard therapy, but randomized to MP × 3 or PE × 7. The patients treated with PE had better outcomes at 1 and 5 years, supporting a role for PE in the management of this patient group.⁶⁷

A second study focused on the withdrawal of CYC and replacement with the steroid-sparing agent, azathioprine (AZA).⁶⁸ Many patients with AAV suffer relapses, and cumulatively, CYC leads to the development of neoplasia and has a high infection risk. European patients in remission at 6 months were either switched to AZA or maintained on CYC. The group using AZA had a similar maintenance of remission with fewer infectious side effects, supporting a role for AZA as maintenance therapy.

In many practices, mycophenolate mofetil (MMF) has superseded AZA as a steroid-sparing antiproliferative agent, but in AAV, there have been no head-to-head trials or studies focusing on the relapse rate in patients maintained on MMF. However, 2 small single-center studies used MMF in place of CYC in conjunction with prednisone and reported remission and relapse rates similar to CYC.^{69,70} This suggests that MMF may be an acceptable, alternative, primary therapy in patients with milder disease; however, further evaluation in RCTs with longer-term follow-up in patients with AAV is required

before MMF can be considered first-line therapy in the management of AAV with CGN.

Another management problem facing the clinician has been whether to preemptively treat patients in remission who have rising ANCA titers. Small cohort studies suggest that rising PR3 titers predicted relapse, but MPO ELISA titers do not correlate as well.⁷¹ With current ELISAs and IF testing for PR3, positive assays and/or rising titers are associated with relapse, but the test is neither highly specific, nor completely sensitive. Nevertheless, in many patients, titers of PR3 can reflect disease activity. Current best practice would not involve preemptive high-dose steroid therapy for patients in remission with rising PR3 titers, rather, closer monitoring of patients for symptoms and signs, with consideration of curtailing any tapering regimen and reinstating small increases in maintenance therapy doses for those with consistently rising titers.

Anti-B cell therapy: The fact that ANCAs are implicated in the pathogenesis of AAV with CGN, and the fact that plasmapheresis (which removes ANCAs) is effective in the induction of remission in patients with severe disease, has led to increased interest in B cell-specific depletion as a therapy in this patient group. Although plasma cells are the B-cell derived cell-type involved in the production of antibodies, intermediate cell types between B and plasma cells also produce some antibodies. Several studies indicate that anti-B cell antibody therapy with rituximab (anti-CD20 humanized antibodies) reduces ANCA titers. However, as described above, in addition to antibody production, B cells in mice have also been shown to play a central role in antigen presentation and, therefore, initiation of autoimmune responses.⁵⁸

Rituximab was developed >10 years ago to treat Hodgkin lymphoma.⁷² The approved indications broadened to include other lymphomas and lymphoproliferative disorders; however, it has also been shown to be effective in autoimmune diseases such as autoimmune hemolytic anemia. Whereas cytotoxic agents and other antibody therapies also target B cells, among other lymphoid cells, one substantial advantage of rituximab over other cytotoxic therapies is its safety profile. Many large studies indicate that rituximab does not lead to increased risks of infection or neoplasia,⁷² and it is generally well-tolerated with relatively minor reactions related to the infusion.

Several small studies have used rituximab in conjunction with steroids as rescue therapy in patients with relapsed AAV with CGN who have either failed CYC therapy or were previously exposed to maximum doses of CYC.⁷³⁻⁷⁵ In these studies, rituximab was highly effective at inducing and maintaining remission. An ongoing, prospective, NIH-sponsored RCT using rituximab as primary therapy in patients with AAV and CGN recently completed recruitment and its outcome is eagerly awaited. Most patients show recovery of peripheral blood B cells counts by 8 months and relapses were closely associated with normalization of B cell levels. Therefore, repeated dosing and monitoring of B cell levels are advised.

Other therapies

Several small studies have investigated the role of therapies targeted against the cytokine, tumor necrosis factor (TNF) α or that specifically target T cells or B cells in patients with severe disease or those who have frequently relapsed on therapy or have failed therapy.

Antibodies or soluble receptor agents blocking TNF α signaling have been partially effective, but with high rates of relapse and serious infectious complications; therefore, although these treatments have gained wide acceptance in the management of rheumatoid arthritis, they cannot be recommended as primary therapies.⁷⁶ CAMPATH-1H antibodies reacting to CD52 on T and B cells have been effective; however, there are concerns that although CAMPATH antibodies are effective, they may result in longer-term immune-compromise and should be reserved for patients with severe disease or pulmonary hemorrhage.⁷⁷

The immunomodulatory therapy, leflunomide, has shown promise in small studies as an alternative to AZA in the maintenance of remission.⁷⁸ Antithymocyte globulin and intravenous immunoglobulin (IVIG) have also been reported to be effective in severe disease or relapse in case reports.

Conclusions

The management of pulmonary hemorrhage in patients with AAV is frequently an emergency or catastrophic situation, where the nephrologist is involved. There are no controlled studies in this patient group but, in addition to supportive measures and standard immunosuppressive therapy, plasmapheresis and pulsed high-dose IV MP are considered acceptable additional therapies, and IVIG and anti-CD52 antibodies have been shown to be effective in case reports.

Note: Supplementary table and figures are available online at www.nephrologyrounds.org.

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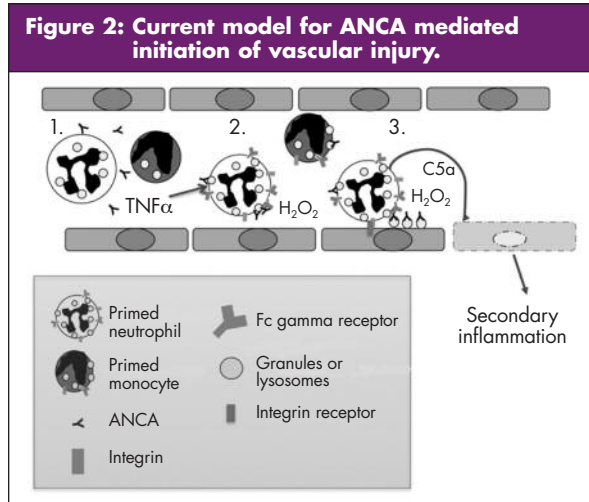
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Table 1: Presentation and frequency of ANCA specificity in the four AAV syndromes				
Disease	Clinical Characteristics	% MPO	% PR3	
Churg Strauss Syndrome	Asthma, eosinophilia, neuropathy, nephritis	30-70	<10	
Wegener granulomatosis	Epistaxis, nephritis, lung lesions	10-30	>70	
Microscopic polyangiitis	Nephritis, alveolar hemorrhage, purpura	30-70	0-30	
Renal limited vasculitis	Nephritis	30-70	0-30	

MPO = myeloperoxidase; PR3 = proteinase 3



1. Quiescent neutrophils and monocytes circulate with ANCA.
2. An inflammatory stimulus such as local TNF α release, primes leukocytes by upregulating cell surface receptors and relocalizing cytotoxic granules to the plasma membrane, exposing autoantigens. In some cases, ANCA binds and couples to the neutrophil surface and may mediate neutrophil activation by Fc γ R mediated signaling.
3. Local release of neutrophil granules leads to local ANCA immune complex formation on the surface of endothelial cells, which further activates neutrophils to release more granules and hydrogen peroxide resulting in endothelial injury. The role of monocytes that also bear ANCA antigens in this process is unclear.

Figure 3: Algorithm for the management of patients with ANCA associated vasculitis with glomerulonephritis. Immunosuppressive therapies should be given in conjunction with standard prophylaxis for PCP infection, fungal infection, osteoporosis, GI ulceration, and urothelial toxicity, and vaccination against pneumococcus and influenza.

