Pulmonary-renal syndromes in the intensive care unit

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Renal disease associated with pulmonary hemorrhage is seen in a variety of clinical disorders (Table 1) and is a common cause of admission to intensive care units. Recent advances in the understanding of the pathogenesis of these disorders have improved the therapeutic options significantly and have favorably influenced the course of many of these disorders. The scope of this article is limited to certain rheumatologic diseases involving both the kidney and lungs, with emphasis on pathogenesis and therapeutic options. Common pulmonary-renal syndromes including anti-glomerular basement membrane (anti-GBM) disease and anti-neutrophil cytoplasmic autoantibodies (ANCA)–associated vasculitis, are discussed.

Anti-GBM disease

In the course of study of the pathologic lesions of influenza, Ernest Goodpasture described the clinical course of a young man who succumbed to pulmonary hemorrhage and acute renal failure following an attack of influenza, in 1919 [1]. The eponym Goodpasture's syndrome introduced by Stanton and Tange [2] is, however, used only for cases of acute pulmonary hemorrhage accompanied by oliguric acute renal failure in which circulating anti-GBM antibodies can be demonstrated. The anti-GBM disease has an estimated incidence of one case per 2 million white persons and accounts for 1% to 5% of all cases primary glomerulonephritis. Approximately 10% to 20% of all cases of crescentic glomer-

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Table 1
Pulmonary-renal syndromes

Glomerulonephritis
Goodpasture's syndrome
Immune complex-mediated glomerulonephritis
Acute silicoproteinosis
Pulmonary-renal involvement in congestive heart failure
Trimatallic anhydride toxicity
Vasculitis syndromes
Wegener's granulomatosis
Microscopic polyangiitis
Churg-Strauss allergic vasculitis
Mixed IgG-IgM cryoglobulinemia
Sarcoid granulomatosis
Collagen vascular diseases
Systemic lupus erythematosus
Systemic sclerosis
Rheumatoid arthritis
Infections
Necrotizing bacterial pneumonitis
Tuberculosis
Lung abscess
Miscellaneous
Pulmonary malignancy–associated glomerulopathy
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Idiopathic pulmonary hemosiderosis

This list includes only disorders in which the lung and kidney are directly involved.

ulonephritis are caused by anti-GBM disease [3,4]. This condition should not be confused with other pulmonary-renal syndromes such as Wegener's granulomatosis, systemic lupus erythematosus, necrotizing vasculitis, and Henoch-Schönlein purpura, because the pathogenesis and therapy are distinctly different in each of these conditions.

Pathogenesis

Lerner, Glassock, and Dixon were the first to demonstrate reproduction of renal and pulmonary lesions in primates, when purified antibodies obtained from kidneys of patients with Goodpasture's syndrome were injected into uni-nephrectomized monkeys [5]. Microscopic examination of the recipient revealed intense staining for human IgG along the GBM, acute renal failure, and pulmonary hemorrhage [5]. More recently it has been demonstrated that the type IV collagen is the most abundant protein in the basement membrane in many organs, including the glomerulus and alveolus. Type IV collagen is composed of at least six genetically distinct chains, designated as $\alpha1$ to $\alpha6$. The $\alpha1$ and $\alpha2$ chains are found in all basement membranes. The $\alpha3$, $\alpha4$, $\alpha5$, and $\alpha6$ chains are much more restricted in distribution. The $\alpha3$ chain is distributed predominantly in the lung,

kidney, seminiferous duct, choroids plexus, optic lens, and the inner ear. Type IV collagen α-chains can be divided into three domains: (1) a noncollagenous N-terminal 7S domain of variable length, (2) a triple-helical domain of approximately 1400 amino acids with a characteristic Gly-X-Y motif, and (3) a C-terminal noncollagenous domain of approximately 230 amino acids. The gene for human α3 type IV collagen is located in the q35-37 region of chromosome 2, and the proteins regulated by this gene replace the α1 (type IV) and α2 (type IV) collagens in the basement membranes during organogenesis [6–9]. Chain mutations of α3 (type IV) collagen results in autosomal recessive Alport's syndrome [10,11], whereas random autoimmune response to native α3 (type IV) NC1-domain collagen results in anti-GBM glomerulonephritis or Goodpasture's syndrome. A genetic susceptibility to human anti-GBM disease has been demonstrated only in studies of twins and to an association with MHC haplotypes mapping to the class II HLA-D region [12]. Anti-GBM disease is more frequently associated with DR alleles than with DQ and DP alleles. Furthermore, this association is more positive with HLA DR15 and HLA DR4 and negative with HLA DR7 and HLA DR1. The latter alleles are dominantly protective [12,13]. The Goodpasture gene (COL4 A5) that has been identified, however, maps to the q36 to q37 site on chromosome 2 [14], whereas the HLA antigen DR2 maps to chromosome 6. This finding may suggest nonstructural peptide processing and presentation to T-cell receptors, facilitating autoantibody formation.

Diagnosis

Demonstration of circulating anti-α3 (type IV) NC1 antibodies (anti-GBM antibodies) in an appropriate clinical setting is the criterion standard for diagnosis [9,15]. A few patients clinically presenting with anti-GBM disease may also have p- or c-ANCA–positive serology. These patients are designated as "double-positive" patients. It is estimated that approximately 20% to 30% of anti-GBM–positive patients may also be positive for p-ANCA or c-ANCA serology. p-ANCA is more frequently associated ($\geq$ 75%) with anti-GBM disease than is c-ANCA. By contrast, however, only 8% to 10% of patients presenting primarily with ANCA diseases (Wegener's granulomatosis) also demonstrate anti-GBM antibodies [16–19]. In either case, serum complement (C3 and C4) levels are usually within the normal range throughout the course of the disease. In double-positive patients the clinical course is more akin to vasculitis than to anti-GBM disease. It my be that in both membranous nephropathy and ANCA vasculitis, renal injury results in an immune response against GBM leading to anti-GBM antibody production. The pathogenic role of such anti-GBM antibodies in the progression of membranous nephropathy and ANCA disease remains to be clarified [16,17,20]. Although renal biopsy is indicated in both anti-GBM and ANCA-related vasculitis, in anti-GBM disease institution of therapy must not await histologic diagnosis. Demonstration of anti-GBM antibodies in an appropriate clinical setting should warrant immediate institution of therapy, especially when accompanied by oliguric renal failure.

Clinical features

General malaise, low-grade fever, weight loss, and arthralgias are frequently reported in anti-GBM disease but are less pronounced than in systemic vasculitis. The degree of anemia is usually out of proportion to pulmonary hemorrhage.

Pulmonary manifestations of Goodpasture's syndrome

Patients most commonly present with hemoptysis that may occur over several months in an episodic manner or as acute and massive hemoptysis leading to respiratory failure. The severity of hemoptysis is variable. It may occur as the sole manifestation, with normal renal function [8,21–23], or glomerulonephritis may occur months later [8]. Chills, chest pain, and fever may accompany episodes of bleeding. Iron deficiency anemia, weakness, cough, and fatigue are common. Alveolar hemorrhage has been reported in association with pulmonary insults such as viral respiratory infections [15,24,25], inhalation of hydrocarbons [26], and exposure to hard metal dust [27] and is also highly correlated with cigarette smoking [28].

Pathologically, acute hemorrhage is seen in the alveolar spaces and small airways, with hemosiderin-laden macrophages (HLM) being a nonspecific indicator of alveolar bleeding. There is interstitial edema as well as lymphocytic infiltrates in alveolar septae and peribronchovascular interstitium. Mild to moderate interstitial fibrosis is usually present. Proteinaceous exudates and hyaline membranes are also seen and may suggest diffuse alveolar damage. Although Goodpasture's syndrome is not commonly considered a vasculitic process, acute neutrophilic infiltrates in alveolar septae with fibrin thrombi characteristic of capillaritis have been described [24,29].

The time course of development and clearance of HLM after alveolar hemorrhage is largely unknown. Animal models of instillation of whole blood into the trachea have detected HLM within 2 to 3 days [30–32], peaking at 7 to 10 days and still demonstrable 60 days later. Macrophages that ingest erythrocytes release iron that is then bound to transferrin, rapidly within the first 24 hours and more slowly in the later phase [33]. In recurrent alveolar bleeding, as in idiopathic pulmonary hemosiderosis, clearance of iron seems to be incomplete, and a significant amount may be sequestered within the pulmonary interstitium [33,34]

Immunofluorescent studies show linear deposits of anti-GBM antibodies in the alveolar wall. These antibodies are typically IgG, but IgA and IgM antibodies have been documented also. The chest radiograph may be normal even in the presence of lung hemorrhage [35]. Bilateral alveolar infiltrates involving the perihilar and lower zones are most commonly seen. Although often bilateral, the infiltrates may appear asymmetric or even unilateral. The upper zones and costophrenic angles are usually spared [36]. Computerized tomography reveals a ground-glass appearance in the areas of hemorrhage. Once bleeding is

controlled, the infiltrates usually resolve over 2 to 3 days, to be replaced by reticulonodular infiltrates along the same distribution. The chest radiograph may become normal within 2 weeks of the bleeding episode [35]. Pulmonary function testing is generally not helpful, with the exception of diffusion capacity of carbon monoxide (D_{CO}), which can be used to determine if new infiltrates indicate pulmonary hemorrhage [37]. Extravascular blood within the air spaces and interstitium take up carbon monoxide and increase D_{CO} [37]; therefore this test has been used to monitor patients for recurrence of alveolar bleeding [38]. Pulmonary function tests after remission may show reduced diffusion capacity and restrictive ventilatory defect.

The role of bronchoscopy in the management of patients with anti-GBM disease is limited. Bronchoalveolar lavage is performed to search for infectious causes of pulmonary hemorrhage or superimposed pulmonary infection. Detection of HLM corroborates alveolar bleeding but is of limited value in differential diagnosis [31]. Transbronchial lung biopsy is rarely indicated.

In patients with Alport's syndrome receiving renal transplantation, circulating anti-GBM antibodies may be detected against host kidney, leading to transplant renal failure. Pulmonary hemorrhage is rare among transplanted Alport's patients, however, because the pulmonary alveolar basement membrane is intact in the transplant recipient.

Renal manifestations of anti-GBM disease

Rapidly progressive acute oliguric renal failure with hematuria and active urinary sediment is the most common manifestation of anti-GBM disease. Urinalysis may show dysmorphic red blood cells and erythrocyte casts. Proteinuria is usually not in the nephrotic range. Serum complement levels (C3, C4, and total complement) are usually within the normal range. In nearly 10% to 20% of patients, renal function as measured by creatinine clearance may be normal at the time of presentation [22,23]

Pathologically, early in the disease, mesangial expansion and hypercellularity may be the sole light microscopic finding. Prominent disruption in the GBM may be seen on electron microscopy at this stage. Soon epithelial crescent formation ensues, with destruction of the GBM. Exudation of growth factors and cellular elements into the Bowman's capsule is thought to play an important pathogenic role in crescent formation. The percentage of glomeruli demonstrating epithelial crescents is variable. Linear binding of IgG on immunofluorescence studies is almost universal in anti-GBM disease [9,29,39]. Linear deposition of IgG in renal biopsies must be interpreted with caution, because a variety of renal diseases, including diabetic nephropathy, may demonstrate linear IgG deposition [40]. In certain cases, both anti-GBM and antibodies against tubular basement membrane (anti-TBM) can be detected. Such lesions are usually accompanied by poly-morphonuclear and macrophage infiltration of the interstitium [41]. The prognostic significance of tubulo-interstitial nephritis associated with anti-GBM

disease merits further evaluation. Deposition of C3 may be detected in nearly 70% of cases but is not of any prognostic significance [41]. Demonstration of epithelial crescents in more than 50% of the glomeruli in the biopsy specimen is considered a poor prognostic sign of renal recovery. Similarly, a serum creatinine level of 7.0 mg/dL or higher at initiation of therapy is also considered a poor prognostic sign of renal recovery.

Ten percent to 20% of patients have been reported to have circulating anti-GBM antibodies but normal renal function as assessed by creatinine clearance. Most such patients tend to have lower titers of circulating anti-GBM antibodies than do patients with renal impairment [68]. Microscopic hematuria, proteinuria, and hypertension are universal findings in such patients, however [22,23].

Predisposing factors to anti-GBM disease

A variety of environmental factors have been implicated as having a pathogenic role in anti-GBM antibody production. Exposure to environmental hydrocarbons has been linked to the development of anti-GBM antibodies [26]. Similarly, development of pulmonary hemorrhage in anti-GBM disease seems to be linked to cigarette smoking, because pulmonary hemorrhage is rare in nonsmokers with anti-GBM disease. Therapy with D-penicillamine in patients with Wilson's disease was reported to be associated with serious pulmonary hemorrhage and rapidly progressive renal failure [42]. Although light microscopy revealed crescentic glomerulonephritis, immunofluorescence did not invariably show linear deposition of IgG in these cases. Idiopathic membranous nephropathy with normal renal function may evolve into acute oliguric renal failure with anti-GBM antibodies but with few pulmonary manifestations [43]. Immunofluorescence of renal biopsy in this situation may not show linear deposition of IgG, because of pre-existing subepithelial deposits of membranous nephropathy. Immunoglobulin G from such tissue injected into living monkeys, however, reproduces classic anti-GBM disease with linear IgG deposits in the primate recipients [43]. Damage and exposure of the basement membrane by preformed immune complexes of membranous nephropathy is postulated to invite autoantibody formation against native basement membrane. Although less common, the converse process (ie, conversion of histologically confirmed Goodpasture's syndrome into membranous glomerulonephritis) has also been reported [44].

Acute crescentic glomerulonephritis associated with anti-GBM antibody has been reported in individuals receiving extracorporeal shockwave lithotripsy for nephrolithiasis [45]. Acute glomerulonephritis develops several weeks to months following shockwave therapy; the cause-and-effect relationship between the clinical entities remains to be established. Nonetheless, all the described patients expressed either HLA DR2 or HLA DR15 specificity. None of the reported cases presented with pulmonary hemorrhage. It is suggested that in all these cases the presence of these alleles predisposes to the development of anti-GBM disease following a precipitating environmental exposure [12,13].

Therapy

Therapy should be initiated without undue delay once diagnosis is suspected and anti-GBM antibodies are demonstrated in patient's serum. Conventional treatment with prednisolone alone is of little value. Pulse methylprednisolone must be combined with cyclophosphamide and plasma exchange [3,9,39,46].

Pulse methylprednisolone should be given intravenously in a dose of 30 mg/kg body weight (not to exceed 3 g in a single dose) on alternate days for three doses. Diuretics should not be given 3 hours before or 24 hours after methylprednisolone administration. Intravenous methylprednisolone should be followed by oral prednisone for 12 months, with rapid taper of the dose to a maintenance dose of 0.0625 mg/kg body weight/day.

Treatment with oral cyclophosphamide should be started at a dosage of 2.0 mg/kg body weight per day. The dose should be reduced by 0.5 mg/kg every 3 months. Cyclophosphamide must be withheld if the white blood cell count is 3500/mm^3 or less or the platelets count is 100,000 mm^3 or less. At least 144-liter plasma exchanges must be performed daily or on alternate days. The plasma should be replaced with 5% human albumin [3,9,39,46].

This regimen has become the standard therapy in anti-GBM disease. In one prospective study, however, pulse methylprednisolone and immunosuppression with cyclophosphamide were compared with a combination of pulse methylprednisolone and immunosuppression with plasma exchange. The outcomes were not significantly different, bringing into question the value of plasma exchange [39]. Nonetheless, a more recent report supports the inclusion of plasma exchange in the treatment of anti-GBM disease [4,47]. Anti-GBM antibodies disappeared more rapidly in patients receiving plasma exchange than in patients receiving immunosuppression alone [3,39,47]. The correlation between decline in serum anti-GBM antibodies following plasma exchange and favorable renal outcome is weak, however [3,39,47]. Further analysis suggests that the number of crescents in the renal biopsy and the baseline serum creatinine level correlated best with the outcomes. Most patients with serum creatinine levels of 6.0 mg/dL or lower responded favorably to therapy. For patients who were dialysis-dependent at the time of diagnosis of anti-GBM disease or who had nearly 100% crescents on renal biopsy at the time of diagnosis, aggressive therapy was, until recently, uniformly unrewarding. Recent protocols employing immunoadsorption in addition to immunosuppression report complete renal recovery even in patients with 100% epithelial crescents on renal biopsy and those who are dialysis-dependent at the time of diagnosis [48,49]. These data suggest a hopeful alternative to conventional therapy in patients with advanced and more aggressive anti-GBM disease.

Many other modalities of therapy have been tried unsuccessfully in Goodpasture's syndrome, including IL-2 receptor antagonists, antibodies to a variety of cell surface adhesion molecules, and immunoregulating proteins such as CTLA4-Ig [50–53]. The possibility that anti-GBM antibodies can be absorbed from the serum using recombinant α_3 (type IV) NC1 domain is an exciting possibility that is awaiting clinical confirmation [54].

In patients who present with a baseline creatinine level of 6.0 mg/dL or higher, who demonstrate 50% or more crescents on renal biopsy, or who are dialysis-dependent at the time of diagnosis, pulmonary hemorrhage is best controlled by supportive care, a short course of steroids, and plasma exchange. Cyclophosphamide has not been shown to ameliorate pulmonary hemorrhage independently. Renal transplantation must await disappearance of circulating serum anti-GBM antibodies.

Careful follow up, with yearly measurements of serum creatinine and anti-GBM antibodies levels, is required in patients successfully treated for anti-GBM disease. Acute elevation of serum anti-GBM antibodies may be a harbinger of recurrent disease. There are 14 reported cases of recurrence of Goodpasture's syndrome after clinical resolution of the disease. In these patients the most common precipitating factor for recurrence of pulmonary hemorrhage was continued cigarette smoking [55–57].

Pulmonary-renal small vessel vasculitis (SVV) syndromes

The Chapel Hill consensus conference for nomenclature of systemic vasculitis [17] that affects the kidneys and lungs is adapted in the following discussion. It is now well recognized that different vasculitides affect various organs preferentially. For example, large vessel vasculitis (ie, giant cell [temporal] arteritis, Takayasu arteritis, polyarteritis nodosa, and Kawasaki disease) does not involve the kidney directly but may cause renal dysfunction indirectly by involving large vessels. In contrast, small vessel vasculitis (ie, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis) typically involves the kidneys and lungs. In Henoch-Schönlein purpura and essential mixed cryoglobulinemia, renal involvement is not accompanied by pulmonary involvement. Furthermore, inflammation in leukocytoclastic vasculitis is limited to cutaneous vessels, without the presence of systemic vasculitis, glomerulonephritis, or pulmonary hemorrhage. This discussion is limited to the pathogenesis, clinical features, and therapy of small vessel vasculitis [16,17,20].

Pathogenesis of anti-ANCA–related vasculitis

The demonstration of ANCA has greatly facilitated the understanding of the pathogenesis of small vessel vasculitis and has provided a tool for monitoring therapeutic efficacy. Most patients with Wegener's granulomatosis, microscopic polyangiitis, or Churg-Strauss syndrome demonstrate either c- or p-ANCA in their blood. The c-ANCA is directed against a serine proteinase called proteinase3 (PR3-ANCA), whereas 90% or more of p-ANCA is directed against perinuclear myeloperoxidase. In Wegener's granulomatosis, the ANCA is predominantly (65%) c-ANCA or PR3-ANCA; a minority of patients (20%) may be p-ANCA– or MPO-ANCA–positive. By contrast, patients with microscopic polyangiitis and

necrotizing glomerulonephritis without SVV are more frequently positive for p-ANCA or MPO-ANCA than for c-ANCA or PR3-ANCA [16,17,20]. The relative distribution of various ANCA in Churg-Strauss syndrome is unclear, because relatively few patients have been studied [16,17,20].

In a few clinical conditions, ANCA may be positive but without either glomerulonephritis or pulmonary disease (Table 2) [4]. In these conditions p-ANCA is directed more towards lactoferrin or elastase than towards myeloperoxidase.

Clinical features

General symptoms

Nearly 90% of patients with SVV present with constitutional symptoms (ie, fever, arthralgias, myalgias, and weight loss preceded by a flulike syndrome). Nearly 25% of patients may present with symptoms of mononeuritis multiplex with sensory and motor involvement. Gastrointestinal ulceration unresponsive to conventional therapy is seen in one third of patients with ANCA-associated SVV. Rupture of aneurysmal dilatation of small mesenteric vessels may present as acute abdomen or peritonitis [16,17]. Admission to the ICU may be required for consequences of pulmonary hemorrhage, septicemia following paranasal sinusitis, uremia from renal failure, or acute abdomen from mesenteric vasculitis.

Pulmonary manifestations

The respiratory tract is involved at least 50% of cases of ANCA-associated SVV. Pathologically, small airways, alveolar capillaries, arterioles, and pulmonary venules demonstrate evidence of necrotizing inflammation with granulomas [16,17]. This pathologic lesion is more common in c-ANCA−positive patients than in p-ANCA−positive patients. Nodular or cavitary lesions are more commonly seen in Wegener's granulomatosis and Churg-Strauss syndrome than in microscopic polyangiitis. These lesions may be tiny, requiring spiral computed tomography (CT) for detection. Pulmonary hemorrhage sometimes occurs in these cavitary lesions, leading to exsanguination. Such pulmonary hemorrhage is an ominous sign of poor prognosis.

Table 2
Antinuclear antibody−positive conditions without renal or pulmonary involvement

Ulcerative colitis
Rheumatoid arthritis
HIV infection
Chronic liver disease
Systemic lupus erythematosus
Schönlein-Henoch purpura
Polymyositis
Sjögren's syndrome

Paranasal sinusitis is seen in nearly one third of patients with Wegener's granulomatosis and microscopic polyangiitis. Paranasal sinus bony erosions by granulomatous infiltration are a common cause of superinfection with *Staphylococcus aureus*. Bleeding from the nasal cavity may mimic hypertensive emergency. Patients with Wegener's granulomatosis may present with hoarseness of voice or strider caused by subglottic inflammation.

Renal manifestations

Renal biopsy usually shows evidence of glomerular capillaritis with granulomas. Clinically, the presentation of ANCA-associated SVV may range from subtle proteinuria-hematuria with normal renal function to explosive acute oliguric renal failure with red cell casts. Some patients present with chronic renal failure with proteinuria-hematuria and red cell casts in urine. Chronic smoldering glomerulonephritis is the usual presentation. The degree of proteinuria-hematuria may vary depending on the disease activity, however. Unfortunately, most patients have advanced renal failure at the time of presentation (creatinine levels $\geq$ 4.0 mg/dL). Some patients may present with intermittent proteinuria-hematuria mimicking IgA nephropathy. On renal biopsy, focal necrotizing glomerulonephritis is the usual presentation. Healing of this lesion leads to focal segmental glomerulosclerosis, with heavy proteinuria and less hematuria [16,17].

Therapy

Remarkable progress has been made in the treatment of Wegener's granulomatosis and other ANCA-positive SVV with the addition of cyclophosphamide to traditional high-dose steroid therapy. Although regimens in different centers vary slightly, induction therapy is usually initiated with intravenous methylprednisolone at 7 mg/kg on 3 consecutive days[. Induction therapy is completed by the administration of prednisone, 1 mg/kg per day for 1 month[. In the second month, prednisone is switched to an alternate-day schedule, and the dose is reduced by 10 mg/week[. Thus, most patients receive 60 mg prednisone or less on alternate days [58].

In some centers, particularly in Europe, plasmapheresis or plasma exchange (twice daily for 7 days) is added to methylprednisolone therapy. Plasmapheresis has been shown to be particularly effective in patients with significant pulmonary hemorrhage and in patients with advanced renal failure [59,69]. Whether plasmapheresis provides additional benefit to that provided by intravenous methylprednisolone alone is the subject of an ongoing randomized, clinical trial in the United States. Nonetheless, in patients with severe pulmonary hemorrhage with attendant mortality rates of approximately 50%, plasmapheresis seems to provide additional benefit and is thus recommended. In a few patients, pulmonary

hemorrhage recrudesces. In such patients, pooled intravenous immunoglobulin may ameliorate persistent pulmonary hemorrhage [60].

Another approach is to use cyclophosphamide either intravenously or orally. Intravenous cyclophosphamide is given in doses of 0.5 mg/kg at monthly intervals[. Oral cyclophosphamide is given at doses of 2 mg/kg per day with vigilant surveillance to prevent leukopenia. In a randomized, controlled trial in France, the intravenous and oral forms of cyclophosphamide administration were equally beneficial [58]. Not surprisingly, the incidence of side effects was higher in the group receiving oral cyclophosphamide, perhaps reflecting the higher cumulative dose of the drug received.

A third approach is to treat ANCA-positive SVV patients with high-dose oral prednisone and oral cyclophosphamide and then switch to oral azathioprine to avoid drug-induced osteoporosis and bone marrow toxicity. Azathioprine is continued for an additional 12 months, and in rare instances, for a longer term[. A recent report attests to the efficacy of anti-CD20 chimeric monoclonal antibody therapy in chronic relapsing c-ANCA–associated Wagener's granulomatosis [61].

It is not yet known how long drug therapy in ANCA-associated SVV should be continued. It seems prudent, however, to continue therapy for at least 6 months[. If the patient is in complete clinical remission, cyclophosphamide therapy may be stopped. Otherwise, therapy should be continued for at least 1 year [66].

Adjuvant therapy

The importance of rigorous control of hypertension in ANCA-associated SVV cannot be overemphasized, because hypertension is an independent risk factor for progression of renal disease. Angiotensin II-converting enzyme blockade is ideally suited as an antihypertensive therapy. Oral supplementation with calcium and vitamin D are essential to prevent corticosteroid-induced osteoporosis. Cyclophosphamide administration is associated with gonadal failure. Concomitant administration of luprolide acetate along with cyclophosphamide seems to reduce gonadal failure. Similarly, administration of testosterone seems to ameliorate cyclophosphamide-induced azoospermia [62]. In patients with Wegener's granulomatosis, long-term oral therapy with cyclophosphamide is associated with increased risk of transitional cell carcinoma of the bladder patients ($\geq$ 15%) [63]. It is not clear, however, that intravenous administration of cyclophosphamide would reduce the incidence of transitional cell carcinoma of the bladder. Trimethoprim-sulfamethoxazole as an adjuvant is effective in preventing relapse of upper respiratory tract manifestations of ANCA-associated SVV [64] but has no effect on the recurrence of renal manifestations.

Response to therapy

Nearly 75% to 80% of patients not requiring dialysis respond to initial therapy that includes cyclophosphamide. The rate of response, however, declines to 50%

or less in patients receiving initial therapy while on dialysis. Nonetheless, it is gratifying t that most patients treated initially while receiving dialysis recover enough renal function to discontinue dialysis for extended periods of time. Patients with c-ANCA seem to respond better to therapy than patients with p-ANCA. Relapse after therapy seems to be more common in patients with c-ANCA than in patients with p-ANCA [58]. The trend towards development of end-stage renal disease is also less in patients with c-ANCA than in patients with p-ANCA [58]. In at least in one report [59], infection and neutropenia following cyclophosphamide administration was the most common cause of death (36%) in the first month of therapy, emphasizing the need for careful monitoring of neutrophil counts and dose adjustments.

Predictive factors for recurrence

The most common factors associated with recurrence of ANCA-associated SVV are c-ANCA positivity, paranasal sinus involvement, and an increase in the serum creatinine level of 1.0 mg/dL or more at the end of treatment. Age, gender, and race are not predictors of recurrence or relapse [58].

Alternative regimens

Therapeutic protocols that include methotrexate were not encouraging and should not be tried [67]. Mycophenolate mofetil (MMF), a relatively new immunosuppressive drug, has shown some efficacy for maintenance of remission. Recrudescence of disease activity has been reported, however, when MMF is discontinued. The efficacy of MMF in SVV is the focus of an ongoing clinical trial. Tumor necrosis factor receptor antagonists are also undergoing clinical trials.

Renal transplantation in systemic vasculitis

Despite improved therapy and better understanding of the natural history of the disease, nearly 66% of patients with SVV will require renal replacement therapy in less than 4 years of initial presentation. It has been more than 2 decades since successful renal transplantation in ANCA-associated SVV was first described. In nearly 18% of transplant recipients, SVV has been reported to recur [65]. There was no difference in the relapse rate between patients maintained with or without cyclosporin A or between those patients with or without measurable ANCA titers at the time of transplantation. The recurrence rate was similar in c- and p-ANCA–positive patients [65]. Response to cyclophosphamide is uniformly encouraging.

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