Wegener Granulomatosis (Granulomatosis with Polyangiitis): Evolving Concepts in Treatment

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ABSTRACT

Wegener granulomatosis (WG), the most common of the pulmonary granulomatous vasculitides, typically involves the upper respiratory tract, lower respiratory tract (bronchi and lung), and kidney, with varying degrees of disseminated vasculitis. The term Granulomatosis with Polyangiitis (Wegener) was recently proposed to replace the older term, WG. The term granulomatosis with polyangiitis can be abbreviated to GPA, with the idea that the eponym Wegener would be omitted over time. Cardinal histologic features include a necrotizing vasculitis involving small vessels, extensive “geographic” necrosis, and granulomatous inflammation. Clinical manifestations of WG are protean; virtually any organ can be involved. The spectrum and severity of the disease are heterogeneous, ranging from indolent disease involving only one site to fulminant, multiorgan vasculitis. The pathogenesis of WG has not been elucidated, but both cellular and humoral components are involved. Circulating antibodies against cytoplasmic components of neutrophils [anti-neutrophil cytoplasmic antibodies (c-ANCAs)] likely play a role in the pathogenesis, and often correlate with activity of the disease. Treatment strategies are evolving. Cyclophosphamide (CYC) plus corticosteroids (CSs) is the mainstay of therapy for generalized, multisystemic WG. Historically, the combination of CYC plus CS was used for a minimum of 12 months, but concern about late toxicities associated with CYC has led to novel treatment approaches. Currently, short-course (3 to 6 months) induction treatment with CYC plus CS, followed by maintenance therapy with less toxic agents (e.g., methotrexate, azathioprine) is recommended. Further, methotrexate combined with CS may be adequate for limited, non-life-threatening WG. Recent studies suggest that rituximab may be useful for induction therapy or CYC-refractory WG. The role of other immunomodulatory agents (including trimethoprim-sulfamethoxazole) is also explored.

KEYWORDS: Wegener granulomatosis, granulomatosis with polyangiitis, granulomatous vasculitis, pulmonary vasculitis, capillaritis, anti-neutrophil cytoplasmic antibodies, geographic necrosis

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WEGENER GRANULOMATOSIS (GRANULOMATOSIS WITH POLYANGIITIS)

Wegener granulomatosis (WG), the most common of the pulmonary granulomatous vasculitides, typically involves the upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea), lower respiratory tract (bronchi and lung), and kidney, with varying degrees of disseminated vasculitis.1–5 In November 2010, the boards of directors of the American College of Rheumatology (ACR), American Society of Nephrology (ASN), and the European League Against Rheumatism (EULAR) recommended a gradual shift from the term WG.6 The term granulomatosis with polyangiitis (Wegener) was proposed to replace WG.6,7 This change was triggered by evidence that Dr. Friedrich Wegener was a member of the Nazi party before and after World War II.7,8 The term granulomatosis with polyangiitis can be abbreviated to GPA, with the idea that the eponym Wegener would be omitted over time.6

Major histological features of WG/GPA include a necrotizing vasculitis involving small vessels (ie, arterioles, venules, and capillaries), extensive “geographic” necrosis, and granulomatous inflammation.2,9–11 Clinical manifestations of WG are protean; virtually any organ can be involved. The spectrum and severity of the disease are heterogeneous, ranging from indolent disease involving only one site to fulminant, multiorgan vasculitis leading to death. Many of the “classical” features of the disease may be lacking early in the course, but may evolve months or even years after initial presentation.1–4 Given the rarity of WG, and nonspecificity of symptoms, the diagnosis is often missed for several months after the initial symptom(s).5 In a previous publication in this journal, we discussed WG in depth.1 In this article, we focus on advances in therapy since that publication.

Epidemiology

The annual incidence of WG has been rising over the decades from <1 per million in the 1970s to current estimates of 4 to 12 cases per million.12,13 Published annual incidence rates (per million) were 4.1 in Spain,14 8.4 to 10.3 in England,14,15 12 in Norway,13 Published prevalence rates (per million) include 23.7 in Paris,16 30 in the United States,17 95.1 in Norway,13 112 in New Zealand,18 160 in southern Sweden.19 WG affects predominantly Caucasians.12,13 The peak incidence is in the fourth through sixth decades of life;2,3,5,17 children or adolescents are rarely affected.1,20,21 There is no gender predominance.4,15

Pediatric Age Group

WG in children is rare,1,20–22 but the incidence may be increasing.23 An epidemiological study in Alberta, Can-ada, from 1994 to 2008 cited an annual incidence of WG in children of 0.93 cases/million from 1994 to 2003 that increased to 6.39 during 2004 to 2008.23 Renal involvement is less common in childhood cases (53 to 79%)20–22 compared with adults (>80%).1–3 Subglottic stenosis was noted in 48%22 and 41%21 of cases of WG in children in two series.

Historical Aspects

In a previous publication in this journal, we discussed historical aspects of WG in detail.1 Excellent reviews of diagnostic criteria for WG and other vasculitides have been published.24,25 Serum antibodies against cytoplasmic components of neutrophils (c-ANCAs), initially described in the 1980s, are present in most patients with WG and often correlate with active disease.1,2,26,27 However, c-ANCAs are not specific for WG,1 and treatment strategies should not be based exclusively on c-ANCAs.1

Clinical Features

UPPER AIRWAY INVOLVEMENT

Upper respiratory tract symptoms occur in more than 90% of patients with WG.1–4,28 Chronic sinusitis, epistaxis, and otitis media are often the dominant clinical features of WG.2,4,28 Sinus computed tomographic (CT) scans are abnormal in over 85% of patients with WG.1,2 Characteristic features include thickening or clouding of the sinuses (75%) and erosion or destruction of sinus bones (25 to 50%).1,2 Magnetic resonance imaging (MRI) scans of the sinuses are less sensitive than CT in detecting bony destruction.1 Air–fluid levels suggest secondary pyogenic infections.2,4

Otologic involvement occurs in 30 to 50% of patients with WG.1,2,4 Otalgia, otitis media, chronic mastoiditis, or hearing loss occurs in 15 to 25% of patients.1–3 Hearing loss may reflect vasculitis of the cochlear artery, chronic otitis media, perforation of the tympanic membrane, or chronic mastoiditis.1,2 Adjunctive surgical procedures (eg, myringotomy tubes) may be helpful in patients with chronic mastoiditis and otitis media.30 Salivary1,31,32 and parotid glands1,33,34 are rarely involved.

The nasopharynx is involved in 60 to 80% of patients with WG.2,3,29,35 Clinical manifestations include epistaxis, nasal septal perforation, nasal congestion or pain, nasal crusting, mucosal ulcers,2,4,30 and saddle nose deformity.2,3,29

Sore throat or hoarseness may reflect ulcers or granulomatous involvement of the pharynx or vocal cords.1,2 “Strawberry gingival hyperplasia” is a rare manifestation of WG.30

A meticulous ears–nose–throat (ENT) exam by an experienced otolaryngologist is warranted in any patient
with suspected WG; suspicious lesions should be biopsied. However, histological confirmation of WG may be difficult. Biopsies of ENT lesions often demonstrate nonspecific findings of necrosis and chronic inflammation. The cardinal histological features of vasculitis or granulomatous inflammation may be lacking. Biopsies of nasal septal perforations are rarely diagnostic. Generous biopsies of involved sites are critical to substantiate the diagnosis. If upper respiratory tract biopsies are nondiagnostic, biopsies of other sites may be required.

WG involving the upper respiratory tract should be treated with cytotoxic agents and corticosteroids (CSs), consistent with WG at other sites. Adjunctive therapy (eg, myringotomy tubes, sinus drainage procedures) may be necessary in some patients.2,29

OCULAR INVOLVEMENT

Ocular involvement occurs in 20 to 50% of patients with WG. Clinical symptoms may result from primary vasculitis of the retinal vessels or from extension of the granulomatous process from the soft tissues or sinuses into the orbit. Conjunctivitis, episcleritis, and scleritis occur in 15 to 20% of patients with WG. Necrotizing keratitis, corneoscleral perforation, posterior uveitis, and optic neuritis are rare but potentially serious complications. Rarely, vasculitis of the posterior ciliary arteries supplying the optic nerves may lead to visual loss. Conjunctivitis or episcleritis often responds to topical corticosteroids; involvement of the deeper ocular structures warrants systemic CS and cytotoxic therapy. Proptosis from a retro-orbital granulomatous inflammatory process develops in 10 to 22% of patients during the course of the disease. Compression or primary involvement of the optic nerve may lead to blindness in 2 to 9% of patients. Granulomatous involvement of the orbit may cause pain, swelling, proptosis, oculomotor palsies, blurred vision, diplopia, and reduction of eye motility. Sinusitis is present in >85% of patients with proptosis due to WG. Nasolacrimal duct obstruction occurs in 25 to 52% of patients with orbital WG. Disease localized to the orbit may be difficult to diagnose because serum ANCA s are often negative. Orbital biopsies in WG demonstrate the cardinal features of necrosis, granulomatous inflammation, and vasculitis in a minority of patients. Adjunctive surgical techniques may be required for mass lesions encroaching the orbit or optic chiasm.

INVOLVEMENT OF TRACHEA AND BRONCHI

Granulomatous involvement of the trachea or major bronchi leads to stenosis in 10 to 30% of patients with WG. Symptoms include dyspnea, wheezing, stridor, and change in voice. Stenosis of large airways may develop years after the initial diagnosis of WG and may develop in the absence of manifestations of WG at other sites. Concomitant involvement of the nasopharynx or sinuses is nearly invariably present. In one series of 43 WG patients with subglottic stenosis (SGS), saddle nose deformity was present in 47%. Tracheal stenosis is usually circumferential and localized, extending 3 to 5 cm below the glottis. However, more extensive involvement of the distal trachea or mainstem bronchi may occur. Flow-volume loops may detect upper airway obstruction but are insensitive. With tracheal (subglottic) stenosis, both inspiratory and expiratory limbs of the flow-volume loop are truncated (flow-rate limitation) (Fig. 1). When stenosis is suspected, flexible fiberoptic bronchoscopy (FFB) should be performed. Circumferential narrowing of the trachea due to scarring is the most common finding; acute inflammation is noted in one quarter of patients with SGS (26%). Histological confirmation of tracheal or endobronchial WG is difficult; biopsies usually demonstrate nonspecific changes (e.g., necrosis or inflammation). Further, serum titers of c-ANCA do not correlate with endobronchial inflammation. Thus, in the appropriate clinical context, the diagnosis of tracheal or endobronchial involvement in patients with known WG must be presumed, even when histology is not definitive. Spiral (helical) CT scans using thin sections and tracheobronchial reconstruction images are useful to

Figure 1 Wegener granulomatosis. Flow-volume loop demonstrating truncation of both inspiratory and expiratory limbs due to a fixed, anatomical narrowing of the proximal trachea (subglottic stenosis) in a 28-year-old male with WG. Cyclophosphamide had been discontinued 4 months earlier after he had been in continuous remission for nearly 18 months. Dyspnea, due to subglottic stenosis, was the initial manifestation of recrudescent WG. Reproduced with kind permission of Mosby, St. Louis. From Lynch and Quint.
assess the extent and severity of tracheobronchial involvement\(^53,55\) (Fig. 2). Importantly, progressive tracheal or bronchial stenosis can develop even when the disease is quiescent at other sites.\(^50–52\)

Severe stenosis of large airways requires urgent and aggressive intervention.\(^52,56\) Life-threatening upper airway obstruction can develop.\(^50,51\) Disease localized to the airways may not respond to medical treatment. In this context, treatment modalities include CO\(_2\) or Nd:YAG laser, dilatation, intratracheal corticosteroid injections, placement of airway stents, laryngeal-tracheal reconstruction, partial tracheal resection, and tracheostomy.\(^2,50–52,56–58\) Silastic stents may provide sustained relief of symptoms in some patients but are associated with numerous complications.\(^51,59\) Tracheal reconstruction may be required in patients with severe tracheal stenosis refractory to medical therapy.\(^50,52\)

**LUNG INVOLVEMENT**

Pulmonary involvement is noted in 55 to 90% of patients with WG.\(^2,3,39,60,61\) Pulmonary manifestations include asymptomatic nodules or infiltrates on chest radiographs or CT scans cough, dyspnea, impaired pulmonary function, bronchostenosis, and diffuse alveolar hemorrhage.\(^2,3,39\) Pulmonary function tests (PFTs) may demonstrate airflow obstruction, restriction, or mixed patterns.\(^1\) Abnormalities on chest radiographs are noted in more than 70% of patients during the course of the disease.\(^1–3,39,62\) Single or multiple nodules or nodular infiltrates are characteristic; cavitation occurs in 20 to 50% (Figs. 3, 4, 5 and 6).\(^1,2,39,62\) Fluffy alveolar or consolidation may reflect granulomatous inflammation (Figs. 7, 8 and 9) or alveolar hemorrhage (Figs. 10 and 11).\(^63–65\) Enlarged intrathoracic lymph nodes are rare (\(\leq 2\%\)) on conventional chest radiographs\(^1\) but are detected by CT in 20% of patients with WG.\(^66\) Chest CT scans typically reveal multiple pulmonary nodules (with or without cavitation); other features of active WG include focal infiltrates, consolidation, or ground-glass opacities (GGOs).\(^52,66\) Additional manifestations of

![Figure 2](image-url)  
**Figure 2** Wegener granulomatosis. Three-dimensional shaded surface display created from helical computed tomographic data shows severe stenosis of the left main-stem bronchus (arrow) in a patient with WG. Reproduced with kind permission of Mosby, St. Louis. From Lynch and Quint.\(^54\)

![Figure 3](image-url)  
**Figure 3** (A) Wegener granulomatosis. Posteroanterior chest radiograph demonstrates focal cavitory nodule in the superior segment of the left lower lobe in a 15-year-old boy with sinusitis, glomerulonephritis, and high-titer anti-neutrophil cytoplasmic antibody. The lesion resolved following treatment with oral cyclophosphamide and prednisone. (B) Wegener granulomatosis. Coronal view of the same patient showing a left lower lobe cavitory lesion.
WG include mass lesions (Figs. 12A, B and C), pleural effusions, stenosis of trachea or bronchi, atelectasis, septal bands, parenchymal scarring, irregular pleural thickening. With treatment, GGOs, cavitating nodules, nodules >3 cm in diameter, or consolidation typically resolves or regresses whereas linear lines persist, reflecting fibrosis.

Because of small sample size, the yield of endobronchial or transbronchial lung biopsies to diagnose WG is low (3 to 18%). Cytologies of bronchoalveolar lavage (BAL) fluid in patients with WG may demonstrate necrotic debris, acute inflammation, multinucleated giant cells, epithelioid cells, and hemosiderin-laden macrophages. Transthoracic core needle biopsy (guided by CT or fluoroscopy) may reveal inflammation or vasculitis, but specificity is suboptimal. With few exceptions, bronchoscopic or percutaneous needle aspiration biopsies are inadequate to substantiate the diagnosis.

Surgical lung biopsy (SLB) is optimal to establish a firm diagnosis of pulmonary WG. When focal pulmonary infiltrates or nodules are present, vasculitis and necrotizing granulomas are found on SLB in more than 90% of patients. A review of 87 SLBs in pulmonary WG cited the following features: vascular
inflammation (acute or chronic) in 94%, parenchymal necrosis (84%), scattered giant cells (79%), areas of geographic necrosis (69%), granulomatous microabscesses with giant cells (69%), neutrophilic microabscesses (65%), poorly formed granulomata (59%), capillaritis (31%), and fibrinoid necrosis (11%).10 Bronchial or bronchiolar abnormalities included nonspecific chronic inflammation (64%), acute inflammation (51%), bronchiolitis obliterans (31%), and follicular bronchiolitis (28%).10 Additional nonspecific features observed in WG include cryptogenic organizing pneumonia (COP),71,72 eosinophilic infiltration,72 chondritis involving bronchial cartilage,73 and interstitial fibrosis.10

Figure 8  Wegener granulomatosis. Posteroanterior chest radiographs from a 70-year-old woman demonstrate extensive airspace consolidation, particularly involving the right lung. Sinus and lung biopsies demonstrated areas of necrosis and granulomatous vasculitis. Although she initially improved with medical therapy, she died 6 weeks later of opportunistic infection.

Figure 9  Photomicrograph of open lung biopsy. Nearly complete obliteration of a blood vessel with granulomatous vasculitis consistent with Wegener granulomatosis. Note the multinucleated giant cell within the vascular lumen.

Figure 10  Alveolar hemorrhage due to Wegener granulomatosis. Posteroanterior chest radiograph from a 13-year-old girl demonstrates extensive, confluent, bilateral alveolar infiltrates. She presented with severe dyspnea, hemoptysis, microscopic hematuria, and proteinuria. Open-lung biopsy demonstrated massive pulmonary hemorrhage and capillaritis but no granulomas. Review of a prior sinus biopsy demonstrated extensive necrosis and inflammatory exudate with occasional multinucleated giant cells but no definite vasculitis. Pulse methylprednisolone, followed by oral prednisone and cyclophosphamide was instituted. Her disease remitted promptly. Reproduced with kind permission of Wolters Kluwer. From Lynch and Raghu.236

Figure 11  Alveolar hemorrhage due to Wegener granulomatosis. Posteroanterior chest radiograph from a 67-year-old man demonstrates extensive, bilateral alveolar infiltrates. Complete recovery was achieved with cyclophosphamide and corticosteroid therapy.
ALVEOLAR HEMORRHAGE
Diffuse alveolar hemorrhage (DAH) due to capillaritis of the pulmonary microvasculature is a rare but potentially fatal complication of WG.\textsuperscript{1,61,65} In this setting, rapidly progressive glomerulonephritis (RPGN) is present in $>$90% of patients.\textsuperscript{64,65} Chest radiographs in DAH demonstrate bilateral alveolar infiltrates; the classic nodular or cavitary lesions of WG are lacking\textsuperscript{64} (Figs. 10 and 11). SLB has no role to diagnose DAH. Typically, SLB in DAH reveals nonspecific features of alveolar hemorrhage and inflammation and necrosis of the alveolar capillaries and walls (termed capillaritis)\textsuperscript{65} (Figs. 13A, B, C and D). Granulomatous vasculitis or extensive parenchymal necrosis is usually not found.\textsuperscript{65} For severe DAH, the risk of SLB outweighs the benefit. A presumptive diagnosis of DAH can often be made on the basis of clinical and radiographic features, circulating c-ANCAs, and bronchoscopy with BAL. Bloody or serosanguinous BAL fluid, large numbers of hemosiderin-laden macrophages, and absence of infectious etiologies support the diagnosis of DAH (Fig. 14). Biopsy of extrapulmonary sites of involvement may substantiate the diagnosis. If microscopic hematuria or renal failure is present, percutaneous renal biopsy may be warranted. Pauci-immune RPGN is characteristic of WG in the context of DAH.\textsuperscript{1} When severe DAH is suspected, we advise prompt treatment with intravenous (IV) “pulse” methylprednisolone (1 g daily for 3 days).\textsuperscript{1,64} Cyclophosphamide (with or without plasmapheresis)\textsuperscript{1,74} is appropriate once a firm diagnosis of WG has been established.

**Figure 12** (A) Wegener granulomatosis. Posteroanterior (PA) chest radiograph demonstrating right upper lobe mass in a 36-year-old woman with leukocytoclastic vasculitis, fever, sinusitis, and cough. Reproduced with kind permission of Wolters Kluwer. From Lynch and Raghu.\textsuperscript{236} (B) Computed tomographic scan from the same patient reveals a mass lesion in the anterior segment of the right upper lobe with areas of focal necrosis (see arrows). Transbronchial lung biopsies demonstrated granulomatosis vasculitis with extensive necrosis and a polymorphous inflammatory cell infiltrate consistent with WG. (C) PA chest radiograph from same patient 5 weeks after initiation of therapy with cyclophosphamide and prednisone showing near complete resolution of right upper lobe mass.
Figure 13  Photomicrograph. Capillaritis and pulmonary hemorrhage in Wegener granulomatosis. (A) Numerous neutrophils hug alveolar capillaries associated with recent alveolar hemorrhage. (B) Early fibrinoid necrosis of alveolar wall associated with capillaritis. (C) Pulmonary hemorrhage with capillaritis. (D) Linear band of degenerating neutrophils from zone of necrotizing capillaritis.
RENAL INVOLVEMENT

Glomerulonephritis (GN) (pauci-immune) occurs in 70 to 85% of WG patients during the course of the disease, but renal insufficiency (serum creatinine > 2.0 mg%) occurs in only 11 to 17% of patients at presentation. Extrarenal manifestations usually precede the renal manifestations, often by several months. Microscopic hematuria, proteinuria, or red cell casts precede elevations in serum creatinine. The characteristic renal lesion of WG is a segmental focal GN. The onset and course of renal involvement are variable. The course may be indolent (progressing over months to years) or fulminant, progressing to end-stage renal failure (ESRF) within days to weeks. Dialysis-dependent ESRF develops in 11 to 32% of patients with WG. Aggressive and prompt institution of therapy with CS and cytotoxic agents is mandatory to avert irreversible renal damage. Even in oliguric renal failure, substantial recovery of renal function can be achieved. However, chronic dialysis-dependent renal failure is more common in patients with severe loss of glomeruli on initial renal biopsy. Renal transplantation may be considered for patients with ESRF provided WG is quiescent. Recurrence of WG has been rare following transplantation.

CENTRAL OR PERIPHERAL NERVOUS SYSTEM INVOLVEMENT

Central or peripheral nervous system involvement occurs in fewer than 4% of WG patients at initial presentation but develops in 10 to 54% during the course of the disease. Patterns of central nervous system (CNS) involvement include (1) primary CNS vasculitis, (2) extension of granulomatous inflammation from contiguous structures (eg, nasopharynx, sinuses, orbit), and (3) granulomatous lesions involving brain or meninges. Mononeuritis multiplex or polynueuritis is most common, accounting for > 50% of neurological manifestations. Cerebral or meningeal involvement occurs in 2 to 8% of patients with WG. Meningeal thickening or enhancing lesions on CT are usually focal, adjacent to nasal, orbital, or sinus disease. Clinical CNS manifestations include cerebral infarction or hemorrhage, cranial nerve palsies, focal deficits or seizures, diabetes insipidus (secondary to granulomatous
involvement of the hypothalamus,\textsuperscript{1,91} pituitary insufficiency,\textsuperscript{92} altered mental status,\textsuperscript{93} cortical atrophy,\textsuperscript{94} chronic headaches,\textsuperscript{94} an visual loss.\textsuperscript{2,87,94} Two series comprising 324\textsuperscript{87} and 85 patients\textsuperscript{39} cited cranial nerve palsies in 6.5\% and 9.4\%, respectively. Mild cognitive impairment has been noted in some patients with WG; in this context, brain MRI scans reveal multiple periventricular or juxtacortical white matter lesions.\textsuperscript{93} Involvement of the spinal cord microvasculature may cause quadriparesis or paraparesis.\textsuperscript{1,87,94,95} Vasculitis of the CNS is rarely confirmed histologically because of inaccessibility or risks associated with biopsies.\textsuperscript{1,94,95} The diagnosis is usually supported by histological confirmation at extraneural sites or by noninvasive studies [e.g., electromyogram (EMG), MRI or CT scans of the brain or spinal cord].\textsuperscript{1,94} Findings on MRI scans include diffuse or focal dural thickening and enhancement, discrete lesions, infarcts, nonspecific white matter areas of high signal intensity, enlarged pituitary gland with infundibular thickening, and cerebral atrophy.\textsuperscript{1,94,95} In some patients, biopsy of the sural nerve or other affected nerves may substantiate the diagnosis.\textsuperscript{87}

**SKIN INVOLVEMENT**

Cutaneous lesions are present in 14 to 50\% of patients during the course of the disease.\textsuperscript{1–3} Manifestations include palpable purpura, subcutaneous nodules, papules, petechiae, ulcers, and nonspecific erythematous or maculopapular rashes.\textsuperscript{1,2,96} Skin biopsies may demonstrate granulomatous vasculitis with necrosis; however, leukocytoclastic vasculitis (LCV) is more common.\textsuperscript{1,2,97} In a series of 46 patients with WG and dermatological manifestations, LCV and chronic inflammation were each noted in 31\% of skin biopsies; granulomatous vasculitis was never observed.\textsuperscript{97} Subcutaneous nodules reflect granulomatous inflammation, whereas petechiae and purpuric or hemorrhagic lesions indicate vasculitis.\textsuperscript{1} Skin changes may parallel the course of the systemic disease and have prognostic significance.\textsuperscript{2,97} LCV often correlates with active, generalized disease, whereas granulomatous inflammation can be found even when the systemic disease is quiescent.\textsuperscript{97} Cutaneous lesions in WG are associated with a higher incidence of articular and renal involvement compared with WG patients without cutaneous involvement.\textsuperscript{1}

**CARDIAC INVOLVEMENT**

Cardiac involvement is rarely documented antemortem, but prevalence rates of 8 to 15\% have been estimated.\textsuperscript{1–3,98} Any portion of the heart may be involved, but coronary arteritis and pericarditis are the most common clinical features.\textsuperscript{1,98} Necrotizing vasculitis or granulomatous inflammation involving the myocardium or coronary arteries may give rise to conduction defects,\textsuperscript{99} fatal arrhythmias,\textsuperscript{100} cardiomyopathies,\textsuperscript{1,2} or coronary arterial aneurysms.\textsuperscript{101} Necrotizing vasculitis affecting cardiac valves has been described.\textsuperscript{1,98}

**INVOLVEMENT OF LARGE VESSELS**

Involvement of large arteries is rare in WG, but anecdot al cases of WG involving the internal carotid artery,\textsuperscript{102} abdominal aorta (with dissection),\textsuperscript{103} or mesenteric arteries\textsuperscript{104} have been published.

**GASTROINTESTINAL INVOLVEMENT**

Gastrointestinal (GI) manifestations were cited in 4 to 10\% of patients with WG.\textsuperscript{2,3,105–107} However, histological confirmation of WG involving the GI tract has rarely been documented antemortem.\textsuperscript{105–108} A review of 59 necropsies in patients with WG cited GI tract involvement in 23 (39\%).\textsuperscript{109} Rarely, GI involvement (e.g., colitis, bleeding) may be the presenting feature of WG.\textsuperscript{107} Rare cases of hepatic\textsuperscript{110,111} or splenic\textsuperscript{112,113} involvement have been cited. Splenic infarcts have been documented at necropsies or on abdominal CT (low attenuation lesions with peripheral enhancement).\textsuperscript{1,113}

**OTHER ORGAN INVOLVEMENT**

Constitutional symptoms (e.g., malaise, fatigue, fever, weight loss) occur in 30 to 80\% of patients with WG and may be the presenting features.\textsuperscript{1,2} Non-deforming polyarthritis involving medium- and large-size joints occurs in two thirds of patients and parallels activity of the systemic disease.\textsuperscript{1,2}

**Histopathology**

The cardinal histopathological features of WG include a necrotizing vasculitis affecting arterioles, venules, and capillaries; granulomatous inflammation; foci of parenchymal necrosis; microabscesses; fibrosis; and acute and chronic inflammation.\textsuperscript{2,9} Irregularly shaped (geographic) necrosis surrounded by granulomatous inflammation is characteristic (Figs. 16A, B). Multinucleated giant cells, epithelioid cells, and collections of histiocytes impart a granulomatous character to the inflammatory process, but well-formed sarcoid-like granulomas are rare in WG.\textsuperscript{2,9} (Fig. 9). Vascular walls are infiltrated (and may be destroyed) by mononuclear cells and neutrophils, with occasional multinucleated giant cells and eosinophils (Figs. 17A, B). Fibrinoid necrosis and thrombosis within vascular lumens are early findings\textsuperscript{9} (Fig. 18). Later, fibrosis of vascular walls may result in stenosis or obliteration of the lumens,\textsuperscript{9} Because granulomas and small vessel vasculitis may be observed with infections (particularly due to mycobacteria or fungi), special stains should be performed in any granulomatous or necrotic lesion to exclude infectious causes.\textsuperscript{9}
Laboratory Features

Anemia, thrombocytosis, or leukocytosis occurs in 30 to 40% of patients with WG. Leukopenia or thrombocytopenia is rare in untreated patients but may develop as a consequence of cytotoxic therapy. Serum complement levels are normal or elevated. Striking increases in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are characteristic of active, generalized disease, and usually correlate with disease activity. However, ESR or CRP can be normal with active disease, particularly when only a single site is involved. Serial determinations of the ESR or CRP are useful to monitor the course of the disease but are nonspecific. Autoantibodies directed against cytoplasmic components of neutrophils (c-ANCAs) are helpful in the initial diagnosis of WG and to monitor response to therapy. Increases in c-ANCA levels were noted in more than 90% of patients with active generalized WG, and in 40 to 70% of patients with active regional disease. Among WG patients with c-ANCAs, >90% are directed against proteinase 3 (PR3); <10% are directed against myeloperoxidase (MPO) or other antigenic epitopes. Changes in c-ANCAs usually correlate with disease activity, and are unaffected by intercurrent infections. However, c-ANCA titers persist in 30 to 40% of patients even after complete clinical remissions were achieved. Further, increases in c-ANCA titers do not necessarily predict relapse. Serial c-ANCA assays provide useful adjunctive information to clinical data, but treatment...
Pathogenesis of WG
The cause of WG is unknown. The presence of granulomas and vasculitis suggests an exaggerated cellular immune or hypersensitivity response, but no identifiable etiologic agent has been identified. The preponderance of disease in the upper and lower respiratory tract suggests that inhaled antigen(s) may initiate the cellular immune response. T cells, monocytes, and neutrophils comprise key cellular elements, suggesting that both cell-mediated and neutrophil-mediated immune mechanisms are operative. Early injury is likely mediated primarily by neutrophils, whereas mononuclear phagocytes and lymphocytes are involved in the late phases of the vasculitic process. Circulating PR3-ANCA are present in 70 to 93% of patients with untreated WG, suggesting a role for these autoantibodies in the pathogenesis and evolution of WG. The role of genes in influencing susceptibility to WG has not been elucidated, but major histocompatibility complex (MHC) alleles or genetic polymorphisms may play contributory roles. The pathogenesis of ANCA-associated vasculitides is reviewed extensively by Drs. Nachman and Henderson in the first article in this issue.

Treatment
Prior to the introduction of effective therapy, mean survival among patients with untreated active WG was less than 6 months; more than 80% of patients died within 3 years of onset of symptoms, usually of progressive renal failure. Corticosteroids ameliorated many of the inflammatory manifestations of WG but were associated with only modest gains in survival (mean survival of only 12.5 months). Seminal studies at the National Institutes of Health (NIH) in the 1970s employing oral cyclophosphamide (CYC) (1 to 2 mg/kg/day) combined with CS (prednisone 1 mg/kg/day, with taper) fundamentally improved the prognosis of WG. Prednisone was gradually tapered and discontinued by 6 to 9 months. Cyclophosphamide was continued for a minimum of 1 year past remission and was then tapered and discontinued. With this regimen, favorable responses were noted in 70 to 95% of patients, with 5-year mortality rates of <15%. Relapses were noted in 30 to 70% of patients following cessation or tapering of therapy, but reinstitution of therapy was usually efficacious. However, sequelae of vasculitis (eg, cerebrovascular accidents, myocardial infarction, renal failure, hypertension) or complications of CYC (eg, opportunistic infections, neoplasms) contributed to late mortality and morbidity. Recognition of treatment-related toxicities and the chronically relapsing nature of the disease led to a search for less toxic therapeutic options. Recent regimens adopt an initial “induction phase” [to assure complete remission (CR)] followed by less intense “maintenance” therapy (to minimize long-term toxicities).

Staging of Disease
Treatment options for WG are stratified according to acuity, extent, site(s), and severity of disease. Severe WG is defined as disease that affects critical organs [eg, kidneys, pulmonary hemorrhage, central nervous system (CNS), etc.] or is life threatening. The current use of the term limited WG implies that there is no immediate threat to the patient’s life or irreversible damage to affected organ(s). Objective criteria are critical to assess disease activity and therapeutic responsiveness. The Birmingham Vasculitis Activity Score (BVAS) is a disease-specific activity index for WG. A modified BVAS was shown to be a valid, disease-specific activity index for WG, with good inter- and intraobserver variability.

Remission-Induction Therapy
We believe that CYC and CS are the preferred induction therapy for severe, generalized WG. IV “pulse” CYC achieves remission rates comparable to daily oral CYC, but has been associated with higher relapse rates. Recently, a multicenter European study randomized 149 patients with newly diagnosed generalized AAV to IV pulse CYC (n = 76) or daily oral CYC (n = 73) (both combined with CS). Time to remission and percent of patients achieving CR were similar between groups. Overall, CRs were achieved in 88.1% receiving IV pulse CYC compared with 87.7% receiving oral CYC. The cumulative dose of CYC was lower among those receiving pulse versus oral therapy (8.2 g vs 15.9 g, p < 0.001). A prospective study by French investigators (WEGENT trial) treated 159 patients with newly diagnosed AAV (WG, n = 32 or MPA, n = 8) and ≥1 unfavorable prognostic factor with IV CYC plus CS as initial induction therapy. Complete remissions were achieved in 126 (79.2%); one stopped therapy (allergy); 32 were refractory (WG, n = 24; MPA, n = 8). Eleven patients died early (median 2.5 months), either of uncontrolled disease, infections, or both. Among patients failing induction therapy with IV CYC, 20 were switched to oral CYC, with favorable responses in 15 (75%) (combined with infliximab in one patient). Hence oral CYC may be effective as rescue therapy for patients failing IV pulse CYC, but additional agents (particularly biologics) may be required. This initial induction regimen (CYC and CS) is continued for 3 to 6 months until complete remissions have been achieved.
achieved. At that point, less toxic agents [e.g., methotrexate (MTX), azathioprine (AZA), or mycophenolate mofetil (MMF)] can be substituted for CYC; this maintenance regimen is continued for a total of 12 to 18 months. Further, for patients with mild or limited WG and preserved renal function, MTX,98,140–142 MMF,143 or leflunamide (LEF)139 can be utilized in place of CYC as induction therapy.1,133 If patients fail to respond to these agents, CYC/CS should be substituted. Alternatively, rituximab (discussed in detail later) can be used in lieu of CYC for induction therapy or for treatment of CYC-refractory cases.2,143,144 Some granulomatous manifestations of WG (e.g., subglottic stenosis, proptosis, sinus or orbital involvement) may require adjunctive therapy via surgical or interventional techniques (e.g., laser). Trimethoprim-sulfamethoxazole (T/S) may have an adjunctive role to reduce relapse rates in WG (generalized or limited).1,146,147 Chronic persistent “grumbling” disease despite CYC/CS may require additional treatment options such as rituximab or infliximab (discussed later).

Specific Therapeutic Agents

CYCLOPHOSPHAMIDE

Cyclophosphamide, an alkylating agent with diverse effects on cellular and humoral immunity,2,129,138 is the initial treatment of choice for generalized WG,1,129,138 However, given its myriad toxicities152 (e.g., bone marrow suppression,153 heightened susceptibility to infections,152 bladder carcinoma,126,128 lymphoproliferative disorders,2,128 and other malignancies,128,154,155 and infertility150,152), less toxic agents are preferred for patients with mild or localized disease.

Intermittent high-dose IV pulse CYC in WG may reduce toxicities compared with daily oral CYC but may be less effective.4,123,124,136,138,156,157 Several studies reported similar remission rates with oral or IV pulse CYC, but relapses were more common with pulse CYC. It is possible that reducing the time between cycles may improve prognosis, but this has not been studied.

METHOTREXATE

Oral or IV MTX, administered once weekly, can be used as (1) induction therapy for patients with mild to moderate (non-life-threatening) WG,1,74,148,149 (2) maintenance therapy for patients who have achieved CRs after initial treatment with CYC,2,129,138 and (3) induction or salvage therapy for patients experiencing adverse effects from CYC.153,161 Acute renal failure, DAH, serum creatinine > 2.0 mg%, and chronic liver disease are contraindications to MTX.141,161 The dose of MTX is 15 to 25 mg once weekly (orally or parenterally); prednisone is administered concomitantly (initial dose 1 mg/kg/day, with gradual taper).153,158,161,162 With this regimen, remissions were achieved in 59 to 88% of cases.3,141,160–163 Late relapses were noted in 36 to 66%, usually after discontinuation of MTX.3,130,141,160–163 In this context, reintroduction of MTX plus CS usually induced remissions.153,158 Five-year mortality rates with MTX were low (3.7 to 14%).1,3,141,160–163 MTX has myriad potential toxicities (heightened susceptibility to infections, stomatitis, GI and hepatitis toxicities), but lacks bladder toxicity and is not oncogenic.150,152 Because the kidneys are the major route of MTX elimination, toxicity is increased in the presence of renal insufficiency.152 The concomitant use of MTX and T/S 160 mg/800 mg twice daily may cause severe pancytopenia.153 However, low-dose T/S (80/400) thrice weekly is safe,1,153 and we use this as prophylaxis against Pneumocystis jirovecii.
AZATHIOPRINE
AZA, a purine analogue with protean immunosuppressive effects, is less effective than CYC and should not be used as primary therapy for WG. However, AZA (1 to 3 mg/kg/day orally) has a role as maintenance therapy in patients who remit with CYC and CS. In a randomized trial by the European Vasculitis Study Group of AAV, AZA was as effective as CYC for maintenance of remissions following induction of CR with CYC/CS. In that study, 155 patients with AAV were treated with daily oral CYC/CS as induction therapy for 3 to 6 months. Ninety-five patients (61%) had WG; 60 (39%) had MPA. Overall, 94% had renal involvement. With this induction regimen, 144 patients (93%) achieved CRs within 6 months. After CRs were achieved, patients were randomly assigned to maintenance therapy with either oral CYC (1.5 mg/kg/day) (n = 73) or AZA (2 mg/kg/day) (n = 71) [both in addition to low-dose prednisolone (10 mg/day)]. After 12 months of therapy, maintenance therapy was changed (in both groups) to AZA (1.5 mg/kg/day) and prednisolone (7.5 mg/day) for an additional 6 months. At 18 months, relapse rates were similar between cohorts (15.5% with AZA; 14% with CYC (p = 0.65). Other outcome measures (eg, Vasculitis Damage Index scores, quality of life, CRP or ESR, rate of adverse effects) were similar with AZA or CYC. Only two patients in each group developed ESRF. Only eight patients died (5% mortality); seven deaths occurred within the first 3 months, during the induction phase with CYC/CS. A subsequent prospective, open-label multicenter trial compared AZA and MTX as maintenance therapy for AAV. In that study, 159 patients with WG or MPA were initially treated with IV pulse CYC plus CS; 126 (79%) achieved CR. These 126 patients were randomized to maintenance therapy with either oral AZA (2 mg/kg/day) (n = 63) or oral MTX (0.3 mg/kg once weekly, maximum dose 25 mg weekly) (n = 63) for 12 months. Outcomes (adverse effects, mortality, relapse rates) were similar with both agents. Relapse rates were similar [36% with AZA; 33% with MTX (p = 0.71)]. Twenty-four months after randomization, relapse-free survival rates were 71.8% in the AZA group and 74.5% in the MTX group. A recent randomized open trial of MMF or AZA as maintenance therapy for AAV cited a higher relapse rate with MMF [(42/76) 55%] compared with AZA [(30/80) 37.5%]. These studies support CYC/CS for initial induction therapy in severe or generalized WG, followed by early switch (within 3 to 6 months) to less toxic agents once CRs have been achieved. AZA has myriad potential toxicities (principally bone marrow suppression, heightened susceptibility to infections, and GI toxicities) but lacks bladder toxicity and has low oncogenic potential. The decision about whether to use MTX or AZA for remission maintenance must be made on an individual patient basis.

MYCOPHENOLATE MOFETIL
MMF, an inhibitor of purine synthesis, has been used both to maintain or to induce remissions in WG. In one study, nine patients with WG were treated with MMF (2 g/day) following induction of remission with CYC/CS. One patient relapsed during the 15-month study period. In a prospective study, 14 patients were treated with daily CYC plus CS to induce CR, followed by MMF as maintenance therapy. Six patients relapsed (43%) at a median of 10 months after achieving CR. In another trial, 12 patients with AAV (seven had WG) were treated with MMF; 10 had failed at least two courses of CYC and/or AZA. All patients improved (by BVAS) at 24- and 52-week time points. MMF was discontinued in three patients; one relapsed. Another patient relapsed while on MMF. Although comparative data are limited, we believe MMF is less effective than AZA or MTX to maintain remissions in AAV.

LEFLUNOMIDE
LEF, an inhibitor of the enzyme dihydroorotate dehydrogenase, was used as maintenance therapy for 20 patients with generalized WG in a phase 2, open-label study. All had remitted with CYC/CS. Overall, disease activity was unchanged during a median follow-up of 1.75 years. A multicenter, prospective, randomized trial compared LEF versus MTX to maintain remissions in WG patients following induction of remissions with CYC. The study was terminated because there were more relapses within 6 months in the MTX group (13 of 28) compared with LEF (six of 26 relapsed). Adverse effects were more frequent in LEF-treated patients. Henes et al treated five patients with refractory WG with rituximab (4 weeks) and maintenance therapy with LEF. CRs were achieved in four patients at 6 months; three patients relapsed, but all remitted with re-treatment with rituximab. In a retrospective analysis, 51 WG patients with “minor relapses” while on maintenance monotherapy with either MTX (n = 36) or LEF (n = 16) were treated with combination therapy with MTX plus LEF. Remissions were achieved in 43 of 51 (84%) with combination therapy, but only 14 achieved sustained remission. Further, MTX + LEF treatment was discontinued in 18 of 51 (36%) patients because of adverse effects. Additional studies are required to determine the role of LEF as therapy for WG.

CHLORAMBUCIL
Chlorambucil, an alkylating agent related to CYC, was used to treat WG in early studies, with anecdotal successes, but is oncogenic and has myriad
T/S may reduce relapse rates in patients with WG, but it is of doubtful value as primary therapy. Non-randomized studies suggested that T/S may have a role in patients with indolent but progressive WG or for limited “initial phase” WG. However, T/S did not induce remissions or reduce relapse rates in patients with generalized WG. Nonetheless, a role for T/S in ameliorating the course of the disease is plausible. In a placebo-controlled, randomized trial, T/S (160/800 mg twice daily) reduced relapse rates in patients with WG who were in remission following treatment with CYC/CS. These data are intriguing, but the impact of T/S on WG remains controversial. The mechanism of action of T/S is not known, but could reflect antimicrobial or immunomodulatory effects. The most important role of T/S may be to prevent pneumonia due to Pneumocystis jirovecii, a complication of immunosuppressive therapy. Thrice weekly T/S (80 mg/400 mg) is highly efficacious and cost-effective.

Treatment of Refractory Disease
Disease unresponsive to conventional therapy can be treated with cytolytic agents, monoclonal antibodies, or other immunosuppressive agents, but data are limited. Anecdotal responses were cited with inhibitors of tumor necrosis factor-α, rituximab (an anti-CD20 chimeric monoclonal antibody directed against B cells), high-dose IV immunoglobulin (IV IgG), alemtuzumab (CAMPATH-1H), (a monoclonal antibody directed against CD52), humanized anti-CD4 antibodies, anti-thymocyte globulin (ATG), deoxyspergualin, etoposide, cyclosporin A, rapamycin, and autologous hematopoietic stem cell transplants, but data are limited to small uncontrolled series and anecdotal cases.

TUMOR NECROSIS FACTOR-α INHIBITORS
Inhibitors of tumor necrosis factor-α (TNFα) have been used to treat WG, but data are limited. Etanercept, comprised of two p75 TNFα receptors coupled to the Fc portion of a monoclonal human IgG1, binds TNFα in a one-to-one fashion. In an early pilot study, 20 WG patients were treated with etanercept (in addition to standard therapy) for 6 months. Remissions were achieved in 16 (80%), but major flares developed in three patients while on etanercept. The Wegener Granulomatosis Etanercept Trial (WGET) randomized 180 patients with WG to either etanercept (25 mg subcutaneously twice weekly) or placebo in addition to standard therapy with CYC or MTX. Patients were followed for a minimum of 12 months. The rate of sustained remissions, number and severity of disease flares, and quality of life (QOL) were similar between etanercept- and placebo-treated groups. Solid organ cancers developed in six patients in the etanercept group but in no control patient. Based on this study, etanercept has no role as therapy for WG.

Conversely, infliximab, a chimeric mouse/human monoclonal antibody that inhibits TNFα, may be effective as therapy for WG. Five clinical trials and anecdotal case reports suggest a possible role for infliximab in refractory WG. Among patients with AAV failing conventional therapy, IV infliximab was associated with favorable responses in 10 of 12. In five of six and five of six patients, respectively. In one open-label trial, 32 patients with AAV (19 with WG; 13 with GPA) received infliximab (5 mg/kg body weight) plus conventional therapy as induction (n = 16) or adjunctive therapy for patients with persistent disease (n = 16). For the first group, infliximab was administered on day 0, 2 weeks, 6 weeks, and 10 weeks and was then stopped. For the group with persistent disease, infliximab was continued every 6 weeks for a total of 12 months. Remissions were achieved in 14 patients (87.5%) in each group. Others cited responses to infliximab in three of four WG patients with CNS involvement refractory to conventional therapy. Josselin et al treated 15 patients with vasculitis (including 10 with WG) with infliximab for a median of 8 months. By day 45, remissions were achieved in all 15 (CR in 11). Although immunosuppressive therapy was continued in all but one patient, 10 patients relapsed, three while receiving infliximab. These various studies suggest that infliximab may have a role to treat selected WG patients refractory to conventional therapy. However, dosages and frequency of dosing were variable in these various series, and the optimal regimen is not known. We are unaware of data assessing adalimumab, another TNF-α inhibitor, as therapy for AAV. TNF-α inhibitors have potential serious toxicities including opportunistic infections, lymphoproliferative and solid malignancies, induction of autoimmune disorders, vasculitis, or interstitial lung diseases.

RITUXIMAB
Rituximab, a chimeric monoclonal antibody that binds CD20 on the surface of B cells and promotes B lymphocyte depletion, has been used to treat AAV, with favorable responses. In early uncontrolled studies of AAV refractory to conventional therapy, favorable responses to rituximab were cited in 11 of 11 patients and 10 of 10 patients, respectively. Rituximab (RITUX) may be less efficacious as therapy for granulomatous manifestations of WG. Aries et al treated...
eight patients with active WG refractory to treatment with CYC/CS plus TNF-α blockade. Rituximab was administered every 4 weeks in combination with CYC (n = 5) or MTX (n = 2). All manifested granulomatous features [retroorbital granulomas (n = 5), bronchostenosis (n = 2), pulmonary nodules (n = 1)]. Despite depletion of B lymphocytes, only three patients remitted (two complete). Consistent with previous observations, “granulomatous” manifestations regressed more slowly than constitutional or “vasculitic” symptoms. In another study of refractory/relapsing WG, RITUX combined with CS and immunosuppressants induced remissions in six of eight patients; one relapsed 1 year after stopping RITUX and responded to a second cycle. In a retrospective study, 34 patients were treated with RITUX for refractory WG affecting ears, nose, throat, or eye. CRs were achieved in 21 (62%); partial remissions (PRs) in nine (26%); no response in four (12%). In a retrospective study, 10 patients with ophthalmic WG refractory to conventional therapy were treated with RITUX. All patients had failed at least three different immunosuppressive agents; five had failed anti-TNF therapy. All 10 improved with RITUX. Rituximab was efficacious in a WG patient with necrotizing scleritis. Investigators in the United Kingdom (UK) retrospectively assessed 65 patients with refractory AAV treated with RITUX. Dosing regimens included four infusions of 375 mg/m² body surface area each week, or two infusions of 1 g each 2 weeks apart. CRs were achieved in 49 (75%), PRs in 15 (23%). Immunosuppressive medications were withdrawn in 62% of patients. Among 49 patients experiencing CR, 28 relapsed (57%). B cell return preceded relapse in 14 of 27 patients (52%). ANCA levels fell following RITUX, but relapse was not associated with rise in ANCA levels. Re-treatment of relapses was usually effective. A recent open-label randomized trial by the European Vasculitis Study Group (RITUXIVAS trial) compared RITUX versus IV pulse CYC as induction therapy for AAV. Forty-four patients with newly diagnosed AAV and renal involvement were randomized in a 3:1 ratio to RITUX (n = 33) or CYC (n = 11). Rituximab was administered at a dose of 375 mg/m² weekly for 4 weeks. In the RITUX group, patients received CS and two pulses of IV CYC. These patients did not receive AZA to maintain remission. Patients in the control group received IV CYC for 3 to 6 months, followed by AZA. Corticosteroid regimens and cumulative dosages did not differ between the two groups. Remission rates were similar. Sustained remissions were achieved in 25 of 33 (76%) patients in the RITUX group and nine of 11 (82%) controls (p = 0.68). Median time to remission was 90 days in the RITUX group and 94 days in the control group (p = 0.87). Serious adverse effects occurred in 14 patients receiving RITUX group (42%) and four controls (36%) (p = 0.77). Six of 33 patients in the RITUX group died (18%) as did two of 11 (18%) in the control group (p = 1.00). A multicenter, double-blind study (RAVE trial) randomized 197 patients with AAV to either RITUX (375 mg/m² weekly for 4 weeks) (n = 99) or oral CYC (2 mg/kg/day) (n = 98) for remission induction. The primary end point was remission of disease without the use of prednisone at 6 months. In the RITUX group, 63 of 99 (64%) met the primary end point compared with 52 of 98 (53%) in the control group (differences between groups were not significant). However, among AAV patients with relapsing disease, RITUX was more effective than CYC; the primary end point was achieved in 34 of 51 (67%) patients receiving RITUX and in only 21 of 50 (42%) in the control group (p = 0.01). Among patients with WG, 46 of 73 (63%) assigned to RITUX and 37 of 74 (50%) assigned to CYC reached the primary end point (p = 0.11). Among patients with microscopic polyangiitis, 16 of 24 (67%) in the RITUX group and 15 of 24 (62%) in the control group reached the primary end point (p = 0.76). Among the subset of patients with major renal disease or alveolar hemorrhage, RITUX was as effective as CYC. These various studies suggest an important role of RITUX as therapy for WG and other AAVs. However, whether RITUX should be used with CS alone or CS combined with IV CYC has not been clarified. The role for long-term maintenance therapy has not been studied. Further, the potential for serious complications with RITUX (eg, progressive multifocal progressive encephalopathy, infections, malignancies) is a concern. Additional studies are required to assess indications for RITUX, appropriate dosing and frequency of administration, role for concomitant therapy, and long-term side effects. Nonetheless, we believe RITUX has an important role for treating relapsing WG or AAV, and may be considered as first-line therapy for initial treatment of WG or AAV.

HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN

Intravenous immune globulin (IVIG) exhibits myriad immunomodulatory effects, including regulating T cell function, blockade of Fc receptors, preventing binding of activated complement components C3b and C4b, modulating cytokine production, neutralizing autoantibodies (including ANCA). High-dose IVIG (0.5 mg/kg/day for 4 days) was shown to be efficacious in diverse autoimmune and inflammatory disorders and may have a role to treat AAV refractory to or intolerant of conventional therapy. In several studies, favorable responses were noted with IVIG (alone or combined with CS and/or immunosuppressive agents) in 45 to 77% of patients with AAV. In one placebo-controlled trial, patients with relapsing AAV were treated with a single course of IVIG. Favorable responses were noted in 14 of 17 (82%) receiving IVIG and six of 17 (35%) receiving placebo. In another study, 22 patients with relapsing AAV (19 had WG) were treated with IVIG monthly for
6 months;\textsuperscript{228} All received concomitant CS; immunosuppression was maintained at existing levels or reduced. After 9 months, 17 patients (77\%) had achieved CR. Side effects of IVIG were mild and transient. These studies suggest that IVIG may have a role in selected patients with AAV refractory to conventional therapy, but trials comparing IVIG with other salvage therapies have not been done.

\textbf{ANTITHYMOCYTE GLOBULIN}

ATG has been used to treat WG refractory to other agents. In one study, three of four patients with severe orbital WG responded to rabbit ATG (two partial; one complete).\textsuperscript{187} In an open-label study, 15 patients with refractory WG were treated with ATG.\textsuperscript{229} Prior to receipt of ATG, patients had received a mean of 5.2 different therapies without control of disease. Favorable responses to ATG were cited in 13 (87\%) (partial in nine; complete in four); relapses occurred in 47\%.\textsuperscript{229}

\textbf{DEOXYSPERGUALIN}

Deoxyspergualin, a synthetic immunomodulatory agent with effects on lymphocytes, macrophages, and neutrophils, has been associated with clinical responses in open-label studies in patients with relapsing WG.\textsuperscript{188–190,230} In a prospective, open-label, multicenter European trial, 44 patients with relapsing or refractory WG and previous therapy with CYC or MTX were treated with subcutaneous (SC) deoxyspergualin.\textsuperscript{190} Deoxyspergualin (0.5 mg/kg/day) was self-administered SC for up to 21 days each cycle, with a minimum drug-free period of 7 days between cycles for a total of 6 cycles. After completion of 6 cycles, AZA (plus CS) was substituted as maintenance therapy. Remissions were achieved in 42 of 44 patients (95\%); 20 (45\%) were CR. Relapses occurred in 18 patients (43\%). Two relapses occurred during treatment with deoxyspergualin; the other relapses occurred in the 6-month period when patients were receiving maintenance therapy with AZA or MMF. Two patients died. Adverse effects were noted in 53\%. Another open-label prospective study of deoxyspergualin in 44 patients with crescentic GN (including AAV) cited improvements in proteinuria and hematuria after 4 weeks.\textsuperscript{231} In a murine model of AAV, deoxyspergualin was equivalent to CYC, and superior to MMF, in attenuating nephritis.\textsuperscript{232} Additional randomized trials are required to assess the role (if any) of deoxyspergualin to treat WG.

\textbf{WG IN THE ELDERLY}

WG in the elderly (age \( \geq 65 \) years) is associated with an increased mortality rate\textsuperscript{136,233} and more frequent complications of therapy.\textsuperscript{233} Because of the heightened susceptibility to opportunistic infections in elderly patients,\textsuperscript{233} less aggressive immunosuppressive therapy is warranted in this age group.\textsuperscript{234} Further, initial induction therapy with agents less toxic than CYC (such as MTX) can be considered in patients with localized or less severe disease.\textsuperscript{1}

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