Clinical Manifestations and Treatment of Wegener's Granulomatosis

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KEYWORDS

• ANCA-associated vasculitis • Wegener's granulomatosis
• Clinical manifestations • Treatment

Wegener's granulomatosis (WG) is a rare autoimmune disorder of unknown etiology that is characterized by granulomatous inflammation and antineutrophil cytoplasmic antibodies (ANCA)-associated small-vessel vasculitis (AAV).[1,2] WG has a broad clinical spectrum that ranges from predominantly granulomatous manifestations restricted to the respiratory tract (localized disease) to severe, life-threatening necrotizing vasculitis affecting many organs, with a predilection for lung and kidney involvement (alveolar hemorrhage and crescentic glomerulonephritis). In WG, ANCA are mainly directed against Proteinase 3 (PR3); there is strong evidence from in vitro studies that ANCA play a crucial role in the mediation of small-vessel vasculitis.[3,4] It has been hypothesized that WG starts as localized disease of the respiratory tract with granulomatous inflammation that later generalizes into small-vessel vasculitis.[5,6] This concept has been endorsed by the EULAR (European League Against Rheumatism)/EUVAS (European Vasculitis Study Group) definition of disease stages[7] to facilitate consistent conduct of clinical trials and to provide evidence-based guidelines for stage-adapted therapy regimens.[8] As a result of EUVAS and other trials, recommendations for therapy for AAV have been published recently,[8] but new data are constantly available, providing evidence for the use of new therapies to reduce treatment toxicity and improve patients' outcome.

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CLINICAL MANIFESTATIONS
Classification Criteria, Epidemiology, Disease Stages, and Outcome

Incidence rates of 6 to 12 per million per year are reported for the United Kingdom, Germany, and Norway,[9–11] which have been confirmed at stable rates for the United Kingdom and Germany. Lower rates have been found in Southern Europe, such as in Spain (2.95/million/year).[12] In a recent United Kingdom study, the annual prevalence was reported to have increased from 28.8 per million in 1990 to 64.8 per million in 2005,[9] suggesting that survival is increasing due to improved therapy and care. WG is even more common in southern Sweden, with a point prevalence on January 1, 2003 of 160 per million.[13] Additional detailed data on the incidence and prevalence of WG are provided in the article by Holle and colleagues elsewhere in this issue.

Of interest is that a Japanese study reported an overall incidence of ANCA-associated renal vasculitis similar to that in Europe, but all patients were classified as microscopic polyangiitis (MPA); no cases of renal WG and Churg-Strauss syndrome were detected.[14] Nevertheless, there is evidence of WG occurring in Japan as described by Japanese ear/nose/throat (ENT) units.[15] Thus, Japanese patients may show a special phenotype of WG that does not progress to generalized renal vasculitis. Whether this phenotype corresponds to the definition of localized disease remains to be clarified.

According to a concept proposed by Fienberg,[5] WG starts as granulomatous disease and subsequently progresses to generalized vasculitis; this concept has been incorporated in the definition of disease stages introduced in 1995,[16] which has been updated several times. In the current definitions[7] (**Table 1**), the localized stage, defined as manifestations restricted to the upper and/or lower respiratory tract with no signs of systemic vasculitis, is differentiated from the systemic disease stages (early systemic, generalized, and severe disease). The early systemic stage is considered nonlife threatening, whereas in generalized disease organ function is at risk of compromise. In the severe disease stage, organ failure has already occurred (creatinine >500 μmol/L or approximately 5.7 mg/dL). Definitions of activity stages have also been updated lately and are intended to facilitate the conduct of clinical trials, and are very useful for treatment decisions in everyday practice.[7] Controlled trials initiated by the EUVAS have been performed for remission induction and maintenance for several disease stages in AAV and provide valuable evidence for stage-adapted therapy, and may also have an impact on the outcome of AAV.

Older age (>50 years), kidney involvement (with impaired renal function), pulmonary manifestations at diagnosis, and absence of ENT involvement are associated with an adverse outcome and increased mortality.[17–19] Whereas several studies published in the 1990s showed an increased mortality in WG patients compared with the general population with standardized mortality ratios (SMR) of 3.7 to 4.8,[20–23] a decrease in the SMR at 5 years' disease duration was reported from a recent Swedish population-based cohort of WG and MPA diagnosed before 1996 and after 1996 (from 2.5 to 1.6, respectively).[24] In addition, in a recent study assessing a population of patients with various vasculitides with disease onset in the 1990s, no increased SMR was reported for women younger than 60 years.[25]

The rate of end-stage renal disease (ESRD) varies among cohort studies, ranging from 23% of patients at 15 months to 23% at 10 years.[26] A decline in the rate of end-stage renal failures was reported[24] in a recent study, which may contribute to a reduction of mortality.

Shorter periods of remission induction and the increasing use of intravenous instead of oral cyclophosphamide (Cyc) or alternative treatments may account for a reduction

Table 1
Definition of disease stages in AAV according to EULAR

Clinical Subgroup	Systemic Vasculitis Outside ENT and Lung	Threatened Vital Organ Function	Other Definitions	Serum Creatinine (μmol/L)
Localized	No	No	no B-symptoms ANCA typically neg	<120
Early systemic	Yes	No	B-symptoms ANCA neg or pos	<120
Generalized	Yes	Yes	ANCA pos	<500
Severe	Yes	Organ failure	ANCA pos	>500
Refractory	Yes	Yes	Refractory to standard therapy	Any

Abbreviations: neg, negative; pos, positive.

Adapted from Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small-vessel vasculitis. Ann Rheum Dis 2009;68:310–7; with permission.

in the cumulative Cyc dose as reported by Eriksson and colleagues[24] and to a reduction of Cyc-related side effects such as infections and malignancy. Using the current definition of remission,[7] this stage is achieved by 90% to 94% of patients, which highlights the efficacy of standard therapy for the induction of remission. Time to remission is usually less than 6 months,[26] but relapse is frequent (18%–40% at 24 months in WG) and remains a major issue: Eriksson and colleagues[24] found no decline in relapse rates in patients diagnosed before 1996 compared with after 1996.

Yet, an increased awareness of AAV may be a factor for improved survival, as a significant shortening of the interval from first symptoms to diagnosis was reported by recent studies.[24,27]

Localized Disease Manifestations/Upper and Lower Respiratory Tract Involvement

Upper respiratory tract involvement affecting the nasal and oral cavity, sinuses, trachea, and bronchi is reported to occur in 75% to 93% of patients at diagnosis[17,28] and in up to 99% of patients during the course of the disease.[17] Rhinosinusitis is the typical manifestation of WG leading to nasal bloody discharge, crusting, and epistaxis. Nasal crusting ("golden crusts") is a typical finding of endoscopic evaluation (**Fig. 1**), although it is not specific for WG. A standardized assessment to rate endonasal activity does not yet exist but is under investigation. Granulomatous inflammation/masses may also be found in the nasal cavity and sinuses, and may lead to bone erosion and cartilage destruction causing saddle nose deformity, which is reported in up to 28% of patients (**Fig. 2**).[17] Conductive hearing loss may be caused by direct involvement of the middle ear mucosa, or by dysfunction of the Eustachian tube due to mucosal involvement of the nasopharynx. The most dreaded granulomatous manifestation in localized disease is orbital granuloma/masses (seen in up to 15% of cases[29]). Orbital granuloma/masses may develop from inflammatory tissue invading from the sinuses, or may develop as a retroorbital mass in isolation. Orbital granuloma/masses are associated with severe complications such as infiltration or entrapment of ocular muscles and impairment of ocular motility, as well as optic nerve compression and atrophy with subsequent blindness. Orbital granuloma/masses are usually unilateral (>80%), but may affect both orbits in up to 14% of patients.[30] Some patients develop orbital

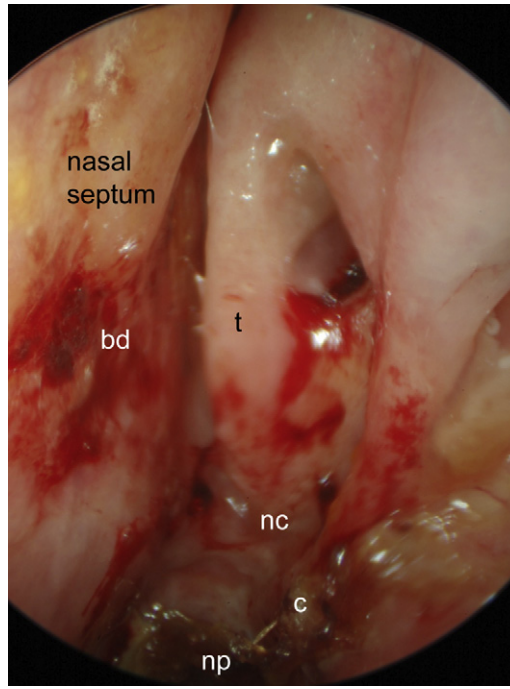

Fig. 1. Endoscopic view of the left nasal cavity (nc) of a WG patient demonstrating crusts (c) and bloody discharge (bd). np, nasopharynx; t, turbinate.

socket contracture, probably as a result of scar formation or fibrosis following immunosuppressive therapy.[31] Orbitonasal fistulas may also develop. Oral manifestations are rare and occur as ulcerative stomatitis (up to 10%[29]) or hyperplastic gingivitis; subglottic stenosis is the typical laryngeal involvement (12%–15%)[17,29]; and stenosis of smaller bronchi and mucosal ulcers of the tracheobronchial tree may also occur.

The overall incidence of pulmonary involvement is between 60% and 85%. The characteristic manifestations are granulomatous masses, alveolitis, and capillaritis, leading to diffuse alveolar hemorrhage (DAH). Pulmonary nodules and/or granuloma have been described on conventional radiography in around 60% of patients.[29] Alveolitis is related to diffuse or interstitial infiltrates. Active disease is associated with an increased neutrophil count in the bronchoalveolar lavage fluid (BAL fluid)[29,32] and diffuse infiltrates; an elevation of CD4+ T lymphocytes may also be found, mainly in conjunction with interstitial infiltrate.[32] DAH has been reported to occur in 7% to 45% of WG patients. Typically, hemoptysis and dyspnea are common symptoms, however, a significant proportion of patients have no history of hemoptysis. Chest radiographs usually reveal bilateral alveolar shadowing (**Fig. 3**); a ground-glass pattern is typically seen on computed tomography (CT). DAH can be confirmed by fiberoptic bronchoscopy, which shows diffuse bleeding arising from the pulmonary parenchyma with increasingly bloody lavage fluid and hemosiderin-laden macrophages. Bleeding may be severe, leading to hypovolemic shock and respiratory insufficiency. Mortality of DAH is estimated at 60%.[33,34]

In general, high-resolution CT (HRCT) may be a useful adjunctive diagnostic procedure to follow pulmonary manifestations. Cavitating nodules/masses with a diameter

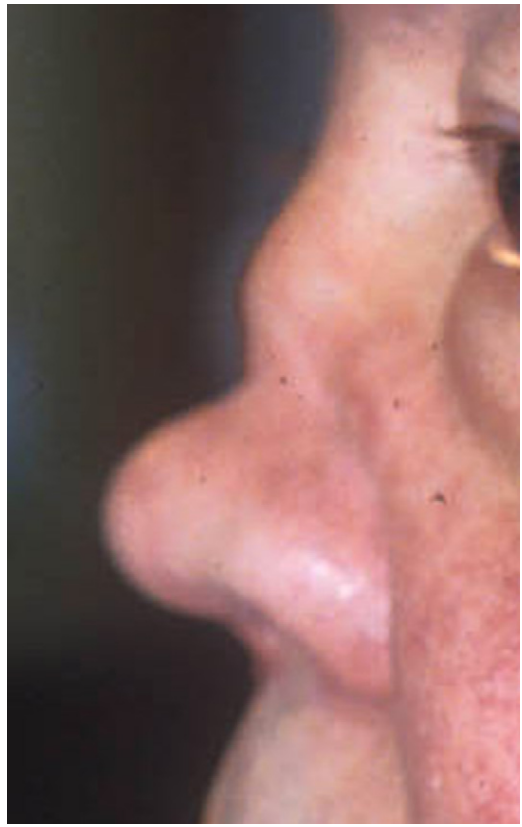

Fig. 2. Saddle nose deformity.

of greater than 3 cm on HRCT and parenchymal opacification are considered active lesions.[35,36]

Kidney Involvement

Glomerulonephritis is reported in 38% to 70% of patients[17,28,29,37] and is the hallmark of generalized disease (**Fig. 4**). Initial renal function may predict renal survival.[22] Approximately 10% to 20% of patients[17,22,29,37] develop end-stage renal failure requiring hemodialysis despite immunosuppressive therapy. Renal involvement/impairment is associated with poorer survival.[26] Diagnosis of renal involvement should be confirmed by biopsy, which usually reveals focal necrotizing glomerulonephritis with both intra- and extracapillary deposits.

Other Organ Manifestations

Most patients suffer from constitutional symptoms such as fever (23%–30% at presentation, 50% during disease course),[29,37] weight loss of more than 10% (50% during disease course),[29] and fatigue (61% at presentation)[37] when presenting with early systemic or generalized disease. Furthermore, musculoskeletal symptoms (arthralgia, arthritis, myalgia; 20%–60% at first presentation, up to 77% during disease course)[17,22,29,37] and ocular manifestations (52%–61%) are frequent complaints.[17,29]

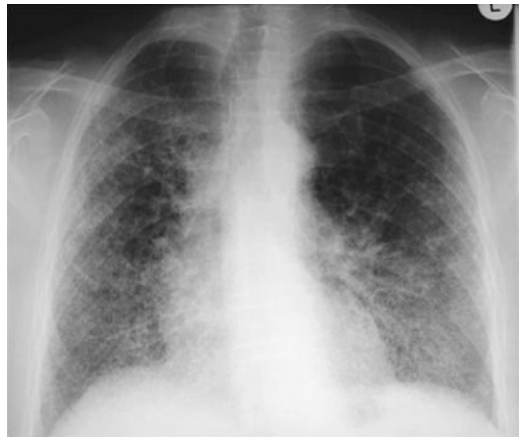

Fig. 3. Chest radiograph of a patient with diffuse alveolar hemorrhage.

Eye involvement manifests predominantly as (epi-)scleritis and conjunctivitis. Dacryocystitis and orbital granuloma may also develop (see above). Peripheral nervous system involvement occurs in 15% to 40% of patients,[17,29] usually as mononeuritis multiplex or sensorimotor polyneuropathy. In a prospective study on patients with generalized WG and standardized neurologic evaluations, most patients (83%) developed peripheral neuropathy within the first 2 years of the disease; symptoms of peripheral neuropathy may be the first signs of WG. Patients suffering from peripheral neuropathy were more often male (61%), older at onset (median age 53 years), had a larger disease extent, and had a higher ANCA titer compared with patients

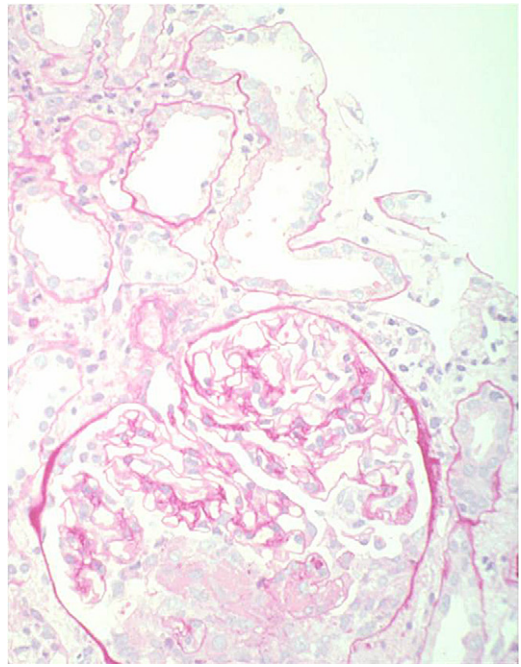

Fig. 4. Crescentic glomerulonephritis.

presenting without peripheral neuropathy. Symmetric polyneuropathy was slightly more frequent (55%) than mononeuritis multiplex (47%) in this study.[38] Skin manifestations such as palpable purpura, vesicles, papules, and subcutaneous nodules are also frequent (30%–46%)[17,29]; digital ischemic lesions or necrosis may develop.

Involvement of the central nervous system (CNS) is not common (7%–11%).[17,29,39] According to Drachman[40] and Seror and colleagues,[39] 3 distinct pathogenic mechanisms of CNS manifestations are described: First, there may be invasion of granulomatous tissue from the sinuses and/or orbit into surrounding tissues, thereby affecting CNS structures such as the optic nerve (by orbital granuloma), other cranial nerves (such as nervus facialis), meninges, and pituitary gland. Second, granulomatous inflammation can develop in CNS tissues itself, for example, in the meninges (hypertrophic pachymeningitis), the parietal bone, the pituitary gland, and the brain. Third, small-vessel vasculitis of cerebral and intraspinal vessels may occur. Pachymeningitis may be completely asymptomatic and develop without any signs of extracranial disease (in up to 40%), but is usually accompanied by chronic headache and sometimes cranial nerve palsies. Meningismus, seizures, limb palsies, and encephalopathy develop in less than 25% of patients. Meningitis of the spinal cord is also rare, but is typically associated with paraplegia. Meningitis may be demonstrated on magnetic resonance imaging (MRI); lumbar puncture usually reveals pleocytosis with lymphocytic predominance and/or increased protein. Granulomatous inflammation of the pituitary gland can induce central diabetes insipidus; manifestations such as intracerebral or subarachnoid hemorrhages, transient ischemic attacks, strokes, ischemic myelopathy, and arterial or venous thromboses may be caused by CNS vasculitis. Diagnosis of CNS involvement in WG may be challenging, as MRI changes and lumbar puncture may yield nonspecific results. Biopsy may be considered in unclear situations.

Clinically apparent heart involvement is rare in WG (6%–20%), but quite frequently reported on postmortem examination.[41] Thus, despite autopsy studies revealing pericarditis and coronary vasculitis in 50% of patients,[41,42] most patients have no clinical signs of cardiac disease. In a small series, subclinical pericardial effusions seen on transthoracic echocardiography were observed in 55%.[42] Tamponade of the pericardium requiring invasive procedures or myocardial infarction are only occasionally reported. Granulomatous myocarditis has been demonstrated in 25% of patients on autopsy; congestive heart failure and dilated cardiomyopathy are only rarely reported to occur. Valvulitis and arrhythmias have been published in case reports.[41,42]

Gastrointestinal manifestations are reported in only a few of the cohort studies[17,43] with rates between 1.7% and 5%; mesenteric vasculitis may lead to serious complications such as mesenteric ischemia and infarction. An overview of organ manifestations reported in cohort studies of more than 100 patients is shown in **Table 2**.

TREATMENT

Remission Induction

Cotrimoxazole (trimethoprim-sulfamethoxazole) is used by some for remission induction (and maintenance) in upper airway disease or localized disease; however, it is less effective in sustaining remission in generalized WG.[44,45]

For early systemic disease, methotrexate (MTX) has been shown to be effective in several open studies[46–50] and one controlled trial (NORAM, nonrenal alternative treatment with MTX[51]). Remission rates of 59% to 89.8% were reported with relapse rates of 37% to 89.8% after 10 to 29 months. Of importance is that the definition of early

Table 2
Organ manifestations developing during longitudinal follow-up of cohorts comprising more than 100 patients with Wegener's granulomatosis

Organ Involvement (%)	Hoffman et al, 1992[29] (n = 158)	Anderson et al, 1992[28] (n = 265)	Reinhold-Keller et al, 2000[17] (n = 155)	Abdou et al,[a] 2002[37] (n = 701)	Stone, 2003[43] (n = 180)
Upper respiratory tract	92	75	99	Sinus: 68 Nose: 51 Ear: 43	90
Lung	85	63	64	62	75
Kidney	72	60	70	38	68
Heart	6	<4	~20	N/A	3.7
Skin	46	25	>30	27	38.5
Central nervous system	8	N/A	<10	N/A	5
Peripheral nervous system	15	N/A	40	N/A	14
Gastrointestinal tract	N/A	N/A	<10	N/A	6.8
Joints	67	29	77	57	81
ANCA positive	N/A	N/A	84	77	73

Abbreviation: N/A, not available.
[a] Percentages are given for organ manifestations at diagnosis.

systemic disease varies among studies, and MTX dose and duration of therapy were variable in the studies, which therefore cannot be directly compared. Early systemic disease is currently defined as nonorgan threatening disease with a maximum creatinine level of less than 120 μmol/L (1.4 mg/dL). In the NORAM study, WG and MPA patients with even higher creatinine values (<150 μmol/L or 1.7 mg/dL) were enrolled. These patients were randomized to receive either oral cyclophosphamide (Cyc; at 2 mg/kg body weight/d) or oral MTX for 12 months plus glucocorticoids. After a follow-up of 18 months, relapse rates did not differ significantly (MTX group 89.8% vs Cyc group 93.5%); however, time to remission was longer in the MTX group in patients with extensive disease ($P = .04$) or pulmonary involvement ($P = .03$). Furthermore, the relapse at 18 months was more frequent in the MTX group (69.5% vs 46.5%) and occurred earlier (13 vs 15 months, $P = .023$), which should be taken into consideration when deciding on an individual patient's treatment in early systemic disease. In general, relapse rates were very high in the NORAM trial, probably as a result of the (early) cessation of therapy after 12 months.

In generalized disease, Cyc has been the mainstay for remission induction for many years, which is currently being challenged by recent preliminary data from controlled trials assessing the efficacy of rituximab compared with Cyc.[52,53] Cyc has been widely used for remission induction since the 1970s and its efficacy was suggested by open studies[54]; there are no controlled trials comparing Cyc with placebo to prove efficacy of this treatment, as this would be unethical. Four controlled trials addressed efficacy and toxicity between oral and intravenous Cyc,[55–58] with a meta-analysis of the first 3 trials also available.[59] In the first 3 trials, similar rates of remission were documented in both arms; however, intravenous Cyc had the advantage of a lower cumulative dose as well as fewer side effects such as infection and leukopenia. The meta-analysis confirmed these findings but also stated that intravenous Cyc may be associated with a higher relapse rate. In the latest trial,[58] CYCLOPS (Randomized Trial of Daily Oral versus Pulse cyclophosphamide as Therapy for ANCA-associated Vasculitis), 149 AAV patients with renal involvement (creatinine <500 μmol/L or 5.7 mg/dL) were randomized to intravenous pulse Cyc (15 mg/kg pulse every 2–3 weeks until remission plus 3 months) or to oral Cyc (initially 2 mg/kg/d until remission, then 1.5 mg/kg/d for 3 months) and then switched to azathioprine (Aza; 2 mg/kg/d plus low-dose glucocorticoid). There was no difference in the remission rate at 9 months (pulse Cyc 78.7% vs oral Cyc 88.1%) and in median time to remission (in both groups 3 months) as well as the development of end-stage renal disease, serious adverse events, and adverse events. There was a significant difference in the cumulative Cyc dose (8.2 vs 15.9 g, $P<.001$) and the episodes of leukopenia. Of note, there were 13 relapses in the pulse Cyc group compared with 6 in the oral Cyc group; however, the study was not powered to detect differences in relapse rates.

Very recent data, which have only been presented in abstract form to date,[52,53] showed equal efficacy of rituximab compared with Cyc, but need to be interpreted with caution as they are preliminary and long-term data are still lacking. The RAVE trial[52] compared oral Cyc (2 mg/kg/d for 3–6 months) for remission induction in AAV (creatinine <4 mg/dL) to 4 weekly infusions of 375 mg/m^2 of rituximab. In both arms, patients initially received 3 pulses of 1 g methylprednisolone, were tapered off glucocorticoids by 6 months, and received azathioprine for remission maintenance for 18 months. Of 197 patients included, 84 patients on rituximab and 81 patients on Cyc completed 6 months. After 6 months, there was no difference in the induction of remission (defined as BVAS/WG = 0 on no glucocorticoids): 64% of patients in the rituximab group and 55% of the Cyc group achieved this primary end point. Therefore, the RAVE trial demonstrates that rituximab is not inferior to oral Cyc in severe AAV for

the induction of remission (see the article by Holle and colleagues elsewhere in this issue for further exploration of this topic). Similar results were demonstrated in the RITUXVAS trial,[53] assessing the efficacy of rituximab (375 mg/m^2 4 times weekly) plus 2 Cyc pulses compared with Cyc pulses for 3 to 6 months alone (44 patients, 3:1 randomization). Patients in both arms received concomitant glucocorticoids, which were stopped after 12 months; furthermore, patients on Cyc pulse therapy were switched to remission maintenance with azathioprine after 3 to 6 months. In this trial there were no differences in the primary end point (remission at 12 months) (76% vs 82%). From this trial it was concluded that the combined Cyc-Rituximab regimen is not inferior to Cyc pulse alone and that rituximab was efficient in sparing Cyc pulses. Data from these 2 studies provide the first evidence for an alternative, noninferior treatment to Cyc for remission induction of severe AAV. This new treatment option should be especially considered in young patients to preserve fertility. Nevertheless, further studies and long-term data will be needed to confirm these preliminary data.

The efficacy of mycophenolate mofetil (MMF) for remission induction in generalized AAV with creatinine levels less than 500 μmol/L (5.7 mg/dL) has been assessed in a small randomized controlled trial of 35 patients,[60] in which patients received either MMF or Cyc. Surprisingly, complete remission was achieved in 77.8% in the MMF group versus 47% in the Cyc group, and renal recovery was 44% versus 15%, respectively. At present, MMF is being investigated for remission induction in active, newly diagnosed MPA and WG and is being compared with pulse Cyc therapy in a larger randomized controlled trial (randomized clinical trial of mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis, MYCYC) initiated by the EUVAS.

Severe (generalized) disease is defined as organ failure, in particular occurring as respiratory or renal failure (creatinine >500 μmol/L or 5.7 mg/dL). Plasma exchange (PE), in addition to standard remission induction, has been shown to improve renal survival compared with methylprednisolone (MP) pulses (MEPEX trial).[61] In 137 newly diagnosed WG and MPA patients with a creatinine level greater than 500 μmol/L, dialysis independence at 3 months was significantly higher in the PE group compared with the MP group (69% vs 49%) and the difference was sustained after 1 year; however, there was no difference in patient survival between the 2 groups. This is in line with former studies,[62,63] which showed benefit in renal but not overall survival in patients with initial dialysis dependence or high creatinine levels. No controlled trials are available with respect to alveolar hemorrhage and PE; however, a retrospective analysis of 20 patients with alveolar hemorrhage who received PE reported resolution of alveolar hemorrhage in all patients.[64] PE is currently recommended by the EUVAS in the treatment of severe renal disease (creatinine >500 mmol/L) in addition to standard remission induction. The British Society of Rheumatology suggests PE be used in the treatment of alveolar hemorrhage.[65] A randomized controlled trial initiated by the EUVAS and the American VCRC (Vasculitis Clinical Research Consortium) to investigate the efficacy of PE in less severe generalized disease (creatinine <500 μmol/L) is currently underway (PEXIVAS trial).

Maintenance

Maintenance therapy is essential because of high relapse rates, which have been documented even under maintenance therapy (18%–40% at 24 months). MTX, Aza, leflunomide (Lef), and MMF have been suggested as options for maintenance therapy in the EUVAS recommendations, mainly based on randomized controlled trials such as CYCAZAREM (for Aza) and LEM (for Lef).[66–68] Shortly after the EUVAS recommendations, the results of WEGENT, a randomized controlled trial comparing MTX and

Aza, were published.[68] In CYCAZAREM (Randomized Trial of Cyclophosphamide vs Azathioprine during Remission in ANCA-positive Systemic Vasculitis), 144 AAV patients with WG, MPA, or renal limited disease in the generalized disease stage (creatinine <500 μmol/L) initially received remission induction with oral Cyc at 1.5 mg/kg/d plus glucocorticoids, and were then randomized (after successful remission induction) to either continue Cyc or to be switched to Aza (2 mg/kg/d). After 18 months, there was no difference in relapse (13.3% vs 15%), renal function, and rate of end-stage renal failure, demonstrating that Aza is a safe option for (short-term) maintenance therapy in AAV. Long-term data from retrospective studies suggest that maintenance with Aza may be associated with a higher relapse rate compared with Cyc, particularly if the ANCA status remains positive, but long-term Cyc is definitely not an option for remission maintenance due to its toxicity. In the future, intermittent use of rituximab may be an alternative for maintenance therapy; this is currently being investigated in the MAINRITSAN trial (Maintenance of Remission using Rituximab in Systemic AAV): After remission induction with oral or pulse Cyc, patients receive either rituximab 500 mg every 6 months or azathioprine 2 mg/kg/d. Recruitment is ongoing.

In the WEGENT study, 126 patients with WG or MPA received either oral MTX or Aza for maintenance after remission induction with intravenous Cyc. There was no significant difference in relapse-free survival and toxicity between the 2 treatment regimens. The data from this study were not included in the EUVAS recommendations, as this study was published later. Based on this study, the authors believe that the level of recommendation and grade of evidence for MTX should be upgraded from level 2b, grade B to level grade 1b, grade A. In a smaller controlled trial (LEM) including only WG patients (64 patients) comparing MTX with Lef for maintenance, the relapse rate was significantly higher in the MTX group (20 mg/wk orally) compared with the Lef group (30 mg/d orally) (46% vs 23%), which led to an early termination of the study.

MMF is not considered in the EUVAS recommendations but may be used for maintenance of remission. However, it should not be considered as first- or second-choice option, as preliminary data from a controlled EUVAS trial (IMPROVE) demonstrated significantly higher relapse rates for MMF (55%) compared with Aza (38%).[69] In uncontrolled prospective and retrospective trials, the use of MMF for maintenance was associated with high relapse rates (48% and 49%, respectively).[70–72]

Cotrimoxazole (trimethoprim-sulfamethoxazole) may be an option for maintenance of upper airway manifestations in WG, but is less efficient in preventing relapse than MTX.[73]

Maintenance therapy should be continued for at least 18 months. The British Society of Rheumatology recommends to continue maintenance therapy for 24 months and, if the ANCA status remains positive, for even as long as 5 years.

Wegener's Granulomatosis Etanercept Trial

The Wegener's Granulomatosis Etanercept Trial (WGET) trial investigated the effect of etanercept as additional treatment to standard therapy during remission induction and maintenance.[74] One hundred and eighty patients were randomized to etanercept; there were no significant improvements in remission rates and time to remission at the end of follow-up. In addition, there were more treatment-related complications in the etanercept-treated patients; 6 patients who received etanercept and standard therapy with Cyc developed solid malignancies. Etanercept should therefore not be used in addition to standard therapy for remission induction and maintenance. No conclusion can be drawn, however, as to whether etanercept may or may not be

useful as an alternative treatment by itself for remission induction and maintenance or in refractory disease.

Treatment of Refractory Disease

Treatment options in refractory disease include rituximab and infliximab as well as intravenous immunoglobulins (IVIG), deoxyspergualin, and antithymocyte globulin (ATG); however, most of the treatments lack evidence from controlled trials.

At present, rituximab is probably the most frequently used drug in refractory disease. Sixteen open-label studies on rituximab in refractory disease have been published so far.[75–89] In the largest study[88] comprising 65 patients, 75% achieved complete remission, 23% partial remission, and there was no efficacy in only 2%. Furthermore, rituximab enabled glucocorticoid reduction from a median of 12.5 mg/d to 9 mg/d (at 6 months) and the withdrawal of immunosuppression in 62% of subjects. Nevertheless, relapse occurred in half of the patients who achieved full remission. First reports on the use of rituximab in granulomatous manifestations pointed to a lack of effectiveness,[80] but recent studies report remission rates of up to 80% in granulomatous manifestations such as retroorbital granuloma.[89] Further studies are needed to clarify this issue.

Remission rates of 70% to 88% have been reported from 4 open-label studies of infliximab in refractory AAV,[90–93] but patient numbers were small and treatment duration as well as follow-up was short. Moreover, in the largest study (32 patients),[93] a high rate of infections (21%) was noted. Remission in 13 of 15 patients was observed in an open study of ATG in refractory AAV patients.[94] However, relapse rates and side effects were high (relapse in 7 patients after 21.8 months, infections in 5 patients, serum sickness in 2 patients).

Deoxyspergualin was investigated in 3 open trials,[95–97] with remission rates of 70% to 100% (after 6 cycles of therapy) reported. In the largest study[97] a high rate of side effects and relapses were documented (43% relapse after median 170 days of remission despite maintenance with Aza).

IVIG represents another treatment option. Apart from 3 open studies demonstrating a beneficial effect on AAV, a small randomized placebo-controlled trial (34 AAV patients)[98] showed a significantly higher rate of remission in the IVIG-treated group compared with placebo (15 vs 6 remissions, $P = .015$); however, this effect was not maintained beyond 3 months. IVIG may in particular be used in refractory situations and concomitant infection to treat both conditions.

MMF was efficient in the induction of remission in recurrent, cyclophosphamide-resistant AAV or in patients with contraindications for Cyc, as shown by small open studies.[72,99,100] It should not be considered as a first-line option, because preliminary results of the IMPROVE trial (see Maintenance section) may cast doubts on the efficacy of MMF not only for maintenance but also for remission induction, especially in refractory disease.

Concomitant Glucocorticoid Therapy

Glucocorticoid (GC) therapy is a mainstay of therapy for remission induction and maintenance. For remission induction, prednisolone/prednisone at 1 mg/kg/d is recommended[7] for 1 month, followed by a stepwise tapering to less than 15 mg/d after 3 months of therapy. There are no clear guidelines on the cessation of glucocorticoids; during remission, GC doses should not exceed 10 mg/d. The practice of an early cessation of GC in recent United States studies may be responsible for higher relapse rates (eg, in WGET) compared with EULAR/EUVAS studies. However, no evidence is available from controlled trials to answer which amount of GC is required for safe remission induction and maintenance and when GC can safely be stopped. Patients

on GC are recommended to receive prophylaxis against osteoporosis.[7] (See **Table 3** for the EULAR recommendations for treatment of AAV.)

Supportive Care

Exposure to Cyc is associated with an increased risk of hemorrhagic cystitis and bladder cancer,[101–103] which may occur several years after the cessation of Cyc. Fluids and mesna should be administered on the day of the Cyc pulse, as recommended by EULAR/EUVAS,[7] and may also be considered in patients receiving oral Cyc.[7] Monitoring for nonglomerular hematuria and regular cystoscopy in case of hemorrhagic cystitis is useful.[7]

Table 3
Summary of the current recommendation for treatment of AAV according to EULAR

Disease Stage	Treatment
Induction of remission	
Early systemic	MTX 15 mg/wk oral/parenteral, increase to 20–25 mg/wk + GC (level 1B, grade B) Folic acid supplementation
Generalized	Cyclophosphamide IV/oral + GC (level 1A/1B, grade A) Duration: 3–6 mo (oral) or 6–9 pulses (IV) (Rituximab may be an alternative)[a]
Severe (Creatinine >500 μmol/L)	Standard therapy for generalized disease + plasma exchange
Concomitant GC	Prednisolone/prednisone 1 mg/kg/d oral Taper to 15 mg/d or less within 3 mo
Maintenance of remission	
After successful induction of remission	Azathioprine 2 mg/kg/d oral (level 1B, grade A) + low-dose GC Leflunomide 20 mg/d oral (level 1B, grade B) + low-dose GC MTX 20–25 mg/wk (level 1B, grade A)[b] + low-dose GC Duration: at least 18 mo
Concomitant GC	Prednisolone/prednisone less than 10 mg/d
Refractory, relapsing and persistent disease	
After failed standard remission induction	IVIG 2 g/kg IV for 5 d Rituximab IV Infliximab 3–5 mg/kg IV 1–2 monthly MMF 2 g/d oral 15-Deoxyspergualin 0.5 mg/kg/d SC until nadir; then stop until leukocyte recovery (6 cycles) ATG 2.5 mg/kg/d IV for 10 d (adjusted to lymphocyte count)

Abbreviations: ATG, antithymocyte globulin; GC, glucocorticoids; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; MTX, methotrexate.

[a] Rituximab is not included in the EULAR recommendations, as results from controlled trials became available later and have so far been published in abstract form.[51,52]

[b] Level 2B, grade B in EULAR recommendations, should be upgraded to level 1B, grade A due to evidence from WEGENT study.[67]

Adapted from Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small-vessel vasculitis. Ann Rheum Dis 2009;68:310–7; with permission.

As Cyc and GC are independently associated with an increased risk of major infections, close surveillance of patients is necessary. Although rates of infections declined in the 1990s, major infections still pose a common problem. Major infections were documented in 24% of patients in a retrospectively analyzed cohort[104]; bacterial infections, especially pneumonias, herpes zoster recurrences, opportunistic infections such as cytomegalovirus reactivation, and pneumocystis pneumonia were most common. In Europe, the use of pneumocystis prophylaxis with Cotrimoxazole (trimethoprim-sulfamethoxazole) is encouraged[7] in all patients receiving Cyc. It may also be useful for patients on high-dose GC.[104] Mupirocin may be used as topical antibiotic treatment for chronic relapsing nasal activity[7] for *Staphylococcus aureus* eradication, but must be considered carefully, as widespread use may lead to resistance against methicillin-resistant *Staphylococcus aureus*. Apart from medication, patient education is an important issue in supportive care. Preliminary data suggest an increase in the patients' knowledge regarding the disease and its therapy after standardized training increases health-related quality of life, self-efficacy, and patient-assessed health status,[105] even if formal proof of an improved outcome of educated vasculitis patients is still lacking.

SUMMARY

WG is characterized by granulomatous lesions and vasculitic disease manifestations. Granulomatous lesions are found in the upper and lower respiratory tract (eg, granulomatous sinusitis, orbital masses, and pulmonary granuloma), whereas vasculitic manifestations occur frequently in lung (alveolar hemorrhage) and kidney (glomerulonephritis). Vasculitis is typically associated with ANCA directed against proteinase 3. WG has been traditionally associated with a poor outcome and increased mortality, as documented by numerous studies; however, recent cohort studies report an improved outcome. Some studies even suggest that the SMR that is no longer increased as compared with the normal population. The improved outcome is probably a consequence of increased awareness leading to an earlier diagnosis and to improved treatment strategies derived from evidence from controlled trials. The treatment regimen is adapted to disease stage and activity. In generalized disease, Cyc is recommended for induction of remission; preliminary evidence from controlled trials suggests that rituximab may be an effective alternative to Cyc, but long-term data are not yet available. PE should be adjunctive treatment in severe disease. In early systemic disease, MTX may be a safe alternative to Cyc for remission induction. Options for maintenance including MTX, Aza, and Lef or MMF may be considered when other maintenance medications are associated with contraindications or have side effects. It is not clear for how long maintenance therapy is required, but periods from 18 months to 5 years have been suggested. Despite maintenance therapy, relapse remains a major problem in the course of WG.

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