

ANCA-associated Vasculitis: Diagnostic and Therapeutic Strategy

Shoichi Ozaki¹

ABSTRACT

Among small-vessel vasculitides, microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), and allergic granulomatous angiitis (AGA) are known collectively as ANCA-associated vasculitis (AAV) because of the involvement of anti-neutrophil cytoplasmic antibodies (ANCA) as the common pathogenesis. Major target antigens of ANCA associated with vasculitis are myeloperoxidase (MPO) and proteinase 3 (PR3). MPO-ANCA is related to MPA and AGA, and PR3-ANCA is the marker antibody in WG. MPO-ANCA-associated vasculitis is more frequent in Japan, whereas PR3-ANCA-associated vasculitis is more common in Europe and USA. ANCA appears to induce vasculitis by directly activating neutrophils. Therefore, no immunoglobulins or complement components are detected in the vasculitis lesions; hence, AAV is called pauci-immune vasculitis (pauci = few/little). Untreated patients with severe AAV with multi-organ involvement have a poor prognosis, which is improved by combination therapy with cyclophosphamide and high-dose corticosteroid. Randomized controlled trials (RCT) regarding induction and maintenance of remission of AAV indicated that the rate of remission induction by the standard regimen is approximately 90% in 6 months, that maintenance of remission can be achieved with oral azathioprine as well as cyclophosphamide, and that methotrexate can be used only for non-renal mild AAV. As these data were obtained mostly in patients positive for PR3-ANCA, caution must be taken in applying these findings to Japanese patients, most of whom are positive for MPO-ANCA. A prospective study is now underway to clarify the effectiveness of the standard regimen in Japanese patients with MPO-ANCA-associated vasculitis. This article describes the diagnostic criteria and the recent evidence-based therapeutic strategy of AAV.

KEY WORDS

allergic granulomatous angiitis, anti-neutrophil cytoplasmic antibody, cyclophosphamide, microscopic polyangiitis, myeloperoxidase, proteinase 3, Wegener's granulomatosis

INTRODUCTION

Vasculitis is defined as inflammation of the vessel walls. Vasculitis develops either primarily or secondary to certain background conditions, such as infection, malignancy, and systemic rheumatic diseases. Primary vasculitis has been classified based on the size of the affected vessels (International Consensus Conference, 1994). Thus, large-vessel vasculitis includes Takayasu's arteritis and temporal arteritis (giant cell arteritis), medium sized-vessel vasculitis includes polyarteritis nodosa (PN) and Kawasaki's disease, and small-vessel vasculitis includes microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), allergic granulomatous angiitis (AGA), Henoch-

Schönlein purpura, essential cryoglobulinemic purpura, and cutaneous leukocytoclastic vasculitis.¹

Among the types of small-vessel vasculitis, MPA, WG, and AGA are separated from the classical PN, and have common characteristics: the affected vessels are arterioles, capillaries, and venules; the most common organs affected are the kidney and lung; they involve anti-neutrophil cytoplasmic antibody (ANCA) as the common pathogenesis.² Therefore, MPA, WG, and AGA are called ANCA-associated vasculitis (AAV). ANCA can be detected by indirect immunofluorescence using ethanol-fixed neutrophils. Two staining patterns are known, perinuclear (P-ANCA) and cytoplasmic (C-ANCA). The major target antigen of P-ANCA associated with vasculitis is

¹Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine.
Correspondence: Shoichi Ozaki, Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Ka-

nagawa 216-8511, Japan.
Email: ozk@marianna-u.ac.jp
Received 24 January 2007.
©2007 Japanese Society of Allergology

myeloperoxidase (MPO),³ while that of C-ANCA is proteinase 3 (PR3).⁴ MPO-ANCA is related to MPA and AGA, and PR3-ANCA is the marker antibody in WG. In Japan, MPO-ANCA-associated vasculitis is more frequent than PR3-ANCA-associated vasculitis, whereas PR3-ANCA-associated vasculitis is much more common in Europe. The mechanism of the development of AAV involves the activation of neutrophils by ANCA.^{5,6} Therefore, no immunoglobulins or complement components are detected in the vasculitis lesions, and hence AAV is called pauci-immune vasculitis (pauci = few or little).

This article mainly describes the therapeutic strategy for AAV.

DIAGNOSIS AND EVALUATION OF AAV

Due to the high toxicity of cyclophosphamide, one of the standard regimens for AAV, a precise and definite diagnosis is required before treating patients with AAV. Diagnostic criteria have been reported by the Research Group of Intractable Vasculitis, Ministry of Health, Labor, and Welfare (MHLW) of Japan.⁷⁻⁹

Renal and pulmonary symptoms are characteristic in microscopic polyangiitis (MPA), and interstitial pneumonitis and pulmonary hemorrhage are common. MPO-ANCA is positive at a rate of 50–75%. Biopsy of the involved organs reveals necrotizing crescentic glomerulonephritis and necrotizing vasculitis of arterioles, capillaries, and venules with few immune deposits. The diagnostic criteria of the Japanese Research Group, MHLW, for MPA⁷ are listed in Table 1. Granulomatous inflammation and asthma are not seen in MPA.¹⁰

Wegener's granulomatosis (WG) is differentiated from MPA by the presence of necrotizing granulomatous inflammation.¹⁰ These lesions preferentially affect the ear, nose and throat (E), lung (L), and kidney (K). The E symptoms include nasal symptoms (purulent rhinorrhea, epistaxis, and a saddle nose), eye symptoms (ophthalmic pain, visual disturbance, and exophthalmia), ear symptoms (otalgia and otitis media), and throat symptoms (pharyngeal ulcer, hoarseness, and laryngeal obstruction). The L symptoms include bloody sputa, cough, and dyspnea, and the K symptoms include hematuria, proteinuria, rapidly progressive renal failure, edema, and hypertension. PR3-ANCA is positive at >90%. Biopsies of the nasal mucosa, lung, and kidney reveal necrotizing granulomatous vasculitis and necrotizing crescentic glomerulonephritis without immune deposits. WG with all of the E, L, and K involvement is classified as the generalized form, while that without K involvement (*i.e.*, E only, L only, or E + L) is classified as a limited form. The therapeutic strategies are different for each form. The diagnostic criteria of the Japanese Research Group, MHLW, for WG⁸ are shown in Table 2.

Allergic granulomatous angiitis (AGA) was first described by Churg and Strauss.¹¹ AGA can be differen-

Table 1 Diagnostic criteria for microscopic polyangiitis (MPA)

1. Symptoms
(1) Rapidly progressive glomerulonephritis
(2) Pulmonary hemorrhage
(3) Other organ symptoms: Purpura, subcutaneous hemorrhage, gastrointestinal bleeding, and mononeuritis multiplex
2. Histological findings
(1) Necrotizing vasculitis of arterioles, capillaries, and venules, and perivascular infiltration of inflammatory cells
3. Laboratory findings
(1) Positive MPO-ANCA
(2) Positive CRP
(3) Proteinuria, hematuria, elevation of BUN and serum creatinine
<Diagnosis>
1. Definite MPA
(1) Positive for 2 or more of the symptoms, and positive histological findings
(2) Positive for 2 or more of the symptoms including the symptoms (1) and (2), and positive MPO-ANCA
2. Probable MPA
(1) Positive for 3 of the symptoms
(2) Positive for 1 of the symptoms, and positive MPO-ANCA

From the Research Group of Intractable Vasculitis, MHLW of Japan (1998)⁷

tiated from the other two diseases by the presence of asthma, eosinophilia, and necrotizing granulomatous inflammation.¹⁰ Within several years after the onset of asthma, manifestations of small-vessel vasculitis develop, such as palpable purpura of the lower extremities, mononeuritis multiplex, abdominal pain, and gastrointestinal bleeding. Eosinophilia and positive MPO-ANCA are seen. Skin biopsy reveals necrotizing vasculitis of small vessels with massive eosinophilic infiltration and extravascular granulomatosis. The diagnostic criteria of the Japanese Research Group, MHLW, for AGA⁹ are shown in Table 3. According to the Research Group, patients with definite histological findings are classified as AGA, whereas those with a typical clinical course, but lacking histological findings, are classified as Churg-Strauss syndrome.

In addition to the precise diagnosis, evaluation of the extent of organ involvement is also important because it determines which therapeutic strategy should be chosen. The Birmingham Vasculitis Activity Index (BVAS)¹² is employed for evaluation of the activity of vasculitis, and the Vasculitis Damage Index (VDI)¹³ for analysis of organ damage.

THERAPEUTIC STRATEGY OF AAV: GLOBAL EVIDENCE

Untreated patients with severe WG with multi-organ

Table 2 Diagnostic criteria for Wegener's granulomatosis (WG)

1. Symptoms
(1) E symptoms
Nose (purulent rhinorrhea, epistaxis, and saddle nose)
Eyes (ophthalmic pain, visual disturbance, and exophthalmia)
Ears (otalgia and otitis media)
Throat (pharyngeal ulcer, hoarseness, and laryngeal obstruction)
(2) L symptoms
Bloody sputa, cough, and dyspnea
(3) K symptoms
Hematuria, proteinuria, rapidly progressive renal failure, edema, and hypertension
(4) Others due to vasculitis
(a) General symptoms: fever (38°C or higher, 2 weeks or longer), weight loss (6 kg or more for 6 months)
(b) Local symptoms: purpura, polyarthritis/polyarthralgia, episcleritis, mononeuritis multiplex, ischemic heart disease, gastrointestinal bleeding, and pleuritis
2. Histological findings
(1) Necrotizing granulomatous vasculitis with giant cells at the sites of E, L, and/or K
(2) Necrotizing crescentic glomerulonephritis without immune deposits
(3) Necrotizing granulomatous vasculitis of arterioles, capillaries, and venules
3. Laboratory findings
(1) Positive PR3-ANCA (or C-ANCA by an indirect immunofluorescence)
<Diagnosis>
1. Definite WG
(1) Positive for 3 or more of the symptoms, including E, L, and K symptoms
(2) Positive for 2 or more of the symptoms, and positive for either of the histological findings
(3) Positive for 1 or more of the symptoms, positive for either of the histological findings, and positive PR3-ANCA/C-ANCA
2. Probable WG
(1) Positive for 2 or more of the symptoms
(2) Positive for 1 of the symptoms, and positive for either of the histological findings
(3) Positive for 1 of the symptoms, and positive PR3-ANCA/C-ANCA

From the Research Group of Intractable Vasculitis, MHLW of Japan (1998) ⁸

involvement have a poor prognosis with up to 90% of patients dying within 2 years.¹⁴ Combination therapy with cyclophosphamide and high-dose corticosteroid, however, induces improvement in >90% of patients with WG and complete remission in 75%.¹⁴ With regard to the induction and maintenance of remission of AAV, 3 randomized controlled trials (RCT) have been reported as summarized in Table 4.¹⁵⁻¹⁷

CYCAZAREM

This RCT, performed in Europe, compared the effectiveness of cyclophosphamide (CYC) and azathioprine (AZA) in maintenance of remission (REM).¹⁵ This study included 155 patients (95 with WG, 60 with MPA), who achieved remission after induction therapy with oral cyclophosphamide (2 mg/kg/day) plus prednisolone (initial 1 mg/kg/day, tapered to 0.25 mg/kg/day by 12 weeks). The rate of induction of remission was 93% in 6 months. The patients were assigned randomly to either continued cyclophosphamide (1.5 mg/kg/day; *n* = 73) or azathioprine (2 mg/kg/day; *n* = 71); prednisolone (10 mg/day) was also given in each regimen. At one year, both groups

were given azathioprine (1.5 mg/kg/day) plus prednisolone (7.5 mg/day).

At 18-month follow-up, the rates of relapse were not significantly different between the two groups (16% *vs.* 14% in the azathioprine and cyclophosphamide groups, respectively). During the remission phase, both groups had a similar number of severe adverse events. In contrast, a significant difference in the rates of relapse was observed between WG and MPA (18% *vs.* 8%, respectively, *P* = 0.03). Thus, this study clearly showed that maintenance of remission can also be achieved with oral azathioprine.

WGET

The Wegener's Granulomatosis Etanercept Trial (WGET) was performed in the USA.¹⁶ This well-designed study of 180 patients with WG (128 with the generalized form; 52 with a limited form) evaluated the effectiveness of etanercept *vs.* placebo to enhance the ability of standard therapy to maintain remission. Patients were assigned randomly to either etanercept (25 mg, subcutaneous injection, twice a week) or placebo groups. Standard therapy was also given in each

Table 3 Diagnostic criteria for allergic granulomatous angiitis (AGA) (Churg-Strauss syndrome)

1. Symptoms
(1) Bronchial asthma and/or allergic rhinitis
(2) Eosinophilia
(3) Symptoms due to vasculitis
(a) General symptoms: fever (38°C or higher, 2 weeks or longer), weight loss (6 kg or more for 6 months)
(b) Local symptoms: mononeuritis multiplex, gastrointestinal bleeding, purpura, polyarthritis/polyarthralgia, and myalgia (muscle weakness)
2. Characteristic clinical course
(1) Symptoms (1) and (2) precede the development of (3)
3. Histological findings
(1) Granulomatous or necrotizing vasculitis of small vessels with marked infiltration of eosinophils
(2) Extravascular granulomas
<Diagnosis>
1. Definite
(1) Positive for 1 or more of the symptoms (1) and (2), and positive for either of the histological findings (Definite AGA)
(2) Positive for 3 of the symptoms, and the characteristic clinical course (Definite Churg-Strauss syndrome)
2. Probable
(1) Positive for 1 of the symptoms, and positive for either of the histological findings (Probable AGA)
(2) Positive for 3 of the symptoms, but not the characteristic clinical course (Probable Churg-Strauss syndrome)

From the Research Group of Intractable Vasculitis, MHLW of Japan (1998)⁹

Table 4 RCT of AAV

RCT	CYCAZAREM ¹⁵	WG ^{ET} ¹⁶	NORAM ¹⁷
Aims	Maintenance of remission CYC vs. AZA	Maintenance of remission Etanercept (Eta) vs. placebo (Pla)	Induction of remission CYC vs. MTX
Patients	Generalized AAV (<i>n</i> = 155) WG: 95, MPA: 60	WG (<i>n</i> = 180) Generalized: 128, localized: 52	Early non-renal mild AAV (<i>n</i> =95) WG: 89, MPA: 6
Protocols	Randomize either CYC (<i>n</i> = 73) or AZA (<i>n</i> = 71) after induction by standard regimen, and follow-up for 12 months	Randomize either Eta (<i>n</i> = 89) or pla (<i>n</i> = 91); all received standard regimen, and follow-up for 27 months	Randomize either CYC (<i>n</i> = 46) or MTX (<i>n</i> = 49); all received standard corticosteroids, and follow-up for 18 months
Results			
• Rates of induction of remission	93%	91% (Eta: 90%, Pla: 92%) (NS)	MTX: 90%, CYC: 94% (NS)
• Rates of relapse	AZA: 16%, CYC 14% (NS) WG: 18%, CYC: 8% (<i>P</i> = 0.03)	Eta: 66/100Pt * year, Pla: 74/100Pt * year (NS)	MTX: 70%, CYC: 47% (<i>P</i> = 0.02)
• Severe adverse effects	AZA: 11%, CYC 10% (NS)	Eta: 56%, Pla: 57% (NS) Malignancy (Eta: 6, Pla: 0)	MTX: 9 cases, CYC: 6 cases (NS)
• Death	8 (7 during the first 3 months)	6 (Eta: 4, Pla: 2)	4 (MTX: 2, CYC: 2)

NS: not significant

regimen: glucocorticoids plus cyclophosphamide in generalized WG or glucocorticoids plus methotrexate in limited WG.

At a mean follow-up of 27 months, the two groups did not differ in their rates of sustained remission (approximately 72%), time to sustained remission, risk of disease flares, or rates of prolonged periods of decreased disease activity. There was a high rate of complications among all patients (56% to 57% in both groups), and only 50% of the patients achieved and maintained remissions throughout the trial. In addition

to lack of efficacy, etanercept was associated with a significantly higher number of solid tumors (six *vs.* zero for placebo).¹⁸ Thus, etanercept was ineffective for the maintenance of disease remission in Wegener's granulomatosis, and considering its increased risk of malignancy, should not be used for the treatment of WG.

NORAM

This European RCT compared methotrexate and cyclophosphamide for both induction and maintenance

of remission of AAV without significant renal involvement.¹⁷ The exclusion criteria were signs of potentially severe systemic disease as manifested by serum creatinine level >1.7 mg/dL, red blood cell casts, severe hemoptysis, cerebral infarction due to vasculitis, orbital pseudotumor, or rapidly progressive neuropathy. The trial enrolled 95 patients with newly diagnosed AAV (89 with WG and 6 with MPA), who were assigned randomly to methotrexate (20 to 25 mg/week orally; $n = 49$) or cyclophosphamide (2 mg/kg/day orally; $n = 46$); all patients received prednisolone. Therapy was tapered gradually and withdrawn by 12 months.

At 6 months, 90% and 94% of patients in the methotrexate and cyclophosphamide groups, respectively, achieved remission, although the time to remission was 2 months longer in the methotrexate group. Among the patients who achieved remission, the relapse rate at 18 months was significantly higher in the methotrexate group (70%) than in the cyclophosphamide group (47%; $P = 0.023$). There was a higher incidence of leukopenia among those treated with cyclophosphamide, and a higher incidence of liver function test abnormalities among those treated with methotrexate.

Thus, methotrexate was as effective as cyclophosphamide for induction of remission in patients with non-renal mild AAV, but was associated with a significantly higher relapse rate. Therefore, methotrexate should probably be used only for non-renal limited disease or for patients truly intolerant of cyclophosphamide.

OTHER TRIALS

The role of plasmapheresis was addressed in an RCT (MEPEX), in which methylprednisolone and plasma exchange were compared.¹⁹ This trial enrolled 151 patients with a new diagnosis of WG or MPA, and necrotizing crescentic glomerulonephritis, who presented clinical signs of severe renal disease defined as oliguria (<400 mL/day), intention to start dialysis within 48 h, and/or serum creatinine level >5.7 mg/dL. The patients were assigned randomly to a plasma exchange group (7 sessions in the first 2 weeks after diagnosis) or intravenous methylprednisolone group (1 g/day for 3 days). In addition, all patients received standard therapy with oral prednisolone (1 mg/kg/day, tapered over 6 months) and cyclophosphamide (2.5 mg/kg/day for 3 months) followed by azathioprine for maintenance. The full results of this trial have not been published, although outcomes have been reported for the 100 patients from whom renal biopsy tissue was available for central analysis.¹⁹ A benefit of plasmapheresis was observed only in the 69 patients who were on dialysis at the time of entry into the study. At one-year follow-up, patients who received plasmapheresis were more likely to be off dialysis (54%) than those who received methylprednisolone

(32%), but there was no significant difference in mortality (29% vs. 21%). Although the effectiveness of plasmapheresis thus remains to be clarified, the currently recommended indications of plasmapheresis are concurrent anti-glomerular basement membrane (GBM) antibodies, pulmonary hemorrhage, and patients requiring dialysis during the acute phase.²⁰

As mentioned above, evidence-based regimens for induction and maintenance of remission are cyclophosphamide, azathioprine, and methotrexate. The effectiveness of sulfamethoxazole/trimethoprim (ST),²¹ mycophenolate mofetil,^{22,23} and cyclosporine^{24,25} has not been proven. AAV in European and American populations is associated predominantly with PR3-ANCA. For example, the three RCT mentioned above included 440 patients with AAV, among whom 374 patients (85%) had WG.¹⁵⁻¹⁷ This is a striking difference from the disease prevalence in Japan, where MPA or MPO-ANCA-associated vasculitis is more common. Therefore, we must be careful when applying the results of these RCT to Japanese patients. In this regard, a prospective study to analyze the effectiveness of the standard regimen for Japanese patients with MPO-ANCA-associated vasculitis is now underway by the Research Group of Intractable Vasculitis, MHLW of Japan, as described below.

THERAPEUTIC STRATEGY FOR AAV IN JAPAN

The therapeutic strategy for treatment of AAV reported by the Research Group of Intractable Vasculitis, MHLW of Japan,⁷⁻⁹ will be reviewed here.

TREATMENT OF MICROSCOPIC POLYANGIITIS (MPA)

(a) Generalized MPA—severe form: This form includes MPA with multi-organ involvement (more than two organs), a renal-pulmonary type (glomerulonephritis plus either limited pulmonary hemorrhage or extended interstitial pneumonitis) and rapidly progressive glomerulonephritis (RPGN). Patients with this form of MPA are treated with a standard regimen to induce remission. This regimen consists of high-dose prednisolone (0.6 to 1.0 mg/kg/day) plus oral cyclophosphamide (0.5 to 2.0 mg/kg/day). Intravenous methylprednisolone (0.5 to 1.0 g/day for 3 days) can be considered. Instead of oral administration, intravenous cyclophosphamide (0.5 to 0.75 g/m², monthly) can also be considered. For the RPGN type, anti-coagulation therapy (heparin at 10,000 units/day or low-molecular heparin at 5,000 units/day) and anti-platelet therapy (dipyridamole at 300 mg/day) are also employed. In patients with impaired renal function (serum creatinine level >1.8 mg/dL) or those more than 60 years old, the dose of cyclophosphamide should be reduced to 75–50%. Remission is evaluated by the BVAS, and, in general, can be achieved within 6 months. Patients who have

attained remission receive maintenance therapy for an additional 1 year. This includes prednisolone (5 to 10 mg/day), and in most cases oral cyclophosphamide or azathioprine (25 to 75 mg/day).⁷

(b) Generalized MPA—most severe form: This form is defined as patients with either diffuse alveolar hemorrhage, intestinal perforation, acute pancreatitis, cerebral hemorrhage, concurrent anti-GBM antibodies, or resistant severe disease. Patients with this form of MPA are treated with plasmapheresis (2.0 to 3.0 L/day for 3 days; several sessions) together with the standard regimen described above. After induction of remission, patients receive the same maintenance therapy as the severe form for 1 year.

(c) Limited MPA—mild form: This form includes a renal-limited type (except RPGN), a pulmonary-limited type (except pulmonary hemorrhage), and other mild forms. To induce remission, patients receive oral prednisolone (0.3 to 0.6 mg/kg/day; 15 to 30 mg/day). Oral immunosuppressive agents (cyclophosphamide or azathioprine; 0.5 to 1.0 mg/kg/day; 25 to 75 mg/day) can also be considered. Maintenance therapy after induction of remission is similar to that in the generalized form.

PROSPECTIVE TRIAL FOR MPA IN JAPAN—JMAAV TRIAL

To establish evidence for Japanese patients with MPO-ANCA-associated vasculitis, the standard protocols for MPA mentioned above have been evaluated in a prospective, open-labeled, and multi-center manner. The Research Group of Intractable Vasculitis and that of Progressive Glomerular Disease, MHLW of Japan, organized a study group, named the Japanese Study Group for MPO-ANCA-associated Vasculitis (JMAAV), which included 27 centers from throughout the country.²⁶ In this trial, patients with newly diagnosed MPA were stratified into those with the severe form, most severe form, or mild limited form of the disease, as defined above. Patients received the regimen according to the therapy protocol, and were followed up for 18 months. The protocol for the severe form is illustrated in Figure 1. The primary end point was induction of remission, and the rates of severe adverse effects, including death and end-stage renal failure, were also evaluated. As secondary end points, the effectiveness and safety of the standard protocols were evaluated. Furthermore, peripheral blood was collected from all assigned patients before and 7 days after the start of initial treatment, and the expression profiles of genes in peripheral blood cells were analyzed using cDNA chips. This comprehensive transcriptome analysis will reveal the key genes associated with the onset of disease or the prediction of remission. The enrollment of patients was completed at the end of September 2006, and 52 patients were enrolled. The follow-up and intensive analysis of patients are currently underway.

TREATMENT OF WEGENER'S GRANULOMATOSIS (WG)

(a) Generalized WG: To induce remission of this form of WG, prednisolone (40 to 60 mg/day) and cyclophosphamide (50 to 100 mg/day) are administered orally for 8 to 12 weeks. In cases of a renal-pulmonary type (including pulmonary hemorrhage) or RPGN type disease, a regimen similar to those for generalized MPA (severe form) is employed. In patients intolerant of cyclophosphamide due to adverse effects, azathioprine (50 to 100 mg/day) or methotrexate (2.5 to 7.5 mg/week) is used. After induction of remission, patients receive maintenance therapy: tapering dose of prednisolone, which is stopped within 8 to 12 weeks, plus cyclophosphamide (25 to 50 mg/day), or prednisolone only (5 to 15 mg/day) without cyclophosphamide.⁸

(b) Limited WG: To induce remission of early and active disease, prednisolone (15 to 30 mg/day), cyclophosphamide (25 to 75 mg/day), and sulfamethoxazol/trimethoprim (2 to 3 tablets/day) are administered orally for 8 weeks. In patients intolerant of cyclophosphamide due to adverse effects, azathioprine (25 to 75 mg/day) or methotrexate (2.5 to 7.5 mg/week) is used. Maintenance therapy after induction of remission is similar to that in the generalized form.

TREATMENT OF ALLERGIC GRANULOMATOUS ANGIITIS (AGA)

Induction of remission can be achieved using corticosteroids. After intravenous methylprednisolone (0.5 to 1.0 g/day for 3 days), prednisolone (40 mg/day) is administered orally for 8 weeks. Prednisolone is then tapered under careful monitoring of clinical symptoms and laboratory findings (especially eosinophil counts). Patients with active angiitis can receive cyclophosphamide or azathioprine (50 to 100 mg/day).⁹ Asthma is treated as usual.

NOVEL THERAPIES OF AAV

The three RCT described above¹⁵⁻¹⁷ yielded induction of remission at rates of approximately 90%. Therefore, true "cyclophosphamide resistance," which is defined as the presence of active disease affecting a major organ despite optimal doses of daily cyclophosphamide and corticosteroids, is rare in AAV. Clinical situations labeled cyclophosphamide resistance are often due to failure to distinguish correctly between active disease and what may present with manifestations similar to active disease, such as permanent damage, the presence of other diseases, or the development of medication toxicities (*e.g.*, infections). These conditions should be ruled out carefully to judge true "cyclophosphamide resistance", for which various novel therapies have been attempted in an open-labeled style.²⁷

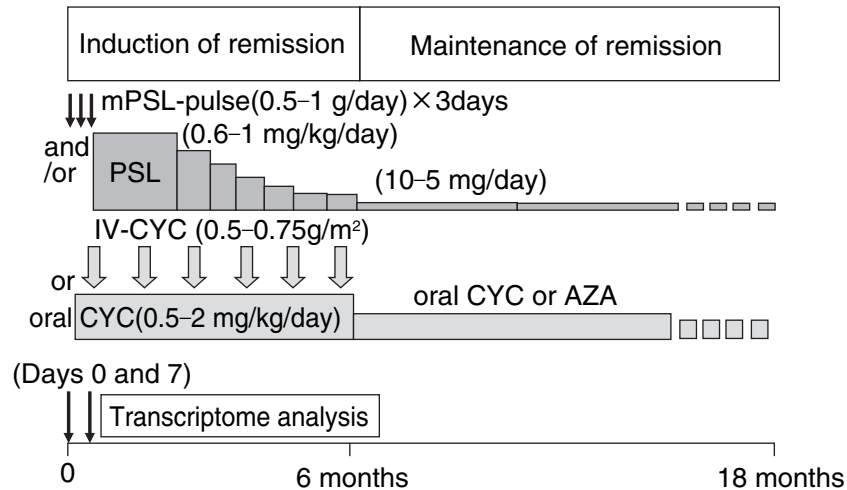


Fig. 1 Protocol of standard regimen for severe form of generalized MPA. This protocol was used in a prospective, open-labeled, and multi-center trial for patients with newly diagnosed severe form of MPA performed by JMAAV.²⁶ The “severe form” is defined as outlined in the text. This regimen consists of high-dose prednisolone (0.6 to 1.0 mg/kg/day) plus oral cyclophosphamide (0.5 to 2.0 mg/kg/day). Intravenous methylprednisolone (0.5 to 1.0 g/day or 3 days) can be considered. Instead of oral administration, intravenous cyclophosphamide (0.5 to 0.75 g/m², monthly) can also be considered. For the RPGN type, anti-coagulation therapy (heparin at 10,000 units/day or low molecular weight heparin at 5,000 units/day) and anti-platelet therapy (dipyridamole at 300 mg/day) are also employed. In patients with impaired renal function (serum creatinine level >1.8 mg/dL) or those greater than 60 years old, the dose of cyclophosphamide should be reduced to 75–50%. Remission is evaluated by the BVAS, and in general can be achieved within 6 months. Patients who have achieved remission receive maintenance therapy for an additional year. This therapy includes prednisolone (5 to 10 mg/day), and in most cases together with oral cyclophosphamide or azathioprine. The primary end point of this prospective trial was induction of remission, and the rates of severe adverse effects, including death and end-stage renal failure, were evaluated. As a secondary evaluation, the effectiveness and safety of the standard protocols were analyzed. Furthermore, peripheral blood was collected from all assigned patients before and 7 days after the initial treatment, and transcriptome analysis of genes in peripheral blood cells was performed using cDNA chips to determine key genes associated with the onset of disease or the prediction of remission.

BIOLOGICAL AGENTS

(a) **TNF blockers:** Biological agents to block tumor necrosis factor (TNF) alpha include etanercept (Enbrel; soluble receptors), infliximab (Remicade; human-mouse chimeric antibody against TNF), and adalimumab (Humira; human anti-TNF antibody). Among these, etanercept was of no additional effectiveness in maintenance of remission and appeared to be associated with a risk of malignancy, as described above.^{16,18} At present, no data are available on the use of adalimumab, and only limited data are available regarding the efficacy of infliximab in AAV. In an open label study, infliximab was administered to 32 patients.²⁸ Infliximab (5 mg/kg, 4 times at weeks 0, 2, 6, and 10) was administered in combination with exist-

ing immunosuppressive agents. Twenty-eight patients (88%) achieved remission within a mean of 6.4 weeks. Serious infections and death were reported in seven and two patients, respectively, while five patients had a relapse at a mean of 27 weeks.

(b) **Anti-B-cell therapy:** It has been suggested that elimination of B lymphocytes with anti-CD20 antibody (rituximab) might have a favorable effect on Wegener’s granulomatosis by removing the cells responsible for producing ANCA.

Rituximab and high-dose glucocorticoids appeared to be of benefit in a study of 11 patients with refractory AAV.²⁹ All patients had refractory disease defined as persistent active disease despite maximally tolerated cyclophosphamide, or a contraindication to

cyclophosphamide therapy. The protocol consisted of high-dose corticosteroids plus four weekly infusions of rituximab (375 mg/m²), with three patients also undergoing plasma exchange. Remission was achieved in all patients, with rituximab being tolerated well. This response was associated with elimination of circulating B lymphocytes, and a decrease in ANCA titer. Remission was maintained during the period in which B lymphocytes remained absent.

The potential benefit of rituximab in treating disease manifestations that are typically not improved by standard immunosuppressive regimens (subglottic stenosis and retrobulbar granulomas) has also been examined. In a preliminary study, eight patients (5 with retrobulbar and 1 with pulmonary/sinus granuloma, and 2 with subglottic stenosis), who had not responded to conventional immunosuppression and anti-TNF antibody therapy, were treated with four weekly infusions of rituximab (375 mg/m²).³⁰ Improvement of disease manifestations was noted in the patient with pulmonary/sinus granuloma and in one of the patients with subglottic stenosis, but in none of the patients with retrobulbar disease.

Further studies of rituximab in patients with WG and/or MPA are needed to better understand its effectiveness, and whether the development of antibodies limits its long-term usefulness; a randomized double-blind trial (RAVE) is currently underway.²⁷

(c) Anti-T-cell therapy: The observation that active systemic vasculitis is mediated in part by T cell-induced injury has led to the evaluation of anti-T cell antibodies in patients with WG who are resistant to or cannot tolerate cyclophosphamide.

In one study, the administration of a combination of two humanized monoclonal antibodies (one directed against CAMPATH-1H, an antigen on all mononuclear cells, and one directed against CD4) led to long-lasting remission in 4 patients with different forms of refractory vasculitis.³¹ This was also accompanied by toxicity that included infusion reactions, infection, autoimmune events, and prolonged lymphocyte depletion.

Among 15 patients with refractory disease, antithymocyte globulin (ATG) resulted in partial or complete remission in 9 and 4 patients, respectively.³² However, 2 patients died 1 and 3 days after the first administration of ATG (due to pulmonary hemorrhage and infection). The role of these experimental therapies remains to be determined.

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG has been studied in only a limited fashion in AAV, and none of the available studies provide clear answers regarding its potential efficacy in this disease. One randomized, placebo-controlled study of 34 patients with AAV found that IVIG (2 g/kg) was associated with a transient improvement in constitutional symptoms, arthralgia, and ENT manifestations.³³ Im-

provement occurred in only 6 of 13 patients who had lung involvement, but no information was provided regarding the presence or response of renal manifestations of the disease. A Japanese group treated 30 patients with MPA (RPGN type), who were positive for MPO-ANCA, with a standard regimen plus IVIG (2 g/kg), and found decreased levels of C-reactive protein and the avoidance of new end-stage renal failure.³⁴ To date, the uncertainty regarding the efficacy of IVIG has led many investigators to be hesitant about its use in systemic vasculitides other than Kawasaki disease.²⁷

OTHERS

Other novel therapies include etoposide,³⁵ 15-deoxyspergualin,^{36,37} intravenous azathioprine,³⁸ radiation therapy,^{39,40} and high-dose myeloablative chemotherapy with stem cell transplantation.⁴¹ Most of these methods, however, are associated with strong adverse effects. In the absence of further data, these experimental therapies should not be used for the treatment of WG or other forms of AAV.

CONCLUSIONS

In conclusion, AAV is one of the best investigated vasculitides, and the clinical significance of ANCA has been clearly demonstrated. A therapeutic strategy has been established, and global evidence has been accumulated by several RCT. Most of these studies, however, have dealt with patients with PR3-ANCA-associated disease, whereas most patients in Japan are associated with MPO-ANCA. Although the evidence for these Japanese patients remains to be established, the prospective, open-labeled, and multicenter trial currently underway by JMAAV will clarify the effectiveness and safety of the standard therapeutic regimen in the near future.

REFERENCES

- Jennette JC, Falk RJ, Andrassy K *et al.* Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* 1994;**37**:187-192.
- Jennette JC, Falk RJ. Clinical and pathological classification of ANCA-associated vasculitis: what are the controversies? *Clin. Exp. Immunol.* 1995;**101**(Suppl 1):18-22.
- Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N. Engl. J. Med.* 1988;**318**:1651-1657.
- van der Woude FJ, Rasmussen N, Lobatto S *et al.* Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985;**1**:425-429.
- Jennette JC, Falk RJ. Pathogenesis of the vascular and glomerular damage in ANCA-positive vasculitis. *Nephrol. Dial. Transplant* 1998;**13**(Suppl 1):16-20.
- Xiao H, Heeringa P, Hu P *et al.* Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J. Clin. Invest.*

- 2002;**110**:955-963.
7. Nakabayashi K, Hashimoto H. Microscopic polyangiitis. In: Hashimoto H (ed). *Clinical Manual for Vasculitis*. Tokyo: Research Group of Intractable Vasculitis, Ministry of Health, Labor, and Welfare of Japan, 2002;24-26.
 8. Yoshida M. Wegener's granulomatosis. In: Hashimoto H (ed). *Clinical Manual for Vasculitis*. Tokyo: Research Group of Intractable Vasculitis, Ministry of Health, Labor, and Welfare of Japan, 2002;30-34.
 9. Tsusaka N. Allergic granulomatous angiitis. In: Hashimoto H (ed). *Clinical Manual for Vasculitis*. Tokyo: Research Group of Intractable Vasculitis, Ministry of Health, Labor, and Welfare of Japan, 2002;27-29.
 10. Jennette JC, Falk RJ. Small-vessel vasculitis. *N. Engl. J. Med.* 1997;**337**:1512-1523.
 11. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *Am. J. Pathol.* 1951;**27**:277-301.
 12. Luqmani RA, Bacon PA, Moots RJ *et al.* Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Qjm* 1994;**87**:671-678.
 13. Exley AR, Bacon PA, Luqmani RA *et al.* Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum.* 1997;**40**:371-380.
 14. Hoffman GS, Kerr GS, Leavitt RY *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann. Intern. Med.* 1992;**116**:488-498.
 15. Jayne D, Rasmussen N, Andrassy K *et al.* A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N. Engl. J. Med.* 2003;**349**:36-44.
 16. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N. Engl. J. Med.* 2005;**352**:351-361.
 17. De Groot K, Rasmussen N, Bacon PA *et al.* Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 2005;**52**:2461-2469.
 18. Stone JH, Holbrook JT, Marriott MA *et al.* Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. *Arthritis Rheum.* 2006;**54**:1608-1618.
 19. de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R *et al.* Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. *J. Am. Soc. Nephrol.* 2006;**17**:2264-2274.
 20. Appel GB, Kaplan AA, Stone JH. Initial and maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis. UpToDate Online, version 14.3
 21. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N. Engl. J. Med.* 1996;**335**:16-20.
 22. Joy MS, Hogan SL, Jennette JC, Falk RJ, Nachman PH. A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis. *Nephrol. Dial. Transplant* 2005;**20**:2725-2732.
 23. Koukoulaki M, Jayne DR. Mycophenolate mofetil in antineutrophil cytoplasm antibodies-associated systemic vasculitis. *Nephron. Clin. Pract.* 2006;**102**:c100-107.
 24. Allen NB, Caldwell DS, Rice JR, McCallum RM. Cyclosporin A therapy for Wegener's granulomatosis. *Adv. Exp. Med. Biol.* 1993;**336**:473-476.
 25. Haubitz M, Koch KM, Brunkhorst R. Cyclosporin for the prevention of disease reactivation in relapsing ANCA-associated vasculitis. *Nephrol. Dial. Transplant* 1998;**13**:2074-2076.
 26. Ozaki S, Nakabayashi K, Tomino Y, Koyama T. A prospective, open-labeled, and multi-center trial of standard protocols for MPO-ANCA-associated vasculitis by Japanese study group for MPO-ANCA-associated vasculitis (JMAAV). *Annual report 2005 of the Research Group for Intractable Vasculitis, Ministry of Health, Labor, and Welfare of Japan.* 2006;199-323.
 27. Rose BD, Appel GB, Stone JH. Alternative agents in the treatment of Wegener's granulomatosis and microscopic polyangiitis. UpToDate Online, version 14.3
 28. Booth A, Harper L, Hammad T *et al.* Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J. Am. Soc. Nephrol.* 2004;**15**:717-721.
 29. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 2005;**52**:262-268.
 30. Aries PM, Hellmich B, Voswinkel J *et al.* Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann. Rheum. Dis.* 2006;**65**:853-858.
 31. Lockwood CM, Thiru S, Isaacs JD, Hale G, Waldmann H. Long-term remission of intractable systemic vasculitis with monoclonal antibody therapy. *Lancet* 1993;**341**:1620-1622.
 32. Schmitt WH, Hagen EC, Neumann I, Nowack R, Flores-Suarez LF, van der Woude FJ. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. *Kidney Int.* 2004;**65**:1440-1448.
 33. Jayne DR, Chapel H, Adu D *et al.* Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *Qjm* 2000;**93**:433-439.
 34. Muso E, Ito-Ihara T, Ono T *et al.* Intravenous immunoglobulin (IVIg) therapy in MPO-ANCA related polyangiitis with rapidly progressive glomerulonephritis in Japan. *Jpn. J. Infect. Dis.* 2004;**57**:S17-18.
 35. Morton SJ, Lanyon PC, Powell RJ. Etoposide in Wegener's granulomatosis. *Rheumatology (Oxford)* 2000;**39**:810-811.
 36. Birck R, Warnatz K, Lorenz HM *et al.* 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J. Am. Soc. Nephrol.* 2003;**14**:440-447.
 37. Schmitt WH, Birck R, Heinzl PA *et al.* Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. *Nephrol. Dial. Transplant* 2005;**20**:1083-1092.
 38. Benenson E, Fries JW, Heilig B, Pollok M, Rubbert A. High-dose azathioprine pulse therapy as a new treatment option in patients with active Wegener's granulomatosis and lupus nephritis refractory or intolerant to cyclophosphamide. *Clin. Rheumatol.* 2005;**24**:251-257.
 39. Eagleton LE, Rosher RB, Hawe A, Bilinsky RT. Radiation therapy and mechanical dilation of endobronchial obstruction secondary to Wegener's granulomatosis. *Chest* 1979;**76**:609-610.
 40. Neviani CB, Carvalho Hde A, Hossamu C, Aisen S, Nadalin W. Radiation therapy as an option for upper airway obstruction due to Wegener's granulomatosis. *Oto-*

laryngol. Head Neck Surg. 2002;**126**:195-196.
41. Kotter I, Daikeler T, Amberger C, Tyndall A, Kanz L. Autologous stem cell transplantation of treatment-resistant

systemic vasculitis—a single center experience and review of the literature. *Clin. Nephrol.* 2005;**64**:485-489.