J Tokyo Wom Med Univ
81 (5) 363～371 (2011)

Review

# Pathogenesis and Treatment of ANCA-associated Vasculitis

**Mitsuyo ITABASHI** and **Kosaku NITTA**

Department of Medicine IV (Director: Prof. Kosaku NITTA), Tokyo Women's Medical University School of Medicine

(Accepted August 23, 2011)

Anti-neutrophil cytoplasmic autoantibody (ANCA) is closely associated with systemic small vessel vasculitis, characterized by segmental vessel wall necrotizing inflammation and a paucity of immunoglobulin deposition. ANCAs are thought to be pathogenetic and to promote the degranulation of neutrophils and monocytes, facilitating endothelial damage. Recent findings have led to a new hypothesis regarding the induction of ANCAs via immune responses against Gram-positive bacteria. During the initial phase of treatment, remission is induced (induction therapy), thereafter, remission is maintained (maintenance therapy). The pharmacotherapy for the two phases differs. Treatment may need to be adjusted according to the disease severity, which in turn depends on the onset age, serum levels of creatinine and C-reactive protein. For induction therapy of generalized and severe disease, steroid therapy and/or cyclophosphamide (CYC) should be the first choice, and plasma exchange should be considered in cases with renal failure and/or life-threatening disease. Alternatively, rituximab may also be used if CYC is contraindicated. To maintain remission, CYC should be replaced by azathioprine. The main causes of death during the induction phase are infection and active vasculitis. As intense immunosuppression increases the risk of infection in association with vasculitis, the prescription of trimethoprim-sulfamethoxazole during induction therapy with immunosuppressive agents may be advisable.

**Key Words**: ANCA, vasculitis, glomerulonephritis, BVAS, prognosis

## Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a life-threatening autoimmune disease characterized by necrotizing vasculitis of small vessels[1]. As shown in Table 1, renal-limited vasculitis (RLV) is commonly observed as a cause of rapidly progressive glomerulonephritis in Japan[2]. Pauci-immune necrotizing glomerulonephritis can be RLV or a renal manifestation of microscopic polyangiitis (MPA). ANCAs with specificity for either proteinase-3 (PR3) or myeloperoxidase (MPO) are hallmarks of ANCA-associated vasculitis. ANCA-associated vasculitis comprises three disease types: Wegener's granulomatosis, Churg－Strauss syndrome, and MPA. The disease types differ with respect to clinical manifestations and histological findings. Granulomatous inflammation is observed in Wegener's granulomatosis and Churg－Strauss syndrome but not in MPA[1)3)4)]. ANCAs themselves are thought to be pathogenetic and to promote the degranulation of neutrophils and monocytes, facilitating endothelial damage[5]. The initial damage leads to a cascade of events, resulting in leukocyte tissue infiltration, T-cell-driven granuloma formation, and further damage. The purpose of this review is to describe the recent advances in the pathogenesis and treatment of ANCA-associated vasculitis.

## Mechanism of ANCA-induced Vascular Damage

ANCAs bind to neutrophils and endothelial cells, having differential but synergistic effects on both cell types. ANCAs bind to membrane-bound PR3/MPO on neutrophils[6]. This interaction with ANCAs results in cell activation and ultimately in the release of cytotoxic superoxide and serine proteases. Membrane-bound MPO/PR3 is expressed constitutively by neutrophils and can be enhanced by proinflammatory cytokines such as tumor necrosis

**Table 1** Total number of patients with rapidly progressive glomerulonephritis

| Diagnosis | Classification | Total n (%) |
|---|---|---|
| Crescentic GN | Anti-GBM antibody-associated GN | 81 (4.6) |
| | Immune-complex-associated GN | 35 (2) |
| | Renal-limited vasculitis | 745 (42) |
| | Overlapped crescentic GN | 31 (1.7) |
| | Undifferentiated primary crescentic GN | 28 (1.6) |
| Primary GN with crescents | Mesangioproliferative glomerulonephritis | 15 (0.8) |
| | Membranous nephropathy | 5 (0.3) |
| | IgA nephropathy | 43 (2.4) |
| | Non-IgA mesangial proliferative GN | 8 (0.5) |
| | Other primary GN | 3 (0.2) |
| Systemic disease-associated | Goodpasture's syndrome | 27 (1.5) |
| | Systemic lupus erythematosus | 66 (3.7) |
| | Wegener's granulomatosis | 46 (2.6) |
| | Microscopic polyangiitis | 344 (19.4) |
| | Other necrotizing vasculitis | 15 (0.8) |
| | Purpura nephritis | 36 (2) |
| | Cryoglobulinemia | 12 (0.7) |
| | Rheumatoid arthritis | 24 (1.4) |
| | Malignant neoplasm | 3 (0.2) |
| | Other systemic diseases | 40 (2.3) |
| Infection-associated | Poststreptococcal acute glomerulonephritis | 10 (0.6) |
| | Abscess | 6 (0.3) |
| | Hepatitis C virus | 2 (0.1) |
| | Other infectious diseases | 20 (1.1) |
| Drug-associated | | 10 (0.6) |
| Others | | 17 (1) |
| Unknown | | 100 (5.6) |
| Total | | 1,772 (100) |

GN: glomerulonephritis, GBM: glomerular basement membrane.

factor-α and interferon-γ[7]. The priming of neutrophils also enhances adhesion to endothelial cells, along with a further increase in membrane MPO/PR3 expression[8]. Thus, degranulation occurs in close contact with the vascular endothelium, resulting in vasculitic damage (Fig. 1). The ANCA-induced release of proteases seems to be the most important factor for vasculitic damage[9]. The interaction of ANCAs with endothelial cells enhances the expression of adhesion molecules like E-/P-Selectin and vascular cell adhesion molecule[10]. ANCAs promote firm and sticky attachments of neutrophils to endothelial cells in these models, leading to enhanced transmigration and damage.

ANCA pathogenesis has been investigated in animal models. Although animal models proving MPO-ANCA pathogenesis are well established, similar efforts for PR3-ANCA have not been successful so far. Xiao et al immunized MPO-knockout mice with murine MPO and transferred anti-MPO-IgG to wild-type and immune-deficient (recombinase-activating gene 2: $RAG2^{-/-}$) mice[11]. Wild-type and immune-deficient mice developed necrotizing crescentic glomerulonephritis, proving a pathogenetic role for MPO-ANCA. The importance of neutrophils and the priming process with proinflammatory agents was also confirmed in this model[12][13].

PR3 was discussed to be the main antigen for cytoplasmic-ANCA, whereas MPO was shown to be the antigenic target of perinuclear-ANCA in patients with vasculitis[14]. The range of ANCA subtypes has been expanded, and additional autoantigens recognized by ANCAs have been found[15]. Recent findings have led to a new hypothesis regarding the induction of ANCAs via immune responses against Gram-positive bacteria[15]. Indeed, chronic nasal carriage of *Staphylococcus aureus* has been demonstrated to increase the risk of disease re-

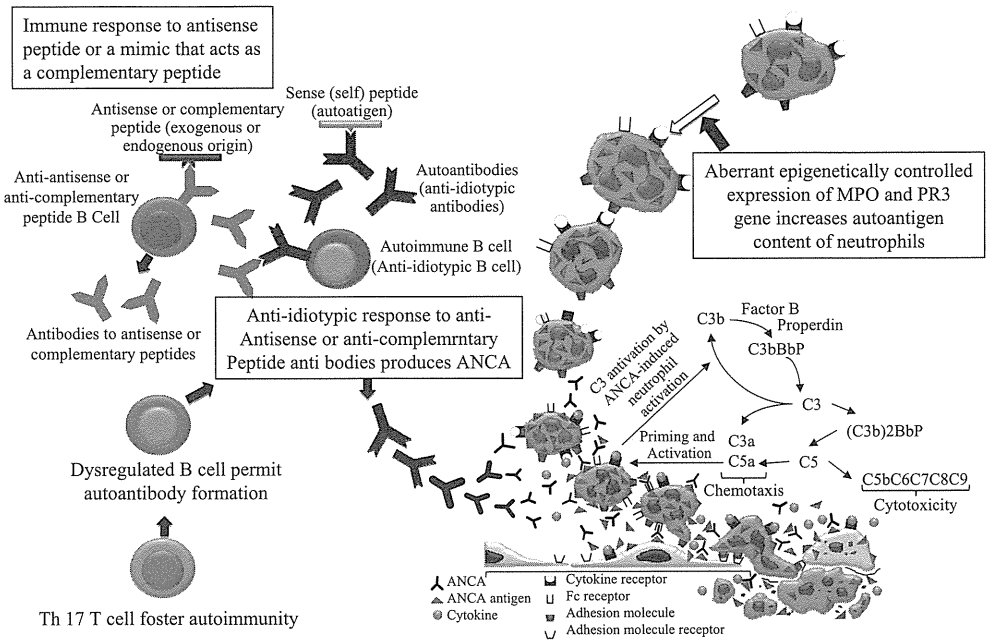


**Fig. 1** Diagram of pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis[8]

lapse[16]. Moreover, Wegener's granulomatosis patients treated with cotrimoxazole are less prone to relapse; in some cases, even remission can be induced by applying cotrimoxazole as a monotherapy[17][18].

## Immune System for Induction of ANCA-associated Vasculitis

T cells are usually found within granulomas as well as in other lesions present in ANCA-associated vasculitis[19]. In accordance with these findings, elevated levels of markers of T-cell activity, such as soluble interleukin-2 receptor have been reported[20]. In addition, ANCA IgG subclasses suggest that a T-cell-mediated subclass switch has taken place[21]. Specific T-cell-targeted therapy is occasionally used in refractory cases and has been demonstrated to be beneficial[22].

Memory T cells are expanded, whereas naive T cells are decreased[23][24]. Recently, Wilde et al demonstrated that a specific subset of effector memory T cells (Tems) expressing CD134 and a steroid-induced TNF-receptor-related protein is especially expanded in Wegener's granulomatosis patients[25]. $CD134^+$ cells were also found in active lesions, suggesting increased migration to inflamed sites. Abdulahad et al demonstrated *Tems* in the urine, suggesting that *Tems* migrate from the circulation to inflammatory lesions during active disease states[26]. *Tems* are powerful immune cells that initiate and sustain immune responses. This T-cell population is long lived and responds quickly to adequate triggers. Moreover, granuloma formation is driven by these T cells[27]. Therefore, *Tems* are believed to play a major pathophysiological role in ANCA-associated vasculitis.

## Pathogenesis and Therapeutic Applications

ANCAs are clearly of major importance to diseases and cause vasculitis, interacting with neutrophils upon specific triggers like bacterial infections. At the same time, *Tems* escaping immune regulation enhance autoantibody production and drive tissue inflammation. Interfering with these pathogenetic mechanisms is crucial, as the patients' outcome is fatal if the disease is left untreated. In Japan, steroids have been used as the first choice for induction therapy[28]. The outcome has improved dramatically since the introduction of cyclophosphamide (CYC) as an induction therapeutic agent for ANCA-associated vasculitis[29]. Most drugs, including steroids, used for treatment have a broad spectrum of activity affecting all effector cells. CYC is one of the most efficient agents available for the

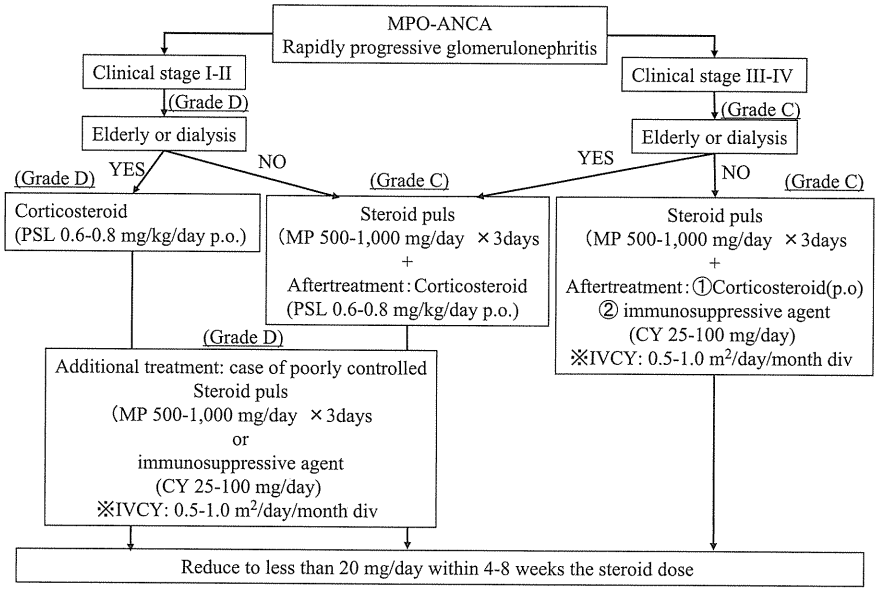


**Fig. 2** Standard therapeutic regimen for anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis recommended by the Japanese Society of Nephrology

treatment of ANCA-associated vasculitis and targets a number of mechanisms described above. It alkylates DNA and thus affects a wide variety of cell types, including leukocytes that lack aldehyde dehydrogenase, an essential enzyme that breaks down the toxic metabolites of CYC. Thus, B-cell suppression is usually observed, and T cells as well as neutrophils are targeted by CYC treatment[30]. This results in the reduction of pathogenetic ANCAs, fewer pathogenetic effector memory T cells, and fewer neutrophils. Azathioprine (AZA), used for maintenance therapy, also interferes with DNA or nucleotide synthesis, affecting dividing cells and thus also pathogenetic lymphocytes. Some of the knowledge gained regarding the pathogenesis of ANCA-associated vasculitis has already been translated into new and specific therapeutic approaches, with presumably fewer adverse effects. Plasma exchange[31] and B-cell depletion using rituximab[30][32] have both been successfully applied for the treatment of ANCA-associated vasculitis and are thought to ameliorate disease by removing autoantibodies or their source.

**Treatment of ANCA-associated Vasculitis**

During the initial phase of treatment, remission is induced (induction therapy), thereafter, remission is maintained (maintenance therapy). The pharmacotherapy for the two phases differs.

**1. Induction therapy**

The most effective and well evaluated drugs used in the induction phase are steroids (prednisolone: PSL) in Japan and CYC in Europe. The Japanese guidelines for ANCA-associated vasculitis are shown in Fig. 2. Of note, CYC is toxic in a dose-dependent manner and is associated with severe adverse effects affecting long-term morbidity as well as mortality, and high cumulative doses above 36 g seem to increase the risk for malignancies such as bladder cancer[33]. Thus, treatment may need to be adjusted according to disease severity (Table 2)[2]. The disease activity depends on the onset age, the serum levels of creatinine and C-reactive protein. In addition, the presence or absence of pulmonary involvement is an important factor. In cases with severe, generalized disease, PSL pulse therapy and/or the intravenous administration of CYC (IVCY) in combination are recommended for the induction of remission. Periodical IVCY reduces the cumulative CYC dosage that is needed and thus the toxicity; the long-term morbidity and/or mortality arising from CYC treatment may also be lowerd[34]. A recent meta-analysis showed that plasma exchange as an adjunctive therapy significantly reduced the risk of end-stage renal disease at 12 months[35]. The re-

**Table 2** Clinical grading for predicting ANCA-associated vasculitis patient prognosis

| Clinical score | Serum creatinine (mg/dl) | Age (years old) | Lung involvement | Serum CRP (mg/dl) |
|---|---|---|---|---|
| 0 | <3 | ≤59 | Negative | <2.6 |
| 1 | 3-6 | 60-69 | | 2.6-10.0 |
| 2 | ≥6 | ≥70 | Positive | >10 |
| 3 | Dialysis | | | |

| Clinical grade | Total score |
|---|---|
| I | 0-2 |
| II | 3-5 |
| III | 6-7 |
| IV | 8-9 |

mission rates were equivalent, but IVCY caused an increased risk of relapse when compared with oral CYC[35].

Removing circulating ANCAs may be beneficial, considering the pathogenetic potential of these antibodies. The addition of plasma exchange may be more effective than steroid pulse therapy for the achievement of renal recovery when used in combination with oral PSL. At 3 months, 69% of the ANCA-associated vasculitis patients in a plasma exchange group were alive and independent of dialysis, as opposed to 49% in the control arm[31]. Furthermore, plasma exchange was associated with a reduction in the risk of progression to end-stage renal disease at 12 months. No differences in patient survival or adverse event rates were observed. A recent meta-analysis by Walters et al[35] confirmed these results, showing that adjunct plasma exchange reduces the risk of requiring dialysis at 12 months after induction treatment. Based on these findings, adjunct plasma exchange is advised in patients with severe renal involvement, alveolar hemorrhage, or other life-threatening organ manifestations.

Rituximab has recently been studied as an alternative therapy to the standard induction protocol with CYC. Two randomized controlled trials (RCTs) have provided evidence that rituximab/PSL is not inferior to CYC/PSL induction therapy[30][32]. The placebo-controlled study enrolled 197 patients with MPA/Wegener's granulomatosis and consisted of two trial arms, in which induction therapy with oral CYC/PSL (n = 99) was compared with rituximab/PSL (n = 98; 4 times, 375 mg/m$^2$)[32]. A total of 55% of the patients in the CYC arm and 64% in the rituximab arm achieved complete remission and PSL treatment was withdrawn after 6 months. There was no difference in the rate of adverse events or relapses within the first 6 months for patients with new-onset disease, whereas in patients with relapsing disease, rituximab was significantly better than CYC. A RCT organized by the European League Against Rheumatism (EULAR) group compared the standard CYC induction protocol to rituximab in patients with severe generalized Wegener's granulomatosis/MPA[30]. These patients were suffering from more severe diseases, as indicated by a median glomerular filtration rate of 18 ml/min/1.73 m$^2$. Patients were either treated with 6-10 cycles of CYC pulses or with rituximab (4 times, 375 mg/m$^2$) in combination with two IVCY treatments. Maintenance therapy with AZA was only given to patients in the CYC group, and the rituximab group did not receive maintenance therapy. A total of 44 patients were enrolled; 33 in the rituximab group and 11 in the CYC group. The outcome was comparable in both groups; 76% of the patients in the rituximab group and 82% of the patients in the CYC arm had entered sustained remission after 12 months. The improvement in renal function during therapy was not different, nor as was the rate of adverse events. These studies provide good evidence of the non-inferiority of rituximab, when compared with CYC, for inducing remission without the burden of long-term toxicity. However, data on the long-term outcome of patients with ANCA-associated vasculitis

are not yet available.

**2. Maintenance therapy**

Maintenance therapy should follow induction therapy, as relapses frequently occur in ANCA-associated vasculitis patients[36]. Falk et al emphasized that a subset of patients with distinct clinical features may not require long-term maintenance therapy[37]. This subset of patients is characterized by the presence of MPO-ANCA and vasculitis without involvement of the respiratory tract, but specific markers allowing reliable identification are not available[38][39]. Thus, at present, maintenance therapy for at least 18-24 months is likely to continue to be recommended by the EULAR and the British Society for Rheumatology[40]. Because of its long-term toxicity, CYC should not be used for the maintenance of remission, as AZA was proven to be as effective as CYC in preventing relapses of Wegener's granulomatosis/MPA patients[40].

Low-dose PSL should be added to maintenance therapy. The duration, however, is debatable. A meta-analysis found a decreased proportion of relapsing patients in studies with long-term steroid treatment (14%), as opposed to studies with the withdrawal of steroids (43%)[41]. As relapses are associated with nasal carriage of *Staphylococcus aureus*, antibiotics may be useful for preventing disease flares[16]. Cotrimoxazole treatment decreases the incidence of relapses in patients with Wegener's granulomatosis and is therefore advised in patients with high relapse rates[17][42].

The time point at which therapy should be switched from induction to maintenance treatment is not well defined. In most studies, induction therapy is switched after clinical remission defined as the absence of clinical symptoms attributable to active vasculitis[43][44]. Interestingly, Slot et al demonstrated that switching to AZA maintenance therapy in patients with clinical remission who exhibit a positive PR3-ANCA titer is associated with significantly higher relapse rates, compared with patients being PR3-ANCA negative at the time of the switch[45]. Hence, ANCA levels at the time of the switch should be studied as a guideline for treatment. Relapses, generally, are treated when clinical symptoms occur. A rise in ANCA levels often precedes disease flares[46].

Taken together, the above findings indicate that therapy for ANCA-associated vasculitis should be adapted according to the phase and severity of disease. For induction therapy in patients with generalized and severe disease, PSL therapy and/or CYC should be the treatment of first choice, and plasma exchange should be considered in cases with renal failure and/or life-threatening disease. Alternatively, rituximab may be used if CYC is contraindicated. To maintain remission, CYC should be replaced by AZA.

**Outcome of ANCA-associated Vasculitis**

Few studies have focused on the prognosis of ANCA-associated vasculitis patients in Japan[28][47]. To improve the prognosis of patients with ANCA-associated vasculitis, we conducted a broad survey of patients and investigated the initial symptoms, laboratory findings, treatment methods and outcomes[28]. We also examined the association between patient survival and the Birmingham Vasculitis Activity Score (BVAS)[48], which is used to evaluate vasculitis activity in ANCA-associated vasculitis. In our study, mortality was significantly associated with disease severity, as assessed using the BVAS. However, no significant differences in organ involvement were observed between those who survived and the patients who died (Fig. 3). At baseline, mortality was associated with an older age, as previously reported[49]. The main causes of death were infection and progressive vasculitis.

Flossmann et al recently reported the long-term patient survival of patients with ANCA-associated vasculitis treated using current regimens[50]. The main causes of death within the first year were infection (48%) and active vasculitis (19%). After the first year, the major causes of death were cardiovascular disease (26%), malignancy (22%), and infection (20%). A multivariable analysis showed that an estimated glomerular filtration rate $<15$ ml/min, an advanced age, a higher BVAS, and a lower hemoglobin level were significant negative prognostic factors for patient survival. Patients with ANCA-associated vasculitis treated with conventional regi-

mens had an increased risk of death, compared with an age- and gender-matched population.

The peripheral white blood cell and/or lymphocyte counts are influenced by immunosuppressive agents. When trimethoprim-sulfamethoxazole was administered, a reduction was observed in the occurrence of *Pneumocystis* pneumonia, and the *Pneumocystis* pneumonia-related mortality rate was significantly reduced[51]. As intense immunosuppression increases the risk of infection in association with vasculitis, the prescription of trimethoprim-sulfamethoxazole during induction therapy with immunosuppressive agents may be advisable.

In the management of patients with anti-MPO-associated vasculitis, Terrier et al evaluated the relevance of monitoring MPO-ANCA levels[52]. According to their study, MPO-ANCA levels were a very useful and relevant surrogate marker of disease activity. In our study[28], despite induction therapy at an early stage, after a mean follow-up period of 22 months, 3 of the 99 patients experienced relapses. MPO-ANCA was elevated at the time of the relapse. Our relapsed patients had never been treated with immune suppressants. Therefore, a maintenance therapy strategy for ANCA-associated vasculitis is important. RCTs focusing on the induction and maintenance of remission of ANCA-associated vasculitis have indicated that the rate of remission induction with the standard regimen is approximately 90% at 6 months and that the maintenance of remission can be achieved with oral AZA as well as CYC[39].

## Future Therapeutic Strategies

The repair of vascular damage is an additional critical point that needs to be considered for upcoming therapeutic options. Vascular repair is thought to be mediated by endothelial progenitor cells (EPCs) present in the circulation[53]. ANCA-associated vasculitis is associated with increased cardiovascular morbidity, and ANCA-associated vasculitis patients have been shown to have a lower frequency of EPCs than healthy controls[54]. Moreover, low amounts of circulating EPCs seem to increase the probability of disease flares[54]. Thus, the promotion of EPC mobilization and function may have a beneficial impact on the disease course. Common drugs such as statins and angiotensin receptor blockers enhance EPC mobilization and should be used as an adjunctive therapy in patients with ANCA-associated vasculitis because of the risk of accelerated atherosclerosis[55]. In addition, erythropoietin can enhance EPC function, and its use should be studied in ANCA-associated vasculitis[53]. In conclusion, several promising candidate therapy may amend the treatment of ANCA-associated vasculitis in the future. Such efforts will hopefully lead to an improved prognosis and a less-toxic therapeutic regimen.

## References


1) **Jennette JC, Falk RJ, Andrassy K et al**: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum **37**: 187–192, 1994
2) **Koyama A, Yamagata K, Makino H et al**: A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. Clin Exp Nephrol **13**: 633–650
3) **Masi AT, Hunder GG, Lie JT et al**: The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum **33**: 1094–1100, 1990
4) **Leavitt RY, Fauci AS, Bloch DA et al**: The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum **33**: 1101–1107, 1990
5) **Falk RJ, Terrell RS, Charles LA et al**: Antineutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci USA **87**: 4115–4119, 1990
6) **Gomez-Puerta JA, Bosch X**: Anti-neutrophil cytoplasmic antibody pathogenesis in small-vessel vasculitis: an update. Am J Pathol **175**: 1790–1798, 2009
7) **Muller Kobold AC, van der Geld YM, Limburg PC et al**: Pathophysiology of ANCA-associated glomerulonephritis. Nephrol Dial Transplant **14**: 1366–1375, 1999
8) **Jennette JC, Falk RJ, Gasim AH**: Pathogenesis of antineutrophil cytoplasmic autoantibody. Curr Opin Nephrol Hypertens **20**: 263–270, 2011
9) **Westlin WF, Gimbrone MA Jr**: Neutrophil-mediated damage to human vascular endothelium. Role of cytokine activation. Am J Pathol **142**: 117–128, 1993
10) **Nagao T, Matsumura M, Mabuchi A et al**: Up-regulation of adhesion molecule expression in glomerular endothelial cells by antimyeloperoxidase antibody. Nephrol Dial Transplant **22**: 77–87, 2007
11) **Xiao H, Heeringa P, Hu PQ et al**: Antineutrophil

cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest **110**: 955–963, 2002
12) **Huugen D, Xiao H, van Esch A et al**: Aggravation of antimyeloperoxidase antibody-induced glomerulonephritis by bacterial lipopolysaccharide: role of tumor necrosis factor-alpha. Am J Pathol **167**: 47–58, 2005
13) **Xiao H, Heeringa P, Liu Z et al**: The role of neutrophils in the induction of glomerulonephritis by anti-myeloperoxidase antibodies. Am J Pathol **167**: 39–45, 2005
14) **Cohen Tervaert JW, Damoiseaux J**: Fifty years of antineutrophil cytoplasmic antibodies (ANCA) testing:do we need to revise the international consensus statement on testing and reporting on ANCA? APMIS **117**: 55–59, 2009
15) **Kain R, Exner M, Brandes R et al**: Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. Nat Med **14**: 1088–1096, 2008
16) **Stegeman CA, Tervaert JWC, Sluiter WJ et al**: Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Ann Intern Med **120**: 12–17, 1994
17) **Stegeman CA, Cohen Tervaert JW, de Jong PE et al**: Trimethoprimsulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. N Engl J Med **335**: 16–20, 1996
18) **Popa ER, Tervaert JW**: The relation between Staphylococcus aureus and Wegener's granulomatosis: current knowledge and future directions. Intern Med **42**: 771–780, 2003
19) **Tipping PG, Holdsworth SR**: T cells in crescentic glomerulonephritis. J Am Soc Nephrol **17**: 1253–1263, 2006
20) **Schmitt WH, Heesen C, Csernok E et al**: Elevated serum levels of soluble interleukin-2 receptor in patients with Wegener's granulomatosis. Association with disease activity. Arthritis Rheum **35**: 1088–1096, 1992
21) **Brouwer E, Tervaert JW, Horst G et al**: Predominance of IgG1 and IgG4 subclasses of anti-neutrophil cytoplasmic autoantibodies (ANCA) in patients with Wegener's granulomatosis and clinically related disorders. Clin Exp Immunol **83**: 379–386, 1991
22) **Schmitt WH, Hagen EC, Neumann I et al**: Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. Kidney Int **65**: 1440–1448, 2004
23) **Marinaki S, Neumann I, Kalsch AI et al**: Abnormalities of CD4 T cell subpopulations in ANCA-associated vasculitis. Clin Exp Immunol **140**: 181–191, 2005
24) **Marinaki S, Kalsch AI, Grimminger P et al**: Persistent T-cell activation and clinical correlations in patients with ANCA-associated systemic vasculitis. Nephrol Dial Transplant **21**: 1825–1832, 2006
25) **Wilde B, Dolff S, Cai X et al**: CD4+CD25+ T-cell populations expressing CD134 and GITR are associated with disease activity in patients with Wegener's granulomatosis. Nephrol Dial Transplant **24**: 161–171, 2009
26) **Abdulahad WH, Kallenberg CG, Limburg PC et al**: Urinary CD4+ effector memory T cells reflect renal disease activity in antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum **60**: 2830–2838, 2009
27) **Lamprecht P, Csernok E, Gross WL**: Effector memory T cells as driving force of granuloma formation and autoimmunity in Wegener's granulomatosis. J Intern Med **260**: 187–191, 2006
28) **Itabashi M, Takei T, Yabuki Y et al**: Clinical outcome and prognosis of anti-neutrophil cytoplasmic antibody-associated vasculitis in Japan. Nephron Clin Pract **115**: c21–c27, 2010
29) **Fauci AS, Haynes BF, Katz P et al**: Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med **98**: 76–85, 1983
30) **Jones RB, Cohen Tervaert JW, Hauser T et al**: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med **363**: 211–220, 2010
31) **Jayne DRW, Gaskin G, Rasmussen N et al**: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol **18**: 2180–2188, 2007
32) **Stone JH, Merkel PA, Spiera R et al**: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med **363**: 221–232, 2010
33) **Faurschou M, Sorensen IJ, Mellemkjaer L et al**: Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol **35**: 100–105, 2008
34) **de Groot K, Harper L, Jayne DRW et al**: Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody associated vasculitis. Ann Intern Med **150**: 670–680, 2009
35) **Walters GD, Willis NS, Craig JC**: Interventions for renal vasculitis in adults. A systematic review. BMC Nephrol **11**: 12, 2010
36) **Mukhtyar C, Flossmann O, Hellmich B et al**: Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis **67**: 1004–1010, 2008
37) **Falk RJ, Hoffman GS**: Controversies in small vessel vasculitis-comparing the rheumatology and nephrology views. Curr Opin Rheumatol **19**: 1–9, 2007
38) **Pagnoux C, Hogan SL, Chin H et al**: Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated smallvessel vasculitis: comparison of two independent cohorts. Arthritis Rheum **58**: 2908–2918, 2008
39) **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 **349**: 36–44, 2003
40) **Mukhtyar C, Guillevin L, Cid MC et al**: EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis **68**: 310–317, 2009
41) **Walsh M, Merkel PA, Mahr A et al**: The effects of duration of glucocorticoid therapy on relapse rate in anti-neutrophil cytoplasm antibody associated vasculitis: a meta-analysis. Arthritis Care Res **62**: 1166–1173, 2010
42) **Stegeman C, Cohen Tervaert J et al**: Co-trimoxazole and Wegener's granulomatosis: more than a coincidence? Nephrol Dial Transplant **12**: 652–655, 1997
43) **Mukhtyar C, Hellmich B, Jayne D et al**: Remission in antineutrophil cytoplasmic antibody-associated systemic vasculitis. Clin Exp Rheumatol **24**: S93–S98, 2006
44) **Hellmich B, Flossmann O, Gross WL et al**: EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis **66**: 605–617, 2007
45) **Slot MC, Tervaert JWC, Boomsma MM et al**: Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. Arthritis Rheum **51**: 269–273, 2004
46) **Tervaert JW, Goldschmeding R, Elema JD et al**: Association of autoantibodies to myeloperoxidase with different forms of vasculitis. Arthritis Rheum **33**: 1264–1272, 1990
47) **Uezono S, Sato Y, Hara S et al**: Outocome of ANCA-associated primary renal vasculitis in Miyazaki predecture. Intern Med **46**: 815–822, 2007
48) **Weidner S, Geuss S, Hafezi-Rachti S et al**: ANCA-associated vasculitis with renal involvement: an outcome analysis. Nephrol Dial Transplant **19**: 1403–1411, 2004
49) **Booth AD, Almond MK, Burns A et al**: Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis **41**: 776–784, 2003
50) **Flossmann O, Berden A, de Groot K et al**: Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis **70**: 488–494, 2011
51) **Green H, Paul M, Vidal L et al**: Prophylaxis of *Pneumocystis* pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc **82**: 1052–1059, 2007
52) **Terrier B, Saadoun D, Sene D et al**: Antimyeloperoxidase antibodies are a useful marker of disease activity in antineutrophil cytoplasmic antibody-associated vasculitides. Ann Rheum Dis **68**: 1564–1571, 2009
53) **Leone AM, Valgimigli M, Giannico MB et al**: From bone marrow to the arterial wall: the ongoing tale of endothelial progenitor cells. Eur Heart J **30**: 890–899, 2009
54) **Zavada J, Kideryova L, Pytlik R et al**: Reduced number of endothelial progenitor cells is predictive of early relapse in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatology **48**: 1197–1201, 2009
55) **Tervaert JWC**: Translational mini-review series on immunology of vascular disease: accelerated atherosclerosis in vasculitis. Clin Exp Immunol **156**: 377–385, 2009

## 好中球細胞質抗体関連血管炎の病態と治療

東京女子医科大学医学部内科学（第四）（主任：新田孝作教授）
板橋美津世（イタバシミツヨ）・新田　孝作（ニッタコウサク）

好中球細胞質抗体（ANCA）は，巣状壊死性血管炎や pauci-immune 型免疫グロブリン沈着を特徴とする全身性微小血管炎に関与している．ANCAs は好中球や単球の脱顆粒による血管内皮細胞傷害の病態を促進すると考えられている．最近の知見では，グラム陽性球菌に対する免疫反応を介して ANCA が誘導されるという新しい仮説が提示されている．治療は初期段階の導入療法，その後の寛解を維持する維持療法の２つに分類される．その２つの段階における薬物療法は異なっている．疾患重症度は，発症年齢，血清クレアチニン値および C-反応性蛋白レベルで規定されている．全身性の ANCA 関連血管炎に対する導入療法として，ステロイド薬やシクロフォスファミド（CYC）が第一選択薬となっているが，腎不全や生命危機に関与する病態では血漿交換療法が施行される．また，CYC 療法が行えない病態では，リツキシマブ治療が代替療法として施行されている．維持療法では，副作用の面から CYC をアザチオプリンに変更すべきである．導入期の主な死因は感染症や活動性の血管炎である．過激な免疫抑制療法は，血管炎に伴う感染症のリスクを増加させるため，トリメトプリム・スルファメソキサゾールを予防的投与することが望ましい．