



# Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in Korea: A Narrative Review

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Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is a group of systemic necrotising vasculitides, which often involve small vessels, and which lead to few or no immune deposits in affected organs. According to clinical manifestations and pathological features, AAV is classified into three variants: microscopic polyangiitis, granulomatosis with polyangiitis (GPA), and eosinophilic GPA. The American College of Rheumatology 1990 criteria contributed to the classification of AAV, although currently the algorithm suggested by the European Medicines Agency in 2007 and the Chapel Hill Consensus Conference Nomenclature of Vasculitides proposed in 2012 have encouraged physicians to classify AAV patients properly. So far, there have been noticeable advancements in studies on the pathophysiology of AAV and the classification criteria for AAV in Western countries. However, studies analysing clinical features of Korean patients with AAV have only been conducted and reported since 2000. One year-, 5 year-, and 10 year-cumulative patient survival rates are reported as 96.1, 94.8, and 92.8%. Furthermore, initial vasculitis activity, prognostic factor score, age and specific organ-involvement have been found to be associated with either all-cause mortality or poor disease course. The rate of serious infection is 28.6%, and 1 year-, 5 year- and 10 year-cumulative hospitalised infection free survival rates range from 85.1% to 72.7%. The overall standardised incidence ratio of cancer in AAV patients was deemed 1.43 compared to the general Korean population.

**Key Words:** Antineutrophil cytoplasmic antibody, vasculitis, Korea

## INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic necrotising vasculitides, which often involve small vessels, and which lead to few or no immune deposits in affected organs.<sup>1</sup> According to clinical manifestations and pathological features, AAV is classified into three variants: microscopic polyangiitis (MPA), granulo-

matosis with polyangiitis (GPA), and eosinophilic GPA (EGPA).<sup>2</sup> GPA and EGPA are identical to what have been called Wegener's granulomatosis and Churg-Strauss syndrome, although GPA and EGPA are more often and widely used.<sup>1</sup> MPA mainly induces rapid progressive necrotising glomerulonephritis, and it occasionally provokes pulmonary capillaritis or alveolar haemorrhage.<sup>1,2</sup> GPA often involves the upper and lower respiratory tracts, and it also affects the kidneys, leading to necrotising glomerulonephritis. EGPA is commonly accompanied by allergic features such as asthma and eosinophilia, and it frequently involves the lungs and skin.<sup>3,4</sup>

Only a few original articles and one review article have reported clinical features and prognosis in Korean patients with AAV since 2000.<sup>5,6</sup> In this review, we searched articles, not case reports, with titles and abstracts including "ANCA," "vasculitis," "microscopic polyangiitis," "granulomatosis with polyangiitis (GPA; Wegener's granulomatosis)," "eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss syndrome)," and "KOREA" in PubMed and analysed them. We primarily

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focused on reclassifying according to new criteria and clinical and epidemiological aspects of AAV in the present review. In addition, we provided relevant indices through which to estimate the current activity and to predict outcomes in Korean patients with AAV.

## A GLANCE AT THE PATHOGENESIS OF AAV

Antineutrophil cytoplasmic antibodies recognise typical antigens in the cytoplasm of neutrophils, myeloperoxidase (MPO) and proteinase 3 (PR3).<sup>7</sup> In healthy individuals, ANCAs exhibit beneficial homeostatic functions, functioning as “natural ANCAs” or “non-pathogenic ANCAs.” Natural ANCAs have lower titres, lower avidity, less subclass diversity, and less capability to activate neutrophil than pathogenic ANCAs.<sup>8</sup> However, when this regulation is broken, ANCAs initiate pathogenic autoimmunity. Endogenous and exogenous stimuli can convert natural ANCAs to pathogenic ANCAs.<sup>9</sup> Pathogenic ANCAs can provoke autoimmune responses in three ways. The first way is by impaired T cell suppression. In AAV patients, CD4+CD25+ T cell numbers are increased, while CD4+FoxP3 T cells are decreased in number. Also, in GPA patients, the expression of PD-1 on circulating T cells is enhanced, while that on renal infiltrated T cells is significantly reduced.<sup>10,11</sup> The second way is by impaired B cells suppression. CD5+ B cells producing IL-10 have regulatory function. In patients with active AAV, the number of circulating CD5+ B cells is decreased, and normalises after remission.<sup>12</sup> The third way is by enhanced B cell-stimulation by ANCA-activated neutrophil. ANCA-activated neutrophil stimulates B cells to produce ANCAs, and it releases ligands for B activating factor of TNF family (BAFF), leading to plenty of circulating ANCAs and enhanced B cell proliferation. In fact, serum BAFF levels are increased during active disease in AAV patients and decreased after remission.<sup>13,14</sup>

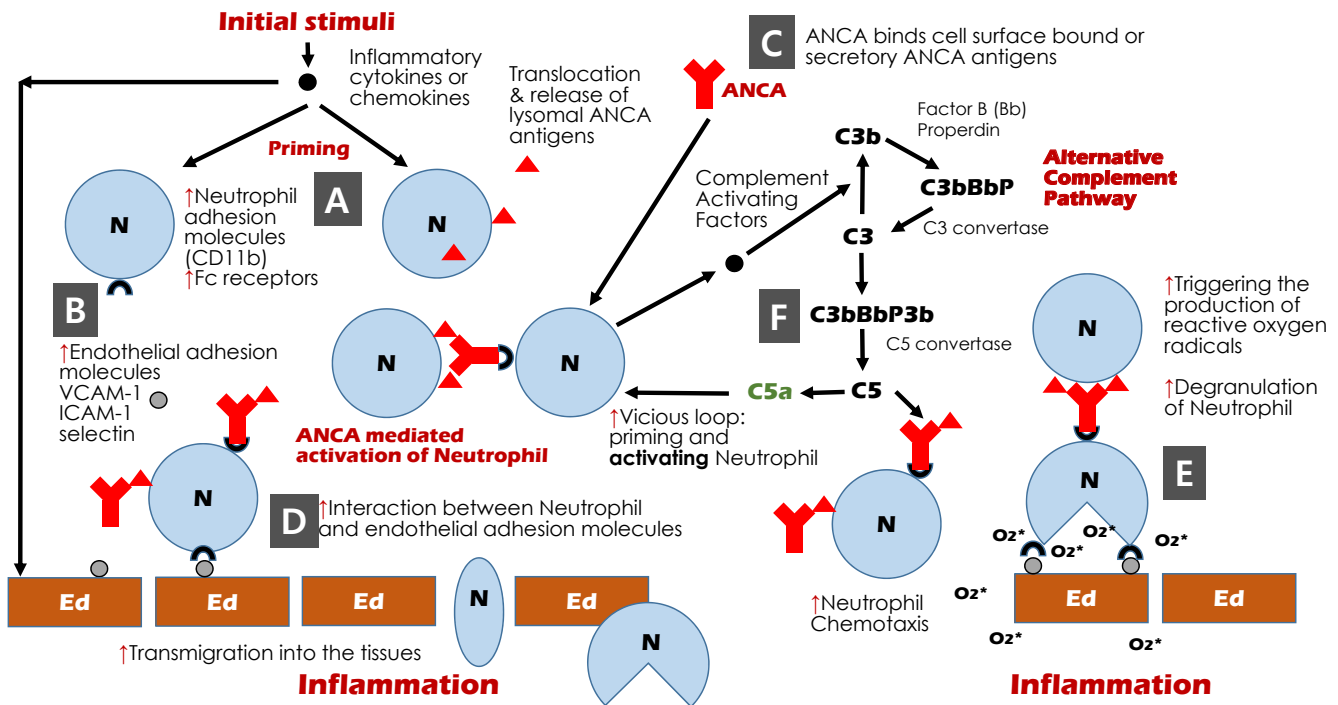
Antineutrophil cytoplasmic antibodies can be generated by two assumed mechanisms: 1) Once infectious organism or medicines, which are considered perpetrators in the pathogenesis of AAV, are processed and presented by antigen-presenting cells (APCs), the release of IL-23 is enhanced and it accelerates the proliferation of Th17 cells and IL-17 production. Increased circulating IL-17 activates macrophages and drives them to secrete pro-inflammatory cytokines, resulting in priming neutrophils. MPO or PR3 in the cytoplasm of neutrophils moves to the surface or are released through lysosomes. Secreted MPO or PR3 can be recognised by APCs and presented to helper T cells.<sup>9,15</sup> Subsequently, helper T cells can transfer the antigenic information to B cells, which produce anti-MPO or anti-PR3 ANCAs or they may differentiate to T effector memory cells, which can participate in granuloma formation.<sup>15</sup> 2) Assuming that antigen 1 is an ANCA antigen mimicking antigen, an antibody response against antigen 1

produces antibody 1. Also, anti-idiotypic responses against antibody 1 may produce antibody 2. Antibody 2 can bind ANCA antigens and induce cross-reaction of priming and activating neutrophils.<sup>9</sup>

Aetiologies of AAV increase pro-inflammatory cytokines or chemokines, which, in turn, may prime neutrophils. Once neutrophils are primed, the expression of neutrophil adhesion molecules (CD11b) and Fc gamma receptors are remarkably enhanced on the surface of neutrophils;<sup>16</sup> cytoplasmic ANCA antigens moves to the surface or they are released through lysosomes (Fig. 1A);<sup>15</sup> and the expression of endothelial adhesion molecules, such as vascular cell adhesion molecule 1, intercellular adhesion molecule 1 and selectins, is enhanced (Fig. 1B).<sup>16</sup> Circulating ANCA binds to the cell surface or secretory ANCA antigens and elicits “ANCA-mediated activation of neutrophils” (Fig. 1C). Thereby, the interaction between neutrophils and endothelial adhesion molecules is strengthened and induces the migration of neutrophils into adjacent tissues (Fig. 1D). Also, “ANCA-mediated activation of neutrophil” triggers the production of reactive oxygen radicals and the degranulation of neutrophils, leading to bulky inflammation on vessel walls as well as in the tissues beyond them (Fig. 1E).<sup>16,17</sup> Alternative complement pathway can also aggravate “ANCA-mediated activation of neutrophils” by forming a loop of complement activating factors to C5a fragment (Fig. 1F).<sup>7,15-17</sup> Moreover, recently, the clinical role of neutrophil extracellular traps in association with MPO-ANCA and IL-18 in the pathogenesis of AAV has been elucidated.<sup>18,19</sup>

## CLASSIFICATION CRITERIA

The American College of Rheumatology 1990 criteria for the classification of AAV (the 1990 ACR criteria) describe EGPA and GPA, but not MPA.<sup>3,4</sup> The 1990 ACR criteria for EGPA include history of asthma, eosinophilia (peripheral eosinophil >10%), mono- or poly-neuropathy related to systemic vasculitis, migratory non-fixed pulmonary infiltrates, paranasal sinusitis, and extravasation of eosinophil on histology. When four of the six items are fulfilled, EGPA can be classified.<sup>4</sup> Criteria for GPA include nasal or oral inflammation, abnormal chest radiography, urinary sediment, and granulomatous inflammation on biopsy. When two of the four items are met, GPA can be classified.<sup>3</sup> The 1990 ACR criteria for EGPA are still reliable for use in determining EGPA.<sup>1,2</sup> However, those for GPA are not specified, and can lead to over-classification, when biopsy-proven granuloma is not available. To overcome these limitations, the algorithm suggested by the European Medicines Agency in 2007 (the 2007 EMA algorithm) and the Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides proposed in 2012 (the 2012 definitions). The 2007 EMA algorithm has a flowchart in the order of EGPA, GPA, MPA, classic polyarteritis nodosa (PAN), and unclassifiable



**Fig. 1.** Mechanism of ANCA-associated vasculitis. (A) Priming and activation of neutrophils, (B) expression of adhesion molecule on endothelial cells, (C) binding of pathogenic ANCA to ANCA-antigens, (D) interaction between neutrophils and endothelial adhesion molecules, leading to extravasation of neutrophils, (E) production of reactive oxygen radicals and degranulation of neutrophils, (F) a loop of complement activating factors to C5a fragment. N, neutrophil; Ed, endothelium; CD, cluster of differentiation; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1; ANCA, antineutrophil cytoplasm antibody; O<sub>2</sub><sup>\*</sup>, oxygen; C, complement; BbP, factor B properdin.

vasculitis, while the 2012 CHCC defines each variant of AAV with clinical and histologic features.<sup>1,2</sup> The new concepts of PAN, based on the 2012 CHCC definitions, are that PAN never provokes glomerulonephritis and it is rarely associated with ANCA. Thus, the presence of glomerulonephritis and any type of ANCA can help to exclude PAN.<sup>1</sup>

We propose supplanted criteria, which are modifications of both the 2007 EMA algorithm and the 2012 CHCC definitions as described in Table 1. Before describing the supplemented criteria, we disclose that we used the same definitions of GPA surrogate markers and renal vasculitis, that were proposed by the 2007 EMA algorithm: GPA markers of lower respiratory tract involvement include fixed pulmonary infiltrates, nodules or cavitations and bronchial stenosis, while those for upper respiratory tract include bloody nasal discharge and crusting or ulcer, chronic sinusitis, otitis media or mastoiditis, retro-orbital mass or inflammation, subglottic stenosis, saddle nose deformity or destructive sinonasal disease. Also renal vasculitis includes haematuria [red blood cell (RBC) casts or >10% RBC dysmorphism] or haematuria ≥2+ or proteinuria ≥2+ on urine stick. When a patient fulfils the 1990 ACR criteria for EGPA, a patient is definitely classified as EGPA. When a patient meets one of the follow three conditions, a patients is classified as GPA: 1) granulomatous and vasculitic features on histology; 2) vasculitic features without granulomatosis on histology and GPA surrogate markers; or 3) GPA surrogate markers without histology and the presence of ANCA. When

a patient exhibits vasculitic features without granulomatosis on histology, but no GPA surrogate markers, or a patient has renal vasculitis and ANCA under the condition of no histology and no GPA surrogate markers, a patient is finally classified as MPA. If a patient cannot satisfy the supplemented criteria, a patient cannot be classified as AAV.

## RECLASSIFICATION

PAN is occasionally difficult to be discriminated from AAV. PAN had three subgroups including cutaneous, classic, and HBV-associated PAN.<sup>20</sup> However, based on the 2012 CHCC definitions, only classic PAN can be classified as PAN. Cutaneous PAN should be reclassified as cutaneous leukocytoclastic angiitis or cutaneous arteritis, and HBV-associated PAN should be reclassified as HBV-associated vasculitis.<sup>1</sup> Park, et al.<sup>21</sup> applied the supplemented criteria to 32 Korean patients with PAN, who were classified according to the 1990 ACR criteria for PAN. Of 32 PAN patients, one patient was reclassified as MPA, as that patient exhibited renal vasculitis and had both MPO- and PR3-ANCA without GPA surrogate markers. Nine of the 32 PAN patients were classified as unclassifiable vasculitis, because they exhibited neither histologic and radiographic evidence of PAN nor the fulfilment of the supplemented criteria for AAV.

EGPA is rarely confused with GPA or MPA, as EGPA exhibits

**Table 1. 2007 EMA Algorithm Modified with 2012 CHCC Definitions (Flowchart from Left to Right)**

ACR for EGPA (1990 ACR)	Histology compatible with 2012 CHCC definition for GPA	Histology compatible with 2012 CHCC definition for MPA and GPA surrogate markers	No histology and GPA surrogate markers and PR3- or MPO-ANCA positivity	Clinical and Histology compatible with 2012 CHCC definition for MPA and No GPA surrogate markers	No histology and No GPA surrogate markers and PR3- or MPO- ANCA positivity and renal vasculitis	Histology compatible with 2012 CHCC definition for cPAN or typical angiographic features of cPAN	
<b>Classified as</b>	EGPA	GPA	GPA	MPA	MPA	cPAN	
<b>Conditions</b>	ACR for EGPA (1990 ACR)	Histology compatible with 2012 CHCC definition for GPA	Histology compatible with 2012 CHCC definition for MPA and GPA surrogate markers	No histology and GPA surrogate markers and PR3- or MPO-ANCA positivity	Clinical and Histology compatible with 2012 CHCC definition for MPA and No GPA surrogate markers	No histology and No GPA surrogate markers and PR3- or MPO- ANCA positivity and renal vasculitis	Histology compatible with 2012 CHCC definition for cPAN or typical angiographic features of cPAN
<b>Classified as</b>	EGPA	GPA	GPA	MPA	MPA	MPA	cPAN
<b>Comments</b>	Necrotizing granuloma with eosinophil infiltrate 1) history of asthma 2) eosinophil > 10% 3) mono- or poly-neuropathy 4) migratory non-fixed pulmonary infiltrates 5) paranasal sinusitis 6) extravasation of eosinophil on histology (4 of 6)	Necrotizing granuloma without eosinophil infiltrate without eosinophil infiltrate with few immune deposit Upper respiratory markers or Lower respiratory markers	Necrotizing vasculitis without granuloma without eosinophil infiltrate with few or no immune deposit Upper respiratory markers or Lower respiratory markers	Necrotizing vasculitis without granuloma without eosinophil infiltrate with few or no immune deposit	No histology and No GPA surrogate markers and PR3- or MPO- ANCA positivity and renal vasculitis	Histology compatible with 2012 CHCC definition for cPAN or typical angiographic features of cPAN	

EMA, European Medicine Agency; CHCC, Chapel Hill Consensus Conference; ACR, American College of Rheumatology; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis, MPA, microscopic polyangiitis; PR3, proteinase 3; MPO, myeloperoxidase; ANCA, antineutrophil cytoplasmic antibody; cPAN, classic polyarteritis nodosa; GN, glomerulonephritis.

typical allergic components, along with vasculitic features. However, patients who are classified as MPA are occasionally reclassified as GPA. On the basis of our clinical experiences, a 29-year-old female patient was classified as MPA due to the presence of MPO-ANCA and renal vasculitis without GPA surrogate markers. However, subglottic inflammation and stenosis, which was incidentally detected on positron emission tomography scan, enabled her to be reclassified as GPA. A 74-year-old male patient, who was classified as MPA, could be reclassified as GPA based on cavitations and nodules in the right lung. A 72-year-old female patient with MPA could be also reclassified as GPA due to chronic and refractory otitis media. So far, final decisions on GPA have often been dependent upon histologic finding of typical granuloma. However, in the real clinical setting, the rate of detection of granuloma in patients suspected of GPA ranges from 20% to 30%. Thus, we suggest that physicians may pay more attention to assessing GPA surrogate markers, when classifying patients as AAV, even in patients who were previously classified as MPA.

## NEW TRIALS OF RECLASSIFICATION

Recently, a new concept for reclassification of AAV into three categories based on the presence of ANCA and its types including MPO-ANCA, PR3-ANCA and ANCA negative vasculitis was recently proposed.<sup>22</sup> Such efforts have been motivated by several needs: First, MPA is classified by the 2007 EMA algorithm and the 2012 CHCC definitions, as MPA does not have clear classification criteria, compared to EGPA and GPA.<sup>1,2</sup> Second, the 1990 ACR criteria for GPA and EGPA are too old to reflect currently developed AAVs. Third, neither MPO-ANCA nor PR3-ANCA was included in those criteria, despite their clinical implications.<sup>23</sup> Moreover, recent studies have supported the distinct entities among MPO-ANCA, PR3-ANCA, and ANCA negative vasculitis.<sup>22,24,25</sup> Even in one AAV variant, patients having MPO-ANCA can present significantly different clinical manifestations from those having PR3-ANCA or no ANCA. Furthermore, responses to immunosuppressive drugs can differ among ANCA types. Yoo, et al.<sup>26</sup> applied this classification method to 133 Korean patients with AAV (79 MPA, 24 GPA and 30 EGPA). Ninety-one patients were reclassified as MPO-ANCA vasculitis, 21 as PR3-ANCA vasculitis and 21 as ANCA negative vasculitis. MPA patients were mainly reclassified as MPO-ANCA vasculitis (82.4%), GPA patients as PR3-ANCA vasculitis (71.4%), and EGPA patients as ANCA negative vasculitis (76.2%). However, ANCA positivity or the type of ANCA had no influence on outcomes of AAV.

The Diagnostic and Classification Criteria for Primary Systemic Vasculitis (DCVAS) and collaborators recently proposed the ACR/EULAR (The European League Against Rheumatism) 2017 provisional classification criteria for GPA. These criteria include nine items, of which five items are clinical vari-

**Table 2.** The ACR/EULAR 2017 Provisional Classification Criteria for GPA

Items	Score
Score for the ACR/EULAR 2017 provisional classification criteria for GPA	Sum ≥ 5
Bloody nasal discharge, ulcers, crusting or sinonasal congestion	3
Nasal polyps	-4
Hearing loss or reduction	1
Cartilaginous involvement	2
Red or painful eyes	1
C-ANCA or PR3-ANCA	5
Eosinophil count ≥ 1 (×10 <sup>9</sup> /L)	-3
Nodule, mass or cavitation on chest imaging	2
Granuloma on biopsy	3

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; GPA, granulomatosis with polyangiitis; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-ANCA.

ables and four items are test variables. Different weights are assigned to each item as shown in Table 2. The score assigned to C-ANCA or PR3-ANCA is the highest among the items. Particularly, nasal polyps and eosinophilia >10% are major negative contributors to the diagnosis of GPA. When the sum of scores is 5 or greater, patients can be classified as GPA (presented at 2016 ACR session: New Classification Criteria for ANCA-associated Vasculitis: implications for clinical practice). Yoo, et al.<sup>27</sup> applied the 2017 provisional criteria suggested by DCVAS to 150 Korean patients with AAV. Three patients, who had been previously classified as GPA, were reclassified as no GPA. All 3 patients had definite histologic evidence of granuloma, but they fulfilled no more items. They were not reclassified as MPA due to granuloma or EGPA due to no history of asthma, eosinophilia or eosinophilic extravasation. Moreover, the 2017 provisional criteria has several limitations that they include no item of kidney involvement for GPA and an item of fixed lung infiltrates is excluded. Meanwhile, one EGPA patient was reclassified as GPA due to sinonasal congestion (3) and PR3-ANCA positivity (5), despite eosinophilia (-3). In this case, PR3-ANCA positivity might be overestimated compared to the 1990 ACR criteria or the 2007 EMA algorithm modified by the 2012 CHCC definitions. Thus, the weight of PR3-ANCA positivity should be readjusted in the near future. In addition, 5 MPA patients were reclassified as GPA and PR3-ANCA also played a major role in the classification of GPA in 2 patients.<sup>27</sup>

### ASSESSMENT OF DISEASE ACTIVITY AND DEFINITIONS OF PROGNOSIS

The disease activity of AAV can be mainly assessed by Birmingham vasculitis activity score (BVAS) (or BVAS for GPA)<sup>28,29</sup> and five factor scores [FFS (1996) and FFS (2009)].<sup>30</sup> Damage derived from AAV can be assessed using vasculitis damage in-

dex (VDI) and combined damage assessment.<sup>31</sup> Functions of patients AAV are evaluated by generalised methods, such as SF-36.<sup>32</sup> BVAS is the most widely used to assess vasculitis activity in AAV. BVAS is composed of nine major items (plus one item of others) including general, cutaneous, mucous membrane/eyes, ear nose throat (ENT), chest (pulmonary), cardiovascular, abdominal, renal and nervous system involvements. The score assigned to the same sub-items can be different depending on the duration and severity of symptoms, such as persistent and newly developed or worsening.<sup>28</sup> The FFS proposed in 1996 includes elevated serum creatinine, proteinuria, severe gastrointestinal (GI) tract involvement, cardiomyopathy and CNS involvement. Meanwhile, the modified version of FFS proposed in 2009 consists of age >65 years, insufficient renal function, severe GI tract involvement, cardiomyopathy and no ENT symptoms.<sup>30</sup> Remission is defined as absence of disease activity attributable to active disease requiring the maintenance of immunosuppressive drugs. Relapse is defined as recurrence or new onset of active disease. Refractory disease is defined as unchanged or increased disease activity in acute vasculitis after 4 weeks of treatment or lack of response or chronic and persistent disease after over 12 weeks of treatment.<sup>33</sup>

### PREDICTORS AT DIAGNOSIS OF PROGNOSIS

In terms of MPA, Oh, et al.<sup>34</sup> first reported the association variables or indices at diagnosis and prognosis in Korean patients with MPA in 2009. Eighteen MPA patients were reviewed, and 10 patients had died. The most common cause of death was diffuse alveolar haemorrhage. BVAS ≥ 19, FFS ≥ 1, age ≥ 66 years and diffuse alveolar haemorrhage at diagnosis predicted all-cause mortality in MPA patients. Ahn, et al.<sup>35</sup> also reported the results of the similar study in 55 Korean patients with MPA. In this study, instead of FFS and diffuse alveolar haemorrhage, cardiomyopathy and interstitial lung disease along with BVAS >9 and old age were predictors of all-cause mortality. In 2017, Oh, et al.<sup>36</sup> reviewed the medical records of 90 Korean patients with MPA, and investigated the association between initial indices and relapse during the follow-up. They insisted that chest (pulmonary) and renal involvement, BVAS ≥ 13.5, and FFS (1996) ≥ 1 at the time of diagnosis were independent predictors of relapse of MPA. So far, MPO-ANCA and PR3-ANCA have been considered to be associated with mortality and relapse in MPA patients, respectively.<sup>37,38</sup> However, ANCA positivity has not been proven as a predictor of poor prognosis in Korean patients with MPA.

In terms of GPA, Kim, et al.<sup>39</sup> reported concrete data regarding clinicopathologic characteristics of Korean patients with GPA. Besides Korean patients with MPA, initial ANCA positivity was significantly associated with renal involvement of GPA and all-cause mortality during the follow-up. Moreover, pa-

tients with ANCA exhibited higher initial BVAS for GPA than those without, and PR3-ANCA mainly contributed to the initial BVAS for GPA. They also compared GPA patients according to histologic patterns and granulomatous and vasculitic types. Patients with the granulomatous type exhibited young age and low frequency of renal involvement, compared to those with the vasculitic type. Yoo, et al.<sup>40</sup> evaluated the predictors of refractory disease during the follow-up in Korean patients with GPA. The optimal cut-offs of BVAS for GPA, and FFS (1996) and FFS (2009) at diagnosis to predict refractory disease of GPA were 9.5, 2, and 2 respectively. In Kaplan-Meier survival analysis, initial BVAS  $\geq 9.5$ , FFS (1996)  $\geq 2$ , and FFS (2009)  $\geq 2$  meaningfully predicted cumulative refractory disease free survival. However, in multivariable Cox hazard model, only BVAS at diagnosis  $\geq 9.5$  was identified as an independent predictor of refractory disease in Korean patients with GPA.

In terms of EGPA, Kim, et al.<sup>41</sup> analysed the clinical features and prognosis in Korean patients with EGPA. They divided EGPA patients according to either ANCA positivity or responses to treatment and compared organ involvements between the two groups. Between patients with and without ANCA at diagnosis, ANCA-negative patients less frequently exhibited renal involvement. Also, older age, diagnosis at earlier stage, less cutaneous involvement, more respiratory involvement, high C-reactive protein (CRP), and more generalized symptoms were observed in good responders. Meanwhile, in another study, Kim, et al.<sup>42</sup> investigated initial variables associated with relapse during follow-up in Korean patients with EGPA. They first obtained the optimal cut-off of FFS to predict relapse of EGPA as 1. When they divided EGPA patients according to FFS of 1, relapse was identified more frequently in patients with FFS  $\geq 1$  than those with FFS  $< 1$  (68.8% vs. 7.1%).

## MORTALITY

In Western countries, 1-year-, 5-year-, and 10-year-cumulative patient survival rates have been reported as 82–95%, 74–97%, and 89%, respectively.<sup>43</sup> In East Asian countries with similar ethnicities to Korea, 1-year- and 5-year-cumulative patient survival rates were reported at 79.1% and 63.6% in Japan, and 6-month-cumulative patient survival rate was estimated as 78.7% in China.<sup>44,45</sup> In Korea, there have been three reports on survival rate in AAV patients before 2016. The first study reported on all-cause mortality in MPA patients with a rate of 56%.<sup>34</sup> The second study reported that 1-year- and 3-year-cumulative survival rates were 93.9% and 89.2% in MPA patients.<sup>35</sup> The third study reported that 22.2% of GPA patients died during follow-up.<sup>39</sup> In 2016, Lee, et al.<sup>46</sup> investigated long term prognosis in 48 Korean patients with renal vasculitis. Six patients had no ANCAs. In Kaplan-Meier survival analysis, ANCA negativity was a significant predictor of renal survival,

but not patient survival. However, in the multivariable Cox hazards model, ANCA negativity did not affect cumulative renal and patient survivals. In 2018, Mun, et al.<sup>47</sup> investigated the initial predictors of all-cause mortality in 153 Korean patients with AAV. Fourteen patients (9.2%) (7 MPA and 7 GPA patients) died during the mean follow-up of 56.9 months. Seven patients died of bacterial, viral, or fungal pneumonia, and 3 patients died of sepsis. In the remaining patients, cardiac arrest of unknown aetiology, alveolar haemorrhage, H1N1 influenza and biliary infection were causes of mortality. One-year-, 5-year-, and 10-year-cumulative patient survival rates were calculated as 96.1, 94.8, and 92.8% in patients with AAV. In the Kaplan-Meier survival analysis, FFS (2009)  $\geq 2$ , chronic kidney disease stage  $\geq 3$  or end stage renal disease (ESRD), and diffuse alveolar haemorrhage were associated with all-cause mortality in AAV patients. However, in the multivariable Cox hazards model, only FFS (2009)  $\geq 2$  (HR 16.5) and diffuse alveolar haemorrhage (HR 3.7) at the time of diagnosis were left as independent predictors of all-cause mortality.

## SERIOUS INFECTION

Serious infections that require hospitalisation have been reported to occur in 20% to 60% of patients with AAV. The wide variability in serious infection rate may stem from AAV variants, ethnic and geographical differences, antibiotics-prophylaxis and the follow-up duration.<sup>48,49</sup> In addition, old age,<sup>50</sup> immunosuppressive drugs,<sup>51-53</sup> reduced renal function,<sup>54</sup> and no ANCA have been found to be related to serious infections.<sup>55</sup> However, most clinical studies regarding serious infection have been conducted in Western countries and only a few observational studies have been undertaken in Korea. Kim, et al.<sup>39</sup> reported 20 of 45 Korean patients with GPA (44.4%) suffered from various infections, including pneumonia, bacteraemia, septic shock, peritonitis, and so on. Yoo, et al.<sup>36</sup> reported retrospective data on hospitalised infections in 154 Korean patients with AAV. Forty-four of the 154 patients (28.6%) had been admitted for serious infection. One-year-, 5-year-, and 10-year-cumulative hospitalised infection free survival rates were 85.1, 77.9 and 72.7%, respectively. Of 44 patients, there were 56 episodes of hospitalised infection and the most common aetiology was pneumonia (29 episodes), followed by aspergillosis (6 episodes), biliary infection (4 episodes), and pneumocystis jirovecii infection (4 episodes). In the Kaplan-Meier analysis, BVAS at diagnosis  $\geq 20.5$ , FFS (2009) at diagnosis  $\geq 1.5$ , pulmonary manifestation, renal manifestation, MPO-ANCA (or P-ANCA) and ANCA positivity were remarkably associated with hospitalised infection. However, in the multiple Cox hazards model analysis, only BVAS at diagnosis  $\geq 20.5$  and pulmonary involvement were predictors of serious infection.

## CANCERS

So far, various autoimmune diseases with chronic inflammatory burdens have been shown to be associated with an increase in the development of cancers. Among autoimmune diseases, rheumatoid arthritis (RA), systemic lupus erythematosus, Sjogren syndrome, systemic sclerosis, and idiopathic inflammatory myopathies are well-known to be linked to cancer occurrence.<sup>57-60</sup> Not only autoimmune systemic inflammation driven by AAV, but also immunosuppressive drugs for AAV may impair immune surveillance and recognitions of cancer cells or act as direct oncogenic aetiology.<sup>61,62</sup> Cancers occur more frequently in AAV patients than the general population [standardised incidence ratios (SIRs) from 1.6 to 2.4].<sup>63-66</sup> Common cancer types are urinary tract cancer, skin cancer and haematological cancers.<sup>63-65</sup> The overall SIR of cancer in AAV patients, however, tends to be reduced due to more safe therapeutic regimens and decreased exposure to both AAV itself and oncogenic immunosuppressive drugs.<sup>67</sup> Yoo, et al.<sup>68</sup> first provided the incidence and types of cancers in 150 Korean patients with AAV (81 MPA, 38 GPA, and 31 EGPA). Four of 150 AAV patients (2.7%) had cancers with the mean follow-up duration of 50.7 months. Each AAV patient exhibited four different cancers, including gastric cancer, lung cancer, prostate cancer, and Non-Hodgkin lymphoma. The gap-time from diagnosis of AAV to cancer development was less than 1 year in two patients. The overall SIR of cancer in AAV patients was 1.43 compared to the general Korean population, but it was not statistically significant. Age at diagnosis of cancer, gender, and AAV variants did not influence SIRs.

## INDICES AT DIAGNOSIS FOR ACTIVITY AND PROGNOSIS

We have discovered that initial vasculitis activity, prognostic factors, and organ-involvement at diagnosis could be associated with the prognosis of AAV. Here, three laboratory variables to estimate the current vasculitis activity, as well as outcomes of AAV, will be introduced. The advantage of the use thereof is that they are currently measured in routine blood tests. First, the consumption of neutrophils can increase the number of immature granulocytes, which is called a granulocytic shift to the left.<sup>69</sup> Delta neutrophil index (DNI) is a leukocyte sub-fraction, which is automatically measured by subtracting the fraction of mature polymorphonuclear leukocytes from the sum of MPO-reactive cells.<sup>70</sup> DNI has been reported to be associated with conditions, in which mature neutrophils are consumed, such as sepsis and disseminated intravascular coagulation.<sup>71</sup> Recently, Yoo, et al.<sup>72</sup> suggested an association between DNI and either current BVAS or relapse in 97 Korean patients with AAV. They indicated that DNI could reflect current BVAS and that DNI  $\geq 0.65\%$  could predict a higher rate of

relapse during follow-up of AAV. Second, RBC distribution width (RDW) is a value of heterogeneity in the size of circulating RBCs. RDW is clinically used to discriminate various types of anaemia.<sup>73</sup> In the meantime, RDW has been considered to be linked to inflammatory burden in systemic rheumatic diseases.<sup>74,75</sup> Kim, et al.<sup>76</sup> reported that RDW was correlated with current vasculitis activity only in GPA patients among 150 Korean patients with AAV. In the Kaplan-Meier survival analysis, RDW  $\geq 15.4\%$  and absence of ENT manifestations were associated with a higher incidence of refractory disease in GPA. Furthermore, in the multivariable Cox hazards analysis, only RDW was an independent predictor of refractory disease of GPA during follow-up. Third, mean platelet volume (MPV) is a marker to reflect platelet distributions in the peripheral circulation. MPV increases as platelet production increases and decreases with reduced production of platelets.<sup>77</sup> MPV exhibits a biphasic pattern in that MPV mainly increases in low-grade inflammation, while it often decreases in high-grade inflammation.<sup>78</sup> Kim, et al.<sup>79</sup> elucidated that MPV was independently and inversely associated with current BVAS in multivariate linear regression analysis in 88 Korean patients with MPA. They also provided the optimal cut-off of MPV for predicting severe MPA (MPV  $\leq 8.85$  fL) and demonstrated that MPV increased along with improvement of vasculitis activity.

In addition, several ratios consisting of two or three laboratory variables at diagnosis of AAV have been proposed for assessing vasculitis activity at diagnosis as well as prognosis during follow-up. Kim, et al.<sup>80</sup> applied systemic immune-inflammation index (SII) [SII=platelet count $\times$ neutrophil count/lymphocyte count] to AAV patients. They elucidated that SII at diagnosis  $\geq 1573.56$  could estimate severe AAV at diagnosis and predict the poor outcome in AAV patients. Ahn, et al.<sup>81</sup> proved that neutrophil to lymphocyte ratio and albumin to globulin ratio might be useful for assessing the current activity and relapse in AAV patients. Park, et al.<sup>82</sup> also provided evidence that platelet to lymphocyte ratio might be associated with the current activity of AAV. Furthermore, it has been recently reported that albumin to globulin ratio was inversely associated with all-cause mortality in MPA patients, and CRP to serum albumin ratio could be a risk factor for all-cause mortality in AAV patients.<sup>83,84</sup> On the other hand, in the pathogenesis of AAV, primed and activated neutrophils release complement-activating factors and they, in turn, cleave complement 3 (C3) into C3a and 3Cb.<sup>85</sup> Thus, it could be assumed that serum C3 level may be negatively correlated with AAV activity. Choi, et al.<sup>86</sup> clarified that serum C3 level  $< 90$  mg/dL was associated with both activity and poor prognosis of AAV.

## OTHERS

### Cardiac function

Cardiovascular manifestations as an item of BVAS consists of

loss of pulses, valvular heart disease, pericarditis, ischaemic cardiac pain (or ischaemic heart disease), cardiomyopathy and congestive heart failure.<sup>28,29</sup> Cardiovascular manifestations occasionally occur in AAV, and its incidence rates differ for both AAV variants and ANCA types (5–49%).<sup>23</sup> Initial involvement of the heart was reported to be related to poor prognosis.<sup>30,87</sup> Recently, Ahn, et al.<sup>88</sup> reported the results of echocardiography performed 3 months before and after diagnosis of AAV in 89 Korean patients. They compared echocardiographic results in AAV patients with those in age- and gender-matched healthy controls. AAV patients showed lower mean left ventricular ejection fraction (LVEF) than controls (64.0% vs. 69.1%). They also exhibited left ventricular diastolic dysfunction more frequently than controls with a higher mean E/E' ratio (11.7 vs. 8.8). Furthermore, measuring right ventricular systolic pressure (RVSP), which can estimate the presence of pulmonary arterial hypertension, the authors indicated that MPA and EGPA patients, but not GPA patients, showed enhanced RVSP than controls. However, there were no significant differences in LVEF, E/E' ratio and RVSP among patients with MPA, GPA and EGPA.<sup>88</sup> Physicians should be encouraged to perform echocardiography within 3 months after diagnosis of AAV.

### Outcome of kidney transplantation

Renal involvement frequently occurs in AAV patients (90–100% in MPA, 50–80% in GPA, 31–51% in ANCA positive EGPA, and 4–16% in ANCA negative EGPA).<sup>23</sup> Pauci-immune crescentic and necrotising glomerulonephritis are the typical histological findings.<sup>89</sup> Renal involvement of AAV may rapidly progress to ESRD in up to 40% of patients.<sup>90,91</sup> In these cases, kidney transplantation may be more valuable than dialysis maintenance.<sup>92,93</sup> So far, histological features, age, PR3-ANCA positivity, and creatinine clearance rate at kidney transplantation were reported to be poor prognostic factors.<sup>94</sup> Recently, Park, et al.<sup>95</sup> first reported the outcome of kidney transplantation in 144 Korean patients with AAV. Of 144 AAV patients, four AAV patients (3 female patients with MPA and 1 male patient with EGPA) underwent kidney transplantation, and they were followed up for more than 2 years. Time-gap from diagnosis of AAV to ESRD ranged from 1 to 48 months and that from AAV to kidney transplantation was 2 to 95 months. One kidney recipient with MPA underwent renal biopsy three times due to renal dysfunction. Renal histology revealed rejection rather than relapse of MPA. There was no relapse or graft failure in the four Korean kidney recipients with AAV. The authors concluded that renal outcomes of kidney transplantation was good and that kidney transplantation could be recommended as a safe and efficient therapeutic modality in patients with ESRD related to AAV.<sup>95</sup>

### Rheumatoid factor false positive

Rheumatoid factor (RF) is a typical antibody in RA and it can

increase the accuracy of the classification as RA.<sup>96</sup> However, RF can be falsely detected in various medical conditions amplifying immunoglobulin G (IgG) production.<sup>97</sup> AAV is also a medical condition augmenting the production of IgG, particularly ANCAs. Thus, it can be reasonably speculated that RF can be frequently detected in AAV patients. Moon, et al.<sup>98</sup> reviewed the medical records and laboratory data 128 Korean patients without RA at the time of diagnosis of AAV and counted the number of patients with RF. The rate of RF false positivity was 39.1% in AAV patients. In multivariable analysis, cutaneous manifestation was the only independent predictor of RF false positivity in EGPA patients, but not in MPA and GPA patients. They explained the link between cutaneous manifestation and RF false positivity via three hypotheses: First, combination of RF with cryoglobulin is associated with skin vasculitis.<sup>99</sup> Second, immune-complex deposition of IgG-RF and complement 3 in the dermal-epidermal junction drives dermatitis.<sup>100</sup> Third, IgA-RF immune complex induces silent dermatitis.<sup>101</sup> Also, they explained the link between RF-induced dermatitis and EGPA by the potential association between RF and eosinophilia, leading to eosinophilic pneumonia.<sup>102</sup> However, RF false positivity did not have an influence on the outcome of AAV or the development of RA.<sup>98</sup>

### Liver related issues

Although liver is one of the major organs with plenty of capillaries like lungs and kidneys, hepatic involvement of AAV might have been underestimated due to non-specific symptoms.<sup>103</sup> However, AAV can theoretically induce the hepatocellular damages and enhance the potential of liver fibrosis similar to autoimmune hepatitis and primary biliary cirrhosis.<sup>104,105</sup> For predicting liver fibrosis, aspartate aminotransferase to platelet ratio index (APRI) and an index of fibrosis (FIB-4) are widely used.<sup>106</sup> Lee, et al.<sup>107</sup> recently reported that AAV may provoke subclinical but significant liver fibrosis at diagnosis using APRI and FIB-4, and suggested FFS  $\geq 1$  at diagnosis as a predictor of liver fibrosis. Furthermore, they also reported that resolved HBV infection could influence vasculitis at diagnosis and relapse after remission in EGPA patients.<sup>108</sup>

## CONCLUSIONS AND FUTURE STUDIES

So far, there have been noticeable advancement in studies on pathophysiology of AAV and the classification criteria for AAV in Western countries. However, studies analysing clinical features of Korean patients with AAV have only been conducted and reported since 2000. Nevertheless, Korean physicians have rapidly adapted to world-wide changes, and have applied new concepts and classification criteria to Korean patients with AAV. In this review, we found several major features in Korean patients with AAV. First, initial vasculitis activity, prognostic factor score, age and specific organ-involvement



seem to be associated with either all-cause mortality or poor disease course. ANCA positivity appears to be related to mortality only in GPA. Second, the overall mortality rate during follow-up of AAV has been reported to be 9.2%. Furthermore, 1-year-, 5-year-, and 10-year-cumulative survival rates were reported as 96.1, 94.8, and 92.8% in a considerable number of AAV patients. Third, the rate of serious infection was described as 28.6% and 1-year-, 5-year-, and 10-year-cumulative hospitalised infection free survival rates ranged 85.1% to 72.7%. Fourth, the overall SIR of cancer in AAV patients appeared to be 1.43, compared to the general Korean population.

Nevertheless, previous studies analysing clinical features and prognosis in Korean patients with AAV have several limitations of a retrospective study-design and a small number of patients. Furthermore, there is no nation-wide cohort of AAV in Korea yet. Thus, a prospective future studies with a larger number of patients by establishing a Korean nation-wide cohort of AAV patients will provide more valuable epidemiologic information and the opportunity to participate in international clinical trials.

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