Current Concept and Epidemiology of Systemic Vasculitides

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ABSTRACT
Although a new classification algorithm for systemic vasculitides was proposed by Watts et al. and the Chapel Hill Consensus Conference (CHCC) was updated in 2012, there are currently no validated diagnostic criteria for systemic vasculitides. The Diagnostic and Classification Criteria for Vasculitis study (DCVAS) is a global study to develop and improve the diagnostic criteria for systemic vasculitides. The epidemiology of systemic vasculitides differs widely among countries. For example, in the case of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, patients with microscopic polyangiitis (MPA) and with positivity for MPO-ANCA are predominant in Asian countries, whereas patients with granulomatosis with polyangiitis (GPA) and with positivity for PR3-ANCA are predominant in northern Europe and the United States. Interstitial lung disease (ILD) occurs more frequently in Asian patients compared with patients in Europe. The incidence and the prevalence of large-vessel vasculitis also differ significantly. Giant cell arteritis (GCA) occurs frequently in northern Europe, unlike Takayasu arteritis (TAK). The ethnic and regional differences in the incidence, prevalence and clinical characteristics of patients with vasculitis should be recognized when we diagnose and treat patients with vasculitis using criteria, and should also be considered when interpreting the results from clinical studies.

KEY WORDS
antineutrophil cytoplasmic antibody-associated vasculitis, Chapel Hill Consensus Conference nomenclature of systemic vasculitides, epidemiology, large vessel vasculitis, polyarteritis nodosa

A HISTORY OF THE CLASSIFICATIONS AND DEFINITIONS OF VASCULITIDES
Systemic vasculitides are pathologically identified by the inflammation of blood vessel walls, and cause various organ disorders depending on the size of the affected blood vessels. Since Kussmaul and Maier reported an autopsy case with polyarteritis nodosa in 1866, several types of systemic necrotizing vasculitis have been reported. The first classification of vasculitis was proposed by Zeek in 1952.¹,² After the disease concept of Wegener’s granulomatosis (WG) was reported,³ DeRemee et al. proposed the ELK classification (upper respiratory tract, lung and kidney) for WG.⁴ In 1990, the American College of Rheumatology (ACR) published criteria for classifying vasculitides to facilitate communication among researchers.⁵ The criteria classified seven types of primary vasculitides; giant cell arteritis (GCA), Takayasu arteritis (TAK), WG, Churg-Strauss syndrome (CSS), polyarteritis nodosa (PAN), Henoch-Schönlein purpura and hypersensitivity vasculitis.⁶⁻¹² The criteria for PAN, WG and CSS have a specificity of 86.6%, 92.0% and 99.7%, respectively, with a respective sensitivity of 82.2%, 88.2% and 85.0%. However, the criteria were established before the general use of antineutrophil cytoplasmic antibody (ANCA) testing, and the most significant problem with these criteria is that they do not distinguish microscopic polyangiitis (MPA) from PAN. Rao et al. reported the limitations of the criteria for the diagnosis of vasculitis.¹³

In 1994, Jennette et al. published the results of the Chapel Hill Consensus Conference (CHCC) on the
THE EUROPEAN MEDICINES AGENCY ALGORITHM

In 2007, Watts and colleagues proposed a new four-step algorithm for the classification of ANCA-associated vasculitides and PAN (the European Medicines Agency algorithm: EMA algorithm).17 The algorithm utilizes the ACR 1990 criteria, CHCC 1994 definitions and surrogate markers to sequentially classify CSS, WG, MPA and PAN. In the algorithm, the ACR criteria and Lanham criteria for CSS are applied first (step 1) to select patients with CSS. As step 2, the ACR criteria for WG, the CHCC definitions and the surrogate markers for WG are applied to diagnose WG. If histological evidence is not available, but surrogate markers are present and ANCA is positive, then patients are classified as having WG. The CHCC 1994 definitions for MPA and surrogate markers for renal vasculitis distinguish MPA from PAN (Steps 3 and 4) (Fig. 1). Because of the poor specificity, the algorithm did not include the ACR criteria for PAN.

The algorithm obtained classifiers’ agreement in 92.3% of the cases of WG, 93.4% of cases of MPA, 95.4% of cases of CSS and 76.9% of the cases of PAN. Two reports were published that evaluated the algorithm, and both of them concluded that the algorithm was useful and practical for epidemiological studies.18,19

THE CHAPEL HILL CONSENSUS CONFERENCE NOMENCLATURE OF VASCULITIDES (CHCC 2012)

In January 2013, the international CHCC published revised nomenclature and definitions of vasculitides (CHCC 2012). They emphasized again that CHCC is a nomenclature system, and not a classification system for clinical research, nor a diagnostic system that can be used to direct clinical management.20 In addition to the three categories described in the CHCC 1994 (large-vessel vasculitis, medium-vessel vasculitis and small-vessel vasculitis), they added new four categories; variable vessel vasculitis, single organ vasculitis, vasculitis associated with systemic disease and vasculitis associated with probable etiology (Fig. 2, Table 1).

Large-vessel vasculitis, including TAK and GCA, was defined as vasculitis affecting the aorta and its major branches more often than other vasculitides, whereas any size artery might be affected. It was concluded that these types of arteritis could not be distinguished by pathological findings, except for the difference in the age of onset.

Medium-vessel vasculitis, including PAN and Kawasaki disease (KD), was defined as vasculitis affecting the main visceral arteries and their branches. PAN is defined as necrotizing arteritis of the medium or small arteries without glomerulonephritis or vasculitis in the arterioles, capillaries or venules, and the

Nomenclature of Systemic Vasculitis.14 They adopted names and definitions of vasculitides based on the size of the affected vessels, and categorized vasculitides into large-vessel vasculitis, medium-vessel vasculitis and small-vessel vasculitis, including MPA. Although they emphasized that the nomenclature and the definitions did not provide diagnostic or classification criteria, both the ACR criteria and CHCC definitions have been used in parallel to diagnose vasculitis by many clinicians, leading to an overlapping diagnosis of PAN and MPA.

Sorensen et al. created new criteria by using the CHCC 1994 definitions and surrogate parameters to diagnose primary vasculitis,15 although a prospective vasculitis register found that the Sorensen diagnostic criteria for MPA were not very useful.16
criteria clearly stated that it could not be associated with ANCA based on a report describing that ANCA is typically absent in patients with PAN.  

Among small-vessel vasculitides, ANCA-associated vasculitis (AAV) was distinguished from the other types of small-vessel vasculitis called “immune complex vasculitis,” including anti-glomerular basement membrane (anti-GBM) disease, cryoglobulinemic vasculitis, IgA vasculitis and hypocomplementemic urticarial vasculitis (anti-C1q vasculitis). Patients clinically considered to have AAV without ANCA were referred to as having ANCA-negative AAV. Immune complex small-vessel vasculitis is defined as vasculitis with moderate to marked vessel wall deposits of immunoglobulin and complement components, predominantly affecting small vessels. These deposits differ from the few or no immune deposits in vessel walls, which is characteristic for ANCA-associated vasculitides. When appropriate, immune complex vasculitis can be categorized as vasculitis associated with probable etiologies (e.g., hepatitis C virus-associated cryoglobulinemic vasculitis) or as a vasculitis associated with systemic disease (e.g., lupus vasculitis or rheumatoid vasculitis).  

Variable vessel vasculitis is defined as vasculitis with no predominant size of the affected vessels. Behçet’s disease and Cogan’s syndrome are categorized as variable vessel vasculitis, rather than vasculitis associated with a systemic disease.  

In the CHCC 2012 definitions, efforts were made to replace eponyms with suitable non-eponymous terms. The eponyms “Wegener’s granulomatosis” and “Churg-Strauss syndrome” were replaced by granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). The eponym Henoch-Schönlein purpura was also replaced by IgA vasculitis. “Goodpasture’s syndrome” has been used in the past for the clinical entity associated with diffuse pulmonary hemorrhage and rapid progressive glomerulonephritis with anti-GBM antibodies, but the use of “anti-GBM disease” was advocated in the CHCC 2012. These changes in the names of vasculitides have already been widely accepted. The eponyms “Behçet’s disease” and “Cogan’s syndrome” were added as types of variable vessel vasculitis.

**THE ACR/EULAR DIAGNOSTIC AND CLASSIFICATION CRITERIA FOR VASCULITIS STUDY (DCVAS)**

Although the ACR 1990 criteria and CHCC 2012 definitions have been widely used as diagnostic criteria for systemic vasculitis by clinical researchers and physicians, there are currently no appropriate criteria to diagnose systemic vasculitis. The diagnostic criteria with updated classifications based on the increased understanding of the pathophysiology, and with newly widespread diagnostic test tools, are required for not only clinical researchers, but also for practicing clinicians.

Lionaki et al. found substantial discrepancies in the allocation of patients between the CHCC definitions and...
Table 1  Names for vasculitides adopted by CHCC 2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Names</th>
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<tbody>
<tr>
<td>I. Large-vessel vasculitis (LVV)</td>
<td>Takayasu arteritis (TAK)</td>
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<td></td>
<td>Giant cell arteritis (GCA)</td>
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<tr>
<td>II. Medium-vessel vasculitis (MVV)</td>
<td>Polyarteritis nodosa (PAN)</td>
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<td></td>
<td>Kawasaki disease (KD)</td>
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<td>III. Small-vessel vasculitis (SVV)</td>
<td>ANCA-associated vasculitis (AAV)</td>
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<td></td>
<td>Microscopic polyangiitis (MPA)</td>
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<td></td>
<td>Granulomatosis with polyangiitis (GPA)</td>
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<td></td>
<td>Eosinophilic granulomatosis with polyangiitis (EGPA)</td>
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<td></td>
<td>Immune complex small-vessel vasculitis</td>
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<td></td>
<td>Anti-GBM disease</td>
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<td></td>
<td>Cryoglobulinemic vasculitis (CV)</td>
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<td></td>
<td>IgA vasculitis (IgAV)</td>
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<td></td>
<td>Hypocomplementemic urticarial vasculitis (HUV)</td>
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<td>Variable vessel vasculitis (VVV)</td>
<td>Behçet’s disease (BD)</td>
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<td></td>
<td>Cogan’s syndrome (CS)</td>
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<td>Single-organ vasculitis (SOV)</td>
<td>Cutaneous leukocytoclastic angiitis</td>
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<td>Cutaneous arteritis</td>
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<td>Primary central nervous system vasculitis</td>
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<td>Isolated aortitis</td>
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<td>Others</td>
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<td>Vasculitis associated with systemic disease</td>
<td>Lupus vasculitis</td>
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<td>Rheumatoid vasculitis</td>
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<td></td>
<td>Sarcoid vasculitis</td>
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<td></td>
<td>Others</td>
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<tr>
<td>Vasculitis associated with probable etiology</td>
<td>Hepatitis C virus-associated cryoglobulinemic vasculitis</td>
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<tr>
<td></td>
<td>Hepatitis B virus-associated vasculitis</td>
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<td>Syphilis-associated aortitis</td>
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<td>Drug-associated immune complex vasculitis</td>
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<td>Drug-associated ANCA-associated vasculitis</td>
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<td></td>
<td>Cancer-associated vasculitis</td>
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<td>Others</td>
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and the EMA algorithm in a retrospective study of 502 patients with ANCA-associated vasculitis. Sixty-four percent of the cases classified as MPA by the CHCC definitions were categorized as having GPA by the algorithm, and the proportion of patients considered to have GPA by the algorithm was significantly higher than those in the CHCC definition (65% vs. 23%, p < 0.0001). The authors of that study also revealed that neither system could predict relapse among patients with ANCA-associated vasculitis with renal disease, and that the ANCA phenotype could provide a more useful tool for predicting relapse. Lyons et al. investigated the genetic basis of ANCA-associated vasculitis, and provided preliminary support for the concept that proteinase 3 (PR3)-ANCA-associated vasculitis and myeloperoxidase (MPO)-ANCA-associated vasculitis are distinct autoimmune syndromes.23

Recently, Hoffman and Calabrese published a review article suggesting that the classification of vasculitis merely based on the size of vessels could fail to consider that the vessels of the same caliber in different locations have specialized roles in response to stimuli, injury and repair that determine the disease patterns.24 They also stated that an improved understanding of the unique territorial vulnerabilities of vessels could form the basis of new hypotheses for the etiopathogenesis of vasculitis.

The imaging techniques used as diagnostic tools for systemic vasculitis have also developed rapidly. The usefulness of computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) in patients with TAK has been reported.25,26 The use of ultrasound and positron emission tomography CT (PET-CT) may also be established to diagnose and evaluate TAK and GCA.27,30
The ACR and the European league against rheumatism (EULAR) have made an international effort to develop new diagnostic criteria for systemic vasculitides. The study is named the “Diagnostic and Classification Criteria of Vasculitis (DCVAS)” study, and the goal of the study is to develop and improve the diagnostic criteria for ANCA-associated vasculitis, PAN, TAK and GCA. They will analyze more than 2,000 patients with vasculitis not only based on the traditional approach involving vessel size for the classification of vasculitis, but also on clinical data, ANCA testing, biopsy and imaging data. The first patient was recruited into the DCVAS in 2010, and the development of a new internationally unified diagnostic and classification criteria for both researchers and clinicians is expected.

**EPIDEMIOLOGY OF ANCA-ASSOCIATED VASCULITIS**

The regional and ethnic differences in the clinical features of patients with primary systemic vasculitides have been well known. For example, in the case of ANCA-associated vasculitis, there have been some reports suggesting that the incidence and clinical characteristics differ geographically. The incidence and the prevalence of GPA are significantly higher in reports from northern Europe (Norway and Germany), while MPA is predominant in reports from southern Europe (Spain), whereas the incidence of GPA and MPA were equal in a report from Sweden.

Fujimoto et al. performed a population-based study to show the incidence of primary renal vasculitis, and revealed that the incidence of renal vasculitis did not differ between Japan and European countries, although patients with GPA or EGPA were not detected in the study in Japan. A prospective study was subsequently performed to compare the incidence and characteristics of ANCA-associated vasculitis between Japan and Europe using the same definitions. Patients were classified using the EMA algorithm. There was no significant difference in the annual incidence of ANCA-associated vasculitis between Japan and the UK (22.6 vs. 21.8/million adults), whereas the annual incidence of MPA in Japan was higher than that in the UK (18.2 vs. 6.5/million adults), while GPA was predominant in the UK (14.3/million adults) compared with the incidence in Japan (2.1/million adults). There were also significant differences in the ANCA phenotype; the ratio of pANCA/MPO-positive patients was significantly higher in Japan than the ratio in the UK (83.7% and 30.0%, respectively, p < 0.001), while there were significantly fewer cANCA/PR3-positive patients in Japan (7.0% and 58.0%, respectively, p < 0.001). A high ratio of MPO-ANCA positivity to PR3-ANCA positivity was also reported in other Asian countries.

In 2014, Sada and colleagues published the results of a nationwide prospective cohort study of remission induction therapy in Japanese patients with AAV (RemIT-JAV), and also showed that MPO-ANCA-positive MPA, including renal-limited vasculitis, was the most common form of ANCA-associated vasculitis in Japanese patients, and that one-half of the patients with GPA were positive for MPO-ANCA in Japan. The reports from China and Taiwan also revealed that MPA was predominant among the patients in these countries with ANCA-associated vasculitis.

Besides the differences in the incidence and the prevalence, the characteristics of the affected organs in patients with ANCA-associated vasculitis also vary widely between Europe and Asian countries. Sugiyama and colleagues published a report describing the characteristics of MPA and GPA in Japan using the database of the Ministry of Health, Labour and Welfare (MHLW) from 2006 to 2008. This study revealed that 73.7% of Japanese patients with MPA had pulmonary involvement and 11.3% presented with pulmonary hemorrhage. A high prevalence of interstitial pneumonia in patients with ANCA-associated vasculitis in Asian countries was also indicated in other retrospective studies. Of note, less than 10% of patients with ANCA-associated vasculitis in European countries had ILD. Some reports previously indicated that interstitial lung diseases (ILD) developed more frequently in MPO-ANCA-positive patients with ANCA-associated vasculitis than in PR3-ANCA-positive patients, suggesting that the differences in the prevalence of ILD between Asia and Europe may results from the ANCA phenotype.

The RemIT-JAV study revealed that ANCA-associated vasculitis patients with ILD tended to be categorized as having lower disease activity by the Birmingham Vasculitis Activity Score (BVAS). The BVAS is a standard tool to evaluate the clinical disease activity in patients with systemic vasculitis, and is widely used not only by physicians, but also by clinical researchers. The BVAS is based on symptoms and signs in nine separate organs. It is noteworthy that ILD is not included in the BVAS scoring system. Although a report concluded that the BVAS was a useful tool for determining the disease activity and outcome in Japanese patients with MPA, further investigations are required to analyze the long-term prognosis in ANCA-associated vasculitis patients with ILD, and to clarify whether the BVAS scoring system can be applied to all patients with ANCA-associated vasculitis in terms of the variety of regional and ethnic differences in the clinical characteristics.

Sreih et al. published a report comparing the clinical characteristics of patients with ANCA-associated vasculitis between Hispanics and Caucasians living in the same geographical area. They revealed that Hispanics with ANCA-associated vasculitis present with more severe disease activity and more severe organ injuries compared to Caucasians. Although some
studies have been performed to analyze the genetic background of ANCA-associated vasculitides, further research in different ethnic groups is required to reveal the effects of genetic factors on the clinical characteristics and prognosis of ANCA-associated vasculitides.

**Epidemiology of Polymyalgia Rheumatica**

The populations of patients with PAN in some old reports were not homogeneous because they included patients with MPA; hence it is difficult to discuss the ethnic and regional differences in the incidence, prevalence and the clinical characteristics of PAN. The annual incidence of PAN in Spain diagnosed using the CHCC 1994 and in Sweden using the EMA algorithm were both 0.90/million adults, and the prevalence was approximately 30/million adults in Europe. Pagnoux et al. described the characteristics of a large number of patients with PAN, which was well distinguished from MPA. Of the 348 patients with PAN, 123 patients had hepatitis B virus (HBV)-related PAN. The mean age at diagnosis was 51.2 ± 17.3 years (±SD), and the ratio of males to females was 1.7 (220/128). Fibrinoid necrosis of interstitial medium-sized arteries was detected in four of the 11 patients who underwent a renal biopsy. They also revealed that the patients with HBV-related PAN presented more severe disease activity compared with patients with non-HBV-related PAN. However, relapse occurred more frequently in patients with non-HBV-related PAN than in patients with HBV-related PAN. Recently, it was reported that loss-of-function mutations of adenosine deaminase 2 (ADA2) could cause PAN vasculopathy. This may underlie some of the differences in different populations.

**Epidemiology of Large-Vessel Vasculitides**

TAK was first reported by Takayasu in 1908. Although patients with TAK have been reported from all over the world, the prevalence and the annual incidence of TAK have been limited. Previous reports revealed that patients with TAK are predominant in Asian countries compared with Western countries, although the low prevalence of TAK makes it difficult to estimate the accurate incidence and prevalence of the disease. The guidelines for the management of vasculitis syndrome by the Japanese Circulation Society (JCS 2008) reported that more than 5,000 patients with TAK were registered in the MHLW registry, so the prevalence was more than 0.004%. Moreover, the distribution of vascular involvement reportedly differs among regions. In Japan and South America, cervical and thoracic arterial lesions are prevalent, whereas abdominal lesions are more common in Israel and other Asian countries.

The HLA-B52 haplotype is well known to be closely associated with TAK not only in Japan, but also in other countries. In Japan, the prevalence of the HLA-B52 allele in healthy controls is higher compared with that in other countries, which might be responsible for the high prevalence of TAK and the higher prevalence of HLA-B52 in patients with TAK than in other countries. The correlation of other HLA alleles with TAK has been also reported.

On the other hand, the incidence and prevalence of giant cell arteritis (GCA) is significantly higher in northern Europeans than in southern Europeans and Asians. The annual incidence of GCA in Scandinavian countries was reported to be over 20/100,000 people over the age of 50, whereas a lower incidence rate of approximately 10/100,000 was reported in Italy and Spain. In Asia, much lower incidence and prevalence rates were reported. Kobayashi et al. reported the results of a nationwide survey, and showed that the point prevalence of GCA in Japan was 690 patients in 1997.

Some genetic factors might affect these differences in the incidence and prevalence of GCA. For example, patients with GCA showed an increased frequency of DR4 compared with controls in a report from Italy. The HLA-DRB1*0401 and HLA-DRB1*0404 alleles (components of the DR4 gene) were predominantly detected in GCA patients, and were less frequently detected in Japanese healthy controls compared with American healthy controls. This might explain one of the reasons for the low incidence and prevalence of GCA in Japan.

A study of a large number of Japanese patients with TAK showed a significant female predominance (the female to male ratio was eight to one), and some reports from other countries indicated the same results. However, a report comparing the characteristics of patients with TAK in Japan and India revealed a significantly lower ratio of female to male patients with TAK in India than the ratio in Japan. GCA affects females two to three times more often than males, and this rate is similar all over the world.

Some studies have demonstrated an overall increase in the incidence of GCA. The increase might be dependent on the improvements in the diagnostic tools, especially imaging tools such as CTA, MRA and PET. The development of new diagnostic criteria for TAK and GCA is required, and as described above, the DCVAS is trying to develop and improve the criteria for systemic vasculitides, including large-vessel vasculitis.

**Conclusions**

We herein reviewed the current classification criteria and definitions for systemic vasculitides. These are used to categorize and diagnose patients with vasculitis, although they were not developed as diagnostic criteria. Hence, international groups are making an effort to establish new internationally unified diagnos-
tic and classification criteria. Global evidence has been established for the treatment of some types of systemic vasculitis based on randomized controlled trials. However, the ethnic and regional differences in the incidence, prevalence and clinical characteristics of patients with vasculitis should be recognized when we apply the results of studies to each patient. Further international studies are required to reveal how the ethnic and regional differences are related to pathogenesis, and to establish individualizing therapies for systemic vasculitides.

REFERENCES

32. Luqmani RA, Suppiah R, Grayson PC, Merkel PA, Watts R. Nomenclature and classification of vasculitis - update on the ACR/EULAR diagnosis and classification of vascu-
Allergology International Vol 63, No4, 2014 www.jsaweb.jp


69. Mehra NK, Jaini R, Balamurugan A et al. Immunogenetic


