The utility of the ACR/EULAR 2017 provisional classification criteria for granulomatosis with polyangiitis in Korean patients with antineutrophil cytoplasmic antibody-associated vasculitis

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ABSTRACT

Objective. *We applied the ACR/EULAR 2017 provisional classification criteria for granulomatosis with polyangiitis (GPA) to 150 Korean patients with previously diagnosed antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and investigated how many patients with AAV were reclassified as GPA.*

Methods. *We included patients with 30 GPA, 30 eosinophilic GPA (EGPA) and 90 microscopic polyangiitis (MPA) patients. Patients can be classified as GPA, when the sum of scores is more than 5.*

Results. *At diagnosis the mean age of 150 patients with AAV was 60.1 years old, and 101 patients (67.3%) were women. Overall, 33 of 150 patients with AAV (22.0%) were classified as GPA according to the 2017 provisional criteria for GPA. The 2017 provisional criteria for GPA dropped to 10.0% of previously diagnosed GPA patients and the major factor to drop 3 GPA patients was the deletion of 2 items of the 1990 criteria, urinary sediment and infiltrates on chest radiograph. Meanwhile, one of 30 patients with EGPA (3.3%) and 5 of 90 patients with MPA (5.6%) were newly classified as GPA based on the 2017 provisional criteria for GPA. We could also find that items of the 2017 provisional criteria to contribute to reclassifying EGPA and MPA patients as GPA were PR3-ANCA, mass-like lung lesion and nasal congestion in Korean patients with AAV.*

Conclusion. *The use of the 2017 provisional criteria for GPA excluded 10.0% of previously classified GPA patients and newly classified 3.3% of EGPA patients and 5.6% of MPA patients as GPA in Korean patients with AAV.*

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic necrotising vasculitis (1). AAV included three variants: granulomatosis with polyangiitis (GPA), eosinophilic GPA (EGPA), and microscopic polyangiitis (MPA) (1). GPA usually involves upper and lower respiratory tracts and kidneys (2, 3). EGPA is commonly exhibits allergic features involving skin and lung (4, 5). MPA typically provokes rapidly progressive necrotising glomerulonephritis and pulmonary capillaritis (1, 6, 7).

So far, the American College of Rheumatology (ACR) 1990 criteria for the classification of AAV have been the most widely used for classifying patients as GPA and EGPA, but not MPA (3, 5). The ACR 1990 criteria include no detailed item of proteinase 3 (PR3)-ANCA (cytoplasmic ANCA (C-ANCA)) or myeloperoxidase (MPO)-ANCA (perinuclear ANCA (P-ANCA)) (1, 8). In addition, the fact that the clinical manifestations of GPA and MPA are similar makes it difficult to differentiate between the two diseases, although both the prognosis and the optimal therapeutic regimen differ depending on variants of AAV or ANCA types (8, 9). With these reasons, needs for the new classification criteria for AAV have been raised to date.

Recently, a joint working group of Diagnostic and Classification Criteria for Primary Systemic Vasculitis (DCVAS) and collaborators, including the ACR, the European League Against Rheumatism (EULAR) and the vasculitis foundations, proposed the ACR/EULAR 2017 provisional classification criteria for GPA (presented at 2016 ACR session: New Classification Criteria for ANCA-associated Vasculitis: implications for clinical practice). These criteria for GPA feature a total of nine items, of which five are clinical variables and four test variables. Different risk scores are assigned to each item; the sum of

Table I. Application of the ACR / EULAR 2017 provisional classification criteria for GPA to 150 patients with AAV.

	Total Scores for the ACR / EULAR 2017 provisional classification criteria for GPA														
	-3	-2	0	1	2	3	4	5	6	7	8	10	11	13	14
AAV (n=150)	3	4	54	8	33	14	1	8	3	2	6	5	5	3	1
GPA (n=30)						3		3	3	1	6	5	5	3	1
EGPA (n=30)	3	4	11	3	2	5	1	1							
MPA (n=90)			43	5	31	6		4		1					

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; GPA: granulomatosis; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

Table II. Three GPA patients not fulfilling and 8 EGPA and 5 MPA patients satisfying the ACR / EULAR 2017 provisional classification criteria for GPA.

Patients number	Total Scores	Bloody nasal discharge, ulcers, crusting or sino-nasal congestion (3)	Nasal polyps (-4)	Hearing loss or reduction (1)	Cartilaginous involvement (2)	Red or painful eyes (1)	C-ANCA or PR3-ANCA (5)	Eosinophilia ount ≥ 1 c($x10^9$/L) (-3)	Nodule, mass or cavitation on chest imaging (2)	Granuloma on biopsy (3)	Previous Diagnosis	Reclassification
1	3									Yes	GPA	No GPA
2	3									Yes	GPA	No GPA
3	3									Yes	GPA	No GPA
4	5	Yes					Yes	Yes			EGPA	GPA
5	7						Yes		Yes		MPA	GPA
6	5						Yes				MPA	GPA
7	5	Yes							Yes		MPA	GPA
8	5	Yes							Yes		MPA	GPA
9	5	Yes							Yes		MPA	GPA

GPA: granulomatosis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; C-ANCA: cytoplasmic antineutrophil cytoplasmic antibody; PR3-ANCA: proteinase 3- antineutrophil cytoplasmic antibody.

scores ranges from 7 to 17. For establishing these criteria for GPA, MAP and EGPA served as comparators. In comparison with the 1990 criteria, the discriminative capacity of the 2017 provisional criteria for GPA was shown to be better (sensitivity 90.7% and specificity 93.5%). However, as the new provisional criteria are not fully defined or formally published, and clinical trials planned to validate the criteria awaits more participants, it is useful to explore the accuracy and the discriminative capacity of the criteria in different populations. Hence, in the present study, we used the 2017 provisional criteria for GPA to evaluate 150 Korean patients with previously diagnosed AAV, and we investigated how many GPA patients would be reclassified as GPA. We also determined how many MPA and EGPA patients became newly classified as GPA based on the new provisional criteria.

Patients and methods

We collected data on 150 patients (30 GPA, 30 EGPA and 90 MPA patients), who had been classified as AAV according to the inclusion criteria as follows: i) patients who had been first classified as AAV from October 2000 to August 2016 at Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital; ii) patients who had fulfilled the 2012 revised Chapel Hill Consensus Conference for MPA, and who had satisfied the ACR 1990 criteria for the classification for GPA and EGPA; iii) patients who had the results of PR3-ANCA and MPO-ANCA by the enzyme-linked immunosorbent assay (ELISA) at diagnosis and those who had not both; iv) patients of whom medical records included the sufficient contents to determine the score for the new criteria for GPA. This study was approved by the Institutional Review Board of Severance Hospital (4-2016-0901). Each patient was scored using the 2017 provisional criteria for GPA as follows: 3 points for bloody nasal discharge, ulcers, crusting or sino-nasal congestion; -4 points for nasal polys; 1 point for hearing loss or reduction; 2 points for cartilaginous involvement; 1 point for red or painful eyes; 5 points for C-ANCA or PR3-ANCA; -3 points for eosinophilia; 2 points for nodules, mass or cavitation on chest imaging; and 3 points for granuloma on biopsy. When the sum of scores is more than 5, the patient can be classified as GPA.

Results

The mean age at diagnosis of the 150 AAV patients was 60.1 years; 101 (67.3%) were female. First, we used the 2017 provisional criteria for GPA to evaluate all patients, and found that 33 patients with AAV (22.0%) were classified as GPA. We next used the 2017 provisional criteria for GPA to evaluate patients with each variant of AAV. The new criteria clearly reclassified 27 of 30 GPA patients (90.0%) as GPA. However, three GPA patients (10.0%) were not reclassified in this way. In addition,

1 of 30 patients with EGPA (3.3%) and 5 of 90 patients with MPA (5.6%) were newly classified as GPA (Table I).

Three GPA patients, who did not fulfilled the 2017 provisional criteria for GPA, exhibited granuloma on biopsy; their scores were thus 3. One EGPA patient exhibited sino-nasal congestion (3 points), PR3-ANCA positivity (5 points) and eosinophilia (-3 points). The sum of scores of 5 thus reclassified that patient as suffering from GPA. Moreover, although five MPA patients who met the 2017 provisional criteria for GPA showed no evidence of granuloma on biopsy, two had PR3-ANCA (5 points) and the other three patients exhibited both sino-nasal congestion (3 points) and masses on chest imaging (2 points), yielding summed scores ≥ 5. Three cases of lung masses were all confirmed by biopsy, revealing fibrotic changes that were not granulomas (Table II).

Discussion

In this study, we first applied the ACR/EULAR 2017 provisional classification criteria for GPA to Korean patients with AAV, and found that 10.0% of GPA patients were not reclassified as GPA, and that 3.3% of EGPA patients and 5.6% of MPA patients were newly classified as GPA. First, we examined three GPA patients who did not satisfy the 2017 provisional criteria. At diagnosis, all had exhibited urinary sediments suggestive of micro-haematuria, and granulomatous inflammation on biopsy (of two kidneys and one lung). In addition, two had exhibited fixed infiltrates on chest radiograph (3). The provisional criteria do not include any item of urinary sediment, and pulmonary item excludes fixed infiltrates. With these reasons, three GPA patients were not reclassified as GPA despite definitive histological results. Moreover, no patient was reclassified as MPA (because their histologic features were those of granuloma), nor were they reclassified as EGPA (because they had no history of asthma, eosinophilia, or eosinophilic extravasation apparent on biopsy) (1, 5). Thus, we are of the view that the system must be revised in the context of granuloma evident on biopsy.

Of these three patients, two patients had MPO-ANCA, but one had no ANCA, at diagnosis. Recently, AAV has been subdivided into three new categories based on ANCA types: MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis (10, 11). Thus, we suggest that two patients with MPO-ANCA might be considered as having MPO-ANCA vasculitis and the single patient with no ANCA might be categorised as exhibiting ANCA negative vasculitis.

We next examined one EGPA patient newly classified as GPA. At diagnosis, the patient had exhibited asthmatic symptoms, >10% eosinophilia, pulmonary non-fixed infiltrates and a paranasal sinus abnormality (5). According to the 2017 provisional criteria, the patient had both sino-nasal congestion (3 points) and eosinophilia (-3 points), yielding a final score of 0. However, the patient scored 5 because of PR3-ANCA positivity, and was thus reclassified as GPA. The extent of PR3-ANCA positivity might be overestimated in this case. Thus, we are of the view that the PR3-ANCA score should be readjusted.

Finally, we examined five MPA patients newly classified as GPA. Two had PR3-ANCA but lacked items associated with negative point scores including nasal polyp and eosinophilia; their summed scores were thus more than 5. Although the points allotted to PR3-ANCA positivity and granuloma evident on biopsy are relatively high, the combination nasal symptoms and lung manifestations caused 3 MPA patients to be newly assigned to GPA in the absence of PR3-ANCA positivity and granuloma evident on biopsy.

We concluded that the major contributor to elimination of three genuine GPA patients, using the 2017 provisional criteria, was the deletion of two items of the 1990 criteria, namely, urinary sediment and infiltrates evident on chest radiograph (3). In addition, use of the 2017 provisional criteria reclassified EGPA and MPA patients as GPA: the relevant criteria were PR3-ANCA positivity, mass-like lung lesions and nasal congestion in Korean patients with AAV. Particularly, as the 2017 provisional criteria is not the definitely validated classification criteria for GPA, more efforts should be devoted to the clinical implications associated with use of the new criteria.

In conclusion, use of the 2017 provisional criteria for GPA excluded 10.0% of previously classified GPA patients and newly classified 3.3% of EGPA patients and 5.6% of MPA patients as GPA in Korean patients with AAV. Therefore, the ACR/EULAR 2017 provisional classification criteria for GPA require adjustment in terms of their application to not only patients previously classified AAV patients, but also patients under suspicion of AAV.

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