Editorial

Subclassifying ANCA-associated vasculitis: a unifying view of disease spectrum

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How to best subclassify ANCA-associated vasculitis (AAV) has been a long-standing debate. The original concept of AAV, combining granulomatosis with polyangitiis (GPA) and microscopic polyangiitis (MPA), paid tribute to the shared clinical and histopathological features of GPA and MPA and their tight links with positive ANCA serology and similar treatment modalities. Conversely, because GPA has additional granulomatous features — with characteristic manifestations of the ear, nose and throat (ENT) tract and pulmonary nodules and masses — AAV can also be considered a fabricated entity devoid of a common underlying pathogenesis. GPA and MPA also have different clinical courses, MPA with a higher risk of mortality and GPA more frequently a remitting-relapsing course (1, 2).

More recently, several studies suggested that predicting clinical outcomes was more accurate when AAV subsets were classified by the specific ANCA profile into proteinase 3 (PR3)-AAV and myeloperoxidase (MPO)-AAV. Even though PR3-ANCA and MPO-ANCA mostly go hand in hand with the clinical diagnoses of GPA and MPA, respectively, a subset of patients with AAV has divergent clinical-serological patterns. With such an ANCA-based classification, PR3-AAV predicted relapsing disease and MPO-AAV higher mortality (1, 3). The rationale for an ANCA serology-based subclassification was further supported by evidence of genetic susceptibility (4), differences in inflammatory cytokine profiles (5), and response to rituximab (6) more closely linked with serological than clinical categories.

The publication by Deshayes et al. in this issue dampens any enthusiasm about the advantage of subclassifying AAV as PR3- and MPO-AAV. The authors' retrospective analysis of a single-center cohort with AAV found that relapse-free remission was better predicted by the clinical phenotypes of GPA or MPA. Because of the relatively limited sample size, 150 patients, the study likely cannot dismiss the observations from larger studies that the separation based on ANCA specificity provides better risk stratification than do clinical categories. The Deshayes et al. study still conveys that no single clinical or serological descriptor may perfectly embrace the outcomes of AAV for individual patients.

The dilemma may stem from the misconception that AAV consists of 2 individual subsets. A cluster analysis, which gave the impetus for the Deshayes et al. study, actually identified 3 main AAV subsets, namely non-renal AAV, renal PR3-AAV, and renal MPO-AAV, with low mortality-high relapse, intermediate mortality-intermediate relapse and high mortality-low relapse risk, respectively (2). Whether such a separation in 3 groups would have changed the conclusions of the Deshayes et al. study cannot be determined from their article. The separation of renal and non-renal subsets has strong face validity given that renal disease or impaired renal function is a well-established determinant of high mortality in studies of AAV (7) or GPA alone (2, 8, 9). That the unfavorable prognostic impact of renal disease also holds true for GPA alone supports GPA itself as a protean entity.

Observations indicating a clinical interaction between ENT and renal disease lend further support to the idea that AAV cannot simply be dichotomized. ENT and renal involvement are prominent organ manifestations found in 50% to 80% of patients with AAV and reflect the granulomatous and vasculitic disease components, respectively. Studies of AAV or GPA only indicated that as compared with patients with no ENT involvement, those with ENT involvement showed less frequent renal disease (10), better renal function (8, 10, 11), milder renal tissue lesions (11) and longer survival (8-10). The possibility that these observations merely reflect delayed diagnosis in the absence of ENT symptoms, and thus more pronounced renal damage, is contradicted by data showing that ENT and kidney involvement predict opposite relapse risks. ENT disease is associated with increased relapse risk (12), whereas impaired renal function decreases relapse risk (10, 13) with a "dose–response" relationship (13).

Hence, AAV may represent a continuum of disease phenotypes anchored at predominantly granulomatous and predominantly vasculitic disease patterns, with relapse risk linked to the granulomatous component and mortality to the vasculitic component. The granulomatosis–vasculitis balance may be driven by age-related immunological factors in light of observations in GPA that ENT involvement is associated with relatively younger age at disease onset (8, 10). ANCAs appear more closely associated with vasculitis given the infrequent ANCA negativity in patients with renal involvement (14) and the predominantly granulomatous phenotype in the few cases with ANCA-negative AAV (15). Why PR3-ANCA are more tightly linked to a granulomatous-vasculitic phenotype and MPO-ANCA to a pure vasculitic response is elusive, but genetic factors might play a role (4).

Thus, the main challenge is to transpose this mechanistic concept into clinically pertinent and practical subcategories. Defining the vasculitis part by renal involvement

alone is too restrictive and does not capture other, yet less frequent, small-vessel vasculitis-related presentations, such as alveolar hemorrhage, mononeuritis multiplex and scleritis. Such symptoms have been individualized as "severe" manifestations, reflecting their inherent organ- or life-threatening nature, as opposed to non-vasculitic and less severe manifestations (16). Given that ANCA specificity further gauges the granulomatous versus vasculitis burden, AAV could then be trisected in "non-severe", "severe PR3-AAV" and "severe MPO-AAV", representing the predominantly granulomatous, mixed granulomatous-vasculitic and predominantly vasculitic patterns of AAV (**Figure**). This separation may be the best compromise that incorporates clinical, histopathological, serologic and prognostic aspects and is therapeutically relevant. EULAR/ERA-EDTA management guidelines endorse that non–organ-threatening AAV can be treated with less toxic remission-induction therapies and PR3- or MPO-ANCA positivity could affect the duration of remission-maintenance therapy. Indeed, the expert panel indicated that PR3-AAV might require longer remission-maintenance therapy, thereby admitting greater confidence in the use of serological than clinical parameters to determine relapse risk (17).

The study by Deshayes et al. may unintentionally lead to a more unifying concept of AAV as a disease entity that spans a spectrum of clinical phenotypes. This implies the abandonment of the GPA-MPA classification that lacks granularity and, as highlighted by the 5% of patients with MPA and ENT involvement in the authors' report, is vulnerable to conflicting classifications. Because subclassifying a disease with a phenotypic continuum is in principle imperfect, the AAV subclassification we propose may be only one step in an iterative process and could prove false if the causes of AAV are eventually discovered or subtypes are identified with cutting-edge genomic and transcriptomic profiling. Regardless, adopting from now on a more harmonious and relevant nomenclature provides opportunities to better characterize AAV at individual and cohort levels and further increase our understanding of the pathogenesis and best-management principles of this disease.

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Figure. Schematic subcategorization of AAV in 3 clinically-relevant disease categories defined by clinical features and ANCA specificity.