

## Does One Size Fit All?



In 1954, when Godman and Churg reviewed 22 published cases with granulomatosis with polyangiitis (GPA; previously Wegener granulomatosis), it was concluded that patients suffered from a triad of pathological features: (1) systemic necrotizing angiitis, (2) necrotizing granulomatous inflammation of the respiratory tract, and (3) necrotizing glomerulonephritis<sup>1</sup>. At that time, the insidious onset of the disease was already appreciated. From these first cases, it was postulated that it should be possible to make an early diagnosis before the full-blown disease is manifest. In 1966, Carrington and Liebow presented the first patients with more limited forms of GPA<sup>2</sup>. These cases were identical in clinical and pathologic manifestations when compared to the extended form of the disease except for the absence of renal involvement. Most importantly, it was questioned whether this limited form represents a unique and separate entity or an earlier state of the same disease. Nearly 5 decades later, this question is still valid.

Nonetheless, the European Vasculitis Society (EUVAS) set out in the 1990s to harmonize treatment strategies for the different stages of disease. It was agreed that immunosuppressive treatment should reflect the severity of the disease<sup>3</sup>. During the last decade, results from clinical trials have been published, and more recently, data on longterm followup of patients included in these trials have been reported. In this editorial, we will discuss whether there are indeed different disease states in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and question whether treatment should be tailored to these states.

### So, what different sizes are there?

Since the seminal paper of Carrington and Liebow, several definitions have been used to characterize the severity and/or extent of the disease. The classification of the EUVAS group and the Wegener's Granulomatosis Etanercept Trial (WGET) group are best known and will be discussed here (Figure 1)<sup>3,4</sup>.

The EUVAS group arbitrarily categorized patients as

having localized, early systemic, generalized, renal severe, or refractory disease<sup>3</sup>. This classification tries to reflect the postulated (natural) progress of the disease, although refractory disease is included as well, and it is clear that these patients cannot be classified as such at presentation. The WGET group classified their patients as "limited" in the absence of disease features that pose immediate threats either to a critical individual organ or to the patient's life, and otherwise as "severe"<sup>4</sup>. The WGET group classified patients based on the need of directly initiating maximal therapy, which may be more pragmatic for the clinician who needs to decide between an aggressive [i.e., cyclophosphamide (CYC) or rituximab] or a milder form of treatment [i.e., methotrexate (MTX)]<sup>5</sup>.

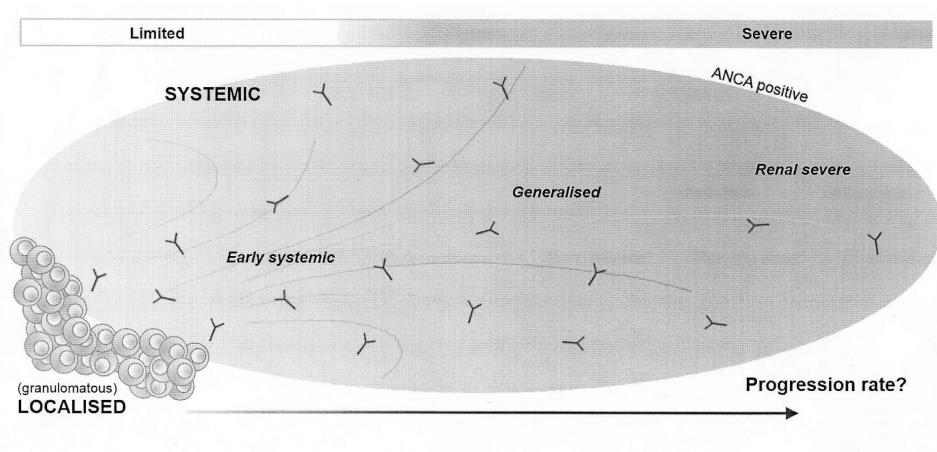
It is evident that there is an overlap between the classification systems. The patients originally presented by Carrington and Liebow as limited can hardly be described as "limited" using the definitions of the WGET or EUVAS, because 6 of 16 patients died from the vascular and granulomatous disease quickly after diagnosis<sup>2</sup>. Although there is agreement between the EUVAS and the WGET in the classification of most patients, there are also differences. Most notably, patients with biopsy-proven necrotizing glomerulonephritis can be classified as limited according to the WGET if renal function is not (yet) impaired; however, these patients are classified as generalized according to the EUVAS classification<sup>6,7</sup>. Otherwise, sensory neuropathy is classified as severe according to the WGET, but may occur in early systemic disease according to the EUVAS. Moreover, these definitions are general terms and are thus open to subjective interpretation. For example, pulmonary hemorrhage may be treated as either limited or severe at the discretion of the physician in the absence of data on progression<sup>4</sup>.

### Which differences matter?

What do the classifications tell us? Do they reflect differences in the underlying pathophysiology? A positive

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*See New features of vasculitis after diagnosis, page 1905*



*Figure 1.* Disease states in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, shown at the bottom as the (natural) progression from localized to renal severe disease according to the EUVAS group; and the classification according to the WGET group, shown at the top, into limited or severe disease. There is evidence that the pathophysiology differs between localized disease and systemic disease. Grayson, *et al* have shown that patients with early systemic vasculitis frequently develop new “severe” manifestations, highlighting that patients with early systemic disease suffer from the same disease as patients with generalized disease. We propose that the classification of disease state should focus not on initial presentation, but more on the biologic behavior of the disease, and hence the disease progression rate should also be included.

ANCA is more often found in patients with generalized disease compared to patients with localized disease<sup>8,9</sup>. In addition, T cells have a differential response in disease states: a Th1 pattern in localized disease and a Th0/Th2 pattern in generalized disease<sup>10</sup>. Histology demonstrates that localized disease is primarily granulomatous<sup>11,12</sup>, while severe manifestations, such as alveolar hemorrhage or necrotizing glomerulonephritis, are predominantly of a vasculitic character. Interestingly, Holle, *et al* showed that vasculitis was also present in 32% of biopsy specimens from patients with localized disease, supporting the view that localized and generalized are indeed the same disease<sup>11</sup>.

Can a patient with localized ANCA-negative disease progress to ANCA-positive generalized disease? By studying granulomatous nasal lesions, Voswinkel, *et al* found evidence that this might be the case<sup>13</sup>. VH gene analysis revealed enhanced selection and affinity maturation of B cells in granulomas, suggesting that autoreactive B cells could possibly produce ANCA directed against proteinase 3 locally. Importantly, however, none of the ANCA-negative patients with localized disease became ANCA-positive during followup in this study<sup>13</sup>.

Findings suggest that there are differences in pathophysiology between different disease states. However, this evidence is restricted to localized versus systemic disease but not between early systemic versus generalized disease, 2 disease states that are both ANCA-positive<sup>8</sup>.

### Patients change size

In the current issue of *The Journal*, Grayson, *et al*, report

their findings on the occurrence of new features of vasculitis that developed after a diagnosis was made and therapy was instituted<sup>14</sup>. Four hundred ninety (59%) of 838 patients with different forms of vasculitis experienced at least 1 new manifestation during followup, and 224 (46%) of these patients developed a new “severe” manifestation.

Even though these findings will not surprise most vasculitis experts, there are some limitations in the generation of data in this study. Most importantly, how accurately were patients assessed at diagnosis? It is known that vasculitis experts find more manifestations compared to general physicians. In addition, retrospective assessment is prone to recall bias. Moreover, the accuracy of the assessment is dependent on the diagnostic methods used. For instance, we found that detailed cardiac evaluation revealed a 62% prevalence of cardiac involvement in our patients with eosinophilic GPA (previously Churg-Strauss), while only 26% had clinical symptoms<sup>15</sup>. Finally, whether a manifestation is caused by active vasculitis is not always evident nor can it always be proven.

It can be questioned whether the findings in the study by Grayson, *et al* are indeed due to progression of the disease or due rather to differences in assessment at the time of diagnosis versus during followup. The authors, however, dealt with this issue by using predefined classification criteria and standardized collection of followup data. Therefore, we feel that it is safe to conclude that patients with a limited form of vasculitis could progress to severe disease during followup and therefore indeed represent an early state of the severe form. However, this study did not answer the question of whether patients

with ANCA-negative localized disease progressed to ANCA-positive generalized disease.

### Which treatment is the right fit?

CYC has been proven to be very effective in inducing remission in AAV. Longterm exposure, however, has been associated with an increased risk of treatment-related comorbidities, such as malignancy. To reduce CYC exposure, patients with early systemic disease were treated with a milder treatment regimen, i.e., MTX instead of CYC. In the NORAM (Nonrenal Wegener's Granulomatosis treated Alternatively with MTX) trial, MTX was not found to be inferior compared to CYC to induce remission<sup>15</sup>. However, results from the longterm followup are disappointing<sup>16</sup>. Patients treated with MTX tended to relapse more often and received corticosteroids, CYC, and other immunosuppressive agents for longer periods during followup compared to the group of patients initially treated with CYC. It was concluded that first-line treatment with MTX was associated with less effective disease control than CYC-based induction therapy<sup>17</sup>. Or, in other words, any advantage gained from treatment tailored to the disease state at initial presentation is lost during followup. However, because MTX and/or CYC were discontinued after 12 months of treatment, an alternative conclusion from the NORAM study could be that the use of MTX for 12 months only is too short and hence is associated with an extremely high rate of relapse after treatment discontinuation<sup>18</sup>.

### New approaches are needed

ANCA-associated vasculitis has changed from a fatal disease to a chronic illness, but the classification of disease states did not change accordingly. The findings from Grayson, *et al* question the validity of the current classifications, which focus on initial presentation, because the disease state may change during followup. This suggests that patients with early systemic disease essentially have the same disease as patients with generalized disease and that patients with early systemic disease may either progress at a slower pace or be earlier diagnosed. These observations suggest that every patient with systemic disease requires aggressive treatment (either CYC or rituximab<sup>19</sup>) to induce stable remission. Patients with early systemic disease, however, may be treated with a milder agent with less treatment-related morbidity, but this approach induces less effective disease control during followup.

We propose that the classification of disease should focus not so much on the initial presentation, but on the biologic behavior of the disease. Can we already use current knowledge of the prognosis from genetic studies or from biomarkers<sup>8</sup>? For example, factors such as ANCA serotype, nasal carriage of *Staphylococcus aureus*, and Fcγ receptor polymorphisms are associated with a higher relapse rate<sup>8,20,21</sup>.

We suggest focussing on identifying patients who are prone to relapse, in order to guide therapy accordingly.

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