Testing for antineutrophil cytoplasmic antibodies (ANCAs) in patients with systemic vasculitides and other diseases

To the editor,

In the excellent study recently published in the *Annals of the Rheumatic Disease*,[1] Damoiseaux *et al* showed a high diagnostic performance of antigen-specific immunoassay for the detection of myeloperoxidase (MPO) and proteinase 3 (PR3) antineutrophil cytoplasmic antibodies (ANCAs). These data challenge the role of indirect immunofluorescence in the ANCA testing algorithm. In our centre, we have discarded ANCA indirect immunofluorescence more than a decade ago. Therefore, new data showing the feasibility of screening by antigen-specific immunoassay have a particular value for us. In the recent series of 284 patients with ANCA-associated vasculitides, we have detected ANCAs by this approach in 96.9% of patients with microscopic polyangiitis (MPA) but only in 72.7% of patients with granulomatosis with polyangiitis (GPA) (table 1). The latter result can be explained by a relatively high occurrence of localised GPA in our series,[2] since a rate of ANCA positivity reached 92.2% in patients with renal GPA.

ANCA testing should be performed only in the clinical context since PR3-ANCA and MPO-ANCA can be found in the other conditions than vasculitis, for example, infective endocarditis,[3] tuberculosis,[4] primary sclerosing cholangitis[5] and interstitial lung diseases.[6] The results of several studies suggest that in such patients, ANCAs have not been merely a chance finding and may be clinically relevant, for example, a high prevalence of ANCAs was identified in unselected patients with infective endocarditis (24%). Seropositive patients presented more commonly with a subacute form of infective endocarditis leading to multiple valve involvement and a more frequent renal impairment.[3] Recent evidence indicates that a proportion of patients with idiopathic pulmonary fibrosis who were MPO-ANCA positive at diagnosis or who subsequently seroconverted can develop MPA.[7] The incidence of MPA tended to be lower in patients treated than not treated with corticosteroids though the difference did not reach statistical significance. In the other study, PR3-ANCAs were detected in a significant proportion of patients with primary sclerosing cholangitis compared with other liver diseases including primary biliary cirrhosis and autoimmune hepatitis. PR3-ANCAs were not solely related to underlying inflammatory bowel disease and may be a specific biomarker for primary sclerosing cholangitis.[5]

Damoiseaux *et al* suggested that ANCA-associated vasculitides may be classified based on the ANCA serotype since recent studies have shown that PR3-ANCA and MPO-ANCA diseases are strongly associated with distinguishable genetic alleles, phenotypic differences and differences in risk of relapse and response to immunosuppressive treatment. However, not all studies confirm a predictive value of ANCA specificity in patients with ANCA-associated vasculitis. Miloslavsky *et al*[8] in a pooled analysis of the Wegener's Granulomatosis Etanercept Trial and the Rituximab in Associated Vasculitis (ANCA) (RAVE) trial were unable to demonstrate the important clinical differences between patients who were MPO-ANCA positive and PR3-ANCA positive and with GPA. A relapse rate in patients who were MPO-ANCA positive and with GPA was higher than in patients who were MPO-ANCA positive and with MPA at 12 and 18 months. Therefore, in this patient cohort, a risk of relapse was associated more closely with the disease type than with ANCA specificity.

GPA and MPA have many overlapping features, and nosological diagnosis per se usually does not determine a choice of treatment.[9] Nevertheless, patients with GPA frequently present with extravascular granulomatous lesions (orbital pseudotumour, necrotising rhinitis and persisting lung infiltrates) that are not seen in MPA. Predominant granulomatous lesions may have impact on the choice of immunosuppression, for example, rituximab may be less effective for the induction of remission in such patients.[10] Up to 15%–25% of patients with GPA present with the localised form of disease that is restricted to the upper respiratory tract, eyes and ears. These patients have better survival and require less aggressive remission induction treatment compared with that in renal or other organ-threatening disease.[9] They usually show predominant granulomatous lesions and, therefore, may be less responsive to rituximab. Moreover, ANCA negativity is more prevalent in patients with the localised GPA.

The ANCA specificity-based classification will apparently be more user friendly than a nosological scheme, but will it improve treatment? ANCA specificity may predict a risk of relapse but its predictive value for outcomes, such as end-stage renal disease or death is low, if any. Patients who are PR3-ANCA positive may require longer maintenance treatment, for example, at least 36 months as opposed to 24 months in patients who are MPO-ANCA positive. However, according to the latest European League Against Rheumatism/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) recommendations for the management of ANCA-associated vasculitis, a choice of initial remission-induction treatment depends on the presence of organ or life-threatening disease.[9] ANCA specificity was not incorporated in these recommendations. Moreover, it was stated that structured clinical assessment rather than ANCA testing should inform decisions on changes in treatment for ANCA-associated vasculitis. This statement was added in the context of serial ANCA testing as a means of predicting future relapse. However, it seems to be relevant for the treatment choices in general.

ANCA presence and specificity not only aids diagnosis of ANCA-associated vasculitis but also may have important value as a guide for immunosuppressive treatment. Nevertheless, different histological and clinical features of ANCA-associated vasculitis are more relevant for treatment decisions than any laboratory parameter (predominant granulomatous lesions, localised vs generalised disease, renal vs non-renal vasculitis, relapsing vs non-relapsing disease, etc).

In conclusion, Damoiseaux *et al* data warranting a revision of the international consensus on screening for ANCA are of significant value for rheumatologists caring for patients GPA and MPA.

Table 1 Results of ANCA testing in 284 patients with ANCA-associated vasculitis, n (%)

	All patients (n=284)	GPA (n=220)	MPA (n=64)
PR-ANCA	145 (51.1)	127 (57.7)	18 (28.1)
MPO-ANCA	63 (22.2)	27 (12.2)	36 (56.3)
Both types	9 (3.2)	5 (2.2)	4 (6.2)
Undifferentiated	5 (1.8)	1 (0.5)	4 (6.2)
Negative	62 (21.8)	60 (27.3)	2 (3.1)

ANCA, antineutrophil cytoplasmic antibody; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR, proteinase.

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