Accurate Relapse Prediction in ANCA-Associated Vasculitis—the Search for the Holy Grail

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doi: 10.1681/ASN.2014080817

The discovery of ANCA in the 1980s has kindled three decades of intense collaborative clinical and translational research in vasculitis.1,2 These efforts have generated a better understanding of the pathogenesis of the various forms of vasculitis, modifications of nomenclature and classification reflecting these advances, and, most important, better-tolerated treatment approaches tailored more specifically to patients’ individual disease presentation.3–6 Yet, we still have no cure for the ANCA-associated vasculitides, and effective and safe prevention of relapses is front and center of current clinical trial activity and investigation. Several biomarker candidates have been explored for their correlation with disease activity of ANCA-associated vasculitis in the hope that they might be useful for predicting relapses, but none has been investigated as extensively and thoroughly as ANCA itself. Despite this, few topics remain as controversial as the clinical utility of serial ANCA testing to predict relapses.7 In this issue of JASN, Kemna and coworkers provide additional information worth careful consideration by clinicians caring for patients with ANCA-associated vasculitis.8

The diagnostic utility of ANCA testing is now undisputed. The detection of autoantibodies reacting with proteinase 3 (PR3) or myeloperoxidase (MPO) generating characteristic cytoplasmic or perinuclear immunofluorescence staining patterns on ethanol-fixed neutrophils, respectively, have strong positive predictive value for one of the classic ANCA-associated vasculitis syndromes, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPO), or eosinophilic granulomatosis with polyangiitis (EGPA), when occurring in an appropriate clinical setting.

After patients have achieved remission, the most important question at the bedside is how to prevent a relapse most effectively with the least amount of toxicity. Recent randomized controlled trials have shown that the likelihood of achieving remission with a given drug regimen is the same, whether the disease represents a new diagnosis or a relapse.5,9 Subsequent relapses seem to be less severe, presumably because they are recognized more readily.10,11 Nevertheless, to this date, any remission induction therapy regimen relies on the short-term effects of glucocorticoids, which remain indispensable for controlling disease activity until other slower but more definitively acting agents can take a hold of the disease. Moreover, each relapse is associated with the risk of cumulative damage left in the wake of active disease.12 The latter is of particular relevance for patients who are left with impaired renal function after achieving remission. In such patients, even a mild subsequent disease flare can result in the need for RRT. Consequently, each relapse is associated with substantial risk of cumulative iatrogenic and disease-related morbidity.12

Targeting effective and well tolerated remission maintenance therapy to those individuals at highest risk for relapse while minimizing unnecessary exposure in those at lowest risk remains a challenge. The ability to accurately predict relapses with a simple, readily available biomarker represents the holy grail for clinicians caring for patients with ANCA-associated vasculitis and the frontier of discovery for many investigators in the field. The key to optimally targeted maintenance therapy may consist of combining the identification of a disease phenotype at risk for relapse with the appropriate use of readily available validated biomarkers that allow the prediction of relapse in such patients.

Several studies have confirmed that a diagnosis of GPA (versus MPA), PR3-ANCA (versus MPO-ANCA), and having had relapses in the past confer the highest risk for subsequent relapses.13–16 Nevertheless, a substantial proportion of newly diagnosed PR3-ANCA–positive patients with GPA do not relapse, and conversely a subset of patients with MPO-ANCA–positive patients with MPA tend to relapse.

On the basis of observed associations with disease activity, serial ANCA testing has long held the yet-to-be-fulfilled promise to serve as a predictor for imminent relapse. To date, studies on the use of serial ANCA titer determinations have not provided clear answers applicable to all patients; treatment decisions based on ANCA titer changes alone without consideration of other clinical parameters are not advised.7

The paper by Kemna and coworkers in this issue of JASN highlights several issues that complicate any analysis of the clinical utility of serial ANCA testing for the prediction of relapses.8 These include different methods of ANCA testing, the frequency of ANCA monitoring, the definitions of a titer increase, the tools and definitions used to capture disease activity and relapse, the duration of observation, and, most important, the specific clinical phenotype of patients who make...
up the study cohort. Few studies on the clinical utility of serial ANCA testing are similar enough to each other in design, have used the same definitions, or have provided a sufficiently detailed description of the study cohort to allow for a clinically meaningful pooled analysis and comparison across studies. The matter is further complicated by recent observations indicating that the ANCA response to treatment may differ between treatments. Specifically, PR3-ANCA negativity is much more likely after rituximab therapy than after cyclophosphamide therapy despite similar clinical response, whereas the MPO-ANCA response seems to be similar between the different treatment options. Consistent with Kemna and colleagues’ observation that seroconversion from negative to positive has a more significant predictive value for relapse than does a mere increase in titer, serial PR3-ANCA testing in patients with relapsing GPA may be more useful after rituximab therapy than in other clinical scenarios.

We also should not ignore the patient-specific variability of how ANCA levels track with disease activity. Physicians who have followed many patients with ANCA-associated vasculitis over considerable time have seen patients in whom changes of ANCA titer are closely associated with changes in disease activity, whereas there are others in whom there is no detectable association. Such patient-specific differences are “drowned out” in cumulative statistical analyses of patient cohorts and can be detected only if serial ANCA testing is included in the clinical monitoring portfolio of any given patient.

Single-center cohort studies, like the one by Kemna and coworkers, provide useful information that hones our awareness of the different performance of biomarkers in different patient populations, and such observations warrant validation in similar cohorts. From this particular study, we learn that an increase of ANCA titers conveys a higher risk of relapse in patients with renal disease than in patients without renal involvement. We can only speculate whether this is so because ANCAs are pathogenically linked more closely to the severe, capillaritis-related disease manifestations than to nonsevere granulomatous disease manifestations of GPA, or whether this also reflects differences of the ANCA response to different treatments. If treatment for severe disease is having a more pronounced effect on ANCA production than treatment options for nonsevere disease, one could expect a higher rate of conversion to ANCA negativity. Subsequent conversion back to ANCA positivity seems to better predict relapses than do mere increases from a persistently positive baseline or nadir.

One important clinical message for clinical practice confirmed by Kemna and coworkers is that severe disease flares are extremely unlikely in the absence of ANCA.

One advantage of single-center biomarker studies over data obtained in the context of randomized controlled trials is a longer observation period among individual patients, providing the opportunity to capture more relapse events. This is offset by variability of clinical practice over time, lack of binding of the physician who assesses disease activity to treatment and ANCA levels, and lack of standardization of sampling intervals or changes in ANCA testing methods during the observation period. So far, no single publication has been able to convey a definitive answer about the clinical utility of serial ANCA testing for all patients with ANCA-associated vasculitis. Instead, to have a comprehensive picture emerge and allow individualized clinical decision making, we have to integrate the information provided by single-center cohort studies, multicenter prospective controlled trials and observational cohorts while fully recognizing the clinical characteristics of the patients included in each of the studies.

Possibly the most important biomarker predicting an imminent relapse is not a blood test, but the patient himself or herself. As shown in a recent study from the Vasculitis Clinical Research Consortium, an increase in the patient global assessment tool, which captures how patients judge their own disease activity, often precedes the detection of disease activity by the physician by at least 3 months.

In the absence of the elusive biomarker that reliably predicts relapses in each and every patient, the clinician needs to carefully weigh all of the following pieces of information for an individual patient in order to provide the best advice about the patient’s individual relapse risk and best options for their prevention: disease phenotype (GPA versus MPA), ANCA type (PR3 versus MPA), organ involvement (for instance, renal versus nonrenal), treatment exposure (rituximab versus cyclophosphamide or methotrexate), individual ANCA response patterns over time, individual baseline of organ damage from previous bouts of disease activity (for instance, how much additional renal function can the patient “afford” to lose with a subsequent relapse), and last but not least, the patient’s own perceptions.

In conclusion, in the field of ANCA-associated vasculitis we are still far away from having a reliable biomarker that can replace the clinician having to practice the art of medicine.

DISCLOSURES

None.

REFERENCES

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