Do serial ANCA titres predict relapse in ANCA-associated vasculitis?

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Key points
Do serial ANCA titres predict relapse in ANCA-associated vasculitis?

• Antineutrophil cytoplasm autoantibodies (ANCA) are essential for the diagnosis of small-vessel vasculitis.
• Information for and against their usefulness to predict relapse exists.
• Different approaches, using various methods and definitions, have been used to answer the role of ANCA in predicting disease relapse.
• Multinational, multicentric prospective studies are needed to address this question using uniform definitions and preferably the best latest tools for ANCA detection.

Antineutrophil cytoplasm autoantibodies (ANCA) are essential in serologic testing for suspected Wegener granulomatosis (WG). There is evidence that ANCA levels rise during active disease and that in most instances a concomitant decrease accompanies remission. The potential usefulness of diagnostic markers in patients’ follow-up remains a fundamental question unanswered for many types of markers. Some studies indicate that serial determinations of ANCA can predict relapse, which occurs frequently in ANCA-associated vasculitides. Others show that preemptive treatment may be justified when such elevated ANCA titres are observed. Several points remain unclear, however, especially as yet other studies have not found any clear relation between a rise in ANCA values and subsequent relapse. Detailed editorials and reviews have focused on these studies. Nevertheless, and at the risk of inadvertently omitting something, I present in Table 1 information from selected articles that do not support a relation between elevation of ANCA titres and impending relapse. Other studies have been previously cited elsewhere. I would like to explain why the studies so far published conflict about this issue. I will discuss only results from WG or PR3-ANCA positive patients (as measured by ELISA), as information from patients with microscopic polyangiitis or who are P-ANCA and/or MPO-ANCA-positive is even scarcer. Additionally, I try to provide personal insight into the questions that must be answered to resolve this issue.

Factors related to testing methods and populations

STUDY DESIGNS
Most data come from retrospective studies. Only a few studies have prospective or retrospective/prospective designs. This matters, especially when comparing data from different populations under different designs (cohorts, case-control studies).
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**METHODS USED FOR ANCA DETECTION**

Although useful and sensitive for diagnosis, ANCA as measured by indirect immunofluorescence (IIF) is a semiquantitative test and its interpretation is subject to wide variation, even among experienced observers. ELISA has proved a more reproducible tool for assessing whether elevations in ANCA values are related to patient condition, although interassay variability can still be observed. The introduction of capture ELISA may be helpful, as it is more sensitive to change. Nonetheless, results from the limited studies that have so far used this method have not met initial expectations. Test characteristics are very important in this regard, and consideration of the populations to be tested is essential. More information is needed to clarify whether recent methodological developments in ELISA detection of ANCA improves prediction of relapse.

The available studies diverge in their definitions of significant elevations of ANCA titres or values, which range from increases ≥50% to those ≥400%. This suggests that different cut-off values may be useful in different conditions, such as diagnosis or follow-up after reaching remission. These differences in selecting values to define elevated or increased titres affect both the sensitivity and specificity of ANCA testing, and both important in deciding on the need for intervention. Most studies do not even report information about test sensitivity and specificity or cut-off values and do not construct curves of receiver operating characteristics. In the only study which gives detailed information on this subject, an increase in PR3-ANCA levels was found useful for predicting relapses, with 82% sensitivity, 78% specificity, and a positive predictive value of 17%. Another point that has not been sufficiently defined is the exact number of relapses (the relevant clinical variable) related—or not—to an increased ANCA level. In other words, the results presented do not always allow a determination of sensitivity, specificity and predictive values and thus make data comparisons difficult.

Another practical issue that influences results is the frequency of measurements. Some studies leave this to each center’s preference, while in others, mainly the few prospective studies, it is uniform and systematic. It is clear that more frequent measurements could shorten the time between an ANCA increase and clinically evident activity suggesting relapse. In standard clinical settings, however, that might also lead to unjustified costs and disrupt patients’ global well-being.

**DEFINITION OF POPULATIONS’ DISEASE STATUS**

The definitions of disease activity, relapse and remission are fundamental. The availability of validated tools for measuring activity (BVAS and BVAS/WG) has made easier to define relapse and to detect it once the patient has achieved remission. Not all studies have used these scores, however, and the symptoms of vasculitides may be present in other conditions, such as infections. As it is not always feasible to obtain histopathologic proof to demonstrate or confirm disease activity, activity must be uniformly defined if ANCA results are to be related to disease stage. Therefore, once the patient has achieved remission, an exact and preferably consensus definition of relapse is needed for ANCA to serve as surrogate marker of activity. This point is relevant to the rationalization of preemptive treatment based on increased ANCA titres before clinically evident disease is present; it is the supposition of relapse that justifies the possible complications of treatment.

**Relevant biological issues**

Other relevant factors, related to the biological activity and/or interactions of ANCA with other actors (cells, antigens), may account for the lack of consistent results.

**POPULATIONS**

Differences in the prevalence of WG among various populations may reflect dissimilar genetic backgrounds, which may in turn influence the type and magnitude of the immunological response that lead to WG. These genetically determined factors, for example, the diverse expression of Fcγ receptors, cause some elements of immune response to vary. The influence of these intrinsic determinants on the development and amplification of immune responses, including ANCA production, must be considered.

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**Table 1**

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>% elevated before relapse</th>
<th>Sensibility (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Oliviera (7)</td>
<td>33*</td>
<td>16 (capture PR3-ANCA) 78</td>
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</tr>
<tr>
<td>Chan (8)</td>
<td>36</td>
<td>25 (direct PR3-ANCA) 83</td>
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<tr>
<td>Kyndt (9)</td>
<td>12 (direct PR3-ANCA) 400% 3</td>
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<tr>
<td>Nowack (10)</td>
<td>21 (PR3-ANCA par captation)</td>
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* 7.4% MPO-ANCA positive
ANCA ISOTYPING

ANCA detection usually identifies the IgG isotype. There is little information available about the association of other isotypes (IgM, IgA) with various disease manifestations. Regular testing to detect different Ig isotypes is rare. How such detection might improve prediction of various disease characteristics must be determined. Another pertinent topic relates to differences in ANCA IgG subclasses. Studies that have looked for associations between the elevation of different ANCA IgG subclasses and subsequent clinically manifest relapses (mainly IgG3, which has been related to disease activity) have not yielded additional information.

ANTIGENS

Detailed information about the interaction of ANCA and its antigens, mainly proteinase-3 and myeloperoxidase, is not yet available. This fundamental topic may be the “missing half” of the story. It is theoretically possible that even if an ANCA rise precedes or accompanies any disease flare, overt clinical manifestations of disease require some additional interaction between ANCA and their antigens. Some evidence supports this theory. For example, it is well known that patients with WG have a higher percentage of neutrophils expressing more antigen (proteinase-3) on their surface than healthy subjects. This expression decreases when remission is reached. Other aspects of antigen besides target antigen expression on neutrophil surfaces may be important. Only one study reports information about circulating ANCA-antigens and their potential interactions with ANCA. Much more information is necessary, including, for example, the relation between levels of identified ANCA-antigens and disease activity. Circulating myeloperoxidase levels are reported to differ between patients with active disease and those in remission. Methods that use modified target antigens also suggest that their recognition by ANCA may correlate with disease activity better than standard antigens. Study is needed of the in vivo reaction of these modified antigens with PR3-ANCA and its consequences, which appear to be biologically important. The use of recombinant antigens or antigens bearing fundamental epitopes for ANCA-ANCA antigen interactions may alter some fundamental properties of ANCA testing and make it a better marker of disease or disease activity.

Similarly, ANCA interaction with other antibodies in WG patients (i.e., rheumatoid factor) has not been studied sufficiently. This potential mechanism may alter the course of immune response and change ANCA detection itself. Many of the factors mentioned are genetically determined and are probably modified or influenced by external, including environmental factors, as we confirmed in our patients. Knowledge of these variables and understanding of their relations may explain some of the divergences observed. Consideration of these issues may require looking at results from some populations from a different viewpoint. We have reported information from 18 Mexican patients whose ANCA levels were unrelated to their disease activity. Many of them remained in remission for long periods despite very high ANCA levels measured by capture PR3-ANCA ELISA. Much work remains to be done to determine the real value of ANCA measurements in monitoring our patients.

TIME FROM ANCA ELEVATION TO MANIFEST RELAPSE

Some studies report a rise in ANCA values months before relapse is clinically evident. From a biological point of view it is difficult to understand why patients would not develop clinical manifestations until a year after their ANCA values rose, given the major pathogenic role ANCA may play. This suggests that factors besides a rise in ANCA play a role in relapse. For example, antigen concentration, expression on neutrophil cell surfaces, intracellular signaling, environmental factors, and treatment phase may, together or separately, prevent disease activation or at least its clinical detectability, even though ANCA are rising. Some of these factors may in fact be “protective.” Why then should ANCA titre elevation alone justify treatment? Why do some permanently ANCA-negative patients develop flares? Why do some patients remain in remission with elevated ANCA for many years?

Conclusions

Evidence is available both to support and rebut the usefulness of ANCA testing in predicting relapses. The reasons for these discrepancies may be inherent to specific study populations, the methods used for ANCA detection, the definitions of relapse and disease activity or may depend on other relevant, independent, biologically phenomena. Prediction of relapses cannot and should not rely exclusively on ANCA levels. Their combination with other characteristics of ANCA patients may well produce better predictive tools. A sense of urgency is needed to reach a consensus on how to resolve this question. As more data become available, experts can help to design better studies to answer it. Sufficient resources, the best up-to-date validated uniform methodologies for ANCA detection, participation of large numbers of patients and centers, sufficient follow-up and uniform definitions of disease status will be needed. Reaching consensus will enable us to provide better treatment for patients with these devastating diseases. Right now, we do not have a solid basis of...
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Evidence to justify general guidelines about the usefulness of ANCA in predicting relapses, and we cannot choose a definitive approach in either direction. Caution is needed in deciding if ANCA elevation is relevant to individual patients. We must not forget that complications may accompany the treatments used for relapsing disease and that the duration of treatment in such cases is still undefined. In my opinion, the best decision for each individual must come from knowing as much as possible about the pertinent aspects involved in reading and interpreting ANCA tests and from accurate clinical evaluation of patients in their particular settings.

References