Editorial

Antineutrophil cytoplasmic antibodies should not be used to guide treatment in Wegener's granulomatosis

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In 1982, Davies and colleagues reported on their observation of cytoplasmic staining antibodies in 8 patients with segmental necrotizing glomerulonephritis (1). The significance of these antineutrophil cytoplasmic antibodies (ANCA) became evident when van der Woude and associates reported that antibodies reacting with the cytoplasm of ethanol-fixed granulocytes and monocytes were associated with Wegener's granulomatosis (WG) and found a correlation between antibody titers and disease activity (2). This and subsequent studies lead to the question as to whether changes in ANCAlevels could be used to predict relapses and guide treatment.

The theoretic rationale for why it might be attractive to use ANCA in guiding treatment is based upon intervening with a hypothesized sequence of events. If increased levels reliably predicted relapse, a rise in ANCA could prompt medical intervention, thereby averting relapse and preventing disease related morbidity or mortality. The limitation of this argument though, is that treatment in and of itself can also cause morbidity and mortality. Because of this concern, when considering whether ANCA should be used to guide treatment, physicians must carefully consider whether there is sufficient scientific evidence to support that the benefits of basing treatment solely on a change in ANCA outweigh the potential risks.

What is the risk of using ANCA as the sole basis for initiating or increasing therapy?

In the absence of clinical disease activity, the difficulty with basing treatment solely on a rise in ANCA is the potential for some patients who might not have gone onto relapse, to receive unnecessary medications. Cyclophosphamide (CYC) can effectively induce remission of active WG but at the risk of substantial toxicity. In a long-term study of patients who were treated with prednisone and daily CYC given for one year past remission, 42% experienced serious morbidity solely as a result of their treatment (3). CYC can result in acute adverse events such as bone marrow suppression and bladder injury as well as long-term complications including infertility, myelodysplasia, and transitional cell carcinoma of the bladder (4). These collective toxicities are of concern not only because of the risks that they pose, but also because they may preclude further use of CYC or other cytotoxic medications.

The investigation of non-CYC treatment options to induce or maintain remission has steadily increased. Methotrexate (MTX) (5) and azathioprine (AZA) (6) have been successfully utilized for remission maintenance and MTX has the ability to induce remission of non-severe disease (7). While less toxic overall than CYC, these agents are not risk free and can both cause bone marrow suppression. MTX can be associated with pneumonitis and hepatic fibrosis while severe allergic reactions and the potential for lymphoid malignancies may rarely occur with AZA. Glucocorticoids remain a key component of all therapeutic regimens in WG and possess a broad toxicity profile.

All of the therapies used in WG are immunosuppressive and can lead to life-threatening infections from bacterial and opportunistic pathogens. In different therapeutic series, infections have been reported to occur in 10-70% of patients (3, 5-10). In a long-term survival study of WG patients from the American College of Rheumatology

(ACR) Classification Criteria cohort, Matteson and colleagues found infection to be the number one cause of death responsible for 29% of patient fatalities (11). Prophylaxis against *Pneumocystis carinii* pneumonia can eliminate the risk from this specific organism, but other bacterial, viral, fungal, and mycobacterial infections remain important threats to patient health.

What is the evidence for making treatment decisions based solely on a rise in ANCA?

In considering the evidence as to whether treatment based upon ANCAalone justifies the risk of treatment-associated toxicities, 5 questions should be asked:

- Are assays for the measurement of ANCAuniformly reliable?
- Is a rise in ANCAalways associated with relapse?
- Does a rise in ANCA immediately precede relapse?
- Has preemptive treatment been proven to reduce relapses?
- Does preemptive treatment offer the best way to avoid serious consequences?

Are assays for the measurement of ANCA uniformly reliable?

Testing for ANCA in clinical laboratories can be performed by two methods 1) indirect immunofluorescence (IIF) of ethanol fixed neutrophils that is manually interpreted and when positive yields a titered cytoplasmic staining ANCA (cANCA) or a perinuclear staining ANCA (pANCA); 2) target antigen specific enzyme linked immunosorbent assay (ELISA) testing performed by automated machine yielding a numeric value for the level of antibodies to proteinase 3 (PR3) or myeloperoxidase (MPO).

The accuracy and reliability of these assays has been examined in a number of different ways. The EC/BCR Project for ANCA Standardization represented an International collaborative effort with the aim to develop and standardize methods of ANCA testing (12). This project demonstrated that by IIF, ANCA titers could not be compared between different laboratories (13). With regards to target antigen specific testing, while standardization was possible, there remained a coefficient of variation of up to 20-34% between centers (13). A study of 5 commercial ELISA kits by Pollock and colleagues found a wide variation of sensitivity and specificity between different assays (14). Similar findings were observed by Csernok and associates, who examined 11 commercial ELISA kits (15). This variability complicates any interpretation of sequential ANCA results and must raise questions as to the reliability and utility of ANCA as a clinical tool for serial assessment.

Is a rise in ANCA always associated with relapse ?

A critical question asked by clinicians is whether a rise in ANCA can occur without a subsequent relapse. Boomsma and colleagues conducted a prospective study over a two year period in which 100 patients with WG were followed serially with a clinical evaluation every 3 months and an ANCA determination every 2 months by both PR3 target antigen specific ELISAtesting and IIF (16). Of the 85 patients with PR3-ANCA, the level rose in 38 of whom 29% did not go on to relapse at all. This disparity was even more pronounced with IIF, where a relapse did not occur in 43% of patients who had a rise in cANCAtiter. Multiple other series have similarly found that 8-44% of patients did not go onto relapse following a rise in ANCA (5,17-22) (Fig. 1).

Does a rise in ANCAimmediately precede relapse?

The temporal relationship between a rise and ANCA and relapse is also important. A rise in ANCAtiter that occurs concurrently with relapse is superfluous since clinical evidence will confirm the presence of active disease. A rise in ANCA that precedes relapse by many months also is not helpful because unnecessary treatment for additional time can increase medication risk. Therefore, the only time that a rise in ANCA could be helpful would be if it were to reproducibly occur immediately prior to the time of clinical disease activity.

From the study by Boomsma and colleagues, a Kaplan Meier analysis demonstrated that at 12 months, 50% of those who had a rise in ANCA by IIF remained disease free (16). In studies that have examined this temporal relationship exclusively in relapsing patients who had a rise in ANCA, it was observed that the majority of ANCA rises occurred concurrently with clinical evidence of active disease or at a

First Author (reference)	Technique	Percent with ANCA Rise who Did Not go onto relapse
Kerr (17)	IIF	44%
Kyndt (18)	IIF	43%
	ELISA	41%
Langford (5)	IIF	39%
Chan (19)	IIF	35%
Cohen Tervaert (22)	IIF	18%
Egner (20)	IIF	25%
Gisslen (21)	ELISA	8%
	Capture	17%

IIF=indirect immunofluorescence; ELISA=enzyme linked immunosorbent assay

Fig. 1. The frequency of clinical relapse following a rise in titer of ANCA as reported by different studies.

timepoint many months in advance of the relapse (17-19, 22-25) (Fig. 2). These data suggest that even when a rise in ANCA is associated with relapse, it is only in a minority of patients that this rise will occur immediately prior to clinical evidence of active disease.

Has preemptive treatment been proven to reduce relapses?

To date, two studies have directly examined the use of preemptive treatment based upon a rise in ANCA (22,26). While both of these series provided important insights, each of them enrolled 20 patients or less which would be of insufficient size to statistically prove that preemptive treatment can reduce relapse, morbidity, or mortality. Another important observation from one of these studies was the finding that even in the setting where preemptive treatment was applied, relapses still occurred (26). Therefore, it must be questioned as to whether preemptive treatment based on ANCAalone effectively achieves the goal of relapse prevention in all cases.

Does preemptive treatment offer the best way to avoid serious consequences?

The hope of avoiding serious consequences remains a key component of the rationale for using ANCA to guide treatment. How best to minimize serious consequences remains an important issue but one that is difficult to study in a standardized manner. Morbidity and mortality in patients with WG can occur for several reasons: acute tissue injury from active WG or treatment, permanent organ dysfunction from previous WG, complications of therapy that may develop after months or years, and events occurring totally independent of the disease or its management.

Clinical monitoring with regular physician visits, laboratories, and radiographs plays a critical role in preventing or detecting acute injury from WG or its treatment (10). The frequency of such monitoring and the types of testing required are based upon the patient's recent disease status and the medications that they are receiving. Although it remains an unanswered question as to whether regular clinical monitoring can reduce the overall risk of morbidity and mortality more effectively than the use of preemptive ANCA, it provides important advantages. By detecting disease activity at an early point, clinical monitoring can in many instances minimize the potential for relapse related disease consequences while eliminating the use of unnecessary treatment for those who would not have gone onto relapse.

Permanent organ damage can occur as a consequence of WG or from drug toxicity. The issue of damage has been actively explored by investigators from the United Kingdom who developed the Vasculitis Damage Index (VDI) (27). Using the VDI, Exley and colleagues demonstrated that significant damage occurred within 6 months of presentation and that treatment related damage occurred late (28). A similar pattern was observed in a randomized trial involving 155 patients that examined the use of AZA for remission maintenance (6). At the time of initial disease presentation, most patients already had damage as a result of their disease and by the 18 month study endpoint, the VDI score had increased. In their discussion, the authors comment that damage increased during the trial despite control of disease activity reflecting the consequences of vasculitic inflammation and of adverse events. These findings underscore the potential for damage to have already occurred by the time of diagnosis as well as the ability for treatment to be associated with permanent sequelae.

	≥ 12 months	6-12 months	6 months	Post	
First author (reference)	Percentage of patients with rise in ANCA that relapsed within the illustrated time period				
Kerr (17)		24		76	
Kyndt (18)		20 (ELISA) 50 (IIF)		80 50	
Girard (23)		16	17	67	
Peterssen (25)	16		17	67	
Cohen Tervaert (22)	33		67		
Chan (19)			46	45	9
Jayne (24)			72	22	6

Fig. 2. In relapsing patients, examination of the temporal relationship between rise in ANCAtiter and demonstration of clinical disease activity as reported by different studies.

Summary

WG can be associated with serious consequences that can occur as a result of active disease or from the side effects of treatment. If the medications used to treat WG were safe, the risk of exposing even a significant proportion of individuals to unwarranted treatment might be a reasonable approach in light of the nature of the disease process. In the setting of toxic medications though, the use of preemptive treatment based on ANCA alone and the potential for unnecessary exposure to side effects cannot be justified in the absence of compelling evidence. Unfortunately, the medical literature does not support that the benefits of preemptive treatment determined by ANCA outweigh the risks. To treat solely on the basis of ANCA potentially exposes an unacceptably high number of patients to the toxicities of treatment that they would not have needed. It is for these reasons that treatment decisions in WG should not be based on ANCA alone in the absence of clinical evidence of disease activity.

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