Relapse in Anti-Neutrophil Cytoplasm Antibody (ANCA)–Associated Vasculitis

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Clinical relapses are common in anti-neutrophil cytoplasm antibody (ANCA)–associated vasculitis, necessitating repeated treatment with immunosuppressive therapy, and increasing the risks of severe adverse events. Better understanding the basis of relapse would help stratify patients, testing the notion that more treatment may prevent development of relapse, whereas in those at low risk of disease flares, treatment minimization may be appropriate, reducing risks of adverse events, most notably infectious complications and drug toxicity. However, relapse can only occur following remission, and although defining clinical remission may seem straightforward, there is evidence in many remission patients of persistent inflammatory and immunological activity, at levels above those found in healthy individuals. This suggests that we may not truly be achieving disease remission in many patients and these persistent responses may set the patient up for subsequent disease flares. Understanding the underlying pathophysiological basis of disease activity and remission is paramount to help define better biomarkers of relapse, which should positively affect adverse events and patient outcomes.

Relapsed. A deterioration in a patient's condition after a partial or apparently complete recovery; return of a disease, symptom, etc., after an interval of recovery.

—Oxford English Dictionary

ANCA-associated vasculitis, like many autoimmune diseases in which exposed autoantigens persist, follows a relapsing and remitting course, although the disease pattern for individual patients even with similar ANCA subtypes can be extremely variable. Certain susceptibility factors for relapse have been well established, such as proteinase-3–ANCA and clinical features of granulomatosis with polyangiitis; however, we have made few inroads into understanding what the pathophysiological drivers of relapse are, and why they are so different in patients with different ANCA subtypes. In part this is because, although overt disease flare may be clinically and immunologically obvious, subtle immune disease activity may be frequently missed. This subclinical inflammation brings into question what we mean by, and how we define, remission, which is generally based on clinical features, whereas more sensitive immunological or inflammatory phenotypes are not considered. We have introduced scoring systems, such as the Birmingham Vasculitis Activity Score and Birmingham Vasculitis Activity Score for Wegener's granulomatosis, which suggest that disease is in remission when the score is zero, but we cannot always easily differentiate active disease from damage, which means we may not score some features that may portend ongoing inflammation after certain time points. Persistent or mild hematuria, subtle elevations in creatinine, or some ear, nose, and throat symptoms may be related to scarring or active disease and may not be recorded as active or persistent disease in these scoring systems. This may be appropriate, as we now realize that it can take many months for these symptoms or parameters to normalize; however, it emphasises that we need more sensitive biomarkers to inform us of when disease is truly supressed or switched off.

For relapse to occur, first there must be remission, and although we know when patients are overtly *not* in remission, because of ongoing signs and symptoms, it is fair to say we do not have robust definitions of when they really have achieved remission. Using an analogy of an iceberg to represent disease (Figure 1), there may

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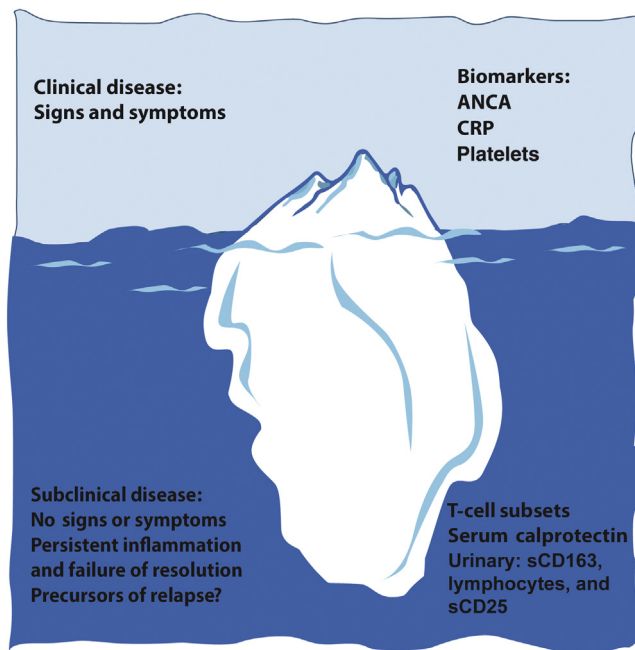
Figure 1. Clinically overt disease and subclinical persistent inflammation in ANCA-associated vasculitis. Current treatment decisions are based on the former and not the latter, as we have inadequate means of following the subclinical disease at the moment. CRP, C-reactive protein; sCD163, soluble CD163; sCD25, soluble CD25.

be a large part of the iceberg that is not visible above the water surface, which could represent the subclinical inflammation defined by various biomarkers, which may persist as overt clinical disease, slowly declines, and patients achieve clinical remission. Some persistent inflammation may result in symptoms that could be interpreted as being due to disease or damage, such as persistent crusting or epistaxis in granulomatosis with polyangiitis, whereas in some cases persistent inflammation may produce no overt clinical signs at all. Conversely, there are some patients who have clearly switched their disease off, and using a variety of parameters show immunological "normality," behaving like healthy individuals. How we measure and define remission will inform us of relapse. For the moment, we are still reliant on clinical parameters, and clear markers of active inflammation, such as elevated levels of C-reactive protein, fibrinogen, and platelets, that are inadequate for optimal customization of therapies.

Known Risk Factors for Relapse

It has been a consistent finding from varied cohort studies and clinical trials that that being cytoplasmic-ANCA or proteinase-3–ANCA positive[1,2] rather than perinuclear-ANCA or myeloperoxidase-ANCA positive was a significant risk for relapsing disease (Table 1). In keeping with the immunological phenotype, patients

Table 1. Recognized risk factors for relapse in ANCA-associated vasculitis

Disease parameters	Management parameters
1. PR3-ANCA	1. Early drug withdrawal at 1 year
2. GPA disease	2. Induction therapy type; see Table 2
3. Higher presenting eGFR	3. Maintenance therapy type; see Table 2
4. *Staphylococcus aureus* nasal carriage	4. Antibiotic prophylaxis with co-trimoxazole
5. ANCA positivity at time of completion of induction therapy	
6. Previous relapses	

ANCA, anti-neutrophil cytoplasm antibody; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; PR3, proteinase 3.

with granulomatosis with polyangiitis have more clinical relapses than patients with microscopic polyangiitis, as do those with involvement of the lungs, upper airways,[1] or cardiovascular system.[2,3] In addition, higher levels of renal function[2] and carriage of nasal *Staphylococcus aureus*[4] appear to confer greater relapse risk, and this is true in both European and Chinese populations.[3,5] In some cohort studies, persistent ANCA positivity at the time of switching from induction to maintenance therapy is associated with an increased risk of future relapse,[6] whereas previous relapses are themselves risk factors for subsequent relapses. Disappointingly, apart from some histological features (including proportion of sclerosed glomeruli and lack of interstitial infiltrates),[7] there are no clear, clinically useful, predictors for renal relapse, which is associated with progression to end-stage renal disease. Importantly, rates of renal relapse, unlike other outcomes in ANCA-associated vasculitis, have remained relatively constant.[8,9] Interestingly, progression to end-stage regnal disease occurs more frequently without overt renal relapses, which may highlight our inadequacies in diagnosing ongoing renal inflammation that may underlie some of what we term chronic kidney disease progression in patients with ANCA-associated glomerulonephritis.[7] Supporting the idea that persistent inflammation promotes some of the progression are data from the Chronic Renal Insufficiency Cohort (CRIC) study that demonstrate more rapid progression of chronic kidney disease (of various causes) in patients with markers of inflammation, such as elevated levels of circulating proinflammatory cytokines (tumor necrosis factor-α) and fibrinogen and lower levels of albumin.[10]

Not All Remissions Are Created Equal: Rates of Relapse

Modern induction regimens are generally very effective at producing disease remission, but which drug is used and which maintenance regimens patients are switched to, are more variable in the ability to maintain it. This tells us that there may be different aspects of the

Table 2. Relapse rates in recent ANCA-associated vasculitis trials

Trial	Compared	Results	Rates of relapse	Reference
CYCAZAREM	CYP vs. CYP/AZA	Same relapse	15.5% vs. 13.7% at 1.5 yr, 52% vs. 36% at 8.5 yr	11
NORAM	MTX vs. CYP	**Greater relapse MTX**	89% vs. 81% at 5 yr	12
CYCLOPS	i.v. vs. ORAL CYP	**Greater relapse with i.v. CYP**	39.5% vs. 20.8% at 5 yr	13
WEGENT	AZA vs. MTX	Same relapse	36% vs. 33% at 2 yr	14
IMPROVE	**AZA vs. MMF**	**Greater relapse with MMF**	**37.5% vs. 55.2% at 3 yr**	15
MAINRITSAN	**AZA vs. RTX**	**Greater relapse with AZA**	**29% vs. 5% at 28 mo**	16
RAVE	RTX vs. CYP/AZA	Same relapse	32% vs. 29% at 18 mo	17
RITUXVAS	RTX/CYP vs. CYP/AZA	Same relapse	42% vs. 36% at 2 yr	18

AZA, azathioprine; CYP, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab.
Trials in bold show significant benefit of one drug versus the other.

immune response that are regulated by particular drugs, or they may do so more or less effectively. Various cohort studies and long-term follow-up of international trials have demonstrated relapse rates that vary between 21% and 89% at 5 years, depending on the induction and maintenance regimens that were used (Table 2[11–18]). More recent trials have suggested that rates can be brought down to as low as 5% at 2 years with use of rituximab,[16] which appears to be a significant improvement compared with previous rates (Table 2).

Induction with either oral cyclophosphamide or rituximab (and glucocorticoids) results in similar relapse rates, but these are greater if intravenous pulsed cyclophosphamide,[13] or methotrexate,[12] are used compared with oral cyclophosphamide, while pulsed cyclophosphamide results in fewer relapses than mycophenolate mofetil induction.[19] However, in addition to which drug is used, the duration of treatment is critical. For example, in the NORAM trial,[12] treatment with either cyclophosphamide or methotrexate was equally effective at inducing remission; however, after 1 year of treatment, cessation of drug was accompanied by significantly higher relapse rate in patients treated with methotrexate. Similarly, maintenance therapy with azathioprine is associated with less risk of early relapse than use of mycophenolate,[15] whereas rituximab maintenance was more effective at preventing relapse than azathioprine.[16] We have not understood what underlies these differences, and uncovering pathways that are variably effected by these various drugs may give us a clue as to what may provoke relapse. In addition, it is unclear how particular maintenance therapy prevents relapse, as there are mixed data suggesting that shorter or longer duration of therapy may be associated with increased or no difference in rates of relapse.[20–22]

ANCA and Relapsing Disease

ANCA has been proposed as a marker of impending disease relapse since the early days of its introduction as

a clinical test.[23] It was shown to be of some value in a single cohort study of patients with renal disease, with an ANCA increase (of more than 200% in the prior 3 months by solid phase assay) giving a hazard ratio of more than 11 for subsequent relapse in the next 18 months,[24] but was less predictive in those with non-renal disease. Persistent ANCA positivity or development of positivity following a negative test showed only modest predictive power in a recent meta-analysis, with the caveat that this contained heterogeneous studies with variable testing strategies.[25] However, using the RAVE dataset, increase titer (doubling of value or reaching an absolute level if previously negative) of proteinase-3–ANCA, by enzyme-linked immunosorbent assay, was clearly associated with subsequent disease flare, but only in those treated with rituximab, with a hazard ratio of 7.9 in those with kidney involvement. There were additional differences in the strength of association depending on the type of enzyme-linked immunosorbent assay used.[26] In addition, in a prospective Japanese cohort, reappearance of myeloperoxidase-ANCA had a significant association with subsequent relapse, with an odds ratio of 26 (95% confidence interval, 8.2–101.0), whereas ANCA persistence was not associated with higher rates of relapse.[27] Differences in myeloperoxidase-ANCA epitope specificity have been reported between acute disease and remission, suggesting there may be differences in antibody pathogenicity that could potentially explain ANCA persistence and clinical disease remission in some patients.[28,29] Standard ANCA measurements during remission remain a feature of clinical practice for many physicians and rising titers may warrant more careful follow-up, but it remains controversial whether that should result in immediate change of therapy.

Subclinical Inflammation and Predicting Relapses

It is clear that many inflammatory pathways are engaged at the time of disease activity and relapse, and some of these never return to normality (seen in

healthy controls) during remission,[30,31] suggesting that they may be the subclinical factors driving relapse. Therefore, either there is a baseline abnormality in these pathways in patients compared with healthy individuals or the immunological pathways may remain turned on at lower levels without inducing overt disease. In part, our inability to predict relapse comes from the reliance on biomarkers that are poor at representing the subclinical inflammation that occurs (Figure 1), such as creatinine, proteinuria, and hematuria in patients with renal disease.

An ideal biomarker to predict relapse in the near future would likely inform of how therapy may be tailored for the individual, minimizing exposure in those less likely to relapse and maintaining higher levels of therapy in those who have greater likelihood of disease flare (although we also need to prove that more treatment will prevent relapse). Optimally, this would be used at the time of disease presentation, during induction therapy or soon after, before deciding on maintenance therapy. Some markers have shown such associations, with variable positive predictive values in cohort studies, but the time lag to relapse may be protracted, meaning that augmented immunosuppression may be delivered to a significant number of individuals for a long period of time, increasing potential adverse events.

Many other biomarkers, including circulating levels of leukocyte subsets (such as B- or T-lymphocyte subsets),[32,33] urinary lymphocytes, or urinary leukocyte proteins[34–37] have been shown to be associated with disease activity, but none have validated as robust markers of subsequent relapse. The most promising biomarkers have been a CD8 T-cell subset that in a single-center study showed a strong association with subsequent relapse in patients with ANCA-associated vasculitis or systemic lupus erythematosus, which requires prospective validation.[38] Another was changes in serum calprotectin levels, which increased while on therapy between baseline and month 3 or 6, in samples from the RAVE trial, again only in those treated with rituximab (like the predictive ability of proteinase-3–ANCA).[39] This suggests that differences exist in suppression of various inflammatory pathways when using different induction regimens, despite similar clinical remission rates, highlighting again that clinical remission is not telling us everything about underlying disease pathway suppression. Perhaps unsurprisingly, since the change in calprotectin was not predictive of relapse in cyclophosphamide-treated patients from RAVE, no association with relapse was found using samples from the MYCYC (mycophenolate vs cyclophosphamide) trial (unpublished data). These data suggest that other biomarkers or combinations of biomarkers could be found that should allow us to predict future disease relapse.

Finally, there are those patients demonstrating prolonged disease-free remission[40] who have become ANCA negative and remain off all immunotherapy, including glucocorticoids, who may truly have switched off all of the subclinical inflammatory and immunological pathways, with some evidence that some of their regulatory cell subsets are numerically restored to levels found in healthy individuals (Oates T, Flores-Barros F, Todd SK, et al. Restablishment of immune tolerance in ANCA-associated vasculitis: a cohort with both sustained undetectable antibody, and disease free remission [abstract]. *J Am Soc Nephrol.* 2016;27:282). This group of patients may provide some clues as to what pathways underpin the subclinical inflammation and predisposition to relapse.

Other Considerations in Relapse Studies

One issue that is not discussed in studies comparing i.v. and oral therapies is compliance with the oral regimen, which can be suboptimal, with rates of noncompliance in many chronic rheumatological diseases estimated at more than 50% and as high as 82%.[41] Although specific data for ANCA-associated vasculitis are lacking, this may be an issue especially in maintenance studies. Assessment of compliance through drug monitoring where possible may help in this regard.

In addition, it is worth considering that unblinded trials of therapy withdrawal may be hindered by the risk of bias in defining a clinical event as a disease relapse if it is known that the patient is not on treatment, rather than a transient infection, for example.

Future studies defining optimal regimens and duration of treatments should consider these issues, by potentially blinding physicians to treatments, using hard (inflammatory or immunological) endpoints, and making attempts at confirming compliance.

Summary

We still rely on clinical definitions of remission and these are not clear-cut or uniform. We need better, more granular inflammatory and immunological profiles to really understand disease states. These should provide better markers of disease quiescence, activity, and potentially markers that can predict short- or long-term relapse. Only then will we be able to truly customize therapy for individual patients, minimizing risks of adverse events by appropriately reducing therapies in some, and reducing risks of relapse in others by appropriately augmenting therapies.

DISCLOSURE

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