Biomarkers in Vasculitis

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An intense search is underway for better ways to support treatment decisions in the vasculitides. Here are the most promising candidate biomarkers for identifying active disease and predicting relapse.

The primary systemic vasculitides, a heterogeneous group of multisystem syndromes characterized by the caliber of the blood vessels involved and the organ systems affected, are clinically challenging. Many of them follow an unpredictable, relapsing course that can lead to permanent damage, while there is no good way to differentiate active disease from infection or prior damage or to predict disease flares. This makes it difficult to plan treatment, weighing the benefits of potent immunosuppressive medications against the potential toxicities.

We urgently need good biomarkers to distinguish active disease from damage or infection and to predict relapse, treatment response, and prognosis. Existing options are unsatisfactory.

In the prototypic small-vessel vasculitis, antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), the autoantibodies for which it is named are unsuitable as biomarkers of disease activity. A recent meta-analysis concluded that the data is insufficient to support using persistently positive or rising ANCA titer alone to guide treatment decisions.1 Also, traditional acute-phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) lack sufficient sensitivity and specificity to predict relapse in a clinically significant manner.2,3

An intensive search for better biomarkers is now under way. Most of the potential biomarkers in AAV are "not ready for primetime," as they are not yet commercially available or validated in large, prospective cohorts.4

Among the most promising candidates:

- **Subsets of B and T cells**, both implicated in the pathogenesis of AAV, may prove useful to discriminate active disease from remission.

Compared to AAV patients in remission or healthy controls, patients with active AAV show higher levels of activated (CD19+/CD38+) B cells,5 while patients in remission show higher levels of CD25+ regulatory B cells than healthy controls or those with active disease.6

Also, decades-long followup of Mayo Clinic patients treated repeatedly with rituximab for refractory AAV reveals that all observed flares occurred in those with B cell reconstitution, concurrent with a rise in levels of PR3, a type of ANCA.7 While time to B-cell reconstitution varied between patients, the authors concluded that for some patients taking rituximab the combination of B cell reconstitution and PR3 level can serve as a biomarker for relapsing disease.

Activated T cells are detectable in the sera of AAV patients with both active and quiescent disease, but transcriptome analysis has identified CD8+ T cell expression profiles that divided patients into two distinct subgroups differing only in their risk of relapse.8
• **Activation of the alternative complement pathway** is also implicated in AAV pathogenesis. Patients with active renal AAV show higher circulating plasma levels of C5a, a common pathway component, and of **fragment Bb**, a measure of alternative pathway activation, than do those in remission or healthy controls.\(^9,10\)

• **Well-characterized longitudinal cohorts from therapeutic trials offer a rich resource to identify and verify other potential biomarkers for AAV**. For instance, recently, Monach et al attempted to find candidate serum biomarkers for AAV using data from participants in the RAVE (Rituximab in ANCA-Associated Vasculitis) trial.\(^11,12\) They identified three proteins **CXCL13 (BCA-1)**, **matrix metalloproteinase-3 (MMP-3)** and **tissue inhibitor of metalloproteinases-1 (TIMP-1)** that may distinguish active AAV from remission better than ESR and CRP. The specificity of these markers for AAV versus other sources of inflammation remains to be seen.

In the **large vessel vasculitides**, Giant Cell Arteritis (GCA) and Takayasu Arteritis (TA), elevations of traditional inflammatory markers are not specific for active vasculitis (and may be affected by therapy). As with AAV, several biomarkers found promising for GCA and TA will require validation in larger cohorts and standardization of measurement techniques to prove their clinical utility:

• **The pro-inflammatory cytokine IL-6** is elevated in the arterial lesions and the peripheral circulation in GCA and TA. IL-6 levels in the serum correlate with disease activity.\(^13\) This observation may inform therapy: A large study using IL-6 blockade with tocilizumab is under way for the treatment of new and relapsing GCA.\(^14\)

• Levels of **another pro-inflammatory cytokine, IL-17**, are also increased in the inflammatory lesions in active GCA. They may predict response to glucocorticoid treatment.\(^15\)

• Certain circulating proteins including several **matrix metalloproteinases** have been suggested to be useful biomarkers for TA disease activity.\(^16\)

• Radiologic biomarkers can also help in determining disease activity in TA. Several studies including a recent meta-analysis suggest the **FDG-PET scan** can detect disease activity in TA patients, even while they are taking immunosuppressive therapy.\(^17,18,19\)

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