Serum calprotectin as promising diagnostic aid in predicting relapse in proteinase 3-antineutrophil cytoplasmatic antibodies-associated vasculitis

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The recently published article of Pepper and colleagues (1) focuses on the deficit in diagnostic aids for predicting recurrent disease in antineutrophil cytoplasmatic antibodies (ANCA)-associated vasculitis (AAV). Although the diagnostic value of ANCA in AAV is well established and undisputed, the clinical benefit of ANCA for disease monitoring seems to be limited to targeted determination in patients clinically suspected for relapse (2,3), in patients with renal disease (4), and in patients that received plasmapheresis for severe AAV (5).

New biomarkers for prediction of recurrent AAV disease remain of major interest. Relapses in AAV are common and can lead to irreversible organ damage, higher risk of infections and chronic comorbidities, secondary to vasculitis or its treatment (6-8). Patients who were diagnosed before development of advanced renal insufficiency have a better prognosis. Combining identification of the disease phenotype at risk for relapse with appropriate use of readily available validated biomarkers that can predict relapses should guide an optimally targeted maintenance therapy. Several studies have found that a diagnosis of granulomatosis with polyangiitis (GPA) [versus microscopic polyangiitis (MPA)], proteinase 3 (PR3)-ANCA [versus myeloperoxidase (MPO)-ANCA] and having had relapses in the past confer the highest risk for subsequent relapses (3).

New insights into the pathogenesis of AAV expand not only the therapeutic options but also the diagnostic tools to predict AAV flares. Despite the central role of ANCA antibodies in AAV pathogenesis, also other biomarkers of the inflammatory process are drawing attention, like inflammatory cytokines (IL-1) (9), complement factors (C5a) (10) and the percentage of CD5+ B cells (11,12).

Calprotectin has gained widespread interest in studies of acute and chronic inflammation and associated diseases. Calprotectin is a heterodimeric complex of 2 S100 calcium-binding proteins, myeloïd-related protein (MRP)-8 (S100A8) and MRP-14 (S100A9), expressed in granulocytes and monocytes. Calprotectin is an important proinflammatory factor of innate immunity acting as endogenous damage-associated molecule regulating myeloid cell function via toll-like receptor-4 activation (13). Its release at sites of inflammation makes calprotectin a potent acute-phase reactant, with normal serum levels in the range of 1–6 mg/L which can increase more than 100-fold with active inflammation (14).

Fecal calprotectin is a sensitive and specific marker of intestinal inflammation, and its analysis is universally accepted and applied for diagnosis and follow up of inflammatory bowel diseases (15,16).

Plasma calprotectin may also be a clinically useful biomarker in several other inflammatory rheumatic diseases, including Still's Disease, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus, primary Sjögren's syndrome and juvenile idiopathic arthritis (17). A recent systematic review by Abildtrup and colleagues, including 17 studies (1988–2013) with 1,065 patients enrolled, addresses calprotectin as an indicator of disease

activity in rheumatoid arthritis (RA). A high calprotectin concentration is found in synovial fluid obtained from the joints of RA patients. Because of its low molecular weight (36.5 kDa), calprotectin diffuses into the circulation, where it can be measured, keeping in mind the short half-life of 5 hours (17,18). Because serum calprotectin directly reflects inflammation in the synovium, serum calprotectin is a more sensitive biomarker of disease activity in RA than conventional inflammatory indices such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Patients with active RA have elevated blood calprotectin levels, which decrease significantly with effective therapy (18). For this reason, serum calprotectin has been proposed as a promising biomarker to predict response to biological therapy in active RA patients at baseline and could be used to monitor response to treatment (19). Furthermore, serum calprotectin levels were independently associated with radiographic progression in RA and high baseline calprotectin levels predict future erosive damage (18).

Relative limited data can be found on the diagnostic role of calprotectin in vasculitis. The study of Croce and colleagues, which was performed in an experimental murine model of vascular injury, demonstrates that serum calprotectin broadly regulates vascular inflammation and controls the inflammatory response at several levels, including regulation of macrophage and neutrophil accumulation, macrophage cytokine production and regulation of vascular smooth muscle cell proliferation (20). Earlier studies examining calprotectin in vascular inflammation found high serum levels in acute Kawasaki disease and the authors concluded that circulating calprotectin levels might be a predictor of the severity of vasculitis (21). Elevated serum levels of calprotectin were also observed in patients with Behçet's disease (BD), a form of systemic vasculitis. However, these serum levels did not correlate with CRP levels, ESR, white blood cell count or BDCAF score (BD current activity form) (22). In the study of Kawasaki and colleagues, serum calprotectin levels were associated with the severity of renal injury and endothelial cell dysfunction in Henoch-Schönlein purpura (HSP) patients (23).

When systemic vasculitis also involves the gastrointestinal system, as might be the case for Takayasu arteritis, HSP, AAV, polyarteritis nodosa and BD, high fecal calprotectin levels can be indicative for active gastrointestinal disease (24).

Earlier studies of Pepper and colleagues already reported elevated serum calprotectin levels in patients with active generalized AAV compared to patients in remission and healthy controls. Persistently elevated calprotectin levels were also found in patients who went on to relapse (25), which is comparable to the non-responders in RA treatment (19).

In their most recent study, Pepper et al. (1) addressed the question whether calprotectin can be used as a biomarker to predict AAV relapse. For AAV patients who attained complete remission, defined by a Birmingham Vasculitis Activity Score for GPA (Wegener's Granulomatosis) (BVAS/WG) of 0 and the successful discontinuation of prednisone, serum calprotectin levels were measured at baseline and at months 1, 2 and 6 following treatment initiation. Patients were treated either with oral cyclophosphamide and glucocorticoids or with rituximab and glucocorticoids. Patients in the cyclophosphamide group were switched to maintenance therapy with azathioprine if complete remission was achieved between month 4 to 6. Not only the level of calprotectin, but also the relative changes in serum levels over time correlated with the duration of complete remission and time to relapse. A total of 144 patients, 93 with PR3-ANCA and 51 with MPO-ANCA, were included in the analysis. As only 6 MPO-ANCA patients relapsed, the analysis was focused on the PR3-ANCA cohort. A significantly higher risk of relapse was associated with an increase in calprotectin between baseline and month 2 and 6 for all patients, suggesting that an individual patient's level of calprotectin from the time of diagnosis stratifies the patient's relapse risk. Subgroup analysis demonstrated that patients treated with rituximab and with increased levels of serum calprotectin at baseline had the greatest risk for future relapse. This is in concordance with the previous observation that elevated serum calprotectin levels predict relapse in rituximab treated RA patients (19). Nevertheless, some patients treated with cyclophosphamide/azathioprine, relapsed despite decreases in serum calprotectin, which requires further investigation.

The results of Pepper et al. (1) on the role of calprotectin in predicting AAV relapse are promising and merit further investigation.

Footnote

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