Predicting Renal Relapses in ANCA-GN: Can We Rely on Urinary CD4+ T Cells?

By Andreas Kronbichler and Cecilia Barnini

Effective therapies to manage antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides have transformed a fatal disease into a relapsing-remitting disease. Predictors of relapses, identified in numerous studies, include ear, nose, and throat involvement; proteinase 3 (PR3)-ANCA positivity; granulomatosis with polyangiitis as the disease phenotype; preserved kidney function prior to relapse; and the use of maintenance agents other than ciclosporin (1).

Analyses of patients recruited into the earlier European Vasculitis Society trials, who were followed for over 5 years, indicated that the occurrence of a renal relapse significantly predicted the risk of kidney failure with a subhazard ratio of almost 9 (2). This finding clearly underlines the importance to avoid disease relapses, and especially renal relapses, to limit the loss of nephrons and thus reduce the risk of kidney failure. A candidate biomarker should ideally associate with disease activity and should become detectable or increase in the months before a relapse occurs. Furthermore, it needs to distinguish risk of disease activity of ANCA-glomerulonephritis (GN) from potential differential diagnoses, such as acute kidney injury (AKI) due to infectious complications or drug-induced AKI. In addition, a candidate biomarker would ideally be easily measurable, and its predictive capacity should be confirmed by independent research groups.

Urinary soluble CD163 (sCD163) has emerged as a promising biomarker, with the ability to distinguish between active disease and remission, active ANCA-GN and other glomerular diseases, and AKI and different causes and to predict renal relapse. At a diagnostic cutoff of 253 ng/mL, a 2021 study by Moran et al. (3) reported an area under the curve of 0.95, with a sensitivity of 96.8% and a specificity of 96.8% to detect renal relapse. In a more recent study by Sonnemann et al. (4), flow cytometry assessment of urinary T cells of 95 patients, of whom 52 had active ANCA-GN, revealed that CD3+, CD4+, and regulatory T cell counts were significantly higher during phases of active renal disease compared with urine samples obtained during remission. Detection of CD3+ T cells and regulatory T cells outperformed other experimental markers such as urinary sCD163, monocye chemotactractant protein 1, and complement C5a in the urine, whereas a dipstick analysis showed a more robust diagnostic performance. In a follow-up study—the prospective PRE-FLARED (Urine T Lymphocytes Predict Renal Flares in Patients With Inactive ANCA-Associated Glomerulonephritis) study—the authors investigated whether urinary T lymphocyte assessment would predict renal flares within 6 months of assessment. For this purpose, 102 patients in remission were recruited. Patients with a subsequent renal relapse (n = 10; 9.8%) had higher detectable urinary CD4+ lymphocytes (811 cells per 100 mL of urine) compared with those with a stable remission (38 cells per 100 mL of urine) by using a cutoff of over 490 CD4+ T cells, a sensitivity of 60%, and a specificity of 97.8%, with an area under the curve of 0.88. Measurement of CD4+ T cells predicted renal relapse more accurately as widely available biomarkers, such as ANCA titers, proteinuria/albuminuria, and hematuria. The addition of PR3-ANCA to urinary CD4+ T lymphocytes yielded better diagnostic accuracy (5).

The findings of PRE-FLARED are highly relevant, and urinary CD4+ T cell analysis might further help to identify patients at risk of subsequent disease relapses. This would have direct implications on management of patients with ANCA-GN, as the analysis might identify a subset of patients who will require long-term maintenance therapies. In the therapy of ANCA-GN, the ultimate goal must be avoidance of renal relapses, given their impact on kidney failure risk. Independent confirmation of measurement of urinary T lymphocytes to predict relapses and eventually a clinical trial with the aim to stratify patients according to their levels of CD4+ T cells in the urine are required to further personalize treatment approaches in ANCA-GN (Figure).

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References

Figure. ANCA-GN: From pathophysiology to clinical implications

A complex interplay of different environmental and genetic factors, infectious complications, and certain drugs can induce ANCA-associated vasculitis. There is an underlying loss of immunologic tolerance, which leads to the production of ANCA, and the increase in inflammatory cells, which reside around areas of inflammation. This phenomenon needs to distinguish risk of disease activity of ANCA-glomerulonephritis (GN) from potential differential diagnoses, such as acute kidney injury (AKI) due to infectious complications or drug-induced AKI. In addition, a candidate biomarker would ideally be easily measurable, and its predictive capacity should be confirmed by independent research groups.

Urinary CD4+ T cells: A novel predictive biomarker for renal flares in patients with ANCA-associated vasculitides

Conclusion: Urinary CD4+ T cells are a new and promising biomarker for ANCA-associated vasculitides. They may help to identify patients at risk of subsequent renal relapses and to stratify them for the management of these diseases. AUC, area under the curve; BVAS, Birmingham Vasculitis Activity Score; MPO, myeloperoxidase.