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Anti-GBM disease: A model for autoimmune kidney diseases

The renewed interest in anti-GBM disease is spurred by the detection of autoantibodies in other forms of glomerulonephritis and has led to an exciting development in studies on pathogenesis as well as diagnosis and management. The newly published review [1] by Professor Mårten Segelmark, gives a comprehensive update on Anti-GBM disease subgroups, pathogenesis and therapies. "A must read for all nephrologist", explains Professor Denis Fouque, editor-in chief of Nephrology Dialysis and Transplantation (NDT), the journal in which the review was published.

For many years anti-GBM disease was thought to be the only kind of glomerulonephritis driven by autoantibodies. Now it has become evident that autoantibodies also play an important part in ANCA-associated nephritis, membranous nephropathy and IgA-nephritis. This has renewed the interest in anti-GBM as a model for autoimmune kidney diseases. The discovery of the B-cell epitopes led to the development of rapid immunoassays for the detection of circulating anti-GBM. This has enabled early diagnosis, which has had an impact on the prognosis.

A large percentage of patients with anti-GBM disease also have myeloperoxidase-ANCA (MPO-ANCA). As a group, double-positive patients are older, and they have more prodromal symptoms. This opens up a window of opportunity for early diagnosis, but it is questionable if double-positive patients have a better overall renal prognosis. The clinically most important aspect of double positivity is the increased relapse risk, making maintenance immunosuppressive therapy warranted for double-positive patients.

There are also several reports of overlap between membranous nephropathy and anti-GBM disease. Such patients usually have nephrotic-range proteinuria in combination with crescentic glomerulonephritis. It has been suggested that membranous nephropathy might trigger an autoimmune response against the cryptic anti-GBM epitopes. However, there are no cases described with simultaneous anti-PLA2R antibodies and antibodies to type IV collagen. An alternative explanation is that some anti-GBM antibodies

preferentially deposit on the subepithelial side of the GBM, thereby mimicking the immune complexes seen in membranous nephropathy.

Cyclophosphamide is today the standard therapy to stop the autoantibody production. Historical data indicate that cyclophosphamide substantially shortens the time circulating antibodies are present. This reduces the risk of flares with nephritis and pulmonary haemorrhage, and enables renal transplantation at an earlier time point. In ANCA-associated vasculitis it has been shown that targeting B-cells with rituximab leads to a more rapid decline of circulating antibodies. There are reports of the use of rituximab in anti-GBM disease, but no head-to-head comparison.

Plasma exchange is used to lower levels of circulating autoantibodies. However, each session only removes about one third of the IgG in the body. Thus it takes several days to reach non-toxic levels. Immunoadsorption techniques have been employed as an alternative. This leads to a more rapid decline of the antibodies, but it is not clear in how many patients this would make a difference in outcome.

"In conclusion, the detection of autoantibodies in other forms of glomerulonephritis, renewed the scientific interest in anti-GBM disease, which now serves as a model in the research of autoimmune kidney diseases", explains Segelmark. Professor Denis Fouque, editor-in chief of Nephrology Dialysis and Transplantation (NDT) adds: "The review is a `must read´ for all nephrologist!"

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[1] Segelmark M et al. Anti-GBM disease – an update on subgroups, pathogenesis and therapies. Nephrol Dial Transplant 2018; https://doi.org/10.1093/ndt/gfy327

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