Low Serum C3 Pauci-Immune Glomerulonephritis: High Histopathological Activity and Lower Rates of Response to Standard Therapies

To the Editor: We thank you for the opportunity to respond to the letter by Pr Jean-François Augusto.

Low serum complement pauci-immune glomerulonephritis (PIGN) is increasingly being recognized as an entity with distinct characteristics, in terms of its clinical picture and response to currently used immunosuppressive regimens. Patients with low serum complement were shown to have highly active glomerular and tubulointerstitial lesions (i.e., crescents, interstitial leukocyte infiltration, and fibrinoid necrosis in vessel walls). Low complement PIGN was shown to be more frequently resistant to therapy with high-dose glucocorticoids and either cyclophosphamide or rituximab. In general, although referring to fewer than one-fourth of patients, treatment resistance remains problematic, as it is associated with end-stage kidney disease and death. Classic risk factors associated with this outcome include advanced age, female gender, black ethnicity, and severe renal disease. However, these data clearly suggest that hypocomplementemia per se defines a noteworthy subset of patients with a high probability for nonresponsiveness to immunosuppressive treatment. Clinically, this is important from 3 aspects: first, it would be reasonable to know what proportion of those patients who experience treatment resistance overall correspond to patients with hypocomplementemia at diagnosis; second, as the renal lesions are highly active in low serum C3 PIGN, one might postulate that they represent relatively new and theoretically reversible kidney injury if appropriate therapy is given; and third, the fact is that standard of care is not effective in this particular setting. Therefore, additional and/or targeted therapeutic intervention(s) are required to regulate the complement system and avoid organ or life-threatening disease. Glucocorticoids, the traditional nonselective anticomplement medication and the targeted antagonist of C5a receptor, avacopan, are both able to restrain complement. The anaphylatoxin C5a, produced by the final complement pathway, is determinant to drive the disease in animal models. The potential of avacopan to reduce the need of glucocorticoids was demonstrated in the CLEAR study, and the CLASSIC trial provided a positive assessment regarding safety and tolerability, when administered in addition to the standard therapy. Hence, avacopan seems likely to play a principal role in the management of patients with low serum C3 PIGN, but it remains to be elucidated if it should be given as an add-on therapy or as a substitute to glucocorticoids, initially or subsequently, or in both occasions and indefinitely.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)
Supplementary References.


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