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LETTER TO THE EDITORS

Treatment of DEAP-HUS—seeking the best strategy

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Sirs:

We gratefully acknowledge the opportunity of responding to the letter by Bagga et al. [1] in which they comment on our report on the use of eculizumab in two DEAP-HUS (deficiency in *CFHR1* and *CFHR3* and CFH-autoantibody-positive) patients and our discussion of treatment options [2]. These authors claim that the "prompt use of immunosuppressive agents and plasma exchange (PLEX) are useful for improving outcomes in pediatric patients with anti-complement factor H-associated HUS" and should be considered "standard of care."

The comments made by Bagga et al. in their letter are based on their recently reported experience in 138 patients with CFH-autoantibody-mediated hemolytic uremic syndrome (HUS) [3]. The authors advise PLEX in combination with immunosuppression for acute management and immunosuppression alone for chronic management. Treatment options used in their study include: (1) PLEX, (2) PLEX + intravenous immunoglobulin, (3) steroids, (4) steroids + cyclophosphamide, and (5) steroids + rituximab and, thereafter, maintenance immunosuppression with either (1) steroids + mycophenolate mofetil or (2) steroids + azathioprine. Of note, 41 of the reported patients had an adverse outcome, 33 were dialysis dependent, and 20 died. The authors report 55 % renal survival at longest follow-up.

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Despite the significant difference in patient numbers between our study and that of Bagga et al. [1], we respectfully refute adopting the reported experience as "standard of care." Randomized controlled prospective trials or—if not feasible due to ethical or other practical considerations—a broad expert consensus are inevitable before any treatment can be adopted as "standard of care."

We also wish to re-emphasize the rationale for the treatment approach presented in our study. Regardless of the initiating event—genetic or acquired—pathogenetic progression in complement-mediated thrombotic microangiopathy is due to loss of control of activation of the complement alternative pathway, in particular its terminal sequence. With that, the main treatment principle consists in re-establishing proper complement control. In DEAP-HUS, where anti-CFH autoantibodies have been shown to abolish CFH C-terminal function (similar to CFH mutations of the C-terminus), this can be achieved either by removing the initiating event (i.e., by removing or reducing the antibody load) or by blocking complement progression (e.g., by eculizumab). We opted for the use of eculizumab, which has been found to be highly successful in prospective treatment trials in atypical HUS (aHUS) patients with acute and chronic presentation. Compared to different treatment strategies, eculizumab has been found to be superior in re-establishing complement control both ex vivo/in vitro when testing aHUS plasma collected during plasma versus eculizumab treatment in a hemolysis assay, and in aHUS patients previously unresponsive to PLEX.

Besides its benefit in primary complement-mediated diseases, eculizumab has also proven useful in patients suffering from autoimmune diseases caused by non-complement-specific antibodies with secondary complement involvement, such as antiphospholipid syndrome, antibody-mediated rejection, neuromyelitis optica, and myasthenia gravis.

However, there is obviously also a role for PLEX and immunosuppression in the treatment of DEAP-HUS, and we foresee a stepwise approach to the treatment of DEAP-HUS consisting of the use of eculizumab to re-establish complement control and prevent (early) relapses (induction) and the use of PLEX and immunosuppression to permanently reduce the antibody burden (maintenance). Of note, we do not recommend the combination of eculizumab and PLEX (unless following a proper re-dosing protocol). Maintenance therapy will have to be informed by close antibody titer monitoring—a challenge in itself as an international standard for determining CFH autoantibody titers has not been established yet and comparing antibody titers measured against different (laboratory specific) standards is meaningless.

The optimal combination of complement control (eculizumab), antibody depletion (PLEX), and immunosuppression needs to be prospectively studied in a larger cohort of DEAP-HUS patients to define a final treatment algorithm for DEAP-HUS—a task of particular importance as access to eculizumab is still problematic in some countries.

References

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