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Letter

Complement inhibition in severe COVID-19 – Blocking C5a seems to be key: Author's reply

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We thank Lim and colleagues [1] for questioning how best to modulate complement pathway to improve outcomes of patients with COVID-19. In our study, we found that in patients with severe COVID-19, eculizumab treatment associated reduction in soluble C5b-9 paralleled the reduction of the concentrations of circulating proinflammatory cytokines and arterial lactate [2]. To explore the effects of eculizumab treatment on the second limb of the terminal complement pathway, we retrospectively measured C5a concentrations at baseline, day-1 and day-7 in 44/80 patients (14/45 and 30/35 in the eculizumab free and treated, respectively). At baseline, C5a concentrations varied fairly from 7 to 200 ng/mL. In the eculizumab treated patients C5a median (IQR) concentrations were 38 (19–89) ng/mL, 24 (17–38) ng/mL and 24 (15–56) ng/mL, at baseline, day-1 and day-7, respectively (Kruskal-Wallis, $P = 0{\cdot}72$). The median concentrations of C5a did not statistically differ between eculizumab-treated and eculizumab-free patients at day-1 (Wilcoxon test, $P = 0{\cdot}93$) and day-7 ($P = 0{\cdot}14$). The reason for incomplete terminal pathway inhibition by eculizumab in patients with severe COVID-19 is unclear. These findings may contrast with eculizumab associated reduction in systemic and lung inflammation, and survival improvement. This retrospective analysis may lack of sufficient power as samples were missing for about one out of 2 patients. On the other hand, strong activation of complement may have played a role in insufficient inhibition of the terminal complement pathway by eculizumab as previously suggested in complement-mediated diseases [3]. Median concentrations of C3a was 338 ng/mL (IQR: 194–718). Further studies may clarify the potential benefit of monoclonal antibodies targeting specifically C5a [4] or C5aR1 [5] in patients with severe COVID-19.

Declaration of Competing Interest

Djillali Annane and Lamiae Grimaldi-Bensouda have no conflicts to declare. Veronique Fremeaux-Bacchi: reports non-financial support from Alexion Pharmaceuticals Inc. during the conduct of the study; grants and personal fees from Alexion, personal fees from Roche, personal fees from Apellis, and personal fees from Biocryps outside the submitted work.

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