The opening salvo of anti-complement therapy against COVID-19

Lancet Rheumatol 2020
Published Online
September 28, 2020
https://doi.org/10.1016/S2665-9913(20)30353-2
See Online/Articles
https://doi.org/10.1016/S2665-9913(20)30341-6

The COVID-19 pandemic remains unrelenting as the autumn of 2020 approaches. Despite many clinical trials underway to find effective treatments for COVID-19, few studies have yielded positive results. Increasing evidence shows diffuse activation of the complement pathway in severe COVID-19 infections, from increased serum levels to widespread deposition in autopsy specimens.[1-4] Initial case reports and case series using complement inhibitors in COVID-19 have shown promising results.[5-8] The complement pathway, a key effector of the innate immune system, has emerged as a nidus of investigation in this pandemic.[9]

In brief, the complement cascade can be activated by three pathways (classical, lectin, and alternative), which converge on the terminal complement pathway at C3. The terminal pathway results in anaphylatoxins, C3a and C5a, and the membrane attack complex (MAC), C5b-9. The anaphylatoxins are potent activators of neutrophils and monocytes. The MAC disrupts pathogen cell membranes. The dysregulation of this pathway is hypothesised to underlie severe COVID-19 complications.

In *The Lancet Rheumatology*, Alexander Vlaar and colleagues[10] report the first randomised controlled clinical trial investigating a complement pathway inhibitor for severe COVID-19. 30 patients (22 [73%] men and eight [27%] women) were randomly assigned to receive IFX-1, an investigational drug that inhibits C5a (n=15), or standard of care (n=15). The primary endpoint of mean relative change in the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air (PaO_2/FiO_2) on day 5 was not significantly different between groups (difference −24% [95% CI −58 to 9], p=0·15). The heterogeneity of oxygenation levels in COVID-19 made this a problematic endpoint, as the authors discuss. Nevertheless, the trial shows the safety and tolerability of IFX-1 in patients with severe COVID-19—an important milestone.

The secondary outcomes reported are notable. In IFX-1-treated patients, there were fewer pulmonary embolisms (two [13%] patients in the IFX-1 group *vs* six [40%] in the control group) and fewer cases of renal impairment (none *vs* two) than in the control group. The IFX-1 group had a significantly lower estimated 28-day mortality rate versus the control group (adjusted hazard ratio for death 0·65 [95% CI 0·10–4·14]). This small exploratory study does not have enough power to draw conclusions about these endpoints, but data certainly are hypothesis generating.

An important caveat is that pharmacokinetic and pharmacodynamic analysis, including C5a, are absent in this study and are planned to be published separately. Investigators using the C5 complement pathway inhibitors eculizumab and ravulizumab have significantly increased their dose and dosing frequency in the acute setting of COVID-19 compared with the doses approved for use in atypical haemolytic uremic syndrome. Whether IFX-1 in this trial successfully inhibited complement C5a in the setting of severe COVID-19 is uncertain at this time.

The next step for IFX-1 is proceeding with the phase 3 trial, informed by the trial by Vlaar and colleagues. The randomised, placebo-controlled, phase 3 trial aims to enrol 360 patients with COVID-19 who have been intubated less than 48 h, with 28-day all-cause mortality as the primary endpoint.

Other clinical trials are underway investigating other inhibitors of the terminal complement pathway against COVID-19, including C3 inhibitors—AMY-101 (NCT04395456) and APL-9 (NCT04402060); C5 inhibitors—eculizumab (NCT04346797 and NCT04355494), ravulizumab (NCT04369469 and NCT04390464), and zilucoplan (NCT04382755); and a C5a receptor inhibitor—avdoralimab (NCT04371367). Furthermore, C1 esterase inhibitors, which block the classical complement pathway, are under investigation—conestat alfa (NCT04414631) and ruconest (NCT04530136).

Beyond the fundamental question of whether anti-complement therapy improves outcomes in COVID-19, the ongoing clinical trials hopefully will address both critical and nuanced questions in the campaign against COVID-19 over the ensuing months.

First, what is the optimal time to start anti-complement therapy during COVID-19 infection? Early use in the viral phase of COVID-19 might block critical antiviral responses of the innate immune system. Late use in patients on mechanical ventilation might be after significant complement-mediated injury has already occurred.

Second, which complement pathway protein is the most effective target against COVID-19?

Third, will treatment with anti-complement therapies increase the risk of complications from other infections? Although no safety issues were recorded in this trial, larger studies or different targets might have different risk profiles. Scarcity of MAC can increase the risk of encapsulated bacterial infections.

Fourth, does inhibition of complement decrease thrombotic events or other complications?

Fifth, is complement inhibition beneficial to any patient with severe COVID-19 or only to a subset of patients with a genetic predisposition to complement pathway dysregulation?

Sixth, the trial by Vlaar and colleagues[10] was done before data showing benefit in COVID-19 from remdesivir and dexamethasone. Whether anti-complement therapy will offer incremental or synergistic benefits with these therapies remains to be established.

Complement inhibitors are promising potential therapies for COVID-19 and, indeed, might emerge as crucial therapies in other severe viral infections. Future studies will show whether IFX-1 or another anti-complement therapy could be an effective approach against COVID-19.

I declare no competing interests.

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