## Efficacy matters: broadening complement inhibition in COVID-19

We and others have proposed the use of anti-complement agents for the treatment of COVID-19;[1] thus, we read with great interest the Article by Alexander P J Vlaar and colleagues[2] reporting the results of an exploratory, randomised phase 2 trial of IFX-1, an anti-human C5a monoclonal antibody, in patients with severe COVID-19. Here, we discuss plausible explanations for IFX-1's inefficacy in this study.

One major concern is the choice of the primary endpoint, the percentage change in $PaO_2/FiO_2$ from baseline to day 5, which was assessed well before the anticipated pharmacodynamic window of IFX-1. In addition, as acknowledged by the authors, the trial was not powered to show statistically significant differences in clinical endpoints, eventually jeopardising any conclusion, even on secondary endpoints. The possible biological efficacy of IFX-1 was not adequately investigated by extensive assessment of key inflammatory markers (eg, C-reactive protein) related to the effect of C5a blockade on hyperinflammation. In fact, upstream complement inhibition at the C3 or C5 level leads to a rapid decline in the concentration of serum inflammatory markers in patients with COVID-19.[3,4]

Monitoring plasma C5a concentrations would enable a reliable assessment of the drug's effective therapeutic concentration. Inclusion of pharmacokinetic and pharmacodynamic measurements would have also been informative (eg, the ability of IFX-1-treated plasma to block C5aR1-dependent responses in appropriate assays), helping to resolve issues related to drug plasma residence, target saturation, dosing, and efficacy.

We believe that the selection of a complement target with a narrow therapeutic scope, such as C5a, is contradictory to mounting evidence indicating that COVID-19 thromboinflammation is fuelled by multiple elements of the complement cascade that remain operative during anti-C5a treatment (eg, C3, C3a–C3aR1, and C5b-9).[4,5] For instance, C3 inhibition offers broader control of thromboinflammation driven by neutrophil extracellular traps in patients with COVID-19 than does C5 inhibition, partly explaining the small impact of IFX-1 on coagulation and indicating that D-dimer analysis might not be a uniformly predictive or reliable marker of coagulation in patients with COVID-19.[4]

Considering that high neutrophil numbers are associated with poor prognosis in COVID-19, the projected non-interference of IFX-1 on neutrophil counts might signify that anti-C5a treatment is not the optimal way to treat COVID-19-associated neutrophilia. In fact, blockade of other complement components, acting upstream of C5a, might be a more robust and favourable clinical approach (eg, blockade of C3-mediated signalling with therapeutics like AMY-101). Thus, even if apparently disappointing, the results of this trial indicate that broader, rather than narrower, complement inhibition might be more beneficial for the treatment of COVID-19.

JDL reports that he is the founder of Amyndas Pharmaceuticals, which develops complement inhibitors for therapeutic purposes, inventor of a broad patent portfolio that describes the therapeutic use of complement inhibitors, some of which are developed by Amyndas Pharmaceuticals, inventor of the compstatin technology licensed to Apellis Pharmaceuticals (ie, 4(1MeW)7W/POT-4/APL-1 and pegylated derivatives such as APL-2/pegcetacoplan and APL-9), and has received consulting fees from Achillion, Baxter, LipimetiX, Ra Pharma, Sanofi, and Viropharma. RTC has acted as a speaker for Alexion Pharma Brazil. AMR has received research support from Alexion Pharmaceuticals, Novartis, Alnylam, and Ra Pharma, lecture fees from Alexion, Novartis, Pfizer, and Apellis, and has served as a member of advisory investigator boards for Alexion, Roche, Achillion, Novartis, Apellis, and Samsung, and as a consultant for Amyndas. All other authors declare no competing interests.

*Dimitrios C Mastellos, Panagiotis Skendros, Rodrigo T Calado, Antonio M Risitano, *John D Lambris*
**lambris@pennmedicine.upenn.edu**

Division of Biodiagnostic Sciences and Technologies, INRASTES, National Center for Scientific Research "Demokritos", Athens, Greece (DCM); First Department of Internal Medicine and Laboratory of Molecular Hematology, University Hospital of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece (PS); Department of Medical Imaging, Hematology and Clinical Oncology, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil (RTC); Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy (AMR); Hematology and Hematopoietic Stem Cell Transplantation Unit, AORN San Giuseppe Moscati, Avellino, Italy (AMR); and Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-6100, USA (JDL)

Published **Online**
December 14, 2020
https://doi.org/10.1016/S2665-9913(20)30423-9

1 Risitano AM, Mastellos DC, Huber-Lang M, et al. Complement as a target in COVID-19? *Nat Rev Immunol* 2020; **20:** 343–44.
2 Vlaar APJ, de Bruin S, Busch M, et al. Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. *Lancet Rheumatol* 2020; **2:** e764–73.
3 Peffault de Latour R, Bergeron A, Lengline E, et al. Complement C5 inhibition in patients with COVID-19—a promising target? *Haematologica* 2020; **105:** 2847–50.
4 Mastellos DC, Pires da Silva BGP, Fonseca BAL, et al. Complement C3 vs C5 inhibition in severe COVID-19: early clinical findings reveal differential biological efficacy. *Clin Immunol* 2020; **220:** 108598.
5 Skendros P, Mitsios A, Chrysanthopoulou A, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. *J Clin Invest* 2020; **130:** 6151–57.

## Authors' reply

We thank Dimitrios C Mastellos and colleagues for their interest in our exploratory, phase 2 randomised controlled trial[1] in 30 patients with severe COVID-19. The authors offer their interpretation of the inefficacy of IFX-1, arguing that upstream inhibition of the complement cascade could be superior to inhibiting C5a. We are surprised that the authors avoid discussing the efficacy signals and group differences generated in our study, and instead argue based on uncontrolled observational data relating to upstream complement C3 inhibitors. We do not think their conclusion is substantiated. As stated by regulatory bodies like the US Food and Drug Administration, in phase 2 studies, researchers administer the drug

Published **Online**
December 14, 2020
https://doi.org/10.1016/S2665-9913(20)30424-0