Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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)

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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

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to a group of patients with the disease or condition for which the drug is being developed to refine research questions and design new phase 3 research protocols. Typically, as in our study, these trials are not large enough to show that the drug is beneficial, but rather suggest efficacy trends and concepts.

In COVID-19, the secondary induction of a systemic hyperinflammatory state with immunothrombosis and endothelial damage in the lungs and other organs, including the kidney, appears to be a main driver of morbidity and mortality. Accumulating evidence points towards a key role for C5a-induced neutrophil activation in disease pathogenesis in critically ill patients with COVID-19.[2] C5a can be produced by conventional complement activation cascades, but also through direct enzymatic cleavage via proteinases, especially those of the coagulation pathways such as thrombin and plasmin. Because a hypercoagulable state is often observed in patients with severe COVID-19, a large proportion of C5a generated by this enzymatic activation can be expected. C5a made via these enzymes would not be blocked by upstream blockers such as the C5 inhibitor eculizumab.[3] Therefore, a targeted blockade of C5a might offer tighter control of C5a in COVID-19 than might an upstream blockade. Thromboinflammation driven by neutrophil extracellular traps has been shown to be a C5a–C5aR-dependent process in COVID-19.[4] This study provides support to our hypothesis that C5a induces the release of tissue factor by neutrophils, the link between C5a and coagulation, and a potential positive feedback loop for more C5a generation.[1] The observed increase in D-dimer concentrations early after C5a inhibition with IFX-1 should be seen within the context of thromboinflammation driven by neutrophil extracellular traps, C5a generation, and coagulation.

The exploratory phase 2 part of the PANAMO trial showed that C5a inhibition with IFX-1 was safe in patients with severe COVID-19.[1] The observed favourable effects of IFX-1 on mortality, kidney function, lactate dehydrogenase concentrations (a marker of tissue damage), and lymphocytopenia are preliminary because the study was not powered on these endpoints, but they do support investigating C5a inhibition with IFX-1 in a phase 3 trial using 28-day mortality as the primary endpoint. The phase 3 part of the PANAMO trial has been initiated (NCT04333420). Importantly, the effects of the C5a inhibitor IFX-1 do not automatically apply to other C5a inhibitors or inhibitors blocking other complement factors in upstream activation pathways. Conclusions on the potential superiority of treatment approaches from very small, non-controlled studies—such as the three patients treated with AMY-101—should be avoided or handled with care. To our knowledge, our data are the first published data of a complement inhibitor from a randomised controlled clinical trial in patients with COVID-19.

The declaration of interests remains the same as in the original Article.

*Alexander P J Vlaar, Sanne de Bruin, Matthijs C Brouwer, Diederik van de Beek
a.p.vlaar@amsterdamumc.nl

Department of Intensive Care (APJV, SdB) and Department of Neurology, Amsterdam Neuroscience (MCB, DvdB), Amsterdam UMC, University of Amsterdam, Amsterdam 1100DD, Netherlands

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Genetic IL-6R variants and therapeutic inhibition of IL-6 receptor signalling in COVID-19

The COVID-19 pandemic, caused by infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major challenge for treating physicians as long as neither a vaccine nor an available therapy is generally effective. Patients with SARS-CoV-2 often display hyperinflammation, and several small studies reported a benefit when patients were treated with tocilizumab, a monoclonal antibody targeting the interleukin (IL)-6 receptor (IL-6R).[1,2] However, the phase 3 COVACTA trial did not show an improvement in clinical status in patients with COVID-19-associated pneumonia nor a reduction in patient mortality with tocilizumab, suggesting that IL-6 blockade might not be beneficial in all COVID-19 patients.

In their Correspondence in *The Lancet Rheumatology*,[3] Jonas Bovijn and colleagues analysed seven genetic IL-6R variants in the context of COVID-19. Of these, only one single nucleotide polymorphism, rs2228145, which encodes the non-synonymous IL-6R variant Asp358Ala, has been functionally analysed,[4] whereas data for the other, mostly intronic, variants are lacking. These variants have previously been shown to be associated with reduced serum concentrations of C-reactive protein and fibrinogen and increased serum concentrations of IL-6 and soluble IL-6R (sIL-6R).

Because these clinical features are also present in patients undergoing anti-IL-6R therapy, Bojvin and colleagues conclude that the genetic IL-6R variants mimic therapeutic inhibition of IL-6R signalling.[3] Their analysis convincingly shows that the IL-6R variants are associated with a lower risk of rheumatoid arthritis and coronary heart disease, and interestingly also