GLOBAL SCIENCE LIBRARY

COMMENTARY

Trends in Pulmonary and Respiratory Medicine

Possible Immunopathological Sequelae of Severe COVID-19 Immunotherapy: The Lesser of Two Evils?

Andrew W. Taylor-Robinson[1-3*]

[1]*School of Health, Medical & Applied Sciences, Central Queensland University, Brisbane, Australia*
[2]*College of Health and Human Sciences, Charles Darwin University, Casuarina, Australia*
[3]*College of Health Sciences, Vin University, Gia Lam district, Hanoi, Vietnam*

Keywords: *COVID-19, SARS-CoV-2, angiotensin-converting enzyme 2, interleukin, cytokine, immunotherapy, treatment, immunopathology*

Eighteen months into the COVID-19 pandemic the number of people infected with SARS-CoV-2 is still increasing worldwide [1], rapidly in many countries, due to a spike in incidence related to community transmission of a hitherto locally unseen variant of this beta-coronavirus. The global confirmed case mortality statistic continues to escalate in the face of a steady roll out of immunization programs with one or other regulatory authority-approved efficacious vaccine [1]. As infected individuals may experience a potentially life-threatening course of infection, especially those in high-risk groups such as the elderly, people with health conditions and pregnant women, there remains an urgent need for effective drug therapy for severe COVID-19. Due to the sheer scale of the public health crisis caused by the pandemic, the consensus of the global biomedical research community is that time is too short to develop novel specific agents. Thus, existing antivirals or immune modulators with known safety profiles are gaining traction as the fastest route to treat hospitalized cases of COVID-19 [2]. Compounds that have already been tested in other indications now have priority, in particular those shown to be effective in treating infection with the closely related coronaviruses that are the causative agents of SARS and MERS.

Severe clinical cases of SARS-CoV-2 infection are characterized by the overexpression of inflammatory cytokines leading to patient death. This may be attributed to a virus-induced acute severe systemic inflammatory response known as a 'cytokine storm' [3]. Several very different therapeutic approaches are in the treatment pipeline for COVID-19: antiviral compounds that inhibit SARS-CoV-2 RNA synthesis; those blocking entry of the virus particle into the host cell; and immunomodulators that are supposed to reduce a cytokine storm and associated pulmonary damage – which are pathological sequalae observed in fulminant disease. Of note, no drug is yet approved for COVID-19. In recently updated guidance, the World Health Organization stated that "there is no current evidence to recommend any specific anti-COVID-19 treatment" and that use of investigational therapeutics "should be done under ethically approved, randomized, controlled trials" [4].

SARS-CoV-2 is a single-stranded RNA beta-coronavirus. Potential targets are non-structural proteins such as protease, RNA polymerase and helicase, but also accessory proteins [2]. Coronaviruses do not use reverse transcriptase. There is a total of only 82% genetic identity between SARS-CoV and SARS-CoV-2. However, the strikingly high genetic homology for one of the key enzymes, the RNA-dependent RNA polymerase, which reaches around 96% [5], suggests that substances effective for SARS may also be active against COVID-19.

Most coronaviruses attach to cellular receptors via the spike protein that protrudes from their outer membrane. Within a few weeks of the outbreak being first reported, the mechanism of entry of SARS-CoV-2 into the target cell was elucidated [6,7]. Similar to SARS-CoV, SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) receptor, a surface protein that is scarcely present in the circulation but widely expressed in multiple organs and – in the respiratory system – on lung alveolar epithelial cells. The affinity of SARS-CoV-2 for ACE2 receptor appears to be higher than that shown by other coronaviruses. The hypothesis that ACE inhibitors promote severe clinical manifestations of COVID-19 through increased expression of ACE2 receptor remains unproven and is subject to investigation [8].

In the first large study of the clinical characteristics of laboratory-confirmed COVID-19, in a cohort of 1,099 hospital inpatients in China, hypertension was associated with an increased risk of severe disease (24% versus 13% for uninfected, matched controls) [9]. Together with diabetes, hypertension was the coexisting condition that posed the highest risk of complications [9,10]. However, comedication was not recorded in this investigation, since when several medical societies and authoritative reviews came out to explicitly advise against discontinuing the use of ACE inhibitors [11-13]. Furthermore, the binding of SARS-CoV-2 to ACE2 appears to lead to an imbalance in the endocrine renin–angiotensin–aldosterone system (RAAS) that regulates blood volume and systemic vascular resistance, which together influence cardiac output and arterial pressure. Studies in animal models have shown that during the course of pneumonia this imbalance could even be favourably affected by ACE inhibitors [14,15]. The biological plausibility of the salutary effects of RAAS inhibitors is intriguing and several trials of patients with COVID-19 receiving the hypertension drug losartan (Cozaar®) are now either underway or being planned. The first trial to be published has indicated at the very least no deleterious effect, and often an improved clinical outcome, of giving RAAS inhibitors to COVID-19 patients with high blood pressure [16].

While stand-alone administration of existing antiviral drugs is most likely to prevent mild COVID-19 cases from becoming severe, adjuvant strategies will be imperative in the therapy of

severe fulminant disease. Human coronavirus infections may induce excessive, aberrant, and ultimately ineffective host immune responses that are associated with severe lung damage [17]. Similar to SARS and MERS, some patients with COVID-19 develop acute respiratory distress syndrome (ARDS), a phenomenon that is often associated with a cytokine storm [3]. This dysregulated immune response is characterized by elevated plasma concentrations of various interleukins, chemokines and acute phase proteins, resulting in inflammation-induced damage and acute pulmonary failure. ARDS has a high mortality rate and so most intensive care patients require mechanical ventilation with a high concentration of oxygen.

In order to address the hyperinflammation observed in COVID-19, the different roles of interleukin (IL)-6 warrant attention [18]. Similar to during SARS, this key cytokine may play a pivotal role in the pathogenesis of COVID-19. Hence, anti-inflammatory drugs such as chloroquine, hydroxychloroquine and tocilizumab that are reported to confer inhibitory effects on IL-6 expression, have been proposed to be of potential immunotherapeutic benefit [18,19]. While preliminary studies have claimed their effectiveness in reducing clinical manifestations associated with COVID-19, these repurposed drugs may not reliably show desired indications due to immunopathological complications related to their use [20-22]. In such a situation, this may be considered the 'lesser of two evils' of the title, an English language idiom that refers to the less unpleasant of two poor choices.

IL-6 is a major pro-inflammatory cytokine the exaggerated expression of which in the event of viral pathogenesis leads to a cytokine storm [23]. Care should be taken to suppress global expression of IL-6 because it has both pro-inflammatory and anti-inflammatory effects, the balance of which depends on its local concentration and the physiological conditions in vivo. IL-6 receptors can exist in both soluble (sIL-6R) and membrane-bound (IL-6R) forms. Depending on concentration, IL-6 can bind to either sIL-6R or IL-6R. Formation of an IL-6-sIL-6R complex initiates a pro-inflammatory cascade whereas that of an IL-6-IL-6R complex promotes an anti-inflammatory pathway [24]. A study published prior to the latest coronavirus pandemic explained why and how inhibition or blockade of both sIL-6R and IL-6R to restrict IL-6 production may not achieve desired outcomes during viral crisis [25]. In the event of a cytokine storm, the unregulated expression of pro-inflammatory cytokines occurs, for which control is urgently required. Therefore, a drug or combination of drugs is needed that will act in a specific manner to inhibit only IL-6-mediated pro-inflammatory responses [26].

A range of host-specific immunotherapies aim to limit the immense damage that is caused by the dysregulation of pro-inflammatory cytokine and chemokine reactions [27]. IL-1-blocking agents, such as disease-modifying antirheumatic drugs anakinra (Kineret®) or the JAK-2 inhibitors baricitinib (Olumiant®), tofacitinib (Xeljanz®) and upadacitinib (Rinvoq®), are also an option [3,27]. These immunosuppressive therapies may potentially act synergistically when combined with antivirals. Several marketed drugs are being discussed, including those to lower cholesterol, for diabetes, arthritis, epilepsy and cancer, but also antibiotics. They are said to modulate autophagy, promote other immune effector mechanisms and the production of antimicrobial peptides. However, clinical data are pending for most strategies [28].

Tocilizumab is a monoclonal antibody that targets IL-6R. Tocilizumab (RoActemra® or Actemra®) is used to treat rheumatic arthritis and has a good safety profile. At least one uncontrolled, retrospective study has been published, showing encouraging results in 20 patients with severe COVID-19 and elevated IL-6 levels [24]. The initial dose should be 4-8 mg/kg, with the recommended dosage being 400 mg (infusion over more than 1 hour). Controlled trials are underway as well as for sarilumab (Kevzara®), another IL-6R antagonist. There is no doubt that tocilizumab should be reserved for patients with severe disease for whom other therapies have failed. However, some case reports have suggested that IL-6-blocking treatment given for chronic autoimmune diseases may even prevent the development of severe COVID-19 [29].

Siltuximab (Sylvant®) is another anti-IL-6-blocking agent. However, this chimeric monoclonal antibody targets IL-6 directly rather than the receptor. Siltuximab has been approved for idiopathic multicentric Castleman's disease, a rare lymphoproliferative disorder. First results of a pilot trial in Italy ('SISCO trial') have shown encouraging results [30]. According to interim data [31], from the first 30 patients treated with siltuximab and followed for up to seven days, one-third of patients experienced a clinical improvement with a reduced need for oxygen support and a further 13 patients (43.3%) saw their condition stabilize, indicated by no clinically relevant changes. Of note, on day 4 after siltuximab treatment a reduction in level of the chemokine IL-8 and of the acute phase protein pentraxin 3, both important mediators of the innate immune response, was associated with improved survival and ventilatory outcomes in patients hospitalized for COVID-19 [32]. Further to these encouraging findings, a phase III randomized clinical trial is currently ongoing to confirm, qualify or refute the efficacy and safety of this IL-6–neutralizing monoclonal antibody in the treatment of patients with ARDS [33].

In order to address the treatment plan for COVID-19 it should be remembered that the disease manifestations are not caused simply by an imbalance of a single biomolecule. Rather, they reflect an overall dysfunction of the convoluted and intricate immune system due to cytokine imbalance and other associated, complex, immunopathological events that are triggered by SARS-CoV-2 infection. Therefore, research into the development of an immunotherapeutic strategy predicated on an anti-IL-6-blocking agent should recognize the advantages of a combinatorial approach over a reductionist, single drug-based therapy. For instance, an anti-inflammatory regimen could be given in combination with an anti-thrombotic drug such as heparin. In any event, extremely careful evaluation of a clinical trial to treat severe COVID-19 based on the proposition discussed here is recommended to determine the therapeutic potential. The benefits need to be balanced against the cost of any side-effects – with a view to making as palatable as possible what should always be the 'lesser evil' of treatment.

Acknowledgment

My research collaborator Abdullah Mahmud-Al-Rafat of Incepta Vaccine Ltd., Dhaka, Bangladesh, is warmly thanked for sharing his expert views on immunotherapy of infectious viral diseases over several years.

Conflicts of interest

The author declares no competing issues of interest.

References

1. COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University. Available at: https://coronavirus.jhu.edu/map.html. Last updated 4 June 2021.
2. Gil C, Ginex T, Maestro I, Nozal V, Barrado-Gil L, et al. COVID-19: drug targets and potential treatments. *J Med Chem*. 2020; 63: 12359-12386.
3. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020; 395: 1033-1034.
4. World Health Organization. COVID-19 Clinical management: living

guidance. 25 January 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Accessed 4 June 2021.
5. Morse JS, Lalonde T, Xu S, Liu WR. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem.* 2020; 21: 730-738.
6. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020; 181: 271-280.e8.
7. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020; 579: 270-273.
8. Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system? A call for epidemiologic investigations. *Clin Infect Dis.* 2020; 71: 870-874.
9. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020; 382: 1708-1720.
10. Fu L, Wang B, Yuan T, Chen X, Ao Y, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect.* 2020; 80: 656-665.
11. Bavishi C, Maddox TM, Messerli FH. Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. *JAMA Cardiol.* 2020; 5: 745-747.
12. European Society of Cardiology. 13 March 2020. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. Available at: https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. Accessed 4 June 2021.
13. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020; 382: 1653-1659.
14. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res.* 2020; 81: 537-540.
15. Sun ML, Yang JM, Sun YP, Su GH. Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020; 43: 219-222.
16. Meng J, Xiao G, Zhang J, He X, Ou M, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect.* 2020; 9: 757-760.
17. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol.* 2017; 39: 529-539.
18. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol.* 2020; 214: 108393.
19. Silva JC, Mariz HA, Rocha LF Jr, Oliveira PS, Dantas AT, et al. Hydroxychloroquine decreases Th17-related cytokines in systemic lupus erythematosus and rheumatoid arthritis patients. *Clinics (Sao Paulo)*. 2013; 68: 766-771.
20. Paliani U, Cardona A. COVID-19 and hydroxychloroquine: is the wonder drug failing? *Eur J Intern Med.* 2020; 78: 1-3.
21. Furlow B. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. *Lancet Rheumatol.* 2020; 2: e592.
22. REMAP-CAP Investigators; Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med.*. 2021; 384: 1491-1502.
23. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy.* 2016; 8: 959-970.
24. Xu X, Han M, Li T, Sun W, Wang D, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. 2020; 117: 10970-10975.
25. Mahmud-Al-Rafat A, Majumder A, Taufiqur Rahman KM, Hasan AMM, Islam KMD, et al. Decoding the enigma of antiviral crisis: does one target molecule regulate all? *Cytokine.* 2019; 115: 13-23.
26. Mahmud-Al-Rafat A, Asim MMH, Taylor-Robinson AW, Majumder A, Muktadir A, et al. A combinational approach to restore cytokine balance and to inhibit virus growth may promote patient recovery in severe COVID-19 cases. *Cytokine*. 2020; 136: 155228.
27. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet.* 2020; 395: e35-e36.
28. Ruscitti P, Cipriani P, Liakouli V, Carubbi F, Berardicurti O, et al. The emerging role of IL-1 inhibition in patients affected by rheumatoid arthritis and diabetes. *Rev Recent Clin Trials.* 2018; 13: 210-214.
29. Mihai C, Dobrota R, Schröder M, Garaiman A, Jordan S, et al. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. *Ann Rheum Dis.* 2020; 79: 668-669.
30. Gritti G. US National Library of Medicine study record details: An observational study of the use of siltuximab (SYLVANT) in patients diagnosed with COVID-19 infection who have developed serious respiratory complications (SISCO). ClinicalTrials.gov identifier: NCT04322188. Last updated 1 June 2020.
31. Rees V. Siltuximab – testing a potential COVID-19 therapy. 16 April 2020. Available at: https://www.europeanpharmaceuticalreview.com/article/116863/siltuximab-testing-a-potential-covid-19-therapy/. Accessed 4 June 2021.
32. Gritti G, Raimondi F, Bottazzi B, Ripamonti D, Riva I, et al. Siltuximab downregulates interleukin-8 and pentraxin 3 to improve ventilatory status and survival in severe COVID-19. *Leukemia*. 2021; 24: 1-5.
33. Rees V. Phase III study to confirm efficacy of siltuximab as COVID-19 therapy initiated. 18 December 2020. Available at: https://www.europeanpharmaceuticalreview.com/news/137456/phase-iii-study-to-confirm-efficacy-of-siltuximab-as-covid-19-therapy-initiated/. Accessed 4 June 2021.

***Correspondence:** Prof. Andrew W. Taylor-Robinson, Infectious Diseases Research Group, School of Health, Medical & Applied Sciences, Central Queensland University, 160 Ann Street, Brisbane, QLD 4000, Australia, Tel: +61 7 3295 1185, E-mail: a.taylor-robinson@cqu.edu.au

Rec: 18 May 2021; **Acc**: 10 Jun 09 2021; **Pub**: 14 Jun 2021

Trend Pulm Resp Med. 2021;1(1):104
DOI: 10.36879/TPRM.21.000104