LETTER TO THE EDITORS

SARS-CoV-2 pandemic and the need for transplant-oriented trials

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To the Editors,

After the first reported case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Wuhan, China, in December 2019, the contagion has spread rapidly and has become a global pandemic [1]. There are as of yet no published studies beyond the case series describing the incidence and clinical course of COVID-19 in transplant recipients, a population potentially at high risk due to the ongoing immunosuppression and higher risk of comorbidities [2]. This pandemic has had a major impact in transplant physicians and healthcare workers as well [3], and this crisis has meant reducing or even interrupting transplant program activity, with a subsequent impact on patient morbidity and mortality that is still hard to quantify.

In contrast with the current bleak situation at our hospitals, these challenging times have unequivocally shown how lively and collaborative the medical community is. Healthcare professionals and scientists across the globe have rapidly shared the results of their studies, leading to a prompt identification of the virus, the development of assays for patient screening, and the initial definition of its pathogenic mechanisms. Over the last few months, we have witnessed an unprecedented proliferation of clinical trials designed to test the efficacy of different molecules in preventing viral replication and restraining the uncontrolled inflammatory response associated with COVID-19 (Table 1). Importantly, these clinical studies are directly testing in humans the hypotheses generated using in vitro and in vivo animal models in a truly translational endeavor. Despite the sometimes unsuccessful efforts to treat this infection and the unavoidable lag required to generate an effective vaccine, this experience testifies to the critical role that basic, mechanistic studies play in improving human health.

Most trials allow participation of transplant recipients, but they are not designed to address the specific questions the transplant physicians are facing. While post hoc analyses may allow to define characteristic responses in transplant patients, ad hoc trials are urgently needed in transplant patients. Should immunosuppression be reduced to unleash the antiviral response or maintained to prevent uncontrolled inflammatory response? Should certain immunosuppressive drugs be maintained based on their supposed antiviral effects? Is the antibody response different in transplant patients? These are only some of the questions warranting crucial answers.

This crisis has shown how vulnerable we are and foreshadows that our community and humanity at large will face more of these emergencies in the future. However, the great collaborative effort of the scientific community and the highly translational approach of the clinical studies are a true demonstration of National Institutes of Health (NIH)’ mission, seeking “fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability” [4]. This experience proves that scientists in numerous fields can fruitfully interact and leverage their own expertise to make the world healthier and a safer place. The transplant community should have a leading role in this effort to understand COVID-19 pathophysiology in the unique population of organ recipients on chronic immunosuppression.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose as described by Transplant International.
Table 1. Main treatments currently being tested on COVID-19 patients.

| Drug                                             | Mechanism of action                                                                 | Registered trials (n) | Rationale*                  |
|--------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------|-----------------------------|
| **Antivirals and antimalarials**                 |                                                                                      |                       |                             |
| Arbidol                                          | Inhibitor of virus-mediated fusion with target membrane                             | 9                     | *In vitro data*             |
| Bromhexine hydrochloride                         | Transmembrane protease serine inhibitor                                             | 2                     | *In vitro data*             |
| Camostat mesilate                                | TMPRSS2 inhibitor                                                                     | 3                     | Animal models of SARS-CoV   |
| Chloroquine                                      | Increases endosomal pH                                                                | 46                    | *In vitro data*             |
| Danoprevir                                       | HCV NS3 protease inhibitor                                                             | 1                     | FDA approved for HCV infection |
| Darunavir                                         | Protease inhibitor                                                                     | 2                     | *In vitro data*             |
| Favipiravir                                       | RNA-dependent RNA polymerase inhibitor                                               | 9                     | Animal models of Zaire Ebola virus |
| Hydroxychloroquine                               | Increases endosomal pH                                                                | 109                   | *In vitro data*             |
| Hydroxychloroquine + azithromycin               | Increases endosomal pH                                                                | 29                    | *In vitro data*; Single-arm trial showed reduction of viral load at day 6 postinclusion. |
| Interferon, interferon α2β, interferon α1β       | Initiate JAK-STAT signaling cascades                                                 | 27                    | *In vitro data*             |
| Lopinavir/ritonavir                               | Protease inhibitor                                                                     | 31                    | *In vitro data* and animal models of MERS-CoV; RCT trial with negative results in severe COVID-19 |
| Nitric oxide gas                                 | Inhibits viral protein and RNA synthesis                                             | 8                     | *In vitro model of SARS-CoV|
| Oseltamivir                                      | Viral neuraminidase inhibitor                                                         | 10                    | FDA approved for influenza A and B infection |
| Remdesivir                                       | Nucleoside analog inhibitors                                                         | 9                     | *In vitro and animal models of SARS-CoV and MERS-CoV |
| **Anti-inflammatories**                          |                                                                                      |                       |                             |
| Baricitinib                                       | JAK/STAT inhibitor                                                                    | 5                     | *In vitro data*             |
| Bevacizumab                                       | Monoclonal antibody against VEGF                                                     | 3                     | Increased VEGF in blood of patients |
| Clazakizumab                                      | Humanized monoclonal anti-IL-6 antibody                                              | 3                     | Humanized monoclonal anti-IL-6 antibody |
| Colchicine                                        | Inhibition of the assembly of the NLRP3 inflammasome                                 | 5                     | Animal models of influenza virus infection |
| Convalescent plasma                              | Plasma with specific antibody                                                        | 28                    | Studied in outbreaks of H1N1 influenza virus SARS-CoV-1, MERS-CoV |
| Eculizumab                                        | Humanized anti-C5 monoclonal Ab                                                     | 2                     | Complement activation in COVID-19 Animal models of neurodegenerative disease |
| Fingolimod                                        | Sphingosine-1-phosphate receptor regulator                                            | 1                     | Animal models of arthritis, nephrotic nephritis and idiopathic thrombocytopenic purpura |
| Intravenous immunoglobulin                       | Block FcR activation                                                                 | 8                     | FDA approved for idiopathic pulmonary fibrosis |
| Kineret (Anakinra)                               | Interleukin-1(IL-1) receptor antagonist                                              | 5                     | FDA approved to treat rheumatoid arthritis and neonatal-onset multisystem inflammatory disease |
| Naproxen                                         | Inhibitor of both COX-2 of influenza A virus NP                                      | 1                     | *In vitro data*             |
| Pirfenidone                                       | Inhibits IL-1β and IL-4                                                               | 1                     | FDA approved for the treatment of myelofibrosis, polycythemia vera, and graft-versus-host disease |
| Ruxolitinib                                       | JAK 1 and JAK 2 inhibitor                                                             | 6                     | Humanized animal model of acute inflammation |
| Sarilumab                                         | Recombinant human anti-IL6R monoclonal Ab                                            | 8                     |                             |
Table 1. Continued.

| Drug               | Mechanism of action                                                                 | Registered trials (n) | Rationale*                                                        |
|--------------------|-------------------------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------|
| Siltuximab         | Anti-IL-6 chimeric monoclonic antibody                                                | 3                     | FDA approved for idiopathic multicentric Castleman’s disease     |
| Stem cells therapy | Anti-inflammatory and immune regulatory functions – induction of immune tolerance in autoimmune T cells and restore immune balance and homeostasis | 20                    | Animal models of influenza virus infection                         |
| Steroids, methylprednisolone | Inhibits the gene expression of multiple cytokines (e.g. IL-1, IL-2, IL-6, IFN-gamma and TNF-alpha) | 13                    | Potent anti-inflammatory activity; possible negative impact on viral load |
| Thalidomide        | Reduces TNFα                                                                        | 2                     | *In vitro data*                                                   |
| Tocilizumab        | Recombinant humanized anti-IL-6R monoclonal Ab                                       | 22                    | Recombinant humanized anti-IL-6R monoclonal Ab                   |
| Vitamin C          | Antioxidant properties                                                              | 13                    | Animal models of asthma                                           |
| Others             |                                                                                     |                       |                                                                   |
| Carrimycin         | Macrolide antibiotic                                                                | 1                     | *In vitro data*                                                   |
| Heparin            | Anticoagulant                                                                       | 5                     | FDA approved for prophylaxis or treatment of thrombosis          |
| Losartan           | Angiotensin II receptor blocker                                                     | 8                     | Animal models of SARS-CoV                                         |

ACE, angiotensin-converting enzyme; COX-2, cyclooxygenase-2; HCV, hepatitis C virus; IL-6R, interleukin-6 (IL-6) receptor; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; TMPRSS2, transmembrane serine protease 2; TNFα, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

The research of the clinical trials has been done using the following keywords: COVID, COVID-19, SARS-CoV-2 or novel coronavirus, together with the name of each drug (https://clinicaltrials.gov. Accessed on April, 20 2020)*. For testing in COVID-19.

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