LETTER TO THE EDITORS

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

Gianluigi Zaza[1] (iD), Claudia Benedetti[1], Miguel Fribourg[2] (iD), Umberto Maggiore[3], Jamil Azzi[4], Leonardo V. Riella[4] & Paolo Cravedi[2] (iD)

1 Renal Unit, Department of Medicine, University Hospital of Verona, Verona, Italy
2 Department of Medicine, Icahn School of Medicine at Mount Sinai, Translational Transplant Research Center, New York, NY, USA
3 UO Nefrologia, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliera-Universitaria Parma, Università di Parma, Parma, Italy
4 Renal Division, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA
E-mail: paolo.cravedi@mssm.edu

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* 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
Fingolimod	Sphingosine-1-phosphate receptor regulator	1	Animal models of neurodegenerative disease
Intravenous immunoglobulin	Block FcR activation	8	Animal models of arthritis, nephrotoxic nephritis and idiopathic thrombocytopenic purpura
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 idiopathic pulmonary fibrosis
Ruxolitinib	JAK 1 and JAK 2 inhibitor	6	FDA approved for the treatment of myelofibrosis, polycythemia vera, and graft-versus-host disease
Sarilumab	Recombinant human anti-IL6R monoclonal Ab	8	Humanized animal model of acute inflammation

Table 1. Continued.

Drug	Mechanism of action	Registered trials (n)	Rationale*
Siltuximab	Anti-IL-6 chimeric monoclonal 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.

REFERENCES

1. Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of Covid-19 – studies needed. *N Engl J Med* 2020; **382**: 1194.
2. Coates PT, Wong G, Drueke T, *et al.* Early experience with COVID-19 in kidney transplantation. *Kidney Int* 2020. https://doi.org/10.1016/j.kint.2020.04.001 [Epub ahead of print].
3. Michaels MG, La Hoz RM, Danziger-Isakov L, *et al.* Coronavirus disease 2019: implications of emerging infections for transplantation. *Am J Transplant* 2020. https://doi.org/10.1111/ajt.15832 [Epub ahead of print].
4. Available at: https://www.nih.gov/about-nih/what-we-do/mission-goals. Accessed on March, 30 2020.