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.

PREFACE

COVID-19 MINISYMPOSIUM: TOWARD A STRATEGIC ROADMAP

A roadmap is defined as a strategic plan that defines a goal or desired outcome and includes the major steps or milestones needed to reach it. This communication tool usually includes a list of tasks to achieve a strategic initiative. In the clinical setting it may be considered to include a series of algorithms containing critical decision points for therapeutic interventions. Because of the wide variety of pre-existent and concomitant disease processes as well as the panoply of transplant procedures, it is easy to become mired in details during this enterprise. However, we must search for cohesive features in a strategic rationale to achieve successful outcomes.

The pandemic with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; coronavirus disease 2019 COVID-19), an RNA virus, poses major challenges to the transplant enterprise from donation to operation and peri-operative care to long-term follow-up, including treatment of afflicted cases.

CLINICAL BIOLOGY

SARS-CoV-2 hooks onto cells via the membrane protein angiotensin-converting enzyme (ACE) 2 receptor, whose gene is encoded within the X chromosome. The protein is present on the surface of cells in the lung, endothelium, heart, kidney, and intestines. After the virus spike complex attaches and fuses to the cell membrane, it gains intracellular entry with ensuing infection. In a mouse experimental model, which has been created by insertion of the ACE2 receptor into the murine genome, the virus replicates in the nose, throat, pulmonary alveolae, trachea, and brain, as well as in higher doses, in the digestive tract, often as an asymptomatic infection.

ORGAN DONATION

Numerous Transplantation Societies have recommended against the use of organs from afflicted individuals as evidenced by a positive viral test which can now be performed relatively rapidly. This opinion assumes the presence of transmittable virions in potentially transplantable organs. However, preliminary studies (with both COVID-19 and other common RNA respiratory viral infections) suggest that in the absence of severe infection, there is a low incidence of virions in non-respiratory tissues or peripheral blood. Clearly at the present state of knowledge, the use of COVID-19-positive donors must require negative results of tissue biopsies that have been subjected to real-time polymerase chain reactions for nucleic acid detection and/or immunochemistry or electron microscopic evaluations for virions, since the disease process may produce secondary effects, such as hepatocellular or renal injury, in noninfected, potentially transplantable organs.

By its very nature, the pandemic produces a variety of other considerations in the donation process. On the one hand, shelter-in-place regulations are likely to reduce the supply of donors from auto accidents or murder-related causes. On the other hand, in much of the country the intensive care resources necessary to effectuate organ donation may be preoccupied with the infected populations. The impact on donation among the centers in The Northern Italy Transplant Program is described in this issue by Cannavó et al [1]. To be assured of a COVID-19-negative organ, prolonged preservation may be necessary, as described in a liver transplant case by Schneeberger and colleagues in Bogensperger et al [2].

TREATMENT OUTCOMES

The risk factors for an adverse outcome of COVID-19 infection (hypertension, diabetes and obesity) are conditions associated with upregulation of ACE2. In addition they are common features among the transplant population as well as well-known side effects of calcineurin antagonist/steroid regimens. While these regimens might be expected to dampen host anti-viral response on the one hand, they may be at least partially protective against the cytokine storm response to infection.

Clinical roadmaps for transplant patients during the COVID-19 pandemic are described in this issue: Management of personnel as described by Thiessen et al [3]; identification of potential recipients by Virmani et al [4]; alterations of patterns of patient care as described by Binda et al [5]; Niriella et al [6], and Monaco et al [7]; including detection of allograft injury by Garg et al [8]. Quite reassuring has been the physical and psychological resilience of transplant recipients, reported by Zgoura et al [9] and Lupi et al [10]. The emerging widespread applications of telemedicine in clinical practice as described by Abuzeineh et al [11] has been accompanied by the wider use of Zoom conferences to improve local and international physician interactions.

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This issue also contains descriptions of patient outcomes. The low incidence and modest mortality rate among multi-organ recipients in The North Italy Program is described by Passamonti et al [12] and reviewed by Aziz et al [13]. Individual centers report their series of kidney (Lum et al [14]; Kocak et al [15]; Hasanoglu et al [16]; Aziz et al [17]), organ (Christensen et al [18]), or liver (Fraser et al [19]; Pahari et al [20]) transplantations. In addition, individual cases are presented following kidney (Adrogué et al [21]; Yamada et al [22]; Taha et al [23]), liver (Mathiasen et al [24]), lung (Renaud-Picard et al [25]), and heart (Vaidya et al [26]) transplantations.

The University of California at Los Angeles series [14], including 41 afflicted renal transplant recipients who most often presented with fever, dyspnea, and cough, revealed hospitalization to be necessary in 63.4% of subjects, with a 9.8% mortality rate and a 26.9% incidence of acute kidney injury.

Reviewing published experiences in liver transplantation, Fraser et al [19] noted fever, dyspnea, and diarrhea as their most frequent symptoms at presentation. Among the 77% of recipients who required hospitalization, 40% experienced moderate and 36% experienced severe disease, with a 19.3% fatality rate at a median of 11.5 days.

Of great concern is the failure of some patients, particularly those requiring intensive care, to recover from the illness within 2 to 3 weeks. These individuals may display breathlessness, weakened cardiac output, neuropathic and autonomic dysfunction as well as psychologic "brain fog" symptoms as part of the chronic fatigue syndrome.

TREATMENT

Prophylaxis by vaccination seems to be rapidly approaching routine practice. While vaccines are likely to protect the majority of the normal population, application to transplant patients may be more problematic, not only because of their blunted, iatrogenic dysfunctional immune responses, but also because of the possibility of mis-intended autoimmune reactions to putatively benign viruses carrying the immunogen or their included adjuvants.

Our knowledge of protective immune responses in the general population has many gaps. Presumably the B cell response of neutralizing antibodies mediates resistance. The strongest evidence for a B cell response is the apparent benefit of treatment with convalescent plasma, or preferably tailored monoclonal antibodies. However, there appears to be concern about the durability of this response. While antibodies to SARS viruses are known to be detectable in blood for 2 years after infection, reports of re-infections with COVID-19 suggest that at least some patients' responses were more transient. Adding to this uncertainty, available antibody tests to detect neutralizing forms are not yet sufficiently reliable, arguing against application of "immunity passports."

The current treatments which have been adapted from their clinical scenes, are at best only moderately effective. Patients with moderate disease not requiring mechanical ventilation appear to experience attenuated courses after a 5- to 10-day intravenous course of remdesivir, which has been given emergency use authorization by the United States Food and Drug Administration (FDA). This agent appears to be more efficacious than other antivirals such as lopinavir/ritonavir, the latter of which has an adverse interaction with calcineurin antagonists.

The FDA has also granted Emergency Use Approval for convalescent plasma, which was successfully used in a lung transplant patient at The University of Chicago [27]. However, one must bear in mind that donated plasma may contain alloantibodies. A more robust therapy appears to be the cocktail of two genetically designed monoclonal antibodies such as that produced by Regeneron, AstraZeneca and Eli Lilly. The participation of T cells in recovery is unclear.

Considerable progress has been achieved to counter the cytokine release syndrome associated with overwhelming host responses to infection. Dexamethasone has received FDA recognition for this use. Tocilizumab, a recombinant humanized monoclonal IgG_1 antibody directed against the Interleukin-6 Receptor, has previously been approved for treatment of severe rheumatoid arthritis and for life-threatening cytokine storm syndrome. Anecdotal reports suggest its beneficial effects in responses to COVID-19. Similarly, addition of a 4 mg dose of the Janus kinase-1 and -2 inhibitor baricitinib to remdesivir further reduced the time to recovery compared with remdesivir alone.

The obvious option to prescribe available ACE2 receptor blockers is contraindicated due to their likely serious adverse effects on blood pressure and to enhance inflammation. Progress in pharmacotherapy of COVID-19 may be facilitated by the availability of the mouse strain with human ACE2 receptor insertion. One avenue for further investigation is decoy soluble ACE2 receptors, which have been shown to reduce the viral load in cell culture and to preserve respiratory function in animal models.

PROSPECTUS

The Minisymposium presented in this issue includes early approaches to organ transplantation in the COVID-19 era. These initial efforts in the enterprise to formulate robust roadmaps to deal with the pandemic will undoubtedly be facilitated by data from national and international registries of affected patients. As we progress in this challenging era, *Transplantation Proceedings* will continue to host Minisymposia that include articles providing novel insights into the impact of COVID-19 disease among these special patients.

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