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CASE ANECDOTES, COMMENTS AND OPINIONS

Comment on "Epidemiological and clinical characteristics of heart transplant recipients during the 2019 coronavirus outbreak in Wuhan, China" by Ren et al

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The study by Ren et al[1] suggests that heart transplant recipients (HTR) do not have a substantially higher rate of coronavirus disease 2019 infection than the general population. This finding is not surprising because immunosuppressive treatment used in HTR favors specific viral infections such as cytomegalovirus or herpes simplex virus infections much more than community-acquired respiratory viruses. For instance, there were only 3 lung infections owing to influenza among 1,073 infectious episodes that occurred in 620 consecutive patients with heart transplantation at Stanford Medical Center between December 1980 and June 1996.[2] In our cohort, since 1985, only 1 of 243 HTR who survived more than 90 days after transplantation required invasive mechanical ventilation for a community-acquired respiratory virus. This patient was classified as obese, with diabetes, and had graft failure. Moreover, to the best of our knowledge, there were no reported cases of severe coronavirus infections in HTR before the current pandemic.

What we do know is that several of the proposed drugs for coronavirus disease 2019 infection have significant interactions with calcineurin blockers. Azithromycin and hydroxychloroquine are CYP3A4 inhibitors and significantly increase cyclosporine concentrations.[3] Lopinavir–ritonavir association is a strong CYP3A4 inhibitor that can increase both tacrolimus and cyclosporine concentrations.[4] Watchful monitoring of calcineurin blocker levels is, thus, necessary if these drugs are used.

References

1. Ren ZL, Hu R, Wang ZW, et al. Epidemiological and clinical characteristics of heart transplant recipients during the 2019 coronavirus outbreak in Wuhan, China: a descriptive survey report. J Heart Lung Transplant, in press.
2. Montoya JG, Giraldo LF, Efron B, et al. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis 2001;33:629-40.
3. Lee JY, Vinayagamoorthy N, Han K, et al. Association of polymorphisms of cytochrome P450 2D6 with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis Rheumatol 2016;68:184-90.
4. Vogel M, Voigt E, Michaelis HC, et al. Management of drug-to-drug interactions between cyclosporine A and the protease-inhibitor lopinavir/ritonavir in liver-transplanted HIV-infected patients. Liver Transpl 2004;10:939-44.

Endothelin receptor antagonists for pulmonary arterial hypertension and COVID-19: Friend or foe?

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Coronavirus disease 2019 (COVID-19) poses a threat to individuals with chronic health conditions who are more likely to develop severe pneumonia and death. Those with pulmonary arterial hypertension represent such a high-risk group. Severe COVID-19 presents with respiratory failure secondary to immunopathologic injury likely due to a combination of direct cytopathic effects of the virus in concert with an aberrant immune response. The interplay between these 2 components has recently been better understood. Indeed, the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) genome encodes 8 accessory proteins designated open reading frame (ORF) with identified functions. In particular, the ORF-3a protein initiates necroptosis once oligomerized by RIP3, allowing it to form a potassium-sensitive channel inserted into late endosomal, lysosomal, and trans-Golgi network membranes.[1] RIP3-driven oligomerization of ORF-3a plays a critical role in driving necrotic cell death, independent from and hijacking RIP3-MLKL necroptotic signaling. There is considerable evidence that an abundance of necroptosis perpetuates pathogenic inflammation and drives tissue injury.[2] Fatal cases of SARS-CoV-2 infection similarly show significant lung damage in response to inflammation, which may very well be driven by necroptosis.[3] Endothelin (ET)-1 effects on cell survival and death may vary depending on the cell type, concentrations, and disease conditions. In contrast to low-physiologic doses, high levels of ET-1 usually trigger activation of necroptotic gene expression.[4] For this reason, patients with pulmonary arterial hypertension may be

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prone to activate the necroptotic pathways. Furthermore, under inflammatory and endotoxemic stress conditions, as in SARS, ET-1–mediated effects are shifted to promote necroptosis through a potent and long-lasting RIP-3 activation,[4,5] thereby enhancing oligomerization of the ORF-3a protein and increasing the catastrophic effects of the proinflammatory necroptotic cell death on SARS-CoV-2 pathogenesis. Blocking of ET receptors with bosentan was able to inhibit the necroptosis pathway in experimental models of microvascular endothelial cells.[5] As ET receptor antagonists counteract the vicious circle of ET-1–mediated RIP-3 activation and propagation of the proinflammatory necroptotic cell death, as it happens in the worst form of SARS, we propose that it seems safe to continue ET receptor antagonists in patients on treatment with this class of drugs.

References

1. Yue Y, Nabar NR, Shi CS, et al. SARS-coronavirus open reading frame-3a drives multimodal necrotic cell death. Cell Death Dis 2018;9:904.
2. Moriwaki K, Chan FK. RIP3: a molecular switch for necrosis and inflammation. Genes Dev 2013;27:1640-9.
3. Franks TJ, Chong PY, Chui P, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. Hum Pathol 2003;34:743-8.
4. Vanlangenakker N, Vanden Berghe T, Vandenabeele P. Many stimuli pull the necrotic trigger, an overview. Cell Death Differ 2012;19:75-86.
5. Abdul Y, Ward R, Dong G, Ergul A. Lipopolysaccharide-induced necroptosis of brain microvascular endothelial cells can be prevented by inhibition of endothelin receptors. Physiol Res 2018;67(Suppl. 1): S227-36.

Clinical distancing of hospitalized patients with advanced heart failure and cardiac transplantation during COVID-19

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Our hospital system includes a central 825-bed, short-term, acute-care teaching facility where heart transplantation is performed under regulatory approval. Located 5.5 miles north of this main campus is a 107-bed cardiac specialty hospital, which operates on a single-bed concept that allows patients to remain in the same bed throughout their hospital stay. All rooms allow for the entire spectrum of care, including hemodynamic monitoring, peri-operative and intensive care, and complete cardiac and device management. At the onset of the expected surge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), all elective cardiac surgeries and procedures were cancelled on both campuses. Because the central hospital was to be redesigned for the care of patients with COVID-19, we administratively decided to transfer all patients with advanced heart failure and cardiac transplant and services to the peripheral specialty hospital in an effort to protect immunosuppressed and vulnerable patients from exposure to SARS-CoV-2. The specialty hospital did not have a single case of COVID-19 at the time of this writing.

To accomplish this goal, on March 31, 2020, the United Network for Organ Sharing Membership and Professional Standards Committee's subcommittee granted our requested temporary change of geographic location for the cardiac transplantation program to the specialty hospital.

In addition to post-transplant patients, those transferred included 1 patient awaiting transplantation, 1 patient with severe rejection, and several other patients requiring intensive care unit care owing to recent implantation of ventricular assist device (VAD) or device complication of a previously implanted VAD. Cardiac transplant physicians and surgeons continued to care for patients on both campuses, with rotation adjustments to minimize exposure between the campuses. Experienced cardiac transplant critical care nurses accompanied patients on transfer and have continued to provide critical care support at the specialty hospital.

All patients were transferred without complication or worsening illness. Concurrently, we began admitting all post-transplant patients and patients with VAD with non–SARS-CoV-2 medical illness to the specialty hospital. Patients who have symptoms suggestive of SARS-CoV-2 infection and those under investigation continue to be admitted to the central hospital. Similarly, all patients with trauma or need for neurosurgical evaluation continue to be admitted to the central hospital as well. As of now, the 1 hospitalized listed patient underwent successful cardiac transplantation at the specialty hospital.

All employees of the specialty hospital were screened daily for self-reported symptoms through an online reporting system. Employees with symptoms suggestive of viral infection were tested at a testing center remote to the hospital and did not return to work unless symptoms resolved and testing was negative. Routine testing for asymptomatic carrier status has not been performed. Personal protective equipment has been widely available, and appropriate personal protective equipment has been used by all with patient contact (surgical mask for routine care and examination, N95 mask and face shield for invasive procedures such as bronchoscopy). The hospital has imposed a no-visitor policy.

As of now, our experience with this new paradigm has been successful and without significant complications. We propose that other multihospital systems with the option of transitioning advanced heart failure services to another institution consider this approach to preserve patient safety and outcomes. The success of such an initiative will require evaluation of outcomes once the threat of the pandemic settles down.

Myocardial edema in COVID-19 on cardiac MRI

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