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EDITORIAL COMMENT

Courage in the Face of Catastrophe

COVID-19 in Heart Transplant Recipients Northern Italian Registry*

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"[I]n Italy, for thirty years under the Borgias, they had warfare, terror, murder and bloodshed, but they produced Michelangelo, Leonardo da Vinci and the Renaissance. In Switzerland, they had brotherly love, they had five hundred years of democracy and peace - and what did that produce? The cuckoo clock."

—Graham Greene, *The Third Man* (1)

Early in 2020, Northern Italy was the European epicenter of the coronavirus disease-2019 (COVID-19) pandemic, with a prevalence of disease in the general population of 7 cases per 1,000 people. As there was little knowledge of disease prevention, diagnosis, and treatment, the health care system quickly became overwhelmed and, as of the end of June 2020, nationally more than 70% of cases and nearly 80% of deaths occurred in Northern Italy. Despite these extraordinarily difficult circumstances, my Italian colleagues had the wherewithal to organize a prospective, multicenter registry aimed at understanding the prevalence and case fatality rate of COVID-19 in heart transplant (HT) recipients, with the secondary objectives to evaluate hospitalization rates and duration and intensive care unit requirements.

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In this issue of *JACC: Heart Failure*, Bottio et al. (2) report that, of 2,676 HT recipients alive before the onset of the pandemic, 53 subjects had a reverse transcription polymerase chain reaction nasopharyngeal swab that was positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (2). Of those 53 subjects, 93% were symptomatic, 73% required hospitalization, and 26% died, a case fatality rate double that of the general population. An important question is whether the findings in those subjects are applicable to the overall HT population. Notably, the mean age of the patients was 62 years, and the average time from HT was 10.5 years. These features are remarkably similar to those of a smaller case series from a single academic center in New York City (3). Older, long-term HT survivors have a greater prevalence of the underlying conditions that worsen the outcomes of COVID-19 in the general population (4). In fact, the report by Bottio et al. (2) states that older age, diabetes mellitus, peripheral vascular disease, lower estimated glomerular filtration rate, and higher New York Heart Association functional class were significantly associated with in-hospital mortality. Factors specific to HT recipients, such as cardiac allograft vasculopathy score and previous percutaneous coronary intervention also predicted higher in-patient death rates. Obesity, another risk factor consistently associated with poorer COVID-19 outcomes, was conspicuously rare in both Northern Italian and New York City case series of HT recipients positive for SARS-CoV-2 infection (2,3). Therefore, it is possible that obese HT recipients with otherwise similar comorbidities may have experienced even poorer outcomes.

A critically important cohort missing from both of those case series is that of new HT individuals. In a single-center report, of 3 patients who developed COVID-19 disease within 6 weeks of HT, 2 had severe illness, defined as requirement for intensive care unit, mechanical ventilation, or death, which was

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associated with severe lymphopenia and elevated inflammatory markers. Of 8 kidney transplant patients with COVID-19 undergoing home monitoring, the 2 who succumbed to COVID-19 were in their early post-operative period, and both had received antithymocyte globulin within the preceding 5 weeks (5). Data are sorely missing in new organ recipients, whose vulnerability to the ravages of COVID-19 may be heightened by recent heart allograft ischemia-reperfusion injury and higher intensity of immunosuppression.

In the paper by Bottio et al. (2) dosages of immunosuppressive drugs were reduced in all 38 hospitalized HT recipients. Anti-metabolites were decreased in more than 50% of patients, and calcineurin inhibitor (CNI) dosages were reduced in approximately 20% of subjects. Scant information for dosage adjustments of corticosteroids is provided, which were still part of the immunosuppression regimen in 50% of the patients despite their late post-HT status. Overall, the report lacks the description of a clear rationale for the changes made in each immunosuppressive drug class.

With respect to anti-metabolites, such as mycophenolate mofetil and azathioprine, it is unknown if these medications should be reduced or eliminated in all solid organ transplant recipients with COVID-19 or if their dosage reduction should be dictated by lymphocyte counts. Although no association between lymphopenia and outcomes was reported in the Northern Italian study, lymphocyte counts below normal have been associated with greater severity and more rapid progression of illness both in the general population and in small case series of HT and kidney transplant recipients.

Considerations of CNI may be entirely different. Some aspects of the immune response to SARS-CoV-2 are eerily similar to those occurring with allograft rejection: viral (or donor major histocompatibility complex antigen) uptake by antigen-presenting cells is followed by presentation of epitopes from structural and non-structural viral proteins (or donor major histocompatibility complex molecules) to T cells. This is followed by activation of cytotoxic and helper T cells (6). The latter produce cytokines, predominantly interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-α), which enhance recognition and killing of infected cells (or allograft cells). The CNI block calcineurin from enabling nuclear translocation of the nuclear factor of activated T-lymphocytes promoter, which upregulates gene expression of IL-2 and other inflammatory cytokines. Therefore, given the immune response to SARS-CoV-2 and CNI's mechanism of action, what is the rationale for decreasing the dosages of these drugs in solid organ transplant recipients with COVID-19? Notably, cyclosporine has been shown to have in vitro activity or possess mechanisms purported to inhibit SARS-CoV-2. Whether CNI can temper the immune dysregulation occurring in cases of severe COVID-19 is unknown. The high case fatality rate in the Northern Italian cohort despite reduced immunosuppression, suggests that only prospective studies can assess whether each individual immunosuppressive agent is protective or deleterious in organ transplant recipients with COVID-19.

TABLE 1 Potential Topics for a Task Force Charged With the Production of a Consensus Statement on the Care of Heart Transplant Recipients With COVID-19

- Precautionary measures
- Education of patients and caregivers
- Indications for hospitalization and transfer to the heart transplant center if patients are initially hospitalized elsewhere
- Structured approach to clinical phenotyping with focus on:
  - Time after heart transplant
  - COVID-19 stage
  - Comorbidities
- Laboratory evaluation at presentation and during follow-up
- Echocardiographic monitoring with focus on:
  - Heart allograft function
  - Suspected SARS-CoV-2 myocardial damage
  - Presence of pericardial effusion
- Rejection surveillance (schedule, endomyocardial biopsy, gene profiling, donor cell-free DNA)
- Structured Approach to modulation of immunosuppression
  - Calcineurin inhibitors
  - Antimetabolites
  - Proliferation inhibitors
  - Corticosteroids
- Surveillance for cardiac allograft vasculopathy
- Recommendations on COVID-19 therapies based on evolving information from clinical trials
- Systematic evaluation of drug-drug interactions
- Ongoing evaluation of safety for heart transplant recipients of vaccines as they become clinically available

COVID-19 = coronavirus disease-2019.

The absence of information for troponin I (TnI) levels coupled with the assertion that none of the HT recipients with COVID 19 had allograft dysfunction is perplexing. According to the authors, all deaths, except for a single instance of multiorgan failure, were caused by respiratory failure in patients with normal echocardiographic heart allograft function (2). However, because endomyocardial biopsies could not be performed in an already overwhelmed health care system, the presence of underlying rejection and COVID-19-related myocardial inflammation cannot be excluded. Therefore, lack of data for biomarkers of myocardial injury and histopathologic findings is a key limitation of the report. Among 305 patients with laboratory-confirmed COVID-19 enrolled in New York City and Milan, 62% were deemed to have myocardial

injury, defined as any elevation of cardiac Tn at the time of clinical presentation or during their hospitalization. In-hospital mortality rates were 5.2%, 18.6%, and 31.7%, respectively, in subjects without myocardial injury, isolated elevation of TnI, and myocardial injury associated with echocardiographic abnormalities. These abnormalities included regional or global left ventricular dysfunction, diastolic dysfunction, right ventricular dysfunction, and pericardial effusion (7). Given the absence of biomarker and echocardiographic details, the true consequences of COVID-19 infection in heart allografts remain unknown. In the general population, COVID-19 can progress from mild disease characterized by constitutional symptoms to the moderate stage defined by pulmonary involvement and finally to the severe illness complicated by multiorgan damage. The Northern Italian HT recipients who required hospitalization were clearly at the severe level of COVID-19 disease, making it imperative that allograft function, progression of cardiac allograft vasculopathy, and extracardiac organ function be meticulously monitored over time in the surviving patients.

COVID-19 "specific" pharmacological treatment included hydroxychloroquine in 80% of the HT recipients, ritonavir/lopinavir in 50%, intravenous corticosteroids in 21% and prophylactic broad-spectrum antibiotics in 83%. A single subject received tocilizumab. As presented, the data in this small sample of patients preclude any conclusion on whether these pharmacological approaches had any disease-modifying effects. As of this writing, clinical trials in hospitalized patients with COVID-19 have shown no clear benefit of hydroxychloroquine. Use of the protease inhibitor lopinavir/ritonavir did not show benefit compared with standard care in a randomized, controlled open-label trial of 199 hospitalized patients with severe COVID-19 disease. In 243 moderately ill patients with COVID-19, tocilizumab was ineffective in preventing the need for mechanical ventilation or death. In contrast, the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial, showed that, compared to 4,321 subjects assigned to receive usual care, the 2,104 patients treated with dexamethasone had a significant reduction in 28-day mortality. This benefit, however, occurred only in patients symptomatic for more than 7 days and those requiring mechanical ventilation (8). Based upon these data, it would be interesting to know if the outcomes were different in the patients enrolled in the Northern Italian registry who received intravenous corticosteroids during hospitalization versus those who did not.

In addition to showing uncommon courage in the face of catastrophe, the report by Bottio et al. (2) lays bare our lack of knowledge of diagnosis, monitoring, and treatment of HT recipients infected with SARS-CoV-2. It is unrealistic to think that randomized controlled trials can address individual knowledge gaps in this area (**Table 1**). Therefore, this is a call to HT professionals to convene a multidisciplinary group with the responsibility for evaluating the constantly changing information, identifying the most critical knowledge gaps, and providing recommendations for a consistent approach to the care of HT recipients with COVID-19.

AUTHOR DISCLOSURES

Dr. Costanzo has reported that she has no relationships relevant to the contents of this paper to disclose.

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