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Islet cell transplantation: the effects of COVID-19 pandemic

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Abstract

Background: **Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 coronavirus is a worldwide epidemic. Estimates of the infection vary by country and region, and US reports over a quarter of the total COVID-19 cases, reported worldwide. COVID-19 has made a significant impact on organ transplantation, in general, and islet cell transplantation, in particular. Islet cell transplantation has been proven a viable cell replacement strategy for treatment of patients with impaired awareness of hypoglycemia, and severe hypoglycemia and is now approved as standard of care in Canada, Europe, Japan and Australia. Clinical success of an islet transplant is largely dependent on the quality of a deceased donor pancreas. Hence, careful selection and testing of potential organ donors are of critical importance. The threat of COVID-19 transmission has either significantly slowed down or completely shut down islet transplant programs in most US transplant centers.**

Materials And Methods: **Literature regarding COVID-19 infection rates and mitigation strategies, National Institutes of Health, American Society of Transplantation and UNOS (United Network for Organ Sharing) recommendations regarding donor organ testing for SARS-CoV-2 and resource allocation were reviewed.**

Conclusions: **Impact of local COVID-19 transmission and changing epidemiology of the disease, availability of resources that include protective equipment, donor procurement teams and adequate donor testing, impact of immunosuppression regiments on COVID-19 infection, as well as local regulations, are issues that should be critically assessed prior to reopening islet transplant programs.**

Introduction

A cluster of cases with pneumonia-like illness due to a novel beta-coronavirus termed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was first detected in Wuhan City, China, in December of 2019[1,2]. On March 11, 2020 the World Health Organization (WHO)[3] classified the disease associated with the virus, COVID-19, as a pandemic. As of the time of writing of this article, over 25 million cases and almost 860,000 deaths have been reported worldwide, with over 25% of the cases and close to 190,000 deaths occurring in the US. Estimates of the infection and death rates vary by country and region. Although most patients with COVID-19 remain asymptomatic or exhibit mild symptoms, a small subset of patients progress to severe disease that requires hospitalization[1,4]. Severe COVID-19 progressing to acute respiratory organ failure (ARDS) is associated with a hyper-inflammatory response, cytokine storm and immunothrombosis, with mortality rate in excess of 40%[5-7]. Rapid spread of the virus in the US, variable infection rates, sparse availability of reliable testing methods, and a sub-set of COVID-19 patients progressing to severe disease with ARDS, forced a number of organ and cell transplant programs, including islet transplant, to slow down or come to a halt.

Islet Transplantation

Allogeneic islet transplantation has been demonstrated as an effective option for patients with unstable type 1 diabetes (T1D) who experience hypoglycemia unawareness and have problematic hypoglycemia leading to severe hypoglycemia[8-10], and represents an effective therapeutic alternative to exogenous insulin delivery and pancreas transplantation[11]. The Diabetes Control and Complications Trial (DCCT) demonstrated that, in patients with T1D, intensive insulin replacement therapy can control blood glucose levels to certain extent[12]. Pancreas transplantation can also correct T1D, but is associated with major surgery, general anesthesia, post-transplant management of pancreatic secretions, and transplant-associated mortality and morbidity. Islet transplantation can be performed using a percutaneous approach (interventional radiology) to implant the graft, does not require general anesthesia, and is associated with minimal morbidity[13,14]. Most experienced islet centers report comparable clinical outcomes for pancreas and allogeneic islet transplantation[15]. Following islet transplant, patients report near normalization of glucose homeostasis, and improvements in protein and lipid metabolism. Subjects also regain hypoglycemia awareness and, therefore, can prevent episodes of severe hypoglycemia. Improvement (near normalization) of glucose metabolism should lead to the delay of onset and reduction of the progression of chronic complications of retinopathy, neuropathy, nephropathy, microangiopathy, and macroangiopathy[15,16].

Development of the Ricordi automated method for islet isolation[17] and the novel immunosuppression protocols[9,18], as well as reports of achievement of near normal metabolic control, improvement in the awareness of hypoglycemia, prevention of hypoglycemia, improvement in diabetes quality of life (QOL) demonstrated in islet transplant recipients[19,20], led to wider implementation of allogeneic islet transplantation in the US. At this time, allogeneic islet transplant is an approved therapy for a T1D patients with brittle T1D in Canada, Europe, Australia and Japan[21]. Despite significant improvements in immunosuppression protocols and notable advancement achieved in the islet isolation methodology, success of an islet cell transplant is closely related to the quality and quantity of transplanted islet cells. In fact, pancreatic islet mass, i.e. the number of islet equivalents (IEQ) transplanted per kilogram of recipient body weight, is one of the most critical parameters that correlates with the success of clinical islet cell transplantation[22,23]. Careful donor selection, therefore, is paramount for a successful islet isolation, where a sufficient number of islets of high quality can be isolated.

Impact of COVID-19 on islet transplantation

Despite the fact that allogeneic islet transplantation has been widely accepted as a viable therapeutic option for T1D patients with problematic hypoglycemia, it is important to note that an islet transplant is not a life-saving procedure. As COVID-19 rapidly spread worldwide, many islet isolation centers have halted their clinical activity due to the uncertainty regarding availability of testing for SARS-CoV-2 infection, variable rate of transmission by region and country, challenges with donor screening and organ recovery, availability of resources, and impact of COVID-19 on transplant recipients and the success of islet transplant.

COVID-19 results in multi-organ damage associated with the expression of ACE-2 receptor in various organs, including pancreas and pancreatic islets. As previously demonstrated, localization of ACE-2 to endocrine tissue suggests a possible association between viral-induced damage to the pancreatic islets and acute diabetes[24]. In fact, a recent retrospective analysis of 85 patients with COVID-19 admitted at a single center showed that more than two-thirds of those who died had diabetes[25]. Additional studies have reported that in addition to lung, trachea and bronchus, SARS-associated coronavirus (SARS-CoV) and the novel SARS-CoV-2 can be detected in multiple tissues including exocrine and endocrine tissue of the pancreas[26,27]. Additional studies are necessary to substantiate these findings and elucidate the underlying mechanism for pathological changes in pancreatic islets. These data have major implications in terms of islet transplantation, including donor selection and recipient outcomes, and emphasize the critical importance of reliable nucleic acid testing methods for SARS-CoV-2 detection in donor pancreatic endocrine and exocrine tissue.

Testing for SARS-CoV-2 and donor screening

Early in the course of COVID-19 transmission, most of community and academically based hospitals, as well as community health centers have gradually shut down all elective procedures, while trying to battle the ever-increasing number of patients presenting with COVID-19. In the US, COVID-19 testing has been slow to materialize. The National Institute of Health (NIH) have been involved in multiple wide-ranging collaborative efforts towards the development of diagnostic strategies from the moment when it became clear that SARS-CoV-2 infection represented a global threat. However, their efforts were limited by the lack of funding which was not appropriated by US Congress until April of 2020. By that time, hundreds of thousands of people were testing positive for the virus. At the same time, there were serious challenges with test performance, accessibility and turnaround time[28]. As of July 2020, depending on the region and state, diagnostic testing in the US was oscillating between 520,000 and 823,000 tests a day, while the goal was to achieve 5 million test per day by June, and 20 million per day by July[28].

Considering challenges with COVID-19 testing, the American Society of Transplantation (AST), in their guidance for donor organ testing[29], made several recommendations. Taking into an account that none of COVID-19 tests have demonstrated 100% sensitivity or specificity AST recommended a combination of screening strategies. These included: (i) epidemiologic and clinical screening of potential organ donors, (ii) Nucleic Acid Testing (NAT) of at least a single sample collected from upper or lower respiratory tract within 3 days of procurement, (iii) NAT testing of whole blood or plasma, recommended as a confirmatory test for RT-PCR (reverse transcription polymerase chain reaction) performed on nasopharyngeal specimens. A recent study reported that among 1070 specimens collected from 205 patients with COVID-19, bronchoalveolar lavage fluid specimens showed the highest positivity rates of 93%, followed by sputum (72%), feces (29%), and blood (1%)[30]. With 15-20% false negative rates reported for currently available confirmatory RT-PCR tests for COVID-19 infection in respiratory specimens, a number of rapid diagnostic tests (RDT) with the aim to test for COVID-19-associated IgG and IgM antibodies, and viral antigens, have been developed[31]. In addition, ELISA-based qualitative and quantitative laboratory-based tests, neutralizing antibody tests and chemiluminescent immunoassays have become available. A number of RDT have been approved by the FDA in the last few months [31]. Due to the fact that organ donors must be screened and tested rapidly, RDT and ELISA-based tests seem to be the most desirable for Organ Procurement Organizations (OPOs), as they take the least amount of time to complete. Considering that over 80% of individuals that test positive for COVID-19 remain asymptomatic, many are unaware of their exposure to SARS-CoV-2 [5]. This directly impacts how organ donors in general, and pancreas donors utilized for islet cell transplantation, in particular, should be tested.

Although the risk of a COVID-19 infection from an infected living or deceased donor is unknown at this time, it is critical that islet cell donors are tested according to AST recommendations, utilizing both blood and nasopharyngeal specimens. Additionally, to prevent transplanting islet cells derived from deceased donors with undiagnosed COVID-19, results of this testing should be available before an organ donor is allocated for an islet cell transplant. Irrespective of the test results, especially in highly impacted areas, the rates of community penetration and transmission should be carefully considered. Donor COVID-19 status should be taken into account, especially if there is evidence of recent suspicious upper respiratory illness and chest X-ray with ground glass infiltrates. All available up-to-date information must be considered to assess the risk of potential COVID-19 donor-to-recipient transmission in the setting of islet cell transplantation. Deceased donors without any risk factors, that test negative for SARS-CoV-2 should be considered as potential donors for islet cell transplantation. Organs from deceased donors that have recovered from COVID-19 infection, had resolution of all symptoms for over 28 days prior to organ donation, and tested negative for SARS-CoV-2 at the time of organ procurement should also be considered as potential donors. Deceased donors with intermediate risk factors that include residing or traveling to/from an area with known or high rate of COVID-19 transmission, direct contact with known or suspected case of COVID-19, confirmed COVID-19 diagnosis within the last 28 days, clinical symptoms suggestive of COVID-19 infection, or active infection should be ruled out.

Resources

As islet cell transplant is an elective procedure, serious consideration should be given to resource availability issues. These include availability of personal protective equipment (PPE), which played a significant role at the beginning of the COVID-19 pandemic; availability of hospital staff, donor ICU beds, donor organ retrieval team, and other critical components in the peri-and post-transplant period.

As COVID-19 spread throughout the US, a number of reports of infected health care workers emerged. Accumulated data clearly demonstrates that the virus is secreted through the airway of an infected individual and is spread via person to person transmission. Hence, to prevent transmission, respiratory barriers such as N95, KN95, surgical masks, and face shields and/or combination thereof are necessary to prevent the spread of the virus.

According to the CDC, one way to prevent the spread of COVID-19 is by social distancing and/or isolation. While these options are not always available to donor organ recovery teams, one way to prevent the spread of the virus is to avoid travel with the objective of donor organ recovery. ATS recommends that the responsibility for donor organ retrieval be given to local organ procurement teams. Once a donor organ is retrieved, it can be shipped to the local center for transplantation or further processing, as in the case with islet cell transplantation. Although there might be quality issues related to the level of experience of the donor organ recovery team, these should be discussed ahead of time to minimize errors and improve donor organ quality. After the donor organ is packaged, personnel handling the donor organ must change their scrubs, PPE and wash areas of the skin exposed during organ procurement, according to the CDC recommendations.

Availability of sufficient laboratory space where islet cell isolation can be performed should be addressed. Islet isolation is a complex procedure that involves multiple steps. It takes 5-6 hours to perform and adequately document, and requires at least 3 highly skilled operators. Considering current CDC and WHO [3, 32] guidelines for social distancing, individual centers will be forced to make decisions regarding reopening their islet isolation facilities in the manner that's safe for center staff and products designated for transplant.

Recipients of allogeneic islet cell transplants

Social distancing, isolation, wearing a mask in public areas, regular hand hygiene are all effective mitigation strategies in prevention of a COVID-19 respiratory infection. Remaining unaffected by the virus should be a priority for all potential islet cell transplant recipients with T1D. An informed consent process between the transplant candidate and medical decision maker should be initiated before placing a patient on the transplant waitlist. Subjects should agree to adhere to CDC guidelines for preventing COVID-19 infection. For those patients that do test positive for the virus, their status on the transplant waitlist should be changed to inactive until they have negative confirmatory COVID-19 PCR testing. The duration for which a negative PCR result is considered valid and the number of re-tests required for patient re-activation on the transplant waitlist should be left to the discretion of the individual transplant center.

The need for immunosuppressive drugs in recipients of islet allografts is another critical issue to consider. As islet cell transplantation remains an investigational procedure in the US, the impact of immunosuppression on COVID-19, if the recipient develops the disease, needs to be included in the consenting process and clearly documented in the consent form. The need for immunosuppression and islet cell transplantation should be weighed against the potential for deleterious impairment of anti-microbial immunity necessary to fight the COVID-19 infection.

Conclusions

As infection rates decline regionally and COVID-19 testing becomes more reliable and accessible, US based islet transplant centers will need to start making individual decisions regarding safe re-opening protocols and availability of sufficient PPE, good quality donors, sufficient laboratory space that can accommodate personnel needed to perform islet cell isolation, and the timing of islet cell transplantation. Issues impacting these decisions should include the level of circulating infection in individual center-specific areas. The status of organ procurement varies by region depending on the availability of viral testing, of procurement teams, and of uninfected deceased donors. Local healthcare infrastructure and capacity issues may also impact transplantation. The current COVID-19 outbreak is unpredictable, and the virus is still circulating in most communities, in the US. In fact, some areas, especially those located around large universities, are experiencing resurgence of COVID-19 cases at the present time. Islet transplant centers will need to follow and comply with local/regional applicable regulations and will have to adapt to changing epidemiology and new information regarding COVID-19 treatment and testing.

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