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On February 21, 2020, when the first locally transmitted case of coronavirus disease 2019 (COVID-19) was confirmed in the town of Codogno, the Lombardy province of Lodi became the center of Italy’s coronavirus outbreak. The next day the town was immediately put under lockdown, together with 10 others across the province, which lies just south of Milan. On March 8, the entire Lombardy region went into lockdown with the rest of the Italy, and it quickly became a red spot on the world map of the COVID-19 pandemic. As of May 4, there were 78,105 confirmed coronavirus cases (0.776% of the Lombardy resident population vs a national prevalence of 0.350%), and the death toll was 14,294, according to official figures, but likely both data are significantly underestimated. At the time of finalizing this report, in Lombardy and across Italy, the curve of new cases is slowly flattening. Italy’s lockdown expired on May 3; however, easing all restrictions at this time would be premature and some limitations have been extended.
Based on the detailed observation of several cases and discussions with colleagues treating COVID-19 patients, it was clear that COVID-19 pneumonia is a specific disease, with distinctive features. Specifically, alveolar viral damage is followed by an inflammatory reaction and by microvascular pulmonary thrombosis. This implies that part of the tissue damage in patients with SARS-CoV-2 infection is likely due to the activation of the complement cascade and innate immune reaction. The first pathophysiologic steps that are hypothesized are cellular damage induced by the viral replication with release of proinflammatory alarmins, activation of resident macrophages, activation of the complement cascade through the lectin pathways, or locally formed immune complexes. These events not only directly cause damage but further recruit leucocytes responsible for a massive release of proinflammatory cytokines and additional severe vascular endothelial cell damage associated with microvascular thrombosis. The name microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome (MicroCLOTS) was recently proposed to define these pathophysiologic chain of events. According to this model, preliminary studies have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection triggers a cytokine storm, which, in turn, increases the levels of a variety of cytokine/chemokine. Increased circulating levels of inflammation biomarkers were found in patients with COVID-19 pneumonia, including C-reactive protein (CRP), ferritin, erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6). Furthermore, patients in the intensive care unit (ICU) had documented higher cytokine levels of interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-10 (IL-10), granulocyte colony-stimulating factor (GSCF), interferon gamma-induced protein 10 (IP-10), chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-C motif) ligand 3 (CCL3), and tumor necrosis factor alpha (TNFα) than those of non-ICU COVID-19 patients. A pattern of tissue damage consistent with complement-mediated microvascular injury was described in the lung and/or skin of individuals who died with severe COVID-19. SARS-CoV-2 nucleocapsid protein (N protein) was found to bind the mannose-binding lectin serine protease 2 (MASP-2), the key serine protease in the lectin pathway of complement activation, resulting in aberrant complement 5 activation. Either suppressing complement activation or blocking the N protein:MASP-2 interaction was shown to be able to alleviate lung injury in vitro and in vivo. Concordantly, complement hyperactivation was also observed in COVID-19 patients, and a promising suppressive effect was observed when the deteriorating patients were treated with anti-C5a monoclonal antibody. Moreover, significantly increased levels of D-dimer and fibrinogen/fibrin degradation products have been associated with poor prognosis of COVID-19. In fact, some patients with severe COVID-19 infection can develop a coagulopathy meeting criteria for disseminated intravascular coagulation (DIC) with fulminant activation of coagulation and consumption of coagulation factors. Concordantly, the autopsic analysis of lung tissues of patients with COVID-19 showed the presence of fibrin thrombi of small arterial vessels (diameter <1 mm) in 33 of 38 cases, half of them with >25% of tissue involvement. For those who work in the field of islet transplantation this cascade of events is quite familiar, as one cannot fail to recognize the presence of an impressive similarity with the immunological/inflammatory reaction after the islet infusion in the portal vein. Early innate inflammatory reaction strongly affects islet engraftment and survival after intraportal infusion. This early immune response is triggered by ischemia-reperfusion injury and instant blood mediated inflammatory reaction (IBMIR) occurring hours and days after islet infusion. Evidence in both mouse models and in human counterparts suggests the involvement of coagulation, complement system, and proinflammatory chemokines/chemokines, as in the case of MicroCLOTS (Table 1). Identification and targeting of pathway(s), playing a role as “master regulator(s)” in postislet transplant detrimental inflammatory events, could now be potentially useful to improve COVID-19 outcome and vice versa. Obviously, the 2 conditions have some specificities that have guided the choice of experimental treatment. MicroCLOTS, has a viral infection as a cause, requiring caution with the immunosuppressive activity of certain treatments. On the other hand, IBMIR is associated with a surgical procedure (even if minimally invasive, such as islet transplantation) requiring caution with the anticoagulation and antivasculogenic activity of certain treatments. Despite these differences, there is a significant overlap in the need for treatments able to modulate inflammation and thrombotic risk. It is useful, at this critical time, to understand on the one hand what we can suggest based on our experience in the field of transplantation and on the other hand, what we can learn from the clinical experience ongoing in the therapy of COVID-19. Looking at the trials testing pathways of common interest (Table S1), we may provide some suggestion. Among the many anti-inflammatory candidates for the treatment of COVID-19, apparently anti-TNF antibodies are not being evaluated. Anti-TNF treatments (such as etanercept or infliximab) are widely used in islet transplantation to target IBMIR, are potentially effective, widely available, and have a well-established safety profile. This treatment opportunity should be tested in patients with COVID-19 at the time of hospital admission to halt or decrease progression of respiratory insufficiency and prevent the need for intensive care support. Considering other treatments under evaluation to avoid IBMIR in islet transplantation (although not yet commercially available) the chemokine receptor 2 (CXCR2) inhibitor reparixin appears of interest. In fact, numerous studies have confirmed a key role of CXCR1/CXCR2 receptor as potential therapeutic target in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Neutrophil infiltration of the lung is controlled by a complex network of chemokines that are released by a variety of cell types. Alveolar macrophages are a major source of chemokines in the alveolar space and produce IL-8, growth-regulated oncogene (GRO)-related peptides, and chemokine 5 (CXCL5; also known as epithelial neutrophil-activating protein [ENA]-78). High concentrations of IL-8 in broncoalveolar lavage (BAL) fluid from ARDS patients are associated with increased neutrophil influx into the airspace. Some studies have shown that IL-8 in BAL fluid is bound to IL-8 autoantibodies (anti-IL-8/IL-8 complexes) and BAL fluid concentrations of these complexes exhibits chemotactic and proinflammatory activity and correlate with the
development and outcome of ALI. In rodents, the most relevant chemokines for neutrophil recruitment into the lung are keratinocyte-derived chemokine (KC, also named CXCL1) or cytokine-induced neutrophil chemoattractant (CINC; the rat homolog to KC) and macrophage inflammatory protein-2 (MIP-2, also named CXCL2). Similar to IL-8, CXCL1, CXCL2, lipopolysaccharide-induced CXC chemokine (LIX, also named CXCL5), and lungkine (CXCL15) bind to CXCR2. Inhibition or knockout of CXCR2 receptor diminishes neutrophil influx into the lung. In contrast to the multiple CXC chemokines only 2 CXC chemokine receptors, CXCR1 and CXCR2 have been shown to mediate the response to CXC chemokines in human neutrophils. Whereas human CXCR1 binds to CXCL6 and CXCL8 (IL-8) with a high affinity, human CXCR2 binds also to CXCL6 and IL-8, as well as several CXC chemokines (GRO-α, GRO-β, GRO-γ, CXCL1, CXCL2, CXCL3), ENA-78 (CXCL5), and CXCL7. At the San Raffaele Hospital in Milan, Italy, we treated 4 patients with ARDS caused by COVID-19 pneumonia and with the clinical indication for intubation and mechanical ventilation, with reparixin IV infusion (2.772 mg/kg body weight/hour) into a central vein for 5 days. The first patient started treatment on March 24, 2020 and the last on March 31, 2020. At the time of finalizing this report, all patients are alive.

### TABLE 1 Pathophysiology of the tissue damage of patients infected with SARS-CoV-2 or infused with pancreatic islets

| Triggering event | Microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome (MicroCLOTS) | Instant blood-mediated inflammatory reaction (IBMIR) |
|------------------|---------------------------------------------|-----------------------------------------------|
| Extension        | Lung and (sometimes) systemic               | Liver                                         |
| Outcome          | Not self-limiting                           | Self-limiting                                  |
| Complement activation | Cellular damage with release of proinflammatory alarmins; activation through the lectin pathways or locally formed immune complexes, activation of resident alveolar macrophages, | Cellular damage with release of proinflammatory alarmins; activation of resident Kupffer cell, islet derived tissue factor |
| Leucocyte recruitment | Via C3a and C5a formation, chemokine release | Via C3a and C5a formation, chemokine release |
| Local release of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, CCL-2, CXCL10 | Yes | Yes |
| Endothelial damage | Yes | Yes |
| Blood release of tissue damage factor | Lactate dehydrogenase > aspartate and alanine aminotransferase | Aspartate and alanine aminotransferase > lactate dehydrogenase |
| Coagulatory cascade activation | Increased levels of D-dimer and fibrinogen/fibrin degradation products | Increased levels of D-dimer and fibrinogen/fibrin degradation products |
| Increased inflammation-related biomarkers | C-reactive protein (CRP), ferroprotein, erythrocyte sedimentation rate (ESR), fibrinogen, neutrophils | CRP, ferroprotein, ESR, fibrinogen, neutrophils |

**Abbreviations:** CCL-2, chemokine (C-C motif) ligand 2; COVID-19, coronavirus disease 2019; CXCL, keratinocyte-derived chemokine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
end of the disease spectrum. In order to have an optimal risk-benefit balance, it is therefore important to identify the most suitable patient and the best time for intervention with anti-inflammatory approaches. In our experience, the first criterion is related to the ARDS severity. ARDS patients are classified as mild (200 mm Hg < PaO$_2$/FiO$_2$ ratio ≤300 mm Hg), moderate (200 mm Hg < PaO$_2$/FiO$_2$ ratio ≤300 mm Hg), or severe (PaO$_2$/FiO$_2$ ratio ≤100 mm Hg). Early treatment with anti-inflammatory drugs should be limited to hospitalized patients with mild-moderate ARDS, whereas the indication for treatment in patients with severe ARDS requiring mechanical ventilation must be considered with extreme caution. The second criterion is the presence of an hyperinflammatory state documented by the following: lactate dehydrogenase (LDH) > normal range, CRP ≥100 mg/L or IL-6 ≥40 pg/mL, serum ferritin ≥900 ng/mL, and serum crosslinked fibrin (XDP) >20 mcg/mL. The third criterion is the absence of uncontrolled bacterial/fungal infection, severe comorbidities, and conditions at high risk of immediate infectious complications (such as diverticulitis).

We have a lot to learn about the treatment of IBMIR from the results that will be obtained in the COVID-19 treatment trials. In fact, the COVID-19 pandemic is pushing the clinical testing of many potentially useful treatments. Among these, the treatment
with anti-IL-6 is of great interest. IL-6 is a soluble mediator that has roles both as a pro-inflammatory cytokine and as anti-inflammatory cytokine, including various biological effects on inflammation, immune response, and hematopoiesis. Preliminary data suggest that the treatment with humanized antihuman interleukin-6 receptor antibodies tocilizumab or sarilumab is associated with an improvement in respiratory and laboratory parameters and could be a safe option in hospitalized adult patients with severe COVID-19. Controlled trials in patients with severe illness are urgently needed to confirm the definite benefit with IL-6 target therapy. In this direction, results from tocilizumab came from an independent controlled French study (CORIMUNO-19 clinical trial platform) conducted at the Assistance Publique-Hôpitaux de Paris involving 129 subjects. Patients were selected based on hospitalization for moderate or severe COVID-19 pneumonia. The primary end point was the combination of the need for ventilation (mechanical or non-invasive) or death on Day 14. The primary efficacy end point was achieved in the tocilizumab arm. Detailed results have not been published yet but given the context of the pandemic, the researchers and the sponsor felt obliged, from an ethical point of view, to communicate this information (April 27, 2020), while awaiting peer review and while continuing the longer follow-up of these patients. In the same time, preliminary results from the phase 2 portion of an ongoing phase 2/3 trial evaluating sarilumab were also released by Regeneron Pharmaceuticals, Inc and Sanofi. Analysis of the phase 2 portion of the trial demonstrated that sarilumab rapidly lowered CRP meeting the primary end point, but the drug had no notable benefit on clinical outcomes. However, there were positive trends in the “critical” patients (defined as requiring mechanical ventilation or high-flow oxygenation or treatment in an ICU) and the Independent Data Monitoring Committee recommended a continuing ongoing phase 3 trial only in the more advanced “critical” group of COVID-19 patients.

The role of anti-IL-6 therapy in islet transplantation is still controversial. In the pig to non-human primate (NHP) islet xenotransplantation model, the anti-IL-6 tocilizumab can delay revascularization of the transplanted islets, although this effect had no significant correlation to the overall islet graft survival, and in some reports IL-6 was shown to protect pancreatic islets from inflammatory cytokine-induced cell death and functional impairment, both in vitro and in vivo. On the other hand, IL-6 has been reported to amplify activation of coagulation through upregulation of tissue factor on innate immune cells and resulted as one of the most relevant factors released after intraportal islet infusion. The result of the effect of IL-6 blockade on MicroCLOTS will likely support considering the use of this molecule in the field of islet transplantation. Similarly, the Janus kinase (JAK) inhibitor tofacitinib was recently suggested as a possible replacement for tacrolimus in a highly translatable NHP islet transplantation model, and good results in COVID-19 treatment would accelerate its incorporation in human allogeneic islet transplantation protocols.

In conclusion, scientific organizations across the world are fighting the COVID-19 pandemic. Islet transplantation, and more generally the transplantation scientific community, could contribute to this fight by suggesting strategies for innovative approaches. At the same time, in the near future an enormous quantity of clinical and translational data will be available on the control of inflammation, complement activation, and microthrombosis activation. These data represent a legacy that it will be our responsibility to transform into innovation in the transplant field. It will be our contribution to change a dramatic event into advancement for the transplant community and ultimately for our patients.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.