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PERSONAL VIEWPOINT

COVID-19 and islet transplantation: Different twins

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For those who work in the field of islet transplantation, the microvascular coronavirus disease 2019 (COVID-19) lung vessels obstructive thrombo-inflammatory syndrome (recently referred to as MicroCLOTS) is familiar, as one cannot fail to recognize the presence of similarities with the instant blood mediated inflammatory reaction (IBMIR) occurring in the liver hours and days after islet infusion. Evidence in both MicroCLOTS and IBMIR suggests the involvement of the coagulation cascade and complement system activation and proinflammatory chemokines/cytokines release. Identification and targeting of pathway(s) playing a role as "master regulator(s)" in the post-islet transplant detrimental inflammatory events could be potentially useful to suggest innovative COVID-19 treatments and vice versa. Scientific organizations across the world are fighting the COVID-19 pandemic. Islet transplantation, and more generally the transplantation scientific community, could contribute by suggesting strategies for innovative approaches. At the same time, in the near future, clinical trials in COVID-19 patients will produce an enormous quantity of clinical and translational data on the control of inflammation and complement/microthrombosis activation. These data will represent a legacy to be transformed into innovation in the transplant field. It will be our contribution to change a dramatic event into advancement for the transplant field and ultimately for our patients.

KEYWORDS

clinical decision-making, clinical trial design, cytokines/cytokine receptors, editorial/personal viewpoint, immune regulation, infection and infectious agents – viral, infectious disease, islet transplantation

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.

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CRP, C-reactive protein; IBMIR, instant blood mediated inflammatory reaction; LDH, lactate dehydrogenase; microCLOTS, microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome; NHP, non human primate; PaO_2/FiO_2, ratio of arterial partial pressure of oxygen/fraction of inspired oxygen; XDP, serum crosslinked fibrin.

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Based on the detailed observation of several cases and discussions with colleagues treating COVID-19 patients, it was clear that COVID-19 pneumonia[1] is a specific disease, with distinctive features.[2] Specifically, alveolar viral damage is followed by an inflammatory reaction and by microvascular pulmonary thrombosis.[3] 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.[4,5] 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.[6] The name icrovascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome (MicroCLOTS) was recently proposed to define these pathophysiologic chain of events.[5] 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.[7-9] Increased circulating levels of inflammation biomarkers were found in patients with COVID-19 pneumonia, including C-reactive protein (CRP), ferroprotein, erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6).[10] 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 α (TNFα) than those of non-ICU COVID-19 patients.[7] 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.[11] SARS-CoV-2 nucleocapsid protein (N protein) was found to bind the mannan-binding lectin serine protease 2 (MASP-2), the key serine protease in the lectin pathway of complement activation, resulting in aberrant complement 5 activation.[4] 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.[4] Moreover, significantly increased levels of D-dimer and fibrinogen/fibrin degradation products have been associated with poor prognosis of COVID-19.[12] 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.[13] Concordantly, the autoptic 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.[14] 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.[15] 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.[16] Evidence in both mouse models and in human counterparts suggests the involvement of coagulation,[17] complement system,[18] and proinflammatory chemokines/cytokines,[19] 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.[20] 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.[21,22] 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).[23,24] 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).[25,26] High concentrations of IL-8 in broncoalveolar lavage (BAL) fluid from ARDS patients are associated with increased neutrophil influx into the airspace.[27] 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

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

	Microvascular COVID-19 lung vessels obstructive thrombo-inflammatory syndrome (MicroCLOTS)	Instant blood-mediated inflammatory reaction (IBMIR)
Triggering event	Alveolar viral infection	Microembolization of tissue, ischemia reperfusion damage
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.

development and outcome of ALI.[28] 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.[29] 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.[30] 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. Specifically, 1 of the 4 patients was never intubated and discharged from hospital, and 3 of them are currently intubated: 1 in stable condition and 2 with improving lung function (see Table 2). From a hematochemical standpoint, during treatment with reparixin, we observed an improvement or at least stabilization of the inflammatory markers (CRP, procalcitonin, and ferritin) and of the tissue damage markers (lactate dehydrogenase, aspartate and alanine aminotransferase). Based on this experience, we are now approved by the Italian Medicines Agency (AIFA) to conduct an adaptive phase 2/3, randomized, controlled multicenter study on the efficacy and safety of reparixin for the treatment of hospitalized patients with COVID-19 pneumonia.

Safety of anti-inflammatory therapies in patients with COVID-19 pneumonia is a matter of discussion. In contrast to islet transplantation COVID-19 is an infectious disease, often in elderly patients and patients with comorbidities. There is concern that anti-inflammatory biologics and immunosuppressants might compromise viral clearance and increase the risk of bacterial or fungal superinfections. However, this concern does not seem to be confirmed by the first available evidence and there are data suggesting that the low degree of immunocompetence in patient did not induce serious complications and that it could even have offered an advantage in the prevention of severe forms.[31,32] Preliminary analysis shows that patients with inflammatory bowel disease or rheumatoid arthritis who are already on anti-TNF treatment are not at increased risk of respiratory or life-threatening complications from SARS-CoV-2 compared with the general population.[33,34] Moreover, anti-inflammatory treatments in animal models with severe viral pneumonia induce beneficial effects without compromising viral clearance[35] and decreasing the susceptibility to secondary bacterial superinfection.[36] However, concerns about safety are important when considering therapies for a new and still partially unknown disease. The possibility of a late detrimental impact of anti-inflammatory treatment in COVID-19 cannot be excluded because after respiratory viral infection, superinfections with other organisms could occur at the most severe

TABLE 2 Characteristics of the 4 COVID-19 patients with severe bilateral pneumonia at hospital admission treated with reparixin

	Pt1	Pt2	Pt3	Pt4
Age	63	57	62	47
Sex	M	M	M	F
Comorbidity	Diabetes	Hypertension, dyslipidemia	Hypertension, dyslipidemia, obstructive Sleep apnea	Diabetes, cardiovascular disease, mood disorder
Ongoing treatment	Insulin	Angiotensin II receptor blockers, statin	Aspirin, angiotensin II receptor blockers, statin	Insulin, aspirin, nitrate
Hospital admission				
Symptoms	Fever, cough, dyspna	Fever, cough, diarrhea, anosmia, dysgeusia, dyspnoea	Fever, dyspnea	Fever, dyspnea
Time of symptoms onset[a]	Day −14	Day −7	Day −10	Day-7
Oxygen saturation (SpO2)	89%; Start CPAP	89%; Start CPAP	87%; Start CPAP	84%; Start CPAP
Chest X-ray	Bilateral pneumonia	Bilateral pneumonia	Bilateral pneumonia	Bilateral pneumonia
Reparixin treatment				
Time[a]	Day +4	Day +3	Day +5	Day +2
Dose	IV infusion (2.772 mg/kg body weight/hour) for 5 days			
PaO_2/FiO_2 ratio (mm Hg)	105	129	127	-
White blood cell, $\times 10^9$/L	16.2	6	7.5	10.5
Lymphocyte count, $\times 10^9$/L	0.9	0.6	0.6	0.8
Neutrophil count, $\times 10^9$/L	14.5	4.9	6.2	8.6
Platelet count, $\times 10^9$/L	497	390	273	491
Creatinine, mg/dL	0.77	0.97	1.89	0.53
Lactate dehydrogenase, U/L	535	472	331	513
C-reactive protein, mg/L	342.8	127.4	81.8	339.8
Serum crosslinked fibrin, µg/mL	1.99	4.31	2.07	10.56
Serum ferritin, ng/mL	1202	1467	2978	461
IL-6, pg/mL	196	—	23	—
Follow up				
Status[a]	Alive at day +45	Alive at day +42	Alive at day +44	Alive at day +41
Admitted to ICU[a]	Yes, day +6	Yes, day +3	No	Yes, day +8
ICU discharged[a]	No	No	—	No
Hospital discharged[a]	No	No	Yes, day +22	No

Abbreviations: COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; ICU, intensive care unit.
[a]All times are calculated considering the day of hospitalization as day 0.

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 mmHg), 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.[37,38] 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 noninvasive) 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,[39] 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.[40] 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.[22] 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 efficacy is likely to be of great interest. In fact, the JAK3 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.[41]

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*.

AUTHOR CONTRIBUTIONS

GL and LP equally contributed to the writing of the manuscript.

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SUPPORTING INFORMATION

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

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