Improving the Outcomes of Immunocompromised Patients With Coronavirus Disease 2019

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Recent case studies have highlighted the fact that certain immunocompromised individuals are at risk for prolonged SARS-CoV-2 replication, intrahost viral evolution of multiply-mutated variants, and poor clinical outcomes. The immunologic determinants of this risk, the duration of infectiousness, and optimal treatment and prevention strategies in immunocompromised hosts are ill defined. Of additional concern is the widespread use of immunosuppressive medications to treat COVID-19, which may enhance and prolong viral replication in the context of immunodeficiency. We outline the rationale for 4 interrelated approaches to usher in an era of evidence-based medicine for optimal management of immunocompromised patients with COVID-19: multicenter pathogenesis and outcomes studies to relate the risk of severe disease to the type and degree of immunodeficiency, studies to evaluate immunologic responses to SARS-CoV-2 vaccines, studies to evaluate the efficacy of monoclonal antibodies for primary prophylaxis, and clinical trials of novel antiviral agents for the treatment of COVID-19.

Keywords. COVID-19; SARS-CoV-2; immunocompromised; monoclonal antibody; vaccine.

Immunocompromised patients are at increased risk for severe and fatal coronavirus disease 2019 (COVID-19) outcomes. In a multicenter study of over 400 solid organ transplant (SOT) recipients with COVID-19, 78% required hospitalization, 34% required intensive care, and 27% required mechanical ventilation [1]. Hematopoietic cell transplant (HCT) recipients also experience high rates of COVID-19–related complications, with up to 15% of patients requiring intubation [2]. Additionally, some studies have shown that mortality rates of SOT and HCT recipients with COVID-19 range between 20% and 30%, [1, 2], although more recent studies of SOT recipients, including a study showing comparable outcomes between SOT recipients and non-SOT controls [3], have shown lower mortality rates (4.4%–9.6%) [3, 4]. Patients with solid tumors, human immunodeficiency virus (HIV), and primary immunodeficiencies are also at high risk for severe outcomes, intubation, and death [5, 6]. By contrast, data in patients receiving immunosuppression or biologic agents for rheumatological and autoimmune conditions are more reassuring, with many studies showing clinical outcomes similar to those of the general population [5]. However, the use of the anti-CD20 monoclonal antibody rituximab and specific immunosuppressive medications (eg, sulfasalazine, azathioprine, cyclophosphamide, cyclosporine, mycophenolate, or tacrolimus) have been associated with worse outcomes compared with the use of methotrexate or disease-modifying antirheumatic drugs [7].

Complementing the clinical outcomes data, several case reports and case series have described prolonged viral replication and evolution of mutated variants in immunocompromised individuals [8–17]. Although limited in scope, these studies have provided initial insights into the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in immunocompromised patients, including the extent of viral replication and mutation within the host, the duration of infectious virus shedding, and the potential for transmission to others. Here, we highlight the serious consequences of SARS-CoV-2 infection in immunocompromised patients and recommend actions to fill knowledge gaps, prevent transmission, and ultimately improve patient outcomes.

PROTRACTED COVID-19 IN IMMUNOCOMPROMISED PATIENTS

We identified 14 patients across 10 studies who have been reported to have continued SARS-CoV-2 replication lasting longer than 20 days, with a median duration of 71 days (range, 21–143), indicating severely impaired ability to clear the infection [8–17]. Fifty percent (7 of 14) of patients had an underlying hematological malignancy [8–10, 13, 14]. The remaining predisposing conditions were SOT (N = 2) [12, 15], advanced HIV infection (CD4 count = 0 cells/mm^3) [15], antiphospholipid syndrome (receiving prednisone, cyclophosphamide, and rituximab) [11], prostate cancer [17], rheumatoid arthritis (receiving rituximab) [15], and X-linked agammaglobulinemia (N = 1 each) [16]. Pneumonia was present in most patients, and SARS-CoV-2 antibody responses were minimal to absent. Impaired B-cell and possibly T-cell function from immunosuppressive therapies

are thought to be the main reasons for the inability to clear the virus. Variability in the duration of infectious virus shedding has been noted, and larger studies are needed to better define the duration of and risk factors for prolonged shedding of infectious virus.

Perhaps the most striking feature of protracted infection in immunocompromised patients is intrahost viral evolution and generation of multiply-mutated viruses. Several studies have shown the emergence of deletions in the N-terminal domain (NTD) of the spike glycoprotein gene (S gene) and mutations in the receptor binding domain (RBD) of the S gene and in other regions of the SARS-CoV-2 genome, all within the same host in the absence of reinfection [8, 9, 11, 13, 14]. Many of these mutations, such as deletions at residues 69–70 and 141–144 of the S-gene NTD and the E484K and N501Y mutations in the RBD would later be identified in late 2020 in the heavily mutated SAR-CoV-2 lineages B.1.1.7, B.1.351, and P.1, first reported in the United Kingdom, South Africa, and Brazil, respectively [18]. That these variants emerged independently and were first identified in immunocompromised hosts in mid-2020 has led some to propose that their origin was in individuals with prolonged infection. These highly mutated variants are thought to be transmitted more efficiently because of greater affinity of the mutated spike proteins to the angiotensin-converting enzyme 2 receptor. The mutated variants may also be less sensitive to neutralization by monoclonal antibodies [19] and sera from convalescent donors [14] or from recent vaccine recipients [20]. It has also been proposed that NTD deletions in the S gene emerged as a result of immune selection following administration of convalescent plasma [14], though this observation has not been universal [10].

Taken together, these findings highlight features unique to immunocompromised patients with COVID-19 and underscore deficiencies in the current approach to management. For instance, because immunocompromised individuals can transmit infectious virus for longer than 20 days, a stringent approach to COVID-19 precautions may be prudent in these patients. We recommend that test-based strategies similar to those proposed by revised Centers for Disease Control and Prevention (CDC) guidelines [21] be implemented even if the frequency and duration of prolonged infectiousness has yet to be completely characterized, as such interventions have the potential to prevent transmission of SARS-CoV-2 variants to healthcare workers and others. In parallel, research efforts should focus on identifying surrogates for viral replication and infectivity, such as cycle threshold values or other biomarkers [22]. In addition, a larger umbrella of studies should be conducted to fill knowledge gaps about the pathogenesis, prevention, and treatment of COVID-19 in immunocompromised patients. Accordingly, we recommend the rapid implementation of the 4 interconnected research strategies discussed below (Table 1).

Table 1. Recommendations to Address Key Knowledge Gaps Related to Coronavirus Disease 2019 in Immunocompromised Patients

Knowledge Gap	Focus of Research
SARS-CoV-2 biology in immunocompromised patients	Defining risk of severe and fatal disease by the type and degree of immunodeficiency
	Managing preexisting immunosuppressive therapies in immunocompromised patients with COVID-19
	Quantifying viral replication dynamics including plasma RNAemia and viral burden in respiratory tracts
	Determining duration of infectiousness
	Determining frequency of intrahost viral evolution
	Profiling immune responses to SARS-CoV-2 infection
Efficacy of COVID-19 vaccination in immunocompromised patients	Longitudinal studies of antibody, B-cell, and T-cell responses in vaccinated immunocompromised patients
	Determining safety and efficacy of vaccines, with a focus on allograft rejection and risk factors for vaccine failure
	Evaluating the mechanisms of vaccine-breakthrough infections
Efficacy of pharmaceutical interventions for COVID-19 prevention in immunocompromised patients	Studies of pre- or postexposure prophylaxis using monoclonal antibodies
	Studies of pre- or postexposure prophylaxis using direct-acting antivirals
Best practices for management of COVID-19 in immunocompromised patients	Observational studies of the impact of immunomodulatory therapies on clinical outcomes of immunocompromised patients with COVID-19
	Observational studies of the risk of opportunistic infections associated with the use of immunomodulatory therapies
	Clinical trials in immunocompromised patients of antivirals that have activity against SARS-CoV-2 (eg, small molecules and antibodies)
	Clinical trials of adoptive transfer of SARS-CoV-2 T cells in immunocompromised hosts

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

PROSPECTIVE PATHOGENESIS AND OUTCOME STUDIES

Centers that care for large cohorts of immunocompromised individuals should coordinate their efforts to study the pathogenesis of COVID-19 in these populations. A collective effort through large, well-established networks is necessary to quickly generate meaningful data beyond case reports or case series. These studies should be designed to collect longitudinal specimens and clinical outcomes from patients with varying levels of immunodeficiency, including SOT recipients, HCT recipients and other patients with hematological malignancies, patients

receiving chemotherapy for cancer, patients with B-cell aplasia (such as anti-CD20 monoclonal antibody recipients), patients with autoimmune or chronic inflammatory conditions, patients living with HIV, and patients with congenital immunodeficiencies. The purpose of these studies should be to investigate the risk of severe and fatal disease by the type and degree of immunodeficiency; the optimal strategies for managing preexisting immunosuppressive therapies (such as discontinuing or dose-reducing antirejection medications, neoplastic therapy, or biologic agents) in immunocompromised patients with COVID-19; viral replication dynamics including plasma RNAemia and viral burden in respiratory tracts; the duration of infectiousness by culturing of longitudinal specimens or measuring surrogates of infectivity; the frequency of intrahost viral evolution; and immune responses to SARS-CoV-2, with a focus on antibody production, neutralization, and durability; T-cell responses to COVID-19; and specific clinical risk factors associated with blunted immune responses to COVID-19 (eg, type of immunosuppression) and the risk for reinfection. These studies will not only further guide the duration of COVID-19 transmission-based precautions but will inform the treatment and prevention strategies described below. Additionally, these data will provide guidance for the safety of resuming immunosuppressive therapies in patients with malignancies and other conditions that require immunosuppression.

STUDIES OF COVID-19 VACCINATION IN IMMUNOCOMPROMISED PATIENTS

COVID-19 vaccines that are available in the United States have shown greater that 66%–90% efficacy in preventing COVID-19. However, immunosuppressed patients were excluded from the phase 3 trials that led to the emergency use authorization (EUA) of the vaccines. While administration of the mRNA and adenovirus vector vaccines is expected to be generally safe, there are some concerns that upregulation of immune responses following COVID-19 vaccination in SOT recipients may trigger allograft rejection [23]. Furthermore, the immunogenicity and protective efficacy of these vaccines are likely to be lower than those of immunocompetent individuals, thereby putting vaccinated immunocompromised patients at continued risk for "breakthrough" SARS-CoV-2 infection [23].

These efficacy concerns have been corroborated by early findings of observational studies in which immune responses to the mRNA vaccines were evaluated. For instance, SARS-CoV-2 antibodies were detected in only 17% of 436 SOT recipients (in whom the effects of mycophenolate or azathioprine were particularly detrimental) and 6.2% of 145 kidney transplant recipients after administration of a single dose of an mRNA COVID-19 vaccine [24, 25]. Additionally, a study of 67 hematological malignancy patients who had received 2 mRNA vaccine doses showed that 46% of individuals failed to produce antibodies against the SARS-CoV-2 spike protein [26], a finding that

contrasts with the essentially 100% seroconversion rate seen in phase 1 and 2 mRNA vaccine trials of healthy volunteers [27]. In contrast, patients with autoimmune diseases appear to have robust responses to mRNA COVID-19 vaccines, with up to 74% of patients developing antibody responses after 1 vaccine dose, although the use of anti-CD20 monoclonal antibodies or mycophenolate was associated with vaccine failure [28].

These early reports should be expanded upon through large, longitudinal studies of immunocompromised patients, in which antibody levels, neutralization titers, and durability of both measures, as well as deeper immune profiling including T-cell responses, should be assessed. Additionally, these studies should be designed to allow for biosampling during COVID-19 breakthrough infections. These data will help inform guidelines for vaccination, postvaccine serological monitoring, and other prophylaxis for immunocompromised hosts. Importantly, in light of current CDC guidance appropriately permitting relaxed precautions among vaccinated and low-risk unvaccinated individuals [29], immunosuppressed patients should be advised to continue wearing masks and practicing social distancing, regardless of prior COVID-19 or vaccination status.

STUDIES TO OPTIMIZE PREVENTION OF COVID-19

Since emerging data suggest that immunocompromised patients are not expected to generate robust antibody or memory B-cell responses to COVID-19 vaccines, preventive efforts that either replace or complement COVID-19 vaccination should be explored. An appealing alternative to vaccination is the use of monoclonal antibodies or other direct-acting antivirals to prevent COVID-19. In an unpublished study of more than 900 participants residing in or working at nursing homes [30], the monoclonal antibody bamlanivimab significantly lowered the risk of nursing home residents developing COVID-19. Similar strategies using monoclonal or polyclonal antibodies targeting wild-type and mutated SARS-CoV-2 variants should be explored for the primary prevention of COVID-19 in immunocompromised patients. However, the sustainability of this approach may be limited by the emergence and spread of resistance to monoclonal antibodies such as bamlanivimab [31], which may result in failure of this agent to prevent COVID-19. Consequently, the potential spread of variants with resistance to monoclonal antibody therapy should be vigilantly monitored.

Prophylaxis of immunosuppressed patients with oral agents, such as the novel COVID-19 antiviral molnupiravir (NCT04405739) or repurposed medications such as fluvoxamine (which has shown promise in early COVID-19 treatment trials; NCT04342663), if shown to be effective in clinical trials, would be an appealing alternative to monoclonal antibody prophylaxis. Although postexposure prophylaxis against influenza using oseltamivir has been established as the standard of care for nearly 2 decades, studies using oral agents such a

hydroxychloroquine for the prevention COVID-19 have not shown efficacy [32, 33]. Additional work in COVID-19 prevention, particularly among vaccine nonresponders, is needed.

STUDIES TO OPTIMIZE MEDICAL MANAGEMENT OF COVID-19

The publication of the RECOVERY trial, which showed a significant reduction in mortality among patients with COVID-19 who received dexamethasone [34], resulted in a paradigm shift in the medical management of COVID-19, whereby immunomodulation and not antiviral therapy has become an accepted clinical practice standard. The concept of immunomodulation has been solidified by clinical trial data demonstrating a mortality benefit of interleukin (IL)-6 inhibitor therapy (eg, tocilizumab or sarilumab) in nonmechanically ventilated critically ill patients with COVID-19. As a result, there has been strong interest in the continued study of immunomodulatory drugs to treat COVID-19. A multitude of immunosuppressive medications are being evaluated (generally as adjuncts to dexamethasone), such as IL-1 or tumor necrosis alpha inhibitors and other cytokine inhibitors and immunomodulators. Current guidelines endorse the use of dexamethasone and IL-6 inhibitor therapy in subgroups of patients with COVID-19 without excluding immunocompromised patients [35], even though these patients were generally excluded from clinical trials. By contrast, antiviral development appears slower, perhaps due to the lag time needed to discover and develop new small molecule inhibitors that are potent, safe, and effective. Given that immunosuppressed patients are at risk for protracted SARS-CoV-2 infection, concerns have been raised about whether immunosuppressive therapies may promote chronic infection and worse outcomes, including selection and transmission of new SARS-CoV-2 variants. Additionally, clinical trial data of the downstream consequences of aggressive immunomodulatory therapy on the risk of opportunistic infections with antimicrobial-resistant bacteria, invasive fungi, and viruses are lacking [34, 36]. Thus, centers that use corticosteroids, tocilizumab, sarilumab, and other immunosuppressive agents, particularly among immunocompromised patients, should publish their clinical outcomes data, with an emphasis on infection-related outcomes not captured by clinical trials.

Studies among immunocompromised hosts should ideally be focused on identifying direct-acting antivirals that markedly reduce SARS-CoV-2 replication, be they small molecules or antibodies. The use of monoclonal antibodies, which are already available for administration to both immunocompromised and immunocompetent patients in the United States via an EUA, should now be expanded via clinical trials to encompass settings beyond those outlined in the EUA (eg, early hospitalization, supplement oxygen requirement in patients with prolonged replication), with a focus on immunocompromised patients who may benefit the most from them. Although the efficacy of the RNA polymerase inhibitor remdesivir has been questioned due to conflicting data [37, 38], remdesivir and other antivirals such as molnupiravir (NCT04405739) should also be studied in clinical trials of immunocompromised hosts who may reap the greatest benefit from such interventions. Indeed, while some have argued that the antiviral oseltamivir may only have modest efficacy against influenza, transplant recipients with influenza who are treated with oseltamivir have a significantly reduced risk of lower tract disease, hypoxemia, intensive care unit admission, and death [39]. A poignant example of a SARS-CoV-2 antiviral treatment that may benefit immunocompromised patients preferentially over others is convalescent plasma. Although general enthusiasm for convalescent plasma has waned due to contradictory and mostly negative trials, a recent study showed a mortality benefit of convalescent plasma in hematological malignancy patients with COVID-19 [40]. The risk of selecting immune escape variants with convalescent plasma or monoclonal antibodies or the development of antiviral resistance during therapy should be better defined in larger longitudinal studies. Finally, immunocompromised patients may be ideally suited for the study of adoptive transfer of allogeneic SARS-CoV-2–specific T-cell therapy (NCT04401410). Trials of antivirals in immunocompromised hosts should include quantification and sequencing of SARS-CoV-2 RNA in the respiratory tract and bloodstream to assess the reduction in viral replication and selection of resistant variants with antiviral therapy.

PATH FORWARD

In conclusion, the fastest way to usher in a new era of evidence-based medicine to manage immunocompromised patients with COVID-19 is to leverage the collective clinical and research expertise of health centers that care for these patients. Only then can we abandon empiricism, intuition-based medicine, and the excessive influence of anecdotal case reports to provide transplant, cancer, and other immunocompromised patients with the best evidence-based care.

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