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EDITORIAL

Unveiling COVID-19 treatment strategies for immunocompromised individuals: Therapeutic innovations and latest findings

1 | COVID-19 AND RECENT THERAPEUTICS

In the past 3 years, targets for therapeutics and strategies for prevention against coronavirus disease 2019 (COVID-19) were identified and developed based on the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and clinical outcomes of infection. Therapeutics for COVID-19 regarding disease time course, symptoms and interventions, different stages of the SARS-CoV-2 lifecycle, and COVID-19-associated immunomodulatory effects were discussed by Toussi et al.[1] Drug treatment of COVID-19 infection regarding mild-to-moderate COVID-19 disease in the outpatient setting, patients hospitalized with mild-to-moderate disease, patients hospitalized with the severe and critical disease were recently reviewed by Lui and Guaraldi.[2] Immunotherapeutics for COVID-19 include the transfusion of high-titer COVID-19 convalescent plasma (CCP), treatment of anti-SARS-CoV-2 monoclonal antibodies (mAbs) to COVID-19 outpatients to prevent progression to severe disease or to people who have a high risk of severe outcomes for pre-exposure prophylaxis purpose. Antivirals for SARS-CoV-2 include inhibitors for main protease (Mpro, also known as 3C-like protease, eg nirmatrelvir/ritonavir), spike protein, and genomic RNA synthesis (eg remdesivir and molnupiravir). Anti-inflammatory and immunomodulatory therapies for COVID-19 include the treatment with corticosteroids, Janus-associated kinase inhibitors (JAKi), interleukin (IL) inhibitors (eg IL-1i and IL-6i) targeting IL or IL receptor along or in combination with antivirals. In addition, vitamin D supplementation as a strategy for the treatment and prevention of COVID-19 disease onset and progression had been noted.[3]

2 | CONSIDERATIONS FOR COVID-19 PATIENTS IN IMMUNOCOMPROMISED POPULATIONS (ICP)

About 3% of the population have immunosuppressed conditions,[4] including people with primary immunodeficiencies and secondary immunodeficiencies, consisting of people with solid-organ transplants, metastatic cancers, hematologic malignancies, advanced or untreated HIV (human immunodeficiency virus) infection, those receiving cancer chemotherapy, and patients with autoimmune diseases receiving immunosuppressive biologics and medications.[5] Patients in this heterogenous group had a higher risk of COVID-19-related hospitalization, severe COVID-19, or death[6] and tend to have higher risk for opportunistic infections.[7] In addition, prolonged SARS-CoV-2 infection and persistent viral replication in ICP not only cause long duration of symptoms but also risk of emergence of antiviral-resistant or vaccine-escaped variants, prolonging the pandemic.[8] Although COVID-19 treatment guidelines had been proposed to manage patients with different severities and clinical cohorts,[9] a consensus on COVID-19 patients in ICP was lacking and the information was limited.

Immunocompromised individuals are at higher risk of severe COVID-19 outcomes. Vaccination remains a critical preventive measure for this vulnerable population. Although some may have a reduced response to vaccines, receiving the recommended doses can still provide some level of protection and potentially mitigate severe disease.[10] Given the potential for diminished vaccine response, immunocompromised individuals should be considered for booster doses based on local guidelines and emerging data. In addition to vaccination, immunocompromised individuals should strictly adhere to preventive measures, including wearing masks, maintaining physical distance, practicing good hand hygiene, and avoiding crowded or poorly ventilated settings. In addition, all close contacts, including household members and healthcare workers who provide care for ICP, are encouraged to get vaccinated.[9,11] Clinicians can closely monitor their condition, assess potential symptoms, and detect any COVID-19 complications early. In cases of exposure to COVID-19, immunocompromised individuals may require specific isolation or quarantine measures, depending on their risk profile. The management of COVID-19 in ICP necessitates an individualized approach. Clinicians must carefully consider the patient's specific immunocompromised condition, medical history, and risk factors to determine the most appropriate treatment plan. In severe COVID-19 cases among ICP, antiviral therapies such as remdesivir may be considered. The decision to use antiviral drugs should be based on clinical judgment and consultation with specialists from multidisciplinary areas. For high-risk individuals, including immunocompromised patients, certain

monoclonal antibody treatments have been granted emergency use authorization.[1,2] Early administration of these treatments can potentially reduce disease progression and hospitalization rates. In severe COVID-19 cases with significant inflammatory responses, corticosteroids like dexamethasone may be used under close medical supervision.[1] The use of CCP therapy in specific severe cases of COVID-19 among immunocompromised patients may be considered on a case-by-case basis early in the pandemic. However, it is suggested there is insufficient evidence to recommend either for or against the use of high-titer COVID-19 CCP for the treatment of COVID-19 in ICP.[9,11] Therapeutic recommendations for antiviral or immunomodulator therapy of adults with varying severities of COVID-19 are summarized in Table 1. The differences in treatment between patients with and without immunocompromised status are also summarized in Table 1. For more details of the therapeutic management differences, please refer to sections "Therapeutic Management of Nonhospitalized Adults With COVID-19", "Therapeutic Management of Hospitalized Adults With COVID-19" in reference 9, and section "Management of Patients With COVID-19 Who Are Immunocompromised" in reference 11. For more strategies regarding ICP including prevention of COVID-19, adjusting chronic immunosuppressive therapies, and therapeutic management of nonhospitalized and hospitalized immunocompromised patients with COVID-19, please refer to the "Special Considerations in People Who Are Immunocompromised" section of COVID-19 Treatment Guidelines proposed by COVID-19 Treatment Guidelines Panel at the U.S. National Institutes of Health.[9,11]

TABLE 1 Therapeutic recommendations for antiviral or immunomodulator therapies for adults with varying severities of COVID-19.[a]

Disease severity	Patient disposition	Recommendations
Nonhospitalized adults with mild to moderate COVID-19 who do not require supplemental oxygen	All patients	• All patients should be offered symptom management. • The Panel recommends against the use of dexamethasone or other systemic corticosteroids in the absence of another indication
	Patients who are at high risk of progressing to severe COVID-19[b]	Preferred therapies. Listed in order of preference: • ritonavir-boosted nirmatrelvir (Paxlovid) • remdesivir Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate: • molnupiravir
Hospitalized adults with COVID-19 but do not require oxygen supplementation	All patients	The Panel recommends against the use of dexamethasone or other systemic corticosteroids for the treatment of COVID-19
	Patients who are at high risk of progressing to severe COVID-19[b]	Remdesivir
Hospitalized adults with COVID-19 and requiring conventional oxygen	Patients who require minimal conventional oxygen	Remdesivir
	Most patients	Use dexamethasone plus remdesivir. If remdesivir cannot be obtained, use dexamethasone
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add oral baricitinib or intravenous tocilizumab to 1 of the options above
Hospitalized and requires HFNC oxygen or NIV	All patients	Dexamethasone should be administered to all patients. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): • oral baricitinib • intravenous tocilizumab Add remdesivir to 1 of the options above in certain patients
Hospitalized and requires MV or ECMO	All patients	Dexamethasone should be administered to all patients. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • oral baricitinib • intravenous tocilizumab

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIV, noninvasive ventilation.

[a]Contents of this table were adapted from table 2 of reference 9.

[b]For a list of risk factors, including immunocompromised conditions, please refer to the Centers for Disease Control webpage at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. For examples, type I and type II diabetes mellitus, heart failure, asthma, primary immunodeficiencies, obesity, etc.

Children have a milder disease course of viral infection than adults generally, including SARS-CoV-2 infection. However, they might develop COVID-19-associated multisystem inflammatory syndrome.[12] Previous results showed that children treated with immunosuppressive drugs have similar clinical presentations and outcomes to the general pediatric population.[13] In contrast, other results suggest that immunocompromised children have a higher risk of severe COVID-19 in high-risk immunocompromised children by underlying diseases.[13] Thus, continuous monitoring in immunocompromised pediatric patients to prevent serious illness is needed.[14]

3 | RECENT RESULTS RELATED TO COVID-19 PATIENTS WITH UNDERLYING DISEASE

COVID-19 patients with underlying disease, such as rheumatoid arthritis (RA), and corticosteroids treatment, are at higher risk of severe disease, and mortality.[15] It is recommended that eligible RA patients receive the SARS-CoV-2 vaccination while their disease is in a quiescent state.[16] Additionally, pediatric patients with inflammatory rheumatic diseases are advised to get vaccinated.[17] Our recent results suggested that RA with JAKi users are at significant risk of hospitalization, death, or composite adverse outcomes, especially higher mortality among those without COVID-19 vaccination.[18] Brown et al[19] suggested that the combination of remdesivir with CCP or anti-SARS-CoV-2 mAbs resulted in a higher viral clearance rate than those receiving remdesivir monotherapy and no therapy in COVID-19 patients with underlying immunodeficiency. Martinez et al[20] suggested that prolonged infusion with 30 consecutive days of remdesivir without dexamethasone, which is beyond the duration authorized or approved by the Food and Drug Administration, cured a case of 5-month persistent COVID-19 in a patient with immunocompromised conditions. Trottier et al[21] reported successful treatment of persistent SARS-CoV-2 infection in an immunocompromised patient using an extended course of remdesivir in combination with nirmatrelvir/ritonavir. In a very recent article, the co-administration of molnupiravir and nirmatrelvir/ritonavir (NMV/r) successfully treated a follicular lymphoma patient with immunocompromised status and persistent SARS-CoV-2 infection. The combination therapy resulted in a quick clinical and virological recovery without concerns of tolerability and toxicity.[22] Lindahl et al[23] described a follicular lymphoma patient receiving chemotherapy with persistent SARS-CoV-2 viral shedding and relapsing COVID-19 pneumonia. The patient was treated with repeated courses of NMV/r. The patient remained afebrile and polymerase chain reaction tests negative without any observed adverse effects after prolonged course of NMV/r treatment.

In a panel of ICP make up of patients, 59.1% with solid organ transplant, 22.7% with hematopoietic cell transplant, 11.4% with hematologic malignancy, and 6.8% with autoimmune disease, neutralizing capacity against Omicron variants of CCP from recently recovered and vaccinated donors was evaluated.[24] They concluded that in the context of the Omicron era, administering high-titer post-vaccine CCP has demonstrated safety in hospitalized immunocompromised patients with COVID-19, and the 30-day mortality rate was found to be low. There is now a strong rationale for conducting randomized controlled trials to evaluate the use of post-vaccine CCP in immunocompromised patients, both as an early and late treatment option, as well as for pre-exposure prophylaxis and post-exposure prophylaxis. Considering the widespread availability of CCP and its potential to effectively treat and mitigate the emergence of new viral variants, these studies should be regarded as a crucial public health priority.

4 | CONSENSUS OF COVID-19 IN ICP

In the next issue of *International Journal of Rheumatic Diseases*, a consensus group comprising multidisciplinary experts from China suggested 13 recommendations for the clinical management of immunocompromised patients exposed to SARS-CoV-2 infection and COVID-19 patients in ICP. They cover laboratory diagnosis, risk assessment, treatment strategies, health management during the convalescent period, and prevention measures. Each recommendation is accompanied by a comprehensive literature list, highlighting current relevant clinical findings. The recommendations consider various factors such as implementation benefits, associated risks, available alternatives, and areas requiring further clarification. While there are still many unknowns that necessitate additional investigation, this article offers updated guidance to clinicians for enhancing clinical outcomes in ICP with COVID-19.

AUTHOR CONTRIBUTIONS

JJT: resources. LTL and JJT: writing—original draft. LTL and JJT: writing—review and editing. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in US NIH at https://www.covid19treatmentguidelines.nih.gov/. These data were derived from the following resources available in the public domain: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, https://www.covid19treatmentguidelines.nih.gov/ and Special Considerations in People Who Are Immunocompromised, https://www.covid19treatmentguidelines.nih.gov/special-populations/immunocompromised/?utm_source=site&utm_medium=home&utm_campaign=highlights.

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