Review

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Update on COVID-19 Therapeutics for Solid Organ Transplant Recipients, Including the Omicron Surge

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Abstract. Major changes have occurred in therapeutics for coronavirus-19 (COVID-19) infection over the past 12–18 mo, most notably in early outpatient therapy. In most cases, solid organ transplant recipients were not included in the original clinical trials of these agents, so studies of real-world outcomes have been important in building our understanding of their utility. This review examines what is known about clinical outcomes in solid organ transplant recipients with newer therapies. SARS-CoV-2 monoclonal antibodies for early treatment or prophylaxis have likely prevented many hospitalizations and deaths. In addition, convalescent plasma, the oral drugs nirmatrelvir/ritonavir and molnupiravir, remdesivir for early outpatient treatment, anti-inflammatory therapy, and investigational virus-specific T-cell therapy will be discussed. Finally, the later consequences of COVID-19, such as secondary infections, long COVID symptoms, and persistent active infection, are identified as areas for future research.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) therapeutics for solid organ transplant (SOT) recipients have evolved over time.[1-6] This overview is not a systematic review, but rather a summary of newer therapeutic developments for clinicians. The National Institutes of Health[7] and the World Health Organization[8] have published guidelines for COVID therapeutics, but randomized trial evidence in transplant recipients has been scant. Retrospective studies have provided a growing real-world experience, but there are many areas that remain to be investigated, to improve outcomes for SOT recipients.[9]

Previously,[1] we contrasted the early pandemic (when hydroxychloroquine, azithromycin, and lopinavir-ritonavir were used) with the more recent period (when remdesivir and dexamethasone became prominent). Inpatient therapies have also included anti-inflammatory agents such as tocilizumab and baricitinib,[3] and convalescent plasma was often used in the early pandemic.[10] Since early 2021, there have not been major changes in the paradigm for treatment of severely ill inpatients with COVID-19.

By contrast, the real revolution has been in early COVID-19 treatment, starting in late 2020 with the introduction of SARS-CoV-2 monoclonal antibodies (mAbs) for treatment of mild-to-moderate COVID-19.[11] Two oral drugs (nirmeltravir/ritonavir and molnupiravir),[12-13] as well as a 3-d outpatient protocol for remdesivir,[14] and a randomized trial of high-titer convalescent plasma in outpatients,[15] have expanded the options for treatment of early COVID. This review will examine what we know about each of these newer therapies in terms of clinical utility, risks, and benefits in SOT recipients. Finally, the difficult problem of persistent infection without viral clearance will be discussed (Table 1).

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SARS-CoV-2 MONOCLONAL ANTIBODIES FOR TREATMENT

Antibody responses to COVID vaccines in SOT recipients are often suboptimal, especially after 1 or 2 doses of vaccine.[16-18] Although antibody responses improve with successive doses of vaccine,[19-25] some patients continue to have low or negative antibody levels, and breakthrough COVID-19 infections have been reported after vaccination.[17,26,27] The largest study of breakthrough infections, involving >40 000 transplant recipients in the United Kingdom with over 4000 COVID-19 infections, compared unvaccinated patients with those who had received 2 doses of ChAdOx1-S or BNT162b2 vaccine.[17] Vaccination was not found to be associated with reduced risk of infection. The unadjusted case fatality rate was 9.8%; vaccination was associated with a 20% reduced risk of death (particularly after ChAdOx1-S vaccine). Thus, 2 doses of

TABLE 1.

Recent COVID therapeutics: brief summary

Therapy	Route	Indications	Comments
Sotrovimab	IV or IM	Early outpatient treatment	Effective against BA.1, BA.1.1; reduced activity vs BA.2
Bebtilovimab	IV	Early outpatient treatment	Effective against BA.1, BA.1.1, BA.2
Nirmatrelvir/ritonavir	Oral	Early outpatient treatment	Potentially severe drug-drug interactions
Molnupiravir	Oral	Early outpatient treatment	Not for use in pregnancy
Remdesivir (3-d outpatient course)	IV	Early outpatient treatment	Logistics may be challenging
Convalescent plasma	IV		Early use of high-titer plasma showed benefit
Tixagevimab/cilgavimab	IM	Pre-exposure prophylaxis	More active against BA.2 than BA.1 or BA.1.1

COVID, coronavirus disease.

COVID-19 vaccine was found to confer some degree of protection but much less than in the general population.[17] This has stimulated interest in passive immunotherapy for treatment or prophylaxis of immunocompromised individuals, either in the form of laboratory-produced mAbs or convalescent plasma from individuals with COVID-19 who have recovered (see below).

The first introduction of SARS-CoV-2 mAbs, starting with bamlanivimab in November 2020, was for treatment of early COVID-19 infection. Casirivimab/imdevimab, bamlanivimab-etesevimab, sotrovimab, and most recently bebtelovimab have followed successively. In the United States, these agents received emergency use authorizations (EUAs) from the US Food and Drug Administration (FDA), for early treatment of outpatients who had risk factors for severe illness, who had mild-to-moderate symptomatic COVID-19, who were not hypoxemic, and were within 10 d of symptom onset (now 7 d). In some countries, use was restricted to inpatients. Although the original clinical trials of these agents did not include many immunocompromised patients, it is likely that this group benefits the most from mAb therapy, given their immunocompromise and suboptimal responses to COVID vaccines.[11] Retrospective studie summarized below suggest that mAb treatment in SOT recipients is associated with reduced risk of hospitalization, reduced likelihood of progression to severe infection, and probably reduced mortality.[11] However, with the constantly evolving landscape of the pandemic, and a succession of new dominant variants, the utility of each monoclonal has changed over time. For example, bamlanivimab was originally administered by itself, then later when it was no longer effective as a single agent, was given together with etesevimab, and ultimately was not used at all. With the advent of the Omicron variant, starting in December 2021, most of the existing mAbs were found to have greatly reduced activity, with the exception of sotrovimab. Sotrovimab is active against the Omicron BA.1 and BA.1.1 subvariants, and previous variants, but has reduced activity against the BA.2 subvariant, so after BA.2 became the dominant variant, the FDA has revoked the EUA of sotrovimab throughout the United States. As of this writing, in April 2022, only bebtelovimab, which has activity against BA.2, has an EUA for early outpatient treatment in the United States.

All of these mAbs are antispike antibodies that bind to the receptor-binding domain of the SARS-CoV-2 spike protein, and thus interfere with the virus's entry into the cell. Bamlanivimab, casirivimab, imdevimab, and etesevimab bind in such a way to interfere with the ACE-2 receptor, whereas sotrovimab binds to a more highly conserved site on the receptor-binding domain and does not interfere with the ACE-2 receptor. It has been thought that sotrovimab was likely to be more resilient to variants because of binding to this highly conserved site, which also renders sotrovimab active against other sarbecoviruses, including the original SARS-CoV-1 virus as well as Middle East respiratory syndrome coronavirus.[28]

Although clinical trial data in SOT recipients were lacking, the uptake of mAb therapy in the transplant community was immediate and enthusiastic. Thus, what is known about benefits and risks of mAb in SOT recipients comes largely from retrospective, mostly single-center studies, well summarized as of October 2021 in a review by Dhand and Razonable.[11] Early on, Dhand et al[29] reported on 10 SOT recipients who had received bamlanivimab, and in a separate report, casirivimab/imdevimab,[30] under EUA. None progressed to severe disease or required hospitalization.[29,30] Yetmar et al[31] reported on 73 SOT recipients, approximately three-fourths of whom received bamlanivimab and the rest casirivimab/imdevimab, through January 2021. Nine (12.3%) required hospitalization and only 1 required intensive care unit (ICU) admission; none required mechanical ventilation and there were no deaths or episodes of rejection.[31] Other groups have reported similar results, with no evidence of rejection or severe adverse events related to mAb administration, and overall a low rate of hospitalization and progression to severe disease.[32-41] Klein et al[42] also pointed out that unfortunately, Black and Hispanic patients were less likely to receive mAbs for early COVID, and were more likely to require hospitalization. In over half of these patients, the reason for not receiving mAbs was either having symptoms for >10 d, or already requiring hospitalization.[42] In any case, these results highlight the health inequities that were evident throughout the pandemic and indicate a pressing need for systems to make early treatment more accessible to all who are eligible.

An inherent difficulty of these retrospective studies is the absence of a truly comparable control group.[11] If contemporaneous patients are chosen, those who did not receive mAbs did not receive it for a reason (eg, not meeting criteria, refusal, logistics, and limited supply), and this group may not have been comparable to the group that did receive mAbs. And if historical controls are chosen (eg, before the availability of mAbs), this introduces the problem of changing management between different eras, and sometimes

different viral variants. To address this issue, Gueguen et al[43] performed a propensity-matched study of 80 kidney transplant recipients who received mAbs for early COVID between February 2021 and May 2021, in terms of hospitalizations, ICU admissions, and mortality within 30 d. These patients were treated with bamlanivimab, bamlanivimab-etesevimab, or casirivimab-imdevimab, and were compared with 155 propensity-matched controls with covariates of age, sex, time since transplant, immunosuppressive therapy, initial symptoms, and comorbidities. The mAb group had less frequent hospitalizations (35% versus 49.7%, $P = 0.032$), ICU admissions (2.5% versus 15.5%, $P = 0.002$), and deaths (1.25% versus 11.6%, $P = 0.005$), and no patient in the mAb group required mechanical ventilation.[43] Although not a randomized trial, this study provided evidence that SOT recipients do benefit from early treatment with mAb, to prevent progression to severe disease.

Several studies have reported outcomes in SOT recipients who were given sotrovimab, which became more frequently used after the onset of the Omicron surge in December 2021. The first report of use of sotrovimab in an SOT recipient was in a pregnant woman.[44] Subsequently, Pinchera et al[45] reported favorable outcomes in a group of 15 SOT recipients who received sotrovimab. Most recently, Cochran et al[46] reported on SOT recipients who were referred for sotrovimab during the Omicron surge, in a nurse-practitioner and nurse-led program that screened 269 newly COVID-19-positive SOT recipients within a few weeks. Of 88 patients who received sotrovimab, 26% required admission and 2% died, which compares favorably with earlier data from the same center[47] and to multicenter registries from earlier in the pandemic.[48,49] However, this was before the emergence of Omicron subvariant BA.2 and, thus, represented sotrovimab outcomes for SOT recipients with Omicron BA.1 and BA.1.[46]

Given the limitations of retrospective studies, some academic/industry partnerships have designed studies to more rigorously elucidate the utility of mAbs in immunocompromised patients. Unfortunately, however, the pace of the pandemic has complicated some of these efforts. A multicenter study of casirivimab/imdevimab for preexposure prophylaxis in immunocompromised patients (NCT05074433) was closed to enrollment in December 2021, shortly after being launched, because of the rise of Omicron and the discovery that casirivimab/imdevimab, which had been highly effective for Delta and previous variants, was not active against Omicron. Several sotrovimab trials have been launched, including a study of sotrovimab for preexposure prophylaxis in immunocompromised patients (NCT05210101), although these were designed before the rise of the BA.2 subvariant. It is nonetheless commendable that industry is now turning its attention to rigorously designed clinical trials directed primarily at immunocompromised patients.

MONOCLONAL ANTIBODIES FOR PROPHYLAXIS

The first mAb to be used for prophylaxis was casirivimab-imdevimab, which received an EUA in the United States for postexposure prophylaxis in August 2021. This was on the basis of a trial in the general population, which showed a relative risk reduction of 81.4% in household contacts of an individual with COVID-19 infection who received this postexposure prophylaxis.[50] However, this authorization was discontinued, along with the use of casirivimab-imdevimab for treatment, in late December 2021, when Omicron became the dominant variant.

Preexposure prophylaxis with casirivimab-imdevimab was not authorized under EUA in the United States, but in France was authorized by the National French Health Authority.[51,52] In this context, Dimeglio et al[51] reported on 182 SOT recipients who had low or undetectable antibody responses to vaccines, and who received 2 doses of casirivimab/imdevimab 1 mo apart as preexposure prophylaxis during the Delta variant surge. This was highly successful, as no patient who received this preexposure prophylaxis developed COVID-19, whereas 13 of 296 (4.4%) of those who did not receive casirivimab/imdevimab developed COVID, of whom 3 had severe disease and 1 died.[51] More recently, Kamar et al[52] reported 1 patient (out of 436 who had received casirivimab/imdevimab for preexposure prophylaxis) who had breakthrough infection with the Omicron variant despite high levels of anti-S antibody. Again, it appears that this use of casirivimab/imdevimab was highly effective during the Delta surge, which speaks to the utility of preexposure prophylaxis as a concept in vulnerable patients.

More recently, starting in December 2021, the long-acting combination mAb tixagevimab-cilgavimab was authorized by the FDA for preexposure prophylaxis, the only agent so far to receive an EUA for this indication in the United States.[53] The trial that led to the EUA, which was a randomized trial of tixagevimab-cilgavimab versus placebo for preexposure prophylaxis, was performed before the rise of the Omicron variant, included few immunocompromised patients, and had relatively few events in the placebo group.[53] However, given the vulnerability of immunocompromised patients, and their suboptimal responses to vaccination, the FDA elected to target this group for tixagevimab/cilgavimab.[53] Given its long duration of activity (6 mo), adverse events were collected out to 6 mo in the original trial. There was a small number of serious cardiac adverse events in the tixagevimab/cilgavimab group (22 of 3470 or 0.6%), which was higher than in the placebo group (3 of 1700 or 0.2%), including myocardial infarctions, heart failure, and arrhythmias.[53] The significance of this is unclear, but this may play a role in some patient and physician decisions about this agent, especially in patients with underlying cardiac disease. More information in real-world use will be welcome, especially as many SOT recipients have underlying cardiac conditions or risk factors.

The true efficacy of tixagevimab/cilgavimab in prevention of COVID-19 in SOT recipients is not yet known. The individual components tixagevimab and cilgavimab have considerably reduced activity against Omicron, but the combination has activity and appears more active in vitro against BA.2 than against BA.1 or BA.1.1 subvariants.[54] There may therefore be more reason to receive tixagevimab/cilgavimab in the current timeframe, when BA.2 is the dominant subvariant. Many patients have been eager to receive this preexposure prophylaxis, viewing it as the key to their successful re-entry into life and community, after having severely restricted their activities throughout the pandemic. However, clinicians have cautioned patients not to abandon safety measures as yet, until we learn more about how protective tixagevimab/cilgavimab actually is.

In this regard, a recent study by Benotmane et al[55] from Strasbourg, France, reported the incidence of breakthrough COVID-19 in kidney transplant recipients who received tixagevimab/cilgavimab at a dose of 150 mg/150 mg. In this cohort, 39 of 416 (9.4%) of patients developed COVID-19 despite preexposure prophylaxis.[55] All but 1 of these 39 were symptomatic; 14 of 39 (35.9%) required hospitalization, 3 (7.7%) required ICU admission, and 2 (5.1%) died from COVID-related acute respiratory distress syndrome.[55] In 15 cases where in viral sequencing was performed, only 1 was BA.2, and the others were BA.1 or BA.1.1 subvariants.[55] The US FDA has since declared the recommended dose to be 300 mg/300 mg instead of 150 mg/150 mg, for reasons of efficacy. It is not known what the incidence of symptomatic COVID-19 would have been in the study by Benotmane et al,[55] had they not received tixagevimab/cilgavimab. One can look at these data as either being favorable (in that >90% of prophylaxed patients did not develop COVID-19) or concerning (in that >9% did develop breakthrough infections and over 1 of 3 of these patients required hospitalization, with 2 deaths).[55] By contrast, in the first 7 wk of the Omicron surge at our center (when most of our SOT recipients had not yet received tixagevimab/cilgavimab), Cochran et al[56] reported that only 90 of 347 (26%) SOT recipients with COVID-19 required hospitalization, and 8 of 347 (2%) died. As more centers begin to publish their data, we look forward to a more detailed understanding of the protective role of tixagevimab/cilgavimab.

CONVALESCENT PLASMA

Convalescent plasma, derived from blood collected from donors who have recovered from COVID-19, has been in use since early in the pandemic, and received an EUA in the United States in August 2020. Although some randomized trials such as the large RECOVERY trial did not show benefit in terms of survival or other outcomes,[57] there appears to be more benefit if given early, and when using high-titer convalescent plasma.[58,59] Most recently, Sullivan et al[15] performed a randomized, placebo-controlled, multicenter trial of convalescent plasma for early treatment of COVID-positive adult outpatients in the general population, which demonstrated that COVID-19-related hospitalizations within 28 d were significantly less likely in the convalescent plasma group (17 of 592 or 2.9%) as compared with the placebo group (37 of 589 or 6.3%), a relative risk reduction of 54%. As a result, early use of high-titer CP is now generating renewed interest. Although the above trial was not specifically focused on immunocompromised patients, it seems likely that this group would benefit even more than those in the general population, who have robust antibody responses after vaccination.

Although randomized trials of convalescent plasma have not been directed toward immunocompromised patients, several case series have attempted to assess its potential utility in this population.[10,60-62] Fung et al[60] reported on 4 patients (3 SOT and 1 with hematologic malignancy) all of whom improved, Naeem et al[61] reported on 3 kidney transplant recipients who recovered, and Gupta et al[62] reported on 10 kidney transplant recipients, 9 of whom recovered, after receiving convalescent plasma. Rahman et al[10] reported on 13 SOT recipients early in the pandemic, who were hospitalized and had COVID-19 pulmonary involvement. Convalescent plasma was administered at a median of 8 d after symptom onset; 8 of 13 (62%) had improvement in oxygen requirements, 9 of 13 (69%) were discharged from the hospital and 3 died.[10] Rodionov et al[63] reported on 14 immunocompromised patients (including 8 organ transplant recipients) who received convalescent plasma at 5–14 d after diagnosis; 12 (86%) were discharged from the hospital and 2 (14%) died of secondary infections. Sait et al[47] at our center reported a low mortality of 5.6% in 77 hospitalized SOT recipients with COVID-19 between March and November 2020. Although this low mortality was likely multifactorial, one feature of this cohort was that 44 of 77 (57%) received convalescent plasma.[47]

To overcome the limitations of case series, Cristelli et al[64] performed a propensity-matched cohort study in kidney transplant recipients with COVID-19, in which 58 of 456 (13%) of patients received a single unit of convalescent plasma at a median of 6 d from symptom onset, and 116 others were selected as controls. The authors found no differences in survival, oxygen requirement, or mechanical ventilation; however, the convalescent plasma used was not uniformly high-titer, and there was a trend toward a higher proportion of survivors receiving high-titer plasma.[64] Senefeld et al[65] pooled data from 75 published studies reporting on immunocompromised patients who had received convalescent plasma through April 2021, and reported that overall, this provided evidence for mortality benefit and rapid clinical improvement. The pooled data included 66 SOT recipients, of whom 14% died and 68% had rapid improvement in supplemental oxygen requirements.[65]

Overall, there is evidence suggesting potential benefit from convalescent plasma in high-risk immunocompromised patients with COVID-19, but the benefits in survival and rapid improvement are likely most marked when given very early in infection, and with use of only high-titer convalescent plasma.

Another growing use of convalescent plasma has been for the treatment of persistently SARS-CoV-2 PCR-positive patients who are unable to mount enough of an immune response to clear their persistent viral infection. This group includes, in particular, severely B-cell-depleted patients who lack an adequate humoral immune response to COVID vaccines (discussed below in section "Persistent Positivity").

ORAL THERAPIES FOR COVID-19: NIRMELTRAVIR/RITONAVIR AND MOLNUPIRAVIR

Since late December 2021, options for outpatient treatment of COVID-19 have expanded, including EUAs for 2 oral drugs. Nirmatrelvir/ritonavir is a combination drug, as the ritonavir component is necessary to achieve adequate levels of the protease inhibitor nirmatrelvir. This raises issues of potentially severe drug-drug interactions with ritonavir, especially with calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, as well as many other drugs.[66] Since so many transplant recipients are taking tacrolimus-containing immunosuppressive regimens, and anecdotal experiences have been circulating about high tacrolimus levels and adverse

events despite holding tacrolimus, some centers have been very reluctant to prescribe nirmatrelvir/ritonavir at all, for patients on those immunosuppressive medications. Moreover, close monitoring of blood tests can be challenging during an active COVID-19 infection, and requires a designated phlebotomy site that will accept patients with active COVID-19 infection. However, a recent report has described the safe use of nirmatrelvir/ritonavir in 25 adult SOT recipients who were taking tacrolimus (n = 21), cyclosporine (n = 4), everolimus (n = 3), or sirolimus (n = 1).[67] Patients were told to hold tacrolimus and mTOR inhibitors and reduce cyclosporine to 20% of their dose during the 5 d of treatment. Only 4 required hospitalization, and there were no deaths. With a median time of 6 d to the first tacrolimus trough level assessed during or after treatment, no supratherapeutic tacrolimus levels were observed on that first assessment, and no neurologic adverse events occurred. One patient had a tacrolimus trough level of 24.6 ng/mL on day 10 after resuming their usual dose on day 7. The authors concluded that "the clinically significant interaction between NR and immunosuppressive agents can be reasonably managed with a standardized dosing protocol."[67] Supporting this, Wang et al[68] reported on 4 kidney transplant recipients treated with nirmatrelvir/ritonavir using a similar regimen of holding tacrolimus, checking tacrolimus levels on days 2 and 3 and again after completion. Days 2 and 3 tacrolimus levels were close to baseline and then declined to near 0 by days 8 and 9.[68] Despite these reports of manageable tacrolimus levels, it is still advisable to proceed with caution given the potential for toxicity, especially if close laboratory monitoring cannot be accomplished, and given that other options for early therapy are available. Further recommendations are discussed in the American Society of Transplantation's statement on oral antiviral therapy for COVID.[69]

Molnupiravir is an oral ribonucleoside antiviral agent that also has EUA for treatment within 5 d of onset of symptoms and lacks the drug-drug interactions of nirmatrelvir/ritonavir, but also appears less effective although it has not been directly compared with other agents in clinical trials.[7] As yet, there is little information on the risks and benefits of molnupiravir in SOT recipients. It is not recommended for use in pregnancy. Because of efficacy considerations, it was recommended in the NIH Guidelines to be used only if nirmatrelvir/ritonavir, sotrovimab, and remdesivir cannot be used or are unavailable.[7]

NEW INSIGHTS AND NEW USES FOR REMDESIVIR

Remdesivir has been well summarized in previous reviews of COVID antiviral therapies for SOT recipients, so it will be discussed only briefly here.[2,4] It is an inhibitor of the viral RNA-dependent RNA polymerase, and has been frequently used in hospitalized patients who are hypoxemic, as the adaptive COVID-19 treatment trial (ACTT-1) demonstrated a shorter recovery time in patients who required supplemental oxygen but were not intubated.[70] However, some other randomized trials, such as the SOLIDARITY[71] and DisCoVeRy[72] trials, did not show benefit with remdesivir. Because of these mixed results, it is recommended in some guidelines[7] but not others.[8] However, most recently, a multicenter comparative effectiveness study of >96 000 patients, 43.9% of whom received remdesivir, found that remdesivir-treated patients were significantly more likely to show clinical improvement by 28 d (adjusted hazard ratio [aHR], 1.19).[73] This effect was particularly pronounced in patients requiring no oxygen (aHR, 1.30) or low-flow oxygen (aHR, 1.23). Mortality in remdesivir-treated patients on low-flow oxygen was significantly lower in this study (aHR, 0.85).[73]

The initial clinical trials excluded patients with acute kidney injury or eGFR <30 mL/min per 1.73 m^2, and early on, concerns had been raised about whether remdesivir might cause dose-dependent tubular damage or accumulation of the sulfobutylether-beta-cyclodextrin carrier in patients with diminished renal function; however, overall there has not been a major safety signal observed.[74-76] Elec et al[77] reported on acute kidney injury and renal function over time in a group of 42 kidney transplant recipients; the 8 who received remdesivir were more likely to have a lower eGFR at discharge compared to admission, but 75% of those had severe or critical illness. On the contrary, acute kidney injury in a retrospective study by Sait et al[47] resolved more rapidly in patients who received remdesivir than those who did not. Buxeda et al[76] reported on 51 kidney transplant recipients who received remdesivir and found that it was well tolerated and safe in terms of renal and hepatic toxicity, but benefit was more difficult to discern as the mortality was 18.9%. Estiverne et al[78] conducted a retrospective case series of 18 patients with eGFR <30 mL/min/1.73 m^2 who received remdesivir; 9 required mechanical ventilation at the time of remdesivir initiation; and 5 were receiving renal replacement therapy (RRT). Two patients developed high ALT attributed to shock liver; 3 others had abnormal liver function tests judged possibly related to remdesivir. Eight of 13 patients not requiring RRT had improvements in renal function and 5 worsened.[78] In this situation with critically ill patients, and an infection in which clinical trajectories vary widely, it is difficult to know how many of these effects were attributable to remdesivir.

Shafiekhani and colleagues reported that the 102 of 245 SOT inpatients with COVID-19 who received remdesivir had an improved survival and shorter hospital stay when compared with those receiving other antivirals; however, the comparators were drugs such as lopinavir-ritonavir, and many patients also received tocilizumab and steroids.[79] The authors did not see any adverse impact of remdesivir on renal or liver function. On the other hand, Winstead et al[80] followed sequential cycle thresholds in a group of 30 kidney transplant recipients with COVID-19 and found no difference in time to a negative PCR between those who did or did not receive remdesivir, nor was there a difference in cycle threshold between the first and second PCR tests, suggesting against an impact of remdesivir on rapid clearance of viral load.

Although it was considered a drug for hospitalized patients for much of the pandemic, a recent randomized trial in 562 patients, of a 3-d course of outpatient remdesivir (the PINETREE Study), showed an 87% lower risk of hospitalization or death, with adverse events similar to those in the placebo group.[14] Although only 5% of patients in this study were immunocompromised, this study did reinforce the idea that remdesivir, administered early, may help to prevent progression to severe disease in patients with risk factors. Logistics of a 3-d course of

outpatient IV infusions may be challenging to implement, but this does represent another option, especially when a suitable mAb is not available.

In all, a growing body of literature suggests that there is no major safety issue in administering remdesivir, including to patients with low eGFR or acute kidney injury and SOT recipients. Whether toxicity may occur in individual cases is difficult to discern, given multiple confounding factors in severely ill patients. At this point, abnormal renal function should not be considered a contraindication to remdesivir. However, remdesivir should be discontinued if the ALT level increases to >10 times the upper limit of normal, or if there is evidence of liver inflammation, per current guidelines.[7]

UPDATES ON ANTI-INFLAMMATORY THERAPY

The inflammatory phase of COVID-19 is marked by elevations in markers such as C-reactive protein, ferritin, D-dimer, and interleukin-6. Consequently, anti-inflammatory agents including IL-6 receptor inhibitors (eg, tocilizumab), dexamethasone, and JAK inhibitors (eg, baricitinib) have been employed to mitigate the pulmonary inflammation that is the hallmark of this phase. Fernández-Ruiz and Aguado[3] have previously reviewed the use of anti-inflammatory agents in SOT recipients with COVID-19.

Tocilizumab has had an up-and-down history throughout the pandemic. After initial enthusiasm, several randomized trials cast doubt on benefit, only to be followed by such studies as the REMAP-CAP study, in which both tocilizumab and sarilumab were associated with improved outcomes in terms of days free of respiratory and cardiovascular organ support.[81] In terms of outcomes in SOT recipients, Pérez-Sáez et al[82] found a high mortality rate (32.5%) in 80 kidney transplant recipients with severe COVID-19 who were treated with tocilizumab early in the pandemic. However, survivors had a greater decrease in C-reactive protein after tocilizumab, suggesting a possible benefit of its anti-inflammatory effect.[82] Bodro et al[83] reported on 33 kidney recipients of whom 42% received tocilizumab and 12% anakinra; there were no differences in ICU admissions, mortality, or respiratory infections, but ordinal severity score was lower in those who had received anti-inflammatory therapy. Pereira et al[84] performed a propensity-matched study in which tocilizumab was not associated with better survival, or other measures of improvement. Recently, Yamani et al[85] have compared SOT recipients in Saudi Arabia who did or did not receive tocilizumab (25 versus 21 patients respectively). Despite being older and having higher inflammatory markers at presentation, patients who received tocilizumab had a shorter hospital stay, although there were no differences in mortality or mechanical ventilation.[85] Although it has been difficult to discern a consistent benefit in the literature, some clinicians continue to turn to tocilizumab in particular situations, for example if a patient is in the upswing of the inflammatory phase, and is not responding to dexamethasone.

Dexamethasone has become well established as therapy for patients with COVID-19 requiring supplemental oxygen, since the RECOVERY trial showed a lower mortality in patients on dexamethasone (as compared with usual care) who required supplemental oxygen or mechanical ventilation.[86] It does not appear to benefit patients not requiring supplemental oxygen. Questions remain about risk for secondary infections after dexamethasone; one retrospective study did not find any statistically significant difference in secondary infections in 90 d of follow-up, in hypoxemic patients who did or did not receive dexamethasone.[47] However, more data would be welcome.

THERAPEUTICS FOR COMPLICATIONS OF COVID-19: SECONDARY INFECTIONS AND LATE CONSEQUENCES

The risk of secondary infections, concomitant with and in the aftermath of a COVID-19 episode, has been high for SOT recipients, but there is no consensus on which patients should receive empiric therapy or prophylaxis. Clinicians should have heightened diagnostic awareness for these possibilities. In the multicenter retrospective study by Kates et al,[48] bacterial infections were diagnosed in 8%, bloodstream infections in 6.1%, and invasive fungal infections in 0.3% of 376 hospitalized SOT recipients with COVID-19, with follow-up to 28 d. In the case series by Sait et al,[47] invasive fungal infections were more common, being diagnosed in 7 of 77 (9%) of SOT inpatients with COVID. Permpalung et al[87] performed a case-control study of lung transplant recipients with COVID-19, and found a higher incidence of secondary bacterial infections (29.2% versus 6.3%, $P = 0.008$), and for-cause bronchoscopies compared with controls, although there was no significant difference in invasive fungal infections. COVID-associated pulmonary aspergillosis has been associated with worse outcomes, in terms of ordinal severity of disease scores and length of intubation in mechanically ventilated patients, and may be underdiagnosed.[88] Clancy and Nguyen[89] have developed a framework using positive and negative predictive values of COVID-associated pulmonary aspergillosis diagnostic criteria, to assist clinicians in assessing which patients might be candidates for empiric antifungal therapy.

Late consequences of COVID-19 may continue to unfold, weeks to months after the original episode. Duivenvoorden et al[90] reported on 912 kidney transplant recipients who had recovered from COVID-19; 83.3% had regained their functional status within 3 mo. However, a subset of patients continues to experience debilitating symptoms, including neurocognitive symptoms, for which management is challenging.

PERSISTENT POSITIVITY

There is increasing recognition that some immunocompromised patients, particularly those who are severely B-cell depleted, can have persistent active COVID-19 infection for many weeks or months with low cycle thresholds, complex courses, and virologic failure despite multiple prior therapies.[91-94] Although previous descriptions were primarily in oncology and HSCT recipients, some SOT recipients also remain persistently SARS-CoV-2 PCR-positive[95] and may have low cycle thresholds at day 20 or after, indicating potential for transmission, despite improvement or resolution of symptoms.[96] This is to be distinguished from the common phenomenon of late detection of virus by PCR with high cycle threshold, likely representing the detection of a small amount of residual viral genome that is not replication-competent. In addition, reinfections can

be distinguished from persistent infection by sequencing of the virus.[97] A study comparing sequencing, in cases of reinfection versus persistent positivity, found that reinfection most often occurs in immunocompetent individuals, whereas persistent positivity occurs in immunocompromised individuals in whom accelerated viral evolution and escape mutations can emerge.[97]

Patients who have long-term positive SARS-CoV-2 PCR's and low cycle thresholds, indicative of active, replicating, transmissible virus, represent a dilemma both for the individual and for society. Such patients may enter the inflammatory phase well after initial infection.[98] In other words, the clinical trajectory of the illness may not proceed by the usual COVID-19 timetable; they can become extremely ill late in the course. In addition, they may transmit viral infection after they are considered to be no longer infectious, as shown by a case report in which transmission from one immunocompromised patient to another occurred on day 28 of illness.[99] The public health implications for society are that they are potential transmitters of a virus that may have undergone mutations during its long tenure in that individual, under the influence of associated therapeutics that may have been received.[100] To stem the spread of new variants arising in such circumstances, it is imperative to devise effective ways of treating these patients and achieving viral clearance.

Remdesivir alone may not be successful in clearing persistent viral infection in B-cell-depleted patients.[91] Convalescent plasma was reported by Hueso et al[101] in a case series of 17 B-cell-depleted patients, and resulted in clinical improvement in all but 1 patient; there was 1 death. Hueso et al[102] also went on to perform a propensity score analysis of 112 B-cell-depleted patients and found that receiving convalescent plasma was associated with decreased mortality. Combinations of direct-acting antiviral therapy (such as remdesivir) and passive immunotherapy (mAbs or convalescent plasma) have been successfully used in some patients, in case reports and small case series.[92,93,103] However, concerns have also been raised about the potential for mutations to occur during a long period of persistent infection, and even to be driven by therapies received, including convalescent plasma. Kemp et al[100] reported on 23 sequential whole-genome viral sequences in a patient with lymphoma, who had received rituximab, and had multiple courses of remdesivir and convalescent plasma during an ultimately fatal 103-d course. During and after 2 courses of remdesivir, the viral population was relatively stable, but after convalescent plasma, dynamic viral evolution occurred, and a strain became dominant that featured a substitution in the S2 subunit and a deletion in the S1 N-terminal domain of the spike protein; this waned but then recurred after convalescent plasma was given again later.[100] As yet, there is no consensus on the optimal treatment of persistently positive patients. Further study of this issue in rigorously designed clinical trials would be of value.

FUTURE DIRECTIONS FOR THERAPEUTICS

Virus-specific T-cell therapy is emerging as an option for treatment of a variety of transplant-related viral infections. A recent case report described an unvaccinated heart transplant recipient with refractory COVID-19, who remained hypoxemic despite remdesivir, dexamethasone, and tocilizumab, and who had a rapidly rising nasopharyngeal viral load.[104] After treatment on a compassionate use protocol with ALVR109, an off-the-shelf SARS-CoV-2-specific T-cell therapy, the patient experienced both virologic and clinical improvement.[104] It will be of interest to see if this therapeutic modality will be effective, either alone or as an element of combination therapy, in clearing long-term active SARS-CoV-2 infection.

CONCLUSIONS

COVID therapeutics have evolved substantially over the past 12–18 mo, with the largest changes being in early treatment of patients with mild-to-moderate COVID. In particular, mAb therapy has likely resulted in the prevention of many hospitalizations and deaths in the immunocompromised population, although the evolution of the pandemic variants and subvariants has nullified the previous utility of several monoclonals over time. With the advent of preexposure prophylaxis with tixagevimab/cilgavimab, there is now another option for prevention. This is particularly important for those who do not mount a robust response to COVID vaccines, given the fact that neutralization of the Omicron variant requires very high levels of antibodies, which may not be routinely achievable even with a fourth dose of mRNA vaccine in transplant recipients.[105] Other recent options for early treatment include 2 oral drugs, nirmatrelvir/ritonavir and molnupiravir (although nirmatrelvir/ritonavir has potentially severe drug-drug interactions), and a 3-d outpatient remdesivir protocol. Convalescent plasma is undergoing a resurgence of interest following recent studies on the early use of high-titer plasma that showed benefit. Despite all of these advances, however, some highly immunosuppressed, primarily B-cell-depleted patients have difficulty clearing SARS-CoV-2 infection and remain persistently PCR-positive with low cycle thresholds, and may develop viral mutations during these lengthy courses. In addition, some patients clear detectable virus but remain symptomatic with post-COVID symptoms, which may be very debilitating. Finding effective treatments for these latter 2 groups (those with persistent positivity, and those with lengthy post-COVID syndromes) will be the next therapeutic frontier for SOT recipients with COVID-19.

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