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Reduction in the risk of progression of solid organ transplant recipients infected by SARS-CoV-2 treated with monoclonal antibodies

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ABSTRACT

Recipients of solid organ transplants (SOT) are at higher risk of infection by SARS-CoV-2 virus especially due to chronic immunosuppression therapy and frequent multiple comorbid conditions. COVID-19 is a potentially life-threatening disease in SOT recipients, with an increased likelihood of progressing to severe disease, with the need of hospitalization, admission to the intensive care unit (ICU) and mechanical ventilatory support. This article presents an updated review of different aspects related to the outcome of COVID-19 in SOT recipients. In unvaccinated SOT recipients, COVID-19 is associated with a high mortality rate, in-patient care and ICU admission, and impaired graft function or rejection in severe disease. In vaccinated SOT recipients even after full vaccination, there is a reduction of the risk of mortality, but the course of COVID-19 may continue to be severe, influenced by the time from transplant, the net state of immunosuppression and having suffered graft rejection or dysfunction. SOT recipients develop lower immunity from mRNA vaccines with suboptimal response. Treatment with mAbs provides favorable outcomes in non-hospitalized SOT recipients at high risk for severe disease, with lower rates of hospitalization, emergency department visits, ICU care, progression to severe disease, and death. However, broad vaccination and therapeutic options are required, particularly in light of the tendency of the SARS-CoV-2 virus to adapt and evade both natural and vaccine-induced immunity.

Keywords: solid organ transplant, COVID-19, SARS-CoV-2, vaccines, immunosuppression, monoclonal antibodies, sotrovimab.

Reducción del riesgo de progresión en receptores de trasplantes infectados por SARS-CoV-2 tratados con anticuerpos monoclonales.

RESUMEN

Los receptores de trasplantes de órganos sólidos (TOS) presentan un alto riesgo de infección por el virus SARS-CoV-2 debido al tratamiento inmunosupresor y múltiples comorbilidades. La COVID-19 puede ser potencialmente mortal en receptores de TOS, con un aumento de la probabilidad de progresión a enfermedad grave. Este trabajo presenta una revisión actualizada del impacto de la COVID-19 en receptores de TOS. En los receptores de TOS no vacunados, la COVID-19 se asocia con una alta tasa de mortalidad, hospitalización, ingreso en la UCI y deterioro del injerto o rechazo. En los pacientes vacunados, incluso con pauta de vacunación completa, se reduce el riesgo de mortalidad, pero el curso de la COVID-19 puede continuar siendo grave en función del tiempo desde el trasplante, el estado neto de inmunosupresión y haber sufrido rechazo o disfunción del injerto. Los receptores de TOS presentan una baja inmunogenicidad a las vacunas de ARNm y respuesta subóptima. El tratamiento con anticuerpos monoclonales (AMC) en receptores de TOS no hospitalizados con alto riesgo de enfermedad grave, se asocia con menores tasas de hospitalización, visitas a urgencias, ingreso en UCI, progresión a enfermedad grave y muerte. Sin embargo, se requieren nuevas vacunas y opciones terapéuticas, teniendo en cuenta la tendencia del virus SARS-CoV-2 a adaptarse y a evadir tanto la inmunidad natural como la inducida por la vacuna.

Palabras clave: trasplante de órgano sólido, COVID-19, SARS-CoV-2, inmunosupresión, vacunas, anticuerpos monoclonales, sotrovimab.

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INTRODUCTION

The current pandemic of SARS-CoV-2 infection posed unprecedented threats to global healthy populations, sick patients with any disease, healthcare systems, economic burden, and governments' responsibilities to ensure the health and safety of their communities. The coronavirus disease 2019 (COVID-19) had also had a major impact on solid organ transplantation (SOT), specially on the mortality of these patients, since they are more likely to develop severe forms of the disease as compared to the general population. This may be because they are unable to mount a robust immunity against SARS-CoV-2.

Although effective treatment options and vaccines have been a game changer, the ongoing pandemic continues to pose unique challenges to fully resume disrupted transplantation activities. A population-based study of nationwide cohorts of consecutive kidney, liver, lung, and heart transplants from 22 countries estimated an overall 16% reduction in transplant activity comparing rates in 2020 and 2019 [1]. An analysis of the impact of COVID-19 pandemic on the size of US transplant waiting lists showed an increase in waiting list mortality and decreased transplant and candidate listings [2]. A review of data provided by the US United Network of Organ Sharing (UNOS) [3] comparing monthly transplants in January and February 2020 with those performed during the entire month of April 2020 demonstrated a 35.9% decrease in organs transplanted, with the largest reduction seen in kidney and lung transplants; moreover, increases in waitlist deaths. The impact on organ transplantation also varied with respect to organ type with preferential deferral of kidney transplant candidates who were stable on renal replacement therapy and/or had lower immunologic barriers to transplantation [4]. However, the majority of reports noted a decline in SOT in all organ types, with living donor programs generally suspended or curtailed in many sites [5-7], recent evidence has also shown that there is low risk for a transplant recipient to get infected from an already infected donor, especially in non-pulmonary organs (kidney, liver, and heart) being transplantation a safe practice, with a low risk of transmission, regardless of the presence of symptoms at the time of procurement [8].

From another perspective, transplant recipients may be at a higher risk of infection by SARS-CoV-2 due to the use of immunosuppression, underlying comorbidities, and frequent contact with the healthcare system. However, they are also more likely to be diagnosed early because of a more overt symptomatology than immunocompetent subjects or due to closer follow-up at the hospital or the transplant center. In Spain, in SOT (n = 665) and hematopoietic stem cell transplant (HSCT) (n = 113) recipients diagnosed with COVID-19 until 13 July 2020, the incidence of COVID-19 was twofold higher compared to the Spanish general population [9]. The mortality rate was 27%, with age > 60 years, lung transplantation, and hospital-acquired COVID-19 as risk factors for death. However, during the ongoing pandemic, from 2020 to 2021 mortality in SOT recipients has decreased from 20-25% to 8-10% as a result of increased and early availability of SARS-CoV-2 testing, adherence to non-pharmaceutical interventions (face covering, hand hygiene, physical distancing) to control spread of infection, development of novel treatments, and vaccination [10]. Nevertheless, transplant patients have less post-vaccination protection than the general population, this condition of lower protection should have implications for treatment [8].

Although the COVID-19 pandemic is likely to move to an endemic phase, with vaccination and novel therapeutic options potentially reducing infection rates in SOT recipients [11-13], there are still limited data on the risk of poor outcomes and progression of SARS-CoV-2 infection, response to vaccination, or efficacy of monoclonal antibody therapy in SOT. Therefore, an updated review of recently published relevant studies addressing these aspects is here presented. The aim of the review is to provide clinicians involved in organ donation and transplantation with some updated evidence for an optimal approach to the care of SOT patients in daily practice, in particular in reference to how COVID-19 impacts on

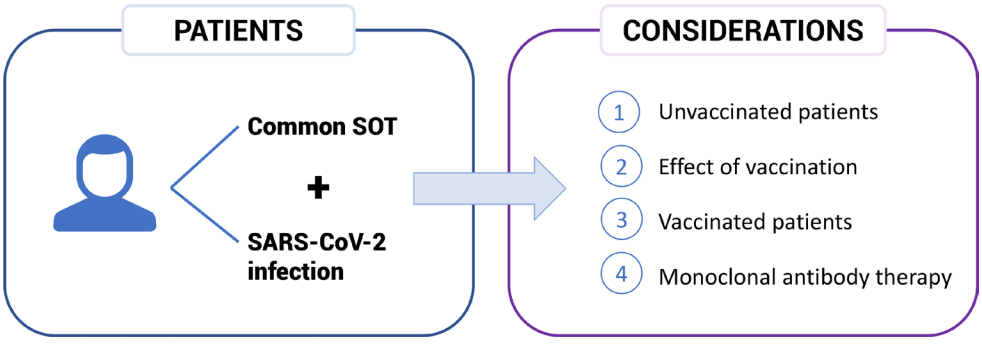

Figure 1 Different aspects of SARS-CoV-2 infection in solid organ transplantation (SOT) recipients include the severity of the disease in unvaccinated in comparison to vaccinated patients, the immune response to vaccines, and the effect of treatment with monoclonal antibodies on the course of the disease.

the overall management of SOT recipients and the use of mAbs as an available treatment to reduce the risk of progression of these patients (Figure 1). It should be noted that even though this review focuses on monoclonal antibodies, there are other treatments available against COVID-19, such as antivirals.

METHODS

A narrative review was carried out to cover all the points of interest to be reflected, being these both the risk of COVID-19 disease progression of SOT patients when infected by SARS-CoV-2 and the use of mAbs as early treatment to avoid COVID-19 progression. The information of interest was divided into four blocks, including: 1) outcomes in unvaccinated SOT recipients, 2) response to SARS-CoV-2 vaccine of SOT recipients, 3) outcomes in vaccinated SOT recipients, and 4) effect of treatment with monoclonal antibodies on the course of COVID-19 in SOT recipients.

The literature search was conducted in MEDLINE/PubMed database in May 2022 using MeSH terms and the following strategy: ((covid[Title/Abstract]) OR (sars-cov-2[Title/Abstract])) AND ((solid organ transp*[Title/Abstract]) OR (transpl*[Title/Abstract]) OR (SOT[Title/Abstract])) AND ((risk[Title/Abstract]) OR (bad outcome*[Title/Abstract]) OR (progno*[Title/Abstract]) OR (hospit*[Title/Abstract]) OR (death[Title/Abstract]) OR (mortal*[Title/Abstract])). Also, (vaccin*[Title/Abstract]) was added in the search of the second and third blocks, and ((monoclonal antibody [Title/Abstract]) OR (mab [Title/Abstract]) OR (treatment [Title/Abstract])) in the search of the fourth block. The search period ranged from June 2021 to May 2022 and was limited to articles published in English. In September 2022, the fourth block search was actualized, extending the search date to that moment. Also, due to updated vaccination programs leading to booster doses, especially in immunocompromised patients, relevant publications that provide key information for the aim of this review, were also allowed to be included. Hematopoietic cell transplant recipients were excluded. Regarding 'article type', no limits were established, although reviews, systematic reviews, and meta-analysis with the largest number of patients and participating centers were prioritized. Reference lists of retrieved articles were checked for additional potentially eligible studies. Full texts were obtained from all articles included in the present review. After excluding publications with the other formats, such as editorials, comments on articles, or opinion studies, the authors met via teleconference for discussion and agreement of the selected bibliography. The authors were not blinded to the authors, institutions, or journals while selecting studies or extracting data.

1. OUTCOMES IN UNVACCINATED SOT RECIPIENTS

In this block, three studies, a systematic review and meta-analysis [14], a structured review [15], and a cohort study [16] were focused on the outcomes of SARS-CoV-2 infection in SOT, whereas another three studies each assessed COVID-19 in specific lung [17], liver [18], and kidney [19] transplant recipients.

The systematic review and meta-analysis [14] included 14 retrospective and 1 prospective studies which had been published in 2020 that provided clinical outcomes of COVID-19 transplant recipients (n = 1485) vs. non-transplant controls. The overall quality of the evidence, according to Newcastle-Ottawa Scale (NOS) ranging from 7 to 9, was moderate. SOT recipients were predominantly male and more likely to present with higher proportions of comorbidities. Transplant recipients with COVID-19 showed as compared with non-transplanted patients a higher risk of admission to the intensive care unit (ICU) (odds ratio [OR] 1.57, 95 % confidence interval [CI] 1.07-2.31, $p = 0.02$) and mortality (hazard ratio [HR] 1.54, 95 % CI 1.03-2.32, $p = 0.037$) (1.40-fold increase odds of mortality than non-SOT recipients). In addition, in three studies that matched SOT recipients with the general population by age, sex, and comorbidities, SOT recipients also showed an increased risk of mortality (HR 1.42, 95% CI 1.01-2.0, $p = 0.046$).

In a structured review of cohort studies, case series, case-control studies, and case reports published in 2020, 164 publications were identified with 3,451 cases of SARS-CoV-2-infected SOT recipients, in which data on outcome were available for 3,353 patients (97.2%) [15]. Main outcomes included hospitalization in 84 % of patients (with SARS-CoV-2 infection recovery in 53.6%), mortality rate of 21.1%, changes in immunosuppressive medication in 57.9%, and disease progression involving an impaired allograft function in 22.6%.

In a study of the largest database on COVID-19 in the United States (National COVID Cohort Collaborative) [16] based on SOT patients who were tested for COVID-19 between January and November 2020, 18,121 SOT patients were identified, 1,925 (10.6%) of whom had a positive test for SARS-CoV-2. The outcome in the 90 days after COVID-19 positivity was analyzed. The presence of COVID-19, compared to SOT patients without COVID-19 positivity, significantly increased the risk of a composite variable (myocardial infarction, stent occlusion/thrombosis, angina, stroke, transient ischemic attack, chronic heart failure or death of any cause) (OR 1.92), as well as the risk of graft loss (OR 79.7), rejection (OR 31.8), death (OR 8.43), acute kidney injury (AKI) (OR 2.35), and graft failure (OR 1.23). Compared with all other organ types, kidney transplant recipients had the highest risk of AKI and graft loss.

COVID-19 is a life-threatening disease for unvaccinated lung transplant recipients. In a single German high-volume lung transplantation center [17], clinical outcomes of 31 recipients with SARS-CoV-2 infection among 1,046 patients followed between March 2020 and May 2021 showed a mortality rate of 39%, and 84% of patients required in-patient care. Pulmonary function parameters worsened significantly, and in patients with pre-existing chronic lung allograft dysfunction, there was a substantial deterioration in graft function, with a mortality rate of 43%. The Charlson Comorbidity Index was a predictor of mortality (4/5.5) (HR 1.5, 95% CI 1.5-2.2, $p = 0.023$).

In a review of eight studies published from January 2020 to January 2021, that evaluated COVID-19 infection in 494 liv-

er transplant recipients, 80% required hospital admission and 17% ICU care (of which 21% required mechanical ventilation) [18]. The overall mortality rate was 17%. Finally, in a systematic review and meta-analysis of 48 observational studies comprising 3,137 kidney transplant recipients with COVID-19 [19], the mortality rate for hospitalized patients was 21%, increasing to 53% among patients admitted to the ICU ($p < 0.0001$) and up to 68% in those who required mechanical ventilation support. In addition, the pooled prevalence of acute respiratory distress syndrome (ARDS) and AKI was 58% and 48%, respectively. There was a higher mortality risk associated with ARDS (OR 19.59), need of ICU care (OR 13.39), mechanical ventilation (OR 3.80), and age ≥ 60 years (OR 3.90).

Take home message

- **Unvaccinated SOT recipients with COVID-19 have a significant high risk of progression to severe COVID-19 disease and mortality.**
- **Impaired allograft function, graft rejection or graft loss are consequences of the severity of SARS-CoV-2 infection.**
- **Intensive surveillance is necessary in unvaccinated SOT patients for severe clinical outcomes.**

2. RESPONSE TO SARS-COV-2 VACCINE OF SOT RECIPIENTS

Vaccines against SARS-CoV-2 have been shown to constitute an important preventive option against COVID-19, especially in fragile patients, such as transplant patients. However, available data indicate that COVID-19 vaccines may be less effective in immunocompromised populations such as SOT recipients, although vaccines are safe and not related to rejection or other major adverse events. For this section of the review, selected reports included two systematic reviews (one with meta-analysis) [20,21], a descriptive review [22], a comparison of antibody titers between SOT recipients and healthy controls [23], three reviews in kidney transplant patients [24-26], one review and meta-analysis in the subgroup of patients receiving anti-CD20 therapies [27], and a retrospective study in liver transplant recipients [28]. Additionally, two prospective cohort study in renal patients [29,32], and two studies in SOT recipients [30,31] were also included to give information about the effect of a third or fourth dose.

A systematic review that assessed the immunogenicity of COVID-19 vaccine after primary complete vaccination in immunocompromised populations, based on 157 studies in 25,209 patients, including 47 studies in 5,974 SOT recipients (23.7%) until August 2021 [20]. Non-response rates, defined as no presence of anti-SARS-CoV-2 spike protein antibodies or absence of neutralizing antibodies, ranged from 19% to 100%, with 35-98% in recipients of kidney transplantation, 19-63% in liver transplantation, 25-88% in heart transplantation, and 59-100% in lung transplantation. Also, most studies found lower non-response rates in cellular than in antibody response. The use of calcineurin inhibitors, antimetabolites, and corticosteroids were associated with higher non-response rates or lower antibody titers. Non-responder status was also associated with older age and lower estimated glomerular filtration rate. The authors found inconsistency in the results with regards to the impact of time since transplantation on vaccine response.

The seroconversion after second dose of COVID-19 mRNA vaccines was evaluated in a systematic review and meta-analysis of 26 studies conducted in 2021 in 3,207 immunocompromised patients and 1,726 healthy controls [21]. Thirteen studies were focused on immunocompromised patients due to SOT, showing that transplant recipients were less likely to develop seroconversion than controls (relative risk reduction [RRR] 0.67, 95% CI 0.53-0.76, $p < 0.01$). No significant differences ($p = 0.55$) were observed in the subgroup analysis based on the type of transplantation (kidney vs. others [heart, lung, and liver]).

A descriptive review based on 24 studies in SOT recipients [22], suboptimal humoral immune responses following two doses of mRNA SARS-CoV-2 vaccine was reported, particularly in kidney and lung transplant recipients (seropositivity rates from 8.2% to 66% and from 10% to 47.4% for kidney and lung transplant recipients, respectively). However, seropositivity rates were higher for liver (37.5 % to 80%) and heart (18.2% to 62%) transplant patients. Among 148 kidney transplant recipients, 35% developed neither humoral nor cellular immune responses. Advanced age and magnitude of immunosuppression correlated to the immune response.

In a single-center prospective observational cohort study of 200 SOT recipients (liver, kidney and lung) and 200 age- and sex-matched controls [23], in which anti-receptor-binding domain (RBD) immunoglobulin IgG was measured after two doses of BNT162b2 vaccine, humoral (36% SOT vs 97.5% controls with positive response, p<0.001) and cellular responses (13.1% SOT vs 59.4% controls with positive response, p<0.001) 6 months after vaccination were inferior in SOT recipients than in healthy controls. Antibody levels increased from first vaccine dose to 2 months but declined from 2 months to 6 months. Statistically significant risk factors ($p < 0.001$) for humoral non-response 6 months after the first vaccine dose were increasing age (risk ratio [RR] 1.23 per decade increase), being less than 1 year from transplantation (RR 1.55), lung (RR 1.63), and kidney (RR 1.70) as type of organ transplantation with liver as reference, the use of mycophenolate (RR 1.54) or corticosteroids (RR 1.45) as immunosuppressive therapy, and *de novo* non-skin cancer as comorbidity (RR 1.52).

Other studies have evaluated the immune response in kidney transplant patients [24-27]. In a systematic review of 18 prospective cohort studies with 2,453 patients, 693 of which were kidney transplant recipients, the antibody response was evaluated 1-6 weeks after receiving the second dose of a mRNA vaccine [24]. The seroconversion rate ranged between 2.5% and 37.5% (overall 27.2%), with advanced age, high-dose corticosteroids in the last 12 months, and maintenance im-

munosuppression regiments including mycophenolate mofetil (MMF) as variables associated with low or absent antibody response. In another review [25], immune response after two doses of anti-SARS-CoV-2 vaccine ranged between 11% and 48%, with longer time from transplantation, first kidney transplant, better kidney function, and less immunosuppression related to more likely to seroconvert. In a meta-analysis of 27 cohort and case-control studies with 1,452 kidney transplant patients and 477 healthy controls, humoral and cellular immune responses ranged from 2.6% to 29.87% and from 5.13% to 59.84%, respectively, for up to 4 weeks post-vaccination completion with mRNA vaccines, whereas all healthy controls maintained ≥ 93% of both responses [26]. Moreover, another meta-analysis of immune responses in patients treated with anti-CD20 antibodies showed a low humoral response rate of 14% for the subset of kidney transplant recipients, which was a lower level of response than other conditions also treated with anti-CD20 such as hematological malignancies or autoimmune diseases. [27]. In patients receiving a liver transplant, alcohol-induced cirrhosis as underlying disease and MMF for immunosuppression have been identify as risk factors for seronegativity [28].

SENCOVAC is a prospective, multicentric study of four cohorts of vaccinated patients with different status of chronic kidney disease (CKD). In an analysis of vaccine response (by measurement of antibody titers), 6 months after the primary vaccination, the authors included 175 kidney transplant recipients who have received, at least, two doses of mRNA vaccine. 118 patients received a third dose. At 6 months, 80% of kidney transplant patients among those who had received a third dose of vaccine (median 125 days after second dose) were categorized as responders vs only 53% of responders among those with only two doses (p=0.002). However, 20% of patients did not respond after a third those [29]. After third dose, patients had higher anti spike antibody titers than those without the third dose (p< 0.001). In addition, 62% of kidney transplant patients that did not respond after two doses, seroconverted after third those. Thus, a third antigenic event seems relevant in this population although still a meaningful size keeps not well protected, not responding to vaccine [29].

Similar results were reported by Kamar et al. after studying, retrospectively, 101 SOT patients (78 kidney, 12 liver, 8 lung-heart, 3 pancreas). There were 40% of SOT patients with detectable anti SARS-CoV-2 IgG before the third dose. After the third those, this percentage increased up to 68%. Among patients that remained seronegative after second dose (n=59), 44% seroconverted 4 weeks after third dose [30].

In a prospective study in Denmark, SOT patients (kidney 73.2%, liver 16.2%, heart 4.7%, lung 3.7%) were included for study of humoral response after BNT162b2 vaccination. 395 and 335 patients were studied after second and third dose respectively. SARS-CoV-2 spike IgG antibodies were detected in 49.4% of patients after two doses and 77.9% after the third dose. The rate of seroconversion was 47.5% after the third dose for those who remained seronegative after second dose (n=200). In terms of quantification, an overall increased in antibody titer was observed after third dose (overall mean increase 831.0 BAU/mL). Factors associated with poor response were increased age, shorter time since transplantation and treatment with prednisolone and proliferation inhibitors [31].

In a further publication, the SENCOVAC study group, analyzed the impact of a fourth dose of vaccine, 12 months after primary vaccination. They included 396 kidney transplant patients (278 with three doses and 118 with four doses). The fourth dose increased the antibody titers in patients with hemodialysis and non-dialyzed patients with chronic kidney disease, but not in kidney transplant patients. Additionally, being a kidney transplant patient was shown to be an independent predictor factor of negative humoral response at 12 months (OR 7.8; p<0.001) [32].

Steroids and mycophenolate mofetil were found to be associated with lower anti-Spike antibody titers (p=0.030 and p=0.004, respectively) [32].

Take home message

- **SOT recipients develop poor response to two doses of COVID-19 mRNA vaccines, with a lower seroconversion rate as compared to healthy population.**
- **Older age, burden of immunosuppressive regimen, maintenance with mycophenolic acid and corticosteroids, less than 1 year after transplantation, and impaired renal function are risk factors for humoral non-response.**
- **Kidney transplant patients increased antibody titers and seroconversion after third dose. However, 20 % of patients did not respond at all and those that did respond had lower antibody titers than other populations.**
- **Fourth dose of vaccine does not seem to meaningful improve the response in kidney transplant patients.**
- **Given the suboptimal immune response to two doses of vaccine, vaccination by at least three doses would be desirable.**

3. OUTCOMES IN VACCINATED SOT RECIPIENTS

The evidence of whether effective anti-SARS-CoV-2 vaccines may significantly reduce the risk of morbidity and mortality-associated with COVID-19 in SOT recipients is unclear [33]. Relevant studies assessed in this block included a retrospective registry-based analysis [34], a cohort study [35], a retrospective multicenter study [36], an observational data linkage cohort analysis [37], and a population-based cohort study [38].

A study that linked four national registries in the United Kingdom was conducted to identify outcomes within 28 days of a laboratory confirmed SARS-CoV-2 infection in unvaccinated SOT recipients and those who had received 2 doses of Pfizer-BioNTech BNT162b2 or Oxford-AstraZeneca ChAdOx1-S vaccine [34]. Vaccination was not associated with reduction

of the risk of testing positive (incidence risk ratio [IRR] 1.29, 95% CI 1.03-1.61), the incidence rate of SARS-CoV-2 infection was 34.4 and 39.2 per 100,000 person-days for unvaccinated and vaccinated SOT recipients respectively. However, vaccinated patients showed a higher chance of survival at 28 days as compared with unvaccinated patients (91.8% vs. 88.8%, $p = 0.002$); after risk adjustment (for type of organ received, time since transplant, sex, age, ethnicity, NHS region, calendar month and, in some analyses, vaccine type), vaccinated patients showed a 20% reduction in the risk of death (HR 0.80, 95% CI 0.63-1.00, $p = 0.05$). Older age, Black ethnicity, lung transplantation, and care location were associated with a higher risk of death.

A cohort study of 449 SOT patients vaccinated with one of the two approved mRNA vaccines at the moment of study (BNT162b2 and mRNA-1273), observed severe course of COVID-19 was common in a small number of SOT recipients (n=15) who tested positive for COVID-19 even after their full vaccination (two doses of mRNA vaccine at the moment of the study) [35]. Fifteen patients (3.3%) tested positive using SARS-CoV-2 PCR, with negative antibody titers in 9 (60%) of them. Seven patients had mild COVID-19, but the remaining 8 (53.3%) required hospitalization, 7 of which had severe disease and 2 of them died. These findings were confirmed in a review of 18,215 fully vaccinated SOT recipients at 17 transplant centers [36], in which there were 151 breakthrough infections (0.83%) defined per Centers of Disease Control and Prevention criteria ≥ 14 days after completing all recommended vaccine doses. Of these 151 cases of breakthrough infections, 87 (57.6%) required hospitalization and 14 patients died, with a mortality rate of 9.3%. Compared with the general population of 101 million fully vaccinated adults in the United States through April 30, 2021, SOT recipients in this study had 82-fold higher risk of breakthrough SARS-CoV-2 infection and 485-fold higher risks of breakthrough infection with associated hospitalization and death.

In kidney transplant recipients, an observational cohort study linking national datasets in Scotland reported that as of September 19, 2021, 5,281 had received two doses of approved SARS-CoV-2 vaccine [37]. There were 814 (15.4%) cases of SARS-CoV-2 infection. Vaccine effectiveness rates were 39% (95% CI 2-58) against infection and 40% (95% CI 0-59) against hospitalization. Within 28 days of a SARS-CoV-2 positive PCR test, the mortality rate among kidney transplant recipients was 10% (compares to < 0.1% of the vaccinated general Scottish population admitted to the hospital or dying due to COVID-19 during the same period). In the multivariate analysis, predictors of breakthrough infection following two doses of SARS-CoV-2 vaccine were kidney transplant (vs. dialysis) and socioeconomic deprivation.

Naylor et al. conducted a population-based cohort study, including 12,842 SOT patients in Canada (kidney, liver, lung, heart and pancreas). Patients were included as for December 2020 and were followed-up until November 2021, as the vaccine program were developed in this population. 54.1% received three doses, with 12.7% who remain unvaccinated. Vaccine effectiveness against severe outcomes (hospitalization or mortality) was shown, again, to be lower in this population vs general population, for both two (54%) and three (67%) doses. However, it was notably improved with the third administration [38].

Take home message

- **The level of protection provided by vaccination from symptomatic SARS-CoV-2 disease in SOT recipients is lower than in the general population.**
- **A primary vaccine course of two doses appears to have a limited effect on COVID-19 and its complications, including hospitalization and fatal outcome.**
- **A third dose notably improves vaccine effectiveness in SOT patients.**
- **Alternative immunization schemes (booster dose, higher doses) and modulation of immunosuppression during vaccination need to be more extensively assessed in SOT recipients.**

4. EFFECT OF TREATMENT WITH MONOCLONAL ANTIBODIES ON THE COURSE OF COVID-19 IN SOT RECIPIENTS

SOT recipients are candidates for the use of anti-spike SARS-CoV-2 monoclonal antibodies (mAbs) for early treatment or prevention of COVID-19 because of special characteristics of this population, particularly chronic use of immunosuppression treatment, multiple underlying medical comorbidities, suboptimal immunogenic response to complete vaccination scheme, and, occasionally, the age of the transplant patient. For all these main reasons, SOT recipients are at higher risk of developing severe COVID-19 with the potential need of care in the hospital including ICU admission, and ultimately to die from the disease. Neutralizing antibodies targeting the spike protein of SARS-CoV-2, such as bamlanivimab-etesevimab, casirivimab-imdevimab, tixagevimab-cilgavimab or sotrovimab have been approved for the treatment of mild-to-moderate COVID-19 in non-hospitalized patients with laboratory-confirmed SARS-CoV-2 infection, who are at high risk of progression or severe disease and/or hospitalization. It is recommended that treatment should be started as soon as possible after a positive test and within 10 days of symptom onset. Also, some mAbs can be used for post-exposure prophylaxis (PEP) (casirivimab-imdevimab) or pre-exposure prophylaxis (PreP) (casirivimab-imdevimab and tixagevimab-cilgavimab).

A number of clinical reviews of the general implications of mAbs against SARS-CoV-2 have been recently published (figure 2) [47-58]. In the particular group of SOT recipients, the use of mAbs, recommended in the outpatient management of mild-moderate COVID-19, has been associated with a lower risk of hospitalizations, emergency department (ED) visits, need for ICU care, mechanical ventilation, and fatal outcomes. Similar benefits have been reported for PEP, treatment of SOT patients with recurrent episodes of COVID-19 and possible

vaccine-breakthrough infection [46]. Studies of mAbs in SOT recipients collected from the literature were divided according to the type of mAbs used: bamlanivimab and casirivimab-imdevimab [47-51], patients were include from March 2020 to September 2021, when the prevalent VOCs and VOIs were those before Omicron (mainly Alpha, Beta Gamma, Epsilon and Delta), and sotrovimab, including patients from September 2021 to August 2022, when the prevalent VOCs were Delta and Omicron BA.1 and BA.2 [52-58]. Most data referred to retrospective case series reports of relatively small study populations.

4.1. Bamlanivimab and casirivimab-imdevimab

Several studies have evaluated bamlanivimab and casirivimab-imdevimab as emergency use in SOT recipients. In a retrospective review from the Mayo Clinic of 73 SOT patients treated with mAbs, between November 2020 and January 2021, most commonly with bamlanivimab monotherapy (75.3%) and completing the full 28-day follow-up period, the rates of ED consultation and hospitalization were 15.1% (63.6% for respiratory symptoms) and 12.3%, respectively [47]. There was one ICU admission not related to COVID-19, no deaths, or advanced respiratory support, and minimal adverse events were reported. Notably, in patients who were hospitalized, mAb administration was later than in those who did not require hospitalization (median 6 days from symptom onset vs 4 days, p=0.03), reinforcing the importance of early intervention with these treatments. The same group of authors also reported data of 28 SOT recipients who presented mild-to-moderate COVID-19 after full vaccination (defined as two doses of mRNA vaccine; except one patient who underwent vaccination with Johnson & Johnson and 4 patients who received a third dose), all patients received casirivimab-imdevimab, with a median time of infusion of 3 days after symptoms onset. ED visits were reported by 4 patients (14.3%) and only 1 patient (3.6%) required hospital admission. No ICU admission or deaths were reported [48].

These results are similar to those obtained in another single-center retrospective analysis of 165 SOT recipients with no records of covid vaccination, 93 of which received mAbs (76.3% bamlanivimab and 22% casirivimab-imdevimab) and 72 did not (comparator cohort) [49]. The 30-day hospitalization rate was 8.7% in the study cohort vs. 15.3% in the comparator cohort, but differences after adjusting for age did not reach statistical significance (OR 0.49, 95% CI 0.18-1.32, $p = 0.16$). None of the patients that received casirivimab-imdevimab were hospitalized but all patients hospitalized in the mAbs group had received bamlanivimab monotherapy. Two episodes of biopsy-proven acute rejection were observed in the mAbs group, but it was unknown whether they could be attributed to mAbs therapy, COVID-19, or immunosuppression adjustments. There were 2 deaths in the comparator cohort and none in the mAbs-treated cohort.

In a single center retrospective review of abdominal transplant patients between February 2020 and February 2021, anti-SARS-CoV-2 mAbs therapy (33/34 received bamlanivimab) was provided to 17 kidney transplant recipients and 17 liver transplant recipients. Only 5 patients required hospitalization, none required ICU admission, and all 34 patients survived [50]. In a comparison of outcomes of abdominal transplant recipients who would have been qualified for mAbs therapy but did not receive the treatment, mAbs reduced the rates of hospitalization from 32% to 15% ($p = 0.045$) and death from 13% to 0% ($p < 0.04$). There were no major adverse reactions [50].

In a single-center analysis of 95 kidney transplant recipients diagnosed with COVID-19 from March 2020 to April 2021, 20 (21%) of which were treated with mAbs (15 bamlanivimab, 1 bamlanivimab-etesevimab, 3 casirivimab-imdevimab and 1 mAb treatment not known). The primary endpoints were hospitalization or ED visits [51]. Antiviral treatment with mAbs was associated with a marked decrease in hospitalization or ED visits (15% vs. 76%, $p < 0.001$; HR 0.216, $p = 0.04$ after adjustment for potential confounders and time-dependent symptom variable). In the multivariate analysis, age, chronic kidney disease, and Hispanic ethnicity were independent factors for hospitalization or ED visits. There were no deaths in the 20 patients treated with mAb whereas there were 8 (10.7%) in the 75 not treated with mAbs.

4.2 Sotrovimab

Several groups have reported their experiences regarding the use of sotrovimab in SOT recipients. In a report of 51 SOT patients who received sotrovimab (during both the Delta- and Omicron-predominant periods), 1 patient experienced progression of COVID-19 symptoms and required 5-days hospitalization. None of the patients required ICU care or died [52]. In this study, patients received sotrovimab on an average of 3.5 days after the onset of symptoms and 2 days after laboratory confirmation of SARS-CoV-2 positivity. 35% of patients in this study were vaccinated with 3 doses, and 45% had an incomplete vaccination regimen (less than 3 doses) with the remained 10% unvaccinated. In another single-center study [53] based on 15 SOT recipients diagnosed with SARS-CoV-2 infection between December 2021 and January 2022 and with a mild to moderate disease, 13 (86.7%) of which had received two or three doses of mRNA COVID-19 vaccines, 2 patients (13.3%) required hospitalization because of rapidly progressive respiratory distress symptoms requiring oxygen therapy. There were no deaths. Sotrovimab infusion was well-tolerated with no reported adverse events. In another single-center prospective cohort study of 300 SOT patients infected with SARS-CoV-2 (51 treated with sotrovimab, of which 80% were vaccinated), it was observed that vaccination ≥3 doses and treatment with sotrovimab are independently protective factors in the progression to severe COVID-19 disease. Regarding sotrovimab treatment, the number needed to treat (NNT) to prevent a patient from requiring supplemental oxygen was 6.64 (95% CI, 4.56 to 13.66), and to prevent one hospitalization was 8.5 (95% CI, 4.83 to 59.1). Once again, there were no deaths in the group of patients treated with sotrovimab [54].

In kidney transplant recipients, a comparison of the clinical outcome of 25 patients with mild-to-moderate Omicron

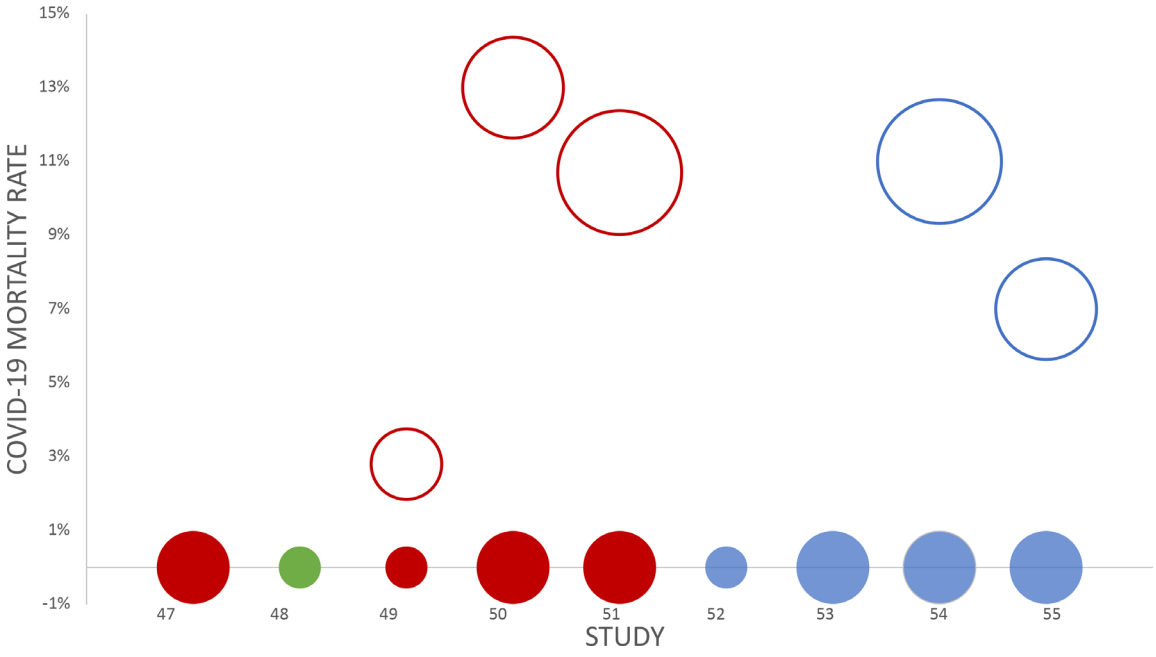

Figure 2 | **COVID-19 progression rates in each study based on treatment or not with mAb**

Colors indicate mAb used for treatment, red: bamlanivimab or casirivimab+imdevimab; green: casirivimab + imdevimab; blue: sotrovimab. Solid fill: mAb treatment (treated group); not solid fill: not mAb treatment (control group). Circles size: hospitalization rate, bigger the circle, higher hospitalization rate:

The numbers of the studies correspond to the reference included in the bibliography section. The patients included in the different studies present different vaccination status. In addition, the outcomes were collected at different dates from the treatment administration, the majority at one-month post-treatment, however, in some studies it is not specified. Three of the publications included in the sotrovimab treatment block have not been included in this graph, one of them is Villanego F, et al. Clin Kidney J. 2022;15(10):1847-55 [56], which at the beginning of the study, 81.7% of the patients were hospitalized, so progression is measured as COVID-19 mortality, being 8.5%. Furthermore, 42% had an oxygen saturation < 95% at admission, and 43,9% of patients were administered >5 days from symptom onset, representing a more severe population and suboptimal administration. Differences were observed between patients treated ≤5 days from the onset of symptoms and those treated >5 days (2.2% vs 16.7%; p=0.020 mortality). The second one, Vathsala A, et al. Transpl Infect Dis. 2022:e13930 [57], where hospitalization is not determined; COVID-19 progression is determined by the need for supplemental oxygen (21.6%; <4 days 14.3% vs ≥4 days 55.6%; p=0.015) and mortality (9.8%). The third publication not included is Negin Farhadian, et al. Immunopharmacol Immunotoxicol. 2022;1-7 [58], since it is a meta-analysis where several publications are included, indicating that sotrovimab treatment reduces the risk of hospitalization (OR 0.29, p<0.001), ICU admission (OR 0.17, p = 0.009) and death (OR 0.15, p=0.010) compared to the control group without mAb treatment.

COVID-19 who received sotrovimab with 100 patients who did not receive sotrovimab showed a reduced rate of hospitalization (4 patients, 16% vs. 35 patients, 35%) and ICU admission (1 patients, 4% vs. 17 patients, 17%), and no patient died as compared to 11% in non-sotrovimab-treated patients. The Kaplan-Meier analysis showed significant differences in mortality (p = 0.044) and severity (measured as mortality and/or ICU admission) of Omicron COVID-19 disease (p = 0.045) between kidney transplant recipients treated or not treated with sotrovimab [55]. Notably, median time from symptoms onset and sotrovimab administration were 5 days, however the 1 patient who suffered COVID-19 progression was administered after 11 days. Overall, 92% of patients had received at least one dose of mRNA vaccine, with 76% and 86% vaccinated with three or four doses in the sotrovimab and control group respectively.

In a Spanish multicenter retrospective cohort study [56], a total of 82 kidney transplant recipients with SARS-CoV-2 Omicron BA.1 infection were treated with sotrovimab, of which was administered early (≤ 5 days from the onset of symptoms) in 46 patients (56.1%). Overall, more than 86.8% of patients had received three doses of vaccine before their COVID-19 diagnosis and 42.6% had an oxygen saturation < 95% at admission. Early treatment was associated with a reduced risk of progression to severe disease with need of mechanical ventilation (2.2% vs. 36.1%, p < 0.001), ICU admission (2.2% vs. 25%,

p = 0.002), and mortality due to COVID-19 (2.2% vs. 16.7%, p = 0.02). In the multivariate analysis, early use of sotrovimab was the only protective risk factor (OR 0.026) for a composite outcome defined as the need for ventilatory support or ICU care or COVID-19-related mortality. There was a good safety profile, even in patients with multiple comorbidities or advanced chronic kidney disease stage.

In another retrospective study of 51 SARS-CoV-2-infected (49% Delta and 51% Omicron BA.1 variants) kidney transplant recipients treated with sotrovimab, 11 (21.6%) progressed to severe COVID-19 disease and 5 (9.8%) patients died. Those who had earlier administration of sotrovimab were less likely to have more severe disease (14.3% of patients administered sotrovimab at < 4 days after symptom onset needed supplemental oxygen therapy vs. 55.6% among those treated at ≥ 4 days [p = 0.015]) [57].

Finally, in a meta-analysis of 6 cohort studies which reports the clinical outcomes of SOT patients treated with sotrovimab vs a control group between January 2021 and August 2022, it was shown that treated patients had a lower frequency of COVID-19 disease progression (Figure 2). Sotrovimab treatment was shown to reduce the risk of hospitalization (OR 0.29, p < 0.001), ICU admission (OR 0.17, p = 0.009) and death (OR 0.15, p = 0.010) compared to the control group without mAb treatment [58].

Take home message:

- **Treatment with the anti-spike available mAbs formulations provides favorable outcomes in SOT recipients at high risk for severe COVID-19 disease.**
- **SOT recipients with SARS-CoV-2 infection treated with mAbs as compared with untreated comparator groups had lower rates of hospitalization, ICU admissions, progression to severe disease, and death.**
- **Early administration (≤ 4-5 days of symptom onset) seems to improve benefits of mAbs treatment.**
- **Treatment with mAbs is safe with a few adverse events generally mild, and no effect on graft losses or rejection.**

CONCLUDING REMARKS

The available evidence based on relevant studies published in the literature reinforces the importance of an early diagnosis of COVID-19 in SOT recipients and completion of a fully anti-SARS-CoV-2 vaccination schedule. Despite a lower rate of humoral and cellular immune response, compared to general population. All studies reviewed, find that repeated doses of vaccination increase the humoral response up to 70 - 80% of transplant patients with detectable antibodies after 3 doses. The third dose seems to be key for this population, with remarkable rates of seroconversion after its administration. However, despite vaccination, a considerable percentage of this group remains at high risk and should be treated soon after COVID-19 diagnosis. Among current available therapeutic options, mAbs have been shown to be both effective and safe in this population. Treatment of COVID-19 with mAbs in SOT recipients, in particular early treatment after diagnosis, is associated with a reduced likelihood of progression to severe COVID-19. Reduction of the risk of severe disease entails decreases in hospitalization, ICU care, ventilatory support, ED visits, mortality, and, very especially to take into account in this immunosuppressed population, the reduction or avoidance of the risk of opportunistic infections by multiresistant hospital bacteria and by fungi that cause invasive fungal infection (CAPA, CAM) with high intrinsic mortality promoted by SARS-CoV-2.

Although neutralizing capacity of some mAbs have been reported to be reduced against new circulating variants, it is not known, how in vitro neutralization data correlates with clinical efficacy. This is specially noting in the case of sotrovimab, a mAb that has a double mechanism of action, not only neutralizing but also with effector function that is mediated by the Fc region of the mAb [59]. This effector function has been shown, in animal models, to be an additional protection mechanism beyond virus neutralization, being critical for the maintenance of its activity against SARS-CoV-2 variants that reduced its neutralizing activity such us BA.2 [60-66]. Several recent studies in real practice, have shown the same effectiveness data of the antibody against Omicron BA.2 vs BA.1, being BA.1 a variant against which sotrovimab neutralization capacity is not impacted [60, 61]. In addition, some preprints have been published showing maintained clinical efficacy for BA.5 also [62]. Same kind of not peer reviewed works, have reported that effector function is maintained for other variants with higher fold changes such us BQ.1.1 [63], and that sotrovimab is able to reduce viral load in animal models for this variant [63,64]. Although more evidence and continuous surveillance is needed, to monitor a potential impact in the effectiveness of these therapeutic mAbs, they are an important therapeutic option, especially in SOT patients, who can be excluded from other therapeutic options because of interactions with concomitant medications.

Findings of the present review are timely and informative to the transplant community. The ability to draw firm conclusions is limited by the retrospective nature of data collection, the absence of a control group and the limited number of participants in most studies. It is difficult to use this data to estimate comparative effectiveness of mAbs therapies in SOT recipients exposed to or infected with SARS-CoV-2 and at high risk of developing severe COVID-19, however the weight of evidence is in favor of a benefit of mAb treatment. It is necessary to continue to explore the best approach in preventing severe COVID-19 in this vulnerable SOT patient population in the context of limited immunogenicity of vaccines and possible surge of COVID-19 infections.

Successful utilization of anti-SARS-CoV-2 mAbs requires a multidisciplinary team approach, close monitoring for efficacy and tolerability, and awareness of circulating variants.

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CONFLICTS OF INTEREST

F.J. Candel has presented conferences in meetings sponsored by GSK, MSD, Pfizer, Correvio, Astellas, Gilead, Meiji and Shionogi; M. Salavert has presented conferences in meetings sponsored by Angelini, Gilead, GSK, MSD, Menarini, Pfizer, Tedec-Meiji and Shionogi; D. Lorite Mingot, M. Manzano Crespo, P. Pérez Portero and R. Cuervo Pinto are employees of GSK, and hold shares in the company.

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