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Respiratory infection. Approach to SARS-CoV-2 infection in transplant patients

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Clinical experience in the treatment of COVID-19 with monoclonal antibodies in solid organ transplant recipients

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ABSTRACT

Solid organ transplant (SOT) recipients are at high risk for complications from coronavirus disease 2019 (COVID-19). SOT recipients mount lower immunological responses to vaccines than general population and are at high risk for breakthrough COVID-19 infections. Passive immunotherapy in the form of anti-Spike monoclonal antibodies (MoAbs) may be an alternative for the prophylaxis and treatment of COVID-19 in these patients. SARS-CoV-2 has evolved by accumulating resistance mutations that have escaped the neutralizing action of most MoAbs. However, MoAbs directed at more conserved epitopes and that maintain effector functions could maintain efficacy in the treatment of these patients. According to published data, SOT recipients with low anti-spike antibody responses to vaccination could benefit from the use of MoAbs in pre-exposure prophylaxis, in the treatment of COVID-19 mild to moderate and severe COVID-19 with less than 15 days of symptom duration and low oxygen requirements. Combination therapy could be more effective than monotherapy for the treatment of mild-to-moderate SARS-CoV-2 infection.

Keywords: COVID-19, SARS-CoV2, Solid Organ Transplant recipients, Monoclonal Antibody.

BACKGROUND

Solid organ transplant (SOT) recipients are at high risk for complications from coronavirus disease 2019 (COVID-19) [1]. Several studies performed early in the pandemic suggest high rates of hospitalization, intensive care unit (ICU) admission, and mortality. Lung transplant recipients appear to have the greatest severity [2]. Over the time, the prognosis of these patients has improved, mainly due to prevention measures, the development of new antivirals and vaccination. Although after each new dose of vaccine, the proportion of recipients with antibody and celular responses rises, SOT recipients mount lower immunological responses to vaccines than general population and are at high risk for breakthrough COVID-19 infections [3-5]. In this setting, passive immunotherapy in the form of anti-Spike monoclonal antibodies (MoAbs) may be an alternative for the prophylaxis and treatment of COVID-19 in these patients.

EVOLUTION OF VARIANTS AND SUSCEPTIBILITY TO MoAbs

MoAbs are specific immunoglobulins produced in the laboratory by purifying the circulating B lymphocytes from convalescents from a SARS-CoV-2 infection and cloning the antibodies from the cells with specificity against the epitope selected as a therapeutic target. Subsequently, the MoAbs obtained undergo a selection process to identify those with the greatest affinity and neutralizing capacity.

From previous experience with other coronaviruses that cause severe acute respiratory syndrome (MERS and SARS), the Spike protein(S) was selected as the main target of these MoAbs, and in this way block cellular infection. Most of the neutralizing response after infection is concentrated within this Spike protein, specifically in the receptor binding domain (RBD), and within this receptor in the region that physically contacts the cellular receptor ACE2, called Receptor Binding Motif (RBM). The SARS-CoV-2 virus is constantly evolving, evading the host's immune response. In the different circulating variants of the virus, resistance mutations have mainly been selected in the RBM regions, which has led to a decrease in the neutralizing capacity of the different MoAbs with specificity against that binding site.

Among the MoAbs that have been available in our setting, casirivimab/imdevimab, tixagevimab/cilgavimab, or regdanvimab with specificity against RBM regions have lost their

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neutralizing capacity against the new variants. Sotrovimab is a MoAbs developed from serum from a SARS-CoV-1 infected survivor that shares a highly conserved epitope also on the Spike protein of SARS-CoV-2. This MoAbs blocked the ACE2 binding site outside of RBM which accumulated fewer escape mutations so it maintains effectiveness, although decreased, against the new omicron subvariants. Therefore, it is necessary to consult the sensitivity of the MoAbs to the predominant circulating variants at all times in order to indicate their use.

Although the main function sought in these mAbs is the ability to neutralize infection, there is increasing information indicating that the effector functions of antibodies could play an important role in protection against the most severe forms of COVID-19. This protection would be related to the functions of cytotoxicity, phagocytosis and stimulation of the cellular response mediated by antibodies. All of these effector responses reside fundamentally in the interaction of the crystallizable fragment (Fc) of immunoglobulins with the entire family of anti-Fc receptors present in different populations of immune cells [6]. Sotrovimab contains a 2 amino acid Fc-modification that is designed to improve bioavailability in the respiratory mucosa and preserve effector functions. Recent studies in vitro and in mice showed that sotrovimab binds avidly to all Omicron variants, promotes Fc dependent effector functions and protects mice challenged with BQ.1.1, the variant displaying the greatest loss of neutralization. Therefore, MoAbs with conserved Fc-dependent effector functions may contribute to protection against disease caused by emerging variants through elicitation of effector functions [7].

PRE-EXPOSURE PROPHYLAXIS

Some MoAbs have demonstrated effectiveness in pre-exposure prophylaxis in high-risk populations, although these clinical trials include a very small number of immunocompromised patients and SOT recipients are not represented [8,9]. A multicenter retrospective cohort study evaluated the efficacy of tixagevimab/cilgavimab in vaccinated SOT recipients in a real-world setting during the Omicron period. The study compared 222 solid organ transplant recipients (SOTRs) who received tixagevimab/cilgavimab for pre-exposure prophylaxis and 222 vaccine-matched solid organ transplant recipients who did not receive tixagevimab/cilgavimab. More than 50% of the patients in both groups had kidney transplants, but lung, liver and heart recipients, and multi-organ transplant recipients were also included. Breakthrough SARS-CoV-2 infections occurred in 11 (5%) of SOT who received tixagevimab/cilgavimab and in 32 (14%) of SOT in the control group ($p<.001$). Stratified analysis by organ type showed a significantly lower incidence of SARS-CoV-2 infection in kidney and lung transplant recipients who received tixagevimab/cilgavimab compared to those who did not, the number of patients included with transplants of other organs was very small, so no statistically significant differences were found. The efficacy of a dose of 150-150 mg of tixagevimab/cilgavimab was also compared to 300-300 mg and it was observed that the incidence rate of breakthrough SARS-CoV-2 infection was higher in those who received the lower dose. No significant differences were found in the incidence of breakthrough infection between the tixagevimab/cilgavimab and control groups in the subgroup of SOTRs who had prior SARS-CoV-2 infection [10]. An observational study in kidney transplant recipients at a single center showed no significant difference in the risk of symptomatic breakthrough Omicron infection between those who received tixagevimab/cilgavimab compared to those who had high-titer anti-spike antibody responses to vaccination but did not receive tixagevimab/cilgavimab [11]. According to these results, the recipients who would benefit most from the use of MoAbs in pre-exposure prophylaxis are those with low anti-spike antibody responses to vaccination.

MILD TO MODERATE COVID-19

MoAbs have reduced hospitalisation or death in outpatients with mild to moderate COVID-19 in high-risk patients, including immunocompromised patients [12,13].

We do not have randomized clinical trials in patients with SOT, but several observational studies and case series have been published. Dhand et al reported their experience regarding the use of sotrovimab in 51 SOT recipients (most of them during the Omicron-predominant period) with at least 21 d of follow-up. These include 28 kidney, 11 liver, 9 heart, 2 liver/kidney, and 1 heart/kidney recipients. Only one patient experienced progression of COVID-19 symptoms requiring 5-d hospitalization and steroid therapy. Five patients required hospitalization unrelated to COVID-19 diagnosis. None of the patients required intensive care or died [14].

In another report of 88 patients who received one intravenous dose of 500 mg of sotrovimab (35 kidney, 18 lung, 17 heart, 15 liver, and 3 dual-organ recipients), ten percent (9/88) required hospitalization for COVID-19 after sotrovimab, including 1 admitted on the same day as infusion and 1 for a cerebrovascular accident 2 w after infusion. Of these 9 patients hospitalized after sotrovimab, 8 did not require supplemental oxygen and 1 required 2 L/min of oxygen via nasal cannula. No episodes of graft rejection or graft loss were observed, and no patients in this cohort required mechanical ventilation or died [15].

Probably the largest series corresponds to the retrospective cohort study by Yetmar et al, which included 361 SOT recipients, 92 (25.5%) receiving bebtelovimab and 269 (74.5%) receiving sotrovimab. The most common transplanted organ was the kidney (42.4%), 21,9% liver, 17,2% heart, 5,8% lung and 44 (12.2%) had received multiple transplanted organs. 3,3% of patients who received bebtelovimab and 3% of patients who received sotrovimab required hospitalization for COVID-19, including three (0.8%) who were admitted to the ICU (all of them received sotrovimab). Four patients died within 30 days of COVID-19 diagnosis; one was unvaccinated, one was fully vaccinated without a booster dose, and two were fully vaccinated with a booster. Two had received bebtelovimab and

the other two had received sotrovimab. The causes of death were an acute respiratory failure from progressiveCOVID-19, subarachnoid hemorrhage, and two were from unknown causes. The patient who died from progressive COVID-19 was fully vaccinated, boosted, and received bebtelovimab [16].

The main limitation of these studies is that they are observational studies without a control group. Kamar et al compared the outcome of SOT patients who were given monoclonal antibodies to an historical control group. Sixteen SOT patients (12 kidney, 1 simultaneous kidney-pancreas, 1 combined kidney-liver, and 2 heart-transplant patients) that presented after February 25, 2021 were treated with monoclonal antibodies, while the 32 remaining patients that presented before this date were considered as a control group. After a follow-up of 39 (10–74) d after the injection of monoclonal antibodies, none of these 16 patients developed a severe respiratory illness defined by the need for high oxygen support, while 15 of the 32 control patients developed a severe respiratory illness (46.9%, P = 0.007), requiring high flow nasal oxygen (n = 7) or orotracheal intubation (n = 8). Three patients from the control group deceased during follow-up [17].

Although we only have observational and retrospective studies, most of them without a control group, from the results obtained we can conclude that the use of MoAbs in SOT recipients with mild to moderate COVID-19 reduces the rate of progression and death.

SEVERE COVID-19

The use of MoAbs in hospitalized COVID-19 patients is controversial. While RECOVERY adaptative trial showed that MoAbs could reduce 28-day mortality in patients admitted to hospital with COVID-19 who were seronegative (and therefore not able to mount a humoral immune response), TICO platform trial found that MoAb LY-CoV555 did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure [18,19].

Few studies have evaluated the efficacy of treating hospitalized patients with severe COVID-19 (requiring oxygen therapy) with MoAbs in immunosuppressed patients. A spanish multicenter retrospective cohort study included 32 patients, 15 out of them were SOT recipients (9 lung, 4 kidney, 2 heart and 1 liver) aimed to describe the safety and efficacy of sotrovimab in severe COVID-19 immunocompromised hosts between October 2021 and December 2021, in a setting with predominance of mutant-rich variants. Most of them were fully-vaccinated but anti-spike antibodies were undetectable. At sotrovimab infusion, all patients had bilateral interstitial pneumonia with low flow nasal cannula oxygen supplementation. Only one transplant patient had respiratory progression and none died. in the cohort as a whole it is observed that PaFi greater than 210 at infusion was associated with a lower rate of respiratory progression (11.5% (3/26) versus 66.7% (4/6), p=0.005) and those receiving sotrovimab within the first 14 days from symptom onset had a lower progression also (12.0% (n=3/25) vs 57.1% (n=4/7), p=0.029) [20]. Therefore, immunocompromised patients (including SOT recipients) hospitalized for severe COVID-19 with less than 15 days of symptom duration and low oxygen requirements may benefit from MoAb treatment.

COMBINATION THERAPY

Cellular immunity is a key contributor to acute disease control and determinant for the severity of the disease. However, a loss of humoral immunity, even with preserved cellular immunity, is a significant contributor to the risk of impaired SARS-CoV-2 clearance [21]. As we have previously indicated, SOT recipients frequently show a low rate of anti-Spike (anti-S) immunoglobulin G (IgG) seroconversion after full vaccination. This insufficient humoral response leads to a prolonged viral replication, which ultimately causes a more extended and severe COVID-19. In this setting, the use of passive immunization treatments, such as MoAb, in combination with direct-acting antivirals could overcome the humoral deficit and prolonged viral replication in these patients.

Our experience, which is pending publication and which we partially reported in the 2023 ECCMID, includes 304 immunocompromised patients with mild-moderate SARS-CoV2 infection, of which 114 were SOT recipients (69 lung, 20 liver, 16 heart and 12 kidney), 21 received combination therapy with sotrovimab 500 mg single dose plus either a 3-day course of remdesivir or a 5-day course of nirmatrelvir/ritonavir and 93 received monotherapy with remdesivir, nirmatrelvir/ritonavir or sotrovimab. Most of them were fully vaccinated (90,1%) with a median time since last dose of 5 months (3-7 months). During follow-up (90 days) 4 SOT patients (3 lungs and 1 liver) presented COVID-19 progression to severe COVID-19 and 1 lung transplant recipient died, all of them had received monotherapy. All patients who progressed to severe COVID-19 had anti-S IgG titers less than 750 BAU/mL. Therefore, in SOT recipients with low vaccination response combination therapy including sotrovimab plus an antiviral agent may be more effective than monotherapy for the treatment of mild-to-moderate SARS-CoV-2 infection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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