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

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Therapeutic strategy in the transplanted patient

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ABSTRACT

The SARS-CoV-2 infection prognosis has dramatically changed as a result of population vaccination and the surge of omicron. However, there are still specific populations at risk of progression to severe diseases that require hospitalization or even at risk of death. The kidney transplant population is one of them. Consequently, when compatible symptoms appear, an early diagnosis should be sought in order to start specific antiviral treatment as soon as possible to avoid clinical deterioration of the patient. Antivirals have shown, in transplant patients, a decrease in the rate of hospitalization and death, especially with their early administration.

KEYWORDS: kidney transplant, COVID-19, donation

INTRODUCTION

The prognosis of SARS-CoV-2 infection has dramatically changed as a result of population vaccination, the immunity acquired naturally due to the infections suffered and the circulation of the omicron variant, with a lower pathogenic power. However, there are still hundreds of deaths every week in Europe, despite a low circulation of the virus, and the mortality of hospitalized patients for COVID-19 has been described as 7%, doubling the mortality rate of the influenza virus infection [1].

There are several risk stratification scores, both clinical [2-4] and analytical [5], which make it possible to identify patients at risk of progression, to select those who can be discharged adequately, avoiding inappropriate admissions, and safe avoiding patient return visits [6] and improving the quality of care provided in the different COVID-19 patient´s phenotypes described [7,8]. An outpatient care model with a high-resolution consultation after emergency discharge is effective for patients with COVID-19 without respiratory failure with clinical or analytical markers of unfavourable evolution [9].

At this time, most of the population suffers a mild viral infection, but there are specific groups that present a risk of poor evolution and may require hospital admission or even death. The vulnerable population is well identified: 1) elderly patients; 2) patients with comorbidity, especially when several accumulate; and 3) immunocompromised patients [10]. Although, due to the volume of patients, most complications are observed in elderly patients [11,12], immunosuppressed patients, including kidney transplant recipients, represent a population at high risk of progression to severe disease.

RISK OF PROGRESSION IN THE TRANSPLANTED PATIENT

Transplant patients are especially vulnerable to presenting poor clinical results due to their state of immunosuppression. This risk is particularly high among those who received immunosuppress treatment, those with a history of a neurological condition, and those with chronic kidney disease [10].

Coll E et al. showed that the incidence of SARS-CoV-2 infection in Spanish solid organ transplant and hematopoietic stem cell transplant patients was twice that than the one of the general population, with a median interval from transplant of 59-month, and the patients at highest risk were those with a lung transplant [13]. The mortality of the patients in this study was high, standing out 46% in lung transplant recipients, 28% in kidney transplant recipients, and 22% in liver and heart transplant recipients. However, the population included in the study is prior to the availability of vaccines and effective antiviral treatments.

Finally, it is important to remember that the duration of the immune response in transplant patients after the third

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dose of the vaccine decreases significantly, so booster doses are required [14].

ANTIVIRAL TREATMENT EFFICACY

We currently have 2 antiviral treatments that have shown high efficacy in preventing the appearance of complications in SARS-CoV-2 patients infected when administered in the initial stages: nirmatrelvir/ritonavir and remdesivir. The latter has also shown its effectiveness in preventing mortality in severe patients who require hospital admission.

Considering patients with mild or moderate disease, administration of nirmatrelvir/ritonavir within the first 5 days of symptoms has shown a lower hospitalization rate among the general population who received it compared to those who did not, with a reduced risk of 51%. This beneficial effect has been observed even in those patients who had received ≥3 mRNA vaccines against COVID-19, observing a 50% risk reduction, and for all age groups depending on the comorbidity they presented [15]. Schwartz et al reported the results of an analysis of real-life data showing a 51% reduction in mortality in patients treated with nirmatrelvir/ritonavir [16].

Antiviral treatments have also shown efficacy in the solid organ transplant population with mild or moderate disease, with a reduction in the rate of hospitalization or death at 30-day follow-up from 30% to 10% in treated patients compared to those who did not receive specific treatment [17-19].

Limited data and guidelines exist for the use of nirmatrelvir/ritonavir in tacrolimus-stabilized solid organ transplant recipients for the treatment of mild to moderate coronavirus disease. This is due to concerns about the effect of using it concomitantly with calcineurin inhibitors, due to significant drug-drug interactions between ritonavir, a strong cytochrome P4503A inhibitor, and other cytochrome P4503A substrates, such as tacrolimus. Dewey KW et al reported their experience with patients discontinuing tacrolimus and starting nirmatrelvir/ritonavir 10 to 14 hours after the last dose of tacrolimus. Tacrolimus was discontinued and then restarted at a modified dose 48 hours after completion of nirmatrelvir/ritonavir therapy. No patient experienced tacrolimus toxicity or acute rejection within 30 days of cessation of nirmatrelvir/ritonavir treatment. The authors conclude that nirmatrelvir/ritonavir can be used safely with close monitoring of tacrolimus levels and appropriate dose adjustments [20].

The advantage of using remdesivir in this population profile, such as kidney transplant recipients, is the absence of significant drug interactions and the possibility of using it in patients with renal failure. There are several studies showing the efficacy of a 3-day course of remdesivir, administered within 7 days of symptom onset, in preventing severe disease in patients with COVID-19 who received a solid organ transplant. Receiving remdesivir significantly reduces the hospitalization rate in outpatients who received it and in preventing clinical worsening in transplant patients who were hospitalized for reasons other than COVID-19 [21]. A study that included kidney, lung, liver, and heart transplant recipients, who were mostly vaccinated against COVID with ≥3 doses, showed that early administration of remdesivir significantly decreased the hospitalization rate, with the number of patients needed to treat to prevent a hospitalization of 15, and no patients who received early remdesivir requiring ICU admission or died. Therefore, it could be concluded that the early administration of 3 doses of remdesivir independently reduced the severity of the disease [22]. Finally, it should be noted that the studies recently carried out with remdesivir have led to the authorizing of its administration in patients with renal failure, given that the studies carried out have shown its safety in participants with severely reduced renal function [23].

Regarding patients with severe disease requiring hospitalization, studies have shown the benefit of remdesivir administration to prevent disease progression and the need for mechanical ventilation, as well as reducing mortality [24]. The sooner antiviral treatment is started, the greater the protective effect we can expect, but we must not forget that immunosuppressed patients can present viral replication even weeks after the onset of symptoms. A recent retrospective routine clinical practice study of hospitalized immunocompromised adults with COVID-19 in the US showed that initiation of remdesivir within the first two days of hospital admission was associated with significant reductions in mortality at 14 and 28 days, regardless of the circulating variant and the clinical situation of the patient [25].

DONATION FROM PATIENTS WITH COVID-19

The decision to transplant organs from donors with SARS-CoV-2 infection must be considered seeking a balance between the risk of disease transmission to the recipient and the scarcity of available organs. However, it seems safe in the short term in terms of death and graft loss [26]. A preliminary Spanish experience supports the safety of the use of organs other than the lungs from SARS-CoV-2 PCR positive donors, in line with other previous series, establishing that if the cause of death was not COVID-19, the donation could be considered [27]. A recent systematic review showed that the use of organs, except the lung, from donors with SARS-CoV-2 infection appears to be a safe practice, with a low risk of transmission, regardless of the presence of symptoms at the time of collection. Low viral replication (Ct > 30) was safe among non-lung donors, even if they had persistent symptoms at the time of collection [28].

CONCLUSION

Kidney transplant patients are at increased risk of SARS-CoV-2 infection and poor clinical outcome. Early diagnosis of this infection should be sought in order to start specific antiviral treatment as soon as possible. In patients with mild or moderate disease, antiviral treatment administered in the initial phases of the disease has been shown to protect them from progression, avoiding hospitalization and death. In pa-

tients with severe disease, administration of remdesivir decreases the risk that patients will die or require mechanical ventilation. The presence of SARS-CoV-2 infection does not necessarily prevent the deceased from being a candidate for donation, so they should be considered as a potential donor.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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