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SARS-CoV-2 infection in solid organ transplant recipients: Experience with molnupiravir

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ABSTRACT

Solid organ transplant recipients (SOTR) constitute one of the groups at highest risk for the development of severe COVID-19. However, evidence on the effectiveness of treatments for SARS-CoV-2 infection in this group of patients is scarce. Molnupiravir is an orally administered antiviral drug that has demonstrated effectiveness in reducing the risk of progression to severe COVID-19 in high-risk outpatients, mainly in the unvaccinated population. Although its effectiveness is lower than that of other antivirals, on many occasions it is the only therapeutic option in transplant recipients given the absence of pharmacological interactions with immunosuppressive treatment, the oral route of administration and the good safety profile.

Keywords: molnupiravir, transplantation, COVID-19

INTRODUCTION

Coronavirus disease (COVID-19), caused by SARS-CoV-2, continues to be a significant cause of morbidity and mortality worldwide. With the emergence of less virulent viral variants and widespread vaccination, the incidence of severe forms of SARS-CoV-2 infection is concentrated in certain high-risk populations, such as immunosuppressed patients, including solid organ transplant recipients (SOTR). In the last two years, different therapeutic options for SARS-CoV-2 infection have been developed, targeting both severe forms of the disease and preventing progression in mild forms in high-risk patients. The therapeutic arsenal includes corticosteroids and immunomodulators, monoclonal antibodies and antiviral drugs such as remdesivir, nirmatrelvir/ritonavir, and molnupiravir.

Molnupiravir is a drug with antiviral activity whose mechanism of action consists in the induction of an accumulation of mutations in the viral genome by means of its incorporation into the RNA chain through RNA polymerase. It is administered as a prodrug, requiring two enzymatic steps to transform into the active form (beta-D-N4-hydroxycytidine-triphosphate) [1]. It is administered orally, and the recommended dosage is 800 mg every 12 hours for 5 days. It is a drug with a good safety profile, showing an adverse event rate similar to placebo in the MOVe-OUT pivotal clinical trial [2].

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MOLNUPIRAVIR VERSUS OTHER TREATMENTS

Molnupiravir versus monoclonal antibodies. The main advantage of molnupiravir over monoclonal antibodies is that it retains its antiviral activity against the different circulating variants of SARS-CoV-2. However, most of the monoclonal antibodies on the market lose neutralizing capacity against the new variants that are currently the most common (mainly Omicron BQ 1.1) [3].

Molnupiravir versus other antiviral drugs. Unlike the orally administered antiviral nirmatrelvir/ritonavir, molnupiravir has no relevant drug interactions and does not require adjustment for renal or hepatic function. This is especially relevant in SOTR, in whom the administration of ritonavir increases the levels of other drugs metabolized through cytochrome P450, such as calcineurin inhibitors or mTOR inhibitors.

The main advantage over remdesivir is the oral route of administration, which facilitates outpatient treatment in patients with mild SARS-CoV-2 infection. On the other hand, remdesivir is not recommended in patients with glomerular filtration rate < 30 ml/min or elevated liver enzymes.

However, molnupiravir has some disadvantages compared to other antiviral drugs. Although no comparative clinical trials have been performed between them, in pivotal clinical trials evaluating effectiveness versus placebo in non-hospitalized, unvaccinated patients with mild SARS-CoV-2 infection, mol-

nupiravir showed a relative risk reduction of hospitalization or death at day 28 of 30% [2] versus 89% for nirmatrelvir/ritonavir [4] and 87% for remdesivir [5].

On the other hand, molnupiravir is contraindicated during pregnancy and lactation as it has been associated with a teratogenic effect in animal models.

THERAPEUTIC POSITIONING

The different international organizations and national health agencies position molnupiravir as a therapeutic option in patients with non-severe SARS-CoV-2 infection at high risk of progression to severe disease, generally as an alternative to other antiviral drugs considered preferential.

In this regard, the *WHO living guidance for clinical management of COVID-19* in its latest update of January 2023 establishes a weak recommendation in favor of the use of molnupiravir for patients with non-severe COVID-19 at highest risk of hospitalization (excluding pregnant and breastfeeding women, and children), similar to the recommendation established for remdesivir but behind nirmatrelvir/ritonavir [6]. As arguments for this recommendation, it points to the absence of long-term data on the safety of molnupiravir in relation to genotoxicity and the possibility of the emergence of resistance.

Similarly, the *COVID-19 Treatment Guidelines* of the US National Institutes of Health, updated in April 2023, places molnupiravir as a therapeutic alternative in nonhospitalized adults with mild to moderate COVID-19 who do not require supplemental oxygen at high risk of progression versus nirmatrelvir/ritonavir and remdesivir, which are considered preferential [7].

In the latest version of the document "*Criteria for evaluating the administration of new antiviral therapeutic alternatives against SARS-CoV-2 infection*", the Spanish Agency for Medicines and Health Products also places molnupiravir as an alternative therapeutic option in cases in which the administration of nirmatrelvir/ritonavir and remdesivir is contraindicated or not possible [8].

Finally, with regard to its availability, it should be noted that molnupiravir is not currently authorized for marketing in the European Union, although it has been recommended for use by the Human Medicines Committee of the European Medicines Agency.

CLINICAL EXPERIENCE

Experience in general population. Several clinical trials have evaluated the clinical and virological effectiveness of molnupiravir, with discordant results depending on the target population analyzed.

The MOVe-OUT trial evaluated the efficacy of molnupiravir in non-hospitalized, unvaccinated mild to moderate COVID-19 adults with a risk factor for progression to severe disease [2]. Molnupiravir demonstrated a reduction in the risk of hospitalization or death from any cause at day 29 (6.8% vs. 9.7%; difference 3% [-5.9% to -0.1%]).

Subsequently, the Phase III PANORAMIC clinical trial evaluated the efficacy of molnupiravir in patients with mild COVID-19 older than 50 years or with any risk factor for progression to severe disease [9]. More than 90% of patients had received at least three doses of the vaccine. In this study, molnupiravir was not superior to the standard of care in the combined endpoint of hospitalization or death within 28 days of randomisation. However, patients who received molnupiravir had an earlier symptomatic recovery. The representation of immunosuppressed patients in the PANORAMIC clinical trial was low (8.5%), and in particular the group of transplanted patients represented 1% of the total population. With regard to virological efficacy, in the AGILE CST-2 clinical trial molnupiravir did not show a greater clearance of viral replication in nasopharyngeal swabs compared to placebo [10].

In some real-life studies conducted during the period when Omicron was the predominant variant, molnupiravir has shown good results. In a retrospective study in hospitalized patients, treatment with molnupiravir was associated with lower 28-day mortality and need for corticosteroid and immunomodulatory therapy, with maximum benefit in patients older than 80 years who received molnupiravir within 5 days of symptom onset [11]. However, in this study, information on the vaccination status of the patients included was not available. In the same way, in another Propensity Score-matched cohort study conducted in non-hospitalized patients with any risk factor for progression to severe disease, treatment with molnupiravir was associated with a lower risk of severe COVID-19 or death at 28 days in the subgroups of non-vaccinated patients and in patients older than 75 years of age [12].

Experience in immunosuppressed patients including solid organ transplant recipients. There are few data on the use of molnupiravir in immunosuppressed patients, as they were often excluded from studies or their proportion of the total population was low.

In a post-hoc analysis of the MOVe-OUT clinical trial in the subgroup of immunosuppressed patients, molnupiravir was associated with a lower risk of hospitalization or death and increased clearance of infectious virus [13]. However, the results were not significant due to the small sample size (n=55). In most cases the immunosuppression status was active oncologic disease or well-controlled HIV infection; transplant patients accounted for less than 10% of the total.

Experience with molnupiravir in SOTR is scarce. In a retrospective study of 122 SOTR (renal, liver, and cardiac) with mild COVID-19, treatment with molnupiravir was associated with a 44% relative risk reduction of hospitalization or death [14]. In contrast to these findings, another retrospective multicenter study analyzed outcomes of 218 lung transplant patients with mild COVID-19, and only age and glomerular filtration rate < 30 ml/min were independent risk factors were associated with an increased risk of severe disease [15]. None of the treatments administered (molnupiravir, sotrovimab or remdesivir) had an

impact on outcomes. Different case series, with mainly kidney transplant recipients, without comparator, showed that molnupiravir resulted in improvement of clinical symptoms with no serious side effects [16-18]. Finally, in another case series of kidney transplant recipients, the results with molnupiravir were similar to remdesivir in the rate of progression to severe disease [19]. Neither treatment was associated with adverse effects or interaction with immunosuppressive therapy.

CONCLUSIONS

Molnupiravir is an antiviral with a good safety profile, which has been shown to reduce the rate of hospitalization and death due to COVID-19 in some selected populations, although with a lower efficacy compared to other available treatments.

Its main advantages over other therapeutic options in SOTR are its oral administration, its low rate of adverse effects and the absence of drug interactions with immunosuppressive treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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