Update on the management of SARS-CoV-2 infection

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Antiviral therapy and immunotherapy of COVID-19

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ABSTRACT

The pharmacological treatment of COVID-19 has evolved in the months since the description of the disease. Published observational studies and, above all, clinical trials have highlighted drugs that are useful as well as ruled out any benefit from other drugs used at the beginning of the pandemic. The pathogenesis of the disease has suggested that patients may benefit from the administration of both antivirals, mainly in the earliest stages, and anti-inflammatory/immunomodulatory medications in more advanced stages. We present a short review of the drugs used and under investigation for the treatment of COVID-19.

Keywords: COVID-19, SARS-CoV-2, remdesivir, tocilizumab, antivirals, immunomodulators

COVID-19 is a public health challenge, responsible for enormous morbidity and mortality in the population. The causative agent is a coronavirus (SARS-CoV-2) for which effective antiviral treatments were not known, even based on experience with patients infected with other coronaviruses that cause similar respiratory diseases (SARS-CoV, MERS-CoV). The knowledge that has been acquired about the pathogenesis of the disease has highlighted the need to administer effective antiviral treatment against the coronavirus but also drugs with anti-inflammatory / immunomodulatory activity that will alleviate the complications that appear in the second phase of the disease. Herein we briefly review the pathogenic aspects of the disease on which proposals of therapy are based, as well as the drugs that have been evaluated, including those that have been shown to be effective, those in which effectiveness has been ruled out, and those that are currently under investigation.

COVID-19 STAGES

Soon in the course of the pandemic, Siddiqi and Mehra made a proposal for staging the course of the disease for clinical and therapeutic purposes (Figure 1) [1]. According to this proposal, COVID-19 would have an initial phase dominated by viral replication and a late phase in which the appearance of inflammatory phenomena marks the course of the disease. These two phases overlap in an intermediate phase. In the early-middle stage of COVID-19, when active replication of the virus is eventually present in all patients, the use of an antiviral to halt the propagation is justified. Moreover, the early use of these types of compounds may prevent progression to the inflammatory phase and subsequent complications, and can even reduce the risk of mortality. In the middle-late-stage, anti-inflammatory/immunomodulatory therapy has demonstrated efficacy in diminishing mortality and its use is justified. The use of both antiviral and immunomodulators seems to be warranted for a successful management of the patients

Antivirals. A significant number of antiviral drugs have been evaluated (Table 1). Currently only remdesivir has been approved as an antiviral drug for the treatment of COVID-19. Its usefulness has been confirmed in clinical trials and in observational studies [2-4] although there have been discrepancies in some studies [5]. Currently, most clinical guidelines from health organizations recommend its use for the treatment of patients with COVID-19 who require oxygen therapy to achieve oxygen saturations greater than 94% and who do not require invasive ventilation [6,7]. A 5-day course appears to be adequate with no differences when a longer, 10-day course is used.

No other drug has been shown to be effective in the treatment of COVID-19 in humans, although various drugs with *in*

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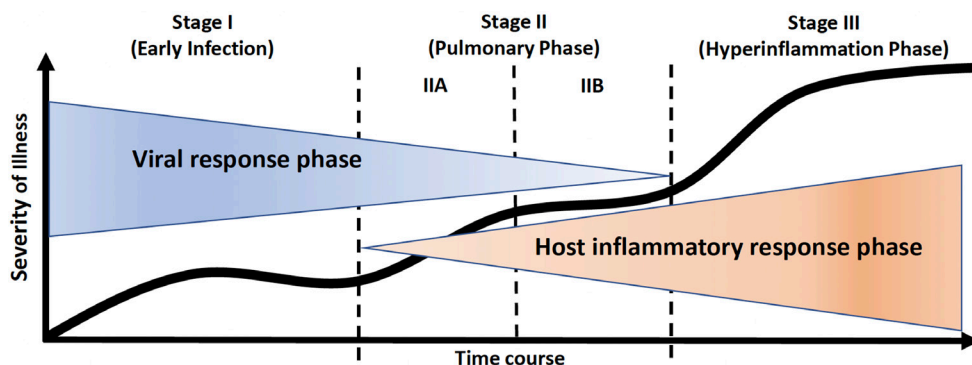E-mail:smguillen@salud.madrid.org

| Figure 1 | Evolution of COVID-19 and proposal of staging [adapted from Siddiqi et al. (1)] |

vitro activity have been used (lopinavir / ritonavir, chloroquine / hydroxychloroquine, azithromycin, betaferon). Clinical studies have shown the absence of benefit from these drugs with an increased risk of toxicity in some cases [8-10]. Other drugs are under investigation. Of special interest, molnupiravir and some monoclonal antibodies (sotrovimab) have shown efficacy in the treatment of mild disease, avoiding clinical progression and the need for hospitalization [11,12].

Anti-inflammatory/immunomodulatory drugs. Anti-inflammatory/immunomodulatory treatment has also been widely explored. Low-dose glucocorticoids for a few days have been shown to reduce mortality in randomized clinical trials

Tabla 1	Key therapeutic classes for the treatment of COVID-19. Drugs under investigation
Antivirals	Immunomodulators
Remdesivir	Corticosteroids, eg, dexamethasone
(Hydroxy)chloroquine	IL-6 inhibitors (eg. tocilizumab)
Lopinavir/ritonavir	IL-1 inhibitors (eg, anakinra)
Interferon	JAK inhibitors (eg, baricitinib)
Azithromycin	Intravenous immunoglobulin
Ribavirin	
Oseltamivir	
Baloxivir	
Favipiravir	
Molnupiravir	
Umifenovir	
Nitazoxanide	
Ivermectin	
Monoclonal antibodies	
Convalescent plasma	

[13]. There is a broad consensus regarding the recommendation to use corticosteroids in patients requiring oxygen therapy, including the most serious patients who require admission to intensive care units and mechanical ventilation, given the benefits observed in mortality. Only patients who are in multi-organ failure seem not to benefit from steroid administration.

In addition to steroid treatment, various immunomodulatory drugs have been evaluated, mainly IL-6 and IL-1 inhibitors and JACK inhibitors. Results with tocilizumab, an IL-6 inhibitor, have been variable. The most recent data and meta-analysis results support its use, especially in patients showing data on inflammatory activity [14,15]. There is less data with anakinra, an IL-1 inhibitor. A recent meta-analysis of randomized clinical trials and observational studies concluded that anakinra could decrease mortality in patients with moderate-severe pneumonia and, as in the case of tocilizumab, especially in the presence of signs of hyperinflammation [16]. Less conclusive are the data with the JAK inhibitors (baricitinib, imatinib), although the studies carried out do not rule out a beneficial effect associated or not with antivirals [17,18].

RECOMMENDATIONS

Despite the coincidence of clinical trials and observational studies in showing the benefits of drug treatment for COVID-19, there are wide discrepancies in all cases, including randomized clinical trials conducted with methodological rigor. These discrepancies have been transferred to the guidelines of scientific societies and health organizations, which have interpreted the results differently and have issued recommendations contradictory on occasions.

With this note of caution, we can dare to affirm that most guidelines are in favor of the administration of antiviral and anti-inflammatory/immunomodulatory drugs for the treatment of COVID-19. Recommendations include administration of remdesivir, steroids, and tocilizumab in population groups in which they have shown benefit in clinical trials.

In a rapidly changing scenario, the interest aroused by the disease has launched clinical trials with other drugs and strategies that, presumably, should improve the management of affected patients in the coming months.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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