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COVID -19: On the threshold of the fifth year. The situation in Spain

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ABSTRACT

Despite having emerged from pandemic status, the incidence of COVID-19 episodes has recently increased in Spain, including pediatric cases and admissions to Intensive Care Units. Several recombinant variants are circulating among us, particularly XBB arising from two Omicron BA.2 sublineages with mutations in the genes encoding the spicule proteins that could increase binding to the ACE2 receptor and be more prone to immune escape. Faced with these, 3 pharmaceutical companies have developed vaccines adapted to the XBB.1.5 sublineage that are already available for administration in our setting with risks that should not be different from those of previous mRNA vaccines and with clearly favorable benefit/risk ratios. They should be applied to patients with potential for poor COVID-19 evolution and to collectives that have a particular relationship of proximity with them. Their application should be understood not only from a perspective of individual convenience but also from that of collective responsibility. The most convenient seems to be a simultaneous immunization of COVID-19 and influenza in our environment. In the therapeutic aspect, there is little to expect right now from antisera, but the already known antiviral drugs are still available and indicated, although their efficacy will have to be reevaluated due to their impact on populations that are mostly immunized and with a better prognosis than in the past. In our opinion, it is necessary to continue to make a reasonable and timely use of masks and other non-pharmacological means of protection.

Keywords: COVID-19, SARS-CoV2, vaccines, recombinant variants, antivirals, masks, influenza, nirmatrelvir-ritonavir, remdesivir, molnupiravir.

COVID-19: A las puertas del quinto año

RESUMEN

Pese a haber salido de la situación de pandemia, la incidencia de episodios de COVID-19 ha aumentado recientemente en España, incluidos los casos pediátricos y los ingresos en Unidades de Cuidados Intensivos. Circulan entre nosotros diversas variantes recombinantes, particularmente la XBB surgidas de dos sublinajes Omicron BA.2 con mutaciones en los genes que codifican las proteínas de la espícula y que pudieran aumentar la unión al receptor ACE2 y ser más propensas al escape inmune. Frente a ellas, 3 empresas farmacéuticas

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han elaborado vacunas adaptadas al sublinaje XBB.1.5 que ya se encuentran disponibles para su administración en nuestro medio con riesgos que no deben ser diferentes a los de las vacunas mRNA previas y con relaciones beneficio/riesgos claramente favorables. Deben aplicarse a pacientes con potencial de mala evolución de COVID-19 y a los colectivos que tienen una particular relación de proximidad con ellos. Su aplicación debe ser entendida no sólo desde una perspectiva de conveniencia individual sino desde la de la responsabilidad colectiva. Lo más conveniente parece hacer una inmunización simultánea de COVID-19 y gripe en nuestro medio. En el aspecto terapéutico hay poco que esperar ahora mismo de los antisueros pero siguen estando disponibles e indicados los fármacos antivirales ya conocidos aunque su eficacia tendrá que reevaluarse por su impacto en poblaciones mayoritariamente inmunizadas y con pronóstico mejor que las de tiempos pasados. A nuestro juicio, es necesario seguir haciendo un uso razonable y puntual de mascarillas y otros medios no farmacológicos de protección.

Palabras clave: COVID-19, SARS-CoV2, vacunas, variantes recombinantes, antivirales, mascarillas, gripe, nirmatrelvir-ritonavir, remdesivir, molnupiravir

INTRODUCTION

Nearly 4 years into the SARS-CoV-2 pandemic infection, COVID-19 is far from being a disease that has been overcome [1-3]. Undoubtedly, the achievements of mass vaccination of a large part of the world's population and antiviral treatment have saved more human lives than few other preventive or therapeutic measures taken with any disease in the past. Nevertheless, COVID-19 episodes continue to occur and continue to cause hospital admissions and ICU stays. Society and the scientific world seem, however, to want to look the other way and much of society, including many practitioners, questions the need and safety of a new round of vaccination, even though new recombinant viral variants threaten the protection of the immune system [4-6] . The role of some previously effective therapeutic measures and their indication under the new circumstances is also questioned.

Therefore, the Committee on COVID-19 and Emerging Pathogens of the Official College of Physicians of Madrid (ICOMEM) has updated the available information on issues such as the incidence of COVID-19 episodes, the viral variants circulating in Spain and the efficacy of antiviral treatments. But fundamentally, the need and safety of a new round of vaccination and its ethical aspects were analyzed. As on previous occasions, the Committee has tried to answer questions that seemed pertinent and opportune at the present time, which are described below.

WHAT DO WE KNOW ABOUT THE EVOLUTION OF THE COVID-19 PANDEMIC THROUGHOUT 2023 BOTH OUTSIDE AND INSIDE SPAIN?

Given the favorable evolution of the COVID-19 pandemic, in March 2022 the surveillance system for this disease was modified to focus on cases diagnosed in the most vulnerable persons (e.g., those over 60 years of age), in high-risk settings (e.g., nursing homes) and in severe cases. In addition, in order to know the trend of mild infections in the general population, the records of acute respiratory infection in Primary Health Care are incorporated into the surveillance. Likewise, the information derived from the sentinel system of Acute Respiratory Infections (IRAS) and Severe Acute Respiratory Infections (IRAG) is incorporated [7].

According to Report No. 181 on the situation of COVID-19 in Spain (the most recent available), prepared by the National Epidemiology Center from data reported by the autonomous communities to the National Epidemiological Surveillance Network [8], the most noteworthy aspects of the recent evolution of the COVID-19 pandemic are the following:

(a) The cumulative incidence and mortality due to COVID-19 in persons aged 60 years and older is stable throughout 2023. The cumulative incidence values correspond to those of "controlled circulation" according to the thresholds defined in the surveillance strategy [7] and mortality remains at the lowest levels since the beginning of the pandemic.

b) The percentage of ICU admissions among hospitalized patients appears to remain stable in all age groups from week 16/2023 to week 23/2023.

c) Case fatality among hospitalized patients is also stable in all age groups from week 16/2023 to week 23/2023 [8].

On the other hand, from Primary Care data [9], in week 35/2023 (first week of September 2023) the incidence rate of COVID-19 in Primary Care was 137.3 cases per 100,000 population, with an increase from week 26/2023 (30 cases per 100,000). The hospitalization rate for COVID-19 stood at 3 cases per 100,000, with increasing fluctuations since week 26/2023 (0.52 cases per 100,000) However, at least for the time being, the hospitalization rate is not higher than that observed in the spring and part of the summer of this same year. Among hospitalized patients, the highest rates are observed in the group over 79 years of age.

Finally, the overall rate of ARI in Primary Care in week 35/2023 stood at 338.2 cases per 100,000 population with upward fluctuations since week 28/2023 (232.7 cases per 100,000). The SARS-CoV-2 positivity rate was 40.6%.

Regarding the global situation, according to data from the latest "Weekly epidemiological update on COVID-19" (1 September 2023) of the World Health Organization (WHO) [10], in the latest 28-day period (31 July to 27 August 2023), more than 1.4 million new cases of COVID-19 and more than 1. 800 deaths, an increase of 38% and a decrease of 50%, respectively, compared to the previous 28 days. Three WHO regions reported increases in the number of cases in the last 28-day period, while two regions reported decreases. While three WHO regions reported decreases in the number of deaths, the Eastern Mediterranean and Western Pacific regions reported increases in the number of deaths. As is well known, currently, reported cases do not accurately represent infection rates due to reduced global testing and reporting.

WHAT IS HAPPENING IN SPECIAL POPULATIONS SUCH AS THOSE REQUIRING INTENSIVE CARE, PEDIATRIC PATIENTS OR PREGNANT WOMEN?

Since the beginning of the SARS CoV-2 pandemic, 56,249 patients have been admitted to Spanish ICUs and since 28/03/2022, 6,736 patients, which represents 0.4% of all patients according to report 181 of the ISCIII- CNE as of June 30, 2023 [11]. At the international level, "Our World Date" of June 7, 2023 shows data on patients admitted to ICUs in the United States (856), Germany (171) and Spain (122) with a trend of increasing cases in the first weeks of September in the United States (1,966 cases) relating to the increase in global cases [12].

The current profile of ICU patients is heterogeneous, with patients with comorbidity and immunosuppression predominating, although healthy patients are also admitted. The clinical characteristics of patients with COVID 19 have evolved since the beginning of the pandemic due to vaccination and changes in therapeutic management. A study evaluating the evolution of patients from June 2021 to March 2023 shows a significant reduction in critically ill patients, with an increase in the age of the most severely ill patients and increased comorbidity without association with the presence or absence of vaccination [13]. Other studies show contradictory results, associating the absence of vaccination or incomplete vaccination with increased need for mechanical ventilation and consumption of ICU resources without influencing mortality [14]. A recent study comparing the evaluation of patients with influenza admitted to ICU with patients admitted for COVID-19 shows in the latter a longer stay and mortality despite being younger patients and with lower severity on admission [15].

The current situation of COVID-19 in the pediatric population in Spain remains controlled and stable in terms of the number of new cases, hospitalizations and mortality [16]. The vaccines against COVID19 have also demonstrated their efficacy and safety in pediatrics and their importance has been fundamental in controlling the pandemic [16,17].

At present (2023-2024) vaccination against COVID-19 is recommended only in children who are at higher risk of complications or serious conditions in case of infection, which are:

- From 6 months-59 months: children with severe immunosuppression and risk groups,

- From 5 years-59 years: people institutionalized in centers for the disabled or closed institutions; immunosuppressed; and cohabitants with people with a high degree of immunosuppression. Also in case of cohabitation with people over 60 years old or with risk factors.

In the case of pregnant women, it is recommended to vaccinate pregnant women in any trimester of gestation and women up to 6 months after delivery, who have not been previously vaccinated during pregnancy, since the benefit of vaccinating pregnant women in the Omicron era has been demonstrated [18].

WHAT VARIANTS HAVE CIRCULATED DURING THIS YEAR IN THE WORLD AND IN SPAIN?

During the year 2023, a new phenomenon has occurred in the evolution of SARS-CoV-2 lineages with the emergence of recombinant variants, resulting from the existence of patients coinfected with more than one strain. Systems have been developed for the optimized identification of these coinfections from whole genome sequences, which allow determining that these recombinant variants have existed throughout the pandemic, contributing to the evolutionary acquisition of diversity in this virus, together with the accumulation of sequential mutations [19]. However, the evolutionary advantages of recombination arise especially when the co-infecting strains are markedly different; hence, attention began to be paid to the recombination phenomenon when the genomic diversity of circulating SARS-CoV-2 was highest, during the Omicron waves, when the BA.1, BA,2 , BA.5 lineages, among others, were prevalent [20].

Among these new variants, the recombinant XBB emerged from the rearrangement of two Omicron BA.2 sublineages, which was a marked immune escape. Its emergence led to a decrease in the prevalence of the Omicron lineages (BA.2, BA.5, BQ, among others) that had dominated the pandemic during 2022. XBB descendants have ended up causing more than 90% of the global cases [21]. Several variants emerged from the evolution of this XBB recombinant, among them, XBB.1.5 was the one that ended up being dominant (globally in February 2023 and in March in Spain). This variant adds to the immune escape provided by its parent XBB, a mutation at position 486 of the gene coding for the spicule, which increases its ability to bind to the ACE2 receptor [22].

This transformation in the epidemiology of the virus has led to the de-escalation of the variants of concern (VOCs) to which we were accustomed [23]. Now, we only have a call for monitoring of several variants of interest (VOI) or variants under monitoring (VUM), which share mutations with those VOCs but without showing increases in severity or immune escape.

This new situation has led to a somewhat different approach to variant monitoring. As opposed to the usual variant/lineage-specific monitoring, there has been a shift to labeling constellations of genetic traits shared by a set of lineages. Following this approach, the latest VOI assignment in August 2023 [23] is an umbrella for several lineages of recombinant XBB.1.5, which share a battery of relevant mutations, hence its definition as XBB.1.5-like. This group, in turn, is divided into those that do or do not add the F456L mutation, which presents some laboratory evidence of association with immune escape. Among the lineages included under this new collective category of VOIs, causing most cases at present, EG.5 (which has derived in EG.5.1) [5] stands out with a particularly high representativeness within the group, which would suggest greater transmissibility.

To these VOIs, we must add VUMs to which we are beginning to pay special attention, although they still accumu-

late a number of identifications below what would justify their consideration as VOIs. Among them, there is BA.2.86, (non-XBB lineage) with scarce representativeness both globally (37 cases in UK) and in our country (4 cases; data 11 September) [24], but which is being monitored as a candidate to succeed in dispersal in the immediate future. Similarly, another non-XBB lineage is monitored that is showing an increasing trend, DV.7.1, which appears to be especially common in Spain (364 of the 960 global sequences, September 2023), with a higher number of mutations (some with immune escape potential) and evolutionary divergence than observed in other lineages.

DO WE EXPECT VARIANTS WITH GREATER VIRULENCE IN THE NEAR FUTURE?

The existence of numerous circulating variants of SARS-CoV-2 arising either by accumulation of sequential mutations in majority variants of Omicron (BA.1, BA.2, BA.4, BA.5 among others), or by recombination among them, makes it difficult to predict their persistence over time, the speed of their dissemination and their virulence [25]. This will depend on the degree of adaptation to the respiratory tract epithelium, its persistence and transmissibility during infection and the possible immunological escape derived from modifications in its spicule. It will also depend on the different impact on vaccinated individuals, on unvaccinated individuals, on those with hybrid immunity (vaccination plus infection) or even on those who, after more than three and a half years of pandemic, have not suffered an episode of COVID-19 and have not been vaccinated [26].

The major selection factor in the evolution of SARS-CoV-2 continues to be the number of infected individuals, the persistence in the infected person and its transmissibility. The first ones (VOC, Alpha, Beta and Gamma, emerged independently in different parts of the world geographically distant from each other [27]. They had a significant number of mutations in their spicule with respect to the original Wuhan strain, only surpassed later by mutations in the Omicron variant. The emergence of the latter variant in November 2021 when Delta was dominant was a surprise in the evolution of SARS-CoV-2. It became classified as a VOC when it was shown to be easily transmitted and widely geographically dispersed. However, the reduced ability to generate severe manifestations, partly due to high vaccination rates in the population, meant that this variant (actually three subvariants BA.1, BA.2 and BA.3) was considered a lesser evil in the evolution of SARS-CoV-2 despite the risk of its persistence over time [28]. Unfortunately, Omicron variants could cause reinfections more frequently than their predecessors, even in the vaccinated population, although not more virulent [25].

A noteworthy aspect is the presentation of the current vaccines and the recommendation by the FDA and EMA to include the Omicron XBB.1.5 variant (or those that generate protection against it) [29]. Therefore, the current emergence of other variants such as EG.5 or EG.5.1 derived from XBB.1.9.2 that present a similar spicule to XBB.1.5 suggests that this vaccine protects against these new subvariants [5]. However, they include the F456L mutation in EG.5 and additionally Q52H in EG.5.1, both of which are associated with lower neutralizing antibody protection and thus may hinder the efficacy of the new ones. They are also associated with greater transmissibility, although not with greater severity [30].

The emergence of new variants with greater virulence will depend on their evolution in undetected reservoirs, either in asymptomatic persons or with minor symptoms or even in animals, and on the chronicity of the infection. In patients with immunosuppression and pharmacological treatment, this emergence can be minimized with combination treatment strategies that reduce the emergence of possible mutations and recombination between different variants [25].

WHAT IS THE IMMUNE STATUS OF THE SPANISH POPULATION AT THIS TIME?

The first seroprevalence studies against SARS-CoV-2 were carried out at the beginning of the pandemic. Between April and May 2020 the population-based eneCOVID study in Spain included 61,075 participants [31] and the overall seroprevalence was 5% with wide variations depending on the geographical area (from 10% in Madrid to <3% in coastal areas). Predictably, most of the population had not yet had contact with the virus.

A second study, in May 2022 in Navarra, including 1,461 persons over 5 years of age [32] estimated that more than 30% of the population had been diagnosed with COVID-19 and more than 90% over 5 years of age had received a complete vaccination regimen. Anti-N antibodies (as evidence of past infection) were detected in 58.9% of the population studied and anti-S antibodies (as evidence of vaccination) in 92.7%. At that time, therefore, most of the population had developed antibodies by natural infection, vaccination or both in this region of Spain. It is very likely that the figures at those dates are extrapolable and will be maintained or have increased by 2023 in the rest of the Spanish population.

Some figures from other countries reflect the situation described in Navarra. In the United States, unpublished CDC data reveal that in the last four months of 2022, 47.7% of the population had acquired hybrid immunity, 22.6% by infection and 26.1% by vaccination. Only 3.6% of the population did not have antibodies against SARS-CoV-2.

Therefore, at this time of post-pandemic and vaccination, only a small percentage of the population would not have antibodies to the virus, although the figure may be higher in older or immunocompromised people.

ARE THERE VACCINES AGAINST THE NEW VARIANTS, WHAT ARE THEY AND WHO PRODUCES THEM?

Vaccination during 2022 was carried out with a bivalent preparation that included the original Wuhan variant and

BA.5, which was the dominant variant. It showed superior protection to monovalent, especially in immunocompromised individuals, although protection decreased over time and could disappear four months after vaccination [33].

Newer Omicron sublineages (XBB.1 and derivatives) have greater immune escape, with which the decline in long-term protection is accelerated. Therefore, WHO and other agencies (EMA, FDA, ECDC and ICMRA) recommend a monovalent vaccine adapted to some sublineage of XBB.1, preferably XBB.1.5, which is the Omicron sublineage with the highest immune escape so far [10,34-36].

Currently, three companies have developed vaccines adapted to the XBB.1.5 sublineage. Comirnaty® (Pfizer) has been approved by the regulatory agencies and is already available for distribution and administration in Spain. Spikevax® (Moderna) is also approved, and Nuvaxovid (Novavax) is still pending approval. All three vaccines have shown neutralizing capacity against XBB.1.5 and also against EG.5.1 (Eris) and BA.2.86 (Pirola) sublineages [37].

WHAT ARE THE BENEFITS AND RISKS OF A NEW VACCINATION?

During the pandemic, clinical trials and epidemiological studies with real-life data have characterized the benefits of different vaccines against COVID19 and pharmacovigilance systems have identified adverse events associated with their use [38]. Since then, independent academic groups and regulatory agencies have conducted many benefit-risk analyses of each vaccine. In general, these analyses compare the benefits of the vaccine, in terms of reduced infections, hospitalizations, ICU admissions, and COVID-19 deaths, as well as deaths from all causes, with the risk of the same type of outcome events (hospitalizations, ICU admission, etc.) resulting from adverse effects of the vaccine. To reduce uncertainty, several scenarios of risk of infection and complications of COVID-19, and of benefits and risks of the vaccine are considered. Analyses are often done separately in each sex, in major age groups, and in some specific population groups, as the risk of COVID-19 complications, and the benefits and adverse effects of vaccination may vary among them [39,40]. In addition, benefit-risk analyses are performed both at the general population level (which includes vaccinated and unvaccinated following a mass vaccination strategy, and which considers potential benefits by reducing transmission in the population, vaccine availability, vaccine coverage, various levels of transmission in the population, etc.) and at the individual level (only in the vaccinated, where simply receiving versus not receiving the vaccine is compared) [41]

In all age and sex groups in which a vaccine has been approved against COVID-19, the benefit-risk ratio has been very favorable. Subsequently, public health authorities have established priority or target groups for vaccination (generally the most vulnerable), which have the best benefit-risk ratio. For the mRNA vaccines adapted to the new SARS-CoV-2 variants to be used in this vaccination campaign, the benefit-risk analyses have considered all available evidence [42], and suggest that the relationship will be very favorable [43]. There are three key elements to this:

i) The updated mRNA vaccines are manufactured with a similar process as the previous formulations. Therefore, the same risks are expected after administration.

ii) The degree of neutralization observed by the updated vaccines appears to be similar to that observed with earlier versions of vaccines against previous variants.

iii) The benefit-risk profile of the previously licensed and approved COVID-19 mRNA vaccines is well known, as they have been administered to hundreds of millions of people worldwide.

Finally, in a mathematical modeling exercise conducted by ECDCs on a vaccination campaign in autumn 2023 with an optimistic scenario of high vaccine uptake among individuals over 60 years of age (target group), it is expected to prevent between 21% and 32% of the cumulative total of COVID-19-related hospitalizations in all ages in all EU countries until February 28, 2024. Prevention benefits are greater when targeting people aged 60 years or older rather than 80 years or older. However, they are similar when the target group is people aged 50 years or older or 60 years or older. This type of evidence, together with other logistical, economic and population acceptability evidence, usually guides decisions on which age groups to vaccinate in order to maximize the benefit-risk ratio [44].

WHO SHOULD BE VACCINATED AND WHEN?

A single dose of the current mRNA vaccines is currently recommended, regardless of whether they are "naive" vaccinees (new, without previous vaccination) or booster vaccinations at any stage of the COVID-19 vaccination schedule. The recommendations are for two risk groups:

* A first group, to decrease complications and morbimortality, in at-risk patients, whether they are "naive", or whether or not they are up to date with their vaccination schedule (if they had recently passed COVID-19, they should wait at least 3 months). They should receive a new dose of vaccine:

- All persons 60 years of age and older regardless of comorbidity and usual residence (domicile/institution).

- Men under 60 years of age with any of the following situations: Long-term inmates in closed institutions such as centers for the disabled or any other type of institution (prisons). It does not include schools, universities.

- Pregnant women in any trimester of gestation and during the puerperium if they are not vaccinated (up to 6 months after delivery).

- Patients with Diabetes Mellitus.

- Morbid obesity.

- Diseases with cognitive dysfunction, especially Down Syndrome and dementia.

- Chronic cardiovascular, neurological, respiratory, chronic kidney disease (including nephrotic syndrome), chronic liver disease (including alcoholism) and chronic coagulation and bleeding disorders.
- Cancer and hematological malignancies.
- Primary or acquired immunosuppression due to infections (HIV), drugs (cortisol, immunosuppressants, ...), asplenia, as well as transplant recipients.

*A second group consists of healthcare and non-healthcare personnel who work or live with risk groups (e.g. students of health sciences, caregivers and family caregivers of the elderly, the disabled or the immunosuppressed). This group also includes state security forces, firefighters, and civil defense. The objective of vaccination in this population group is twofold:

-To reduce the impact and maintenance of critical and essential services to the community: health care and citizen protection.

-To avoid the transmission of disease to risk groups.

The American CDC clearly indicates COVID-19 vaccination of the entire population over 6 months of age with different vaccination protocols. This is undoubtedly a top recommendation, but at the present time it is not well supported by population studies showing a less severe clinical picture than the variants prior to the current Omicron. There is, instead, sufficient evidence that in at-risk populations with an up-to-date vaccination schedule, the morbidity and mortality of COVID-19 is much lower than in the unvaccinated [45-48]. Thus, it seems more reasonable in terms of both clinical and economic efficiency to limit the recommendation to risk groups.

IS IT CONVENIENT TO ASSOCIATE VACCINATION AGAINST COVID WITH VACCINATION AGAINST INFLUENZA?

The loss of protection that occurs months after vaccination against COVID makes it necessary to implement strategies that facilitate periodic revaccination. One strategy for this is simultaneous vaccination for COVID and influenza, which reduces the logistical complication of running two separate campaigns. This approach involves analyses related to safety, due to a possible increase in reactogenicity and adverse effects, and also to effectiveness due to possible interactions in the immune response to both vaccines.

With regard to safety, a trial published in 2022 [49] comparing safety and efficacy in two population groups, one with simultaneous administration of COVID and influenza vaccine and the other with COVID vaccination alone, showed that, although the symptoms related to reactogenicity were greater in the group in which both vaccines were administered simultaneously, the serious or unexpected adverse effects did not differ between the groups. The results have been confirmed in two other trials [50,51] and in a systematic review published in 2023 [52].

There are discrepancies regarding immunogenicity. While some studies highlight similar efficacy with vaccination for COVID-19 alone and with coadministration with influenza [50-52], others indicate lower immunogenicity when the two vaccines are administered together, although efficacy is maintained [53-55]. These studies conclude that further research is needed.

In view of the above, Spanish health organizations recommend simultaneous administration of both vaccines, COVID-19 and influenza [56]. From a practical point of view, there are two circumstances in which joint administration is not advisable: 1) having COVID-19 or having received a dose of the vaccine in the previous three months and 2) if either of the two vaccines could have caused a relevant adverse effect, in which case it seems more prudent to administer them separately or even, considering the risk/benefit balance on an individual basis, to avoid one of the two.

WHAT SHOULD BE THE ANTIVIRAL TREATMENT OF PATIENTS WITH COVID-19 AT THE PRESENT TIME?

Antiviral treatment at the present time has controversial aspects due fundamentally to the fact that we are dealing with a patient population different from the one in which the drugs were originally tested. Most COVID-19 patients today are either vaccinated, have had one or more episodes of COVID-19, or both. Moreover, the circulating virus variants are also not those of yesteryear and past clinical trials may not accurately reflect present circumstances [57]. Rebound episodes have been described, both of clinical symptoms and viral load that were not previously contemplated (1 to 14%, according to different studies), which seems to be favored by antiviral treatment [58-61].

With these premises, we believe that antiviral drugs still have a clear indication in the early treatment of patients with COVID-19 and risk factors for a poor clinical course, particularly when other treatments such as monoclonal antibodies do not seem effective at present. Several institutions have issued recent recommendations on various aspects of treatment and in particular on antiviral treatment [62,63].

Nirmatrelvir-ritonavir (Paxlovid), which received full FDA approval in May 2023, is the antiviral drug of choice for outpatients and the most frequently prescribed antiviral drug. This drug reduces the risk of severe illness, including hospitalization and death, by approximately half in high-risk individuals (elderly, immunocompromised, and patients with underlying neurological and cardiovascular disease), regardless of vaccination status. However, despite its efficacy, many people at increased risk of severe disease are not prescribed this drug. There are believed to be several reasons for this underuse, but the potential for drug-drug interactions and fear of a rebound effect are commonly cited.

It is a drug that acts by inhibiting viral proteases that generate the structural and functional proteins necessary for viral replication. Its oral absorption facilitates its administration and it has mild and transient side effects.

Due to the low levels and short half-life of Nirmatrelvir, it should be coadministered together with Ritonavir, which works as a potent CYP3A inhibitor that boosts plasma levels. It generates incompatibilities with other frequently used drugs and natural preparations, which make it necessary to temporarily suppress or modify their doses, if possible, as in the case of statins or amiodarone. Nirmaltrelvir-ritonavir cannot be used in hepatic insufficiency and cannot be used in severe renal insufficiency (Ccr < 30 ml/mn) and the dose should be reduced in patients with other degrees of renal insufficiency. Nirmatrelvir-Ritonavir can be administered to pregnant women [64-69].

Remdesivir (Veklury) [70] is a broad-spectrum, RNA polymerase inhibitor antiviral that is administered intravenously usually for 5 days in hospitalized patients. Longer courses have not been associated with greater efficacy [71,74-78]. In contrast, shorter treatments (3 days) have also been tested to avoid hospitalization in patients with mild-moderate COVID-19 and with risk factors [70] for poor outcome. Remdesivir is recommended for the treatment of COVID-19 in admitted patients who do not require supplemental oxygen and who are at risk of poor outcome [63]. This includes patients with severe renal failure [79].

Aggregate data on the use of Remdesivir to treat all high-risk patients show a faster recovery time in those who received Remdesivir although there is no conclusive evidence of a survival benefit [80-82].

Remdesivir administration requires monitoring for side effects such as bradycardia or elevated transaminases.

Molnupiravir (Lagevrio), another antiviral previously tested in influenza, is a prodrug that acts as a false ribonucleoside analog, causing errors in RNA sequencing that can induce mutagenesis in the host. This contraindicates its use in pregnant women, especially in the period of embryogenesis and requires contraception during its use up to four days after its elimination and up to three months in men. It is not authorized in children. It is administered orally at a dose of 800 mg every 12 hours, for five days, does not require dose adjustment in hepatic or renal insufficiency, has no significant interactions and is well tolerated.

Nine randomized clinical trials were included in treatment with molnupiravir that enrolled 31,573 COVID-19 patients, of whom 15,846 received molnupiravir. The results of the meta-analysis showed that the molnupiravir group had a higher proportion in terms of clinical improvement and real-time PCR negativity. However, no significant differences were observed in terms of mortality, hospitalization, adverse events and serious adverse events. Its benefit in initial randomized trials, with a non-immunized population has been reduced [83,84], as with the other antivirals [84-86].

The EMA issued a document in February 2023 recommending rejection of marketing of this drug in the European Union.

Where the best therapeutic strategy is less well defined is in the immunosuppressed patient with persistently positive CRP, defined as a patient who remains positive one month after the clinical presentation. In this scenario, prolonged therapies (10 days) with a combination of antivirals (remdesivir, nirmatrelvir/ritonavir and even the use of monoclonal antibodies) have been tested. The evidence regarding their usefulness comes only from observational studies, but the use of remdesivir 200 plus Nirmatrelvir/Ritonavir 10 days in high-risk patients with prolonged COVID-19 or with COVID-19 relapses, may be useful to achieve viral clearance and avoid progression of COVID-19 [87]

The situation, therefore, of antiviral drug use, is in need of new clinical trials that are better suited to the current circumstances of the population. The number of ongoing clinical trials in this field is very high and drugs such as ensitrelvir and VV116 are promising [88-90].

The need to administer dexamethasone in patients requiring oxygen therapy to maintain Sat>93% is well established. Finally, if there is elevation of biomarkers of inflammatory response (CRP > 74mg/L) or clinical failure of dexamethasone, the prescription of tocilizumab or baricitinib is recommended.

WILL IT BE NECESSARY TO RETURN TO NON-PHARMACOLOGICAL PREVENTIVE MEASURES?

The Council of Ministers of July 4, 2023 declared the end of the health crisis caused by COVID-19 in Spain, ending the obligatory use of masks. Despite this, their use is still highly recommended in symptomatic persons with respiratory processes and for individual protection of persons in whom SARS-CoV-2 infection can have very negative clinical repercussions (those over 80 years of age, ≥ 65 years with at least one severe chronic comorbidity or in any situation of immunosuppression or frailty). Masks may be indicated in these and other groups, if there is going to be a prolonged stay in crowded areas or when there is exposure to people with respiratory symptoms. Mask use is also recommended by healthcare personnel during direct clinical care of patients at high risk of poor outcome in case of COVID-19 (ICU, emergency, transplant unit, units or services of clinical care for immunocompromised patients), in primary care and in workers in residential homes for the elderly and people with disabilities [91,92].

From the scientific point of view, there is moderate evidence on the effectiveness of the combination of several of the non-pharmacological measures from observational studies and mathematical models (social distancing, isolation and quarantine, hand hygiene or the use of personal protective equipment and masks) [93-95]. They are generally considered to be effective in reducing virus transmission, reducing the need for hospital beds and the number of COVID-19 cases and deaths [94,96-99].

That said, international agencies and public health entities in different countries could recommend early adoption of non-pharmacological public health interventions for other population groups in the event of a notable increase in virus circulation and reported cases or in the face of the emergence of new, more transmissible and virulent SARS-CoV-2 variants.

WHAT ARE THE ETHICAL ASPECTS OF THE CURRENT RECOMMENDATION FOR VACCINATION AGAINST COVID-19?

Although vaccination against COVID-19 is not mandatory in Spain, special emphasis should be placed on the ethics of responsibility [100,101].

The vaccine is not only administered for personal benefit, but also to achieve the so-called herd protection. It would be an act of individual and collective solidarity where each vaccinated person protects the others. In addition, the responsibility of healthcare professionals is even greater as they contribute to the public debate by strengthening social trust in the healthcare sector, where one of their moral and labor principles is not to harm those they care for, in this case people with a higher risk of complications and morbidity and mortality if COVID-19 is transmitted to them. Unvaccinated healthcare personnel against COVID-19 put the most vulnerable population at serious risk.

The COVID-19 Committee of ICOMEM has pronounced in favor of vaccination in different published documents [100) (101]. However, despite the fact that there are sufficient legal grounds to support mandatory vaccination, the coercive path is not the most efficient, advocating intermediate positions that favor free vaccine adherence.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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