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Real-world experience with therapies for SARS-CoV-2: Lessons from the Italian COVID-19 studies

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SUMMARY

The therapeutic armamentarium that has been made available from the beginning of the emergency phase of the COVID-19 pandemic to date is briefly reviewed, and an overview of the real-world clinical evidence published by the Italian medical and scientific community during the last three years is presented herein. Prior to the introduction of a vaccine for SARS-CoV-2, several treatment options were implemented from the onset given the evidence that a "cytokine storm" was present during infection with SARS-CoV-2. However, with the exception of tocilizumab, baricitinib and perhaps anakinra, most studies with anti-cytokine biological agents in patients with severe COVID-19 did not show any significant clinical improvement or decrease in mortality at day 28. The same is true of several repurposed drugs including ivermectin, lactoferrin, interferon ß-1a, lopinavir/ritonavir alone or combined with hydroxychloroquine, and darunavir/cobicistat, which did not show any benefits in clinical status or mortality. Treatment with neutralizing monoclonal antibodies (mAbs) for COVID-19 is changing continually with the evolution of new viral variants. In Italy, current indications for treatment of COVID-19 outpatients underline that the use of specific mAbs may vary over time depending on the prevalent SARS-CoV-2 variant and the sensitivity to the different mAbs available. Three antiviral drugs against SARS-CoV-2 were studied extensively and initially available in Italy: remdesivir, molnupiravir, and nirmaltrelvir/ritonavir, but at present the latter is the only oral antiviral for SARS-CoV-2 available in Italy. Several real-world studies for the use of nirmatrelvir/ ritonavir in the Italian population have been published. Among the current unmet needs, a clear and universal definition for long COVID along with treatments and prevention are still lacking as is clarity of the pathogenetic mechanisms responsible for it.

Keywords: SARS-CoV-2, COVID-19, real-world, management, Italy.

BACKGROUND

On March 11, 2020, the World Health Organization (WHO) characterized the outbreak of coronavirus disease 2019 (COVID-19) as a global pandemic, and more than three years after, on May 5, 2023, the WHO Emergency Committee determined COVID-19 as an established and ongoing health issue that no longer constitutes a public health emergency of international concern [1]. Initially the outbreak was due to the ancestral strain of SARS-CoV-2 isolated in Wuhan, after which the variants of concern Alpha and Delta began to emerge, which acted on a population that totally lacked immunity. Indeed, the first epidemic wave that hit Italy had an unprecedented impact on healthcare services, especially in critical areas, due to the very rapid increase in cases of infection with SARS-CoV-2 and severe clinical manifestations at a time when no effective drugs or vaccines were available, and the entire population was completely susceptible to infection [2, 3].

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The virus mutated rapidly, with the appearance of new variants having different aggressiveness and transmissibility, although the lethality depended on the setting and characteristics of the population [4, 5]. With the Delta variant, anti-SARS-CoV-2 Spike IgM antibody was found to be associated with both disease severity and risk of death in unvaccinated patients [6]. In the meantime, the immune status of the population changed, due both to the rapid accumulation of infected and recovered subjects and to the introduction of a large vaccination campaign which began at the end of December 2020, with the aim of protecting vulnerable individuals, but at the same time allowing for rapid vaccination of the vast majority of the Italian population. During 2021 and January 2022, vaccination against SARS-CoV-2 led to a significant reduction in the impact of the pandemic in terms of morbidity and mortality, and therefore a decreased burden on hospital services [7]. This led to easing of restrictive measures, such as social distancing and lockdown, in the second half of 2022.

At present, the predominant variants in Europe are Omicron recombinants [8], which are highly transmissible likely due to their ability for immune evasion. Fortunately, these variants are associated with low lethality due to their tropism for the upper airways and less risk of lower respiratory tract infection, together with greater immunity in the general population from prior infection and vaccination [9]. According to data from the GIMBE Foundation (Gruppo Italiano per la Medicina Basata sulle Evidenze), at the beginning of December 2023 the total number of cases of COVID-19 in Italy was 26,415,845, with 193,435 deaths [10]. The rates of hospitalization and the mortality increase with age, with the highest values in those ≥90 years; the rates of admission to intensive care also increase with age [11].

Besides prevention, from the beginning of the pandemic there was an enormous effort by the medical and scientific community to identify therapies that were effective against the virus. When the Omicron variant became prevalent at the beginning of 2022, although associated with less severity and lethality, it continued to cause substantial healthcare burden due to the evasion of immunity and its increased transmissibility combined with a shorter incubation period, leading to a high prevalence of disease and reinfections [12, 13].

In this rapidly evolving scenario, real-world evidence is crucial to interpret the effectiveness and tolerability of therapies outside the rigid framework of randomized clinical trials and is increasingly recognized as an important complement to clinical trials. In the context of COVID-19, one must consider the timing in which the data were retrospectively selected, variation due to different pandemic waves and circulating variants, and changing vaccination and immunity status of the population. Many randomized clinical trials, for example, were carried out in unvaccinated patients and during circulation of the Delta variant. Several subsets of patients were also not included in randomized trials, such as the immunocompromised. Thus, real-world data is needed to gather insight into the effectiveness and safety of therapies as well as for pharmacovigilance. This narrative review will briefly outline the therapeutic armamentarium that has been made available from the beginning of the emergency phase of the COVID-19 pandemic to date, in order to provide an overview of the real-world evidence published by the Italian medical and scientific community during the last three years focusing on monoclonal antibodies (mAbs) and antivirals.

MONOCLONAL ANTIBODIES

Neutralizing mAbs are recombinant proteins that can be derived from the B-cells of convalescent patients or humanized mice; they target the spike protein of SARS-CoV-2 that mediates viral entry into host cells [14]. Most neutralizing mAbs can be used to treat the disease but have no role in its prevention, although tixagevimab/cilgavimab (Evusheld®) is an exception in this regard [15, 16]. A present, the use of mAbs for the treatment of COVID-19 is in continuous debate due to the evolution of variants resulting in reduced susceptibility to mAbs, which is demonstrated by in vitro data showing loss of activity against certain variants and subvariants [17]. Notwithstanding, it is worth considering that mAbs also have "accessory effector actions" that go beyond neutralizing efficacy, which include complement-mediated cytotoxicity, Ab-mediated cytotoxicity, and Ab-mediated phagocytosis. Thus, in addition to the epidemiological situation in establishing the correct target population, better understanding of the optimal timing and dosage for their use is needed to augment their therapeutic action [18].

Between 2020 and 2023, 220 studies on the use of mAbs for treatment of COVID-19 were published by Italian groups and are available on PubMed. In particular, data on bamlanivimab/etesevimab, casirivimab/imdevimab (Ronapreve®), sotrovimab (Xevudy®), and tixagevimab/cilgavimab have been reported [19-25] . Of note, several of these were carried out during the Omicron era, with the result that the response to the vaccine and/or to the drugs was different compared to earlier stages of the pandemic. In patients infected by the Alpha variant, some combination therapies (bamlanivimab-etesevimab and casirivimab-imdevimab) have been reported to be more effective in lowering hospitalization duration vs. monotherapy with bamlanivimab [26]. Falcone *et al*. found that casirivimab/imdevimab was beneficial in patients infected with the Gamma variant [27].

During circulation of the Delta variant, and at the beginning of the Omicron era, the Italian Medicine Agency funded research protocols to acquire new evidence on the efficacy of mAbs in the treatment of COVID-19 patients at an early stage of illness, not hospitalized, with or without risk factors which may worsen prognosis [28]. Among these, MANTICO was a multicentric open-label randomized controlled trial that compared the clinical efficacy of early treatment with bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab in outpatients with mild-to-moderate COVID-19 [29]. Among patients infected with the Delta variant, no progression of COVID-19 was observed, with no differences among treatment groups. Sotrovimab was the most effective against the Omicron BA.1 and BA.1.1 variant, reducing symptoms within 5 days compared to bamlanivimab/etesevimab and casirivimab/imdevimab. This would seem to confirm *in vitro* studies suggesting that sotrovimab retains its neutralization capacity against Omicron BA.1, but has less efficacy against BA.2, BA.4 and BA.5, and BA.2.12.1 [30].

A multicenter retrospective analysis of 268 fragile patients with mild SARS-CoV-2 infection by Bartalucci *et al*. examined the efficacy of sotrovimab and casirivimab-imdevimab and reported that only 22 (8%) patient had unfavorable outcomes defined as increased need for oxygen supplementation and/or death [31]. De Vito *et al*. published the results of a real-life study of 689 patients with SARS-CoV-2 infection who did not receive any treatment (n=348) or who received with sotrovimab (n=341). In all there were 161 (23.4%) cases of disease progression and 65 (9.4%) deaths, with a significant difference between those who were treated or not with sotrovimab ($p < 0.001$). Vaccination [OR 0.21 (95% CI 0.12-0.37)] and administration of sotrovimab [OR 0.05 (95% CI 0.02-0.11)] were both associated with a lower risk of progression to severe COVID-19. [32].

Capoluongo *et al.* carried out a retrospective real-life analysis on the use of tixagevimab-cilgavimab in 42 immunocompromised patients for treatment of COVID-19 [33]. It was reported that patients with hematological malignancies had a lower negativization rate when treated with 10 days after the onset of clinical symptoms. In a real-world experience in booster vaccinated immunocompromised patients studying tixagevimab-cilgavimab as pre-exposure prophylaxis against Omicron BA.5, Schiaroli *et al.* reported that that the combination cannot substitute for vaccination; however, it may be a valid supporting therapy if the recommended douse is doubled. Similarly, in patients with hematological malignancies, Angotzi *et al.* reported that after a median of 4 months, the 3-month cumulative incidence of infection with SARS-CoV-2 was 20% in those administered tixagevimab/cilgavimab compared to 12% in the observation/vaccine group [34]. In 2024, Gidari *et al*. published a study of 72 immunocompromised patients in which the efficacy of tixagevimab/cilgavimab appeared to wane against novel subvariants such as BQ.1, XBB.1.5, XBB.1.16, and EG.5.

In this regard, it should be pointed out that there remains the need to study the effectiveness of mAbs on new variants, along with the need to closely monitor their susceptibility in vitro that could provide the rationale for their use in vivo (if consistent with the doses administered in the therapeutic range or risk toxicity to achieve efficacy in clinical practice) [35]. Indeed, the current recommendations for treatment of COVID-19 outpatients in Italy underline that, due to a constantly evolving epidemiological landscape, the indication for the use of specific mAbs may vary over time depending on the SARS-CoV-2 variant prevalent in the country and the sensitivity to the different mAbs available [36]. More recently, the SIMIT (Italian Society for Infectious and Tropical Diseases) has recommended that early treatment with mAbs be given to fragile patients (immunocompromised, patients with tumors or with chronic

renal impairment) and/or patients who are at high risk [37].

EARLY TREATMENT WITH ANTIVIRALS

Antivirals have the potential to reduce the viral load (VL) and viral spread, as well as affect outcomes of infection. Early use of antivirals, meaning as soon as possible and within 5 days of symptom onset, has the potential to reduce viral replication and the ensuing cytokine storm as well as decrease morbidity, mortality, and the costs of healthcare [38]. Three antiviral drugs against SARS-CoV-2 were initially available in Italy: remdesivir (RDV), molnupiravir (MPV), and nirmaltrelvir/ritonavir (NMV/r), all for adults with COVID-19 who do not require supplementary oxygen therapy and are at risk of progression to severe forms of illness [39]. Criteria to differentiate patients into risk categories have been made available by AIFA [39].

Remdesivir

Remdesivir (Veklury®) is a viral RNA polymerase inhibitor developed by Gilead Sciences in 2017 as a potential antiviral agent given intravenously for Ebola virus. RDV obtained authorization for emergency use for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized patients with pneumonia requiring supplemental oxygen from the U.S. Food and Drug Administration (FDA) in May 2020, and from the European Medicines Agency (EMA) in June 2020 [40]. A conditional approval was obtained by the EMA on July 2020 and full approval by the FDA on October 22, 2020. In December 2021 the indication was also extended to treat non-hospitalized patients with COVID-19 with mild-to-moderate COVID-19 and at risk for progression to severe disease who do not require supplemental oxygen, within 7 days from the onset of symptoms [41, 42].

RDV was approved for early treatment of COVID-19 based on the results of the PINETREE trial [43]. This was randomized, double-blind, placebo-controlled trial involving non-hospitalized patients with COVID-19 with symptom onset within the previous 7 days and at least one risk factor for disease progression. Patients in the active treatment arm received intravenous RDV. In all, 562 patients were randomized, the mean age was 50 years, and the most common coexisting conditions were diabetes mellitus, obesity, and hypertension. COVID-19–related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) patients receiving placebo (HR, 0.13; 95% CI 0.03 to 0.59; p = 0.008). The proportion of adverse events was similar in both groups.

Between 2020 and 2023, 55 studies on the use of RDV for early treatment of SARS-CoV-2 were published by Italian groups and are available on PubMed.

Studies in non-hospitalized patients

To evaluate whether early use of RDV is associated with reduced COVID-19 progression in a homogeneous cohort of patients with mild to moderate COVID-19, a prospective observational study was carried out by Falcone *et al.* [44]. Patients who received early (≤5 days from onset of symptoms) versus late (>5 days from onset of symptoms) RDV were compared; according to this study the early administration of RDV was associated with a 51% of reduction of disease progression [44].

Mazzitelli *et al*. performed a real-life analysis of all patients given early RDV compared to patients who received no antiviral therapy [45]. The analysis included 681 patients with a median age of 66 years. Both vaccination against SARS-CoV-2 and early RDV were associated with a reduced risk of hospitalization. Early RDV was also associated with a shorter duration of positivity for SARS-CoV-2 and related as well as with a lower rate of COVID-19 sequelae vs. the control group. More recently, Scotto *et al*. carried a real-life analysis of early administration of RDV alone or in combination with mAbs to prevent progression to severe COVID-19 in 62 high-risk patients with mild/moderate disease [46]. Overall, 8% of patients progressed to severe COVID-19 with similar rates in patients administered RDV alone (6.7%) or in combination with mAbs (9.4% p=0.531).

Regardless of the treatment of severe cases in a hospital setting, in Italy, the early administration of RDV is currently recommended by AIFA for patients with defined risk factors, within 7 days from symptom onset, to be administered intravenously for three consecutive days in outpatient clinics [36].

Studies in hospitalized patients

In hospitalized patients, a number of comparative, non-randomized and observational studies have demonstrated advantages with the use of RDV for

severe COVID-19 pneumonia for several endpoints [47-49]. In contrast, the monocentric retrospective study by Campogiani *et al*. did not find that administration of RDV (or other antivirals) influenced the VL in hospitalized patients [50]. An Italian registry-based study including all hospitalized patients in Italy with COVID-19 and treated with RDV (16,462 patients) was published by Russo *et al*.; it was reported that mortality at 15 (7.1%) and 29 days (11.7%) was higher than that observed in the ACTT-1 and ACTT-2 trials, which was likely due to the older age of patients [40]. A number of studies in hospitalized patients with mild-moderate COVID-19 published by Italian authors have reported contrasting findings with either positive [51-54] or negative results [55-59].

Molnupiravir

MPV (Lagevrio®) is an orally available, small-molecule ribonucleotide prodrug of β-D-N4-hydroxycytidine (NHC) with potent, broad-spectrum in vitro activity against coronaviruses, including SARS-CoV-2 variants of concern, and a high barrier to the development of resistance that was under development by MSD [60]. In light of the rising rates of infection and deaths due to COVID-19 across the EU, on November 15, 2021 the human medicines committee (CHMP) of the EMA issued advice on the use of MPV to support national authorities who may decide on possible early use of the medicine prior to marketing authorization, for example in emergency use settings, for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of developing a severe form of illness [61]. On December 23, 2021, the FDA approved MPV for emergency as treatment of mild-to-moderate COVID-19 in adults with high risk for progression to severe COVID-19 [62].

The main study presented by the developer to support the application for MPV was a randomized, placebo-controlled trial enrolling 1433 non-hospitalized adults aged 18 years or older with mild to moderate COVID-19 (MOVe-OUT) demonstrated that with COVID-19 receiving MPV showed faster normalization of C-reactive protein (CRP) and oxygen saturation (SpO2), decreased need for respiratory interventions, when hospitalized were discharged a median of 3 days earlier, and needed fewer acute care visits and COVID-19–related acute care visits compared with patients who received placebo [63]. However, the MOVe-IN study in hospitalized patients with COVID-19 did not demonstrate any clinical benefit with the administration of MPV [64].

Between 2020 and 2023, 58 studies on the use of MPV for treatment of COVID-19 were published by Italian groups and are available on PubMed. Observational studies have also been conducted in outpatients. Pontolillo *et al*. reported on a retrospective cohort of 100 patients receiving MPV, with 100.0% compliance to the antiviral treatment. No patient required hospitalization due to worsening of respiratory function or the appearance of serious side effects. The median downtime of VL was 10 days (IQR 8.0–13.0), regardless of the type of vaccination received [65]. Scioscia *et al*. prescribed MPV to 74 patients with COVID-19 (age range 26–96 years), including 10 affected by idiopathic pulmonary fibrosis, which led to regression of symptoms in all patients. No patients were hospitalized and/or showed sequelae [66]. Bruno *et al*. reported on administration of MPV to 168 subjects with an age ≥80 years with COVID-19 and mild-to moderate illness; in this cohort, hospitalizations (12.5%) and mortality (5 deaths) at 28 days remained low [67].

On February 24, 2023, the EMA CHMP formulated a negative opinion regarding MPV due to failure to demonstrate a clinical benefit in terms of reduction in mortality and hospital admissions in the main study in over 1,400 non-hospitalized, unvaccinated adults. Based on the CHMP considerations, despite having verified the absence of details safety issues related to the treatment, the Italian Scientific Technical Advisor Committee (CTS) of AIFA established that - similarly to what has already been decided by most of the European countries in which it was foreseen an emergency distribution authorization – the use of MPV in COVID-19 patients was suspended starting from March 11, 2023 [68]. On June 21, 2023, the developer withdrew its application for marketing authorization for MPV for the treatment of COVID-19 in adults [69].

Nirmatrelvir and ritonavir

Nirmatrelvir and ritonavir (Paxlovid®) is a co-packaged medication developed by Pfizer, and currently the only oral antiviral for SARS-CoV-2 available in Italy. According to the Summary of Product Characteristics, NMV/r is recommended

for adults with COVID-19 who do not require additional oxygen therapy and are at increased risk of progression to severe COVID-19 forms; this oral therapy should be administered as soon as possible after diagnosis, and no later than 5 days after the onset of symptoms [70].

In the EU, NMV/r received conditional marketing authorization on January 28, 2022 and full marketing authorization on February 24, 2023 [71].The FDA approved NMV/r on May 25, 2023 for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19 [72]. Nirmatrelvir inhibits SARS-CoV-2 main protease (Mpro) and has potent pan–human-coronavirus activity in vitro. Mpro is an appealing target because it is essential in the viral replication cycle and has a low probability of off-target activity given the lack of human analogues. Ritonavir has been used as a pharmacokinetic booster of other protease inhibitor antivirals predominantly due its potent inhibition of cytochrome P450 3A4, thus increasing plasma concentrations of nirmatrelvir [73, 74].

NMV/r was approved based on the results of the EPIC-HR study in which 2246 patients at high risk of progression to severe disease were randomized to NMV/r or placebo [75]. Treatment of symptomatic COVID-19 with NMV/r was associated with a risk of progression to severe disease that was reduced by 89% compared to placebo if patients were treated within 3 days from the onset of COVID-19 symptoms. Moreover, when treatment was initiated within 3 days after the onset of symptoms, the VL was lower with NMV/r than with placebo at day 5 of treatment (adjusted mean difference -0.868 log10 copies per mL). This thus reinforces that early treatment is beneficial. In an analysis of data on prescriptions of mAbs and antivirals in England and Italy from December 2021 to October 2022, NMV/r was the most frequently prescribed antiviral in both countries for early treatment of outpatients [76]. In the study by Mazzotta *et al*., NMV/r significantly reduced VL compared to all the other drugs except vs. MPV in strain BA.2. MP was superior to RDV in both BA.1 and BA.2, and to sotrovimab in BA.2. Sotrovimab had greater activity than RDV only against BA.1 [77]. Between 2020 and 2023, 20 studies on the use of NMV/r for early treatment of SARS-CoV-2 were published by Italian groups and available on PubMed.

As already mentioned, differences in real-world studies can be expected compared to randomized clinical trials due to the differences in the populations treated for characteristics such as vaccination status, dominant circulating variants, comorbidities, etc. Several observational studies have attempted to evaluate the effectiveness of various antivirals, since head-to-head clinical trials are lacking. In a retrospective analysis on 257 patients with SARS-CoV-2 infection treated with oral antivirals during the Omicron surge in Italy, 56.8% received MPV and 43.2% were administered NMV/r [78]. There were three hospitalizations with MPV (2.1%) and one with NMV/r (0.9%). The authors reported a low rate of hospitalization, death, and adverse drug reactions, which were lower than those reported in pivotal clinical trials. In a retrospective cohort study on 909 patients prescribed MPV (n=407) or NMV/r (n=502), 124 (13.6%) patients experienced an adverse event, 79% of which were grade 1; 18.5% were grade 2 and only 2.5% were grade 3 [79]. There were also more adverse events in women and in those treated with patients treated with NMV/r. In contrast with the smaller real-world study on 257 patients, in this analysis adverse events were higher than those reported in clinical trials. The real-world study by del Borgo *et al*. on 1118 patients reported that RDV, MPV, and NMV/r all had similar efficacy in inhibiting progression to severe COVID-19 and no serious adverse effects [80].

In a very recent nationwide cohort study from AIFA, Torti *et al*. compared mortality in patients with SARS-CoV-2 infection and at risk for clinical progression who were treated with MPV or NMV/r during the Omicron era in Italy. It was reported that early initiation of NMV/r was associated with a significantly reduced risk of all-cause mortality at day 28 compared to MPV [81]. In particular, the study evaluated 17,977 patients treated with MPV and 11,576 patients with NMV/r, 87% of whom had received a full-course of vaccination. The incidence of crude all-cause mortality was higher with MPV (51.83 per 100,000 person-days) compared to NMV/r (22.29 per 100,000 person-days). This large study contributed to the better understanding of real-life therapeutics for COVID-19 [82].

In another large real-world cohort of 1,342 outpatients (94% vaccinated), no differences were found among treatment with MPV, NMV/r, and RDV in terms of rates of clinical recovery or hospitalization [83]. Another real-world analysis on 562 out-

patients has also been published that compared NMV/r, MPV, and RDV [84]. The primary endpoint was a composite of death or hospitalization and occurred in 0.8%, 1.8%, and 5.1% of patients receiving NMV/r, MPV, and RDV, respectively (ANOVA among groups p=0.012). Other cohort studies (even during the Omicron era) have also suggested that early treatment with antivirals and/or mAbs is associated with a lower risk of hospitalization, progression, and mortality at 30 days, particularly among subjects who are at high risk of disease progression. In a retrospective study of 719 patients, 554 (77%) receiving MPV and 165 (23%) receiving NMV/r, Bruno *et al*. reported that there were no differences between the two antivirals and that early use of these antivirals limited a composite outcome of all-cause hospitalization and/or death at 30 days in patients at high risk of progression [38]. Several additional real-world studies have all confirmed that early antiviral therapy is beneficial in terms of reducing VL as well as preventing hospital admission and/or mortality from COVID-19 [32, 83, 85-88].
Bai *et al*. carried out a retrospective analysis comparing viral clearance in high-risk patients with mild-moderate COVID-19 and treated with MPV (92/376; 43.8%), NMV/r (150/376; 24.7%), or RDV (134/376; 31.5%) [89]. NMV/r was associated with a higher proportion of viral clearance at day 7 and a shorter time to viral clearance compared to MPV and RDV, even after adjustment for age and immunodeficiency. Notwithstanding, there was little difference in clinical recovery rates among the 3 treatments (97.5% for MPV, 98.3% for NMV/r, and 93.6% for RDV).

LONG COVID

The WHO has defined long COVID as the "continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation" [90]. Long COVID may have a vast range of symptoms and affects 10-20% of people infected with SARS-CoV-2. Some authors have suggested that early administration of mAbs and antivirals may lower the risk of developing long COVID [85, 91]. In a retrospective analysis of 649 patients who were treated with mAbs (37%) or antiviral drugs (30%), data on long COVID at 3 months was available for 50% of patients [85]. There was a significant beneficial effect of early use of both antivirals and mAbs on long COVID (any symptoms) [85]. In a retrospective propensity score-matched case-control study of 737 patients at high risk for progression, antiviral agents or mAbs were administered to those not requiring oxygen therapy or hospital admission [91]. Long COVID was reported in 28% of cases, although early use of antivirals and mAbs were both associated with a reduced risk of long COVID. In a survey carried out by telephone among 97 patients with cancer who underwent or not previous treatment with early therapy for SARS-CoV-2, 12 patients (12.4%) referred long COVID with no significant difference between those receiving or not early therapy [92]. In any case, at present there are no therapies approved for long COVID, which is a topic of great interest and warrants further studies to better clarify its pathophysiology and long-term consequences [93]. Long COVID has also been considered by some to be a fourth phase of SARS-CoV-2 infection [94].

ONCO-HEMATOLOGICAL PATIENTS

Among high-risk COVID-19 patients, those with hematological malignancies or who have undergone hemopoietic stem cell transplantation and are immunocompromised have a greater risk of progression to severe forms of COVID-19 compared to the general population [95]. Patients with hematologic malignancies have higher levels of immunosuppression and as a result may develop more respiratory viral infections that are more severe than patients with solid tumors. In addition, persistent positivity for SARS-CoV-2 and increased VL has the potential to lead to delays or temporary discontinuation of oncological therapies. Thus, all these considerations render patients with hematological malignancies worthy of special attention [96-98].
The EPICOVIDEHA survey on over 3000 elderly patients with hematological malignancies infected with SARS-CoV-2 reported that 90-day survival for patients with COVID-19 was 71%, with significant differences between age groups. Moreover, the first pandemic wave mainly affected patients >80 years, while the second wave was more severe for those aged 65-70 years; the third wave was the least severe in all age groups [99]. A retrospective study of patients with hematological malignancies

treated for mild/moderate COVID-19 between March 2021 and July 2022 found that, even though the rate of treatment failure was lower in the Omicron versus the pre-Omicron period (7.8% versus 36.8%, p<0.001), there was still a significant risk of early treatment failure and a high rate of mortality [100]. Minoia *et al*. also reported similar data on patients with hematological malignancies with COVID-19, with all-cause mortality at 90 days of 13.4%, despite early treatment with antiviral agents (NMV/r or MPV) [101].

Encouraging data have been reported on the early use (within 5 days of onset of symptoms) of antivirals alone in vaccinated patients with a variety of solid tumors and undergoing treatment for no more than 5 days in the study by Lasagna *et al*. [102]. These authors presented data on 69 patients with a variety of solid tumors and mild-moderate COVID-19. In all, 49 patients received early therapy and only one patient (14.5%) required hospitalization for COVID-19. In a case series of 10 patients with multiple myeloma receiving NMV/r (n=10) or MPV (n=5), there were two hospitalizations but no deaths [103]. In patients with hematological malignancies, it has also been reported that early antiviral treatment reduced the incidence of pulmonary failure and mortality [101]. However, other authors have reported that early treatment with an antiviral for COVID-19 was not effective in reducing the rate of hospitalization or viral shedding in patients with hematological malignancies [104].

Currently, patients with hematological malignancies are still facing an elevated vulnerability to severe outcomes, resulting in higher rates of hospitalization and mortality over time, underlining the importance of continuous monitoring and targeted interventions to optimize outcomes for this vulnerable group beyond the pandemic phase of COVID-19 [105]. Despite the use of vaccines, monoclonal antibodies and antivirals in the Omicron era, which significantly lessened the impact of the infection, mortality is still high and the incidence of persistent symptomatic forms, which delay the use of chemotherapy, remains elevated [105]. The use of off-label combination antiviral therapies has been found to be effective in treating immunocompromised people with prolonged COVID-19 symptoms and evidence of ongoing viral replication, and could represent the therapy of choice in these high-risk patients, although their optimal management is currently undefined [106].

CONCLUSIONS

Drug development efforts for COVID-19 brought about the authorization of three broad classes of antivirals, RdRp inhibitors (RDV), Mpro inhibitors (NMV/r), and mAbs that can all help to improve clinical outcomes, especially in patients with a high risk of progression to severe disease. Notwithstanding, effective, easy to use, and less costly therapies are still desirable along with agents that are effective against new variants. The development of pan-coronavirus inhibitors would also be an important contribution and could also potentially help prevent future outbreaks of pathogenic coronaviruses. COVID-19 continues to have significant impact on individuals, especially vulnerable and elderly patients. The COVID-19 pandemic was fast moving, and as consequence observational studies have sometimes given contrasting results largely due to the rapidly changing situation in terms of vaccination status and timing and predominant variants of concern, for example. This has made it difficult to quickly understand the real-world utility of different therapies in the treatment of COVID-19, which is further complicated by the fact that many symptoms are self-reported, leading to large heterogeneity across studies. However, overwhelming real-world evidence has shown that early antiviral therapies are beneficial for patients, despite changing variants. There are no surprises in the safety profile of these agents in the real-world, which are well tolerated with few severe adverse events. Among the current unmet needs, a clear and universal definition for long COVID along with treatments and prevention are still lacking as is clarity of the pathogenetic mechanisms responsible for it. Lastly, local, national, and international guidelines should always be updated in a timely manner.

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