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REVIEW



# Antiviral treatment selection for SARS-CoV-2 pneumonia

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**ABSTRACT**

**Introduction:** Therapy of coronavirus disease 2019 (COVID-19) involves evolving algorithms that include drugs aimed at reducing disease progression by counteracting two different, but intertwined processes: (*i*) the damage caused by the virus (with antivirals); (*ii*) the damage caused by a dysregulated host response (with immunomodulatory agents).

**Areas covered:** Herein, we discuss the available evidence on the efficacy and safety of antiviral agents employed over the past months for the treatment of COVID-19, and the reasons to be considered for antiviral selection.

**Expert opinion:** The available evidence from randomized controlled trials (RCT) currently discourages the use of lopinavir/ritonavir, hydroxychloroquine, and interferons, which did not show improved efficacy compared to standard care or placebo. Regarding remdesivir, the current body of evidence may conditionally support its use in COVID-19 patients requiring oxygen supplementation but still not requiring invasive mechanical ventilation. Finally, neutralizing monoclonal antibodies have been proven efficacious in reducing the risk of severe disease development if administered early in the course of the disease to patients at risk of progression. The results of the ongoing RCT will certainly be crucial to further improve our understanding of the optimal place in therapy of antiviral agents for COVID-19.

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SARS-CoV-2; COVID-19; coronavirus; antiviral; remdesivir; hydroxychloroquine; lopinavir/ritonavir

## 1. Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is a systemic infectious process, mostly (but not only) presenting as a respiratory disease, with severity ranging from mild forms to acute hypoxemic respiratory failure needing invasive mechanical ventilation [1–3]. Many physiopathological features of COVID-19 are still unknown, but some major mechanisms have been identified: (*i*) direct virus-mediated cellular cytotoxicity; (*ii*) dysregulation of the renin–angiotensin–aldosterone system; (*iii*) dysregulated host response; (*iv*) endothelial cell injury with proinflammatory and thrombotic cascades; (*v*) fibrotic tissue reaction [4].

The treatment of COVID-19 currently involves continuously evolving algorithms that were initially based on off-label or compassionate administration of drugs aimed at reducing disease progression by counteracting two different, but intertwined processes: (*i*) the damage caused by the virus (with antiviral agents); (*ii*) the damage caused by the dysregulated host response (with immunomodulatory agents) [5–7]. The strategy of aiming at two different targets has not changed over the past 12 months, but now results from large randomized controlled trials (RCTs) have become available to optimize and guide the therapy for COVID-19 with more solid evidence, although further improvements could and will certainly emerge from still ongoing RCTs.

In the present narrative review, we discuss the available evidence on the efficacy and safety of antiviral agents employed over the past months for the treatment of COVID-19, and the reasons to be considered for antiviral selection.

## 2. Methods

The structure of the present narrative review was finally agreed by all authors to be divided into the following main sections: (*i*) lopinavir/ritonavir; (*ii*) umifenovir and favipiravir; (*iii*) remdesivir; (*iv*) hydroxychloroquine; (*v*) neutralizing monoclonal antibodies; (*vi*) other antivirals and agents showing antiviral activity *in vitro*; (*vii*) conclusion; (*viii*) expert opinion. An inductive PubMed search for each section was conducted by different groups of authors, using various combinations of pertinent keywords. Eventually, the different drafts were merged into a final manuscript that was approved by all authors.

## 3. Lopinavir/ritonavir

Lopinavir/ritonavir (LPV/r) is employed for treating infections caused by human immunodeficiency virus 1 (HIV-1). LPV is an HIV protease inhibitor administered in association with ritonavir

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**Article highlights**

- At the very beginning of the COVID-19 pandemic, the use of antiviral agents for treating SARS-CoV-2 infection was mostly based on the promising results of in vitro studies or limited, previous experiences in patients with SARS-CoV infection
- The available evidence from RCT currently discourage the use of lopinavir/ritonavir, hydroxychloroquine and interferons, which did not show improved efficacy compared to standard care or placebo.
- With regard to remdesivir, the current body of evidence may support its use in COVID-19 patients requiring oxygen supplementation but still not requiring invasive mechanical ventilation.
- Research efforts in this field should not be discontinued. Indeed, the results of ongoing RCT will certainly be crucial to further improve our understanding of the optimal place in therapy of antiviral agents for COVID-19.

(which acts as booster, increasing plasma half-life of LPV). LPV is also an inhibitor of the severe acute respiratory syndrome coronavirus (SARS-CoV) main protease, a protein crucial for viral replication which is highly conserved also in SARS-CoV-2 [8,9]. In 2003, two retrospective matched cohort studies indicated a possible favorable effect of LPV/r in patients with SARS-CoV infection [10,11], thus ; thus, it seemed reasonable, at least initially, to evaluate its possible use also in patients with SARS-CoV-2 infection. In this regard, preliminary data in a ferret animal model of SARS-CoV-2 infection showed how LPV/r marginally reduced clinical symptoms but did not significantly impact virus titers [12]. Nevertheless, due to the widespread availability and lack of alternatives, the drug was widely employed in the first phases of COVID-19 pandemic.

Initial retrospective reports described a reduced viral shedding in patients treated with LPV/r plus interferon-α [13], but subsequent larger studies of the same type reported opposite results [14]. In a multicentre, prospective, open-label, randomized, phase 2 trials conducted in Hong Kong, an early triple antiviral therapy with LPV/r plus ribavirin plus interferon-β-1b was safe and more efficacious than LPV/r alone in alleviating symptoms and shortening the duration of viral shedding (7 days vs. 12 days) and hospital stay (9 days vs. 14.5 days) in patients with mild to moderate COVID-19 [15]. Other doubts about any possible true LPV/r efficacy were suggested by a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection conducted in China. In this study, treatment with LPV/r was not associated, in comparison with standard care, with a difference in the time to clinical improvement (hazard ratio [HR] for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80) and mortality at 28 days (19.2% vs. 25.0%; difference, −5.8%; 95% CI, −17.3 to 5.7). Furthermore, the percentages of patients with detectable viral RNA at various time points were similar. Overall, no substantial benefits of LPV/r treatment were observed compared to standard care [16]. Similar results were provided by the RECOVERY trial, a large, randomized, controlled, open-label, platform trial, performed across 176 hospitals in the United Kingdom. In this trial, treatment with LPV/r plus standard care was not associated with a reduction in 28-day mortality (23% vs 22%), duration of hospitalization (median of 11 days in both groups), and progression to invasive mechanical ventilation (4% in both groups) when compared to standard care [17]. Finally, in the large, worldwide, World Health Organization (WHO)-sponsored SOLIDARITY trial, the main outcome of death occurred in 148 of 1,399 patients receiving LPV and in 146 of 1,372 receiving its control (rate ratio [RR], 1.00; 95% CI, 0.79 to 1.25). No differences in the RR for in-hospital deaths were observed even when patients were stratified by age (<50 years, 50–69 years, ≥70 years) and respiratory support (no mechanical ventilation vs mechanical ventilation) at enrollment. Finally, also the secondary outcomes, initiation of ventilation and time to discharge, were not reduced in patients treated with LPV/r. The WHO's living guidelines did not report any difference between LPV/r and standard care in terms of mortality, progression to mechanical ventilation, viral clearance at 7 days, length of hospitalization, and time to symptoms' resolution, recommending against the use of LPV/r in COVID-19 patients [18].

## 4. Umifenovir and favipiravir

Umifenovir (Arbidol®, ARB), is approved for the prophylaxis and treatment of influenza A and B virus infections in China and Russia [19]. ARB inhibits virus-mediated fusion with the target membrane and blocks virus entry into target cells [20]. Activity of ARB against Coronaviridae has been reported *in vitro* [21,22], with a 50% maximal effective concentration and a 50% cytotoxic concentration of 4.11 (3.55–4.73) and 31.79 (29.89–33.81) μM, respectively, and a clear dose-response curve [23].

The whole number of enrolled patients in studies assessing the use of ARB in patients with SARS-CoV-2 infection is quite limited, with conflicting evidence [19]. An RCT evaluated hydroxychloroquine (HCQ) followed by LPV/r in comparison to HCQ followed by ARB, with primary outcomes hospitalization duration and a composite score of clinical improvement at 7 days after admission. The study population was quite limited, being composed of two arms of 50 patients. Overall, the duration of hospitalization in the ARB group was shorter than in the LPV/r arm (7.2 versus 9.6 days) [24].

Favipiravir (FPV) inhibits the RNA-dependent RNA of RNA viruses, and is approved for the treatment of influenza in China and Japan [25]. *In vitro* results showed its ability to inhibit SARS-CoV-2 in Vero E6 cells, with a half-maximal effective concentration of 61.88 μM and a half-cytotoxic concentration >400 μM, prompting several *in vivo* studies [26]. In a Russian adaptive, multicenter, open label, randomized, phase 2/3 clinical trial of FPV versus standard care in hospitalized patients with moderate COVID-19, patients treated with FPV achieved viral clearance (62.5% vs 30% at day 5, 92.5% vs 80% at day 10) and apyrexia faster (median of 2 days vs 4 days) than those receiving standard care only [27]. Conflicting results were provided by other small studies, with some [28–30] suggesting a faster achievement of clinical cure in patients receiving FPV and others not [31]. It should be noted that in some studies FPV has been administered in combination with inhaled

interferon, therefore results must be interpreted with caution given potential confounders [28,31].

## 5. Remdesivir

Remdesivir (RDV or GS-5734) is a prodrug of a nucleotide-analog, a wide-spectrum antiviral that has been developed against the genus *Ebolavirus* [32]. It has *in vitro* activity against Coronaviridae such as SARS-CoV-2, and animal studies have supported its potential beneficial effects [26,33,34]. The mechanism of action of remdesivir ultimately results in the inhibition of SARS-CoV-2 RNA-dependent RNA-polymerase, which is highly conserved across Coronaviridae, thereby representing an important target for antiviral development [35].

Wang and colleagues [36] conducted the first double-blind, placebo-controlled, randomized trial to investigate the efficacy of a 10-day treatment course of RDV in hospitalized patients with an oxygen saturation of <94% in room air (or a PaO2/FiO2 of <300 mmHg) and pneumonia. In this trial, 158 patients were randomized to RDV, and 79 patients to placebo. Time to clinical improvement before day 28, the primary outcome, was not met by RDV (HR 1.23; 95% CI 0.87 to 1.75) [36]. The 28-day mortality rates were 14% (22/158) in the RDV arm and 13% (10/79) in the placebo arm (difference of 1.1%; 95% CI −8.1% to 10.3%).

Subsequently, a double-blind, randomized, placebo-controlled study was conducted in patients with COVID-19 (Adaptive COVID-19 Treatment Trial [ACTT-1]) [37]. Five hundred and forty-one patients were randomized to 10 days of RDV and 521 to 10 days of placebo. The primary outcome measure was time to recovery, and the median period to recovery in patients receiving RDV was 10 days vs. 15 days in patients receiving placebo (RR 1.29; 95% CI 1.12 to 1.49). Participants were also divided into four main subgroups: without supplementary oxygen, with any supplemental oxygen, requiring noninvasive ventilation/high-flow oxygen, and requiring mechanical ventilation or extracorporeal membrane oxygenation. The RR for recovery of these groups were 1.29 (95% CI 0.91 to 1.83), 1.45 (95% CI 1.18 to 1.79), 1.09 (95% CI 0.76 to 1.57), and 0.98 (95% CI 0.70 to 1.36), respectively. In the intent-to-treat population, the HR for 14-day mortality was 0.55 (95% CI 0.36 to 0.83) and the HR for 28-day mortality was 0.73 (95% CI 0.52 to 1.03). Notably, RDV was associated with a reduced 14-day mortality (HR 0.28; 95% CI 0.12 to 0.66) and 28-day mortality (HR: 0.30; 95% CI 0.14 to 0.64) in patients needing any extra oxygen but not requiring MV. Serious side effects were reported in 131 (24.6%) patients who received RDV and in 163 (31.6%) patients who received a placebo.

In the SIMPLE-severe trial, an open-label RCT comparing 5- vs. 10-day courses of RDV, 397 hospitalized patients not receiving invasive mechanical ventilation were enrolled [38]. On day 14, 64% (129/200) and 54% (107/197) of the patients had clinical improvement in the 5- and 10-day groups, respectively [36]. Adverse events (AEs) were distributed equally in the 5-day and 10-day arms, but severe AEs were more frequent in latter [38].

Afterward, Spinner and colleagues randomized patients with mild-moderate COVID-19 pneumonia to three arms: 10-day RDV, 5-day RDV, or standard treatment, respectively [39]. Clinical improvement at day 11 was registered in 70% patients in the 5-day RDV arm (135/193), in 65% of patients in the 10-day RDV arm (126/193) and in 60% of the patients in the standard treatment arm (121/200) [39]. Mortality was 0% (0/191) in the 5-day RDV arm, 1% (2/193) in the 10-day RDV arm, and 2% (4/200) in the standard treatment arm.

Preliminary data have also been provided by the WHO Solidarity trial, a large, global, open-label randomized study involving over 11,000 COVID-19 patients in 405 hospitals in over 30 countries [40]. RDV was one of the four treatment alternatives (with lopinavir/ritonavir, hydroxychloroquine, and interferon beta-1a), each compared with standard care, and the primary outcome was in-hospital mortality. Secondary outcomes were the initiation of ventilation and the duration of hospitalization [40]. None of the four treatments showed any benefit, although one limitation was a lack of data on the duration of symptoms before RDV initiation, and the direction of the effect in the subgroup of patients not requiring invasive ventilation treated with RDV was toward improved survival (see expert opinion below) [40].

## 6. Hydroxychloroquine

At the beginning of the pandemic, the proposal of HCQ for treating COVID-19 patients was based on its possible immunomodulatory effects and *in vitro* anti-SARS-CoV-2 activity [41]. An early small observational retrospective study by Gautret et al. suggested (exploratorily) a possible beneficial effect in reduction of SARS-CoV-2 viral load in specimens from the respiratory tract [42]. However, other subsequent exploratory studies yielded contradictory findings, more often suggesting no beneficial effect on different endpoints [43–45].

In an open-label RCT, 194 participants were randomized to HCQ (400 mg twice daily on the first day, then 200 mg twice daily for a total of 15 days) or standard treatment alone. All patients were hospitalized but not mechanically ventilated at enrollment [46]. With regard to primary endpoints, recovery within 28 days was registered in 54% of the patients in the HCQ arm (52/97) and in 34% of the patients in the standard care arm (33/97) [46]. Overall, 4.1% (4/97) of the HCQ patients and 5.2% (5/97) of the standard group patients required invasive mechanical ventilation by 28 days, and 28-day mortality was 6% (6/97) in HCQ-treated patients and 5% (5/97) in patients receiving standard care alone.

Another open-label RCT randomly allocated hospitalized COVID-19 patients with mild-to-moderate disease into three arms: standard care, HCQ (400 mg twice daily for 7 days) plus standard care or HCQ (400 mg twice daily for 7 days) plus azithromycin (500 mg once daily) plus standard care [47]. With respect to the primary efficacy endpoint, i.e., clinical status at day 15, no advantage was observed for HCQ or azithromycin plus HCQ vs. standard care (OR 1.21, 95% CI 0 to 2.12, and OR 0.99, 95% CI 0 to 1.73, respectively). Overall, 7.5% of HCQ patients (12/159) and 11.0% of HCQ plus azithromycin patients required invasive mechanical ventilation vs. 6.9% (12/173) of those receiving standard care (OR 1.15 for HCQ, 95% CI 0.49 to 2.70, and OR 1.77 for HCQ plus azithromycin, 95% CI 0.81 to 3.87). In-hospital mortality was 4.4% (7/159), 2.9% (5/172), and 3.5% (6/173) in patients in the HCQ, HCQ plus azithromycin, and standard care arms, respectively.

In the RECOVERY RCT, different treatments were evaluated for patients hospitalized with COVID-19, using 28-day mortality as

the primary efficacy endpoint [48]. The 28-day mortality was 27% in the HCQ arm (421/1561) and 25% (790/3155) in the standard care arm (RR 1.09, 95% CI 0.97 to 1.23). In patients without mechanical ventilation at enrollment, an increased risk of disease progression (composite of mechanical ventilation or death) was registered in the HCQ arm (RR 1.14, 95% CI 1.03 to 1.27).

In the WHO Solidarity trial, HCQ was one of the four treatment alternatives (with lopinavir/ritonavir, RDV and interferon beta-1a) [40]. There was no benefit in the primary and secondary outcomes in the HCQ arm as compared to the standard treatment group. Finally, no effect of HCQ on short-term mortality in hospitalized COVID-19 patients was highlighted in two meta-analyses [49,50]. Three RCTs investigated changes in viral load as primary endpoints, also showing no substantial advantages [51–53].

## 7. Neutralizing monoclonal antibodies

Neutralizing monoclonal antibodies (mAbs) bind to the virus with high affinity and interfere with cell entry, as their target is the receptor-binding domain of the spike protein of SARS-CoV-2 (through which the virus interacts with the cell-surface angiotensin-converting enzyme 2 receptors, starting the entry process) [54]. Two combinations are currently available for emergency use in the US and Europe: (i) bamlanivimab plus etesevimab; (ii) casirivimab plus imdevimab. Bamlanivimab was previously available also as monotherapy, but the authorization for emergency use has recently been withdrawn in the USA due to an increased risk of impaired activity in patients harboring some SARS-CoV-2 variants (e.g., those including the E484K mutation) [55].

Neutralizing mAbs are administered to reduce the risk of progression to severe disease, following favorable evidence from RCTs. In a double-blind RCT conducted in 531 outpatients with mild to moderate COVID-19, 2800 mg of bamlanivimab plus 2800 mg were associated with improved decrease of viral load compared to placebo at day 11 (log viral load difference −0.57; 95% CI −1.00 to −0.14). Of note, 0% vs. 13.5% hospitalizations were observed in the subgroup of patients ≥65-year-old receiving bamlanivimab plus etesevimab vs. placebo, respectively [56]. In another double-blind RCT (interim analysis), casirivimab plus imdevimab were compared to placebo in 275 non-severe COVID-19 outpatients with onset of symptoms <7 days [57]. The least-squares mean difference between mAbs and placebo arms in the time-weighted viral load average change was −0.41 $\log_{10}$ cp per mL (95% CI −0.71 to −0.10), with the effect being more marked in serum-negative patients at baseline (−0.56 $\log_{10}$ cp per mL, with 95% CI from −1.02 to −0.11). Medical visits were necessary in 3% vs. 6% of the patients in casirivimab plus imdevimab vs. placebo arms, respectively [57].

## 8. Other antivirals and agents showing antiviral activity *in vitro*

Interferons have been proposed for the treatment of patients with COVID-19 based on their possible immunomodulatory effects and *in vitro* anti-SARS-CoV-2 activity [58]. In the WHO Solidarity trial, interferon beta-1a was administered subcutaneously in three doses of 44 μg over 6 days. The in-hospital mortality was 11.9% (243/2050) in the interferon beta-1a arm vs. 11.0% (216/2050) in the standard care arm, with a RR of 1.16 (95% CI 0.96 to 1.39) [40]. In the subgroup of patients not receiving mechanical ventilation at enrollment, progression to mechanical ventilation or death was similar in the two arms, with a RR of 0.99 (95% CI 0.80 to 1.24) [40]. On October 16, 2020, randomization to interferon beta-1a was ceased for futility [40]. On the other hand, some encouraging results were provided in a phase 2, double-blind RCT comparing nebulized interferon beta-1a (48 patients) vs. placebo (51 patients) for the treatment of hospitalized patients with COVID-19 [59]. The primary endpoint was a change in clinical conditions on the WHO Ordinal Scale for Clinical Improvement (OSCI) scale, with patients on the interferon beta-1a showing better improvement on the OSCI scale on day 15–16 than patients receiving placebo (odds ratio 2.32, with 95% CI from 1.07 to 5.04). No substantial differences were observed between arms in terms of tolerability, and deaths occurred in 0 and 3 patients in the interferon and placebo arms, respectively [59]. Larger RCTs remain necessary to confirm these preliminary positive findings.

The combination of favipiravir plus inhaled interferon beta-1b vs HCQ was evaluated in a RCT on 89 COVID-19 patients with moderate-to-severe COVID-19, showing no differences between the two groups regarding admission to the ICU, time to recovery, and mortality [31].

Daclatasvir (DCV) and sofosbuvir (SOF) are drugs used for treating hepatitis C, which have also been evaluated against SARS-CoV-2, with some promising effects in *in silico* and *in vitro* studies [60,61]. Two small (44 and 68 patients with moderate/severe SARS-CoV-2 infection), open-label RCT were conducted in Iran [62,63]: in one study adding SOF/DCV to standard care was associated with reduced length of hospital stay vs. standard care [62]; in the other one, mortality and ICU admissions were similar in the two arms (sofosbuvir/daclatasvir vs. standard care) [63].

Leflunomide, a pyrimidine synthesis inhibitor, was also evaluated in a single-center RCT [64]. Its use in patients with prolonged viral shedding showed no benefit in terms of the duration of viral shedding of the combination leflunomide/interferon alfa-2a vs. interferon alfa-2a alone [64].

Novaferon, a recombinant interferon-like protein, was evaluated alone or in combination with LPV/r, in patients with moderate to severe COVID-19: data reported a 3-day reduction in time to negative conversion of SARS-CoV-2 molecular tests for patients treated with novaferon alone or in combination with LPV/r compared to the LPV/r monotherapy, a preliminary finding deserving further investigation [65].

Finally, the antibiotic azithromycin has been reported to interfere with virus entry into cells [66]. The largest RCT currently available (1323 patients) is an open-label study conducted on outpatients with suspected COVID-19, with azithromycin resulting not associated with improved recovery compared with standard care alone (HR 1.08; 95% Bayesian credibility interval 0.95–1.23). Similar results were observed in the subgroup of patients with confirmed SARS-CoV-2 infection [67].

## 9. Conclusion

Based on moderate to high certainty of evidence stemming from RCT conducted in patients with COVID-19 that have

become available in the past few months, no substantial beneficial effects of lopinavir/ritonavir and hydroxychloroquine can be identified, whereas a limited, but favorable effect of remdesivir has been described in patients requiring oxygen supplementation still not subjected to invasive mechanical ventilation. Regarding ARB and FVP, large RCTs remain necessary to clearly delineate any possible place in therapy for these two antivirals.

While the available evidence may already be sufficient to support the development of dedicated guidelines, research efforts in this field should not be discontinued. Indeed, the results of ongoing RCT will certainly be crucial to further improve our understanding of the optimal place in therapy of antiviral agents for COVID-19.

## 10. Expert opinion

Selection of antiviral agents for the treatment of patients with COVID-19 has been an evolving process over the past 12 months. At the very beginning of the COVID-19 pandemic, the use of antiviral agents for treating SARS-CoV-2 infection was mostly based on the promising results of *in vitro* studies or limited, previous experiences in patients with SARS-CoV infection. This off-label and compassionate use was nonetheless much debated. On the one hand, the principle of "first, do not harm" certainly held true [7], discouraging the use of drugs outside approved indications without clinical studies providing sufficient evidence in terms of efficacy or effectiveness. On the other hand, at the beginning there were obviously neither clinical studies nor alternative agents for treating COVID-19 patients. From this perspective, in our opinion it was reasonable to consider the use of potentially effective agents (based on preliminary *in vitro* or *in vivo* data) in those patients worsening despite adequate supportive care, also as off-label/compassionate use whenever the patients could not be enrolled in RCTs (that remained the priority, in order to ultimately provide high certainty of evidence to optimize treatment algorithms and improve patients' care) [6].

Over the subsequent months, this scenario has, fortunately, rapidly changed, with the release of results from RCTs. The available evidence from RCTs, described in the previous sections, currently discourage the use of lopinavir/ritonavir, hydroxychloroquine and interferons, which did not show improved efficacy compared to standard care or placebo. With regard to remdesivir, the scenario is more complex. Indeed, while preliminary evidence from the open-label Solidarity RCT does not fully support use of remdesivir even in the subgroup of patients needing oxygen supplementation but not invasive ventilation (i.e., in those patients in whom the drug was efficacious in the ACTT-1 RCT), it is of note that the direction of the effect was toward reduced mortality (RR 0.86, with 95% CI 0.67–1.11), which is in line with the reduced mortality observed in the ACTT-1 RCT in the similar subgroup of patients who were not under invasive mechanical ventilation at baseline (HR for 28-day fatality 0.30, with 95% CI 0.-14–0.64) [37,40]. In our opinion, pending complete results of the Solidarity RCT, the current body of evidence may support the use of remdesivir in patients requiring oxygen supplementation but still not requiring invasive mechanical ventilation, although it should be acknowledged that the true magnitude of this favorable effect still remains controversial.

Eventually, we think three important points should be stressed. The first is that, after only 1 year of COVID-19, we are discussing the use of antivirals on the basis of RCT and not only observational studies. This is extremely important to optimize therapeutic algorithms, and has also shown us once again that, for anti-infective agents, observational studies may be strongly affected by residual and unmeasured confounding, and possibly by publication bias, and should only be considered as hypothesis-generating (i.e., to be confirmed/refuted by RCT, as correctly was the case for antivirals discussed in the present review). The second point is that, in addition to antivirals, immunomodulatory agents have also been (and still are) tested in RCT for the treatment of COVID-19, with well-known positive results for steroid administration in severely ill patients. From this standpoint, we think an intriguing field of research for the future is the combined use of antiviral and immunomodulatory agents, in the context of a balanced approach taking into account the possible different timing of administration and the different patients' phenotypes (based on laboratory or genetic data), which it is plausible may also explain why no antiviral treatment (if evaluated alone independent of immunomodulatory agents) has been proven very efficacious up to now, although this consideration still remains largely speculative pending further dedicated investigation. Finally, neutralizing monoclonal antibodies also interferes with viral activity (e.g., by preventing membrane fusion or by prompting antibody-dependent cell cytotoxicity [68]), and may be an important weapon against SARS-CoV-2 in the early phases of the disease. A proposal of treatment algorithm in patients with COVID-19, including the current role of antivirals pending further RCT results, is shown in Figure 1.

Overall, we truly welcome this new complex scenario, in which classical antiviral agents, neutralizing monoclonal antibodies, and anti-inflammatory or immunomodulatory agents are carving out their place in therapeutic algorithms based on RCT results (i.e., on high-level evidence) [69]. We should continue on this path.

## Declaration of interest

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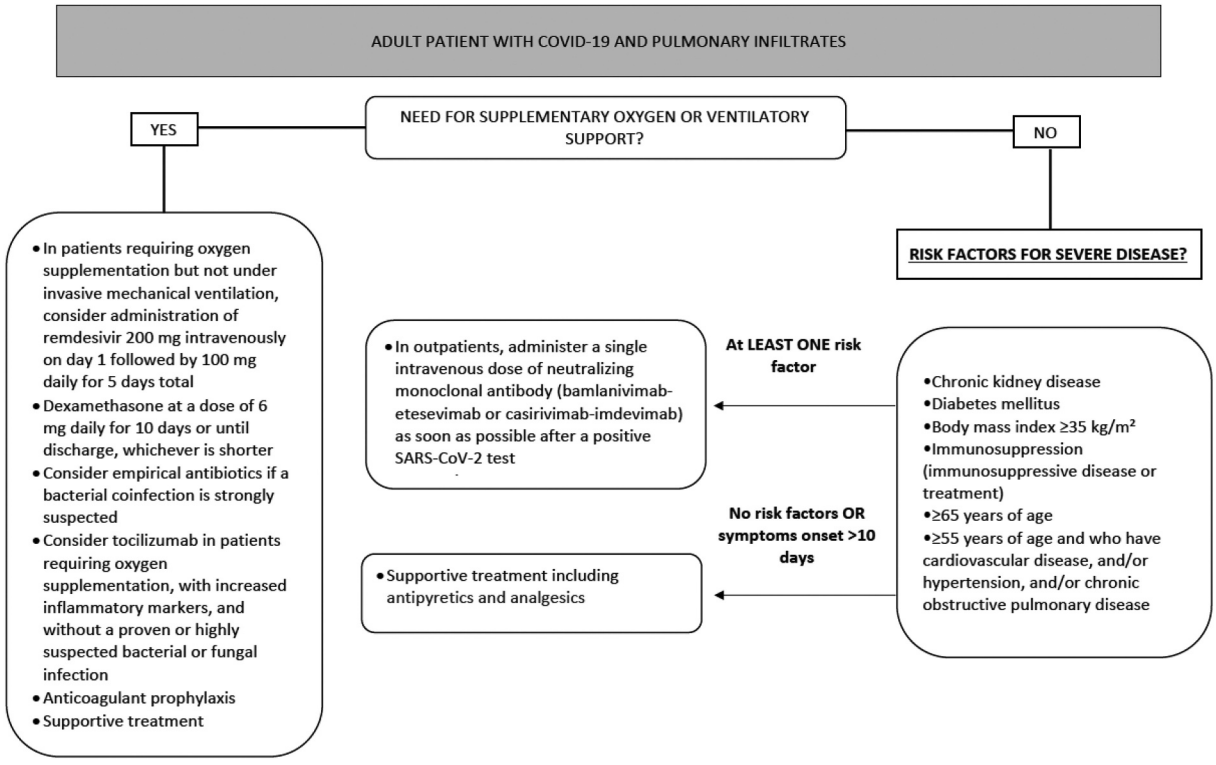


Figure 1. Possible clinical approach to adult patients with COVID-19 and pulmonary infiltrates. Besides antiviral agents and neutralizing monoclonal antibodies, the therapeutic approach to moderate/severe COVID-19 also involves the administration of immunomodulatory and antithrombotic agents. More details on treatments other than antiviral agents are available in currently released guidelines [18,69].

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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