

REVIEW



## Antiviral treatment selection for SARS-CoV-2 pneumonia

Matteo Bassetti <sup>a,b</sup>, Silvia Corcione <sup>c</sup>, Silvia Dettori <sup>a,b</sup>, Andrea Lombardi <sup>d,e</sup>, Tommaso Lupia <sup>c</sup>, Antonio Vena <sup>b</sup>, Francesco Giuseppe De Rosa <sup>c</sup>, Andrea Gori <sup>d,e,f</sup> and Daniele Roberto Giacobbe <sup>a,b</sup>

<sup>a</sup>Department of Health Sciences, University of Genoa, Genoa, Italy; <sup>b</sup>Clinica Malattie Infettive, San Martino Policlinico Hospital - IRCCS, Genoa, Italy;

<sup>c</sup>Department of Medical Sciences, University of Turin, Infectious Diseases, City of Health and Sciences, Turin, Italy; <sup>d</sup>Infectious Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; <sup>e</sup>Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; <sup>f</sup>Centre for Multidisciplinary Research in Health Science (MACH), University of Milan, Milan, Italy

### 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.

### ARTICLE HISTORY

Received 10 February 2021

Accepted 6 May 2021

### KEYWORDS

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 hypoxic 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

**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- $\alpha$  [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- $\beta$ -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)  $\mu$ M, 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  $\mu$ M and a half-cytotoxic concentration >400  $\mu$ M, 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 PaO<sub>2</sub>/FiO<sub>2</sub> 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  $\geq 65$ -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 interfere 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.

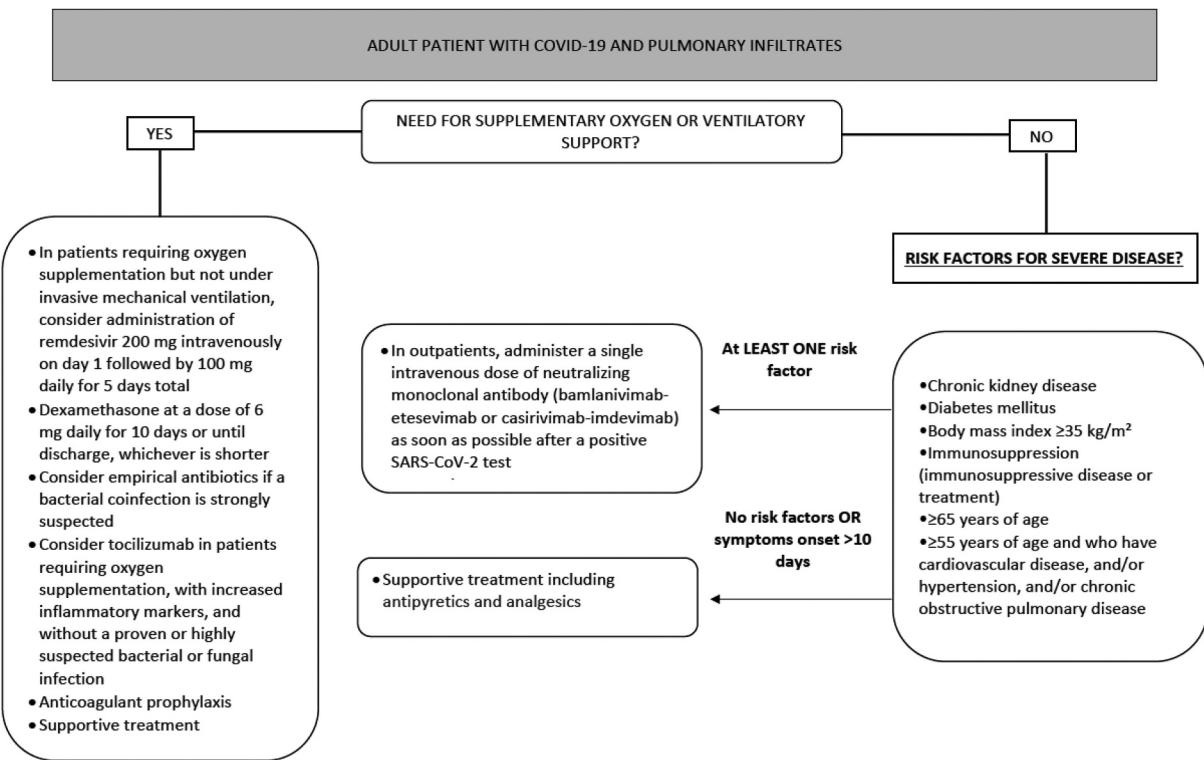
Overall, we truly welcome this new complex scenario, in which classical antiviral agents, neutralizing monoclonal antibodies, and anti-inflammatory or immunomodulatory agents are carving out their place in therapeutic algorithms based on RCT results (i.e., on high-level evidence) [69]. We should continue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

## Declaration of interest

Outside of the submitted work, M Bassetti has received funding for scientific advisory boards, travel and speaker honoraria from Angelini, Astellas, AstraZeneca, Basilea, Bayer, BioMérieux, Cidara, Correvio, Cubist, Menarini, Molteni, MSD, Nabriva, Paratek, Pfizer, Roche, Shionogi, Tetraphase, Thermo Fisher, and The Medicine Company. Outside of the submitted work, D R Giacobbe reports honoraria from Stepstone Pharma GmbH and unconditional grants from MSD Italia and Correvio Italia. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.



**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].

## Funding

This work was not funded.

## ORCID

Matteo Bassetti <http://orcid.org/0000-0002-0145-9740>

## References

- Papers of special note have been highlighted as either of interest (•) or of considerable interest (++) to readers.
- Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med.* 2020 Dec;8(12):1201–1208. .
  - Robba C, Battaglini D, Ball L, et al. Distinct phenotypes require distinct respiratory management strategies in severe COVID-19. *Respir Physiol Neurobiol.* 2020 Aug;279:103455. .
  - Vena A, Giacobbe DR, Di Biagio A, et al. Clinical characteristics, management and in-hospital mortality of patients with coronavirus disease 2019 in Genoa, Italy. *Clin Microbiol Infect.* 2020 Nov;26(11):1537–1544. .
  - Lopes-Pacheco M, Silva PL, Cruz FF, et al. Pathogenesis of multiple organ injury in COVID-19 and potential therapeutic strategies. *Front Physiol.* 2021 Jan 28;12:593223. .
  - Bassetti M, Giacobbe DR, Alberti S, et al. Balancing evidence and frontline experience in the early phases of the COVID-19 pandemic: current position of the Italian Society of Anti-infective Therapy (SITA) and the Italian Society of Pulmonology (SIP). *Clin Microbiol Infect.* 2020 Jul;26(7):880–894. .

- Bassetti M, Pelosi P, Robba C, et al. A brief note on randomized controlled trials and compassionate/off-label use of drugs in the early phases of the COVID-19 pandemic. *Drugs Context.* 2020;9:9. .
- Ac K. Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA.* 2020 May 19;323(19):1897–1898. .
- Liu X, Wang XJ. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. *J Genet Genomics.* 2020 Feb 20;47(2):119–121. .
- Nukoolkarn V, Lee VS, Malaisree M, et al. Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. *J Theor Biol.* 2008 Oct 21;254(4):861–867. .
- Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J.* 2003 Dec;9(6):399–406. .
- Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax.* 2004 Mar;59(3):252–256. .
- Park SJ, Yu KM, Kim YI, et al. Antiviral efficacies of FDA-Approved drugs against SARS-CoV-2 infection in ferrets. *mBio.* 2020 May 22;11(3):3. .
- Zuo Y, Liu Y, Zhong Q, et al. Lopinavir/ritonavir and interferon combination therapy may help shorten the duration of viral shedding in patients with COVID-19: a retrospective study in two designated hospitals in Anhui, China. *J Med Virol.* 2020 Nov;92(11):2666–2674. .
- Choi MJ, Kang M, Shin SY, et al. Comparison of antiviral effect for mild-to-moderate COVID-19 cases between lopinavir/ritonavir versus hydroxychloroquine: a nationwide propensity score-matched cohort study. *Int J Infect Dis.* 2020 Oct 27;102:275–281. .
- Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of

- patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet.* **2020** May 30;395(10238):1695–1704.
16. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med.* **2020** May 7;382(19):1787–1799.
  17. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* **2020** Oct;396:1345–1352.
  18. World Health Organization (WHO). Therapeutics and COVID-19: living guideline, 31 March **2021**. Geneva: World Health Organization; 2020.
  - **Current version of the WHO living guidelines for the treatment of COVID-19**
  19. Lian N, Xie H, Lin S, et al. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. *Clin Microbiol Infect.* **2020** Jul;26(7):917–921.
  20. Boriskin YS, Leneva IA, Pecheur EI, et al. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. *Curr Med Chem.* **2008**;15(10):997–1005.
  21. Brooks MJ, Burtseva EI, Ellery PJ, et al. Antiviral activity of arbidol, a broad-spectrum drug for use against respiratory viruses, varies according to test conditions. *J Med Virol.* **2012** Jan;84(1):170–181..
  22. Khamitov RA, Loginova S, Shchukina VN, et al. [Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures]. *Vopr Virusol.* **2008** Jul-Aug;53(4):9–13.
  23. Wang X, Cao R, Zhang H, et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. *Cell Discov.* **2020**;6(1):28..
  24. Nojomi M, Yassin Z, Keyvani H, et al. Effect of Arbidol (Umifenovir) on COVID-19: a randomized controlled trial. *BMC Infect Dis.* **2020** Dec 14;20(1):954.
  25. Furuta Y, Komono T, Favipiravir NT. (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys Biol Sci.* **2017**;93(7):449–463.
  26. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* **2020** Mar;30(3):269–271..
  27. Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. *Clin Infect Dis.* **2020**. DOI: [10.1093/cid/ciaa1176](https://doi.org/10.1093/cid/ciaa1176).
  28. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering (Beijing).* **2020** Oct;6(10):1192–1198..
  29. Kocayigit H, Ozmen Suner K, Tomak Y, et al. Observational study of the effects of Favipiravir vs Lopinavir/Ritonavir on clinical outcomes in critically ill patients with COVID-19. *J Clin Pharm Ther.* **2020** Oct;46(2):31..
  30. Udwadia ZF, Singh P, Barkate H, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. *Int J Infect Dis.* **2020** Nov 16;103:62–71..
  31. Khamis F, Al Naabi H, Al Lawati A, et al. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. *Int J Infect Dis.* **2020** Nov 9;102:538–543..
  32. Nili A, Farbod A, Neishabouri A, et al. Remdesivir: a beacon of hope from Ebola virus disease to COVID-19. *Rev Med Virol.* **2020** Nov;30(6):1–13..
  33. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med.* **2017** Jun 28;9(396). DOI:[10.1126/scitranslmed.aal3653](https://doi.org/10.1126/scitranslmed.aal3653).
  34. Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature.* **2020** Sep;585(7824):273–276..
  35. Borbone N, Piccialli G, Roviello GN, et al. Nucleoside analogs and nucleoside precursors as drugs in the fight against SARS-CoV-2 and other Coronaviruses. *Molecules.* **2021** Feb 13;26(4):986.
  36. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multi-centre trial. *Lancet.* **2020** May 16;395(10236):1569–1578.
  37. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med.* **2020** Nov 5;383(19):1813–1826.
  38. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med.* **2020** Nov 5;383(19):1827–1837.
  39. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA.* **2020** Sep 15;324(11):1048–1057.
  40. Pan H, Peto R, Henao-Restrepo AM, et al. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 - Interim WHO Solidarity trial results. *N Engl J Med.* **2021**;384:497–511.
  41. Gasmi A, Peana M, Noor S, et al. Chloroquine and hydroxychloroquine in the treatment of COVID-19: the never-ending story. *Appl Microbiol Biotechnol.* **2021** Jan;105(4):30..
  42. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* **2020** Jul;56(1):105949..
  43. Gao G, Wang A, Wang S, et al. Brief report: retrospective evaluation on the efficacy of lopinavir/ritonavir and chloroquine to treat non-severe COVID-19 Patients. *J Acquir Immune Defic Syndr.* **2020** Oct 1;85(2):239–243.
  44. Geleris J, Sun Y, Platt J, et al. Observational Study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* **2020** Jun 18;382(25):2411–2418.
  45. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA.* **2020** Jun 23;323(24):2493–2502.
  46. Abd-Elsalam S, Esmail ES, Khalaf M, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. *Am J Trop Med Hyg.* **2020** Oct;103(4):1635–1639..
  47. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med.* **2020** Nov 19;383(21):2041–2052.
  48. Horby P, Mafham M, Linsell L, et al. RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* **2020** Nov 19;383(21):2030–2040.
  49. Fiolet T, Guihur A, Rebeaud ME, et al. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. *Clin Microbiol Infect.* **2021** Jan;27(1):19–27..
  50. Kashour Z, Riaz M, Garbati MA, et al. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis. *J Antimicrob Chemother.* **2021** Jan 1;76(1):30–42.
  51. Lyngbakken MN, Berdal JE, Eskesen A, et al. A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. *Nat Commun.* **2020** Oct 20;11(1):5284.
  52. Mitja O, Corbacho-Monne M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. *Clin Infect Dis.* **2020**. DOI: [10.1093/cid/ciaa1009](https://doi.org/10.1093/cid/ciaa1009).
  53. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ.* **2020** May;14(369):m1849..
  54. Taylor PC, Adams AC, Hufford MM, et al. Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat Rev Immunol.* **2021**. DOI: [10.1038/s41577-021-00542-x](https://doi.org/10.1038/s41577-021-00542-x).

- .. Comprehensive recent review on available neutralizing monoclonal antibodies for reducing disease progression in COVID-19 patients**
- 55. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021;593(7857):130–135.
- 56. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2021 Feb 16;325(7):632–644.
- 57. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med*. 2021 Jan 21;384(3):238–251.
- 58. Rizk JG, Kalantar-Zadeh K, Mehra MR, et al. Pharmacokinetic-Immunomodulatory Therapy in COVID-19. *Drugs*. 2020 Sep;80(13):1267–1292. .
- 59. Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2021 Feb;9(2):196–206. .
- 60. Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. *Life Sci*. 2020 Jul 15;253:117592. .
- 61. Kim J, Zhang J, Cha Y, et al. Advanced bioinformatics rapidly identifies existing therapeutics for patients with coronavirus disease-2019 (COVID-19). *J Transl Med*. 2020 Jun 25;18(1):257. .
- 62. Abbaspour Kasgari H, Moradi S, Shabani AM, et al. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. *J Antimicrob Chemother*. 2020 Nov 1;75(11):3373–3378.
- 63. Sadeghi A, Ali Asgari A, Norouzi A, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. *J Antimicrob Chemother*. 2020 Nov 1;75(11):3379–3385.
- 64. Wang M, Zhao Y, Hu W, et al. Treatment of COVID-19 patients with prolonged post-symptomatic viral shedding with leflunomide – a single-center, randomized, controlled clinical trial. *Clin Infect Dis*. 2020. DOI: [10.1093/cid/ciaa1417](https://doi.org/10.1093/cid/ciaa1417).
- 65. Zheng F, Zhou Y, Zhou Z, et al. SARS-CoV-2 clearance in COVID-19 patients with Novaferon treatment: a randomized, open-label, parallel-group trial. *Int J Infect Dis*. 2020 Oct;99:84–91.
- 66. Bleyzac N, Goutelle S, Bourguignon L, et al. Azithromycin for COVID-19: more than just an antimicrobial? *Clin Drug Investig*. 2020 Aug;40(8):683–686.
- 67. PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021 Mar 20; 397(10279):1063–1074. .
- Currently the largest randomized study on the effect of azithromycin administration in patients with COVID-19**
- 68. Jiang S, Zhang X, Yang Y, et al. Neutralizing antibodies for the treatment of COVID-19. *Nat Biomed Eng*. 2020 Dec;4(12):1134–1139
- 69. Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. *Eur Respir J*. 2021 Apr 15;57(4):2100048. .
- .. Recently released living guidelines from the European Respiratory Society (ERS)**