



# PHARMACOLOGICAL TREATMENT OF COVID-19

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## INTRODUCTION

Most infections with SARS-CoV-2 are self-limiting, but about 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen. An additional 5% progress to critical illness with hypoxemic respiratory distress syndrome and multiorgan failure that necessitates ventilator support.<sup>1</sup>

Although several approved drugs and investigational agents have demonstrated *in vitro* activity against SARS-CoV-2, and a number have been promoted as potentially effective, most lack proven effectiveness in severely ill patients with COVID-19.

This article will review current data (as of August 14, 2020) on aminoquinolines (e.g. hydroxychloroquine), remdesivir, interleukin 6 (IL-6) inhibitors, and corticosteroids.

## AMINOQUINOLINES: NO PROOF OF BENEFIT

Use of chloroquine and hydroxychloroquine for COVID-19 occurred primarily early in the pandemic. *In vitro* studies suggest they alkalize the phagolysosome, which hampers the low pH-dependent steps of viral replication, including cell membrane fusion and uncoating. Reduction of cytokines and toll-like receptors is also suggested.<sup>2</sup> Dosing of hydroxychloroquine is controversial; pharmacokinetic models suggest that 400 mg orally Q12H x 2 doses, followed by 400 mg orally daily for 5 - 10 days, may be adequate.<sup>2</sup>

The debate started when the media publicized data from an incomplete, non-peer reviewed study in France of 36 patients with ages > 12. Sixteen patients did not receive the drug, 14 patients received hydroxychloroquine 200 mg TID x 10 days, and 6 patients received hydroxychloroquine plus azithromycin 500 mg x 1 dose, then 250 mg daily x 4 days.<sup>3</sup>

At day 6 post-inclusion, 100% of patients treated with the hydroxychloroquine and azithromycin combination were virologically cured compared with 57.1% of patients treated with hydroxychloroquine only, and 12.5% of the control group ( $p < 0.001$ ).

This study was clearly limited in design. The

patients in the combination group had higher cycle threshold (Ct) values (inversely related to viral load), indicating an easier path to virological cure ( $Ct > 35$ ) at day 6. Symptoms ranged from asymptomatic to lower lung respiratory disease. Six hydroxychloroquine patients were not included in the analysis - three were transferred to the ICU, one left the hospital, and one had nausea, resulting in discontinuation of drug treatment.<sup>3</sup> The full cohort of 80 patients in a second publication demonstrated that the combination was not a panacea - at the time of publication, one patient had died, 14 were still admitted, and seven patients experienced adverse events.<sup>4</sup>

With the public fearful, and the Trump White House promoting aminoquinolines, use of the drugs for prophylaxis and treatment became rampant, even though subsequent studies found no benefit from them. More concerning were reports of adverse events, including cardiac arrest, EKG changes, diarrhea, blurred vision,<sup>5,6</sup> and mortality.<sup>7</sup>

The only study that demonstrated a mortality benefit for hydroxychloroquine was a retrospective analysis from the Henry Ford Health System.<sup>8</sup> Between March and May 2020, 2,541 patients with COVID-19 were placed into four groups: no treatment ( $n = 409$ ), azithromycin alone ( $n = 147$ ), hydroxychloroquine alone ( $n = 1202$ ), and hydroxychloroquine plus azithromycin ( $n = 783$ ). The primary outcome was in-hospital mortality. Median age was 64 years (53 - 76); median total hospitalization time was 6 days (4 - 10 days); and median follow-up time was 29 days (3 - 53).

Overall, in-hospital mortality was 18.1% (95% CI 16.6 - 19.7). Mortality by treatment group was: no treatment 108/409 (26.4%; 95% CI 22.2 - 31.0); azithromycin alone 33/147 (22.4%; 95% CI 16.0 - 30.1); hydroxychloroquine alone 162/1202 (13.5%; 95% CI 11.6 - 15.5); and hydroxychloroquine plus azithromycin 157/783 (20.1%; 95% CI 17.3 - 23.0) ( $p < 0.001$ ). Variables such as corticosteroid use (35.7% vs. 38.8% vs. 78.9% vs. 74.4%,  $p < 0.001$ ) and age (68.1 years vs. 63.3 vs. 63.2 vs. 62.3,  $p < 0.001$ )

affected decisions to treat and limit the applicability of these data.

Because of the lack of therapeutic agents early in the pandemic, and perhaps due to political pressure, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for aminoquinolines on April 27, 2020,<sup>9</sup> which was later revoked on June 15, 2020.<sup>10</sup> In addition, several large randomized clinical trials such as DisCoVeRy (May 24),<sup>11</sup> RECOVERY (June 5),<sup>12</sup> ACTG/A5395 (June 20), ORCHID (June 20),<sup>13</sup> and SOLIDARITY (July 6),<sup>14</sup> have halted enrollment. Several key organizations such as Infectious Diseases Society of America (IDSA), National Institutes of Health (NIH), Society of Critical Care Medicine (SCCM), and American College of Physicians do not recommend aminoquinolines outside the context of clinical trials. Entire countries (Italy, Belgium, United Kingdom, France) have halted use outside of clinical trials, or have halted clinical trials altogether. At this time, aminoquinolines have largely fallen out of favor as a potential therapeutic option in COVID-19.

#### REMDESIVIR (VEKLURY®): WHICH PATIENTS ARE LIKELY TO BENEFIT?

Remdesivir is a monophosphoramidate prodrug of an adenosine analogue, intracellularly metabolized to adenosine triphosphate, and it inhibits viral RNA polymerases. Remdesivir has broad spectrum activity against members of several virus families, including filoviruses (e.g. Ebola) and coronaviruses (e.g. SARS-CoV and MERS-CoV). *In vitro* testing demonstrates activity against SARS-CoV-2.<sup>15</sup> Remdesivir is available as an intravenous formulation only. Dosing is 200 mg on day 1, followed by 100 mg daily on days 4 - 9 (5 - 10-day duration).<sup>15</sup>

#### Compassionate Use

Compassionate use and expanded access pathways first became available in the United States on January 25, 2020. The first patient to receive remdesivir was a 35-year old male from Snohomish County, Washington. Improvement in clinical status was documented the day after the drug was administered.<sup>16</sup>

About two months after the first case report, Grein and colleagues reported on the safety and efficacy of compassionate use remdesivir in 61 patients from the United States, Europe, Canada, and Japan. The median age was 64 years (48 - 71), and the median duration of symptoms was 12 days (9 - 15). Fifty-three

of the 61 patients received at least one dose of remdesivir and were included in the final analysis, but only 40 completed a 10-day course of therapy. Thirty of these 53 patients (57%) were mechanically ventilated and four (8%) were receiving extracorporeal membrane oxygenation (ECMO) when remdesivir was initiated. Clinical improvement was most evident in patients requiring low-flow or no oxygen (12/12, 100%) compared with those requiring noninvasive ventilation (5/7, 71%) and mechanical ventilation (16/34, 47%). Early administration of remdesivir was advantageous in this population.<sup>17</sup>

In addition, Gilead has also released data on pregnant and pediatric patients who received compassionate use remdesivir. Of the 77 pediatric patients treated with remdesivir, 73% were discharged from the hospital, 12% remained hospitalized, and 4% died at day 28. Eighty six pregnant and post-partum women were treated with remdesivir—93% and 89% achieved clinical cure, respectively. Median time to recovery was 5 days for women who were not on invasive oxygen support and 13 days for women who required mechanical ventilation at baseline.<sup>18</sup>

#### ACTT

The first stage of the Adaptive COVID-19 Treatment Trial (ACTT) trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) is a randomized, double-blind, placebo-controlled trial assessing the efficacy of a 10-day course of remdesivir in patients with severe COVID-19. The trial was conducted in 60 countries in North America, Europe, and Asia. Patients were randomized 1:1 to remdesivir or placebo; randomization was stratified by disease severity and site.<sup>19</sup>

The first stage of the ACTT trial evaluated remdesivir compared to standard of care. Of the 1,107 patients assessed for eligibility, 1,049 received randomly assigned intervention (531 remdesivir, 518 placebo). As of April 28, 2020, 301 patients had not reached the primary outcome or death; therefore, the current data are preliminary. The most common comorbidities were hypertension (49.6%), obesity (37.0%), and diabetes (29.7%). The most common baseline ordinal category score was 5 (hospitalized; requiring any supplemental oxygen), which included 222 remdesivir patients (41.0%) and 199 placebo patients (38.1%).<sup>19</sup>

Patients receiving remdesivir had a statistically significant shorter time to recovery compared with those on placebo (11 days vs. 15 days; RR 1.32; 95% CI 1.12

– 1.55;  $p = 0.001$ ). The benefit in time to recovery was primarily driven by patients in ordinal category 5 at baseline (RR 1.47; 95% CI 1.17 – 1.84). However, a test of interaction between treatment arm and baseline ordinal category was not significant. Fourteen-day mortality did not meet statistical significance (7.1% vs. 11.9%; HR 0.70; 95% CI 0.47 – 1.04).<sup>19</sup> Duration of symptoms ( $\leq 10$  days vs.  $> 10$  days) did not affect time to recovery (1.28 [95% CI 1.05 – 1.57] vs. 1.38 [95% CI 1.05 – 1.81]).<sup>19</sup>

Following the initial announcement of these results on April 29, 2020, the decision was made to unblind the study and offer remdesivir to the remaining 169 patients receiving placebo who had not completed the day 29 follow-up visit.<sup>20</sup> Certainly, this decision may affect subsequent data. Due to the results of the ACTT trial, the FDA authorized an EUA of remdesivir on May 1, 2020.<sup>21</sup> Per the EUA, patients with an oxygen saturation of  $\leq 94\%$  on ambient care can receive the drug.<sup>21</sup>

#### SIMPLE Trials

Goldman and colleagues presented the results of a randomized, open-label, multicenter, international trial comparing a 5-day with a 10-day course of remdesivir in severely ill patients, i.e. those with oxygen saturation  $\leq 94\%$  on ambient air or requiring supplemental oxygen (SIMPLE-Severe). Notable exclusion criteria included a baseline need for mechanical ventilation and/or ECMO; creatinine clearance  $< 50$  mL/min (previous trials excluded those with  $< 30$  mL/min); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 5x the upper limit of normal; and concurrent therapy (within 24 hours) with agents that had putative activity against SARS-CoV-2.<sup>22</sup>

There were 397 patients in this study: 200 were randomized to 5 days of therapy and 197 to 10 days. At baseline, patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group ( $p = 0.02$ ). After adjustment for baseline clinical status, there was no significant difference in clinical outcome at 14 days between those who received a 5-day or 10-day course of remdesivir. A post-hoc analysis demonstrated that in patients receiving invasive mechanical ventilation on day 5, treatment for 10 days appeared associated with a lower incidence of 14-day mortality (7/41 [17%] vs. 10/25 [40%]). Caution should be taken in interpreting these findings, as there was no placebo group and no subsequent randomization on day 5.<sup>22</sup> Because

of limited drug supply, a 5-day course became more attractive for frontline providers.

Olender and colleagues were the first to demonstrate a mortality benefit in patients receiving remdesivir. The SIMPLE-Severe cohort ( $n = 312$ ) was compared to a retrospective cohort ( $n = 818$ ) with similar baseline characteristics. At day 14, 74.4% of patients in the remdesivir cohort had recovered compared to 59.0% in the standard of care group (aOR 2.03; 95% CI 1.34 – 3.08;  $p < 0.001$ ). In addition, 7.6% in remdesivir cohort had died compared to 12.5% in the standard of care group (aOR 0.38; 95% CI 0.22 – 0.68;  $p = 0.001$ )—this was a 62% reduced odds of all-cause death.<sup>23</sup>

SIMPLE-Moderate, a phase III trial in moderately ill patients, also evaluated a 5-day ( $n = 191$ ) or a 10-day ( $n = 193$ ) duration of remdesivir compared to standard of care ( $n = 200$ ). Patients receiving a 5-day (OR 1.65; 95% CI 1.09 – 2.48;  $p = 0.017$ ) and 10-day (OR 1.31; 95% CI 0.88 – 1.95;  $p = 0.18$ ) regimens were more likely to achieve clinical improvement compared to standard of care. Full publication is not available at this time.<sup>18</sup>

#### Safety

In general, remdesivir is well-tolerated. It is important to monitor elevation of transaminases, as two patients in a cohort of 61 patients from China discontinued the drug due to ALT elevations.<sup>24</sup> Therapy for 10 days may increase the risk of serious adverse events, but this correlation is not established.<sup>22</sup> Interestingly, in ACTT-1, serious adverse events were less common in the remdesivir arm than the placebo group (21.1% vs. 27%).<sup>19</sup> Sulfobutylether-beta-cyclodextrin (SBECD), the solubilizing agent, may have implications for renal dysfunction, but patients with renal impairment were excluded from trials.<sup>21,22,24</sup> The only known drug-drug interaction is with hydroxychloroquine—decreased concentrations may decrease efficacy.<sup>25</sup>

#### Unanswered Questions

Both the IDSA and the NIH promote use of remdesivir in COVID-19 patients.<sup>26,27</sup> Despite all these studies, several questions remain:

(1) Should all patients receive the drug or just those with comorbidities that increase the risk of progressing to severe disease?

(2) When in the disease course should treatment be initiated?

(3) Does the benefit diminish after a certain

number of days of symptoms?

(4) Is the inpatient or outpatient setting better for administering the drug?

When inventory is limited and the disease burden is high, these questions have important implications.

#### INTERLEUKIN 6 (IL-6) INHIBITORS: SHOULD WE QUELL THE STORM?

The pathogenesis of COVID-19 has been associated with a cytokine storm and elevation of interleukins and tumor necrosis factor. Tocilizumab (Actemra®) and sarilumab (Kevzara®) are recombinant, humanized, anti-human IL-6 receptor monoclonal antibodies that bind and inhibit soluble and membrane bound IL-6 receptors; thereby inhibiting signal transduction and targeting the cytokine storm.<sup>28</sup>

Both tocilizumab and sarilumab are available in intravenous and subcutaneous formulations. Dosing of IL-6 inhibitors is controversial. For tocilizumab, a flat dose (400 mg) or weight-based dose (8 mg/kg; maximum of 800 mg) for one or two doses (12 hours apart) have been used in clinical practice for COVID-19. A total of 324 mg SQ (162 mg SQ x 2 doses) has also been reported in one study.<sup>29</sup> Pharmacokinetic models from chimeric antigen receptor T cell-induced cytokine storm models suggest that a second IV dose may be necessary for adequate plasma levels.<sup>28</sup>

Interest in IL-6 inhibitors was sparked by a multicenter, retrospective, single arm study of 21 severely and critically ill patients conducted by Xu and colleagues in Hubei province, China.<sup>30</sup> A dose of 4 – 8 mg/kg (maximum 800 mg) was utilized. The most common dose was 400 mg and no patients received a second dose.

All 21 patients became and remained afebrile one day after administration, and 19 (91%) had improvement in CT chest imaging. Fifteen of the 20 patients who were receiving oxygen at baseline (75%) had decreased oxygen requirements at day 5.<sup>30</sup>

Generalizability of these findings is limited by the small size of the cohort with only four critically ill patients.

#### Tocilizumab: A mortality benefit?

Three retrospective, observational trials from the University of Michigan,<sup>31</sup> Hackensack Meridian Health System,<sup>32</sup> and Italy<sup>29</sup> appeared to demonstrate a mortality benefit for tocilizumab.

The Michigan study assessed the effectiveness and safety of tocilizumab in 154 patients who required mechanical ventilation; 78 received tocilizumab at 8

mg/kg (maximum 800 mg), and 76 received none. Mortality at 28-days was lower (18% vs. 36%,  $p = 0.01$ ) in the tocilizumab group, at the cost of a higher superinfection rate (54% vs. 26%,  $p < 0.001$ ). Even with a commendable statistical analysis, several factors such as younger age, fewer patients with chronic pulmonary and kidney disease, and lower PaO<sub>2</sub>/FiO<sub>2</sub> ratio in the tocilizumab group, complicate drawing conclusions. In addition, 20 patients (26%) received tocilizumab > 48 hours after intubation, contrary to the protocol. Corticosteroid use was permitted at the discretion of the treating physician (29% vs. 20%,  $p = 0.16$ ), and IL-6 levels were not routinely measured. These unmeasured treatment biases remain crucial limitations.

At Hackensack Meridian (13-hospital system), the impact of tocilizumab was studied in 210 patients compared to standard of care ( $n = 420$ ), after propensity score matching. The Pharmacy and Therapeutics committee created criteria for use of tocilizumab, but administration was at the discretion of the provider. A majority of patients (206, 98%) received 400 mg flat dosing, two (1%) received 8 mg/kg, and two (1%) received other doses; 185 (88%) received one infusion and 25 (12%) received a second infusion. About 45% of each group received corticosteroids ( $p = 0.84$ ). More patients in the tocilizumab group received hydroxychloroquine, azithromycin, or both ( $p = 0.0001$ ) compared to standard care. Tocilizumab was administered a median of 9 days (6 – 12) after the start of patient-reported symptoms, a median of 3 days (1 – 7) from the date of hospitalization, and a median of 0 days (0 – 2) from the date of ICU support. A majority of patients were mechanically ventilated on admission (94% vs. 93%,  $p = 0.50$ ). In-hospital mortality was significantly lower in the tocilizumab arm (49% vs. 61%; HR 0.71; 95% CI 0.56 – 0.89;  $p = 0.0027$ ).<sup>32</sup>

In Italy the findings were similar. In 544 patients (179 tocilizumab, 365 standard of care), a composite of death or invasive mechanical ventilation at 14 days was lower in the tocilizumab arm (7% vs. 20%;  $p < 0.0001$ ). Patients treated with tocilizumab again had a higher rate of new infections (13% vs. 4%,  $p < 0.0001$ ). Notably, the tocilizumab group had significantly lower median age (64 years vs. 69 years,  $p = 0.0064$ ), baseline PaO<sub>2</sub>/FiO<sub>2</sub> (169 mmHg vs. 277 mmHg,  $p < 0.0001$ ), and higher corticosteroid use (30% vs. 17%).<sup>29</sup>

Yet, an additional single-center, propensity-score matched cohort study from Rutgers University demonstrated no mortality benefit. A total of 132 patients (66 tocilizumab, 66 no tocilizumab) were included in

the study. Most received hydroxychloroquine with or without azithromycin (90.9% vs. 89.4%,  $p = 0.770$ ) and patients were required to exhibit severe symptomatology, as defined by  $SpO_2 \leq 94\%$  on room air or requirement of non-invasive or invasive oxygen supplementation. The mean age of the study population was  $63 \pm 16.2$  years and there was no significant difference in the number of patients on a ventilator at baseline between groups (24.2% vs. 18.2%,  $p = 0.405$ ). The mean ferritin was  $1027.4 \pm 957.5$  ng/mL, mean CRP was  $10.9 \pm 6.6$  mg/dL, and mean LDH was  $361.2 \pm 144.1$  U/L. Of the patients who received tocilizumab, 10 patients (15.1%) received 800 mg of tocilizumab, three patients (4.5%) received 600mg of tocilizumab, and 53 patients (80.3%) received 400 mg. Four patients received a second dose of tocilizumab. In terms of all-cause in-hospital mortality, there were 18 deaths (27.3%) in the tocilizumab group and 18 deaths (27.3%) in the no tocilizumab group (OR 1.0; 95% CI 0.465 – 2.151;  $p = 1.00$ ). Selection bias and retrospective design may limit this study; but, mortality benefit, if present, may be marginal at best.<sup>33</sup>

### Conflicting Results

Several clinical trials evaluating tocilizumab and sarilumab have described conflicting results. A press-release by a group in Paris (CORIMUNO-TOCI, NCT04331808) reported that tocilizumab lowered the need for the composite outcome of mechanical ventilation and mortality, while patients are no longer being enrolled in the sarilumab trials.<sup>34,35</sup> Another phase III trial, COVACTA (NCT04320615),<sup>36</sup> demonstrated no benefit of tocilizumab in clinical improvement ( $p = 0.36$ ), mortality ( $p = 0.94$ ), or ventilator-free days ( $p = 0.32$ ). Lastly, results from the TOCIVID-19<sup>37</sup> (NCT04317092), a phase II trial, reported a 30-day mortality rate of 22.4%, with a lack of control group.

Neither the NIH nor the IDSA recommend IL-6 inhibitors outside of clinical trials at this time, as data about them are still highly debated.<sup>26,27</sup>

### CORTICOSTEROIDS: NOT TOO HIGH, BUT NOT TOO LOW

Corticosteroid use in viral diseases is controversial. Theoretically, corticosteroids reduce inflammation-induced lung injury and cytokine storm. Li and colleagues collected more than 60 variables from 206 COVID-19 patients in China to assess the risk factors associated with long-term (> 30 days) positive SARS-CoV-2 tests and viral shedding, and found

that high-dose corticosteroids (80 mg/day mg/day methylprednisolone equivalent), but not low-dose (40 mg/day methylprednisolone equivalent) were associated with delayed viral shedding (aHR 0.67;  $p = 0.031$  vs. aHR 0.72;  $p = 0.11$ ).<sup>38</sup>

### RECOVERY AND METCOVID

A phase III trial from the United Kingdom (RECOVERY – Randomised Evaluation of COVID-19 ThERapY) comparing dexamethasone to standard of care was published in the *New England Journal of Medicine (NEJM)* on July 17, 2020.<sup>39</sup> Dexamethasone has potent anti-inflammatory activity and minimal mineralocorticoid activity, potentially avoiding sodium balance and fluid imbalances, which may be harmful in viral processes.

Standard of care included azithromycin, hydroxychloroquine, lopinavir-ritonavir, and IL-6 inhibitors. Patients were randomized to dexamethasone 6 mg orally or IV daily for 10 days (or until discharge) or standard care in a 2:1 ratio. At baseline, 16% of patients required mechanical ventilation or ECMO, 60% required any form of supplemental oxygen, and 24% did not require oxygen.

Dexamethasone reduced 28-day mortality in mechanically ventilated (29.3% vs. 41.4%; RR 0.64; 95% CI 0.51 – 0.81) patients and in those receiving non-invasive oxygen modalities (23.3% vs. 26.2%; RR 0.82; 95% CI 0.72 – 0.94), but had no benefit among patients who were not receiving supplemental oxygen, and a trend toward harm is suggested (17.8% vs. 14.0%; RR 1.19; 95% CI 0.91 – 1.55). Mortality benefit was also more pronounced in patients with a symptom duration of > 7 days (RR 0.69; 95% CI 0.59 – 0.80 vs. RR 1.01; 95% CI 0.87 – 1.11).<sup>39</sup>

In contrast, MetCOVID, a parallel, double-blind, placebo-controlled, randomized, phase IIb trial conducted in Brazil demonstrated no mortality benefit in patients receiving methylprednisolone 0.5 mg/kg twice daily for 5 days ( $n = 194$ ) compared to placebo ( $n = 199$ ). Mean age of both groups was about 55 years and about a third were admitted to the ICU and required mechanical ventilation. Patients diagnosed with septic shock were permitted to receive hydrocortisone. No patients received remdesivir. Twenty-eight-day mortality was not statistically different between the groups (37.1% vs. 38.2%,  $p = 0.692$ ). Because of high overall mortality rate in Brazil and steroid use in septic patients, a difference may have gone undetected. In addition, the methylprednisolone dose used was

higher than the RECOVERY trial, which suggests the decrease in mortality may be dose dependent.<sup>40</sup>

### Current Recommendations

Based on findings from the RECOVERY trial, the IDSA updated guidelines on June 25, 2020, recommended dexamethasone 6 mg orally or IV daily for 10 days for patients requiring supplemental oxygen or mechanical ventilation. The NIH also recommends dexamethasone at the same dose, and updated its guidelines on July 30, 2020, to suggest corticosteroids at equivalent doses can be used; the benefit of steroids other than dexamethasone is unknown. Both entities recommend against the use of corticosteroids in patients who do not require oxygen.<sup>26,27</sup>

The Society of Critical Care Medicine guidelines, last updated March 20, 2020, recommend low-dose steroids (hydrocortisone 200 mg/day) in

patients with refractory shock and acute respiratory distress syndrome. This dose is equivalent to 7.5 mg of dexamethasone per day.<sup>41</sup>

### CONCLUSIONS

Based on countless publications, of which this review can only provide a sampling, it is evident that aminoquinolines are not a viable therapeutic option for COVID-19. Further research should be targeted at understanding the role of remdesivir in the clinical course of the disease. The role of immunomodulators such as corticosteroids and IL-6 inhibitors is an evolving area of study. Combination therapy (antivirals plus immunomodulators) is being evaluated in clinical trials. Even in a pandemic, critical evaluation of available literature is crucial.

The words of Hippocrates, *do no harm*, should lead us to put the patient first, to advocate for robust clinical trial data, and to oppose misinformation.

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