

Drug Recommendations in the Novel Coronavirus Disease (COVID-19) Treatment and Management Guidelines from the Infectious Diseases Society of America

Masafumi Seki*

Division of Infectious Diseases and Infection Control, Tohoku Medical and Pharmaceutical University, Sendai City, Miyagi, Japan.

*Correspondence:

Masafumi Seki, MD, PhD, Division of Infectious Diseases and Infection Control, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, 1-15-1 Fukumuro, Miyagino-ku, Sendai City, Miyagi 983-8536, Japan, Tel: +81-22-259-1221; Fax: +81-22-290-8959.

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ABSTRACT

Infectious Diseases Society of America recently published the guidelines for treatment of novel corona virus infectious diseases 2019 (COVID-19). There are seven recommendations and additional optical treatments.

Keywords

Hydroxychloroquine, Azithromycin, Lopinavir/ritonavir, Corticosteroid, Tocilizumab, Convalescent plasma, Remdesivir.

Introduction

The novel coronavirus disease (COVID-19) has rapidly become a global threat and many drugs and treatment methods are being investigated. The treatment guidelines announced by the Infectious Diseases Society of America on April 11, 2020 (updated April 13, 2020) have thus attracted much attention [1].

This article briefly summarizes seven drug recommendations, which are presented in the executive summary, as well as Remdesivir, another drug that has attracted attention [2].

- Recommendation 1: Hydroxychloroquine (HCQ) for hospitalized COVID-19 patients.
- Recommendation 2: HCQ plus azithromycin (HCQ + AZM) for hospitalized COVID-19 patients.
- Recommendation 3: Lopinavir/ritonavir for hospitalized COVID-19 patients.
- Recommendation 4: Corticosteroids for hospitalized COVID-19 patients (recommendation against).
- Recommendation 5: Corticosteroids for hospitalized COVID-19 patients with acute respiratory distress syndrome (ARDS).

- Recommendation 6: Tocilizumab for hospitalized COVID-19 patients.
- Recommendation 7: Convalescent plasma for hospitalized COVID-19 patients.
- Other drugs currently undergoing evaluation (including Remdesivir).

Recommendations

Recommendation 1: Hydroxychloroquine (HCQ) for hospitalized COVID-19 patients.

Recommendation 2: Hydroxychloroquine plus azithromycin (HCQ + AZM) for hospitalized COVID-19 patients.

The assessment of Recommendation 1 was mainly based on two randomized controlled trials (RCTs), while that for Recommendation 2 was mainly based on three clinical trials.

For Recommendation 1, improved clinical findings such as radiological progression and decreased viral load have been noted, but both studies suffered from problems including small sample size, the possibility of bias, and no accurate evaluations of mortality rate, progression to acute respiratory distress syndrome (ARDS), or other matters.

With Recommendation 2, the possibility that decreases in viral load and mortality rate can be indirectly expected is suggested, but

similar to Recommendation 1, bias exists in patient stratification and the evidence is not necessarily strong. AZM seems to be used in combination not for the purpose of treating or preventing secondary bacterial pneumonia as an antibacterial agent, but instead with the expectation of second-order actions, such as immunomodulation.

In addition, reported adverse effects include QT prolongation, gastrointestinal symptoms in patients with Systemic lupus erythematosus who routinely use HCQ, decreased renal function, and risks related to cytochrome P450 with AZM. In the end, this is a usage recommendation made in consideration of the risks and benefits.

Recommendation 3: Lopinavir/ritonavir for hospitalized COVID-19 patients

This recommendation is made based on a single RCT and two case studies, all of which suggested improvements in the mortality rate and clinical findings.

On the other hand, a fair number of patients are unlikely to be able to complete a 14-day course of administration because of gastrointestinal symptoms. From this and other considerations, we concluded that careful clinical studies are needed for lopinavir/ritonavir groups as well as for other HIV protease inhibitors.

Recommendation 4: Corticosteroids for hospitalized COVID-19 patients (recommendation against)

Recommendation 5: Corticosteroids for hospitalized COVID-19 patients with ARDS

No studies have yet clarified the specific actions of corticosteroids in COVID-19, and these recommendations are based on data on the frequent use of these drugs, mainly in China, in preventing COVID-19 pneumonia patients from progressing to ARDS. However, a lack of basic data cannot be denied, including that all cases involved pneumonia and that the details of ARDS patients and timings of administration were unclear.

Data and systematic reviews from cases of Severe Acute Respiratory Syndrome (SARS) 2003 (SARS-CoV-1) and Middle East Respiratory Syndrome (MERS) were also considered, raising concerns about delayed viral clearance. Thus, the general use of corticosteroids for hospitalized COVID-19 patients is not recommended.

On the other hand, Recommendation 5 is given based on a report on the possibility that methylprednisolone significantly decreased the mortality rate in ARDS patients (Reference 3). Moreover, patients who are already using steroids (for bronchial asthma, etc.; systemic administration and inhalation) should probably continue using these agents even if they develop COVID-19.

To properly judge the benefits and potential risks (secondary infection from immunosuppression, osteoporosis, etc.) of steroids, RCTs that carefully examine aspects such as dose, administration route, start timing, and usage duration are needed.

Recommendation 6: Tocilizumab for hospitalized COVID-19 patients

The involvement of cytokines, including Interleukin (IL)-6, which thought to be the initiator of the so-called ‘cytokine storm’, in COVID-19 was suggested from the pathologies of SARS and MERS. This recommendation is based on one study in which tocilizumab, an IL-6 blocker, was used in 21 patients with severe or critical COVID-19.

That study seemed to have a large impact due to the fact that no deaths or serious adverse effects were encountered, but concerns have been raised about combination with opportunistic infections such as fungal infections or tuberculosis, or reactivation of hepatitis B virus with the administration of tocilizumab. There are also some concerns regarding the some cases of anaphylaxis, liver damage, or other conditions.

This is a recommendation with a fairly low level of evidence, and caution thus remains warranted in its application.

Recommendation 7: Convalescent plasma for hospitalized COVID-19 patients

Convalescent plasma is considered based on data from a total of 15 patients in two clinical studies. All 5 patients in one study and 3 of 10 in the other were on mechanical ventilation, but no deaths were encountered. A benefit was suggested compared with a control group in which 3 of 10 patients died. There were not considered to have been any serious adverse effects, but some details on aspects such as timing of withdrawal from mechanical ventilation and extubation were unclear, and the recommendation remains weak. Again, further clinical study is needed.

Other drugs currently undergoing evaluation, including Remdesivir Other treatments mentioned are the anti-Human immunodeficiency virus (HIV) drugs darunavir/cobicistat, the combined use of lopinavir/ritonavir and interferon β , convalescent plasma as a prophylactic drug for COVID-19 infection, ribavirin (in vitro data only), the anti-influenza drug oseltamivir, intravenous immunoglobulin, and remdesivir, which has been investigated for the treatment of Ebola hemorrhagic fever.

For Remdesivir in particular, data showed clinical improvements in 36 (68%) of 53 patients in one group (including 9 Japanese), of whom 30 were receiving invasive mechanical ventilation and 4 were receiving extracorporeal membrane oxygenation. Reliable evidence from future RCTs is awaited [2].

Angiotensin-converting enzyme (ACE)-2 is the receptor for SARS-CoV-2, the virus that causes COVID-19, and the use of ACE inhibitors and related angiotensin receptor blockers (ARBs), both of which are antihypertensive drugs, enhances ACE-2 expression. There is thus concern about the possibility that these pharmacotherapies may increase the risk of SARS-CoV-2 infection and exacerbate the condition of COVID-19 patients, but clear clinical data verifying or refuting this hypothesis remain lacking. Concern about the use of NSAIDs has been expressed,

due to similar effects in enhancing ACE-2 expression, but this relationship has not been confirmed.

Conclusion

Many candidate drugs and management methods (centered on respiratory management) will continue to be reported and investigated, and early establishment of effective measures to save many COVID-19 patients is eagerly anticipated.

References

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