Review article

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Global Trend of COVID-19 Treatment

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Received: 1 June 2020
Accepted: 25 June 2020
Published: 30 June 2020

Cite this article as:
Nsanzabaganwa et al. Global Trend of COVID-19 Treatment. Rw. Public Health Bul. 2020; *Rw. Public Health Bul. 2020. 2(2): 13-24.*

INTRODUCTION

Since the virus first emerged in Wuhan, China in December 2019, The COVID-19 pandemic has caused worldwide concern and has become a major public health concern and infected more than 6.5 millions and led to more than 400,000 deaths worldwide [1-4]. Treatments and vaccines have been the focus of the pharmaceutical companies for effectively fighting the pandemic [5].

Currently, there is no effective treatment for COVID-19 but studies are being conducted to develop a cure and vaccines [6]. Drugs approved or licensed for other indications have been used for treatment of the infected cases [7].

Nevertheless, global COVID-19 management trends have proven that timely and proper diagnosis as well as early management of symptoms to minimize the number of infected patients migrating from mild/moderate to severe disease translate, in many countries, to effective management of COVID-19 [4,5].

CURRENT KNOWLEDGE OF MANAGEMENT

Based on the available knowledge, COVID-19 clinical presentation was divided into stages to allow better orientation of the management and symptomatic treatments (Figure 1) [4].

Asymptomatic: Are confirmed cases with positive test for SARS-CoV-2 but have no symptoms.

Asymptomatic patients: are encouraged to self-isolate for a 14-day period and report to healthcare providers if they develop any symptoms [6-8].

Mild Illness: Are confirmed cases who have any of these: fever, cough, sore throat, malaise, headache, muscle pain without shortness of breath, dyspnea, or abnormal chest imaging. If they are healthy with only mild symptoms, no need of specific laboratory evaluations and they can be managed in an ambulatory setting or isolation centers and be closely monitored [4,6,8].

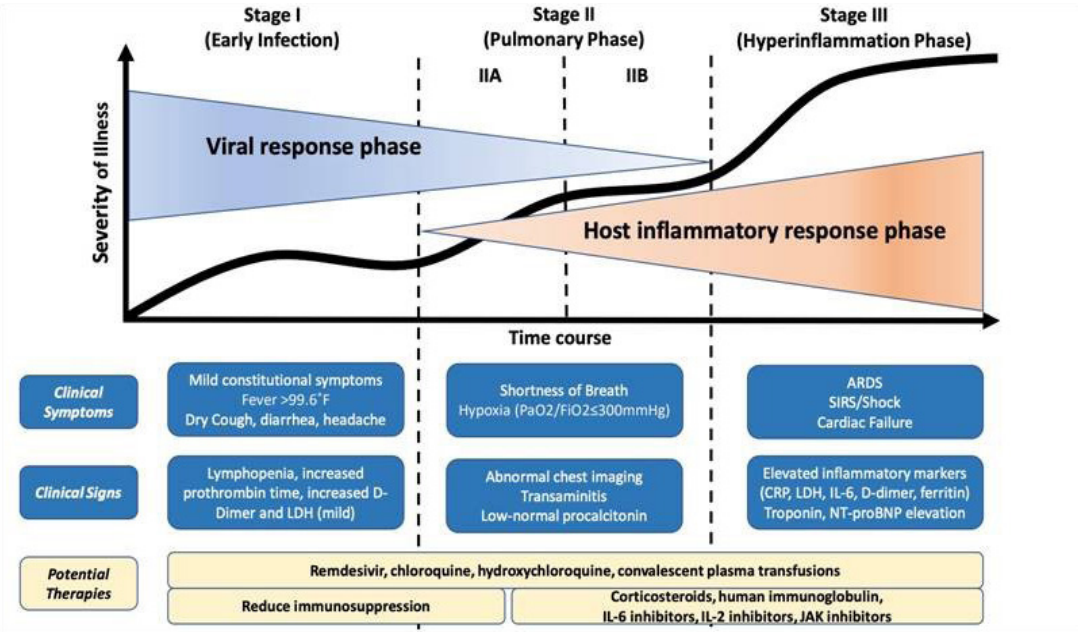

Figure 1: *COVID-19 clinical stages and treatment rationale (Adapted from " COVID-19 illness in native and immunosuppressed states: A clinical−therapeutic staging proposal" by Hasan K. Siddiqi and Mandeep R. Mehra, 2020, Elsevier, January 2020).*

Moderate Illness: Are confirmed cases with lower respiratory disease with oxygen saturation of (SpO2) ≥94% on room air [4,8].

Close monitoring of these patients is recommended and the empiric antibiotic treatment for community acquired pneumonia is used for secondary bacterial pneumonia in these patients [4,7,8]. Clinicians refer to the latest data and updated guidelines for the use of drugs against COVID-19 [4,6].

Severe Illness: Are confirmed cases with respiratory frequency >30 breaths per minute, SpO2 <94% on room air, arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio of <300 mmHg, or lung infiltrates >50% [4,8]. Oxygen therapy should be immediately administered and if pneumonia is suspected, administer empiric antibiotics [3,7]. Laboratory tests like chest x-ray, ultrasound, CT, ECG should be conducted for investigation or evaluation [4]. Clinicians should refer to the latest data and updated guidelines of drugs against COVID-19.

Critical Illness: Are confirmed cases who have respiratory failure, septic shock, and/or multiple organ dysfunction.

These patients are admitted in the intensive care unit (ICU). COVID-19 patients are managed depending on the reason of ICU admission [3,4]. Clinicians use guidelines on the management of critically ill adults with (COVID-19) [4,8] developed by Surviving Sepsis Campaign (SSC).

TREATMENT EVOLUTION FOR COVID-19

There are no approved specific treatments for COVID-19; and all treatments are experimental until proven effective by resuly of clinical trials [9]. Only treatments with high-quality clinical trial data are considered as potential treatment and are based on to inform clinical practice and treatment guidelines.

In an effort to develop the treatment rapidly, scientists have returned to medications already in existence and approved for other diseases.

This is because the development of a new vaccine compound might require a longer period to be developed and approved [1,4].

The existing antivirals are tested to assess their effectiveness against COVID-19 by mainly targeting the virus in its three stages of infection: preventing the virus from entering cells, preventing it from replicating after entering and minimizing the damage to the patient's organs (Figure 1) [1].

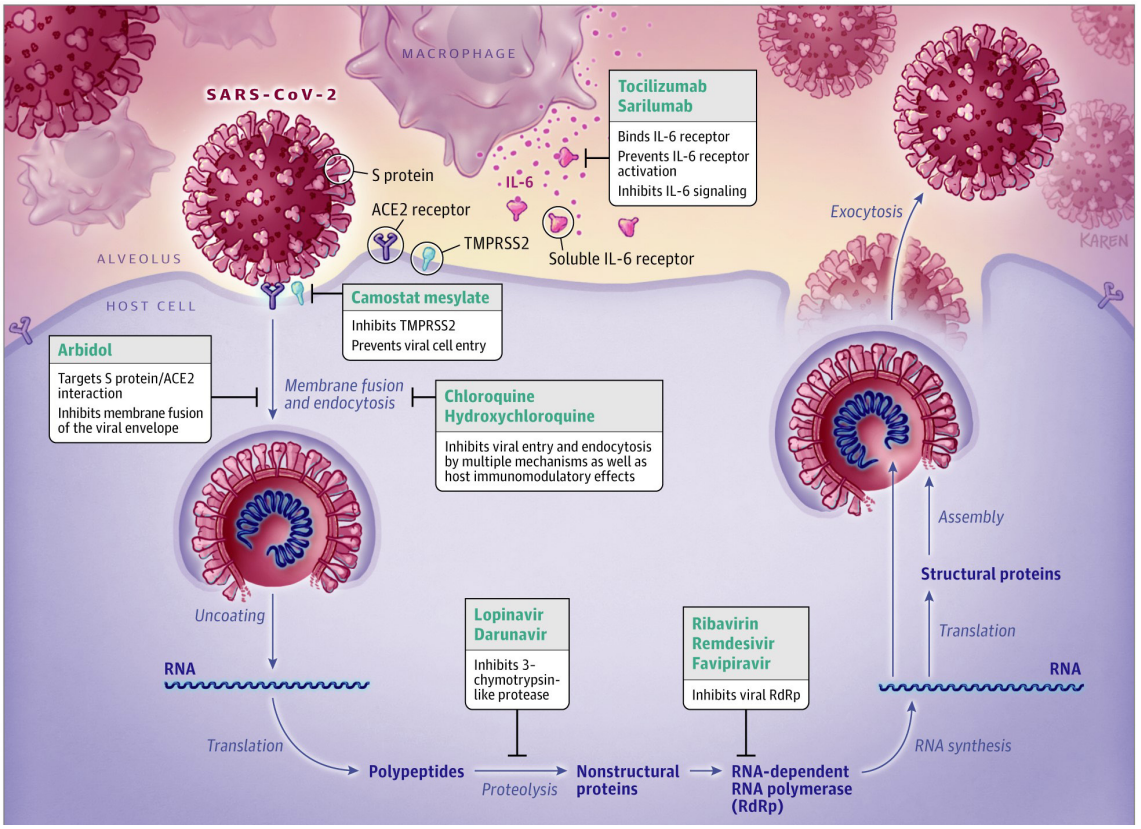

Figure 2: *Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) (Adapted from " Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review" by James M. Sanders, Marguerite L. Monogue, Tomasz Z. Jodlowski, James B. Cutrell, 2020, JAMA, Vol 323, NO: 18).*

Based on the available data, there are 4 drugs (lopinavir/ritonavir, CCR5 inhibitors, remdesivir, tocilizumab), one plasma (convalescent plasma), and a vaccine(mARN) are both used at different levels for the COVID-19 management. These drugs are still under clinical trials to identify their safety and efficacy, and at different level of experimental progress. The healthcare professionals are encouraged to consult the latest data available before prescribing a particular drug [4].

Remdesivir: A nucleotide analogue binding to RNA-dependent RNA polymerase and inhibits viral replication. It is used for hospitalized patients with severe COVID-19 and for COVID-19 patients on mechanical ventilation. Data from randomized controlled trials showed that hospitalized patients with severe COVID-19 symptoms who received remdesivir for 5 days had a shorter time to clinical recovery than those who received placebo. Participants on remdesivir treatment had a 31% faster recovery time compared with those who received placebo, P <.001; and a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group, P = .059) [9,12,13]. There is no sufficient data for mildly and moderately ill COVID-19 patients, and multiple clinical trials are currently underway.

The safety and effectiveness of remdesivir for COVID-19 treatment have not yet been studied in pregnant and pediatric patients. Remdesivir is used in these patients if indicated and if the benefits outweigh side effects [1].

Antithrombotic therapy: COVID-19 associated with thromboembolic disease is globally treated with anticoagulant therapy at the same dose and management of non-COVID-19 patients [1].

Dexamethasone: Researchers at the University of Oxford in England have determined its effectiveness in patients with severe COVID-19 symptoms by reducing the inflammation [1,14]. Mortality reduction by one third was shown in COVID-19 patients on ventilators according to findings shared with WHO but no benefit seen in mildly ill patients [1].

EXPERIMENTAL TREATMENTS AND VACCINE DEVELOPMENT

With continuously growing number of COVID-19 cases and deaths, scientists around the world are racing to develop the treatments and vaccines.

DRUGS

Toculizimab: A humanized monoclonal antibody that inhibits membrane-bound and soluble IL-6 receptors. Already approved by FDA for rheumatoid arthritis and cytokine release syndrome treatment related to chimeric antigen receptor-T cell therapy. It was reported that elevated IL- 6 in severe COVID-19 ia associated with increased mortality. Data (pre-print) on 21 patients with tocilizumab showed fever resolution, decreased oxygen requirement, resolution of opacities on CT scan, and improved patients C-reactive protein (CRP) [15].

Convalescent Plasma: Five convalescent patients from COVID-19 (age 18-60 years old, recovered from SARS CoV-2 infection,asymptomatic for > 10 days, Serum SARS-COV-2 specific ELISA Ab > 1:1000 + neutralizing Ab > 40, at time of donation-negative for SARS-CoV-2, other respiratory viruses, HBV, HCV, HIV, syphilis) volunteered to give their plasma to treat 5 selected COVID-19 patients (critically ill patients age 36-65 years old) with severe pneumonia with rapid progression and high viral load despite antiviral treatment, PaO2/FiO2 < 300, any of the following: mechanically ventilated, shock, multi-organ failure, given at 10-22 day from admission) [16,17,19]. The treatment with convalescent plasma showed normalization of temperature within 3 days, sequential organ failure assessment score (SOFA) score decreased, resolved ARDS at 12 days post transfusion, weaned from mechanical ventilation within 14 days, and discharged from hospital (length of stay: 53 days) 53 days) [16]. The effectiveness of convalescent plasma and hyperimmune immunoglobulin is still under experimentation.

Baricitinib: This is a Janus kinase (JAK) inhibitor which is in Phase 3 of clinical trial to determine its effectiveness against COVID-19 [1].

Bemcentinib: A selective AXL kinase inhibitor developed by BerGenBio and previously proven to be effective against Ebola and Zika viruses. Its effectiveness against SARS-CoV-2 is being studied and it is in phase 2 of clinical trial [18].

Colchicine: This an anti-inflammatory that is being studied to reduce the excessive inflammatory reaction caused by coronavirus thus, preventing the COVID-19 complications.

Lopinavir/ritonavir (Kaletra): HIV medications (lopinavir/ritonavir (in-vitro), darunavir, atazanavir, delutegravir, and efavirenz (molecular docking testing) have shown activities against SARS-CoV-2, and randomized control trial of LPV/RTV versus standard of care for patients with severe COVID showed at 14 days that 13.8% of LPV/RTV recipients decreased drug dosage for side effects [16,19,20].

EIDD-2801: A broad spectrum oral antiviral called EIDD-2801 developed by Ridgeback Biotherapeutics got FDA permission to start clinical trial to determine its use as prophylactic or treatment for COVID-19 [1].

Favipiravir: An antiviral drug approved in Japan as the treatment of influenza. It is in the phase 2 clinical trial [1].

Remdesivir considered a small number of study participants, and lopinavir/ritonavir had different data/modelling studies from in vitro to clinical data. Best data should be well powered, and randomized controlled trials should evaluate potential treatment candidates and determine drugs safety and efficacy [4,11,19].

VACCINES

These are some investigational vaccines being studied in different locations internationally.

BNT162: An mRNA vaccine developed by Pfizer Inc. and BioNTech SE. It is in Phase 1/2 clinical trial in the United States of America (USA) where first participants have been dosed [21].

This is the second dosing after the first completed in the first cohort in Germany [1,21].

AZD1222: It is investigational vaccine against COVID-19 in development and is in phase I/II

clinical trial in England to study its efficacy, safety and immunogenicity [22].

mRNA Vaccine-1273: This vaccine developed by Moderna Inc. has showed positive results in interim Phase 1 and the mouse challenge model. The phase 3 is scheduled to start in July 2020 [23].

INO-4800: This vaccine candidate against COVID-19 developed by INOVIO Pharmaceuticals, Inc., was accepted by FDA to enter phase I clinical trial [24].

In summary, investigational antiviral drugs still need definitive clinical trial data and more scientific research projects are underway to identify safe and effective treatments and vaccine for COVID-19 to slow down and eradicate the pandemic.

Remdesivir is the first antiviral showing promising results for treatment of COVID-19 in well-designed clinical trials.

Multiple studies of hydrochloroquine have shown no beneficial effect, risk of harms and increased mortality have been observed. Convalescent plasma may have benefit for COVID-19, more data is needed. Many vaccine candidates are at different stages of evaluation. Supportive treatments of COVID-19 patients, personal protection and transmission control measures remain the only means available for the fight against COVID-19 pandemic.

REFERENCES

[1] J. S. BPharm, "COVID-19 : Prevention & Investigational Treatments," vol. 11, no. February, pp. 1–11, 2020.

[2] R. A. Raschke, S. L. Till, and H. W. Luedy, "1 2 1 1," vol. 20, no. 2, pp. 95–97, 2020.

[3] Ministry of Health, "Rwanda standard operating procedures for covid-19 outbreak preparedness," pp. 1–84.

[4] T. Guidelines, "Coronavirus Disease 2019 (COVID-19) Treatment Guidelines," vol. 2019, 2019.

[5] "Global research trend in the treatment of the new Coronavirus diseases (COVID-19) : bibliometric analysis.," vol. 33, no. 0, 2020.

[6] Hasan K. Siddiqi, Mandeep R. Mehra, COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal, Elsevier, January 2020.

[7] World Health Organisation, "Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected," pp. 1–11, 2020.

[8] W. Alhazzani et al., Surviving Sepsis Campaign : guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID - 19), vol. 46, no. 5. Springer Berlin Heidelberg, 2020.

[9] T. F. J. Grein, N. Ohmagari, D. Shin et al. "Compassionate Use of Remdesivir for Patients with Severe Covid-19," pp. 2327–2336, 2020.

[10] James M. Sanders, Marguerite L. Monogue et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review, 2020, JAMA, Vol 323, NO: 18.

[11] NIH press release, "NIH begins clinical trial of hydroxychloroquine and azithromycin to treat COVID-19," pp. 19–22, 2020.

[12] P. Vijayvargiya, Z. E. Garrigos, and N. E. Castillo, "Treatment Considerations for COVID-19: A Critical Review of the Evidence (or Lack Thereof)," 2020.

[13] C. Chen et al., "Favipiravir versus Arbidol for COVID-19 : A Randomized Clinical Trial," 2020.

[14] Drugs.com, "Dexamethasone," pp. 1–5, 2020.

[15] X. Xu et al., "Effective Treatment of Severe COVID-19 Patients with Tocilizumab," 2020.

[16] M. Chenguang Shen; ZhaoqinWang; Fang Zhao et al. "Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma," vol. 323, no. 16, pp. 1582–1589, 2020.

[17] C. Dunbar and C. Hillyer, "COVID-19 and Convalescent Plasma : Frequently Asked Questions," pp. 24–25, 2020.

[18] A. Bergenbio and A. S. A. Ose, "Bergenbio ' s Bemcentinib Selected To Be Fast- Tracked As Potential Treatment For Covid-19 Through New National UK Government Clinical Trial Initiative," pp. 19–21, 2020.

[19] B. Cao et al., "A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19," pp. 1787–1799, 2020.

[20] M. JamesM. Sanders, PhD, PharmD; Marguerite L. Monogue, PharmD; Tomasz Z. Jodlowski, PharmD; James B. Cutrell, "Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review," vol. 323, no. 18, 2020.

[21] B. Wire, "Pfizer and BioNTech Dose First Participants in the U . S . as Part of Global COVID-19 mRNA Vaccine Development Program," pp. 19–22, 2020.

[22] AstraZeneca, "AZD1222 Approval status: FDA Approved", Drugs.com,

[23] M. B. Wire and N. Mrna, "Moderna Announces Positive Interim Phase 1 Data for its mRNA Vaccine (mRNA-1273) Against Novel Coronavirus," pp. 4–7, 2020.

[24] INOVIO Pharmaceuticals Inc., "INOVIO Initiates Phase 1 Clinical Trial Of Its COVID- 19 Vaccine," pp. 19–22, 2020.