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Original Article

A Review of Coronavirus Disease-2019 Prophylaxis, Treatments, and Prevention

Adeeba Saleem[1], Henna Mir[1], Divya Srivastav[1], Chetna Joshi[2], Aditya Veer Singh[3], Swathi Pathak[1]

[1]Post Graduate, Department of Public of Health Dentistry, Institute of Dental Sciences, Bareilly, Uttar Pradesh, India, [2]Post Graduate, Department of Oral Medicine and Radiology, D. Y. Patil Dental College and Hospital, Pune, Maharashtra, India, [3]Post Graduate, Department of Public of Health Dentistry, Teerthanker Mahaveer Dental College and Research Centre, Bagadpur, Uttar Pradesh, India

Abstract

Introduction: There is a new world health crisis threatening the public with the spread of Coronavirus Disease-2019 (COVID-19). Since December 2019, when Covid-19 emerged in Hunan seafood market at Wuhan, South China, and rapidly spread throughout the world, the virus outbreak has been declared a public health emergency of international concern by the World Health Organization (WHO).

Materials and Methods: We here summarize the current clinical characteristics data to guide potential COVID-19 about prevention, diagnosis, treatments, and prevention of COVID-19. In this review, the data were extracted from various Research Report WHO guidelines and other articles. It is important to warn readers that COVID-19 publishes new data almost every hour with respect to clinical symptoms, diagnosis, treatment approaches, and outcomes. The disease has caused various degrees of illness around the world.

Results: Patients typically experience fever, cough, sore throat, breathlessness, exhaustion, and malaise, among other symptoms. The illness is treated by general diagnosis, symptomatic treatment, antiviral medicine, oxygen therapy, and the immune system.

Conclusion: It is necessary to identify the potential cases as soon as possible and isolate the suspected people from the confirmed cases of COVID-19, to prevent the potential transmission of infection to other patients and health-care staff.

Key words: Coronavirus, COVID-2019, Respiratory syndrome, Hydroxychloroquine, Azithromycin, Passive immunization

INTRODUCTION

The SARS-CoV-2 pandemic and COVID-19 diffusion are an international public health emergency.[1] Coronaviruses are ribonucleic acid viruses. Importantly, the viruses can infect respiratory, gastrointestinal, hepatic, and central nervous systems in humans.[2] Infection with four of the most common strains of coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) usually results in mild, self-limiting infections of the upper respiratory tract.[3] Other coronaviruses, however, are associated with severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV).

Symptoms of infection are usually nonspecific and include fever, cough, and myalgia, with diarrhea, with or without the subsequent development of dyspnea.[4] Severe cases that include respiratory distress, sepsis, and septic shock have been increasingly reported.[5] One recent systematic review and meta-analysis reported ten observational studies of corticosteroid administration in 6458 influenza-affected patients.[6] The aim was to investigate the effectiveness of various therapies in COVID-19 patients.

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Hydroxychloroquine as Prophylaxis or Treatment

Chloroquine (CQ) is an affordable and fairly safe antimalarial used in India and other malaria-endemic countries for decades. Previous studies showed CQ to be highly effective *in vivo* for the treatment of avian influenza A (H5N1)[7] and *in vitro* against extreme coronavirus acute respiratory syndrome (SARS-CoV).[8,9] HCQ used for the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis has shown to be active against COVID-19 *in vitro*.[7]

Mechanism of Action

It prevents the fusion of the SARS-CoV-2 to host cell membrane[10] and blocks the release of SARS-CoV-2 viral genome.[11] HCQ also has immunosuppressive properties

Corresponding Author: Adeeba Saleem, Department of Public of Health Dentistry, Institute of Dental Sciences, Bareilly, Uttar Pradesh, India.

that can help to minimize the extreme COVID- 19 cytokine storm.[12,13] Although HCQ is relatively safe, it can lead, under adverse conditions, to cardiac disorders such as prolongation of the QT segment, which could lead to myocardial arrest and arrhythmia.[14]

Randomized Clinical Trial Data

Recent *in vitro* studies have shown that SARS-2CoV-2 replication can be inhibited by both CQ and HCQ.[11,10,15] Based on these encouraging *in vitro* data, CQ has been used to test, it is *in vivo* efficacy in multicenter clinical trials involving 100 COVID-19 patients in China. The study concluded that CQ decreased the inflammation of the lungs and shortened the duration of disease without significant adverse reactions.[16] The Chinese analysis of 62 patients found that HCQ shortened the time to recover from chronic conditions.[17]

Hydroxychloroquine and Azithromycin (AZM) Combination

RCT data for the combination of hydroxychloroquine and AZM are not available; however, several RCTs are ongoing.[18] Two case series were reported in France, one reporting benefit[12] and other no benefit.[19] At present, this combination should be used only in the setting of a clinical trial as routine use could lead to severe adverse events with QT prolongation.

Randomized Clinical Trial Data

In addition, two studies conducted in France have indicated that HCQ can reduce the viral load in COVID-19 patients, particularly in combination with AZM.[14,20] These encouraging preliminary studies should have guided the Indian Medical Research Council (ICMR) to recommend HCQ for chemoprophylaxis of asymptomatic health workers who treat suspected or confirmed COVID-19 cases and confirmed patient asymptomatic household contacts.[13] For asymptomatic health workers, the recommended dose is 400 mg twice on day 1, followed by 400 mg once every week for 7 weeks, while for asymptomatic household contacts, the duration is 3 weeks and has to be prescribed by a registered medical practitioner.[13] However, there is no previous research to support the use of CQ and HCQ as prophylaxis to COVID-19. Recently, the US Food and Drug Administration has authorized HCQ for emergency use to treat COVID-19 pneumonia.[21]

Lopinavir/ritonavir

Lopinavir/ritonavir is an approved drug for the treatment of HIV and has been shown to be effective against other novel CoVs such as SARS CoV-1 and MERS Co-V *in vitro*.[22,23] A recent studies indicated *in vitro* activity of lopinavir against SARS-CoV-2.[24]

Mechanism of Action

It inhibits 3-chymotrypsin-like protease enzyme, which is conserved in SARS-CoV-2.[25]

Randomized Clinical Trial Data

One well-done RCT involving 199 patients in China compared clinical outcomes among hospitalized patients with severe COVID-19 infection with lopinavir/ritonavir and standard of care.[26] While in the lopinavir/ritonavir community, the mortality was lower (19.2% vs. 25%) and the duration of the intensive care unit (ICU) stay was shorter (6 days vs. 11 days) relative to the standard of treatment, this was not statistically important. In a second study involving 86 patients with mild to moderate COVID-19 infection in China, lopinavir/ritonavir was contrasted with arbidol (also known as umifenovir) and the 2:2:1 standard of treatment.[27] The results indicated no benefit in clinical outcomes with lopinavir/ritonavir or arbidol compared to standard of care. Additional RCTs are ongoing.[28] At present, routine use of lopinavir/ritonavir is not recommended, and it should be only used in the context of clinical trial.

Major Adverse Effects

Major adverse effects of lopinavir/ritonavir are nausea, vomiting, diarrhea and hepatotoxicity.

Remdesivir

Remdesivir is an analog prodrug of intravenous adenosine nucleotide with activity against many RNA viruses, including SARS CoV-1 and MERS Co-V.[29] It has demonstrated *in vitro* activity against SARS-CoV-2 as well.[30]

Mechanism of Action

It inhibits the viral RNA-dependent RNA polymerase leading to premature termination of RNA transcription.[31]

Randomized Clinical Trial Data

One well-conducted double-blinded RCT from China examined the outcomes in patients with severe COVID-19 disease.[32] In this study, 237 patients were enrolled and randomly assigned to a remdesivir (158 patients) or placebo (79 patients). The primary outcome was the time before day 28 for clinical changes. Receiving remdesivir trials had a quicker duration of clinical progress than those receiving placebo in 10-day studies; however, it was not statistically relevant.[26] Another RCT carried out by the National Institute of Health in the United States announced the findings in a press release, but this research is not published in a peer-reviewed scientific journal.[32] Patients receiving remdesivir had a 31% quicker recovery time than those receiving placebo, according to the press release (median time to recovery 11 days with remdesivir vs. 15 days with placebo; $P < 0.001$). In addition, there was a trend for survival benefit (mortality rate of 8.0% in remdesivir group vs. 11.6% in placebo group [$P = 0.059$]).

There are several other RCTs ongoing.[33] On May 1, 2020, the United States Food and Drug Administration released an emergency use authorization for the use of remdesivir for the care of hospitalized COVID-19 patients, taking into account the findings of the United States National Institute of Health research.[34]

Major Adverse Effects

Major adverse effects of Remdesivir are nausea, vomiting and elevated liver enzymes.

Favipiravir

Favipiravir is an approved drug for the treatment of influenza A in Japan[35] and China[36] with activity against several RNA viruses with pandemic potential.[37]

Mechanism of Action

It inhibits the viral RNA-dependent RNA polymerase halting viral replication.[36]

Randomized Clinical Trial Data

Limited RCT data are available. In one RCT in China, 240 hospitalized patients with moderate-to-severe COVID-19 were randomized to favipiravir or arbidol.[38] There was no major difference in the primary outcome that was a 7-day clinical recovery rate (61% for favipiravir vs. 52% for arbidol; $P = 0.14$).[32] At present, there is insufficient evidence to recommend either for or against the use of favipiravir for COVID-19 treatment. At present, an RCT using favipiravir is planned in India.[39]

Major Adverse Effects

Major adverse effects of Favipiravir are nausea, vomiting, elevated serum uric acid levels, and elevated liver enzymes.

Other Antivirals

Arbidol (umifenovir) is an antiviral agent currently approved in Russia and China for the treatment and prophylaxis of influenza.[35,36] It did not show any benefit over the standard of care[27] or with other agents such as favipiravir in the RCTs which included arbidol;[27,28] however, other trials are ongoing ribavirin has been known to have antiviral activity and was suggested to be one of the possible agents against SARS-CoV-2, and several RCTs are underway.[40] Oseltamivir which is currently approved for the treatment of influenza has limited role in the treatment of SARS-CoV-2.[35]

Ribavirin Major Adverse Effects

Ribavirin major adverse effects are hepatotoxicity, hemolytic anemia, and teratogenicity.[35]

Adjunctive Therapies for Coronavirus Disease 2019

Some adjunctive therapies for supportive care are currently under investigation or are used off-label. These agents may target the virus (e.g., convalescent plasma [CP]) or modulate the immune response (e.g., interleukin (IL)-1 or IL-6 inhibitors) or anti-inflammatory agents (corticosteroids).

Immunoglobulin Therapy or Convalescent Plasma

CP is plasma collected from patients fully recovered from SARS-CoV-2 infection.[41] CP contains antibodies that could help clearing the free virus and the virus from the infected cells. A previous meta-analysis of observational studies showed a reduction in mortality with convalescent plasma or hyperimmune immunoglobulin among SARS-CoV-1 and severe influenza infection.[42]

Mechanism of Action

CP-derived antibodies can neutralize a virus by preventing replication or by binding without interfering with replication.[41]

Randomized Clinical Trial Data

RCT data are not available at present. In case series of two studies with 5[43] and 10,[44] severely ill COVID-19 patients showed promising results. The clinical status of all patients had improved approximately 1 week after transfusion. In addition, the neutralizing antibody titers of patients increased after breathing samples tested negative after transfusion. Many RCTs of CP for COVID-19 infections are underway in various countries.[45] At present, routine use of CP therapy is not recommended for the treatment of COVID-19 outside the clinical trial setting.

Major Adverse Effects

Potential major adverse effect of Immunoglobulin therapy are antibody-dependent enhancement of infection, transfusion-associated acute lung injury, and allergic transfusion reactions.[46]

Anticytokine Agents

Good amounts of data from various studies indicate that cytokine storm plays an important role in severe cases of COVID-19. Therefore, monoclonal antibodies directed against key inflammatory cytokines represent other potential class of adjunctive therapy for COVID-19 infection.[47]

Interleukin-1 and Interleukin-6 Inhibitors

SARS-Cov-2 infects the upper and lower respiratory tract and cause a mild or highly acute respiratory syndrome with a release of pre-inflammatory cytokines, including IL-1 β and IL-6.[48] Similarly, the Janus kinase (JAK) family of enzymes regulates signal transduction in immune cells, and thus, JAK inhibitors could block the cytokine release. Therefore, IL-1, IL-6, and JAK inhibitors could overcome the systemic inflammation associated with severe COVID-19 illness.[49]

Mechanism of Action

It inhibits the amplified immune response and cytokine release.[49]

Randomized Clinical Trial Data

At present, there is no RCT data examining the impact of IL-1, IL-6, and JAK inhibitors on COVID-19-infected patients. RCTs are underway for COVID-19 infection using Anakinra (Recombinant human IL-1 receptor antagonist), recombinant humanized anti-IL-6 receptor monoclonal antibodies (tocilizumab and sarilumab), and siltuximab (recombinant human-mouse chimeric monoclonal antibody that binds IL-6).[50,51] At present, routine use of these agents is not recommended for the treatment of COVID-19 outside the clinical trial setting.

Major Adverse Effects

Main risk of Interleukin-1 and 6 Inhibitors are serious bacterial infections including tuberculosis.

Interferons

Interferons belong to the cytokine family, which have antiviral effects; nonetheless, major interferon toxicities outweigh the possible benefit and are therefore not recommended for COVID-19 diagnosis or as adjuvant therapy.[35] At present, no RCT data as a monotherapy are available.

Major Adverse Effects

Hematological toxicities elevated liver enzymes, nausea, vomiting, and psychiatric problems.

Corticosteroids

Corticosteroids are currently not recommended as adjunctive therapy in patients with COVID-19, except in the case of RCT.[30] The rationale for such recommendation is based on observational studies in patients with SARS CoV-1 and MERS Co-V.

Mechanism of Action

Corticosteroid helps in decreasing the host inflammatory response in the lungs. However, patients with chronic diseases (such as primary or secondary adrenal insufficiency, rheumatologic diseases, asthma, and chronic obstructive pulmonary disease) on chronic corticosteroid therapy (oral or inhalational) should not discontinue the therapy.[30]

Major Adverse Effects

Including delayed viral clearance and increased risk of secondary infections, hyperglycemia, psychosis, and avascular necrosis.[35,52,53]

Coronavirus and Analgesics

Experimental animal studies are ambivalent concerning NSAIDs and paracetamol.

Randomized Clinical Trial Data

A systematic analysis found that rats diagnosed with influenza had an increased risk of mortality following analgesics/antipyretics (i.e., aspirin, paracetamol, and diclofenac).[54] Nonetheless, the same study found no evidence for a similar impact on humans, while criticism was made of the consistency of those studies.

Mechanism of Action

Human volunteers challenged with rhinovirus type[54] given ibuprofen, aspirin, and paracetamol showed that aspirin and paracetamol were associated with suppression of serum antibody and a trend for a prolonged time of viral shedding.[55] Aspirin increased the shedding of virus, but did not alter infection or disease levels.[56] Paracetamol prolongs the actual illness in experimentally infected patients with influenza A[57] and inhibits leukocyte function in *in vitro* experiments.[58]

India Situation

The Ministry of Health and Family Welfare (MoH&FW), Government of India, released their revised guidelines on clinical management of COVID-19 on March 31, 2020. The guidelines suggest that these drugs should be administered under close medical supervision with monitoring for side effects, including QT interval. This therapy is not recommended for children <12 years, pregnant, and lactating mothers.[59] The MoH and FW released an advisory (March 22, 2020) on the use of hydroxychloroquine as prophylaxis for SARS-CoV-2 infection based on the recommendation by the National Task Force for COVID-19 constituted by the Indian Council of Medical Research. The guideline calls for the placement of the following high-risk population with hydroxychloroquine under chemoprophylaxis for (i) asymptomatic health-care staff engaged in the treatment of suspected or confirmed COVID cases and (ii) asymptomatic household contacts with reported laboratory cases.[60] Many centers in different states of India are engaged in RCTs evaluating treatment, prevention, and adjunctive therapies for the management of COVID-19.[61] These clinical trials are mainly evaluating hydroxychloroquine and chloroquine in the prevention of new infection and adverse outcomes and effect of chloroquine in addition to standard therapy in COVID-19 patients. The World Health Organization's Solidarity trial involving four treatment options (remdesivir, chloroquine or hydroxychloroquine, lopinavir with ritonavir, and lopinavir with ritonavir plus interferon) comparing standard of care for hospitalized patients with COVID-19 infection is also ongoing.[61,62] Many other clinical trials include evaluating the effect of Ayurvedic and homeopathic agents on COVID-19 prevention, the efficacy of recombinant Bacillus Calmette-Guerin vaccine in reducing COVID-19 infection incidence and disease severity, and the efficacy and protection of convalescent plasma therapy in serious COVID-19 patients in several centers.[61]

Passive Immunization

PI is a method for obtaining immediate, short-term fortification in patients against infectious agents by adding pathogen-specific anticorps. These specific antibodies can bind to the pathogenic antigens and block their interaction with a cell receptor, which is extremely applicable to viral antigens which facilitate attachment to the target receptors.[63] The patient's body, after exposure to a viral infection, creates large multinational corporations to fight off the virus. Such antibodies in a recovered patient's blood can be obtained as convalescent plasma (CP) and transferred to a newly infected patient's blood where they can neutralize the pathogen, improve the patient's immunity and contribute to blood circulation enucleation in the patient after transfusion.[64] CP gets growing attention as a favored therapeutic tool after large-scale epidemics for several reasons: Collecting a large volume per session, repeated donations are feasible and without any effect on the donor's hemoglobin,[64] which seems to be an appealing approach in the case of COVID-19. There are currently about 1,159,953 patients who have survived and the number continues to grow, and we hope all of them will donate their plasma to end this pandemic. However, donor plasma should be screened for antibody activity and neutralization activity to provide a successful CP infusion. ELISA IgG may be a replacement for neutralization tests in a resource-limited situation.[65]

Safety and Preventive Measures for Dental Health Care Professionals on COVID-19

An alternative to relief symptoms should be provided to patients suspected or confirmed with COVID-19 infections, who need emergency dental treatment in case of tooth pain and/or swelling, antibiotics and/or analgesics. It will allow dental personnel time to prepare and provide dental care with both appropriate and preventive measures to prevent spread of infection. According to the British Medical Journal, the use of ibuprofen became banned on March 17, 2020, because of its interference with immune function. Acetaminophen is an analgesic drug of choice for treating patients diagnosed with COVID-19. The recommendation was endorsed by the World Health Organization (WHO) on March 18, 2020.[66]

In certain emergency cases such as dentoalveolar trauma and fascial space infection, dentists should be aware of the following recommendations:

- Use of disposable dental equipment for cross-contamination preventive measures is mandatory.
- Radiographs: Avoid intraoral radiographs as they can cause gag reflex or cough. Extraoral radiographs (e.g., panoramic radiograph or CBCT) should be done.[65] When intraoral imaging is required, double protections are performed on sensors to prevent cross-contamination.
- Rubber dam will be used for non-surgical endodontic treatment to reduce the splatter generation.
- Dental procedures that generate higher aerosol content, for example, should be avoided for ultrasonic instruments, high-speed handpieces, and three-way syringes.
- Suspected or reported cases of COVID-19 should be treated only in negative pressure rooms or in isolation rooms for airborne infection (AIIRs)[66] and not in routine dental practice.
- Coronavirus survival time is up to 9 days at room temperature on inanimate surfaces or objects, with a greater preference for humid conditions. Therefore, to avoid SARS-CoV-2 spread, dry conditions should be maintained. Recently, approved COVID-19 chemicals should be used for the disinfection.

CONCLUSION

The COVID-19 pandemic is an ongoing public health crisis for which effective therapeutic agents are urgently needed. At the time of writing this commentary, there is no peer-reviewed published evidence from randomized clinical trials of any pharmacological agents improving outcomes in COVID-19 patients. Globally, several clinical trials involving repurposed and novel pharmacological agents for the treatment of COVID-19 are ongoing and thus recommendations may change with new evidence. The positive results of remdesivir against COVID-19 are encouraging; however, the findings from other ongoing remdesivir trials will be critical in establishing its therapeutic efficacy against COVID-19 infection.

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