

CURRENT TREATMENT MODALITIES FOR COVID - 19 - A REVIEW

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ABSTRACT

A novel category of virus belongs to corona virus family found at very first time at Wuhan, China in December 2019. It was mentioned that COVID-19 (Coronavirus disease 2019 name given to this novel virus) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). Since then virus has spread across the globe at very high rate and increasing number of confirmed cases and disease related mortality are being reported. Drugs are needed for prophylaxis and treatment of COVID-19. But there is no current effective strategy to prevent the spread of disease and to treat infection with COVID-19, though several antiviral and immunomodulation drugs are being tested and some preliminary research studies and clinical trials reported significant effect of some drugs to managing patients of COVID-19. Treatment guidelines for COVID-19 also vary between countries. Therefore, more evidence based multicentre clinical trials need to be done to ensure the safety and efficacy of these drugs. Relevant publications both in journals, web, newspaper, and magazine from various database such as PubMed, Scopus, ProQuest, CINAHL and Google scholar searched to visualize publications from inception to 15th June 2020 were searched and manually filtered. This review summarizes evidences regarding treatment strategies that are being tested for the prevention and management of COVID-19.

Key Words: chemical drugs; corticosteroids; COVID -19; hydroxychloroquine; lopinavir; SARS-CoV-2; treatment strategies

INTRODUCTION

The plague of novel corona infection began in Wuhan China and is being sent out to huge number of nations all through the globe. Prior experience of Severe Acute Respiratory Syndrome (SARS) 2003, Middle East Respiratory Syndrome (MERS) 2012 and Pandemic flu obviously show about the critical need of assembling all the wellbeing assets and general wellbeing exercises to limit its potential effect, World health organization (WHO) officially announced novel corona virus as an pandemic to aware international community about the seriousness of this disease on 11th March 2020. On 11 February 2020, WHO reported a name for the new Corona infection sickness: COVID-19. World governments are attempting to set up counter measures to stem conceivable decimating impacts.

At present the remedial alternatives are exceptionally constrained and there is no endorsed antibody or antiviral medication for viably treating Novel Corona Virus disease. With expanding number of cases and passing due to COVID-19 contamination, there is a dire need of creating successful remedial procedure to control the spread of the illness. Yet, no compelling antibody or antiviral restorative intercessions have been affirmed to treat COVID-19 contamination till now. Current way to deal with Corona infection treatment chiefly centres around suggestive and strong consideration. Investigators reviewed it in depth and brought up summed up clinical result, prevention with safety, therapeutic impact of existing helpful procedures for avoidance of transmission and treatment of COVID-19 contamination.

Search strategy and data extraction: Electronic searches were conducted in a total of 3 literature data bases namely PubMed, Scopus, ProQuest, CINAHL and Google Scholar from inception to 15th June 2020. Along with it a close loop on WHO database of publications on COVID-19 kept in consideration. We searched databases using keywords COVID-19, Novel coronavirus 2019, SARS-CoV-2, Co-V, Coronavirus disease 2019, respiratory disease, Chloroquine, Hydroxychloroquine, azithromycin, monoclonal antibodies, corticosteroids, potential interventions, convalescent plasma, and therapeutic interventions. List of references of every single recognized article were screened to discover more applicable articles. For organizing this review we included case series, randomized controlled trials, and observational, interventional studies covering positive COVID-19

patients of any age. Papers with portrayal of medications for COVID-19 treatment were likewise chosen including remarks, news, articles, correspondences, reviews and government reports. We screened out substance drugs, organic treatment and AYUSH which has conceivable valuable consequences for COVID-19 upheld by logical information. Studies were at first chosen dependent on title and theoretical and for important examinations full messages were audited for additional assessment and copies were rejected. A detailed evaluation of relevant articles was carried out and assessed for final inclusion.

ANTIVIRAL AGENTS

Right now there is no particular antiviral treatment for COVID-19. Nonetheless, sedates recently created to treat other viral contaminations are being tried to see its efficacy against the virus that causes COVID-19.

Lopinavir/Ritonavir

In vitro experimental studies confirmed that lopinavir and ritonavir has reduced levels of SARS-CoV and MERS-CoV¹. Jaegyun Lim *et al*² has mentioned in their investigation that using of these two minimize the viral pressure and helped to keep therapeutic benefit in curing of COVID-19 patients. Study by Xiaoting Ye *et al*³ demonstrated that mix treatment with lopinavir/ritonavir could create better adequacy in patients with COVID-19 contamination contrasted with treatment with adjuvant medication alone. So lopinavir/ritonavir can be prescribed to generally high-chance gatherings of COVID-19 pneumonia patients (older or patients with hidden illnesses) from the beginning phase. A randomized clinical trial, where COVID-19 patients got either lopinavir-ritonavir 400 mg/100 mg, orally twice day by day in addition to standard of care, or standard of care alone reported no better outcome of lopinavir-ritonavir regimen as compared to standard treatment⁴. Moreover, adverse reactions related to drug were more among patients treated with lopinavir /ritonavir⁵. These study outcome supporting further investigations by the help of clinical trials to identify and support existing evidence to use lopinavir/ritonavir for patient safety.

Remdesivir

Remdesivir has solid anti-filovirus impact in vitro and certain anti- coronavirus impact through repressing RNA-subordinate RNA synthetize in animal experiments. Holshue *et al* mentioned in their article that COVID-19 patient got treated successfully in USA with Remdesivir drug⁶. A fundamental report by National Institute of Allergy and Infectious Diseases (NIAID) USA indicated that patients who got remdesivir had 31% quicker an ideal opportunity to recuperation than the individuals who got pseudo treatment. Moreover, researchers identified that early remdesivir treatment inception in COVID-19 patients may forestall movement to serious pneumonia^{7,8}. Organization of remdesivir to extreme COVID-19 patients was related with improved clinical result particularly in oxygen bolster status, decreased emergency clinic remain and mortality. Study additionally detailed that during middle follow up timeframe of 18 days, 57% of patients accepting mechanical ventilation were extubated⁹. In extreme COVID-19 patients requiring no mechanical ventilation, 5-day course and 10-day course of remdesivir didn't demonstrated noteworthy contrast in the clinical status. Be that as it may, study couldn't exhibit any greatness of advantage because of absence of placebo control¹⁰. A randomized, double-blind multicentre clinical trial conducted in China uncovered no noteworthy job of Remdesivir in quickening recuperation or decreasing mortality among COVID-19 patients¹¹. Thus, for effective utilization of Remdesivir, quite a good number of clinical trials need to be organized.

Favipiravir

Favipiravir is a viral RNA polymerase inhibitor which has demonstrated effectiveness in the treatment of Ebola and influenza virus^{12, 13,14} and approved in China for COVID-19 treatment¹⁵. A preliminary open label nonrandomized trial on 80 patients in China have exhibited that favipiravir applies an antiviral activity more strong than lopinavir/ritonavir in COVID-19 treatment and distinguished critical decrease in the chance to SARS-CoV-2 viral freedom in patients treated with favipiravir¹⁶. Another examination contrasting the impact of favipiravir and arbidol among 240 patients with COVID-19 found no huge improvement in the clinical recuperation following multi week (favipiravir [61%] versus Arbidol [52%]; contrast in recuperation rate, 0.0954; 95% CI, -0.0305 to 0.2213; P = 0.1396)¹⁷. Reviewers believe that to create sufficient evidence, good number of trails need to be organized to establish the Favipiravir as effective treatment option for COVID-19.

Arbidol hydrochloride (umifenovir)

It is an antiviral agent utilized for the treatment and prophylaxis of flu and other respiratory diseases. Chinese scientists reported that arbidol is effective in inhibiting the pathological impacts of SARS-CoV-2 at a centralization of 10 - 30 $\mu\text{mol/L}$ with multiple times of viral burden in vitro through screening an assortment of antiviral medications¹⁸. A Review companion concentrate among 111 patients from two clinical focuses in China uncovered higher organic transformation (59.2% Versus 40.3%, p= 0.048) and lesser requirement for oxygen treatment in the individuals who got arbidol¹⁹. A retrospective study analyzed the viability of lopinavir/ritonavir (400 mg/100 mg two times every day) or arbidol (0.2 g three times each day) among COVID-19 affirmed patients. Fourteen days after confirmation no popular burden was found in arbidol bunch versus 44% in lopinavir/ritonavir treated gathering. Patients in the arbidol bunch additionally had a shorter length of positive RNA test contrasted with those in the lopinavir/ritonavir gathering (p<0.01)²⁰. Another clinical

preliminary looking at viability of lopinavir/ritonavir (LPV/r) or arbidol monotherapy for treating patients with gentle/moderate COVID-19 found no huge distinction between two medications²¹. Existing information and result of clinical trials still need to be supported by many more clinical trials to identify Arbidol hydrochloride (umifenovir) as an effective treatment for COVID-19.

CORTICOSTEROIDS

Corticosteroids were controlled to patients who created extreme respiratory infection during SARS CoV 2003 and MERS 2012^{22,23}. Significant proportion of patients infected with COVID-19 develops ARDS and requires intensive care with ventilatory support^{24,25}. High dose corticosteroids are the most commonly used adjuvants in the management of ARDS²⁶. A retrospective cohort study led in Wuhan, China among COVID-19 affirmed pneumonia patients set up that treatment with methylprednisolone diminished danger of death among patients who created ARDS (risk proportion [HR], 0.38; 95% certainty span [CI], 0.20–0.72). Specialists likewise saw that patients who got methylprednisolone were sorted as high hazard as per pneumonia seriousness list²⁷. However, in another examination patients treated with corticosteroids experienced multiplied danger of being admitted to an ICU²⁸. Besides, multiplied span of viral RNA for oropharyngeal swabs and excrement in corticosteroids bunch than in controls (15 Versus 8 days, $p=0.013$ and 20 Versus 11 days $p<0.001$) in a retrospective study²⁹. Current interim guidelines from WHO released on January 28, 2020 doesn't support use of corticosteroids unless indicated for another reason³⁰. Accessible writing so far doesn't completely bolster corticosteroids in COVID-19 administration.

INTERFERONS

Recombinant human Interferon (IFN- α) applies antiviral, antitumor and ant proliferative impacts. IFN- α authoritative to cell surface receptors instigates cells to create a scope of antiviral proteins, which hinders viral multiplication in cells and expands insusceptible framework capacity by improving phagocytosis of macrophages. Interferon- α has been broadly utilized in the administration of serious intense respiratory disorder 2003 plague³¹. Type 1 interferon can be suggested as sheltered and viable procedure in the administration of SARS-CoV-2^{32,33}. A retrospective cohort study done in China announced that IFN- $\alpha 2b$ with or without arbidol altogether diminished term of distinguishable infection in the upper respiratory plot and in equal decreased span of raised blood levels for provocative markers IL-6 and CRP³⁴. A prospective randomized controlled trial dexhibited consolidated interferon beta-1b, lopinavir-ritonavir, and ribavirin (14-day mix of lopinavir 400 mg and ritonavir 100 mg each 12 h, ribavirin 400 mg each 12 h, and three portions of 8 million worldwide units of interferon beta-1b on exchange days) was related with diminished term of viral shedding and clinic remain in patients with gentle to direct COVID-19 when contrasted with 14 days of lopinavir 400 mg and ritonavir 100 mg each 12 hourly treatment routine³⁵. Available literature is supporting that Interferons can be a safe and effective therapeutic strategy in COVID-19 management.

AZITHROMYCIN

Azithromycin, a macrolide gathering of anti-toxin is utilized to deal with diseases like bronchitis, pneumonia and Macintosh (Mycobacterium avium complex) contamination. Azithromycin has been utilized as adjunctive treatment because of antibacterial, immunomodulatory and anti-inflammatory impacts in the treatment of some viral respiratory tract diseases. In addition, it has been demonstrated to be dynamic in vitro against Zika and Ebola infections^{36,37}. Adequacy of azithromycin in mix with HCQ for COVID-19 administration has been tried in clinical preliminaries. A clinical preliminary was done in France to evaluate adequacy of hydroxychloroquine in 20 patients, 6 of which were co-regulated with azithromycin. Patients treated with hydroxychloroquine + azithromycin demonstrated most noteworthy virologic fix rate following 6-day treatment. Study additionally announced a 100% viral leeway in nasopharyngeal swabs with co-treatment of hydroxychloroquine and azithromycin³⁸. However contrast findings were reported in a study conducted by Molina etal in France³⁹. What's more, expanded danger of heart harmfulness with joined hydroxychloroquine + azithromycin routine ought to likewise be thought of. Accessible information till now isn't adequate to help the utilization of azithromycin for COVID-19 treatment.

HYDROXYCHLOROQUINE (HCQ)

Chloroquine and hydroxychloroquine are widely utilized in the treatment of malaria and rheumatic diseases. Chloroquine has immunomodulatory activity, which can synergistically upgrade antiviral action. In this way, it has been suggested as successful treatment for COVID-19 because of its anti-inflammatory and antiviral impacts. Chloroquine and hydroxychloroquine are extensively used in the treatment of⁴⁰. Several randomized clinical trials and observational studies have been carried out to evaluate efficacy of chloroquine/hydroxychloroquine in COVID-19 management. An observational study was done in hospitalized patients with COVID-19 found no huge relationship between organization of hydroxychloroquine (600 mg two times every day on day 1, at that point day by day 400 mg for 5 days) and the pace of intubation or death (HR,

1.04; 95% CI, 0.82–1.32)⁴¹. A study by Gautret *et al.* among COVID-19 patients showed that chloroquine essentially diminished the viral burden on day 6 and diminished oxygen necessity and requirement for ICU affirmation^{45,42}. Clinical trials evidenced that in China Gao *et al.* reported that chloroquine is powerful in treating COVID-19 pneumonia patients by improving lung imaging discoveries, advancing an infection negative change, and shortening the illness course⁴³. A retrospective study done by Rosenberg *et al.* on 1438 patients conceded with COVID-19 saw that there was no huge contrast between in-medical clinic mortality in patients accepting hydroxychloroquine alone, azithromycin alone, or the blend of hydroxychloroquine with azithromycin. Heart failure was almost certain in patients accepting HCQ with azithromycin when contrasted with different groups⁴⁴. Despite the fact that huge scope randomized preliminaries are required for better assessment, in view of accessible writing hydroxychloroquine can be savvy treatment for battling COVID-19 pandemic.

CONVALESCENT PLASMA OR IMMUNE PLASMA

Convalescent plasma (CP) is the plasma that is gathered from a contaminated individual and it is bonded into another person as post presentation prophylaxis. Convalescent plasma is aloof immune response treatment which has been utilized to improve endurance rate in past two coronavirus pestilences in the 21st century: SARS in 2003 and MERS in 2012^{45,46}. Experience from those flare-ups shows that Convalescent plasma contains killing antibodies. Besides, numerous examinations detailed diminished medical clinic remain and mortality in patients treated with Convalescent plasma⁴⁷. In the current novel coronavirus pandemic, uncontrolled case arrangement of basically sick patients with COVID-19 and ARDS from China detailed improvement in clinical result with plasma bonding as confirm by weaning off mechanical ventilation, decrease in viral burdens, improved oxygenation and clinical adjustment⁴⁸. In a pilot investigation of 10 patients with extreme COVID-19, specialists found that bonding of gaining strength plasma brought about progress in side effects (for example fever, hack, windedness and chest torment) inside 1-3 days of bonding, diminished viral burden and diminished C–receptive protein⁴⁹. A case arrangement exhibited that gaining strength plasma improved the clinical status of five fundamentally sick patients with COVID-19⁵⁰. However, more clinical trials are needed to establish actual benefit of convalescent plasma in COVID-19 treatment.

STEM CELL THERAPY

Stem cells can advance endogenous injury fix by controlling safe framework, repress intense movement of aggravation in lungs, and aides in soothing manifestations of respiratory trouble. Exploration considers have shown viability of Mesenchymal stem cell in the administration of MERS-CoV⁵¹. Intravenous Administration of allogenic mesenchymal umbilical cord stem cells to a 70 year old female patient showed decreased levels of IL-6 and CRP, increased absolute value of T cells and NK cells, and reduced inflammation of lungs on CT imaging⁵². Another study of mesenchymal stem cell transplantation carried out among seven patients also revealed improvement in clinical symptoms⁵³. In spite of the fact that, stem cell therapy has demonstrated points of interest for fundamentally sick COVID-19 patients, more outcomes are expected to set up viability in COVID-19 treatment.

ANTICOAGULATION

Hypercoagulable state prompting small scale and macrovascular apoplexy happens in COVID-19⁵⁴. Cohort study with COVID-19 distinguished raised D-Dimer level and scattered intravascular coagulation as indicators of most noticeably terrible result⁵⁵. Anticoagulant treatment with low molecular weight heparin was related with diminished mortality and better anticipation among COVID-19 patients⁵⁶. Low molecular weight heparin improved coagulation dysfunction and enhanced anti-inflammatory effects by reducing IL-6 in COVID-19 patients⁵⁷. In view of the accessible writing, either low molecular weight or fractionated heparin is prescribed to COVID-19 patients as thromboembolism prophylaxis.

VITAMINS AND MINERALS

Dietary enhancements plentiful in nutrients and micronutrients are fundamental to support resistant framework which assumes a significant job in the battle against COVID-19. Vitamin C and D includes various significant capacities inside the body. A randomized controlled preliminary completed in USA among 167 patients with sepsis identified with ARDS suggested that organization of ~ 15 g/day of IV nutrient C for 4 days has diminished mortality in these patients⁵⁸. High-portion intravenous Vitamin C has additionally been effectively utilized in the treatment of 50 moderate to extreme COVID-19 patients in China. Extra bolus portion was regulated to patients with basic conditions⁵⁹.

Vitamin D D underpins creation of antimicrobial peptides in respiratory epithelium and lessens provocative reaction to disease with SARS–CoV. Vitamin D insufficiency altogether expanded danger of COVID-19 and mortality related with the condition⁶⁰. In one of cross sectional study at Europe, researchers found that Vitamin D associated with mortality of COVID-19⁶¹. It is fitting to keep up serum 25(OH) D fixations more than 30 ng/ml (75nmol/L), ideally at a level more prominent than 40 ng/ml (100nmol/L) along with adequacy of

micronutrients, zinc, selenium and cell reinforcements to control and to decrease the danger of COVID-19⁶². Meta-analysis of randomized controlled trials have demonstrated that supplementation of oral zinc fundamentally diminishes rate of intense respiratory diseases by 35%⁶³. Without a doubt, great quality eating routine plentiful in vitamin and minerals are basic during COVID-19 pandemic to keep the invulnerable framework sound.

AYUSH

Ministry of AYUSH Government of India endorsed ayurvedic suggestions to help invulnerability and to stop the spread of viral episode. As a team with Committee of Logical and Mechanical Exploration (CSIR), it has begun clinical preliminaries for testing viability of four significant ayurvedic spices ashwagandha, guduchi, yasthimadhu, peepli and another figured medication, 'ayush 64' in battling novel coronavirus⁶⁴. Investigations by Indian Institute of Technology (IIT), Delhi, Japan's National Institute of Advanced Industrial Science and Technology (AIST), states spice (ashwagandha) can be a successful remedial and preventive medication against COVID-19 contamination^{65, 66}. Guduchi or Giloy (Ayurvedic base of eternity) has wondrous recuperating powers. Its capacity to battle a few respiratory and stomach related issues can be very useful in lessening a portion of the manifestations related with COVID-19. Ayush 64 is another medication under testing for COVID-19 which has been solely evolved by the Focal Service functions as a jungle fever battling drug.

Harvard clinical school suggested yoga, reflection and controlled breathing to manage issues identified with crown infection nervousness⁶⁷. Yoga assists with alleviating tension and to decrease dread of crown infection⁶⁸. National Institute of Siddha reported that SRM Medical College and Hospital have effectively treated 13 COVID-19 patients with integrative methodology of Siddha alongside allopathic medication by utilizing Kabasurakudineer⁶⁹. Homeopathy medication Arsenicum album³⁰ can be a prophylactic medication against coronavirus contaminations dependent on the suggestion of the Logical Warning Board (January 28) Service of AYUSH⁷⁰. In any case, information from progressing clinical preliminaries are expected to produce more confirmations.

CONCLUSION

Existing review called attention to numerous clinical trials considered the therapeutic benefit and viability of different antivirals and other treatment techniques in the administration of SARS-COV-2. Anyway till now it isn't evident whether right now accessible restorative intercessions are helpful in improving clinical result of COVID-19 patients or not. Excellent randomized controlled trials are expected to create more evidences on the board of COVID-19. Fundamental attributes of medicine, its signs and unfriendly responses ought to be distinguished to guarantee clinical wellbeing and guide for additional standardized clinical trials and research.

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