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REVIEW ARTICLE

Systemic Review of Potential drugs used for COVID-19 patients

Amarha Naeem[1], Arfa Aziz[1], Huda Tahreem Hashmi[1], Farhat Ijaz[1], Rana Khurram Aftab[2], Rizwana Kamran[1]
[1]CMH Lahore Medical College Institute of Dentistry.Lahore, Pakistan.
[2] Punjab Institute of Cardiology, Lahore, Pakistan.
Corresponding Author's Email: farhat_khurram_rana@cmhlahore.edu.pk

ABSTRACT
To state the potential drugs used for the therapeutic management of the COVID-19 patients. We searched articles from Google Scholar, PubMed and clinical trials.gov and follow the protocols of the PRISMA. There was no eligibility restriction based on the type of study. The search words which were used are anti-viral, anti-bacterial, anti-malarial drugs, Tocilizumab, Remdesivir, ACE inhibitors, Chloroquine/hydroxychloroquine, Fluoroquinolones, and Azithromycin. 69 articles were identified during the literature search from which 26 studies were included in this review. These were clinical trials (n=5), case series (n=1), review articles (n=17) retrospective studies (n=3). Repositioned drugs like Tocilizumab (promising drug in severe infection) Remdesivir (has promising results in early infection) and ACE inhibitors, Fluoroquinolones, Azithromycin (effective to some extent) chloroquine/hydroxychloroquine (not that much effective) against this coronavirus. Until there is no effective treatment repositioning of drugs is an effective short-term strategy.
Keywords: *COVID-19, Coronavirus, Potential drugs*

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INTRODUCTION

COVID-19 is similar to the SARS-CoV and MERS-CoV which belong to the beta-coronavirus family and causing deadly infections during the last two decades.It begins in Wuhan city of China in December 2019 later it became a Global emergency and on 11th March 2020 WHO declared it as a Pandemic. (1)Fast activation of the immune system take place in patients with severe COVID-19.(2)COVID-19 hyper-inflammatory state of body's immune-mediated by mediators interleukins(IL-1, IL-6, IL-12, and IL-18)and tumor necrosis factor-alpha (TNFα).(3)Coronavirus illness showed highly variable symptoms which are fever, dyspnea, or dry cough, which are consistent with lower respiratory tract infection. Loss of smell and taste,GI distress, headache and weakness have also been reported.Acute respiratory distress syndrome if prolonged may cause fibrosis of the lung and progress to respiratory failure. Secondarily, it may lead to multiple organ failure.(4) So far there is no effective proven treatment. Various drugs are recommended for the treatment of COVID-19 by different health authorities in different countries. Here we are highlighting some antiviral, antibacterial, antimalarial, anti-inflammatory drugs and some ACE inhibitors which are efficacious in COVID-19.

METHODOLOGY

We did this systemic review under the guidelines of the PRISMA. We searched the research articles from PubMed, Google Scholar, Clinical trials.gov by the search words anti-viral, anti-bacterial, anti-malarial drugs,Tocilizumab,Remdesivir, chloroquine/hydroxychloroquine, Fluoroquinolones, Azithromycin. There was no eligibility restriction based on the type of study. 69 articles were collected which were screened and accessed for eligibility and many were excluded as described in Fig.1 and only 27 articles were included in it.

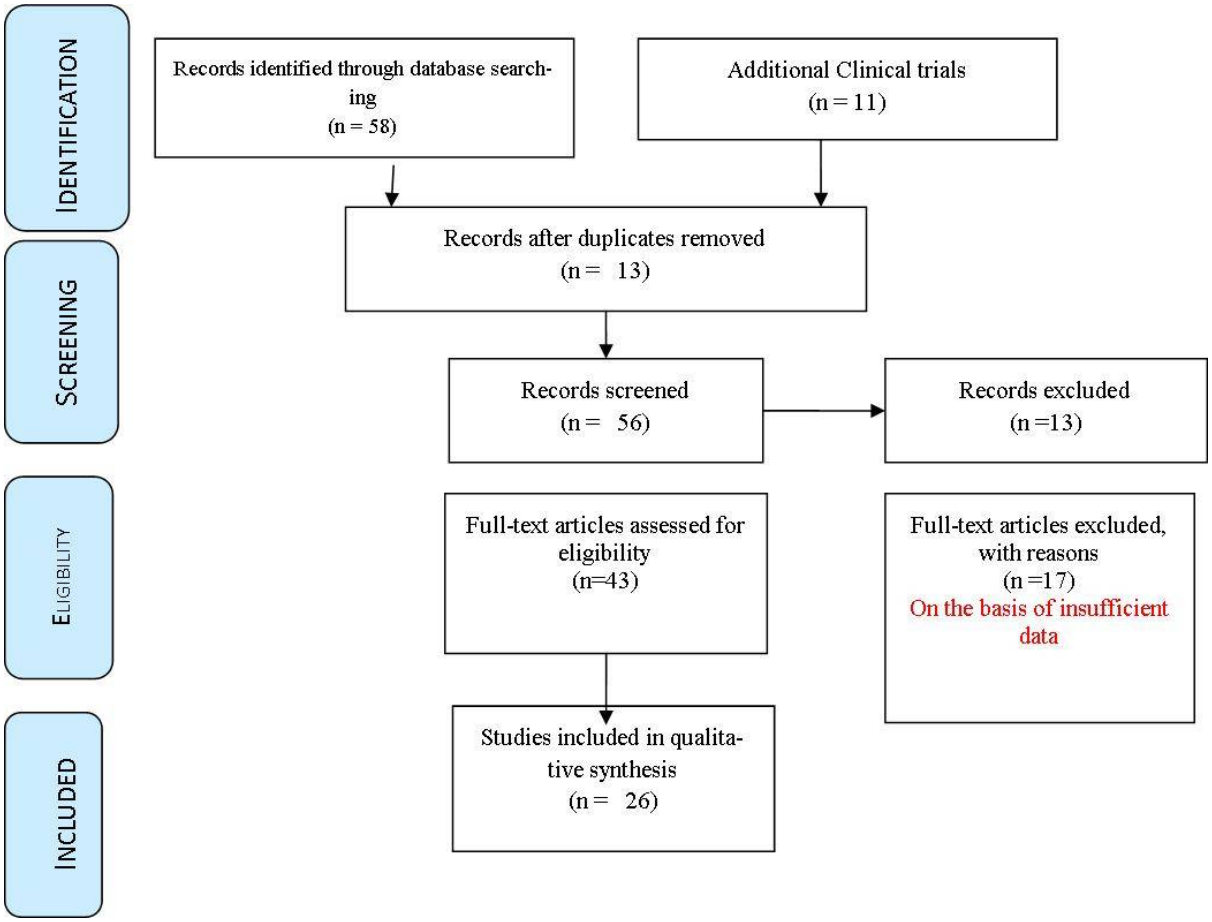

Fig.1 Search result's PRISMA Flow chart

RESULTS

Authors	*Year*	*Study Design*	*Country*	*Outcomes*
Nasonvoe, Samsonovm.	*2020*	*Review Article*	*Russia*	*IL-6 Is Responsible For Cytokine Storm Syndrome In COVID-19 Patients Tocilizumab Inhibits IL-6 And Effective In The Treatment Of COVID-19*
Tadepalli et al	*2020*	*Case Series*	*USA*	*IL-6 Inhibitor Reduces The Rate Of Mortality In Patients*
Toniati et al	*2020*	*Clinical Trial*	*Italy*	*Tocilizumab Produce Rapid, Significant Clinical Improvement In Patients*
Jakob J. Malin et al	*2021*	*Review Article*	*Germany*	*Remdesivir Showsgood Efficacy Against COVID-19 And Other Viral Infections.*
Robin E Ferner et al	*2020*	*Review Article*	*UK*	*Remdesivir Is Effective Against COVID-19 And It Is Involved In The Post-Entry Stage In The Host Cell.*
Marks et al	*2020*	*Clinical Trial*	*UK*	*There Is No Significant Difference In The 5 Days Or 10days Therapy With Remdesivir.*
S. Akhtar et al	*2020*	*Review Article*	*Qatar*	*The Use Of Aceis Is Safe In COVID-19*
A. Aleksova et al	*2020*	*Review Article*	*Trieste, Italy.*	*Should Continue Aceis Treatment In Patients With COVID-19 Infection*
J. Alexandre et al	*2020*	*Review Article*	*France*	*Because Of COVID-19, We Should Not Discontinue The Usage Of Aceis*
J. Alexandre et al	*2020*	*Review Article*	*France*	*Aceis Can Be Used In Covid-19 Infection*
A. Kurdi et al	*2020*	*Retrospective Study*	*UK.*	*The Risk Of Having Covid-19 Is Low With Aceis*
J. Meng et al	*2020*	*Review Article*	*China.*	*Aceis Can Be Used To Treat The Clinical*

				Symptoms Of Covid-19 In Patients Suffering From Hypertension.
S. L. P. Scroggs et al	*2020*	*Review Article*	*USA*	*Fluoroquinolones To Some Extent Can Reduce The Replication Of SARS-Cov-2 When Cultured.*
C. Gagliotti et al	*2021*	*Clinical Trial*	*Italy*	*Antibiotics Can Cause A Reduction In The Transmission Of The Virus*
K. Marciniec et al	*2020*	*Review Article*	*Poland*	*Ciprofloxacin Can Interact With Protease Of Covid-19*
I. Karampela et al	*2020*	*Clinical Trial*	*Italy*	*Fluoroquinolones Can Treat COVID-19 Patients.*
O. Berwanger	*2021*	*Clinical Trial*	*Brazil*	*Azithromycin Can Be Used To Treat COVID-19 Patients*
R. H. M. Furtado et al	*2020*	*Retrospective Study*	*Brazil*	*Azithromycin In Severe COVID-19 Patient Is Not Helpful*
Prof Chris Butler Et al	*2021*	*Retrospective Study*	*Brazil*	*Azithromycin Does Not Help To Reduce Recovery Time In COVID-19 Patients.*
D. Echeverría-Esnal et al	*2021*	*Review Article*	*Spain*	*Azithromycin Is Not Beneficial In The Treatment Of COVID-19.*
Sebastián Ibáñez et al	*2020*	*Review Article*	*Santiago, Chile*	*The Use Of Hydroxychloroquine Or Chloroquine In COVID-19 Is Not Very Effective*
Wei-Yi Ong et al	*2020*	*Review Article*	*Singapore*	*Clinical Trials On Patients With COVID-19 Have Identified Benefits With Chloroquine And Hydroxychloroquine*
Neerajsinha et al	*2020*	*Review Article*	*USA*	*Chloroquine Was Found To Have An Effective Concentration As Well As Cytotoxic Concentration.*
Rashmiranjan Das et al	*2020*	*Reviewarticle*	*New Delhi, India*	*An Increased Risk Of Mortality And Adverse Event Occur With HCQ And Azithromycin Together(Not HCQ Alone*
Anwar M. Hashema et al	*2020*	*Review Article*	*Saudi Arabia*	*CQ/HCQ In COVID-19 Treatment Is Used Both For Ill Patients As Well As Prophylaxis.*
Ohad Oren et al	*2020*	*Review Article*	*USA*	*CQ And HCQ Both Medications Can Induce Cardiotoxicity Only Few Evidence Are There As Safe Drugs*

DISCUSSION

Tocilizumab

It is a monoclonal antibody against the IL-6 receptors. IL-6 potentiates the inflammatory response and its level is particularly high in a patient with severe COVID-19 (having acute respiratory distress syndrome).It down-regulates the IL-6 pathway, which reduces the risk of morbidity and mortality in patients. This is a promising treatment for severe COVID-19 patients(5). It reduces the oxygen requirement drastically reduce and lessens the hospital stay and mortality risk. (3). 100 patients were enrolled for the treatment with the Tocilizumab. 58 patients showed improved clinical outcomes of respiratory condition. 77 patients had stabilized respiratory condition on 10th day, 20 patients died out of 23 patients who had worsened respiratory condition. It shows Tocilizumab produces significant clinical improvement in patients. (6).

Remdesivir:

It is the first FDA-approved promising drug against the COVID-19(7).It is an antiviral broad-spectrum drug. It targets the replication of RNA by inhibiting RNA-dependent RNA polymerase. It doesn't cause any damage to the human RNA Pol II and mitochondrial RNA Polymerase. Nonstructural proteins 12 (nsp12) polymerase is highly conserved along with the coronavirus family. Remdesivir-TP particularly targets nsp12 polymerase multi-subunit RNA synthesis complex. (8) It is a prodrug that converts intracellularly into its active metabolite. Coronaviruses have a proofreading enzyme that corrects errors in the RNA sequence, remdesivir targets this proofreading. (9). A randomized trial on the 397 patients for the use of the remdesivirfrom which 200 on 5 days trials and 197on 10 days trial but it didn't show any significant difference.(10)

ACE Inhibitors (ACEIs):

The SAR-CoV-2 acts on the ACE2 receptor. ACEIs are usually used in the treatment of hypertension, cardiovascular disease and diabetes. (11) ACE2 increases the risk of mortality or severity in COVID-19

infection. it may be helpful as it forms angiotensin. Angiotensin shows anti-inflammatory and anti-oxidative effects and hypertension-induced end-organ damage. (12)ACE2(carboxypeptidase) is a membrane-linked enzyme that acts on angiotensin II and inactivates it by inhibiting its effects. No evidence was found which shows increasing ACE2 can help SARS-COV2 in its entry into the cell.(13)However, high ACE2 protects inflammatory tissue damage due to COVID-19 infection(14)because of COVID-19 we should not abandon the usage of ACEIs(15)Study may suggest the occurrence of COVID-19 is lower in patients treated with ACE inhibitors over a long period. (16)

Fluoroquinolones:

Fluoroquinolones, the derivatives of quinoline, are a synthetic antimicrobial agent, (17). Remarkably, fluoroquinolones show antiviral actions against HIV, VZV, HCV, HSV-2, and poxviruses. (18)This drug repressed SARS-CoV-2 replication by binding to its protease. (19). It inhibits pro-inflammatory cytokines which weaken the inflammatory response. Remarkable, It is an effective agent for the treatment of infection.(20)

Azithromycin:

Azithromycin, which shows antiviral and anti-inflammatory properties, can be used in the treatment of COVID-19(21).This drug inhibits SARS-CoV-2 by acting at various points of the viral cycle. It reduced cytokine production, maintain epithelial cell integrity and preventing lung fibrosis. It decreases the mortality and days of hospitalization in viral infections. Thus it is helpful in COVID-19.(23)Studies show Azithromycin with hydroxychloroquine, is not helpful in COVID-19. It is an extensively available, reasonable drug, and it is safe therefore it might be an option for the treatment of COVID-19. (24). In the trial on 7763 participants, 2582 were under azithromycin treatment and 5181 patients were under usual care alone. The trial took place at 176 hospitals in the UK. The research found azithromycin is not beneficial for the primary outcome of 28-day mortality when added to the standard care regimen.(22)

Hydroxychloroquine and Chloroquine:

Hydroxychloroquine and Chloroquine are the drugs involved in the inhibition of immune activation by reducing cytokine production and decreasing Toll-like receptor (TLR) signaling. CQ has broad-spectrum antiviral activity. CQ interferes with the angiotensin-converting enzyme 2(ACE 2) receptor by the process of glycosylation, therefore the virus cannot bind to its target cell. And one proposed mechanism is that inhibition of activation of p38, mitogen-activated protein kinase (MAPK) occurs by chloroquine in THP-1 cells (25). These drugs are lipophilic and able to cross the blood-brain barrier. Phospholipase A2 isoform is inhibited by them non-selectively.(26). The effects of these drugs include mainly cytokine inhibition, inhibition of viral post-translational modifications, glycosyl-transferases (27). Hydroxychloroquine (HCQ) has no relationship with mortality however HCQ and azithromycin together significantly increase mortality (28). CQ and HCQ chemical structure is closely related. Inhibition of Quinone reductase 2 occurs by CQ which is required for salicylic acid synthesis which is involved in attachment and entry into the host cell. And CQ increases endosomal pH thus inhibiting virus endosome fusion. CQ works as an anti-autophagy and anti-inflammatory agent. CQ/HCQ is also used in prophylactic treatment along with the treatment of patients who are ill with COVID-19(29). Complete AV block is encountered with chloroquine and left ventricular hypokinesia is associated with HCQ. Additional side effects include the hyperpigmentation of the skin, muscular weakness and retinopathy [30].

CONCLUSION

As in the worse situation of COVID-19 when it spreads rapidly and there is no effective therapy and vaccine is only for healthy people not for the infected persons. Repositioning of drugs, symptomatic treatment, are efficient short-term strategies. Repositioned drugs like Tocilizumab (promising drug in severe infection), Remdesivir (promising result in early infection), ACE inhibitors, Fluoroquinolones, Azithromycin and (effective to some extent) chloroquine/hydroxychloroquine (not that much effective) against this coronavirus.

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