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GLOBAL PREVALENCE OF COVID-19: A HOPE ON EMERGING TREATMENT OPTIONS & RESEARCH

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ABSTRACT

Background: Corona virus pandemic is at present a global public health emergency. Starting from China, Italy, America, now it is escalating worldwide. Foremost with individual case and now with 43, 55,456+ cases, this virus is travelling across every region of the world. Due to the dearth of proficient and peculiar treatments, drug repurposing is expected to be the most suitable way to look for analeptic solution. **Objective**: There are many reports which showed the role of various existing drugs in different viral conditions, Evidence about the worth of those drugs in COVID-19 infection is very limited. This systematically evaluated review intends to abridge on hand evidences concerning to the treatment of corona virus infection and how this novel virus is affecting patients undergoing other diseases. **Methods**: The desired and encouraging testifying items for systematically evaluated reviews and meta-analyses (PRISMA) standards were opted. A literature exploration was accomplished utilizing to locate articles for the present scenario and treatment for COVID-19 affected persons. **Results**: We have appended 32 publications in this systematically evaluated review. Each of the articles refer to the role of already existing drugs in restricting the contagion with SARS-CoV-2 and how this novel virus is affecting patients undergoing other diseases. **Conclusions**: There are clinical evidences of usefulness of previously existing medications in patients who are getting infected by COVID-19.

KEYWORDS: COVID-19, Management, Coronavirus, Worldwide, SARS-CoV-2.

INTRODUCTION

An eruption of SARS-CoV-2 or COVID-19 during December in the year 2019, informed in Wuhan, China, which escalate to every zone of China and almost every single country throughout the globe. The figure of human population detected with COVID-19 is multiplying exponentially, and WHO affirmed it a pandemic.[1] The earlier known Wuhan virus, is now Novel Corona Virus (Covid-19), dilated its orbit in South Korea, Italy, Japan, Iran, America and instantly increasing worldwide. Symptomatology of COVID-19 is cognate to previous respiratory viral infections. Cases fluctuate from insignificant to rigorous condition that may lead to critical medical conditions or demise also.[2] No drug has been indorsed by existing governing agencies, which is believed to be pharmacologically effectual for the cure of SARS-CoV-2 infectivity, and study of drugs efficacious in COVID-19 is the pressing priority.[1]

From the reported evidences, it is advocated that SARS-CoV-2 illness is allied with a pro-inflammatory stage depicted by increased level of dissimilar cytokines, with interleukin-1β, IL-2, IL-1Rα, IL-10, GM-CSF, FGF, IP10, G-CSF, PDGF, MCP1, TNFα, MIP1-α and VEGF. Patients with severe illness entailing ICU demonstrate distinctly higher levels of G-CSF, IL-2, IL-10, TNF-α IP10, MCP1, MIP1A and IL-6. Also, levels of IL-6 coordinate with increase in mortality.

Likewise, in grievous COVID-19, a depletion of NK cells, CD4+, CD8+ T- lymphocytes & IFN-γ manifestation in CD4+ cells, has been discerned. Readings of IL-6, IL-10 & TNFα, not directly but inversely correlate with lymphocyte sum, advocating that cytokine release syndrome possibly shackle the adaptative immune retort hostile to SARS-CoV-2 pestilence. High intensities of ferritin were displayed in those patients who needs ICU hospitalization. This endowed rational for the utility of numerous anti-rheumatic medications as potential therapies for this rigorous viral infection, though a direct antiviral influence of few medications is proposed by preliminary experiments, *in vitro.* As chloroquine (CQ) as well as hydroxychloroquine (HCQ) are exercised in COVID-19 infectivity at this time. Tocilizumab, indorsed for the cure of rheumatoid arthritis (RA), is an anti-IL-6 monoclonal antibody and has been exercised with inspiring results in markedly ill patients. Trials are in progress to examine the worth of Tocilizumab on critical COVID-19 patients.[3] To date, no clinical evince is there to encourage the usage of any drug in curing COVID-19.[1]

MATERIALS AND METHOD

A systematically evaluated review of currently published literature was executed to uncover the role of anti-rheumatic, anti-viral and various other drugs in COVID-19 illness. The desired and favorable testifying items for systematically evaluated reviews & Meta-analyses, PRISMA guiding principles were utilized. The publications chosen in this review study incorporated original articles, pre-prints, pre-proofs of the accepted article, letter to editor, expert's opinions and case reports or case series, published from inception till date, which probed the role of various existing drugs in COVID-19. Duplicate papers, posters, and papers lacking in treatment for COVID-19 were excluded.

LITERATURE SEARCH AND DATA SOURCES

We searched the articles from Scopus, Science Direct and Google Scholar, reporting the role of various already existing drugs in COVID-19. Keywords used in search were: "COVID-19", "SARS-CoV-2", "Novel Corona virus", "Treatment", "Worldwide" with a publication time range for last two years up to date. From the articles, abstract & purpose of the article was reviewed. The articles which describe the role of any drug in the treatment of COVID-19 and effect of this infection in other diseases were chosen for full-text review.

SCREENING

Headings (Titles), along with abstracts in the search outcomes, were assessed and screened. Downloaded the manuscript (full-text) of the chosen articles and then extracted the relevant data and material. All the investigators studied the data independently, and attained the consensus with conjoint conversation.

EXTRACTED DATA AND ITS ANALYSIS

Extracted the appropriate data from chosen articles After interpretation of full text, data points were tabulated and presented the outcomes in the form of chronicle sum-ups.

RESULTS

The early search for "treatment for Covid-19, effect of Covid-19 in other medical conditions and Current scenario worldwide" yielded 248 entries, published till 22nd April, 2020. By means of exclusion criteria, 32 articles were finalized for the review. The record included 18 published articles, 3 letters/ correspondence, 2 commentary, 6 pre-proofs of accepted articles, 1 report, and 2 pre-prints (that are not peer-reviewed yet)

articles.

DISCUSSION

The first person to have contracted COVID-19 pestilence, in Hubei province of Wuhan (China) had been reported on 17 November 2020. As of now, the World health organization (WHO) had confirmed a sum of 43, 55,456 cases (subjected to alter in due course), 16, 10,421 recoveries, & 2, 93,090 demises worldwide, which is remarkably high.[2]

As this 2019-nCoV acute and grave respiratory illness is spreading rapidly all around the world, there is quick necessity for the medicines/therapy which would aid the patients sooner than a vaccine is researched. The currently available drugs can be focused which may block the viral infection.[4] Effect of compounds that are under instigation as Anti-SARS-CoV-2 or else previously approved for former medical implementations are evaluated; a number of compounds formerly reported to be efficacious against coronavirus duplication *in vitro*, and several compounds are assessed in clinical trials in COVID-19 infected patients.[6]

Erlotinib and **Sunitinib** (oncology drugs) show antiviral property through the inhibition/ reticence of AAK1. Receptor-mediated endocytosis is the utmost route for the entry of majority of the viruses into cells. AAK1 are well-known endocytosis regulators. AAK1 disruption, in turn, might interrupt the viral passage. Even so, these drugs would not be a secure therapy due to profound adverse-effects, and the reported data infer high doses for the inhibition of AAK1 efficiently.

Baricitinib, janus kinase inhibitor (high binding affinity to AAK1), is another endocytosis regulator. Because for the inhibition of AAK1, plasma levels of baricitinib with therapeutic dosage (2 mg or 4 mg OD) is adequate, we suggest, trials should be performed on patients with 2019-nCoV, to reduce viral entry as well as the inflammation.[4]

Ciclesonide (Alvesco), an inhaled steroid possesses strong antiviral action against SARS-CoV-2. Antiviral as well as anti-inflammatory actions of ciclesonide are expected to be effectual in curing lung injury triggered by coronavirus, that's becoming more serious now. Only ciclesonide showed antiviral effect against COVID-19 as inhaled steroids till now. The usage of steroidal preparations for the COVID-19 therapy is not advised because of the probability of persisting viremia and problems like diabetes, even though systemic dispensation of prednisolone, hydrocortisone, methylprednisolone and dexamethasone are

being measured. An inhaled prodrug Ciclesonide, that remains upon lung surface with minimal rise in blood levels. It is given mostly in pneumonia prior to the severity of illness, and it is presumed that it has effect of abruptly bettering the symptoms of patients and restraining evolution to rigorous pneumonia.

The standard adult dosage regimen is 400 µg OD, and maximum dose is 800 µg BD. As the replication time of virus is 6-8hr, repeated and higher dosage is supposed to be necessary to reach alveoli. To avoid recrudesce of viral infectivity, its continuation is opined for at least 14 days or can be extended. Gasping (inhaling) as intensely as possible will boost its effect, because the virus imitates in alveolar epithelial cells. If the outcome can be confirmed, primary dispensation of ciclesonide is effortless and economical, and is judged to have profound ability. It is significantly apprehended that additional cases of ciclesonide practice will be amassed and analysed in future.[5]

Remdesivir, another antiviral drug (1′-cyano-substituted adenosine prodrug, having activity against paramyxoviruses, filoviruses, and coronaviruses) confirmed recently to show *in vitro* inhibition of 2019-nCoV.[5, 6]

Remdesivir, Lopinavir, Emetine dihydrochloride and Homoharringtonine, were discovered to hinder SARS-CoV-2 duplication in Vero E6 cells under 100 µM with EC_{50}. Some of the medications at present under clinical trials, for instance, favipiravir, ribavirin, baloxavir or oseltamivir, other adenosine indicated no perceptible antiviral efficacy against SARS-CoV-2 *in vitro*. Efficiency of Remdesivir is against SARS-CoV, human coronaviruses (hCoV-OC43 and hCoV-229E), MERS-CoV and SARS-CoV-2. Clinical trials, currently in Phase 4, evaluated its efficacy against COVID-19. Combination of Lopinavir and ritonavir is HIV-I protease inhibitors approved by FDA.

Lopinavir, exhibit more potency in the inhibition of HIV-1 than showed in ritonavir *in vitro* but with insignificant bioavailability *in vivo*.

Ritonavir, displayed inhibition against HIV-I protease as well as against host's cytochrome P450 3A4 enzyme metabolizing lopinavir. Thus, in this type of combination the bioavailability of lopinavir can be prolonged, *in vivo*.

Ribavirin, along with lopinavir or ritonavir was previously recommended for the cure of SARS-CoV infected patients, is under a non-randomised clinical trial. ARDS instigation or

death was lessen in SARS patients, administrating combination drug of lopinavir or ritonavir with ribavirin in comparison to the patients given treatment with corticosteroids and ribavirin. At this point of time, under randomized control trials (RCT), lopinavir/ritonavir displayed proficiency in SARS-CoV-2 patients with or without ribavirin. Antiviral efficiency of lopinavir (EC50 at 26.1 μM) was scrutinized *in vitro,* against SARS-CoV-2 in the past reports, but was not observed with ritonavir. In the ongoing situation, at the dose of 400mg/100 mg BD, lopinavir/ritonavir is advised for the management of patients enduring COVID-19, with or without ribavirin, in China (China National Health Commission, 2020). No substantial aid in hospitalized patients with lopinavir-ritonavir is testified by current RCT than the standard care. Lopinavir therapy in combination with additional effectual drug treatments against SARS-CoV-2 may enhance synergy and hence for the inhibition, reduction in the concentration of lopinavir may be possible.

Homoharringtonine, which is a alkaloid of plant origin stemmed from Cephalotoxus fortune, likewise reported to display potent activity against rhabdoviruses, herpesviruses, coronaviruses and additional viruses viz hepatitis B, echovirus and Newcastle disease virus. Homoharringtonine observed to inhibit SARS-CoV-2 with EC_{50} at 2.10 μM.

Emetine, a determinant of protein synthesis, employed as an anti-protozoan and used in the management of amoebiasis; also bind to ribosomal E site of P. falciparum to inhibit malaria. However, clinical utilization of emetine has been confined due to its potential cardiotoxicity. It was reported to be active against array of RNA as well as DNA viruses, involving Ebolavirus, Zika virus, rabies virus, Cytomegalovirus, HIV-1, bovine herpesvirus 1, echovirus 1, peste des petits ruminant virus, buffalo poxvirus, Newcastle disease virus, Rift Valley fever virus, herpes simplex virus-2 and influenza virus. Also, Emetine was recognized to impede MHV-A59, MERS-CoV, hCoV-OC43, SARS-CoV and hCoV-NL43 *in vitro*. It is observed that at nearly 0.5 μM, emetine may impede replication of SARS-CoV-2 effectually. Combinatory efficiency of emetine and remdesivir *in vitro* is explored to lessen the effectual concentration of distinct compound/ drug below the leading therapeutic plasma levels. Checkerboard assay was used to evaluate drug interaction with this combination (remdesivir and emetine) when consecutively 2-fold diluted (0-50 μM and 0-0.781 μM respectively). This combination at concentrations 6.25 μM and 0.195 μM respectively, may give inhibition of 64.9%, and in vivo testing can be achieved further.[6]

A WHO report, indicate that Remdesivir having expansive potential, and can serve as a

leading candidate against COVID-19. It can be envisaged from remdesivir that it would bring magnificent break throughs to the COVID-19 management, or highly promising for additional viral pestilences in future.[12]

ACE2 and TMPRSS2, the host cell factors, may lead to SARS-CoV-2. As ACE2 expression guard from harm to lungs and SARS-S can impact adversely, which might boost SARS. It can be fruitful in inventing whether CoVID-19 also influences ACE2 expression.[7] These findings may assist in establishing alternatives for the safeguard against Covid-19.

TMPRSS2 inhibitor (Camostat Mesylate), which is a protease inhibitor, is well known to inhibit TMPRSS2, and hypothetically can be effective in preventing the viral pestilence of host cell. Camostat Mesylate used for the cure of pancreatic swelling, in Japan. Also managed to suppress the approach of SARS-CoV-2 infectivity into the lung cells when assessed on SARS-CoV-2 extracted from a patient.[26]

Thromboprophylaxis, Severe hypoxia, diffuse intravascular coagulation (DIC), immobilization and excessive inflammation may induce arterial and venous thromboembolic disease in COVID-19 infected patients. Specific facts of the degree of thrombotic difficulties in SARS-CoV-2 infected patients is vital for seriousness of thromboprophylaxis, specifically for patients in ICU and at extremist thrombotic risk. Ischemic stroke, Acute PE, systemic arterial embolism, deep-vein thrombosis or myocardial infarction in each one of COVID-19 patients had been evaluated who were hospitalized under ICU of 1 Dutch teaching hospital and 2 Dutch university hospitals. In the ICU patients, 31% occurrence of thrombotic issues is surprisingly high. Thus, the strict application of prophylaxis in all ICU patients would be endorsed, with higher-prophylactic doses, notably in the lack of randomized evinces.[8]

IFN-I, Administration of five million U of IFN-α, bis a day, by vapor inhalation, with ribavirin, has been advised to the COVID-19 patients, as per the recommendations in China. In the initial phase of infection, utilization of IFNβ1 may provide a secure and effortless remedy against COVID-19. Mixed efficiency had been observed with similar medications effective in MERS-CoV and SARS-CoV infection, but by *in vitro* analyses it was found that only SARS-CoV-2 might be prominently more receptive to IFN-I as compared to former coronaviruses. More precise facts on the proficiency of this therapy would be expected in the coming future.[9]

Glucocorticoids, the most arguing question is, should GCs be effective through COVID-19 pandemic, if so, which, And in which phase, dosage and route of administration. Current evidences as well as WHO report regarding COVID-19 did not endorsed the usage of GCs routinely for cure of novel corona virus pneumonia before clinical trials.[3] Corticosteroids effectively control inflammation in lungs but restrict immune responses and prevent clearance of pathogens as well.[10] Diabetes, psychosis and avascular necrosis were more associated with corticosteroid treatment in the treatment of SARS. So, it is concluded that there is no single cause to envisage that the COVID- 19 infection could be cured with corticosteroids usage and such trials possibly be unsafe. However, following clinical records, prescribing corticosteroids to right patients at right time can be effectual.[11] Administration of Corticosteroids showed no influence on mortality in both SARS and MERS but slow down the clearance of the coronavirus in lower respiratory tract. Current WHO recommendations advocate that usage of corticosteroids in routine should be averted in COVID-19 patients; lest the patients are evinced for any different reason.[22]

Rheumatologists are fearful that COVID-19 could present a serious threat to their patients especially who are using immunosuppressive therapy are at higher risk of serious outcomes. At present, there is inadequate data, even though researchers are instigating to investigate COVID-19 in people suffering from rheumatic ailments. Prevailing literature propose that there is a significant escalation in critical infections in the patients who cured with classical anti- rheumatic therapies including biologic drugs, glucocorticoids, and Janus kinase (JAK) inhibitors and a great probability of Herpes zoster virus infectivity is there for patients who are taking JAK inhibitors. Although the major bother is the harmful effects of drug therapies used to manage rheumatic ailments, arguments are also coming about the potential effectiveness of some familiar anti-rheumatic drugs. IL-1 inhibitors, JAK inhibitors, Antimalarials, IL-6 inhibitors, leflunomide & i.v. immunoglobulin, all have been listed as probably effective therapeutics for COVID-19. Apposite trials are progressing for their extensive use in COVID-19. Tocilizumabis currently underway phase III trial for COVID-19. Rheumatology COVID-19 repository would facilitate the prompt gathering of the case details from doctors treating patients with rheumatic diseases and is formulated to collect information about the COVID-19 consequences in patients under treatment of rheumatic diseases, specifically those with immunosuppressive therapies; and to hypothesize the developing harms or merits of certain immunomodulatory and immunosuppressive medications in COVID-19 infection.[28]

Naproxen, a determent of COX-2 along with Influenza virus-A nucleoprotein (NP), might possibly have the aptitude of exhibiting antiviral actions against SARS-CoV-2. A current clinical trial indicates lessen mortality confined for H3N2 Influenza viral infectivity, with the combinational therapy of naproxen, clarithromycin and oseltamivir. A clinical trial has begun phase 3 to investigate the benefit of encompassing naproxen taking part in the prevailing therapy of critically COVID-19 infected patients.

NSAIDs and **acetaminophen,** possibly concomitant with the masking of manifestations in COVID-19, also with respiratory and cardiovascular complications. NSAIDs have been enormously used in cases with acute respiratory affliction, and evidences indicate that NSAIDs are linked with escalating probability of stroke plus myocardial infarction. In addition, larger randomized clinical trials encouraged that the NSAIDs can be accountable for the cause of more prolonged ailment when given through respiratory tract infections. Factors like age and presence of concomitants specifically hypertension may produce big threat of hospitalization, precarious disease as well as transience in COVID-19 infected patients. Thus, regular use of NSAIDs cannot be suggested as first line choice for COVID-19 therapy till further research.[3]

Chloroquine (CQ) and **Hydroxychloroquine (HCQ)**, recently carried out clinical trials have confirmed the inherent useful upshots of **CQ** as well as **HCQ** *in vitro* against COVID-19 infection. Early footprints appear to support that CQ may meliorate COVID-19 related pneumonia by blocking pneumonia aggravation, rectification of lung imaging and by reducing the course of disease. CQ and HCQ have been comprehended in the usual therapy worldwide. However, the threat of adverse outcomes cannot be ignored which is highlighted by recent trial reports. In a recent review article, 6 articles and twenty-three in process clinical trials there in China are added. In controlling SARS-CoV-2 replication, CQ found to be successful. Gautret et al. have testified 20 patients were given HCQ therapy (600 mg/day) for 6 days accompanying **Azithromycin,** brought significant pruning of the viral appearance conform to the controls and is diagnosed from nasopharyngeal swabs by polymerase chain reaction (PCR). This indicates that the addition of azithromycin along with HCQ can be more efficient in virus eradication. CQ and HCQ are advised in COVID-19 infected patients, for a very short interval (5–20 days), to reduce the probable risk of serious after-effects. Nevertheless, in critically diseased patients, serious manifestations like acute hypersensitivity and gastrointestinal intolerance may develop due to COVID-19 that requires investigation.

Moreover, CQ and HCQ can be used imperviously in the course of pregnancy.[3]

However, in rheumatology, similar protocols have been recommended by majority of guidelines and parameters i.e., CQ, 500 mg BID or HCQ, 200 mg BID (incorporating those by China and Italy), as the consummate dose regimen has yet to be validate. Although, for the best dosing regimen, *in vivo* clinical trials are vital, initial day loading dose of HCQ at 400 mg BID, following the dose of 200 mg B.D. for subsequent four days is insinuated by a physiologically established pharmacokinetic model and a pertinent plasma concentration should allow to maintain up to ten days. It can be expected that, sooner, a remarkable data to verify the actual potential of the drug on survival and revival of COVID-19 infected patients, would be helpful by the clinical trials. Up till now, because of magnificent safety sketch and expansive practice, their utility remains a backbone of the ongoing therapy.[3]

At the same time, small danger of macular retinopathy cannot be ignored, which devolve on the accumulative dose, and some survey reports on cardiomyopathy as an alarming deleterious effect due to chloroquine also exist, but a survey on SARS-CoV-2-infected persons for these untoward effects by taking chloroquine treatment remains to be achieved. No scientific data has communicated so far which invigorate these findings. Hence, the authentication has not been peer reviewed.[14,16]

Rare but remarkably fatal harms would be noticed in some patients who are widely using hydroxychloroquine, which include fulminant hepatic failure, significant cutaneous adverse reactions, and ventricular arrhythmias (particularly given with azithromycin); overdose is risk taking and cure can be intricate. Although a successful treatment for covid-19 is sorely demanded, but a vaccine or therapy with medications for the prevention is more expected to succeed which can destruct the specific structure of the virus, than existing drugs might be working in the laboratory while lacking data that encourage their clinical use. Better, accurately powered, randomized controlled trials for chloroquine or hydroxychloroquine are essentially required.[17] There must be awareness among the physicians and patients about the severe and lethal effects. Cautiously selection and monitoring of the patients can abate the harms of the treatment.[18]

Leflunomide (LEF), a marketed therapeutic agent belonging to the malononitrile amide family and have been used from years in the therapy of RA, renal transplantation and autoimmune disorders. Teriflunomide, its active form, act by inhibiting protein tyrosine

kinase and by inhibiting proliferation of T-cells. It has been endorsed in the remedy of multiple sclerosis. The antiviral potential of drug at high concentrations was commensurable to ribavirin, however LEF manifest pronounced anti-viral efficiency as compared to ribavirin at lesser concentration. The major dose-limiting adverse-outcomes of LEF therapy includes altered bowel movements, disturbance in liver functions, lung disorders, suppression of immune system, skin rashes and non-scarring alopecia. Besides anti-viral effects in humans, no sufficient data is available on the duration of therapy, appropriate dosage regimen, and target blood concentration of the drug for effective anti-viral activity. Thus, the use of this therapy in COVID-19 is not clear.[10]

Colchicine: Literature survey has reported that SARS-CoV and its associated proteins are dominant catalysts of pro-IL-1β gene transcription and protein ontogenesis, therefore are expected capable of activating NLRP3 inflammasome. The encephalomyocarditis virus 2B or influenza virus M2proteins trigger IL-1βrelease followed by subsequent activation of NLRP3 inflammasome (release IL-1β and IL-18), that can be blocked by colchicine. IL-1β, IL-18, and IL-6 are the chief inflammatory cytokines in the patients with acute coronary syndromes,[13] and administration of colchicines had remarked ability in limiting transcoronary gradients of cytokines to 40%–88%. In the patients of mucocutaneous Behcet's malady, an equivalent depletion in IL-6, IL-8 or TNF-α level was suggested. Additionally, colchicine has known to be efficacious against virus “Flaviviridae” as well as against the “strain of mouse hepatitis virus RSA59”, reducing virus replication. Influence of colchicine and derivatives on HIV load has also been suggested by various studies. SARS-CoV-2 and SARS-CoV are alike and viral replication may influence by microtubule interference. In fact, ARS cognate to COVID-19 occur with an extensive release of inflammatory cytokines and their binding to COVID-19 promote fever, fibrosis and lung inflammation. Thus, it may be fruitful to gain a conquest of IL-1 and IL-6 by suggesting colchicine to gain a therapeutic efficiency against viral infections. Colchicine extensively shows anti-inflammatory as well as marked antiviral effects, and not constrained by an immunosuppressant action. It can work greatly in this outbreak situation worldwide as it is not expensive but very cheap. GIT disturbance has been reported in patients up to10% due to the narrow therapeutic index of colchicine, and persistent incident of diarrhea restrict its utilization in COVID-19 patients. Anyhow, this adverse upshot can be lessened by potential intravenous administration and also hike its bioavailability. It can be urged that colchicine should be trialed in significant COVID-19 patients to restrict viral entry as well as inflammation. Nevertheless, for the

evaluation of the efficiency and safety of colchicine, an open-label, phase 2 research registered COVID-19 patients, has currently encouraged by the Italian Society of Infectious and Tropical Diseases, the Italian Society of Rheumatology and by the Italian Thoracic Society and ratified by the Italian Drug Agency. Inciting upshots are coming up with case report by Gandolfini et al. who medicated a patient with manifestations of systemic inflammation, and given therapy with colchicine (1 mg on eighth day, and 0.5 mg daily subsequently) with ease due to exacerbation of respiratory functions. Patients are stable to date, emphasizing on colchicine as appropriate and ideal choice for patients suffering from COVID-19 infection.[3]

Anakinra (ANK), used in the management of AOSD, RA and other critical autoimmune and autoinflammatory ailment specifically TNF-receptor-associated periodic syndrome (TRAPS). The goal of IL-1Ra therapy is to engage necessary IL-1 receptors with IL-1Ra to snag IL-1 cell signaling.[3]

Rilonacept and **Canakinumab**, also employed in the management of autoinflammatory ailments. Rilonacept is a decoy receptor (having longer duration of action), prohibits the association of IL-1α and IL-1β with surface of IL-1receptor by itself binding to them. It was endorsed for the cure in children above the age of 12 years, adults and also elderly enduring cryopyrin-associated periodic syndromes (CAPS) during year 2008. Canakinumab, is entirely a human anti-IL-1β antibody. It is evident in records that the drug restricts the inflammation by targeting IL-1β inherent immunity route can decline inflammatory tissue impairment since it is manifested in CVS dysfunction like atherosclerosis and diabetes. At present, no confirmation related to its anti-viral properties exists. As broadly depicted, SARS-CoV-19 occur with an extensive release of inflammatory cytokines which may significantly promote immuno-mediated impairment of lungs as well as other organs, leading to acute lung injury (ALI) and, eventually, multi-organ defect. Hence, we can suggest that IL-1 β antagonist's utilization may lower the intensity and mortality linked with SARS-CoV-2 infectivity. Nonetheless, no significant statistics is supporting the utilization of these two compounds as effective anti-viral drugs.

Tumor necrosis factor α inhibitors, the only mode, productive in COVID-19 infection could be lower levels of TNF which are found to be elevated particularly in the crucial phases. Furthermore, interaction with ACE2 receptor is its probable function in COVID-19. Actually, serious respiratory distress associated with SARS-CoV, cognized to be connected

with propensity of SARS-CoV's to suppress ACE2 expression. Additionally, TNF-α-converting enzyme (TACE) - action attune SARS-CoV through cytoplasmic dominion of ACE2 promote viral entry as well as tissue destruction by significant TNF-α release. On the basis of this observation, authors formerly put forward the use of TACE antagonists to deterrent SARS-CoV infection and enervated the awful clinical upshot. Additional studies established that arresting of TNF-α signaling may illustrate usable therapies.[3]

IL-6 invigorates acute-phase natural resistance as well as hematopoiesis and also associated with tortuous pathogenesis of cytokine release syndrome (CRS) and autoimmune ailments such as RA, Systemic Juvenile Idiopathic Arthritis (SJIA), Giant Cell Arthiritis (GCA). CRS, a probable sequel of giving chimeric antigen receptor engineered T cells (CAR-T) immunotherapy, latterly endorsed in the management of B-cell leukemias and lymphomas.[3]

Tocilizumab, is a refined monoclonal antibody focused against IL-6 receptor, is accomplished to lessen and rein the ramifications of perverse release of IL-6 and this is endorsed by FDA & EMA in RA therapy and other ailments.[3]

As COVID-19 come across various clinical likeness evolving in 15% sufferers of ARDS, serious kidney disorder as well as acute cardiac impairment necessitate ICU superintend and IL-6 appears to play a pivotal role which is remarkably aloft accompanying IFN-γ, granulocyte macrophage colony stimulating factor (GM-CSF), IL-2, TNF-α, IL-10 and IL-8 management with Tocilizumab (8 mg/kg *i.v.*) dose was suggested.[3]

A survey of 452 COVID-19 infected patients, who admitted to the Tongji hospital, an elevated inflammatory cytokine levels in critically infected patients were manifested as compared to non-critical patients, including IL-2R, IL-6, IL-8, IL-10, and TNF-α, but still the authenticated reports of trials are highly needed.[3]

IVIg, Manifestation of antiviral IgG concurs in 80% of the patients with inception of serious respiratory disorder was observed. Identical observation also recognized IVIg as a potential agent adroit to impregnate FcR and probably forbid lung impairment in SARS-CoV infectivity. In spite of a systemized review of SARS management evinced vague outcomes in a retrospective investigation of IVIg managed patients, a probable therapy with IVIg in COVID-19 must be assumed/hypothesized.[3]

Arbidol in addition with lopinavir/ritonavir was suggested in a case report, with considerable

recovery in COVID-19 infected patients. Proficiency and security of various antiviral compounds/drugs for the cure of COVID-19 is under assess. 34 clinical trials with antiviral compounds/drugs COVID-19 patients had been inscribed till March 15, 2020.[11]

Convalescent plasma transfusion, A laboratory check suggested that, COVID-19 virus, excluded from broncho alveolar lavage fluxional of a hypercritical case, and neutralized by sera collected from distinct patients. Convalescent patients have pleaded by "The National Health Commission" of China, to come up with their blood to cure COVID-19 viral infection. To verify a favorable neutralization antibody titer, convalescent plasma needs to be collected in two weeks after revival. The obscurity in plasma collection in the course of convalescence restricts its clinical usage. Inventive clinical trials however, are essential to encourage and assess its proficiency and security.[11]

Antibodies, the instigation of vaccines as well as sanative antibodies abutting COVID-19 have major significance. Marking the comparably extortionate distinction of receptor-binding domain (RBD) in SARS-CoV as well as in SARS-CoV-2, cross-reaction of anti-SARS-CoV antibodies with COVID-19 spike protein was appraised. Spike protein is a key persuader of the neutralizing antibodies. Fortuitously, SARS-CoV meticulous human monoclonal antibody CR3022 binds sturdily with COVID-19 RBD. As CR3022 is feasibly a dormant remedial candidate, independently or conjointly with additional neutralizing antibodies, for the anticipation and cure of COVID-19 infection. Nonetheless, instigation of COVID-19 definite antibodies needs a prolong period of time. Implementation of the monoclonal antibodies in the clinical use for novel pathogens in a short time period is not easy.[11]

Vaccine invention is a very long and time-consuming approach, and at present, no vaccines are at hand to fight against this pandemic outbreak. Fortunately, Company proclaimed its hypothetical mRNA vaccine for COVID-19, entitled as mRNA-1273, and is set for the trials on humans. It is under scrutiny for its safety and immunogenicity (Clinical Trials. gov Identifier: NCT04283461). It is exceptionally speedy instigation in the generation of primary vaccine after discovering genetic sequence SARS-CoV-2. Currently, Tianjin University has efficiently established an oral vaccine, by using food-grade harmless *Saccharomyces cerevisiae*as a conveyor and aims to target S protein. In addition, eighteen biotechnology organizations and universities located in China are acting on the vaccines for SARS-CoV-2.[11]

Vitamin D, no testimonies on the significance of vitamin D among infected persons are underlined so far. On the contrary, a huge amount of firm data manifested antiviral action of vitamin D, that can promptly constrain not only viral duplication, but also serve in an anti-inflammatory and immunomodulatory means. Later effects possibly will be decisive for assumptive favorable effects of them during SARS-CoV-2 infectivity, as it seems like that initially SARS-CoV-2 utilizes immune evasion mechanisms, which in certain patients is ensued by immune hyper-reaction and cytokine storm, as a conventional pathogenic mechanism of systemic inflammatory response syndrome (SIRS) and acute respiratory disease syndrome (ARDS) occurrence, despite of etiological factor. Moreover, various research data encourage the efficacy of Vit. D as an adjunct therapy together with antiretroviral compounds in HIV- affected patients. Additionally, pretreatment with vitamin D was proficient in animals with ARDS, which limits the lung permeability by modulating the RAS activity and ACE2 expression. In viral infections, efficacy of vitamin D is also encouraged by the outcomes of a few vitamin D receptor gene (VDR) alleles which are linked with enhanced susceptibility to respiratory and HIV infections.

Owing to dearth of discrete therapy and exigency to perform, these verdicts could be speculatively generalized to SARS-CoV-2 infectivity, rationalizing the utility of vitamin D as a probable adjunct therapy. Recommendation of persistent supplementation as probable prophylaxis could be suggested from the public health aspect. Inquisition on the status of vitamin D and VDR polymorphisms of affected subjects might explain “unusual spreading behavior” of SARS-CoV-2 and enormous clinical outcomes of COVID-19.[15]

Innumerous findings of several viruses logically hypothesize that the supplementation of vitamins C and D may escalate immunity system which can help human in fighting against COVID-19 and its violent influences. Vitamin-D supplementation in higher dose can be advised to deficient individuals, specifically elders, obese, dusty people and residents at higher latitudes. Considering defensive effects of vitamin-D in patients at high risk of chronic ailments such as respiratory tract infections, cardiovascular disease, cancers, diabetes mellitus, and hypertension, specialists hypothesize that supplementation of vitamin D and corresponding rise in serum concentration of 25-hydroxy vitamin D more than 50 ng/ml (125 nmol/l) to a great extent may lower the degree and extremity of a number of viral infections like COVID-19.[25] During the COVID-19 outbreak, everyone should take supplement of vitamin-D to raise the concentrations of 25(OH)D for the prohibition of infectivity and

spread. There is a high need of trials on this hypothesis at present. It has been reported that the higher concentration of 25(OH)D is effective in limiting the probability of infection and death from ARTIs, influenza, CoV and pneumonia. 25(OH) D levels are reduced in winter and the probability of ARTIs is remarkably high. On that account, vitamin D_3 should be initiated prior to winter in order to raise 25(OH) D levels, necessary to prohibit ARTIs. Since a variety of research studies have suggested that continuing vitamin D supplementation shows health benefits without inducing adverse effects, e.g., 2000 IU/d for reducing the risk of cancer and 4000 IU/d for limiting evolution from pre-diabetes to diabetes. Accessible evidences, suggested that supplementation with numerous micronutrients such as vitamins C, vitamin D and Zinc possessing immunity boosting functions would regulate immune function and limit the risk of infection. However, conflicting data still subsist. Further potential clinical trials on humans are needed to establish dosage and synergy of micronutrients in individual people are required to validate the supplementation of micronutrient strength against Covid-19 infection.[30]

Teicoplanin, a glycopeptide antibiotic ordinarily used to manage bacterial infection, proved to be effectual, *in vitro* against Covid-19, and could also be assessed as therapeutic arsenal against COVID-19. At present, this antibiotic is acting efficiently against the infection caused by Gram-positive bacteria, specifically staphylococcal infections. This antibiotic has already exposed efficacy against numerous viruses viz influenza virus, Ebola virus, flavivirus, HIV virus, hepatitis C virus, and CoV such as MERS-CoV and SARS-CoV.[19]

Favipiravir, a broad spectrum anti-viral drug, got approval from Shenzan Health Commission for the management of COVID-19 infectedpatients.[20] Acceptance of these exploratory results now needs a randomized clinical trial.[19, 20,21]

Zinc, Certain manifestations encouraged that intonation of zinc status may be lucrative in COVID-19. *In vitro* experiments imply that Zn2+ boast antiviral activity through prohibition of SARS-CoV RNA polymerase. Circumstantial evidence also evinces that Zn2+ may restrict the activity of angiotensin-converting enzyme2 (ACE2), recognized as the receptor for SARS-CoV-2.[23]

Overproduction of interferon α by zinc may meliorate immunity against virus and also raise its antiviral activity. Zinc boasts anti-inflammatory action by repressing NF-κB signaling and intonation of regulative T-cell functions that may restrict the cytokine storm in COVID-19.

Enhanced Zn status may also diminish the threat of bacterial co-infection by boosting mucociliary clearance and hinder the function of the respiratory epithelium, over and above, control antibacterial effects against *S. pneumoniae*. Uncertain factors in drastic COVID-19, together with obesity, ageing, atherosclerosis, immune deficiency, and diabetes (noted risk groups for zinc deficiency) are soundly consort with zinc status. Thus, Zn may exhibit defensive effect and adjunct therapy for COVID-19.[23] *In vitro* studies demonstrated that escalating intracellular Zn2+ concentration with zinc-ionophores such as pyrithione (PT) can proficiently impede replication of corona viruses. Chloroquine was discovered to be a zinc ionophore.[26] Further potential clinical trials on humans are needed.[23, 26]

Platelet count, a basic and readily accessible biomarker, which is solely linked with the extremity of disease and threat of mortality in ICU. Also, a scant platelet count corresponds to elevated disease extremity scores like Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation II, and Multiple Organ Dysfunction Score. Incidence of thrombocytopenia in up to 55% of patients was divulged during SARS outbreak and was verified as a notable risk factor for mortality. Zou et al. employed only two variables i.e. Platelet count, along with hypoxemia, for originating a SARS presaging model which evinced 96.2% veracity. Current studies seek to scrutinize if platelet count differentiation occurs between COVID-19 cases with or without critical malady, and check out/ analyses if thrombocytopenia may cognate with severe COVID-19. Platelet count may be a simple, inexpensive, expeditious and readily accessible laboratory variable that could effortlessly discriminate between COVID patients with and without critical malady. In addition, it is also reported that thrombocytopenia is incidental with treble risk of severe COVID-19. Howbeit, according to WHO report, notable dissimilarities are discovered between SARS and COVID-19 and pathophysiological mechanisms of each infection are likely to differ.[24]

Future research should focus on confirming these findings and to spot other biomarkers in COVID-19 infections. Further potential research should be oriented to explicate the exact mode underlying the depletion of platelet count in severe COVID-19 patients, also their probable hyper or hypoactivation.[24,26]

Umifenovir, having brand name Arbidol, is an antiviral drug utilized in the therapy of influenza. China and Russia have recommended its practice in the COVID-19 infection, but is not approved in other countries. Furthermore, research should focus on confirming its efficacy.

Leronlimab, is being investigated as a promising drug in COVID-19 infection, by CytoDyn, in phase two clinical trials as a therapy for HIV and has been allocated fast-track approval status by the United States Food and Drug Administration.

Darunavir/cobicistat (PREZCOBIX® HIV medication) has been donated by Janssen Pharmaceutical Companies for its usage in research campaign aiming for discovering a treatment for COVID-19.

Beclabuvir, (an antiviral drug for hepatitis C) has been spotted as foremost candidate for COVID-19 medication, on account of the virtual high throughput screening of scientifically endorsed drugs and the structure of SARS-CoV-2.

Fingolimod, is an immunoregulating drug, frequently used in the therapy of multiple sclerosis. A probable therapy of fingolimod in COVID-19 therapy must be hypothesized.

Simeprevir (protease inhibitor used in the Hepatitis C infection) has been spotted as an inherent candidate to recover for COVID-19 infections. The proficiency and security of various antiviral compounds/drugs for COVID-19 is under assess in ongoing clinical trials.

Treatments to prevent acute lung injury

Acute respiratory distress syndrome (ARDS) is the foremost prevalent impediment in severe COVID-19. This may trigger demise and major challenges, and generally urge admission into critical care.

Thalidomide, is an immunoregulating and anti-inflammatory drug and has been prospecting a promising drug candidate for COVID-19. It blunts the immune response by constraining TNF-alpha expression. Thalidomide employed to medicate a slew of cancers and skin ailments. Clinical trials have initiated phase 1 and 2 to prospect the benefit of inclusion of thalidomide in treating lung injury.

Bromhexine Hydrochloride, a mucolytic physic used to manage chest congestion and cough. It acts via mucus break down and make easy to cough out. The proficiency of this drug for COVID-19 in combination with other treatments is under asses in ongoing clinical trials.

Brilacidin, is being prospecting a promising drug for COVID-19 as it has evinced anti-

inflammatory, antibacterial, and immunomodulatory effects in assorted clinical trials. Various reports insinuate that immunomodulators, such as Brilacidin can act in synergism with antivirals.

Dehydroandrographolide succinate has been endorsed in China for the ministrations of viral pneumonia and upper respiratory tract infirmities, is also used off label in nebulization remedy to eschew the adverse reactions with injection. In-vitro study of animal endorsed that the nebulized drug exhibit promising efficiency in treating lung injury.

Alternative medicine named "Shufeng Jiedu Capsule", a Chinese medication, may alleviate acute lung affliction and legitimize further research. Numerous Traditional Chinese Medicines (eg T89, Huaier) are under clinical trial for COVID-19. Glycyrrhizin, Resveratrol, silvestrol, and baicalin have shown anti-viral effect on coronaviruses in vitro.[26,29,27]

Prediction of worst consequences in COVID-19 transplant patients

If a post-transplant individual goes down with COVID-19, it will be ideal if we have a surrogate marker to anticipate which transplant recipients are highly prone. There was lymphopenia in COVID-19 patients, due to poor prognosticative factor. The explication of lymphopenia in HCT is not elementary but various other non-COVID-19 causes such as non-SARS-CoV-2 viral afflictions, conditioning chemotherapy, awaiting bone marrow amelioration, and transfusion-cognate graft-versus host disease, etc. must be factored and revoke. Also, Huang et al has reported that lesser count of T cells is an appealing indicator of poor prognosticative in COVID-19 post-transplant recipients. Nevertheless, the patients with steroids, cyclosporin-A and mycophenolate mofetil therapy are explored to cause T cell diminution. Therefore, in present scenario there is lack of consummate marker in cancer/HCT patients which could be positively used to predict the clinical course or upshot of COVID-19.

According to assumptions, if SARS-CoV-2 may transmit through blood transfusions, there is no corroboration of transfusion-linked coronavirus reaction in the ongoing pandemic of COVID-19 along with previous outbreaks. Undergoing therapies for cancer and HCT are great psychosomatic aggravation. Profuse evidences are there which encouraged that such patients continually require devoted psychological and pharmacological interventions throughout cancer therapy. In short, we underline the urgent requirement for all the national and international bone marrow transplantation societies to unite, share and dissipate their understanding of transplant patients during this pandemic. This will assist in assimilating

records and frame a guideline to fight COVID- 19 in the case of HCT.[31]

A recent report has also depicted the clinical course of a patient on **hemodialysis** who gets infected by COVID-19. The medical examination of that patient was kindred to deviant symptoms of COVID-19. While the patient deprived of many usual symptoms, like fever, malaise, sore throat, headache, nasal congestion or myalgia, he had cough, dyspnea, and conventional changes of bilateral multiple ground-glass opacities on chest CT scan images. Ratification recommends a positive SARS-CoV-2 virus nucleic acid test. As hemodialysis patients have irregularities of B-cell and T-cell activity, patients might have deviant presentations. Lymphopenia is recurrent in COVID-19 patients and may be a crucial factor confederated disease extremity and mortality in familiar patients. Cao and colleagues documented that the prevalent laboratory deviations were depressed total lymphocytes, sustained prothrombin time, and uplifted lactate dehydrogenase in COVID-19. Given depleted lymphocyte counts in hemodialysis patients chronically, lymphopenia prospectively is not beneficial in spotting SARS-CoV-2 infected individuals. Considering these impediments and high ubiquity of comorbid conditions, prognosis of COVID-19 in patients on hemodialysis is reliant on clinical epidemiology, radiographic detection, and viral nucleic acids examination.[32]

According to numerous articles, lopinavir/ritonavir possibly meliorate the COVID-19 course in patients on hemodialysis, even though this interpretation is quite subjective due to the inadequacy of a control patient. Dose adjustments are not imperative in the medication of patients on hemodialysis, because of liver clearance as well as higher protein binding ability of lopinavir/ritonavir. Regardless, further research studies should be done.[32]

CONCLUSION

The experimental data of *in vitro* studies and those of current clinical trials using numerous existing medications in COVID-19 infection are hopeful and encouraging. Immunocompromised population, pregnant woman, HIV infected persons, and cancer patients are in high danger of acquiring COVID-19 infection. Prognosis of COVID-19 pneumonia in hemodialysis patients is reliant on clinical epidemiology, radiographic detection, and viral nucleic acids examination. An international strategy for permitting the use of these already existing and seems to be promising drugs like CQ, HCQ, lopinavir/ritonavir, Baricitinib and many more discussed here, for COVID-19 should be made, cost effective, easily available, and lesser side effects, under supervision of

qualified medical staff. Future trials with these findings will throw more light for their use and proficiency in COVID-19.

LIMITATIONS

There are some limitations in the present systematic review, including publication data size being limited regarding the role of various existing drugs in the treatment of patients infected with COVID-19 and influence of COVID-19 in Immunocompromised population, pregnant woman, HIV infected persons, and cancer patients. However, under current ongoing emergency circumstances, this review and study can be fruitful to the scientific community as well as to general public.

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