A Rapid Review of the Therapeutic drugs that form the part of the ICMR guidelines for hospitalized patients from the initial onset of the infection in India

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Abstract

Objective of the Study:

To estimate the association between the pharmacological therapies stated in the ICMR protocols of India for COVID-19 compared with usual care or placebo and rate of mortality.

Study Design:

The study design is in the form of a Rapid Review

Methodology:

SysRev™ and manual sheets were used to study the data extracted after applying the necessary inclusion and exclusion criteria. 41 research papers were finally selected after retrieving 395 articles using the designated search terms.

Results:

41 clinical trials and observational studies enrolling 27,043 participants were included; Our results were indicative of a large-scale prophylaxis failure among all the six pharmacological agents. In comparison with SC, the corticosteroids like Dexamethasone and Methylprednisolone fared best, and were able to successfully bring down inflammation due to viral pneumonia and improve mechanical ventilation in hospitalized individuals. Furthermore, TCZ showed promising results when it came to improving pulmonary health and reducing number of deaths in individuals presenting with advanced stage infection.

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I would also like to acknowledge with appreciation the crucial role of the staff at the Dean Henderson library at IIHMR university, who gave me the permission to use its resources and giving permission to use all the necessary tools in the library.

Contents-

List of Tables for doses and main outcomes of the papers studied –

Abbreviations used in the Study –

1. SARS – severe acute respiratory syndrome
2. WHO – world health organization
3. MERS – middle eastern respiratory syndrome
4. ACE- angiotensin converting enzyme
5. ACEI – angiotensin converting enzyme inhibitor
6. ARBs- angiotensin receptor blockers
7. ICMR- Indian council of medical research
8. SC- standard care
9. HCQ- hydroxychloroquine
10. AZM- azithromycin
11. 3CLpro- 3C-like protease
12. CoV- corona virus
13. UK- United Kingdom
14. LPV/r – lopinavir/ritonavir
15. RDV - remdesivir
16. RNA- ribonucleic acid
17. DEX- Dexamethasone

Objective

To estimate the association between the pharmacological therapies stated in the ICMR protocols of India for COVID-19 compared with usual care or placebo and rate of mortality.

Introduction

December of 2019 was witness to numerous furtive instances of a new-found pneumonia leading to "severe acute respiratory syndrome (SARS)" in the "Wuhan*"* city of central China. The "Coronavirus 2 (SARS-CoV-2)" was later recognized to be the cause behind it. The disease caused by this novel virus, on February 11th, 2020, was designated by World Health Organization (WHO) as COVID -19[i]. In a study carried out by Dr Joshua et al. the seven symptoms most indicative for COVID- 19 from over one million samples were "loss/change of smell, loss/change of taste, pyrexia, cough, chills, loss of appetite and muscle aches. Other symptoms that might be present include uncomfortable or sore throat, headache, myalgia, conjunctivitis, and diarrhoea[ii]". With its far-ranging signs and symptoms "SARS-CoV-2" infection, however, has shown to possess a lower rate of fatality at 3.1% than the previously known SARS-CoV-1 at 9.6% & "*Middle East respiratory syndrome* (MERS-CoV)" at 34.4%[iii]. The mode of action of "SARS-CoV-2" viral pathogen is through invading the cells of the individual, also known here as the host, and "initiating the disease by attaching itself to the angiotensin-converting enzyme-2 receptor (ACE-2 receptor)"[iv]. The *ACE-2* gene is known to perform a vital role in "transferring genetic information for the expression of the ACE-2 receptor in both CoV- 1 and CoV- 2"[v]. Hence, greater the number of expressions of the receptors, higher are the chances of contracting the infection. Additionally, certain *ACE-2* gene variants have shown to reduce this strong link between the spike-protein of the coronavirus and the *ACE-2* receptors. Hence, it is believed that modifying this gene could heavily influence the form in which *ACE-2* receptors in human are expressed, which could in turn prove to be critical to our hopes of reducing the severity of the symptoms, and overall outcome of COVID - 19 infection. Those individuals currently on "angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) are associated with a considerably low risk of COVID-19 infection"[vi]. This is possible because ACEI arrests the angiotensin's activity, converting enzymes linked to COVID-19 ACE-2 receptors, thereby reducing the cell invasion. Additionally, ARBs

compete for the ACE-2 receptors, thus resulting in a minimized interaction between the virus and the host's cells.

COVID- 19 suspected patients all over the world are generally being detected suing the "reverse transcriptase-polymerase chain reaction (RT-PCR) assay", the test is carried out using a nasopharyngeal swab or using lavage fluids as test-samples. Additional techniques that have been widely applied by Indian doctors to confirm the presence of the infection have been chest X-ray and enzyme-linked immunoassays (ELISA). Some of the newer development in the diagnostic field involve Lateral flow immunoassays (LFIA), and chemiluminescent assays.[vii]. According to the NIH guidelines "Patients with COVID-19 are considered to have severe illness if they have SpO_2 <94% on room air at sea level, PaO_2/FiO_2 <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%"[viii] . The idea behind any treatment regime for COVID - 19 is the reduction of viral load, improvement of lung function, reduction of fever if present, and overall improvement in the individual's ability to fight foreign pathogens. The pharmacological agents prescribed for Indians with COVID-19, under the ICMR guidelines include a fixed-dose combination of antiviral agents (lopinavir 400 mg/ritonavir 100 mg taken every 12hrs), a broad spectrum ani-viral (remdesivir 100 mg/day), antiparasitic agents (ivermectin 12mg/day), antibiotics including azithromycin (500mg daily), antimalarials, including hydroxychloroquine (600mg daily), dexamethasone (6mg/day) or methylprednisolone (1mg/kg/day) are the corticosteroid options, anti-inflammatory IL-6 blocker like Tocilizumab (8mg/kg/day), and vitamin C (3g daily)[ix].

In recent times, we have been witnessed to growing fears over numerous universally proposed drugs. Foremost among them being Ivermectin, the latest studies have failed to show any clinical benefit from Ivermectin, this has prompted the ICMR to drop Ivermectin from the most recent September Covid-19 drug protocol. The combination of "Lopinavir/ritonavir" which was removed by WHO citing concerns over its effectiveness, are still included as part of the ICMR protocol. This inconsistency in various guidelines has triggered the dire necessity to test other prospective pharmacological agents in search of a cure for patients with COVID - 19. To follow-up on these growing concerns, this review intends to study in depth the clinical trials, along with prospective and retrospective observational studies for the pharmacological agents mentioned in the ICMR drug protocols from January 2020 to September 2021 for COVID-19 infection. A number of systematic and

other reviews exist which have been published in the past. However, our intention is to add to the current existing literature by going through the latest findings related to the above-mentioned drugs and to summarize the efficacy of these drugs for their effect on combatting the COVID - 19 infection.

Methodology

A rapid review method was chosen for the study as it allows us to streamline the steps of a systematic review in a shortened timeframe and hence provide faster, relevant and state-of the art evidence to justify the inclusion of the pharmacological therapeutic options mentioned in the ICMR drug protocols against COVID-19

Information Sources

Relevant information, data and study material were recovered using three biomedical databases which included PubMed, Embase, and MEDLINE. The terms used to retrieve the pool of data were, “clinical trials”, “evidence of efficacy”, “COVID-19”, “randomized controlled trials”, “therapeutic options”, “Hospitalized patients", as well as individual drug names including “hydroxychloroquine + COVID-19”, “ Lopinavir/ritonavir + COVID-19”, “Remdesivir + COVID-19”, “ Corticosteroids + COVID-19”, “Dexamethasone + COVID-19”, “Methylprednisolone + COVID-19”, “ivermectin + COVID-19” and “Tocilizumab + COVID-19”

Study Selection

At first, 395 studies were salvaged from the above-mentioned electronic archives. 136 of them were found to be duplicates and were excluded. Further, 173 papers were excluded for them being in-vitro studies (outside of a living organism), in-vivo animal studies, or pertaining to medicinal plants. Additionally, 45 more articles were excluded because of them being reviews or combination therapies compared amongst each other and not against placebo or standard care and hence efficacy of individual drugs could not be studied. In the end, 41 studies that went on to meet the below-mentioned inclusion conditions were reviewed in more detail.

Inclusion Criteria

Only the studies carried out between January of 2020 and August of 2021 were included. Studies that were written or published in the English language were included as part of the review. We intended to only include parallel randomised controlled trials (RCTs), prospective and retrospective studies comparing the therapeutic agents mentioned in the ICMR protocols against placebo, or standard care (SC). Only studies involving consenting participants that were hospitalised, above 18 years of age and affected by COVID - 19 formed a part of this study. There was a conscious effort to make the study as inclusive as possible and hence, limits were not set in terms of race, class, ethnicity, or gender. Studies were included regardless of the severity of disease or stage of disease progression. Studies only pertaining to the agents described in the ICMR protocols were included, but there were no limitations set on the dose level, the route through which the drug would be administered, or length of intervention. The studies included had standard care or placebo forming the control arms.

Exclusion Criteria

Studies carried on indigenous, or expatriate medicinal plants were excluded. Also, the studies carried out in-vitro, in-vivo animal, and reviews were excluded. Further, cross-over trials, quasi randomised controlled trials were excluded. Pilot studies with a single arm, or studies comparing two different drugs, or two dosages of the same drug also were not considered to be part of this study.

Data Extraction –

The papers recovered after using the above search terms were screened. The second step involved selecting only the studies that fit the inclusion criteria, and lastly data was extracted using the SysRev^{TM} software and manual sheets.

Results

Our results were indicative of a large-scale prophylaxis failure among all the six pharmacological agents. This result was in accordance with the recent ICMR and WHO statements regarding some of their exclusion. Full details of the studies chosen are depicted in the following tables along with their respective drugs.

Hydroxychloroquine with or without Azithromycin

Hydroxychloroquine (HCQ) is an anti-malarial drug; the mode of action of this drug is primarily by boosting the acid level of the medium which is surrounded by the area in which "COVID- 19 *protein-spikes*" act and attach to the *ACE-2* receptors. This heightened acid levels in turn have a degrading effect on the viral spike and thereby bring down the rate of infection and the chances of new and more lethal mutations[x]. Once given in combination with Azithromycin, it is said to have an additive effect as AZM acts by directly blocking the binding of "SARS-CoV-2" pathogen with the *ACE-2* receptors on an individual's affected cell surface[xi]. Hence it was initially believed that HCQ and AZM might hold a spot in the treatment plan to attend to non-severe cases of COVID- 19 infections. However, a trial conducted by Tang et.al in China was not indicative of a therapeutic success among 150 confirmed cases of COVID - 19 patients[xii]. Comparably, improved clinical outcomes over placebo were not observed in a study by Cavalcanti et al among 667 patients in Brazil[xiii]. HCQ also failed to successfully treat 1561 adult individuals in an open-labelled, placebo-controlled, randomised clinical trial performed by Peter Horby et. al in partnership with the "Nuffield Department of Population Health" at the University of Oxford in the UK[xiv]. Other studies like the one by Wesley et.al. also exposed the therapeutic let-down in 479 affected individuals of 34 separate hospitals of the United States[xv]. Alongside these studies, therapeutic failure was also noted in an observational study using mortality as the endpoint of its main outcome, this research was performed at one of the larger medical centres in New York city by Geleris et.al among 1376 patients[xvi].

In contrast, the research carried out by Gautret et al (2020) was able to prove the possible advantages of using HCQ; this study was considered a major breakthrough in the prophylaxis of COVID-19 infection and major governing bodies of various countries had begun endorsing the drug, but it was soon sternly disparaged because of the non-existence of a control arm in

the study. Samia Arshad et al (2020)[xvii] further stated that HCQ alone and in combination with AZM substantially reduced the period of hospice through a multi-centre, retrospective data-based research paper. Chen et al (2020), carried out an early study at Renmin Hospital of Wuhan, China including 62 adults, and revealed that Hydroxychloroquine effectively enhanced an individual's physical status[xviiixix].

The use of HCQ with or without AZM, has also reported to have had an unfavourable impact on an individual's mental status. Overall safety of the individuals taking HCQ has been of growing concern which has only been brought to attention by the rising number of suicide attempts[xx]. The most recent developments have also indicated that HCQ has been associated with mental health disorders such as "depression, psychosis, insomnia, and increased risk of suicide"[xxi]. Moreover, to its detrimental effect on mental health, studies have also linked the use of the drug with a prolonged QT Interval[xxii]. An increased QT interval in the QRS complex can lead to a potentially life threatening arrythmia known as 'Torsades de pointes' which may result in episodes of syncope or sudden cardiac arrest.

Overall, the usage of HCQ alongside and devoid of AZM in the prophylaxis for COVID-19 infections was found to be unsuccessful in preventing or treating COVID - 19 infections of varied severity. This, coupled with health fears surrounding the drug, rightly triggered the WHO to cut out HCQ from its solidarity trials.

S.No.	Intervention	Type of t/t	Type of study	Doses	Main outcome	Reference
1	HCQ	Hospitalised adults with COVID - 19	Randomised, open label, Multicentre Controlled Trial	1200mg/day lasting for 3 days, followed by 800mg daily for next 2 weeks	Statistically in-significant negative conversion of test results was observed.	Tang et al (2020)
2	HCQ + AZM	Hospitalized adults with confirmed COVID - 19	A Multi-centre, observational study was carried out.	Not mentioned	Overall reduction in COVID-19 associated mortality when two drugs were combined.	Samia Arshad et al
3	HCQ	Hospitalised individuals showing positive COVID - 19	Randomized uni-centre, controlled trial.	400mg/day taken till completion of 5 days	Drug efficacy was observed in individuals with moderate severity of disease.	Chen et. al

4	HCQ +- AZM	hospitalized adults with suspected/ confirmed COVID - 19	Multicentre, randomized, open-label, three-group, controlled trial	HCQ-400mg two times daily AZM – 500mg/day for 1 week	Failed to show an improvement in patient condition at day 15 when comparison is made against SC.	Cavalcanti et al.
5	HCQ	Hospitalized patients	A Random, controlled, open-labelled platform trial.	400mg twice daily	No significant difference among control arm and treatment group.	Peter Horby et.al
6	HCQ + AZM	Admitted individuals with confirmed diagnosis of COVID - 19	Uni-centred, controlled trial	HCQ – 600mg/day taken for ten days AZM – 500mg on first day and then 250mg from 2nd day till 5th day	No significant findings in favour of clinical benefit or anti-viral properties	J.M Molina et al.
7	HCQ	In-Hospital individuals having a confirmed COVID – 19 diagnoses.	A Randomized Controlled Study carried out in multiple centres	600mg/12hrs on first day of admission, followed by 400mg/day till 5th day.	No correlation was established between use of HCQ and reduced risk of mortality	Joshua Geleris et.al
8	HCQ + AZM	Hospitalized patients	An open-label, clinical trial	HCQ - 400mg/12hrs everyday AZM – 500mg once daily for 7 days	Statistically significant reduction in viral load was observed	Gautret et al
9	HCQ	Admitted consenting adults with confirmed diagnosis of COVID - 19	A blinded, placebo-controlled randomized trial carried out in multiple centres.	400 mg/12hrs for two doses, then 200 mg/12hrs daily for next eight doses	No significant difference was observed in any of the main or secondary outcomes	Wesley et.al
10	HCQ + AZM	In-hospice adults having confirmed COVID - 19	Retrospective, cohort study carried out in multiple centres.	Was not mentioned	no significant association with in-hospice mortality	Eli et al

Lopinavir (LPV) and Ritonavir (r)

The combination of LPV/r acts by blocking a key CoV protease enzyme, called 3CLPro. "The drug splits the polyproteins during viral replication"[xxiii] and thereby is believed to arrest the multiplication process of SARS-CoV-2 virus and its consequently its spread. Hence, it was widely believed that a combination of LPV/r at the right dosage might prove to be valuable for handling COVID - 19 infections. Research was carried out by Dr Bin Cao (2020)[xxiv] and his team in Shanghai, China involving 199 individuals, an LPV/r combination did not show any significant drop in mortality or negative conversion of COVID-19 nasopharyngeal swabs. Another randomised controlled trial was conducted by Horby et.al (2020)[xxv] where 1616 patients were randomly allocated to receive LPV/r, this study also failed to show any improvement in mortality rates after the course of drug was completed. Additionally, Li et. al (2020)[xxvi], conducted an exploratory randomized controlled study among eighty-six adults in China, which further failed to find any added symptomatic relief from use of LPV/r over standard care. Also, in a study carried out by Pan et.al (2020)[xxvii] involving 1411 patients, no statistically significant difference was observed when it came to the number of deaths amongst the treatment group when evaluated against the control arm.

Conversely, two studies were potentially promising in proving the suppression of viral load, first a paper by Hung et. al[xxviii] among 127 participants showed a quicker median time for obtaining a negative nasopharyngeal swab. Secondly in a study by conducted by Nojomi et.al (2020)[xxix] in a teaching hospital in Iran showed LV/r when given in a combination with HCQ showed significantly contributed to clinical and laboratory improvements.

Additional research needs to be conducted before a concreate inference can be drawn concerning Lopinavir/ritonavir's position as part of prophylaxis or management programs for COVID - 19. As it stands today, the WHO has withheld further research on Lopinavir/ritonavir from their solidarity trial.

S. No	Intervention	Type of t/t	Type of study	Doses	Main Outcome	Reference
1	Lopinavir/Ritonavir	Hospitalized and confirmed COVID - 19	Open label, Randomized Controlled trial	400mg/100mg twice every day meant for the period of 14 days	Significant negative conversion of test samples was not seen	Cao et.al (2020)

2	Lopinavir/Ritonavir	All Hospitalized COVID-19 patients	Randomized, Open labelled trial	400mg/100mg every 12 hrs for 10 days	No significant improvement in mortality	Horby et al., 2020
3	Lopinavir/Ritonavir	Admitted participants having confirmed COVID - 19	Randomized, Open labelled trial	400mg twice daily for 14 days	Shorter duration of treatment	Hung et.al
4	Lopinavir/Ritonavir	In-patient admitted with confirmed covid 19	Randomized, Open labelled trial	400/100mg every 12hr for 7-14 days	No significant advantage over supportive care	Li et. al
5.	Lopinavir/Ritonavir + HCQ	Admitted adults >18yrs with confirmed COVID - 19	Randomized, Open-labelled clinical trial	400mg/100mg every 12hr for 10 days + HCQ 400mg on day 1	significantly contributes to clinical and laboratory improvements	Nojomi et al., 2020
6.	Lopinavir	In -hospice participants with confirmed COVID - 19	Randomized, Open labelled trial	400mg/100mg 12hr every day for 14 days	The drug showed very little improvement which was statistically insignificant	Pan et.al, 2020

Remdesivir (RDV)

RDV, sold under the trade name Veklury™, is a known "monophosphoramidate adenosine analogue that blocks the RNA polymerase enzyme", and in turn arrests the viral RNA synthesis. The drug influences "in-vitro and in-vivo antiviral activity" against a wide variety of families of viral pathogens, including "SARS-CoV-2"[xxx]. Consequently, it was widely thought that RDV might possibly play a role in the management regimes for non-severe cases of COVID - 19. Preliminary findings however using the drug failed to show any significant improvement in outcomes of the disease when evaluated against SC or placebo. Spinner et. al (2020)[xxxi], through their study which comprised of 596 enrolled individuals, saw that those individuals that were on RDV for ten days failed to exhibit a statistically significant progress towards a state of asymptomatic against a randomised SC. However, the ones on a regime that lasts for five days showed superior results when compared to SC. The WHO solidarity

trial spearheaded by Dr Hongchao Pan also comprised of Remdesivir and showed no significant improvement on primary and secondary outcomes[xxxii]. Another study by Yeming et.al comprising of 237 patients also did not show any significant improvement in symptoms or mortality[xxxiii].

On the other hand, Zeno Pasquini et al (2020)[xxxiv] in their study using Kaplan Meier curves showed significant improvement in mortality rates of the patients. Although the study sample only stood at 35 patients, the study by Dr Spinello showed encouraging results after day 10 of remdesivir course[xxxv]. Another research performed after enrolling 1062 confirmed cases of COVID - 19 by Biegel et al in the United States revealed promising findings, a quicker recuperation period and decrease in mortality[xxxvi]. The positive result kick-started the "emergency use and authorization by the US Food and Drug Administration (FDA) and a further endorsement by the European Medicines Agency and the National Health Services in the UK"[xxxvii]. Nevertheless, additional new findings prompted WHO to stop suggesting the usage of RDV for in-hospice individuals having COVID - 19. Subsequently, more trials with a greater sample size are required to appreciate the part RDV could play for the prophylaxis of individuals having COVID - 19.

S.No.	Intervention	Type of t/t	Type of Study	Doses	Key Outcome	References
1	Remdesivir	In-hospice adults above 18yrs having COVID - 19	Randomised, Open-label, phase 3 trial	200mg on day 1 and 100 for next 5-10 days	Patients on 5-day course showed significant improvement	Christoph D spinner et al.
2	Remdesivir	Hospitalized patients above 18yrs with COVID - 19	prospective, open-label, single centred	Not mentioned	Potential to benefit patients that are non-ICU but hospitalized.	Spinello Antinori et al.
3	Remdesivir	Hospitalised adults having confirmed COVID - 19	Randomized, Open labelled trial	200mg at 0^{th} day and 100mg for days1 through 9	No significant effect of remdesivir was observed	Pan et.al
4	Remdesivir	Admitted individuals having confirmed COVID – 19 reports	Randomised, single centred, open-labelled trial	200mg IV at 1^{st} day and 100mg from day 2 onwards	significant beneficial effect on survival.	Zeno Pasquini et.al

5	Remdesivir	Confirmed Covid-19 patients hospitalized	double-blind, randomized, placebo-controlled trial	200mg on day 1 and 100 for the following 10 days	remdesivir was superior to placebo in reducing the recuperation period among the patients	John H. Beigel et.al
6	Remdesivir	Hospitalized patients with confirmed covid 19	randomised, double-blinded, control arm being placebo, multicentre trial	200mg on the 1st day followed by 100mg from day 2 through 10	No significant improvement in symptoms or mortality.	Yeming Wang et.al

Corticosteroids

Dexamethasone (DEX) and **Methylprednisolone** were the two corticosteroids in the ICMR drug protocol against COVID-19. These drugs act by impeding the inflammatory mediators. "It begins with pro-inflammatory genes that encode cytokines, chemokines, cell adhesion molecules, inflammatory enzymes, and receptors"[xxxviii]. The World Health Organization in its latest guidelines strongly suggest the use of corticosteroids following the path-breaking discoveries of the UK recovery group led by Horby et. al (2020) being made public. In the study, DEX surfaced to be the most encouraging therapeutic option discovered so far having successfully decreased the fatality significantly and the period of hospitalization in over six thousand adults having severe COVID - 19. Methylprednisolone also demonstrated to prove a significant easing of respiratory symptoms caused by COVID- 19 in a study among 68 hospitalized individuals by Edalatifard et.al. Additionally, Chaomin et.al, showed how introducing methylprednisolone to the regime reduced the requirement of ventilatory support and thereby reducing number of deaths. Following these positive findings, WHO's team conducting rapid evidence appraisal care therapies (REACT), spearheaded by Dr Sterne stated that "Administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19"[xxxix] .

However, some studies also show the lack of any significant difference in fatality rates among the therapeutic group for corticosteroids and placebo. Wu et.al conducted a study comprising of 1514 enrolled individuals demonstrating no association between corticosteroid use and reduction in hospital mortality. Similar findings were also observed in the study by Li et.al (2020).

S. No.	Intervention	Type of t/t	Type of study	Dose	Main Outcome	References
1	Corticosteroid	Hospitalized patients with covid19	single-centre retrospective observational study,	Methylprednisolone – 80mg/day for 3 days	low-dose corticosteroid t/t was linked to a reduction of deaths in admitted patients.	Chaomin Wu et.al
2	Corticosteroids	Hospitalized having confirmed COVID-19	Randomised bi-centred, clinical trial	40MP equivalent (mg/day)	not significantly associated with increased in-hospital mortality	Wu et.al, 2020
3	Corticosteroids	Hospitalized patients with confirmed covid-19	Retrospective, Cohort Study	20MP equivalent /day	Mortality rates were statistically similar in the two arms	Li et.al, 2020
4	Corticosteroids	Hospitalized individuals showing confirmed COVID-19	prospective meta-analysis of 7 randomized trials	15mg/day Dexamethasone, 1mg/kg/day of methylprednisolone	was associated with lower 28-day all-cause mortality.	(REACT) Team of WHO
5	Corticosteroids	Hospitalized patients with confirmed covid-19	single-blind, randomised controlled clinical trial	Methylprednisolone 250mg/day	could be an efficient therapeutic agent for hospitalised severe COVID-19 patients	Maryam Edalatifard et.al
6	Corticosteroids	Hospitalized adults presenting a confirmed COVID-19 diagnosis	Randomised, double-blinded, Phase IIb, Trial	IV MP 0.5mg/kg for 5days	No significant difference was observed in mortality	Christiane Maria Prado Jeronimo et.al

IVERMECTIN

The drug Ivermectin is a widely used anti-parasitic in the developing countries of the tropical regions to treat worm infections. It is listed under the WHO's essential medicines list. Apart from its anti-parasitic properties it is also used as anti-viral and anti-inflammatory, thus, prompting it's use as part of COVID-19 prophylaxis[xl]. It is believed that Ivermectin opposes the action of "SARS-CoV-2" viral pathogen by blocking the nuclear import of its viral proteins that supress the normal immune response[xli]. Although, in truth the clinical mechanism of action might be multi-modal depending on the stage of the disease. Ahmed et.al[xlii] showed findings after a trial on 72 hospitalized individuals, that the time taken to clear the host body off the virus was quicker after using the drug in contrast to the placebo/SC group. Similar findings were observed when Ivermectin was combined with Doxycycline by Mahmud et.al[xliii], where recovered patients were higher in treatment group.

Other studies failed to prove a substantial difference amongst the therapeutic and control arm. Medina et.al[xliv] conducted a study in 476 adults, showing that the median time of resolution of symptoms was 10 and 12 days in the treatment arm and control arm respectively. Similar findings were seen by Sherief et.al[xlv], where small improvement was seen in discharge time, but this improvement was statistically insignificant. In spite of these discoveries, the National Institutes of Health (NIH) of USA lately asserted "there is insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19,"[xlvi]and the "World Health Organization recommends against its use outside of clinical trials"[xlvii].

S. No	Intervention	Type of t/t	Type of study	Dose	Main Outcome	Reference
1	Ivermectin + Doxycycline	Hospitalized confirmed cases of COVID- 19	randomised, double-blinded, trial using a control arm	Ivermectin - 12mg daily for 5 days, 200 mg doxycycline on 1st day, followed by 100 mg/12hrly for the following 4 days	Showed benefits of single use of Ivermectin on day 5	Sabeena Ahmed et.al

2	Ivermectin + Doxycycline	Hospitalized patients with confirmed COVID-19	randomized, blinded, placebo-controlled trial	Ivermectin - 12mg Doxycycline 100mg twice daily for 5 days	Intervention group recovered earlier	Mahmud et.al
3	Ivermectin	Symptomatic lab confirmed COVID 19	Single site, double-blind, randomized trial	ivermectin, 300 μg/kg of body weight per day for 5 days	findings do not support the use of ivermectin for prophylaxis of mild COVID-19	Medina et.al
4	Ivermectin	Hospitalized volunteers having confirmed COVID- 19	prospective, randomised, single-blinded phase-III study	200mcg/kg body wt./day for five days in solution form	ivermectin can provide a reduction in mortality	Nurullah et.al
5	Ivermectin	Hospitalized patients with confirmed COVID-19	randomized open-label controlled study	12 mg once daily for 3 days	Drug did not achieve significance for any of the endpoints.	Sherief et.al
6	Ivermectin	Hospitalised individuals having a confirmed COVID- 19 diagnosis.	Double-blinded, parallel, Randomised Placebo-Controlled Trial	12mg once daily for 6 days	Did not prove any significant improvement in outcomes	Ravikirti et.al

Tocilizumab (TCZ)

The drug TCZ is a "humanized monoclonal antibody that inhibits the IL-6 receptor. It is generally part of the treatment plan for rheumatoid arthritis and other auto-inflammatory processes. Consequently, TCZ, an IL-6 receptor blocker, may be suitable in treating patients with severe pneumonia"[xlviii]. Salama et. al (2020) "found that the use of TCZ significantly reduced the need for mechanical ventilation and improved lung function among 249 COVID-19 patients"[xlix]. Similar findings were seen by Román et.al[l], where early administration of TCZ was associated with improved oxygenation levels in patients. Barring the study by John H Stone et al (2020), where TCZ use was not associated with reduced mortality or number of ICU admissions, most studies were in favour of TCZ use. Prompting its inclusion in the drug guidelines all over the world.

S. No	Intervention	Type of T/T	Type of Study	Doses	Main Outcome	Reference
1.	TCZ	Hospitalised >18yrs having confirmed COVID- 19	Randomised, multicentre, controlled trial	8mg/kg body weight IV	TCZ reduced the likelihood of progression to mechanical ventilation or death.	Carlo Salama et. al
2.	TCZ	Hospitalized Patient	Randomized, double-blind, placebo-controlled trial	8mg/kg body weight IV	Not effective for preventing intubation or death	John H Stone et. al
3.	TCZ	hospitalised and positive diagnosis for COVID-19.	Retrospective, observation study	8mg/kg/day	was associated with improvement in oxygenation	Román et. Al
4.	TCZ	Hospitalized patients>18 yrs with suspected or confirmed covid 19	Multicentre, retrospective, observational study	Flat doses 1.400mg(30-100kg) 2.600mg(>100kg) SC	Clinical improvement was observed	Christine A Vu et.al
5.	TCZ	Patient admitted in three hospitals	multicentred, retrospective, cohort study	Not mentioned	IL-6, C-reactive protein, fibrinogen, and activated partial thromboplastin time decreased.	Jianbo Tian et al.
6.	TCZ	Confirmed COVID 19 patients admitted in hospital of Iran	prospective open-labelled, not-controlled multicentred trial	320mg (<100 kg body wt.) or 480 mg (≥100 kg body wt.)	Oxygen requirement was markedly reduced upon TCZ t/t	Reza Malekzadeh et al.
7.	TCZ	Hospitalised individuals having a confirmed COVID - 19	Non-control, prospective trial	400mg as single dose, IV	may be a promising agent for patients with severe or critical SARS-CoV-2 infection	Farzaneh Dastan et.al

Discussion

Our research comprises of 41 clinical trials and observational studies with 27,043 participants enrolled to be administered with at least 1 of the 6 pharmacological agents included in the ICMR protocols and comparing these to either standard care or placebo. Since the research methodology also included non-randomized, non-controlled trials, it categorizes as Level VIII evidence.

The studies observed as part of this rapid review indicate grave concerns with several of the suggested management regimens. Chiefly Hydroxychloroquine, which proved to be incapable in effectively curing COVID - 19 and underlined the possible detrimental effect it has on the mental psyche of an individual. The inability of Hydroxychloroquine to bind with the receptors could also suggest that the SARS-CoV-2 virus demonstrates multiple mechanisms of pathogenesis. Henceforth, a more scientifically backed method should be adopted by health experts and governing bodies when proposing management regimes. LPV/r, remdesivir and ivermectin also failed to impede the virus from replicating inside the host. The corticosteroids deployed in the ICMR protocols however were able to substantially decrease inflammation due to viral pneumonia, thereby improving unassisted ventilation and in turn reducing the mortality rates.

Furthermore, TCZ showed promising results when it came to improving pulmonary health and reducing number of deaths in individuals presenting with advanced stage infection. The use of tocilizumab helps in preventing the cytokine storm which is to blame for the ventilatory distress and death. However, conclusions cannot be drawn, and additional research is required to better evaluate the drug’s significance taking into consideration the ambiguous results that have surfaced so far.

Subsequently, doctors and other clinicians should be more careful before trusting any changes made to the treatment protocol until large scale positive findings are released. An additional objective of this rapid review was to instigate more discussions that could result in the advent of newer research-backed prophylactic option.

Conclusions

Barring the five countries of Turkmenistan, Tonga, Tuvalu, Nauru, and North Korea[li] all other countries have reported positive cases of COVID – 19. The novel virus has managed to take over one million lives globally, leaving entire communities and nations economically challenged for a few years to come. Various UN bodies along with partnering countries have taken up massive endeavours to ease the incidence and lower the fatality rates. Several pharmacological agents, as well as repurposed medications, have been in question for clinical trials because of the critical need to cut on the existing mortality rates. Although the use of HCQ was subject to preliminary publicity, corticosteroids with dexamethasone being the main agent and to some extent Tocilizumab have displayed potential to provide symptomatic care to those affected by the disease. Some drugs like Molnupiravir have shown initial promising results to reduce duration and severity of illness but large-scale trial results are awaited.

Till date (October of 2021), not a single pharmacological agent for the treatment of COVID - 19 has shown confirmatory benefits. Thus, highlighting how imperative it is for major stakeholders to adopt and initiate large scale evidence-backed methodologies and not move towards administering unconfirmed medications that may lead to more harm than good.

Limitations to the research

1) The drugs with active clinical trials were not included in the ICMR protocols and hence could not be included in the study

2) This study was not funded, and hence paid articles could be accessed.

3) Tools like Cochrane could have been used to remove bias in the selection of the studies.

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Additional funding was not proposed for completion of this study

Declaration of Competing Interest

I declare that I have no significant competing interests, professional, personal relationships, or financial interests that could have influenced the design or presentation of this study.

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