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Original Research Article

AN ANALYSIS OF EFFECTIVENESS OF VARIOUS DRUGS USED IN THE TREATMENT OF COVID-19 TREATMENT

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Abstract

The world is challenged by the coronavirus disease 2019 (COVID-19) pandemic. Epidemiologists and researchers worldwide are consistently trying to understand and struggle this precarious new disease. Scrutinizing available drug options and developing potential new drugs are urgent needs to control this pandemic. Several intervention strategies are being considered and handled global with limited success, and many drugs are yet in the trial phase. Despite these limitations, the development of COVID-19 treatment strategies has been accelerated to improve the clinical outcome of patients with COVID-19, and some countries have efficiently kept it under control. Recently, different medicine has set the trend in coronavirus treatment. This study aimed to discuss the established COVID-19 treatment strategies available globally by examining their efficacy, potential mechanisms and challenges in predicting a future potential treatment. The findings might enrich the knowledge on medication and its role to managing the COVID-19.

INTRODUCTION

The first reported severe acute respiratory syndrome due to coronavirus-2 (SARS-CoV-2) was in Wuhan, China, in December 2019. Coronavirus disease 2019 (Covid-19) severely endangered the global healthcare systems. The world has observed more than 505 million confirmed cases with more than 6.2 million related deaths in more than 200 nations, areas, or territories as of April 21, 2022. Since the first outbreak of SARS-CoV-2 in China and the declaration of the pandemic, scientists everywhere the globe rushed to develop treatment options and preventive measures for the Covid-19.[1]

Today, many vaccines have been approved and are in different stages of clinical trials. Vaccines are the first line of defense against Covid-19.[2-5]

However, antiviral drugs are designed for SARS-CoV-2 involve various strategies to inhibit viral replication. For example, viral attachment to host cell inhibitor candidates targets spike proteins of SARS-CoV-2 and human angiotensin-converting enzyme 2 (ACE2) receptor interaction mediated viral entry.[6-8]

Another strategy involves inhibiting viral proteases, main protease (Mpro),[9]or 3-like proteases (3CLpro), and papain-like protease (Plpro).[10,11]Furthermore, RNA-dependent RNA polymerase (RdRp) also emerged as a target in anti-SARS-CoV-2 drug design.[12]

Recently, only a few drugs are available against SARS-CoV- 2 for preventative (tixagevimab/cilgavimab) and curative (sotrovimab, bebtelovimab, molnupiravir, and remdesivir, nirmatrelvir/ritonavir) purposes.

Some medications such as Amoxyciline, Doxycycline, hydroxychloroquine, azithromycin, corticosteroids, ivermectinand other drugs also effective. Although the majority of the aforementioned medications have been researched for their effects on a variety of parameters for COVID-19 patients in a number of countries, very little information regarding the efficacy and

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potential mechanisms of these drugs has been gathered from Indian patients.

The current research project was carried out with the goal of determining whether or not the aforementioned medications are effective in the treatment of COVID-19 patients.

CURRENT STATUS OF VARIOUS DRUG THERAPIES IN USE FOR THE TREATMENT OF COVID-19 WITH THEIR POSSIBLE ANTIVIRAL EFFECTS AND MECHANISM OF ACTION

Total numbers of patents included were 524 based on the inclusion and exclusion criteria. Out of these, 383 were male and 141 were female.

This study analyzed the efficacy and potential mechanisms of various treatment protocol for mid, moderate and severe COVID 19 patients. In this study, assessment of various treatment protocols provided the data in support of improvement in inflammatory markers and disease severity markers of COVID 19

Adult patients with mild, moderate and severe COVID- 19 infection, when treated with different drug combinations were more likely to improve in terms of inflammatory markers, disease severity markers and clinical profile

DOXYCYCLINE
Doxycycline increases the pro-inflammatory response after inhibiting NF-jB pathway (Malek et al., 2020; Conforti et al. 2020; Szolnoky 2020)

BIOLOGICAL ACTIVITY/THERAPEUTIC EFFECT
It is a synthetic, broadspectrum tetracycline antibiotic exhibiting antimicrobial activity. Currently, it is also in use for treatment against COVID- 19 disease.

MODE OF ACTION
Chelate zinc from MMPs and on the basis of chelating activity of this antibiotic, it might help in inhibiting SARS-CoV-2.

IVERMECTIN
Ivermectin is generally used for the treatment and control of filarial diseases (Murthy 2019). Recently, its usage against COVID-19 infection showed some positive results and patients response. In vitro study on ivermectin have also been found very effective against positive-sense single-stranded RNA viruses, such as dengue, Zika and yellow fever, via inhibiting the viral replication (Azeem et al., 2015; Choudhary& Sharma 2020; Gotz et al., 2016; Mastrangelo et al., 2012). Similarly, recent report suggested that Ivermectin have a potential to inhibit COVID-19 replication in vitro (Caly et al., 2020). Single dose of Ivermectin was found to reduce the viral load up to 5000 fold in vitro culture within 48 h (Caly et al., 2020),

BIOLOGICAL ACTIVITY/THERAPEUTIC EFFECT
It is a macrocyclic lactone derived from Streptomyces avermitilis with antiparasitic activity such as nematodes, scabies and onchocerciasis (river blindness). Now this drug is also used against SARS-CoV-2.

MODE OF ACTION
Acts and prevents the import (integrase protein and importin (IMP) a/b1 heterodimer) through the rise in antiviral response, inhibits the nuclear import of viral and host protein.

My studies shows Patients in the Mild categories who were prescribed Doxycycline along with Ivermectin other drugs showed significant improvement in SPO2, RR, D-Dimer, PCT, CRP and Ferritin Values.

The SPO2 value raised to 96.37 ± 1.85 at the time of discharge from the value of 94.69 ± 5.94 at the time of admission ($p < 0.0001$; CI 0.87 to 2.48). The RR came down to 17.60 ± 1.27 from the initial rate of 20.22 ± 2.70 ($p < 0.0001$; CI -3.00 to -2.23). D-Dimer value at the time of admission was 1.26 ± 0.65 but at the time of discharge it was 0.34 ± 0.14 ($p < 0.0001$; CI -1.00 to -0.83). PCT value at the time of admission was 1.27 ± 0.10 but at the time of discharge it was 0.04 ± 0.00 ($p < 0.0001$; CI -0.24 to -0.21). CRP value at the time of admission was 13.47 ± 5.27 but at the time of discharge it was 2.41 ± 0.90 ($p < 0.0001$; CI -11.75 to -10.36). Ferritin value at the time of admission was 1044.77 ± 286.98 but at the time of discharge it was 309.83 ± 48.37 ($p < 0.0001$; CI -772.73 to -697.146).

AZITHROMYCIN
Azithromycin have shown good efficacy against SARS-CoV-2 (Kelleni 2020), while acting on different sites of virus life cycle.

BIOLOGICAL ACTIVITY/THERAPEUTIC EFFECT
It is used orally in children for the treatment of acute otitis media, malaria and also against SARSCoV-2

MODE OF ACTION
Interferes with viral entry through binding collaboration between the COVID-19 spike protein and host receptor ACE 2 and block the viral entry.

My studies shows Patients in the Mild categories who were prescribed Azithromycin along with other drugs showed beneficial significant improvement in SPO2, RR, D-Dimer, PCT, CRP and Ferritin Values. The SPO2 value raised to 96.27 ± 1.70 at the time of discharge from the value of 94.76 ± 6.02 at the time of admission ($p = 0.0151$; CI 0.295 to 2.725). The RR came down to 17.74 ± 1.09 from the initial rate of 20.26 ± 2.35 ($p < 0.0001$; CI -3.023 to -2.017). D- Dimer value at the time of admission was 1.123 ± 0.62 but at the time of discharge it was 0.33 ± 0.03 ($p < 0.0001$; CI -0.91 to -0.67). PCT value at the time of admission was 0.27 ± 0.010 but at the time of discharge it was 0.045 ± 0.0001 ($p < 0.0001$; CI -0.226 to -0.223). CRP value at the time of admission was 13.92 ± 5.78 but at the time of discharge it was 2.49 ± 0.89 ($p < 0.0001$; CI -12.56 to -10.29). Ferritin value at the time of admission was 994.26 ± 312.8 but at the time of discharge it was 304.18 ± 46.82 ($p < 0.0001$; CI -751.52 to -628.63).

HYDROXYCHLOROQUINE

The HCQ is the derivative of CQ, and is the first category drug which is working as a therapeutic agent against COVID-19 infection (Beura&Prabhakar 2020; Choudhary& Sharma 2020; Sinha &Balayla 2020).

BIOLOGICAL ACTIVITY/THERAPEUTIC EFFECT

Used in the treatment of malarial and inflammatory activities. It is also now often used as an antirheumatologic agent in systemic lupus erythematosis and rheumatoid arthritis. Currently, this drug is used against SARSCoV-2.

MODE OF ACTION

Inhibits terminal glycosylation of ACE2, the receptor that SARS-CoV-2 target for cell entry. ACE2 that is not in the glycosylated state may less efficiently interact with the SARS-CoV 2 spike protein, further inhibiting viral entry.

Patients in the Mild categories who were prescribed Hydroxycloroquine along with other drugs showed in significant improvement in RR, D-Dimer, PCT, CRP and Ferritin Values. But not significant improvement showed in SPO2 value.

The SPO2 value raised to 95.88 ± 0.87 at the time of discharge from the value of 94.88 ± 5.57 at the time of admission ($p = 0.6019$; CI -2.98 to 4.68). The RR came down to 17.55 ± 1.00 from the initial rate of 21.00 ± 2.78 ($p = 0.0029$; CI -5.53 to -1.36). D-Dimer value at the time of admission was 1.26 ± 0.52 but at the time of discharge it was 0.32 ± 0.12 ($p = 0.0001$; CI -1.31 to -0.56). PCT value at the time of admission was 0.21 ± 0.09 but at the time of discharge it was 0.047 ± 0.0001 ($p < 0.0001$; CI -0.22 to -0.09). CRP value at the time of admission was 12.38 ± 4.83 but at the time of discharge it was 2.35 ± 0.81 ($p < 0.0001$; CI -13.49 to -6.56). Ferritin value at the time of admission was 965.44 ± 242.05 but at the time of discharge it was 329.95 ± 36.68 ($p < 0.0001$; CI -808.48 to -462.49).

METHYLPREDNISOLONE
BIOLOGICAL ACTIVITY/THERAPEUTIC EFFECT

It is a synthetic corticosteroid with anti-inflammatory and immunomodulating properties.

MODE OF ACTION

Methylprednisolone binds to and activates specific nuclear receptors, resulting in altered gene expression and inhibition of proinflammatory cytokine production.

My studies patients in the Moderate category who were prescribed Methylprednisolone, Doxycycline along with other drugs showed significant improvement in SPO2, RR, D-Dimer, PCT, CRP and Ferritin Values.

The SPO2 value raised to 96.37 ± 2.04 at the time of discharge from the value of 92.13 ± 7.44 at the time of admission ($p < 0.0001$; CI 2.37 to 6.10). The RR came down to 18.59 ± 0.98 from the initial rate of 22.85 ± 2.41 ($p < 0.0001$; CI -4.88 to -3.63). D-Dimer value at the time of admission was 1.30 ± 0.64 but at the time of discharge it was 0.51 ± 0.14 ($p < 0.0001$; CI -0.94 to -0.63). PCT value at the time of admission was 0.47 ± 0.12 but at the time of discharge it was 0.045 ± 0.0001 ($p < 0.0001$; CI -0.45 to -0.39). CRP value at the time of admission was 16.13 ± 6.23 but at the time of discharge it was 2.61 ± 0.89 ($p < 0.0001$; CI -15.04 to -11.99). Ferritin value at the time of admission was 1382.1 ± 358.74 but at the time of discharge it was 305.6 ± 56.74 ($p < 0.0001$; CI -1164.27 to -988.72)

FAVIPIRAVIR

This drug is a derivative of pyrazinecarboxamide and it is being developed and manufactured by Fujifilm group. It targets RdRp enzymes, that is important for the transcription and replication of viral genomes (Coomes&Haghbayan 2020).

The mechanism of action of favipiravir is described previously; itacts on viral RNA synthesis as a chain terminator at the specific site, where the RNA is incorporated into the host cell. Furthermore, this drug is not effective against

DNA based viruses. Conversely, this specific property of favipiravir proves to have a positive outcome in the treatment of COVID-19 disease (Asai et al., 2020).

BIOLOGICAL ACTIVITY/THERAPEUTIC EFFECT

It is a pyrazinecarboxamide derivative with activity against RNA viruses. It has been investigated for the treatment of life-threatening viruses such as Ebola virus, Lassa virus, and now COVID-19.

MODE OF ACTION

Targets RNA-dependent RNA polymerase (RdRp) enzymes that are important for the transcription and replication of viral genomes.

My studies shows patients in the Severe category who were prescribed Favipiravir along with other drugs showed significant improvement in SPO2, RR, D-Dimer, PCT, CRP and Ferritin Values.

The SPO2 value raised to 93.14 ± 1.84 at the time of discharge from the value of 82.85 ± 8.49 at the time of admission ($p < 0.0001$; CI 6.45 to 14.95). The RR came down to 18.57 ± 1.33 from the initial rate of 27.04 ± 1.36 ($p < 0.0001$; CI -9.30 to -7.63). D-Dimer value at the time of admission was 1.39 ± 0.54 but at the time of discharge it was 1.72 ± 0.11 ($p < 0.0001$; CI -0.91 to -0.11). PCT value at the time of admission was 1.33 ± 0.11 but at the time of discharge it was 0.069 ± 0.11 ($p < 0.0001$; CI -1.32 to -1.19). CRP value at the time of admission was 18.12 ± 5.10 but at the time of discharge it was 3.13 ± 0.91 ($p < 0.0001$; CI -17.27 to -12.70). Ferritin value at the time of admission was 1632.4 ± 371.16 but at the time of discharge it was 336.43 ± 48.19 ($p < 0.0001$; CI -1461.03 to -1130.90).

REMDESIVIR

Remdesivir belongs to prodrug of an adenosine triphosphate (ATP) analog. Furthermore, after administration it gets metabolized into its active form GS-441,524 (Cao et al., 2020). Its activity against many other viruses such as Lassa fever, Nipah, Hendra, respiratory syncytial, Junin, MERS and SARS coronaviruses has also be seen (Asai et

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al., 2020; Hendaus 2020). However, the mechanism of action of this drug is shown by the inhibition of RdRp enzymes, conceivably through the interruption of RNA chain termination in the host cells (Figure 3) (Augustin et al., 2020). Consequently, it has been suggested that, remdesivir may be one of most useful and effective drug for the treatment of COVID-19 disease (Asai et al., 2020; Ferner& Aronson 2020b).

BIOLOGICAL ACTIVITY/THERAPEUTIC EFFECT

It belongs to prodrug of an adenosine triphosphate (ATP) analog. Its activity against viruses such as MERS, SARS-CoV-1 and SARS-CoV-2 coronaviruses.

MODE OF ACTION

Inhibits RNA-dependent RNA polymerases, conceivably through the interruption of RNA chain termination in the host cells.

My studies shows patients in the Severe category who were prescribed Remdesivir along with other drugs showed significant improvement in SPO2, RR, D-Dimer, PCT, CRP and Ferritin Values.

The SPO2 value raised to 93.17 ± 1.92 at the time of discharge from the value of 82.35 ± 7.36 at the time of admission ($p < 0.0001$; CI 8.98 to 12.65).The RR came down to 18.55 ± 1.10 from the initial rate of 27.19 ± 1.82 ($p < 0.0001$; CI -9.15 to -8.12). D-Dimer value at the time of admission was 1.40 ± 0.64 but at the time of discharge it was 0.75 ± 0.13 ($p < 0.0001$; CI -0.80 to -0.49). PCT value at the time of admission was 1.38 ± 0.09 but at the time of discharge it was 0.046 ± 0.0001 ($p < 0.0001$; CI -1.35 to -1.31). CRP value at the time of admission was 18.82 ± 5.72 but at the time of discharge it was 3.22 ± 0.82 ($p < 0.0001$; CI -16.99 to -14.20). Ferritin value at the time of admission was 1661.3 ± 356.61 but at the time of discharge it was 319.20 ± 46.19 ($p < 0.0001$; CI -1428.99 to -1255.20).

CONCLUSION

Till date, no particular drug has been developed against COVID-19 disease. It is important to develop a specific and novel inhibitor for blocking the viral entry and its replication on the host cells, that will essentially control this pandemic disease. It has been noticed that, there are many clinical trials related to new drugs, drug repositioning studies against novel coronavirus are on track. However, novel approaches like producing combinations therapeutic approaches with different drugs and imunomodulators will probably show a better way in controlling COVID-19 disease.

Furthermore, at this stage, computational approaches could help and lead us in developing or designing new therapeutic drugs at rapid level.

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