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Role of Antiviral Drugs and Monoclonal Antibodies in Treatment of Covid-19

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Abstract

The SARS-CoV-2 virus is the infectious disease known as coronavirus disease (COVID-19), most virus-infected individual with good immune system will recover without need for special care. Meanwhile some patients will get sever infection and need consultation. Sever infection is most common in older patient and patients with chronic disease such as diabetes, hypertension, asthma and other respiratory disease, although several therapeutic strategies have been investigated, the optimal treatment approach for patients with coronavirus disease (COVID-19) remains to be elucidated. This review paper will be concentrated on antiviral drugs and role of different monoclonal antibodies in COVID-19.

Keywords: Antiviral Drugs, COVID-19, Favipiravir, Monoclonal Antibodies, Remdesivir, Paxlovid

Introduction

The SARS-CoV-2 virus is the infectious disease known as coronavirus disease (COVID-19). The majority of virus-infected individuals will experience a mild to severe respiratory disease and will recover without the need for special care. However, some people will get serious illnesses and need to see a doctor. Serious sickness is more likely to strike older persons and those with underlying medical illnesses including cancer, diabetes, cardiovascular disease, or chronic respiratory diseases.

COVID-19 can cause significant illness or death in anyone, at any age People with COVID-19 have reported a wide range of symptoms, from minor discomfort to serious disease. 2 to 14 days after contact, symptoms may start to show anyone can experience minor to major symptoms. Possible symptoms include cold or fever, shortness of breath, fatigue, muscle aches, and headache. Getting enough rest, drinking plenty of fluids, and taking drugs to reduce fever and pain are some strategies that work for COVID-19 as well as the flu.

A targeted drug development approach against SARS-CoV-2. The lines of attack against SARS-CoV-2 are numbered 1-6 and include the drugs, which affect each of the steps:
(1) Fusion (2) translation; (3) proteolysis. (4) translation and RNA replication (5) packaging; and (6) virus release [1].

Different drugs are used in the treatment of COVID-19 ranging from antibiotics like azithromycin and chloroquine and hydroxychloroquine- two oral drugs that have been available and used widely for the prevention and treatment of malaria and in the management of autoimmune diseases.

Both drugs are currently inexpensive. Dexamethasone, a steroid medication, has long been used to treat inflammation caused by a variety of illnesses, including asthma, Crohn's disease, and several malignancies.in addition to vitamin D and anticoagulant therapy in COVID 19 [2]. This review paper is concerned with antiviral drugs and role of monoclonal antibodies in COVID-19 management

Method

In order to conduct this systematic review, we searched the medical literature for studies that discussed the use of immunoglobulin and antiviral medications in COVID-19 patients from October to December 20222, an English only literature search was conducted utilizing the electronic databases of MEDLINE (via PUBMED), EMBASE, SCOPUS, OVID, and Cochrane Library Only publications that had undergone peer review were used in the final Analysis. The "COVID-19" or "SARS-CoV-2" or "coronavirus disease 2019" and "IVIG" or "immunoglobulin" medical topic headings (MeSH) and key words were employed.

Additionally, we looked through the references of the most pertinent review articles for any new research that our original literature search had missed

According to Review of literature

Remdesivir provides a variety of coronavirus- fighting antiviral effects. Remdesivir was once employed as an ebola virus research medication. Remdesivir potential mode of action for treating COVID-19 involves inhibiting viral replication. SARS-CoV-2 replication requires the RNA- dependent RNA polymerases (RdRps) enzyme. Remdesivir is an adenosine analog that inhibits inhibits RdRps. It is a mono phosphoramidite prodrug of remdesivir – triphosphate (RDV-TP).

Remdesivir-TP faces competition from adenosine triphosphate for insertion into viral RNA chains RDVTPS stops RNA synthesis before integrating into viral RNA because it does not cause instantaneous chain termination [3].

Its effectiveness against COVID-19 is the subject of numerous clinical trials being conducted worldwide Remdesivir reportedly improved the clinical conditions of patients with severe COVID-19, according to a US clinical study [4]. In a clinical trial, remdesivir was administered to patients with severe COVID-19, and the results showed symptomatic improvement [5]. For severe COVID-19 ailments, only remdesivir has currently received USFDA approval (Authorization, 2021).

In Japan, Favipiravir is Authorized to Treat Influenza Viruses Favipiravir, a purine nucleotide prodrug that become active as Favipiravir –ribofuransyl triphosphate (favipiravir –RTP) in tissue, operates by blocking the RdRp enzyme of the SARS-CoV-2 it makes it simple to incorporate favipiravir into viral RNA, sparing human DNA and producing its action [6].

Favipiravir was initially employed in Wuhan, where COVID-19 first appeared, to treat the disease. In China, a clinical research found that giving favipiravir to COVID-19 patients resulted in faster viral load clearance and improved lung CT scans than alternative treatment options Patients with mild and severe COVID- 19 symptoms recovered from favipiravir more quickly, according to a Japanese observational research. In India, the DCGI approved favipiravir for patients with mild to moderate COVID-19 [7].

Numerous nations, including Russia, Japan, Italy, Moldova, Bangladesh, Turkey, Egypt, Ukraine, Uzbekistan, and Kazakh, have approved the use of favipiravir in emergencies.

A crucial component of the distribution program run by the U.S. Department of Health and Human Services is ensuring equitable access to COVID-19 medications (HHS).

In December 2021, the Food and Drug Administration (FDA) granted emergency use authorization (EUA) to two oral antiviral drugs, nirmatrelvir/ritonavir (Paxlovid) and molnupiravir (Lagevrio), to help patients with mild to moderate COVID-19 who are more likely to experience severe disease [8].

Oral antivirals were prescribed more frequently overall, rising by 57% from 643 per 100,000 people between April 24 and May 21, 2022, to 1,012 between July 31 and August 28. In comparison to data collected from April 24 to May 21, dispensing during the most recent 4-week period (July 31 to August 28) increased to 315 per 100,000 people (31% of the overall population-adjusted dispensing rates) in zip codes with high vulnerability, 367 (36%) in zip codes with medium vulnerability, and 331 (33%) in zip codes with low vulnerability, which represents increases in dispensing rates of 159%, 48%, and 21%, respectively.

These findings point to a decreasing dispensing gap between zip codes with high susceptibility and those with medium and low vulnerability, while also showing an increase in overall dispensing [9].

This analysis comprised total of eight studies. There were 2440 COVID-19 patients in the drug group, 54 of whom passed away or were admitted to the hospital. A total of 2348 COVID-19 patients, including 118 who Passed away or were hospitalized, were included in the control group.

Oral antiviral medications appeared to be helpful for COVID-19 patients, as measured by the overall odds ratio (OR) of mortality or hospitalization, which was 0.33 (95% confidence interval [CI], 0.22-0.49) for patients in the treatment group and the placebo group [10].

The study comprised 2401 COVID-19 participants from 10 studies including four randomized controlled trials (RCTs) and six non-randomized controlled trials (non-RCTs).

Participants received either IVIG, a placebo, or routine medical treatment (RR0.50.95%CIs0/18-1.36, p=0.17 for RCTs; RR0.95.95%) (CIs 0.61-1.58, p = 0.94 for non-RCTs; low certainty of evidence) The use of IVIG was not linked to a significantly lower risk of mortality.

Although this difference was significant only for studies analyzing mild COVID-19 individuals, IVIG considerably decreased the length of hospital stay (MD 2.24, 95% CIs 3.20/1.27; p = 0.00001; low certainty of evidence).

Between IVIG participants and controls, there was no discernible difference in the prevalence of overall and major adverse events (very low certainty of evidence) [11].

At Day 3, virus isolation among 202 treated individuals was considerably lower in those taking 800 mg of molnupiravir (1.9%) compared to placebo (16.7%) (p = 0.02).

On Day 5, no subjects using 400 or 800 mg of molnupiravir had any viral isolates, compared to 11.1% of participants taking a placebo (p = 0.03).

Participants who received 800 mg of molnupiravir as opposed to a placebo experienced a shorter time to viral RNA clearance and a higher overall percentage of clearance (p = 0.01).

Overall, molnupiravir was well tolerated, and all groups experienced almost the same amount of side effect [12].

Results of the 1433 subjects who were randomly assigned, 716 received the drug molnupiravir, whereas 717 received a placebo. The two groups shared similar baseline traits, with the exception of a sex imbalance.

The interim analysis proved that molnupiravir was superior; the risk of hospitalization for any reason or death up to day 29 was

lower with molnupiravir (28 of 385 participants; 7.3%) than with placebo (53 of 377; 14.1%) (difference, 6.8 percentage points; 95% confidence interval [CI], 11.3 to 2.4; P=0.001).

The percentage of participants who were hospitalized or died through day29 was lower in the molnupiravir group than in the placebo group in the analysis of all participants who had completed randomization (6.8% [48 of709] vs.9.7% [68 of 709] [68 out of 699]; difference, 3.0 percentage points; 95% confidence interval, 5.9 to 0.1) [13].

The results of subgroup analyses were generally similar with these overall findings; however, in several subgroups, such as those with diabetes, low baseline viral loads, and patients with evidence of prior SARS-CoV-2 infection, the point estimate for the difference favored placebo.

Through day 29, 9 deaths were reported in the placebo group and one in the molnupiravir group.

In the molnupiravir group, adverse events were reported by 216 of 710 Participants (30.4%), while 231 of 710 participants (33.0%) were in the Placebo group.

Randomization was performed on a total of 2246 patients; 1120 received nirmatrelvir + ritonavir (nirmatrelvir group), while 1126 received a placebo (placebo group). The incidence of COVID -19 related hospitalization or death by day 28 was lower in the nirmatrelvir group than in the placebo group by 6.32 percentage points (95% confidence interval [CI], 9.04 to 3.59; P0.001; relative risk reduction, 89.1%); the incidence was 0.77% (3 of 38) in the planned interim analysis of patients treated within 3 days of symptom onset (modified intention-to-treat population, comprising 774 of the 1361 [14].

The angiotensin-converting enzyme 2 (ACE2) is the main receptor allowing SARS-CoV-2 entrance into the cell [15].

The ACE2 receptor is found in a variety of cell types and organs, including the mouth and nasal epithelial cells, and its greater expression in the lungs is connected with aging.

This explains, at least in part, the greater viral load and more severe symptoms seen in senior SARS-CoV-2 carriers [16].

The helical region found in the peptidase domain of ACE2 was previously identified for mediating infection of SARS-CoV-1 by identifying the receptor-binding domain of the spike protein (S1-RBD) [17].

Result

The therapeutic target that inhibits ACE2 offers the possibilityof treating SARS-CoV-2 infection [18].

Anti-SARS-CoV-2 treatments at the ACE-2 level, for instance, might be based on interfering with the virus-host ACE2-S1-RBD interface, for instance. Utilizing low compound with the capacity to interact negatively with the dynamic network of protein-protein interactions that is essential for viral entry into the cell.

Antiviral drugs such as sofosbuvir and daclatasvir prevent viral RNA replication by inhibiting the NS5A and NS5B polymerase, respectively. The FDA has approved sofosbuvir and daclatasvir for the treatment of chronic hepatitis C.
Because SARS-CoV-2 shares RNA replication methods with other RNA viruses, it may be possible to suppress SARS-CoV-2 replication with the use of sofosbuvir and daclatasvir [19].

In seven RCTs, COVID-19 was treated with sofosbuvir, daclatasvir, or a combination of sofosbuvir and additional medications.

Although the size of the benefit was sometimes minor, all five RCTs that utilized sofosbuvir/daclatasvir indicated significantly superior outcomes for the treatment group for at least one outcome.

Among the three RCTs utilizing sofosbuvir in combination with other drugs than daclatasvir or patients with moderate to severe COVID-19 [20].

In a conducted a phase 3, multicenter trial to examine the effects of sofosbuvir/daclatasvir with standard of care vs standard of care alone (HCQ and LPV/r at physician discretion) [21].

Due to delay in getting RT-PCR results, sofobuvir/daclatasvir was begun later than the treatment in control arm. 88% (29/33) of patients in the sofosbuvir/daclatasvir arm and 67% (22/33) of patients in the control arm experienced clinical recovery within 14 days of enrollment (P = 0.076).

Patients in the Sofosbuvir/Daclatasvir Group had Shorter Hospital Stays than those in the control group (6 [4-8] days vs. 8 [5-13] days, respectively; P = 0.029), and they had a greater cumulative incidence of discharge from the hospital than the control group did [22].

Monoclonal antibody CR3022 was created using a COVID-19 patient's serum.

The SARS-CoV-2 RBD's conserved epitope is bound by the antibody in spite of the presence of human ACE2, CR3022 is unusual in that it Binds viral RBD and activates host effector cells. As a result, even though infected cells generate a significant amount of ACE2, the mAb has the capacity to eradicate infected cells [23].

Furthermore, CR3022 has been shown to be able to activate NK cells in a manner that is antibody dependent, as well as neutrophil phagocytosis, Monocyte phagocytosis, complement deposition, and neutrophil Activation.

For RBD binding, ACE2 competes with the majority of other neutralizing mAbs.

On the other hand, CR3022 may continue to remove infected cells or viral particles even after the following the infection related upsurge of ACE2 expression [24].

The recombinant protein Ni-NTA, a nickel-charged affinity resin, was utilized to purify the antibodies produced as part of the synthesis of CR3022 in E. coli HB2151 cells [25].

By using ELISA and BLI, it was discovered that CR3022 binds to the SARS-CoV-2 RBD with a KD of 6.3 nM. Recently, it was shown that the drug CR3022 prevented SARS-CoV-2 from interacting with the protein vimentin, which is expressed in human endothelium cells [26].

It is believed that vimentin interacts with the SARS-CoV- 2 spike proteins to ease host cell invasion.

This interaction is thought to encourage the growth of infection and aid in the evolution of COVID-19, particularly the vascular difficulties brought on by the illness unfortunately, preliminary research on CR3022 in mouse and hamster models of COVID-19 has revealed significant inflammatory-related morbidity in CR3022-treated individuals. Before the antibody can be explored in a clinical environment, the authors of the original CR3022 study stress the significance of developing tailored Fc variants of the antibody to minimize treatment-induced pathology and boost protective effects.

The synthesis of CR3022 involved the expression of the protein in E. coli HB2151 cells; the resultant antibodies were then purified using the nickel-based compound Ni-NTA [27].

A completely human anti-SARS-CoV-2 mAb called CT-P59 (regdanvimab) was identified from the plasma of a recovering. Korean patient by the Celltrion Group working on behalf of the Korea Center for Disease Control.

Recombinant DNA technique is used to create the mAb in a CHO cell Line [28].

By attaching to the viral Spike protein RBD region, CT-P59 prevents SARS-CoV-2 particles from entering host cells and preventing the virus from Connecting with host ACE2 receptors Crystallographic findings show that CT-P59 does not bind the highly changeable sites 367, 364, and 436 of the RBD, which may increase the effectiveness of the drug against future SARS-CoV-2 mutations.

Analysis of surface Plasmon resonance, CT-P59 was found to have a KD constant of 27 pM and a strong affinity against the SARS-CoV-2 RBD [29]. In vitro, CTp59 maintained its effectiveness against the problematic Gamma, Delta, Epsilon, and Kappa form [30].

Following successful phase II/III trial results Regikrona, a brand name for CT-P59, was approved as a COVID-19 treatment in the European Union in November 2021.

Monoclonal Antibodies against Anti-IL6 as COVID-19 Therapeutics The cytokine release syndrome (CRS) is characterized by a sudden rise in cytokine levels throughout the body CRS is frequently experienced by individuals receiving immune system therapies like chimeric antigen receptor T-cell therapy, and it is mostly brought on by microbial infections and some medications [31].

One of the main cytokines generated in CRS is interleukin 6 (IL-6), a little polypeptide with four helices.

If released by macrophages, the interleukin has a pro-inflammatory cytokine effect; if synthesized by muscle tissues, it has an anti-inflammatory myokine effect.

Tocilizumab has showed good outcomes in a clinical trial for the Treatment of severe COVID-19 patients in China.

All of the trial participants had a COVID-19 diagnosis of severe or critical.

The severity of COVID-19 symptoms was assessed at baseline and five days after tocilizumab Treatment [32].

The group that received tocilizumab treatment experienced a statistically significant reduction in symptom intensity.

All patients who had a fever have returned to their normal body Temperatures.

In 75% of the patients, the amount of mechanical oxygen required to be Inhaled was reduced, and one patient no longer required oxygen after Treatment.

Absorption of pulmonary lesions could be evident in the lung CT images of 90.5% of the individuals who received treatment [33]

Discussion

With an estimated 269 million confirmed cases and 5.3 million fatalities as of December 12, 2021, the coronavirus disease 2019 (COVID-19) continues to pose a serious threat to healthcare systems around the World [34].

SARS-CoV-2, a virus that causes severe acute respiratory syndrome, is the source of COVID-19. If the infection worsens, SARS-CoV-2 might cause increased immunological and inflammatory responses [35].

As result, a wide range of therapeutic approaches, such as antiviral, antiretroviral, antimalarial, anti-inflammatory, corticosteroid, immunomodulatory, and immunoglobulin Therapy, have been employed to treat the disease at different stages.

Remdesivir may work by preventing viral replication in order to cure COVID-19. The RNA dependent RNA polymerases (RdRps) enzyme is necessary for SARA CoV replication. The data show that remdesivir likely has little to no impact on mortality and raises the percentage of patients who recover in hospitalized individuals with COVID-19.

Remdesivir may shorten the time required for clinical improvement and may result in slight decreases in significant adverse events, but it may also cause slight increases in all types of adverse event the main result was overall and illness severity at entry-divided in-hospital mortality. This result is displayed in figure 2 and the appendix as a function of time since study admission (pp 25–29).

The overall mortality statistics for remdesivir (in all patients) exclude significant benefit or damage but do not reject either moderate effects or no effects on mortality, with more than twice as many deaths as previously.

In the overall remdesivir analysis, of the 8275 patients, 602 (14%) of 4146 patients who were given remdesivir and 643 (15%) of 4129 patients who were given controls died (RR 091 [95% CI 082-102], p=012).

There were 15 palliative discharges in the remdesivir group and 11 in the control group for these analyses of in-hospital mortality.

According to division by disease severity (trend test 21=39, p=005; appendix p. 31), RR was shown to be less favorable in cases of more severe disease.

25 (2%) of the 869 patients who were given remdesivir and 33 (3%) of the 861 patients who were given the control medication died among the 1730 patients who were initially not on oxygen (RR 076 [046-128], p=030) [36].

426 (14%) of the 2918 patients allocated to remdesivir out of 5839 non-ventilated patients receiving low-flow or high-flow oxygen first died compared to 476 (16·3%) of 2921 assigned to control (RR 0·87 [0·76–0·99], p=0·03). Of 706 patients already ventilated, mortality was 42·1% for those assigned to remdesivir (151 of 359) versus 38·6% for those assigned to control (134 of 347; RR 1·13 [0·89–1·42], p=0·32). Among those not already ventilated, 14·1% of patients assigned to remdesivir versus 15·7% patients assigned to control progressed to ventilation (RR 0·88 [0·77–1·00], p=0·04), 11·9% versus 13·5% died (RR 0·86 [0·76–0·98], p=0·02), and 19·6% versus 22·5% died or progressed to ventilation (RR 0·84 [0·75–0·93], p=0·001; figure 3).

Two hundred thirty-one patients (median age 37 years; interquartile range (IQR): 32-44 years; 155 [67%] male) were randomly assigned to the trial, with 112 (48.5%) being placed in the treatment group and 119 (51.5%) being placed in the placebo group.

A stop to enrollment was advised by the data and safety monitoring board due to the interim analysis's failure.

With a hazard ratio of 0.87 (95% CI 0.571-1.326; p = 0.51) for the favipiravir group, the median time to viral clearance was 10 days (IQR: 6-12 days) in the favipiravir group and 8 days (IQR: 6-12 days) in the placebo group.

In the favipiravir group, the median time to clinical recovery was 7 days (IQR: 4–11 days), while in the placebo group, it was 7 days (IQR: 5–10 days) [37].

Receiving Paxlovid was linked to overall hospitalization prevention (aHR = 0.49, 95% CI = 0.46-0.53) including among those who had received 3 mRNA vaccine doses (0.50, 95% CI = 0.45-0.55) and 2 prior mRNA vaccination doses (0.50, 95% CI = 0.42-0.58).

Receiving paxlovid was linked to lower hospitalization rates for people ages 18 to 49 (aHR = 0.59; 95% CI = 0.48 to 0.71); 50 to 64 (aHR = 0.40; 95% CI = 0.34-0.48); and 65 and older (aHR = 0.53; 95% CI = 0.48 to 0.58).

Receiving Paxlovid was linked to lower hospitalization rates among people aged 18 to 49 who had received fewer than three doses of the mRNA vaccine (aHR = 0.75, 95% CI = 0.53 to 1.06) and those who had only one underlying medical condition (aHR = 0.91, 95% CI = 0.58 to 1.44); however, these estimates failed to reach statistical significance [38].

Paxlovid estimated protection to be comparable. The most efficient and practical therapeutic and/or preventive option against COVID-19, monoclonal antibodies have been found to reduce viral load, as well as hospitalization and death rates.

Various mAbs are undergoing various stages of clinical trials in various nations, with some of them having reached stages III and IV.

The FDA has granted emergency approval for the mAb combinations bamlanivimab with etesevimab and casirivimab with imdevimab due to the rising number of cases around the world [39].

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