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MOLNUPIRAVIR AS A PROMISING AGENT AGAINST COVID-19: A REVIEW

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ABSTRACT

Coronaviruses can cause illness in people all around the world. They typically cause respiratory infections ranging from the common cold to more serious diseases like middleeast respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), and infectious disease. Molnupiravir is the first orally available medicine to immediately inhibit SARS-CoV-2 and has the potential to be used for treatment of covid 19. Molnupiravir has a high safety profile, tolerability, and oral bioavailability in humans. Molnupiravir may be available in a patient-friendly oral dose form in the first or second quarter of 2022. Early treatment with molnupiravir lowered the risk of hospitalization or death. Various antiviral drugs that are used for COVID-19 treatment are given in this review. We have also explained the various studies related to molnupiravir that could help researchersin finding the effectiveness of molnupiravir.

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INTRODUCTION

COVID-19

Coronaviruses are a broad group of viruses that can infect both animals and humans. [1]. Seven (7) coronaviruses can cause illness in people all around the world, but the four most prevalent human coronaviruses are 229E, NL63, OC43, and HKU1. They typically cause respiratory infections ranging from the common cold to more serious diseases like Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), and infectious disease [2]. The severe acute respiratory syndrome coronavirus 2 causes this zoonotic disease (SARS-CoV-2). This infectious disease was previously known as Novel Coronavirus-Infected Pneumonia (NCIP) by the WHO, and the virus was called 2019 novel coronavirus by the virus's creators (2019-nCoV). The (WHO) formally renamed the clinical disease COVID-19 (CoronaVirus Disease-19) on February 11, 2020, as stated in a tweet. In December 2019, a COVID-19 outbreak caused by the 2019 new coronavirus (SARS-CoV-2) began in Wuhan, Hubei Province, China, and has since been declared a pandemic [3]. Chronic cough and sneeze produce pulmonary droplets, which carry the virus quickly from one person to another. While transmission can occur before symptoms appear in patients, it is believed to be most contagious when persons are sick. The time between exposure and development of symptoms is usually between two and fourteen days, with an average of 5 days. Fever, cough, sneezing, and shortness of breath are all common symptoms. Pneumonia and acute respiratory distress syndrome are all possible serious conditions. There is currently no available treatment; instead, efforts are focused on symptom relief and supportive therapy. Washing your hands, sanitation, masking mouth when coughing, keeping a 1-meter distance from other people, and monitoring and self-isolation for fourteen days are all recommended preventive actions for persons who fear they are infected [4]. The reverse transcription polymerase chain reaction (RT-PCR) from a throat swab or nasopharyngeal swab is the gold standard for diagnosis. A combination of symptoms, risk factors, and a chest CT scan showing pneumonia-like characteristics can also be used to identify the infection [5].

Corona viruses are named after the Latin word "corona," which means "crown." The name comes from the virus's unusual appearance under an electron microscope, which resembles the solar corona with spherical particles with a rim of projections. They are single-stranded, enclosed, positive-sense RNA viruses that were originally discovered from humans in 1965[6]. Coronavirus is a member of the Corona viridae family, which is known to cause mild respiratory illnesses in people. In 2002 the severe acute respiratory syndrome coronavirus (SARS–CoV), followed by the Middle East respiratory syndrome coronavirus (MERS–CoV) in 2012, and now the severe acute respiratory syndrome coronavirus 2 (SARS–CoV2), there have been three major corona viruses that have caused disease outbreaks. The majority of the early instances of coronavirus were linked to the Huanan seafood entire sale market, which sold aquatic animals and live animals [7]. An unknown beta coronavirus was found in lower respiratory tract samples of these patients using unbiased next-generation sequencing. The virus, which has been given the name 2019–novel Coronavirus (2019–nCoV), was isolated using human airway epithelial cells. Under an electron microscope, the virus had a diameter of 60 to 140 nm and distinctive spikes of 9 to 12 nm, which was identical to the Coronoviridae family. The novel coronavirus was discovered to be phylogenetically more similar to two bat-derived coronavirus strains (88 percent similarity) than coronaviruses that infect people, such as SARS (79 percent similarity) and MERS (50 percent similarity)[8]. On February 11, 2020, the Coronaviridae study group of the International Committee on Taxonomy of Viruses designated the virus SARS–CoV2 based on phylogeny and taxonomy. COVID-19 was declared a pandemic by WHO on March 11, 2020, after an assessment of the situation around the world [9].

The majority of early cases had a history of exposure to wet markets, therefore zoonotic transmission appeared to be a probable explanation. The number of people who had the sickness without being exposed to the market or another person with respiratory symptoms increased by the end of January 2020. The disease's proliferation among people who had never been to Wuhan and among healthcare staff revealed that the virus had passed from person to person. The virus's specific mode of propagation is uncertain. However, as with other respiratory viruses, droplet-borne infection via fomites, either directly or indirectly, is likely to be the most common method of transmission. At present,the reason evidence for air borne transmission of the virus. Although virus particles have been found in symptomatic and convalescing patients' feces, the danger of feco-oral transmission is unknown.

Ivermectin, favipiravir, aspirin, molnupiravir, amodiaquine, zuclopenthixol, and nebivolol are some of the medications used to treat covid 19. By June 2020, an Oxford study had found that the steroid dexamethasone can assist treat COVID-19 individuals who are critically unwell, and by November, scientists were testing hepatitis C medications for their efficacy against SARS-CoV-2. Despite these advancements, the hunt for a very effective treatment that might act on SARS-CoV-2 from the very beginning of the COVID-19 infection yielded little findings.

MK-4482/EIDD-2801 or molnupiravir, according to the majority of researchers, is the first orally available medicine to immediately inhibit SARS-CoV-2 and has the potential to be ground-breaking. The goal of the global scientific and health-care research community has been to either identify new treatment options or vaccinations that can kill SARS-CoV-2 or repurpose established medications to treat and cure the virus without substantial negative effects since the beginning of the COVID-19 pandemic [10].

Molnupiravir

Molnupiravir (development codes MK- 4482 and EIDD-2801) is an orally active investigational antiviral medication that was developed to treat. It is a prodrug of the synthetic nucleoside derivative N4 hydroxy cytidine, and it inhibits viral RNA replication by introducing copying mistakes. Due to its substantial inhibitory impact in cell cultures, molnupiravir was first proposed as a therapeutic treatment for influenza viruses and encephalitic alphaviruses such as Venezuelan, Eastern, and Western horse encephalitis viruses [11]. It appears to act through the "error catastrophe" mechanism, which is based on the idea that increasing the rate of mutation in the viral genome above a biologically tolerable threshold will make the virus fatal and lead to extinction [12].This drug's wide antiviral efficacy is due to its two-step mutagenesis process.

Molnupiravir is an isopropyl ester prodrug that is converted into an active nucleoside analogue -D-N4-hydroxycytidine (NHC) or EIDD-1931 in the plasma by host esterases . The drug's active form is transported throughout the body and then transformed to its 5′-triphosphate counterpart (NHC triphosphate or MTP). This then goes after the virally encoded RdRp, which competes for cytidine and uridine triphosphates and replaces them with M. The RdRp employs the NHC triphosphate as a substrate rather than the cytidine and uridine triphosphates, and then incorporates either A or G into the RdRp active centers, generating stable complexes and avoiding resistant via production of a modified RNA [13].

Molnupiravir is now being tested in a phase III clinical trial for COVID-19 therapy. The medicine is bioavailable in an oral form and could be given to outpatients with COVID-19 in the early stages to reduce the likelihood of hospitalization. In vitro observations revealed that G-to-A and C-to-U transition mutations were dose-dependently increased, as was antiviral efficacy against coronaviruses. As a result, molnupiravir is classified as a mutagenic nucleotide analogue [14].

In the United Kingdom and the United States, Molnupiravir/EIDD-2801 received an IND for influenza as a basis for preliminary data on action against highly pathogenic coronaviruses. The FDA has accelerated pre-IND meetings and coronavirus IND amendments (cross-referral to influenza IND). In the United Kingdom, package submission was based on coronavirus activity paired with the influenza IND. In order to conduct COVID-19 studies, the United Kingdom established an Expert Working Group. The Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM) both issued guidelines on COVID-19 Clinical Trial Applications (CTAs) [15].

Mechanism

Within 24 hours, a novel antiviral medicine has been developed that successfully suppresses the SARS-CoV-2 virus and prevents transmission. MK-4482/EIDD-2801, also known as molnupiravir, is the first orally available medicine to immediately block SARS-CoV-2, according to the researchers, and has the use in corona virus disease. Researchers reported that an orally delivered ribonucleoside analogue inhibitor worked against influenza viruses, and after seeing its efficiency, they chose to repurpose the medicine for use against SARS-CoV-2 [16]. Molnupiravir, the medicine, is now in phase II/III clinical studies, although it has been shown to be effective against the virus in ferrets [17].

Studies which support effectiveness of molnupiravir

Jayk Bernal et al. (2019) stated that new medicines are needed to lower the risk of coronavirus disease progression of Covid-19. Molnupiravir is a small-molecule antiviral prodrug that works against the coronavirus 2 that causes acute respiratory syndrome (SARS-CoV-2). They conducted a phase 3, randomized, placebo-controlled trial to assess the efficacy and safety of molnupiravir treatment initiated within 5 days of the onset of signs and symptoms in non hospitalized, non vaccinated adults with mild-to-moderate Covid-19 and at least one risk factor for serious Covid-19 illness. The trial participants were given either 800 mg of molnupiravir or a placebo twice daily for 5 days. The incidence of hospitalization or death at day 29 was the major efficacy end point, while the incidence of adverse events was the primary safety endpoint. When 50% of the 1550 participants (target enrolment) had been tracked through day 29, an interim analysis was planned. The results of subgroup analyses were broadly similar with the overall findings; however, the point estimate for difference favored placebo in some categories, such as those with evidence of past SARS-CoV-2 infection, those with low baseline viral load, and those with diabetes. Through day 29, one fatality was observed in the molnupiravir group and nine in the placebo group. Adverse events occurred by 216 of 710 people (30.4%) in the molnupiravir group and 231 of 701 people (33.3%) in the placebo group. In at-risk, unvaccinated adults with Covid-19, early treatment with molnupiravir lowered the risk of hospitalization or death [18]. Imran et al.(2021) described the effects of Molnupiravir. According to authors, remdesivir and favipiravir are two of the few therapies available for treating covid 19. As a result, the pharmaceutical sector is working to create novel COVID-19 medicines. Molnupiravir, an orally active RdRp inhibitor, is being tested against COVID-19 in a phase 3 clinical trial. Molnupiravir was first created at Emory University in the United States to treat influenza. This medicine, on the other hand, has shown to be effective against a range of viruses, including SARS-CoV-2. Molnupiravir has a high safety profile, tolerability, and oral bioavailability in humans. Molnupiravir may be available in a patient-friendly oral dose form in the first or second quarter of 2022. Molnupiravir's patent data disclosed approved compound patents and process-related patent applications. They also expect to file patents for oral dosage forms, inhalers, and molnupiravir in conjunction with marketed medications such as remdesivir, favipiravir, and baricitinib. The present pandemic needs a COVID-19 treatment that is patient-friendly, safe, acceptable, and effective when taken orally. According to the authors, molnupiravir fits these criteria and is a breakthrough COVID-19 treatment [19]. Hashemian et al. (2022) worked on molnupiravir as RdRp inhibitors. Rapid mutations in the viral genome allow viruses to elude host immune responses and antiviral medicines, and can lead to viral persistence in host cells. RdRp (RNA-dependent RNA polymerase) is an important enzyme in RNA viruses that helps to synthesize RNA by forming phosphodiester linkages. As a result, RdRp could be a critical therapeutic target in RNA viral diseases like SARS-CoV-2. They highlighted the promising application of RdRp inhibitors in the treatment of RNA virus infections, which have been previously licenced or are presently being evaluated in human clinical studies. Non Nucleoside inhibitors (NNIs) bind to allosteric regions, whereas nucleoside inhibitors (NIs) bind to the active site of RdRp. Given the lack of very effective medications to treat COVID-19, finding a viable treatment for this pandemic is a top priority for researchers all around the world. They look at the data for molnupiravir (MK-4482, EIDD-2801), an antiviral medication originally developed for Alphavirus infections, as a possible COVID-19 preventative and treatment agent. Molnupiravir was in preclinical research for seasonal influenza at the time of the pandemic. When COVID-19 spread rapidly, the development timeframe was accelerated to focus on the pandemic's therapy. To expedite this initiative, real-time consultations with regulators were held. The therapeutic efficacy of RdRp inhibitors is summarized, and molnupiravir is highlighted as a novel small molecule medication for COVID-19 treatment [20].

Adashi et al. (2021) assessed for mulnopiravir for the best timing and dosage, as well as any potential interactions with other COVID-19-controlling medications. Molnopiravir's safety is a major concern that needs to be addressed using large-scale epidemiological data collected during the post-marketing phase. Mulnopiravir is the first oral antiviral medicine to be shown to be effective in attenuating viral RNA and SARS-CoV-2 in the nasopharynx while also being well tolerated and safe. Against COVID-19, oral antiviral medications (such as molnupiravir) have a significant advantage over injectable medicines (remdesivir). The good findings of the initial trials to regulate COVID-19 give us optimism for future clinical trials to be more successful [21]. Pourkarim et al. (2022) studied that the novel coronavirus disease 2019 (COVID-19) first appeared in China in late December 2019 and has since spread to a number of other nations. COVID-19 mortality can be reduced with proper medication. Molnupiravir is an antiviral with anti-RNA polymerase action that is now being studied for the treatment of COVID-19 patients. They also summarized the published research on molnupiravir's mechanism of action, safety, efficacy, and clinical studies in COVID-19 patients [22].According to the study by Vitiello et al. (2021), Large-scale epidemiology data from the post-marketing phase will further help establish the safety profile of molnupiravir. Molnupiravir is the first oral, direct-acting antiviral with a favorable safety and tolerability profile that has been found to be highly effective at reducing nasopharyngeal SARS-CoV-2 infectious virus and viral RNA. Molnupiravir has a significant benefit over antiviral injections that function against COVID-19, such as remdesivir, in that it may be taken orally. Future treatment trials are eagerly anticipated after early analyses revealed excellent outcomes against COVID-19 infection [23].Zarenezhad et al. (2022) also described that molnupiravir as a promising oral drug for the treatment of coronavirus disease. Various therapeutic candidates have been developed during the COVID-19 pandemic; molnupiravir (MK-4482 and EIDD-2801), a novel orally antiviral medication under development for the treatment of COVID-19, is now being studied in the last stage of a clinical trial. Molnupiravir boosts viral RNA mutation replication in both animals and humans. The COVID-19 pandemic is currently one of the world's most serious challenges, resulting in thousands of deaths each year. Many researchers from many disciplines of study, such as organic chemists, medicinal chemists, pharmacologists, and so on, worked together to identify and develop new medications to combat novel coronaviruses (CoV). The immediate therapeutic strategy will be to evaluate an effective small-molecule therapeutic target. Molnupiravir, an oral antiviral medication, was found to be a promising treatment for COVID-19 patients who were not hospitalized. Molnupiravir significantly reduced the risk of hospitalization or death in adults with mild or moderate COVID-19 in phase 1, 2, and 3 clinical trials. Molnupiravir may prove to be a global game-changer in the fight against SARS-CoV-2, according to new research. Finally, the development of this powerful antiviral medicine has piqued the interest of scientists all around the world [24]. Painter et al. (2021) also worked on molnupiravir for covid 19 treatment. Despite the availability of vaccinations, antiviral medicines with potent efficacy against SARS-CoV-2, the virus that causes COVID-19, are still desperately needed. Millions of people are immuno-compromised, and vaccination may leave them unable to produce a fully protective immune response. In addition, a medication to cover developing SARS-CoV-2 variations, against which existing vaccinations may be less effective, is becoming increasingly urgent. They showed how molnupiravir (EIDD-2801, MK-4482), a broad-spectrum antiviral medicine originally developed to treat Alphavirus infections, evolved into a possible COVID-19 preventive and therapy drug. Molnupiravir was in preclinical development for the treatment of seasonal influenza when the pandemic broke out. As COVID-19 spread, the development program's timeframe was accelerated, and the focus changed to coronavirus infection treatment. They suggested that molnupiravir is a good candidate for treatment of covid 19 disease [25].

Other Antiviral drugs for used for COVID-19 treatment

RdRp inhibitors

RdRp (RNA-dependent RNA polymerase) is a conserved enzyme in RNA viruses that plays a critical role in replication [26]. RdRp inhibitors all have varying degrees of antiviral efficacy due to the common protein structure. The RdRp protein of SARS-CoV-2 has the same binding site with the same amino acid residues as coronaviruses [27]. For example, RdRp in SARS-CoV-2 and SARS-CoV has a 96 percent structural similarity. As a result, existing powerful RdRp inhibitors have been thoroughly investigated for the treatment of SARS-CoV-2 [28].

Favipiravir

Favipiravir is converted to its active form, favipiravir-RTP, by phosphoribosylation of the molecule within the tissue. For starters, favipiravir can be used as a RdRp substrate since the enzyme detects it as a purine, causing the virus's protein production to stop. Second, favipiravir can be incorporated into the viral RNA sequence, preventing the virus from replicating further [29]. The broad efficacy of this medicine is explained by these methods of action, as well as the conservation of the RdRp enzyme catalytic domain across various RNA viruses. Favipiravir has recently been shown to cause lethal mutagenesis during influenza virus replication in vitro, indicating that it is a virucidal agent. It's unknown whether SARS-CoV-2 exhibits a similar pattern of behaviour [30].

Remdesivir

Remdesivir is a RdRp inhibitor that has been studied against coronaviruses and was first used to treat the Ebola virus. Early dosing of remdesivir significantly reduced lung damage and viral load in SARS-CoV-2-infected monkeys, according to one experimental research. To cause delayed chain termination, Remdesivir interacts with the virus's RdRp enzyme. In vitro, it was found to be effective against a variety of coronaviruses (including MERS, SARS, bat-CoVs, and modern human CoVs) [31]. Even in the presence of proofreading exonuclease activity, Remdesivir is active against model-coronaviruses SARS, MERS, and murine hepatitis virus (MHV), implying pan-CoV RdRp action [32].

Nitazoxanide

Both a salicylamide and a nitrothiazole moiety are present in nitazoxanide [33]. These moieties could explain the characteristics of nitazoxanide. Anti-infectives such as acetyl benzamide and salicylamide, for example, can work against viruses, parasites, bacteria, and fungus. It can also serve as an anti polymerase in the hepatitis virus and prevent influenza virus penetration and fusion with the host cell membrane. It has antioxidant, analgesic, and anti-inflammatory properties, as well as the ability to influence interleukin production and alter immunological response [34]. Anti-infective, anti-proliferative, and anti-protozoal activity is also demonstrated by the nitrothiazole moiety.

Ribavirin

Ribavirin is a synthetic nucleoside guanosine analogue that has been licensed to treat RNA virus infections such hantavirus, Lassa virus, hepatitis C virus (HCV), hepatitis E virus (HEV), and RSV. Ribavirin and favipiravir together provide anti-coronavirus action. Coronaviruses produce the exonuclease enzyme as a nonstructural protein 14 (nsp14-ExoN). RNA proofreading activities have been discovered in the nsp14-ExoN [35]. As a result, coronaviruses may be resistant to nucleoside analogues. Experiments have shown that ribavirin alone has low anti-coronavirus activity, implying that it should be used in conjunction with NIs to combat RNA viruses [36].

Regulatory Status

Molnupiravir (as EIDD2801) was developed at Emory University's Drug Innovation Venturesat Emory (DRIVE), a non-profit biotechnology organization. Ridgeback Biotherapeutics licensed it, and it is presently being developed further in collaboration with Merck& Co. (in Europe: Merck Sharp & Dohme / MSD). The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have not authorized molnupiravir (FDA) [37].

CONCLUSION

Coronavirus is a member of the Corona viridae family, which is known to cause mild respiratory illnesses in people. They typically cause respiratory infections ranging from the common cold to more serious diseases like Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), and infectious disease. The novel coronavirus was discovered to be phylogenetically more similar to two bat-derived coronavirus strains.Molnupiravir is an oral antiviral drug which is a prodrug of synthetic nucleoside derivative of N4-hydroxy cytidine which inhibits the replication of multiple RNA Viruses including SARS-COV-2. Coronavirus transmission is entirely suppressed in ferrets within 24 hours, according to studies. According to the findings, molnupiravir is the first oral medicine to effectively block SARS-cov-2 and could be used to treat covid-19. As a result, molnupiravir is being recognised as a promising anti-covid-19 agent. We've also discussed the numerous medications that are used to treat coronavirus sickness in these articles.

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