Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 12, Page No: 241-246

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

Use of Ivermectin in COVID-19

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ABSTRACT

The emergence of Coronavirus infection has produced a concerning scenario all across the world. COVID-19 is made up of a single stranded positive sense RNA gene that is wrapped in a crown shaped collection of spike glycoproteins in an external membrane. Depending on the person's genetics, race, age and geographic region, COVID-19 infection can cause a range of symptoms and morbidity. Pulmonary epithelial cell death, thrombosis, hyper coagulation and vascular leak are all part of COVID-19 pathophysiology, which can lead to sepsis in severe instances. As a result of these events, Acute Respiratory Distress Syndrome (ARDS) and lung fibrosis occur. The vital to create a therapeutic approach is to stop COVID-19 from spreading. COVID-19 instances are on the rise every day, yet there is no effective therapy or vaccine available. Several clinical studies are being done in COVID-19 to assess the effectiveness of various drugs and vaccinations. To yet, no one medication has been discovered to be successful for Coronavirus patients. This analysis examines the proof for using ivermectin, an anti-parasitic drug with antiviral properties. Ivermectin, an FDA approved medicine which is used to treat parasitic infection, was lately discovered to have a suppressive impact on Coronavirus. It possesses antiviral activity in vitro and in vivo against a number of viruses, in addition to anti-parasitic capabilities. As a result of this antiviral effect, it has been identified as a potential COVID treatment drug. In vitro, ivermectin was been demonstrated to be inhibitory to RNA and DNA viruses. The goal of this theoretical article is to assess the available information on COVID-19 transcription features and to explain the method of action of ivermectin, which may justify its therapeutic use in COVID-19 treatment.

Key words: COVID-19, Mask, Facemask, SARS-CoV-2, Ivermectin

HOW TO CITE THIS ARTICLE: Ankita Jadhao, Pramita Muntode, Ashok Mendhale, Use of Ivermectin in COVID-19. J Res Med Dent Sci, 2022, 10 (12): 241-246.

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E-mail: ankita345jadhao@gmail.com
Received: 30-Sep-2022, Manuscript No. JRMDS-22-72452;
Editor assigned: 03-Oct-2022, PreQC No. JRMDS-22-72452 (PQ);
Reviewed: 17-Oct-2022, QC No. JRMDS-22-72452;
Revised: 19-Dec-2022, Manuscript No. JRMDS-22-72452 (R);
Published: 27-Dec-2022

INTRODUCTION

In December 2019, a wave of acute atypical respiratory illness patients was reported in Wuhan, China. This swiftly swept throughout China, starting in Wuhan. The new COVID-19 was termed as severe acute respiratory distress syndrome Coronavirus-2 (COVID-19) because to its strong resemblance (80%) to SARS-CoV-2, which gave rise to Acute Respiratory Distress Syndrome (ARDS) and significant fatality between 2002–2003 [1]. The SARS-CoV-2 wave is considered to have started with a zoonotic illness linked to a seafood market in Wuhan, China. Person to person transmission was later shown to have had a significant part in the outbreak that ensued [2]. The Coronavirus is a virus that typically affects the lungs, but it can potentially impact other organ systems. Coronavirus has a single-stranded positive sense RNA that is encased in an external membrane with a crown shaped array of spiked glycoproteins. Coronavirus infection can result in a wide range of symptoms and morbidity, depending on the patients, their genome, race, age and geographic region. Pulmonary epithelial cell death, thrombosis, hyper coagulation and vascular leak are all part of COVID-19 pathophysiology, which can lead to sepsis in severe instances. As a result of these events, ARDS and lung fibrosis occur. Pyrexia, dry cough and dyspnea were among the manifestation of lower airway infection in the first wave series from Wuhan, China [3]. There is no particular treatment available at this time and medical management is primarily supportive. Drug trials have looked at lopinavir ritonavir, remdesivir, hydroxylchloroquine and azithromycin, among other medicines [4-6].

Coronavirus disease (COVID-19) has risen as a global outbreak of crucial priority, driven by the novel severe acute respiratory disorder Coronavirus 2 [7]. 81% of cases are classed as light, in which case home based symptom management and clinical deterioration monitoring are recommended. Despite the availability of symptomatic therapy, a therapeutic drug that can delay infection progression is urgently needed.

LITERATURE REVIEW

Mechanism of Coronavirus disease-19

Quick multiplication of Coronavirus promotes amplification of the immunity, which can result to a cytokine storm, which typically leads in a severe lung inflammation in response to it [8]. As the illness advances, alveolar damage can lead to increased respiratory failure and, eventually, death [9]. Furthermore, assessing the viral load of Coronavirus in the upper airway and Bronchoalveolar Lavage Fluid (BALF) in cases with severe infection reveals elevated loads and longer viral persistence [9-12].

Invasion in host cells

COVID-19 viruses are positive sense single stranded RNA viruses with a single stranded RNA and a 30 kb contained genome. They may infect contaminate of diversity of animals [13]. They are commonly classified into 4 group based on their genetic structure: α-alpha, β-beta, gamma and delta. The α-alpha and βeta Coronaviruses only infect animals [14]. COVID viruses that result in cold and croup are known as human COVID-19 viruses, such as 229E and NL63. Coronaviruses, on the other hand, include the SARS-CoV-2, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV-2) and the COVID-19 is classified to β Coronaviruses. The 5 phases in the Corona virus's life cycle with the patient's cells are attachment, penetration, biosynthesis, maturity and release. After connecting to host cell receptors (attachment), Corona viruses penetrate host cells through endocytosis. COVID-19 has 4 structural proteins: Spike (S), Membrane (M), Envelop (E) and Nucleocapsid (N) [15].

Host response to COVID-19

COVID-19 infection causes symptoms that extent from moderate respiratory distress to serious respiratory syndrome with several organs failure [16]. Coronavirus have been shown to penetrate host cells by receptor mediated endocytosis [17], which happens when the virus's receptor binding domain binds to the homologous receptor on the host cell.

Because the lungs are the first part of body to cause infection with COVID-19 [18,19], it's critical to understand how the virus penetrates the lower airway and which cellular target in the lungs are susceptible to infection. The majority of COVID-19 infected droplets produced by the patient are in the optimal range (1–10 m) for reaching the deeper parts of the lung. Alveolar type 2 epithelial cells indicated the most angiotensin converting receptor-2 relative to other pulmonary cell types, according to a single cell transcriptome analysis of healthy pulmonary tissue samples taken from a range of individuals [20]. Despite modest levels of angiotensin converting receptor-2 production in majority pulmonary tissue, increased angiotensin converting receptor-2 production in alveolar type 2 cells may allow COVID to infect pulmonary tissue. In addition, alveolar type 2 cells function as hosts for the COVID-19 virus and generate greater levels of inflammatory cytokines [21]. Viral envelope proteins get attached to and degrade angiotensin converting receptors-2 receptors, inhibiting normal angiotensin converting receptors 2 function. Coronavirus infection results in ACE-2 abnormalities as well as an inflammation immunological reaction known as a cytokine disturbance, all of which aggravates the patient's comorbidity.

Transmission

The most prevalent form of transmission is now universally recognized as human to human transmission. People who are asymptomatic can potentially spread the infection to others. The most prevalent source of infection, on the other hand, is symptomatic individuals. Transmission occurs when respiratory droplets are disseminated by coughing or sneezing. According to the findings, close contact between persons might result in transmission. This also shows that increasing aerosol concentrations in confined areas might induce transmission [22].

Clinical features

In individuals with a mild illness, manifestation of an upper respiratory passage disease may be evident. A dry cough, a slight pyrexia, nasal blockage, pharyngitis, headache, muscle tenderness and malaise are some of the symptoms. The lack of severe, manifestation such as difficulty in breathing can also be used to diagnose it. In those with moderate disease, cough, difficulty in breathing and tachypnea are frequent respiratory symptoms [22].

Severe pneumonia, ARDS, sepsis and septic shock are all symptoms of a severe illness. Within 24 to 48 hours, patients may experience severe breathlessness, tachypnea (respiratory rate >30/minute), difficulty breathing, SpO_2 93 percent, PaO_2/FiO_2 300 and/or more than 50% lung infection. Fever may be absent or moderate even in the major severe infection of the disease [22].

Ivermectin

This drug is a broad spectrum antibiotic that has been used as anti-parasitic in humans for more than 30 years [23]. *In vitro*, ivermectin has been shown to exhibit antiviral effect against the Zika virus, Influenza A virus, Newcastle disease virus, Chikungunya virus, Yellow fever virus, Dengue virus, Japanese encephalitis virus, BK polyomavirus and Equine herpesvirus type 1 [24]. Because it is produced by the soil bacteria streptomyces avermitilis, ivermectin is also known as an ivermectins [25].

Mechanism of ivermectin

The anti-parasitic medication ivermectin inhibits coronavirus by inhibiting viral proteins from penetrating the nucleus of the host cell [26]. In a simulated pharmacological screening, doxycycline was recently discovered as a putative suppressive of COVID-19 papain-

like protease [27]. Ivermectin is a macro cyclic lactone molecule with 16 members that belongs to the avermectin family [28]. Higher doses and more consistent regimens of ivermectin are regarded to be safe. Higher dosages of ivermectin, such as 120 mg (up to 2,000 g/kilogram) given once or 180 mg (up to 3,000 g/ kilogram) given in divided regimen about a 7 days, were well tolerated and safe [29]. It has also demonstrated antiviral effect against a range of RNA and DNA viruses and it is now being tested in Coronavirus [30].

Ivermectin, a broad spectrum antibiotic with high lipid solubility, has been discovered to have a variety of impacts on parasites, nematodes, arthropods, Flavivirus, mycobacteria and mammals *via* different pathways. This drug is anti-parasitic and antiviral, but it also has an effect on the immunological system of the host. Studies have shown that it can reduce cancer cell growth in addition to controlling glucose and cholesterol in animals. It can also be used in cases when hydroxychloroquine isn't available. In some cases, hydroxychloroquine is restricted in COVID-19 because of the danger of QTC prolongation and the fact that potential antiviral tissue levels take 5-10 days to develop at the highest regular dose [31].

Ivermectin hasn't been connected to any of these negative effects and it's also a less expensive choice [32]. The antiviral mechanism of ivermectin is assumed to be in relation to its regulation of virus and host nuclear protein import. Ivermectin reduces IMP/1 import while enhancing the antiviral response, which is required by the majority of RNA viruses at the time of infection [33]. Ivermectin binds to the import in α (armadillo repeat) state in this process, resulting in thermally stable and a structural alteration in α-helicity that inhibits attachment to import in β-1 [34,35]. Ivermectin's anti-SARS-CoV-2 activity is most likely due to reduction of viral IMP/1 mediated nuclear import, which decreases virus replication and therefore viral burden. [36]. Ivermectin has also been proposed to function as an ionophore [37]. Ivermectin might induce an ionic imbalance that affects the viral membrane's potential, putting its integrity and functionality at risk [38]. As ionosphere substances have been characterized as possible antiviral treatments. Another method of action for ivermectin is considered to be the Trans membrane receptor CD 147. CD 147 has been considered as a key COVID-19 spike protein binding site, along with ACE-2. To examine the possibility for substantial dose response increases, studies suggesting that ivermectin protect COVID-19 spiked protein that gets attached to CD 147 and angiotensin converting enzyme-2 [39] are employed. Another mechanism of action to examine is ivermectin's allosteric modulation of the P_2X_4 receptor.

DISCUSSION

According to Dayer ivermectin is one of the most effective medications for preventing COVID spiked protein from interacting with host cell receptors [40]. According to a research done by Daghir Janabi [41], ivermectin has a high binding affinity for RNA dependent RNA polymerase.

Ivermectin's antiviral effectiveness against coronavirus, the COVID-19 causal agent, was described by Caly, et al. [42]. After a single dose of ivermectin, the growth of an Australian strain of COVID-19 in Vero/HSLAM cells was decreased by 5000 fold. Physicians, academics and health professionals from all over the world have been intrigued by this discovery. However, these data should be treated with care. To begin, the medication was only evaluated on a monkey kidney cells *in vitro* and that was genetically modified to generate human Signaling Lymphocytic Activation Molecule (SLAM), also known as CDW 150 [42]. In addition, ivermectin was stated to lower viral RNA by 5000 times in 48 hours and that the IC_{50} was determined to be 2 μM. This research was the first to look into the activity of ivermectin against coronavirus. According to the researchers, the medicine may have therapeutic potential by suppressing the importin (IMP)/ receptor, which transfers viral proteins in nucleus of the host cell. According to the researchers, human trials are required to confirm the potential advantages of ivermectin in the management of COVID-19. Despite the fact that this was the first trial to indicate that ivermectin is antiviral on COVID-19 [42]. It was shown to be ineffective.

Rajter, et al. studied Coronavirus infected patients hospitalized to a South Florida hospital in a retrospective cohort analysis (n=280). They compared 173 patients who undergone ivermectin treatment (at the minimum one dose of 200 mcg/kilogram *via* oral route along with usual clinical care) to 107 patients who undergone standard management, discovered that ivermectin management was associated with low death rate, especially in who needed more oxygen or ventilator support [43].

We discovered five researches of ivermectin in Coronavirus infection at European Union clinical studies register (2020-001994-66, 2020-001971-33, 2020-002091-12, 2020-001474-29, 2020-002283-32) [44]. Ivermectin is now being examined in at least five studies in India, according to the official website Clinical Studies Registry India (CTRI) [45]. The US clinical research database currently lists 38 research trials in varying stages of the work from several countries. Ivermectin has been used in clinical studies at dosages range from 200 to 1200 micrograms per kilogram of body weight for 3–7 days, with excellent effects in terms of viral load and symptomatology. Two *in vivo* studies have been conducted on ivermectin as single or in combined with doxycycline.

The authors discovered that the ivermectin and doxycycline combine had a higher favorable rate of indicative relief, a shorter recovery time, fewer side effects and better compliance than the hydroxychloroquine azithromycin combination therapy when 116 patients undergone treatment with ivermectin combined with doxycycline (no=60), hydroxychloroquine combined with azithromycin (no=56). For those with

mild to moderate COVID-19 illness, ivermectin was found to be a superior option. In a retrospective analysis of 280 patients with COVID-19 disease undergone treatment with ivermectin (n=173) or standard management (n=107) and a total of 280 patients with Coronavirus infection undergone treatment with ivermectin (n=173) or standard management (n=107) the authors discovered that the ivermectin group had a decreased death rate (25.2 percent vs 15.0 percent, OR 0.52, 95 percent CI 0.29). Patients with severe lung illness (n=75) were managed with ivermectin had a low death rate (38 percent, vs. 80.7%). The researchers also discovered a substantial change in successful extubation rates.

CONCLUSION

Coronavirus epidemic is sweeping the world in danger. It has resulted in more infections and fatalities than either SARS or Ebola. COVID-19, unlike SARS or MERS, is considered to be more infectious. The elderly and immune compromised people are the one who are at risk. The main principle of Coronavirus outbreak is to stop the virus from increasing and to develop therapeutic treatments that improve cure rates while decreasing total mortality. To obtain this aim, an absolute recognition of all aspects of COVID virus is essential in order to avoid or limit potential civilization wide impact.

Ivermectin is an anti-parasitic drug that also works as a broad spectrum antibacterial agent to treat viral infections.

According to early findings, ivermectin, an import in/1/ mediated nuclear import inhibitor, suppressed COVID-19 *in vitro*. Many studies have recognized the involvement of ivermectin in Coronavirus disease. Since a result of these findings, ivermectin might be a probable therapy of choice for Coronavirus infected patients, as it reduced mortality and improved symptoms, according to clinical investigations. Ivermectin is safe in SARS-CoV-2 patients and lowers symptomatology as well as the virus's viral load.

Furthermore, ivermectin in combination with doxycycline looks to be effective. ivermectin's molecular selectivity is highly diverse, as evidenced by its excellent binding properties with both S1 and S2 domains, as well as a CL protease inhibitor site.

A five-day ivermectin regimen ensured in quicker virus clearance when compared to placebo, thus specify that advance treatment with this medicine may minimize virus proliferation in the patients. By 7th day, CRP and LDH, which are indicators of sickness severity, were considerably decreased in the five-day ivermectin group. In the lack of other diseases, a five days regimen of ivermectin therapy resulted in quicker SARS-CoV-2 virus clearance. Ivermectin may have a crucial level of care in a variety of biological processes as a result of its antiviral effect, making it a good option, COVID-19 is one of the viruses that can be treated with this drug. More study is needed for prospective human benefits in current and future pandemics because clinical, In order to assess the result of ivermectin on Coronavirus in a clinical context, more research is required. The FDA put out a statement on April 10, 2020, about administering to oneself of ivermectin in COVID infected patients. Citing a freshly reported *in vitro* analysis. This form of *in vitro* study is most commonly utilized in the recent phase of pharmaceutical evolution, according to the FDA. Furthermore, additional study is required to show the effectiveness and ivermectin's anti-Coronavirus safety in humans in order to develop a preventive or therapeutic window.

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