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Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

PREVENTION, DIAGNOSIS AND TREATMENT ON COVID-19: A REVIEW

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ABSTRACT

Study on prevention, diagnosis and treatment of COVID-19 have been performed. Different protective measures and the steps of minimizing the spreading of COVID-19 have been addressed in this study. The epidemiological history, clinical manifestations and auxiliary examinations, like nucleic acid detection, CT scan, immune identification technology of IgM/IgG, enzyme-linked immune sorbent assay and blood culture diagnosis have been studied. The clinical symptoms and signs of patients infected with SARS-CoV-2 are highly atypical, including respiratory symptoms, cough, fever, dyspnea and viral pneumonia. Investigation on effective treatments through recommendation of suitable drugs and medications has been carried out.

Keywords: COVID-19, Prevention, Diagnosis, Treatment, Remdesivir

1. INTRODUCTION

A novel coronavirus was recognized as a pathogen which resulted in the outbreak of a "Severe acute respiratory syndrome (SARS)"-like viral pneumonia in Wuhan, China in the December of 2019 [1-3]. This was termed as 2019-nCoV by "World Health Organization (WHO)" [4] which was later named as Novel Coronavirus Pneumonia. The virus was renamed as "SARS" coronavirus 2 "SARS-CoV-2" by the "International Committee on Taxonomy of Viruses (ICTV)". This new Coronavirus is now the seventh member of the Coronaviridae known to infect humans. Group of SARS-CoV-2 infection cases were reported to be epidemiologically linked to the Huanan Seafood Wholesale Market, in Wuhan, China [2]. The human transmission nature of 2019-nCoV was proved from the infection of fifteen people of Wuhan hospital from one confirmed patient [3]. On February 9, 2020, a total of 37287 corona patients were confirmed in China and 302 cases were found cumulatively from 24 different countries [1]. The present concern is that "SARS-CoV-2" [5] has spread around the world like the previous two SARS and MERS viruses. It seems to be difficult to understand the clinical characteristics of 2019-nCoV [1]. The study of Ye *et al* [6] examined the clinical characteristics of the "SARS-CoV-2" reactivation. They investigated the clinical records, chest CT scans and other laboratory results for 55 patients with confirmed "SARS-CoV-2" cases in Zhongnan Hospital Wuhan for a one-month period during January-February, 2020 [6]. All these 55 patients had been epidemiologically exposed to COVID-19 and 5 of the reactivated patients were found with the symptoms of fever, cough, sore throat and fatigue. One patient was suffering from progressive "lymphopenia" and "neutrophilia" [6]. But, the "aminotransferase" levels with the 5 patients were observed normal. So, no specific clinical characteristics were observed to distinguish them [6]. The genome of nCoV-2019 has been noticed to have a high similarity with the genome sequence of other SARS-like CoVs [7]. Coutard *et al* [7] "identified a peculiar furin-like cleavage site in the Spike protein of the 2019-nCoV, lacking in the other SARS-like CoVs." A possibility of the role of cleavage site for the preparation of antiviral has been thought by them [7]. The examination of patients and their management has been recommended by Chavez *et al* [8] on the basis of some review work by this group. According to them, the virus responsible for causing COVID-19, transmits from one people to another by close proximity and transmitted through respiratory droplets. COVID-19 matches with the symptoms of other viral infections for upper respiratory disease [8]. Rothan *et al* [9] provided a future direction on COVID-19 after studying the symptoms and treatment related issues on this.

The present research investigates on the details of prevention, diagnosis and treatment of COVID-19. The

objective of this study is to search for different protective measures, clinical manifestations, auxiliary examinations and treatment trials on COVID-19.

2. PREVENTION

The concept of prevention of COVID-19 is to eliminate the source of infection and to remove the origin of transmission of it. COVID-19 is primarily spreads through respiratory droplets and human contacts. Necessary personal protective measures are required to manage the transmission of COVID-19 [10]. According to WHO, the learning on COVID-19, controlling from its spreading and treatment of infected persons are the most steps in preventing from the COVID-19 [11]. The chance of minimizing the spreading of COVID-19 may the feasible with the recommendations as below:

- Home quarantine and avoiding any direct contact with any healthy infected person, which has been called shielding;
- Avoiding non-essential travel;
- Observing social distancing rules like avoiding crowded public places and maintaining a minimum distance of two meters between everybody, especially if they're coughing or sneezing;
- Avoiding shaking hands when greeting others;
- Frequently washing hands for a minimum of 20 s with soap and water or hand sanitizer with a minimum of 60% alcohol, especially after touching common surface areas, using the toilet, or shaking hands, avoiding touching eyes, nose, and mouth with unwashed hands;
- And disinfecting surfaces using household sprays or wipes.

It should be mentioned that due to the long period of time and presence of asymptomatic patients, applying a medical mask (especially N95) or a respirator (especially FFP3) may well be recommended.

Also, sterilizing the used respirator, only reusing it for a limited time, and proper disposal of the used masks, are recommended. Although respirators (the protective classes, including FFP1, FFP2, and FFP3) [12] are produced as single-use items, they might be used again for a limited time unless there's a risk for contamination through the deposition of infectious particles on the surface [13]. When the respirator becomes soiled or wet with bodily fluids or it can now not be appropriately fitted, or if breathing via the respirator becomes difficult, it should be discarded. Also, masks should be discarded after being employed during an aerosol-generating procedure. Until now, manufacturers have had no reason to disinfect masks or to provide masks for repeated use. However, it is important to disinfect masks before reuse. Contamination of the respirator surface may well be prevented through placing a medical mask over it, or wearing a face shield that may be cleaned. Due to large contamination of respirators and surgical masks within the COVID-19 pandemic, several methods may well be considered for the sterilization of used masks, including steam, peroxides or radiation.

Besides, the utilization of medical shields or wearing protective suits is suggested, especially for health care workers. It should be mentioned that wearing gloves in publicly isn't an adequate protection against COVID-19, because gloves can easily be contaminated. So, frequent washing of hands is that the best decision to protect against SARS-CoV-2 infection [14]. A study in six departments of a hospital in Wuhan, China demonstrated that the utilization of N95 masks, disinfectants, and hand washing by doctors and nurses were effective in preventing against COVID-19 infection [15].

In terms of vaccines, there are an oversized number of vaccination strategies against SARS-CoV, MERS-CoV being tested in animals, including a live-attenuated virus, viral vectors, inactivated virus, subunit vaccines, recombinant DNA, and proteins vaccines. Although, until now, there has not been any approved vaccine against SARS-CoV-2, several clinical trials are launched for testing the consequences of varied vaccines against SARS-CoV-2.

3. DIAGNOSIS

Clinical diagnosis of COVID-19 is primarily supported with epidemiological history, clinical manifestations and a few auxiliary examinations, like nucleic acid test, CT scan, immune identification technology of IgM/IgG, enzyme-linked immunosorbent assay and blood culture.

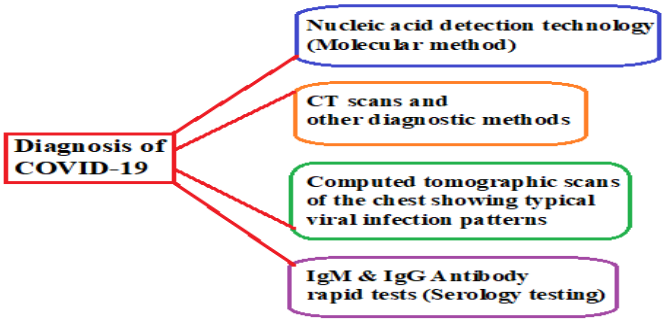

Fig. 1: The diagnosis tools of COVID-19

However, the clinical symptoms and signs of patients infected with SARS-CoV-2 are highly atypical, including respiratory symptoms, cough, fever, dyspnea and pneumonia. Therefore, auxiliary examinations are necessary for the diagnosis of COVID-19, even as the epidemiological history. Fig.1 demonstrates the diagnosis tools of COVID-19.

3.1. Nucleic acid detection technology (Molecular method)

The two commonly used nucleic acid test technologies for SARS-CoV-2 are real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing. The authoritative identification method for SARS-CoV-2 is virus blood culture and high-through put sequencing of the full genome [16]. It was first demonstrated that current SARS-CoV-2-positive plasma didn't show any cross-reactivity with other corona viruses, with the exception of SARS-CoV. However, given the sequence homology between these two viruses (>90%), the cross-reactivity is not surprising. They proposed conducting antibody testing when a qPCR testis negative despite other indications of COVID-19, including symptoms and epidemiology, suggesting a possible failure of those patients to come up with the antibody response, which can have contributed to the disease severity [17].

The current methods of diagnosis by qPCR or deep sequencing-dependent technologies confirm on the presence of replicating virus in sufficient amounts to ensure that sufficient quantities of virus are collected [18]. Three novel real-time COVID-19 RT-PCR assays targeting the RdRp/Hel, S, and N genes of SARS-CoV-2 were developed [19]. But, the appliance of high-throughput sequencing technology in clinical diagnosis is proscribed due to its equipment dependency and high cost. Therefore, RT-qPCR is that the most commonest, effective and easy method for detecting pathogenic viruses in respiratory secretions and blood [20]. Another study showed that the positive rate of SARS-CoV-2 was 91.7% (11/12) within the patients' self-collected saliva by using RT-qPCR (non-probes SYBR based fluorescence signal), which suggests that saliva could be a promising non-invasive specimen for the diagnosis, monitoring, and infection control of patients with SARS-CoV-2 infection [21]. RT-qPCR detection also showed high sensitivity and specificity for SARS-CoV and MERS-CoV infection [22]. But, five patients with negative results of RT-qPCR for SARS-CoV-2 may present with positive chest CT findings, and repeated swab tests (RT-qPCR) eventually confirmed that each one of patients were infected by SARS-CoV-2 [23]. The detection of SARS-CoV using RT-qPCR can only achieve a sensitivity of 50%-79%, betting on the protocol used the sample type and number of clinical specimens collected [24]. Thus, it's essential to enhance the detection rate of RT-qPCR for SARS-CoV-2 infection.

3.2. CT scans and other diagnostic methods

For the diagnosis of COVID-19, although RT-qPCR is particular, its false-negative rate can't be ignored because of the severe consequences of missed diagnosis. Numerous clinicians proposed CT scans should be one necessary auxiliary diagnostic method due to its sensitivity. For people with a high clinical suspicion of SARS-CoV-2 infection with negative RT-qPCR screening, a mix of repeated RT-qPCR tests and chest CT scan could also be helpful. Especially the high-resolution CT for the chest is crucial for early diagnosis and evaluation of disease severity of patients with SARS-CoV-2 [25]. The regular CT images show bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a round edmorphology and a peripheral lung distribution. Lung involvement with a peripheral predominance was also seen in patients with SARS-CoV and MERS-CoV infections, and therefore the chest CT showed that disease progressed with ground-glass opacities and consolidation, which is analogous to that of SARS-CoV-2 infection [26, 27]. With or without vascular enlargement, interlobular septal thickening, and air bronchogram sign are common CT features of COVID-19. The CT findings of COVID-19 overlap with the CT findings of adenovirus infection. There are differences as well as similarities in the CT features of COVID-19 compared with those of the severe acute respiratory syndrome [28].

According to those findings, CT scans have an excellent clinical diagnostic value for COVID-19, especially within the high prevalence area of SARS-CoV-2 infection. However, CT scans even have some shortcomings, like indistinguishability from other pneumonia and within the hysteresis of abnormal CT imaging CT include bilateral multilobar ground-glass opacifcation with a peripheral or posterior distribution, mainly in the lower lobes and fewer frequently within the proper middle lobe. Acute respiratory distress syndrome is that the commonest indication for transferring patients with COVID-19 to the ICU and also the major reason behind death during this patient population [29].

3.3. Computed tomographic scans of the chest showing typical virus infection patterns

At the advanced stage, the CT manifestations of patients are almost like those in other styles of pneumonia and mainly include diffuse lesions in both lungs, are mostly consolidated lesions, and GGOs surrounding consolidated lesions, which are mostly among parenchymal bands and sometimes by a little amount of pleural effusion. This CT appearance is named lung whiteout. The occurrence of viral infection is correlated with the virulence of the virus, the transmission route, and therefore the age and immunological status of the host. In general, the incidence of viral pneumonias is higher in children than in adults. In contrast, COVID-19 commonly occurs in 40- to 60-year-old patients with multiple co morbidities. Chest CT, which is straightforward to perform and readily available, can quickly detect lung lesions and make imaging diagnoses at the first stage. Thus, it's great value in early screening, medical diagnosis and disease severity assessment of COVID-19 [30]. Coronavirus disease 2019 also has to be differentiated from bacterial pneumonia, mycoplasma pneumonia, and chlamydia pneumonia [31].

3.4. IgM & IgG Antibody rapid tests (Serology testing)

Molecular testing is time consuming and need specialized operators, factors that limit their use in reality when the rapid diagnosis is required for fast intervention decisions. An easy to perform serological assay has been assessed to differentiate COVID-19 positive patients from negative subjects, by Li *et al* [32]. Recently, immunoglobulin M (IgM) and IgG antibody detection reagents and SARS-CoV-2 antigen detection reagents established by colloidal gold and enzyme-linked immunosorbent technologies have also been successfully developed and applied for auxiliary diagnosis [33].

4. TREATMENTS

Because of the lack of effective treatments and the need to contain the epidemic, drug repurposing seems to be the best option to obtain therapeutic solution. Some drugs like chloroquine, remdesivir, lopinavir, ribavirin or ritonavir have been shown to be effective in inhibiting coronavirus in vitro. Presently, lopinavir/ritonavir (LPV/r) combination, which was earlier confirmed effective in SARS-CoV and MERS-CoV, has been recommended for the treatment of 2019-nCoV in the latest guidelines [34].

4.1. Remdesivir

Remdesivir (chemical formula: $C_{27}H_{35}N_6O_8P$) is an antiviral medication and is developed by the Gilead Sciences biopharmaceutical company [35]. Remdesivir (RDV, GS-5734), is a novel nucleotide analogue prodrug that has been examined to be an effective pan-CoV antiviral [36, 37]. Recently, remdesivir is being examined as a specific treatment for COVID-19. Wang *et al.* indicated that RDV can inhibit 2019-nCoV infection *in-vitro* and they found positive perspective on successful application of RDV in a 2019-nCoV patient in the United States [38, 39]. A randomized, double-blind, parallel-controlled phase 3 clinical trial of safety and efficacy of RDV is going on in Wuhan (NCT04252664).

This medication has been authorized for the use in the United States in emergency and also approved for use in COVID-19 with severe symptoms, in Japan [40-42]. Application of remdesivir may reduce the recovery time from COVID-19 [43, 44]. Remdesivir diffuses into cells and changed to GS-441524 mono-phosphate, which is then further phosphorylated to its active metabolite triphosphate by nucleoside-phosphate kinases [45]. The injection of this medication is given intravenously [46, 47]. The side effects of use of remdesivir may be liver inflammation, an infusion related reaction with nausea and low blood pressure [48].

4.1.1. Mechanism of action of Remdesivir

The active metabolite of remdesivir, as an adenosine nucleotide triphosphate analog, interferes with the action of viral RNA-dependent RNA polymerase and escapes proofreading by viral exoribonuclease (ExoN) thus leading to a decrease in the production of viral RNA [35, 49]. Its predominant effect is to induce an irreversible chain termination, occurring after five additional bases have been added to the growing RNA chain [50]. The arrest of RNA synthesis in the RNA-Dependent RNA Polymerase of MERS-CoV, SARS-CoV-1, and SARS-CoV-2 occurs after incorporation of three additional nucleotides [51, 52]. This action of remdesivir has led to its classification as a delayed chain terminator [53]. Activation of remdesivir into its active triphosphate metabolite is demonstrated in Fig. 2.

4.2. Hydroxychloroquine and other medications

Hydroxychloroquine (HCQ; Formula: $C_{18}H_{26}ClN_3O$) is applied to inhibit the replication of several DNA and RNA viruses, including the human coronaviruses [54].

HCQ is used to prevent and treat malaria in places where malaria remains sensitive to chloroquine [55]. It is also being studied as a treatment for coronavirus disease 2019 (COVID-19) [56, 57]. In April 2020, the US National Institutes of Health (NIH) began a trial of the medication of HCQ [58, 59]. Wang *et al* also proved the effectiveness of chloroquine in the control of 2019-nCoV [38]. Chloroquine was also tested to inhibit SARS-CoV-2 *in vitro* and its hydroxylated form has been recommended as a possible therapy to treat SARS-CoV-2 patients where other drugs are not working [38].

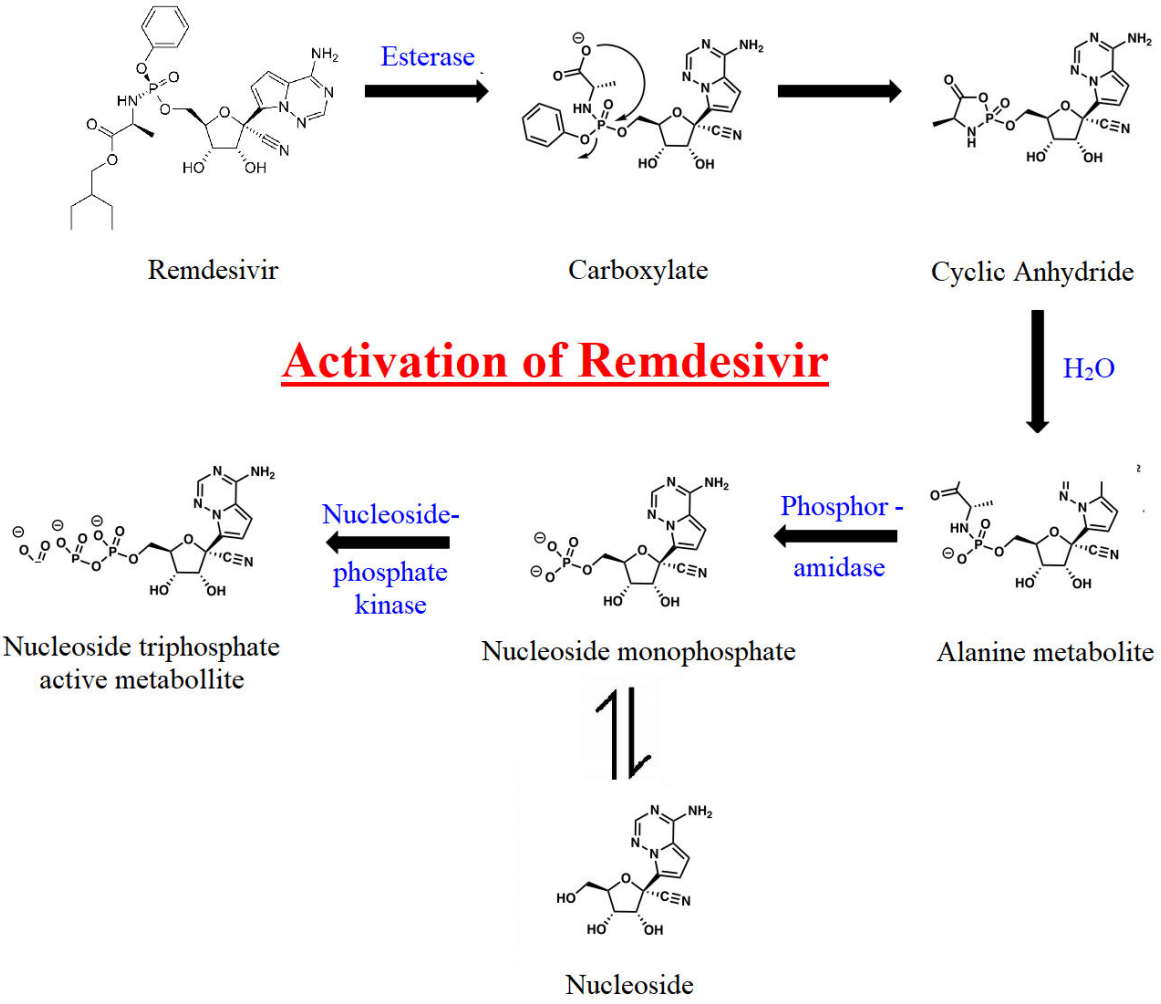

Fig. 2: Activation of remdesivir into its active triphosphate metabolite [53]

A phase 4 clinical trial for Arbidol, which has been found to have broad-spectrum antiviral activity against respiratory viruses had been registered (NCT04246242) for new coronavirus pneumonia [1].

Also, several researches showed that the combination of RDV and mAb could be the ideal treatment for 2019-nCoV [1]. For the first time, Tian *et al*. reported about a SARS-CoV-specific human mAb, CR3022. This mAb could bind potently with the binding domain of the SARS-CoV-2 receptor [60]. Therefore, CR3022 may act as a drug to prevent and treat new coronavirus infection.

Baricitinib, a Janus kinase inhibitor, has the ability to disrupt the receptor mediated endocytosis and therefore stop the entry of virus into the cell. It reduces the potency of the virus to infect lung cells [61]. So, it has become a potential treatment for SARS-Cov-2 infection [61].

Teicoplanin is an antibiotic used to treat staphylococci infection. It has previously been affective against the

first stage of MERS coronavirus viral cycle in human cells [62]. Its activity is also conserved on the SARS-Cov-2, thus teicoplanin can also become a potential drug for treatment of patients infected with this virus [62].

Lopinavir and Ritonavir are both HIV protease inhibitors that interfere with the cleavage of a polyprotein into multiple smaller functional proteins. At the Rajavithi Hospital in Thailand, a combination of oseltamivir (anti-influenza agent) and lopinavir/ritonavir was used by their infectious disease team to successfully improve the status of patients with severe conditions [63].

4.3. Convalescent plasma and monoclonal antibodies

Convalescent plasma and monoclonal antibodies are suggested as probable therapies for the treatment of COVID-19 patients. Convalescent plasma or immune globulins was used to improve the survival rate of patients with SARS, only in those patients whose condition continued to deteriorate even after pulsed steroid therapy [64]. Currently, plasma (from a recovered patient) containing antibodies is transfused to a patient suffering from COVID-19. The donor antibodies might improve the patient's condition, possibly by shortening the length or reducing the severity of the disease. Even though, there have been reports of success from China, there's not much knowledge about how effective it is for treating COVID-19, mainly since no randomized, controlled studies have been done. On March 24, 2020, the FDA began allowing convalescent plasma to be used in patients with serious or immediately life-threatening COVID-19 infections [65]. This treatment is still considered experimental.

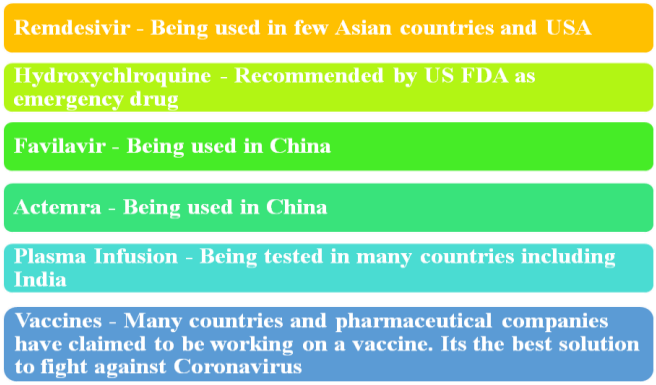

Fig. 3: Medication/treatment being trialled in different places/countries for COVID-19.

Further research indicates potential treatment options like Leronlimab, a humanized monoclonal antibody (CCR5 antagonist), and galidesivir, a nucleoside RNA polymerase inhibitor, both of which have shown survival benefits in many deadly virus infections [1]. Medication/treatment trialled in different places/countries on COVID-19 is summarized in Fig. 3.

5. CONCLUSION

For the controlling of COVID-19 pandemic, drug repurposing seems to be the best option. The drugs such as hydroxychloroquine (HCQ), remdesivir (RDV), lopinavir, ribavirin or ritonavir have been checked to be effective in inhibiting COVID-19 in vitro. RDV has been authorized for the application in the United States in emergency and also approved for application in COVID-19 with severe symptoms, in Japan. Convalescent plasma and monoclonal antibodies have also been proposed as probable therapies for the treatment of COVID-19 patients. More research is required to find out the vaccine and treatment of COVID-19.

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