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A review

The main treatments used for SARS-CoV-2 patients

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ABSTRACT

As the COVID-19 pandemic continues to ravage the world and threaten people's lives, treating infected patients effectively has been one of the top concerns for medical workers around the world. Currently, no medication is recommended to treat COVID-19, and no cure is available. Researchers are testing a variety of possible treatments. Several drugs are being researched in different countries. Most are existing drugs that are being trialled against the virus. Pharmaceuticals undergoing clinical trials to assess their safety and efficacy as potential treatments for COVID-19, include the antiviral nucleotide analogue remdesivir, systemic interferons and in particular interferon β-1a, the antiviral combination lopinavir/ritonavir, the antimalarial chloroquine/hydroxychloroquine, and monoclonal antibodies against components of the immune system such as interleukin-6 (IL-6) and IL-4. It is important that the potential treatments are carefully assessed in randomised controlled trials.

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1. Introduction

Coronavirus is a family of the virus and can cause illness such as the common cold, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [1]. Chinese public health officials announced to the World Health Organization (WHO) that a new and unknown virus caused a disease with symptoms like pneumonia in Wuhan last December 2019 [2]. The WHO is seeking to identify, track and restrict a new disease from the CoV family called CoV disease 2019 (COVID19), which is still affecting many peoples in China and out breaking to other countries. This new virus still affecting many peoples in China and out breaking to other countries. This type of CoV is also spreading in other countries such as Iran, Italy and South Korea [3]. On 30 January 2020, the World Health Organisation (WHO) declared SARS-CoV-2 pandemic as a Public Health Emergency of International Concern [4]. Now, therapeutic strategy for COVID-19 is largely supportive [5]. Several drugs seem to be clinical beneficial, but their efficacy is far from satisfactory. To this end, there are urgent needs to develop COVID-19-specific treatment to alleviate the symptoms and reduce the mortality [6].

2. Treatments of SARS-CoV-2

Until now, no fully proven and specific antiviral treatment for the SARS-CoV-2 infection exists. The treatments that can be administered are those that help fight the symptoms. Some experimental treatments are authorized to be tested with caution. It is mainly about chloroquine and

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hydroxychloroquine (+/- azithromycin), antivirals (lopinavir/ritonavir, remdesivir, umifenovir, favipiravir), immunomodulators (tocilizumab, interferon-β-1a, anakinra), corticosteroid therapy, and plasma therapy.

2.1. Hydroxychloroquine and azithromycin

The treatment that is most talked about during this pandemic is the combination of hydroxychloroquine (a derivative of chloroquine) with azithromycin (an antibiotic).

Preclinical studies have shown that chloroquine phosphate and hydroxychloroquine sulfate inhibit viral activity in vitro. The current study authors report that another of their studies show a synergistic effect when both azithromycin and hydroxychloroquine are used on cells infected with the SARS-CoV-2, at levels similar to the probable concentrations in humans dosed with these drugs. Some studies have also shown that chloroquine reduces fever and leads to an improvement in the CT signs on imaging, as well as delaying the progression of symptoms. This has led some Chinese researchers to recommend a chloroquine-based treatment for COVID-19, of all severities [7, 8].

2.2. Antivirals

2.2.1. Lopinavir/ritonavir

This medicine is an antiretroviral active against the human immunodeficiency virus (HIV). The active component is lopinavir, which belongs to the family of HIV protease inhibitors (antiproteases). By blocking this enzyme, it prevents the virus from reproducing in infected cells, but does not allow its elimination. The other ingredient is ritonavir (antiprotease). The latter is used in this combination by just allowing increasing the concentrations of lopinavir in the body (booster effect) [9].

2.2.2. Remdesivir

It is an anti-viral drug already authorized in the United States. Originally, it is used against Ebola and had already shown benefits in the treatment of Mers and SARS-CoV-1. The study of reports encouraging results with anakinra. Sold under the trade name Kineret®, it is mainly prescribed for inflammatory diseases such as rheumatoid arthritis, rheumatism or Muckles-Wells syndrome, for example. The treatment could act on the thunderstorm of cytokines, an inflammatory mechanism which provokes the overrun of the immune defenses which the researchers think mainly responsible for the severe forms of COVID-19, including its attacks on the organs like the kidneys, the lungs or heart [10].

2.2.3. Umifenovir

Is an antiviral treatment for influenza infection used in Russia and China. The drug has also been investigated as a candidate drug for treatment of hepatitis C [11, 12]. Umifenovir inhibits membrane fusion [11]. It prevents contact between the virus and target host cells. Fusion between the viral envelope (surrounding the viral capsid) and the cell membrane of the target cell is inhibited. This prevents viral entry to the target cell, and therefore protects it from infection [13].

Some evidence suggests that the drug's actions are more effective at preventing infections from RNA viruses than infections from DNA viruses [14]. As well as specific antiviral action against both influenza A and influenza B viruses, umifenovir exhibits modulatory effects on the immune system. The drug stimulates a humoral immune response, induces interferon-production, and stimulates the phagocytic function of macrophages [15].

2.2.4. Favipiravir

Is an antiviral drug being developed in Japan with activity against many RNA viruses. It is a pyrazinecarboxamide derivative witch has shown activity against influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease

virus as well as other flaviviruses, arenaviruses, bunyaviruses and alphaviruses [16].

Activity against enteroviruses [17] and Rift Valley fever virus has also been demonstrated [18]. The agent has also shown some efficacy against rabies, [19] and has been used experimentally in some humans infected with the virus [20].

2.2.5. Arbidol

It is a broad-spectrum antiviral compound that blocks the contact, adhesion and fusion of viral lipid capsules and host cell membranes and blocks the virus replication [21, 22]. In vivo and in vitro experiments confirm that arbidol has inhibitory effects on a variety of respiratory viruses, including enveloped and unenveloped viruses as well as RNA and DNA viruses [23]. A randomized controlled trial gave oral arbidol (200 mg/d) to workers during an influenza epidemic for 10 to 18 days and found that arbidol had significant preventative effects. It blocks the virus from entering host cells and blocks also the initial stages of the virus's pathogenic process, leading to preventative protection [24].

2.3. Immunomodulators

2.3.1. Tocilizumab

It is a recombinant humanised monoclonal antibody of the IgG1 class, which is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor [25, 26]. IL-6 is a cytokine that plays an important role in inflammatory reaction and immune response. The most recent clinical experiences in China suggested that IL-6 is one of the most important cytokines involved in COVID-19-induced cytokine storms [27].

Tocilizumab is recommended for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor T cell therapy [28, 29].

2.3.2. Interferon-β-1a

Interferons (IFNs) are natural chemicals that are secreted as part of the immune response to infections. They activate natural killer (NK) cells and macrophages. The antiviral effect of IFNs express through activating interferon-stimulated gene (ISG) that slow viral replication. Interferon-beta (IFN-beta) is a polypeptide, normally produced by fibroblasts, that has antiviral, immunomodulatory and antiproliferative effects. Binding of IFN-beta to its receptor induces a complex transcriptional response. In immune cells, IFN-beta reduces antigen presentation and T-cell proliferation, alters cytokine and matrix metalloproteinase (MMP) expression, and restores suppressor function. Therapeutic forms of IFN-beta can be produced in bacterial expression systems (IFN-beta1b) or in mammalian cells (IFN-beta1a) [30, 31].

2.3.3. Anakinra

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease [32]. It is also used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis [33].

2.4. Corticosteroid

2.4.1. Dexamethasone

Dexamethasone, a corticosteroid, is similar to a natural hormone produced by your adrenal glands. It often is used to replace this chemical when the body does not make enough of it. It relieves inflammation (swelling, heat, redness) and is used to treat certain forms of arthritis; skin, blood, kidney, eye, thyroid, and intestinal disorders, severe allergies and asthma. Dexamethasone is also used to treat certain types

of cancer [34]. It is a steroidal anti-inflammatory drug used in particular to treat asthma, which reduces mortality in hospital patients with severe respiratory complications "by a third". This is the standard treatment for patients who are to be given oxygen [35].

2.6. Plasma therapy

People who have recovered from COVID-19 develop antibodies, natural defences to the disease in their plasma blood. This plasma can be used to make two preparations. Firstly, convalescent plasma, which is plasma that contains these antibodies. Secondly, hyperimmune immunoglobulin, which is more concentrated, and therefore contains more antibodies. Convalescent plasma and hyperimmune immunoglobulin have been used successfully to treat other respiratory viruses. These treatments (given by a drip or injection) are generally well-tolerated, but unwanted effects can occur [36].

3. Discussion

The SARS-CoV-2 virus emerged in December 2019 and then spread rapidly worldwide. Scientists are endeavouring to find antivirals specific to the virus. Several drugs are currently undergoing clinical studies to test their efficacy and safety in the treatment of COVID-19 disease; some promising results have been achieved thus far. This is a non-randomized observational study on the benefit of the different treatments used for SARS-CoV-2 patients. Hydroxychloroquine is postulated to exert a direct antiviral activity by increasing intracellular pH resulting in decreased phago-lysosome fusion, impairing viral receptor glycosylation. In addition, it has immune-modulating effect by inhibiting toll-like receptor signaling, decreasing production of cytokines especially IL-1 and IL-6 [37]. Prior data also suggests a potential anti-thrombotic effect [38].

Hydroxychloroquine clinical safety profile is better than that of chloroquine (during long-term use) and allows a higher daily dose [39] and has fewer concerns regarding drug-drug interactions [40].

Indeed, azithromycin, a macrolide antibiotic, has in vitro antiviral properties such as decreased viral replication, blocking entrance into host cells, and a potential immunomodulation effect [41]. An in vitro study demonstrated synergistic activity of the combination of hydroxychloroquine and azithromycin against SARS-CoV-2 [42]. Furthermore, the study conducted by Rosenberg showed that among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality [43]. Additionaly, the multinational, observational, realworld study Mehra et *al.*, [44] of patients with COVID-19 requiring hospitalisation found that the use of a regimen containing hydroxychloroquine or chloroquine (with or without a macrolide) was associated with no evidence of benefit, but instead was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19 [44]. The effectiveness of antiviral drugs is relative. On the one hand, the preliminary findings of a study support the use of remdesivir for patients who are hospitalized with COVID-19 and require supplemental oxygen therapy. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should evaluate antiviral agents in combination with other therapeutic approaches or combinations of antiviral agents to continue to improve patient outcomes in COVID-19 [45].

On the other hand, a research study conducted showed that in hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard

care [46]. Indeed, another study showed that comparing with symptomatic and supportive treatment, additional umifenovir has not been found to shorten the duration of SARS-CoV-2 negativity time and improve the prognosis in non-intensive care unit patients. This conclusion needs to be further verified in randomized control clinical trials [47]. However, in [3], favipiravir was being studied in China for experimental treatment of the emergent COVID-19 disease. On March 17 Chinese officials suggested the drug had been effective in treating COVID in Wuhan and Shenzhen [48].

According to Chunguang [49], arbidol was significantly associated with reduced SARS-CoV-2 infection and might play a preventative role among health professionals. This result also has certain significance for other high-risk populations, such as family members of COVID-19 patients and infectious disease control personnel. Indeed, this study reveals that preventative oral arbidol was not significantly associated with the hospitalization rate and duration of positive throat swab of health professionals with COVID-19. Moreover no statistical correlation between prophylactic medication and severe pneumonia which was worth further consideration. Immunomodulatory therapy has the potential to inhibit cytokines and quell the immune dysregulation. Several studies are interested in evaluating the effect of tocilizumab (TCZ) on patients with Covid-19 [49]. Luo [50] evaluate the effect of TCZ therapy in COVID-19 patients in real life. The findings supported the effectiveness of TCZ in the prevention or treatment of cytokine storms induced by COVID-19. In most patients, acute phase reactant levels were decreased and the patients were getting to a stable condition reflected by a later gradual decrease of IL-6 after TCZ administration.

Clinical data showed of study exhibits that the symptoms, hypoxygenmia, and computerized tomography opacity changes were improved immediately after the treatment with TCZ in most of the patients, suggesting that this molecule could be an efficient therapeutic for the treatment of COVID-19 [51]. Indeed, the findings of Guaraldi (2020) showed the treatment with TCZ, whether administered intravenously or subcutaneously, might reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia [52].

Despite SARS-CoV showed resistance to their effects by STAT1 inhibition that blocked IFN signalling, different types of IFN are being evaluated for efficacy in the current pandemic, such as IFN β-1b in combination with lopinavir-ritonavir and ribavirin in mild to moderate COVID-19, and nebulized IFN α-2b with oral arbidol [53]. The Iranian research study suggests that IFN β-1a added to the standard of care increased the proportion of patients discharged by day 14, and reduced the mortality at 28 days. Early administration of the drug improved survival rates. The tolerability and safety profile of the drug was also acceptable [54].

In China, a retrospective cohort study of 77 adults with moderate COVID-19, participants were treated with nebulized interferon alfa-2b, nebulized interferon alfa-2b with umifenovir or umifenovir only. The time to viral clearance in the upper respiratory tract and reduction in systemic inflammation was faster in the interferon alfa-2b groups than in the umifenovir only group. However, the results of this study are difficult to interpret because participants in the interferon alfa-2b with umifenovir group were substantially younger than those in the umifenovir only group (mean age 40 years vs. 65 years) and had fewer comorbidities (15% vs. 54%) at study entry [55]. The World Health Organization (WHO) welcomes the initial clinical trial results from the United Kingdom (UK) that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill

with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with WHO. The benefit was only seen in patients seriously ill with COVID-19, and was not observed in patients with milder disease [35]. The UK RECOVERY trial showed that low-dose dexamethasone (6 mg daily for 10 days) randomized to 2104 patients reduced deaths by 35% in ventilated patients and by 20% in other patients receiving oxygen only compared with patients who received standard of care [56].

Two studies showed that anakinra significantly reduced both need for invasive mechanical ventilation in the intensive care unit and mortality among patients with severe COVID-19, without serious side-effects [57, 58]. Administration of anakinra, which is a recombinant soluble receptor antagonist of IL-1β and IL-1α, in patients with signs of secondary hemophagocytic lymphohistocytosis reduced mortality by 30% [57]. Regarding plasma therapy, clinical data are currently insufficient to evaluate the efficacy of convalescent plasma for the treatment of COVID-19. Safety data from a large, multicenter, expanded access program indicated that uncommon (in <1% of transfusions) but serious risks of convalescent plasma may include transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic reactions, and death. Another theoretical risk is potential for antibody-dependent enhancement (ADE) of infection [59].

The study of Zeng is the first to indicate that convalescent plasma treatment contributes to the discontinuation of SARS-CoV-2 shedding and longer survival in patients with COVID-19 and respiratory failure; however, it cannot reduce the mortality rate in critically ill patients with end-stage COVID-19 [60]. There are multiple clinical trials taking place in several countries. People who have recovered from COVID-19 for more than 28 days, with no transfusion-transmitted diseases and who are not pregnant are eligible to participate. Recipients will be followed throughout their hospitalisation and a month after discharge [61]. There is a large global effort to develop vaccines for protection against COVID-19 and at least ten vaccine candidates have, as of early June, 2020 entered clinical trials, including phase II trials [62].

Safety and immunogenicity data have been reported in the scientific literature for the first-in-human trial assessing a vector-based SARS-CoV-2 vaccine candidate conducted in China and merit further studies [63]. Summarizing this literature search, I think that all these treatments show relative effectiveness depending on the stage of the disease, pathophysiological factors related to the severity of symptoms, health status of patients with SARS-CoV-2. In my opinion, blood plasma therapy is promising, especially when combined with anti-inflammatory treatment to avoid septic shock in patients. Another hypothesis that seems interesting to me is the synthesis of antibodies present in the blood of COVID-19-attendees (healthy or positive carriers) by means of biotechnology. Subsequently, these antibodies will be used intravenously instead of plasma therapy to avoid the problems and limitations of the latter.

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