Propósitos y Representaciones
ISSN 2307-7999
e-ISSN 2310-4635

May. 2021, Vol. 9, SPE(3), e1142
Current context of education and psychology in Europe and Asia
http://dx.doi.org/10.20511/pyr2021.v9nSPE3.1142

RESEARCH ARTICLES

Modern Approaches to the Study of Medicines Used in the Treatment of Patients Diagnosed with Covid-19

Enfoques modernos para el estudio de los medicamentos utilizados en el tratamiento de pacientes diagnosticados con Covid-19

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Received 09-08-20 **Revised** 10-10-20 **Accepted** 12-12-20 **On line** 03-15-21

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Citation:

Gulnara Ramazanovna Gamzatkhanova, Seda Beslanovna Bamatgiriyeva, Vitaly V. Goncharov, Yana Paromova, Ivan Gennadievich Subbotin, Alexander Sergeevich Bronnikov. (2021). Modern Approaches to the Study of Medicines Used in the Treatment of Patients Diagnosed with Covid-19. *Propósitos y Representaciones*, *9* (SPE3), e1142. Doi: http://dx.doi.org/10.20511/pyr2021.v9nSPE3.1142

Abstract

The new coronavirus (COVID-19) was first detected in the city of Wuhan in China in December 2019. Most patients infected with COVID-19 had clinical manifestations of dry cough, fever, shortness of breath, chest pain, fatigue and malaise, pneumonia, and bilateral chest CT infiltration. Soon COVID-19 spread around the world and turned into a pandemic. Now this disease affects many patients around the world. Patients with concomitant diseases have a high risk of COVID-19 infection, the infection is quite severe, leading to organ dysfunction, which is acute respiratory distress syndrome, acute kidney damage, septic shock, pneumonia and death. Currently, the coronavirus disease (COVID-19) is an imminent threat to global public health. Experts around the world are now actively searching for medicines that can stop the infection. Despite the fact that some modern therapeutic drugs have demonstrated quite high capabilities in the field of prevention or treatment of patients with COVID-19, various side effects have occurred during their use. Therefore, a comprehensive assessment of the safety profile of therapeutic agents against COVID-19 is highly relevant.

Keywords: COVID-19, therapeutic medicines, specific therapy, drug adaptive reuse.

Resumen

El nuevo coronavirus (COVID-19) se detectó por primera vez en la ciudad de Wuhan en China en diciembre de 2019. La mayoría de los pacientes infectados con COVID-19 tenían manifestaciones clínicas de tos seca, fiebre, dificultad para respirar, dolor en el pecho, fatiga y malestar, neumonía e infiltración bilateral de TC de tórax. Pronto, COVID-19 se extendió por todo el mundo y se convirtió en una pandemia. Ahora bien, esta enfermedad afecta a muchos pacientes en todo el mundo. Los pacientes con enfermedades concomitantes tienen un alto riesgo de infección por COVID-19, la infección es bastante grave y conduce a una disfunción orgánica, que es síndrome de dificultad respiratoria aguda, daño renal agudo, shock séptico, neumonía y muerte. Actualmente, la enfermedad por coronavirus (COVID-19) es una amenaza inminente para la salud pública mundial. Los expertos de todo el mundo están buscando activamente medicamentos que puedan detener la infección. A pesar de que algunos fármacos terapéuticos modernos han demostrado capacidades bastante elevadas en el campo de la prevención o el tratamiento de pacientes con COVID-19, se han producido varios efectos secundarios durante su uso. Por lo tanto, una evaluación integral del perfil de seguridad de los agentes terapéuticos frente al COVID-19 es muy relevante.

Palabras clave: COVID-19, medicamentos terapéuticos, terapia específica, reutilización adaptativa de fármacos.

Introduction

Coronaviruses are membranous, unsegmented, and single-stranded RNA viruses with a positive meaning. The starting point for the spread of this disease should be considered the end of December 2019, when new cases of pneumonia caused by this virus were first detected in the Chinese city of Wuhan. The most common clinical signs and symptoms in the first and subsequent patients were dry cough, fever, shortness of breath, and bilateral chest CT infiltration. The causative agent of the new coronavirus was first detected using swobs taken from these patients.

This new coronavirus was later named the severe acute respiratory syndrome coronavirus (SARS-CoV-2). Soon this disease was named (COVID-19), and its spread became pandemic.

Most patients infected with COVID-19 have an average age of 50 years, most often the virus affects men. Approximately 25% of infected patients with severe forms of the disease are treated in hospitals, while 10% of these patients require artificial lung ventilation.

Studies of European specialists in Italy showed that COVID-19 prevailed in men (59.8% in men and 40.2% in women), the majority of patients (about 75%) were over 50 years old, approximately 46% of all patients had a mild form of the disease, 25% showed a severe course of the disease,

5% were in a critical situation, and the remaining patients had minor symptoms, unspecified symptoms, or completely absent symptoms (Huang et al., 2020).

According to recently published studies, the most common clinical manifestations in patients with COVID-19 were fever in 83-98% of patients, dry cough in 76-82%, and fatigue or myalgia in 11-44% of them. Other signs and symptoms reported include sore throat, headache, confusion, rhinorrhea, sneezing, ageusia, anosmia, chest pain, hypoxemia, pneumonia, hemoptysis, acute heart failure, neurological complications, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain.

Patients with concomitant diseases are very likely to develop severe infection, which is expressed through acute respiratory distress syndrome, acute kidney injury, septic shock, etc. A severe form of COVID-19 can lead to death due to severe alveolar damage and highly progressive respiratory failure.

CAVID-19 particles can be spread through the airway mucosa and through the fecal-oral route. The virus's nucleic acid was found in excrement samples and saliva. This virus can be transmitted from person to person, and this form of transmission can significantly accelerate the spread of this virus.

Studies have shown that COVID-19 can also be transmitted by an asymptomatic carrier with an incubation period of 1 to 19 days. To prevent the spread of this new virus, hands should be washed frequently, you should not touch your face with unwashed hands, regular disinfection of surfaces is required, social distancing from people with respiratory symptoms is necessary, and other precautions are taken.

Covid-19 diagnostics is also a special feature. According to published reports, in most patients with COVID-19, the absolute value of lymphocytes was reduced, indicating that this new coronavirus (COVID-19) acts more on lymphocytes, especially on T-lymphocytes, like the SARS coronavirus.

COVID-19 can cause a cytokine storm and activate immune responses, which can manifest in changes in the number of white blood cells and immune cells, especially lymphocytes. The clinical outcome of such events will be respiratory distress syndrome, septic shock, and finally, damage to the target organ. COVID-19 can also affect the liver, resulting in hypoproteinemia, increased aminotransferases, and prolonged prothrombin time. Hepatotoxicity can be explained by higher expression of angiotensin converting enzyme II (ACE2) in cholangiocytes, ACE2 can act as an input receptor for COVID-19. It is also assumed that this new virus can directly damage the intrahepatic bile ducts.

Pathological results of a liver biopsy of a patient with COVID-19 showed moderate microvesicular steatosis, as well as moderate portal and lobular activity, which may be the result of direct liver damage from SARS-CoV-2 or hepatotoxicity caused by antiviral drugs.

Almost all patients with COVID-19 were diagnosed with abnormal lung CT. The analysis of studies showed that on average, patients with the considered diagnosis had 10.5 ± 6.4 segments, and the number of affected lung segments was significantly higher in the group of patients with symptoms compared to asymptomatic carriers of the disease (Zang et al., 2020).

CT results showed that patients with COVID-19 may have both bilateral lung damage and peripheral or diffuse lung damage. The most common manifestations of chest CT were matte glass pattern, compaction, and fuzzy borders (Xia et al., 2020).

According to WHO-approved laboratory PCR tests for the diagnosis of COVID-19, the diagnosis is based on a nucleic acid amplification test (NAAT), such as rRT-PCR, which can detect COVID-19 RNA sequence.

Materials and Methods

During the preparation of the work, we analyzed studies related to the use of non-specialized medicines for the treatment of a new coronavirus infection, as well as drugs developed directly for the treatment of COVID-19. The results of clinical studies related to the use of these medicines were also examined.

Results

As already noted, today medical specialists around the world are trying to find the most effective medicine against coronavirus infection. One of the directions in this area was the re-profiling of existing medicines.

The medicine repurposing approach speeds up the drug discovery process and attracts the attention of researchers in a wide variety of fields of science (Zhou et al., 2020). Due to the availability of in vitro and in vivo screening data, complete chemical optimization, toxicity studies, mass production, formulation development, and pharmacokinetic profiles approved by the FDA, the medicine development cycles for coronavirus infection are shortened in this case, since all these critical steps can be bypassed. In addition, there is no need for larger investments, and the safety of repurposed medicines has been proven in preclinical models. Consequently, the main advantages of drug of adaptive reuse are associated with the established safety of known candidate compounds, a significant reduction in the development time and costs associated with the promotion of a particular drug for clinical trials (Ruan et al., 2020).

Most of the repurposed drugs were discovered by accident. In addition to random observations, drug repurposing can be performed using several strategies, including binding assays, phenotypic screening methods, and so on. In (Ruan et al., 2020), a brief overview of various approaches to medicine repurposing was presented.

Table 1. Different approaches to re-purposing drugs for the treatment of COVID-19

Name of approach	Description
Binding assay	Identification of binding interactions of ligands with analysis components
Phenotypic screening	Evaluates a large number of approved or developed medications in various predictive models Evaluation of a number of connections in an array of independent models
Targeted approach	Identifying new indications on the basis of target proteins of the medicine
Scientific approach	Combines known information about the medicine with the prediction of unexplored biomarkers.
Comparative approach	Based on comparing the unique characteristics or "signature" of a medicine with the characteristics of another medicine, disease, or clinical phenotype

Choosing the right approach is a crucial step in repurposing medicines. The possibilities for repurposing drugs are diverse, but much remains to be done to explore them.

Within the framework of the above approaches, various strategies for repurposing medicines are used to determine the effectiveness of known drugs in respiratory viral infectious diseases using both screening of collections of bioactive small molecules and computational methods. The main non-core drugs studied by various specialists for use against COVIND-19 are presented in table 2.

Table 2. Repurposed drugs in clinical development against various indications caused by respiratory viruses

Medicine / composition	Original designation	A new use for respiratory viral infections

Sarilumab	Rheumatoid arthritis	COVID-19
Favipiravir	Flu	COVID-19
Ramdevpir	A wide range of antiviral drugs	COVID-19
Danoprevir / ritonavir	Danoprevir for hepatitis C	COVID-19
Dexamethasone	Ritonavir for HIV	COVID-19-associated acute respiratory distress syndrome
Ivermectin / doxycycline	Immunosuppressant	COVID-19
ASC09 / ritonavir	Ivermectin for parasitic infections	COVID-19
Hydroxychloroquine	Doxycycline for bacterial infections	COVID-19
Methylprednisolone	Ritonavir for HIV	COVID-19
Tocilizumab	Malaria	COVID-19

If an antiviral medicine has the ability to affect a specific pathway used for virus replication and is active against other viruses, it may be useful against COVID-19 (Ragab et al., 2020).

Remdesivir, a broad-spectrum antiviral drug under investigation, has shown promising efficacy in the treatment of MERS and SARS. Several recent studies have reported the effectiveness of remdesivir in the treatment of COVID-19 (Ragab et al., 2020). Similarly, chloroquine (approved for the treatment of malaria) has shown potential for reuse against influenza (Ye et al., 2020), MERS (suppression of virus replication), SARS, and COVID-19 (Ye et al., 2020).

In addition, hydroxychloroquine (HCQ) has shown positive effects in the treatment of COVID-19, as reported in several recent studies (Ye et al., 2020). on March 28, 2020, the food and drug administration (FDA) issued an emergency use allowance (EUA) for the use of chloroquine phosphate and hydroxychloroquine sulfate for the treatment of COVID-19 (Xu et al., 2020). In addition, on May 1, 2020, the FDA granted permission for the use of remdesivir in emergency cases (EUA) for the treatment of COVID-19. However, June 15, 2020 The FDA has withdrawn EUA for emergency use of the oral formulations chloroquine phosphate and hydroxychloroquine sulfate based on current EUA analysis and new scientific data (Xu et al., 2020).

Researcher L. Heimfarthab and her co-authors also studied many classes of drugs to minimize the effects of COVID-19 (Heimfarth et al., 2020). They suggested that some of these drugs, such as chloroquine (CQ) and hydroxychloroquine (HCQ), had caused unnecessary insanity due to their indiscriminate use as preventive measures in a number of countries, including Brazil and the United States.

Although this is not the main goal of most drugs currently used to treat COVID-19, there is growing evidence that the "cytokine storm" can have a significant impact on the development of the disease, especially in patients in critical condition (Heimfarth et al., 2020). However, there is no information on how these drugs can help control important cytokines and promote patient recovery.

Some drugs that have been studied for their potential usefulness in COVID-19 have an anti-inflammatory profile in other diseases and are being tested against hyperinflammation caused by SAR-COV-2 infection.

Knowledge of the molecular targets of drugs in SAR-COV-2 infection and their subsequent effects on immune responses can help pave the way for empirical approaches and trials at this stage. The above authors presented a classification of drugs proposed for the treatment of COVID-19 that can modulate the observed inflammatory process. The classification includes antiviral, anti-rheumatic, anti-inflammatory, antitumor and antiparasitic drugs (table 3). It was noted that all these classes of drugs have a beneficial effect on patients with COVID-19 (Heimfarth et al., 2020).

Table 3. Drugs used in the treatment of COVID-19

Class	Drug, remedy, medicine	Main class	Main mechanism of action	The prevailing COVID-19 management mechanism
Antiviral drugs for the treatment of COVID-19 and affected cytokines				
Antiviral drugs	Atazanavir	Antiretroviral drug	Inhibitor of CYP3A and UGT1A1	It blocks the main protease (Mpro) SARS-CoV-2.
	Favipiravir (Avigan)	Antiviral drug	Competitive inhibitor of RNA-dependent RNA polymerase	It prevents virus replication
	IFN-α2b (interferon)	Antiviral drug Immunomodulatory drug	Formation of an adaptive immune response. Suppression of DNA replication.	It suppresses SARS-CoV and MERS-CoV replication.
	Lopinavir-ritonavir	Antiviral drug	Proteinase inhibitor, proteinase inhibitor, antiretroviral proteinase inhibitor	It suppresses CYP3A-mediated LPV metabolism, inhibits 3CL pro due to SARS-CoV, affecting virus replication and maturation; Ritonavir inhibits the CYP3A metabolism of lopinavir, increasing its plasma concentration It is a protease inhibitor
	Remdesivir	Antiviral drug	Inhibitor RNA-polymerase A nucleoside analogue	Inhibitor RNA-polymerase
	Ribavirin	Antiviral drug	Stops the synthesis of viral RNA	An analogue of nucleosides that interferes with the replication of RNA

				and DNA viruses.
	Umifenovir	Antiviral drug	Inhibition of fusion of the viral envelope and cytoplasmic membrane of the host cell.	It blocks the trimerization of spike glycoprotein of-SARS-CoV-2
Anti-rheumatic and anti-inflammatory drugs for the treatment of COVID-19 and the cytokines they affect				
Anti-rheumatic drugs	Anakinra	Antiarthritic agent	Recombinant antagonist IL-1Ra	Interleukin-1 receptor antagonist
	Baricitinib	Antiarthritic agent	Powerful and selective Janus kinase inhibitor (JAK)	It interrupts passage and intracellular gathering of SARS-CoV-2 into target cells by disrupting AAC 1 It blocks clathrin - indirect endocytosis and thereby suppresses viral infection of cells
	Etanercept	Antiarthritic agent	Inhibitor TNFα	Inhibitor TNFα
	Infliximab	Antiarthritic agent Crohn's disease	Inhibitor TNFα	Inhibitor TNFα
	Tocilizumab	Antiarthritic agent	Inhibitors of receptor IL-6 Monoclonal antibodies against the soluble receptor IL-6	Recombinant humanized monoclonal antibody against IL6R. It binds both soluble and membrane-bound IL6R, by suppressing IL6-indirect signal transmission.
Antiinflammatory drugs	Indomethacin	Non-steroidal anti-inflammatory drug	Non-selective cyclooxygenase inhibitor (COX)	Suppression of virus replication and

				production of infectious virus particles
	Thalidomide	Phthalimides	Immunomodulatory, anti-inflammatory and anti-angiogenic medicine	An immunomodulatory and anti-inflammatory medicine
	Corticosteroids	Non-steroidal anti-inflammatory drug	Suppression of multiple inflammatory genes by binding glucocorticoids with the involvement of histone deacetylase 2 for the activated transcription complex.	It suppresses the transcription factor NFkB.
ACEi and ARB drugs for the treatment of COVIND-19 and the cytokines they affect				
ACEi	Enalapril	ACEi	Angiotensin-converting enzyme inhibitors	It reduces the interaction between the viral protein and ACE 2, affecting the internalization of the virus.
ARB	Losartan	ARB	Antagonist AT_1R	It reduces the interaction between the viral protein and ACE2
	Telmisartan	ARB	Antagonist AT_1R	It reduces the interaction between the viral protein and ACE2
Anticancer, antibiotic, and antiparasitic drugs for the treatment of COVID-19 and the cytokines they affect				
Anticancer drugs	Ibrutinib	Anticancer drug	Covalent inhibitors of TCI	It prevents B-cell activation and transmission of B-cell-indirect signals (suggestion)

	Ruxolitinib	Antitumor and immunomodulatory effects	Janus kinase inhibitors	Janus kinase inhibitors
Antibiotic	Azithromycin	Antibiotic	It binds with the 50S subunit of the ribosome, affecting bacterial protein synthesis.	
Antiparasitic drugs	Chloroquine	Antimalarial drug	Immunosuppression	It changes the pH in lysosomes. It prevents viruses from merging and replicating. Spike (S) - protein blockers of angiotensin-converting enzyme 2 (ACE2)
	Hydroxychloroquine	Anti-malarial drugs anti-rheumatic drugs that modify the disease (disease-modifying anti-rheumatic drug)	Immunosuppression	Inhibition of the SARS-CoV cell receptor (ACE 2), virus membrane fusion in the host, nucleic acid replication, new virus transport, virus release.
	Ivermectin	Broad-spectrum antiparasitic agent Antiviral medicine (*in vitro*)	Inhibitory activity of nuclear transport	Inhibitory activity of nuclear transport
	Nitazoxanide (anitta)	Antiprotozoal drug	It increases the production of interferon alpha and beta interferon	It affects the synthesis of the viral genome It prevents virus entry and prevents N-glycosylation
Others	Colchicine	Antipodagric medicine	Microtubule inhibitor (colchicine blocks microtubule polymerization)	A non-selective inhibitor of NLRP3 inflammasome

				Anti-inflammatory effect

Research by medical specialists from China on the choice and effectiveness of medicines for the treatment of patients with a new coronavirus infection is also interesting. In China, the practice of fighting SARS-CoV-2 over the past four months has fully confirmed that traditional Chinese medicine plays an important role in the prevention and treatment of COVID-19 before the successful development of specific medicines and vaccines. Combined methods of treatment of traditional Chinese medicine and chemical preparations increased clinical effectiveness, reduced the length of hospital stay, and reduced the critical mortality rate (Pan et al., 2020). Therefore, these drugs, including recipes for Chinese herbal compounds, injectable drugs, and natural active ingredients with specific effects for the prevention and treatment of COVID-19, should be generalized and distributed. Prescriptions for Chinese herbal compounds and injectable medications that have tried to prevent and treat COVID-19 in China are listed in table 4 (Pan et al., 2020).

Table 4. Traditional Chinese medicine medications that can potentially be used for the prevention and treatment of COVID-19

Traditional Chinese medicines	Compositions	Indications	Adverse reaction	General usage (for reference only)
Huoxiangzhengqi preparations (capsule, pill, water, liquid for oral administration)	13 types of herbs: Pogostemonis Herba , Perillae Folium , Angelicae dahuricae Radix , Atractylodis macrocephalae Rhizoma , Citri reticulatae Pericarpium , Pinelliae Rhizoma Praeparatum , Magnoliae officinalis Cortex , Poria and others.	Migraines, flu, acute upper respiratory tract infection, heat stroke, functional dyspepsia, etc.	Some people may have skin damage, redness, palpitations, dizziness, rash, itching, disulfiram-like reaction in combination with cephalosporins, etc.	An oral solution of water or HuoxiangZhengqi solution is 5-10 ml once - twice a day. Tablets of 2.5-5 g: once-2 times a day. Capsules are 4 capsules once or twice a day. The diet should be light while taking medication
Jinhua Tsingan Pellets	Lonicerae japonicae Flos , Fritillariae thunbergii Bulbus , Scutellariae Radix , Arctii Fructus , Artemisiae annuae Herba and others.	Various flu : flu a (H1N1)	Uncertain	Take one sachet with boiled water twice a day for 3-5 days or as prescribed by your doctor. Avoid spicy, cold, and fatty food
Lianhua Qingwen Capsule (granules)	13 types of herbs: Forsythiae Fructus , Lonicerae japonicae Flos , Ephedrae Herba , Armeniacae semen Amarum , Gypsum Fibrosum , Isatidis Radix , Dryopteridis crassirhizomatis Rhizoma , Houttuyniae Herba , Pogostemonis Herba and others.	Flu	It usually occurs after the first dose of medication, such as nausea, vomiting, bloating, diarrhea, rash, itching, etc.	Oral administration of 4 capsules or one granule at a time, three times a day. 7-10 days as a course for the mild and common form of COVID-19

Shufeng Jiedu Capsule (granules)	Polygoni cuspidate Rhizoma et Radix , Forsythiae Fructus , Isatidis Radix , Bupleuri Radix , Patriniae Herba , Verbenae Herba , Phragmitis Rhizoma , Glycyrrhizae Radix et Rhizoma	Acute upper respiratory tract infection	Sometimes nausea, rash, dizziness, headache, high blood pressure, etc.	Oral administration of 4 tablets three times a day.
Tablets Fangfeng Tongsheng (granules)	17 types of herbs: Saposhnikoviae Radix , Schizonepetae Spica , Menthae haplocalycis Herba , Ephedrae Herba , Rhei Radix et Rhizoma , Natrii Sulfas , Gardeniae Fructus and others	Urticaria, eczema, constipation	Sometimes an allergic rash	Oral administration, one tablet, twice a day.
Granules Toujie Quwen (from pneumonia #1 on prescription)	16 types of herbs: Scutellariae Radix , Forsythiae Fructus , Lonicerae japonicae Flos , Isatidis Foliu and others	Antivirus	Uncertain	Oral administration, 2 sachets at a time, each sachet 11 g, twice a day.
Tsingfei Paidu Decoction	21 types of herbs: Ephedrae Herba , Armeniacae semen Amarum , Gypsum Fibrosum , Asari Radix et Rhizoma , Bupleuri Radix , Scutellariae Radix , Citri reticulatae Pericarpium and others	Measles, pneumonia	It may occur after inappropriate medication, such as excessive sweating, epigastric discomfort, diarrhea, and increased arterial pressure.	One dose a day, once in the morning and evening (in 40 minutes after meals), take with warm water, three times by a course. If possible, add half a cup of rice soup after each serving.
Huashi Baidu Recipe	14 types of herbs: Ephedrae Herba , Pogostemonis Herba , Gypsum Fibrosum , Armeniacae semen Amarum , Pinelliae Rhizoma Praeparatum , Rhei Radix et Rhizoma , Glycyrrhizae Radix et Rhizoma and others.	Pneumonia	Uncertain	1-2 doses per day, decoction, 100-200 ml each time, 2-4 times a day, oral or nasal feeding
Decoction of Suanfei Baidu	13 types of herbs: Ephedrae Herba , Armeniacae semen Amarum , Gypsum Fibrosum , Pogostemonis	Pneumonia	Uncertain	One dose per day, 400 ml decoction, take 200 ml in the morning and evening, respectively.

	Herba , Artemisiae annuae Herba , Glycyrrhizae Radix et Rhizoma and others			
Ciyanping for injections	Andrographolide ether sulfonate	Acute viral infection of the upper respiratory tract, viral bacterial pneumonia, influenza, acute and chronic bronchitis	Digestive symptoms such as nausea and vomiting.	Viral infection or combined mild bacterial infection: 0.9% sodium chloride injection 250 ml + Ciyanping injection 100 mg 2 times a day
Xuebijing injection	Carthami Flos , Paeoniae Radix Rubra , Chuanxiong Rhizoma , Salviae miltiorrhizae Radix et Rhizoma and Angelicae sinensis Radix	Lung infection	Chest tightness, rash, anaphylactic shock, fever, abdominal pain, nausea, vomiting, drop in blood pressure, etc.	Systemic inflammatory reaction or polyfunctional organ failure: 0.9% sodium chloride injection 250 ml + xuebijing injection 100 ml - 2 times a day.
Shen fu injection	Radix et Rhizoma rubra ginseng and aconiti lateralis radix praeparata extract	Septic, hemorrhagic and dehydrating shock	Uncertain	Shock: injection of 0.9% sodium chloride - 250 ml + injection of 100 ml Shenfu 2 times a day.
Shengmai injection	Ginseng Radix et Rhizoma rubra , Ophiopogonis Radix and Schisandrae chinensis Fructus	Septic shock, coronary heart disease, angina, epidemic hemorrhagic fever, arrhythmia	Allergic rash, back pain	Immunosuppression: glucose injection 250 ml + Shengmai injection 20-60 ml 2 times a day.
Re-injection	Artemisiae annuae Herba , Lonicerae japonicae Flos and Gardeniae Fructus	Upper respiratory tract infection	Individual patients may experience dizziness, chest tightness, dry mouth, diarrhea, nausea, and vomiting. Occasional allergic reactions, such as redness, itching, or a rash all over the body.	Viral infection or combined mild bacterial infection: injection of 0.9% sodium chloride 250 ml + repeated injection of 20 ml 2 times a day
Tanrecin for injections	Scutellariae Radix , Pulvis fetis Ursi , Goat horn , Lonicerae japonicae Flos and Forsythiae Fructus	Acute bronchitis, acute pneumonia (early stage)	Allergies, anaphylactic shock, dizziness, nausea, vomiting, itching, rash, high fever, heart and kidney function disorders, etc.	Viral infection or combined mild bacterial infection: 0.9% sodium chloride solution for injection 250 ml + Tanrecin injection 40 ml 2 times a day
Xingnaojing injection	Moschus , Gardeniae Fructus , Curcumae Radix and Borneolum Syntheticum	Epidemic encephalitis B, hepatic coma	Accidental allergic reactions, including itching, rash, and fever. Sometimes there are adverse symptoms such as tightness in the chest, belching, rapid	High fever with impaired consciousness: 0.9% sodium chloride solution for injection 250 ml + injection Xingnaojing 20 ml 2 times a day.

			breathing and rapid heartbeat.	
Shenmai injection	Ginseng Radix et Rhizoma rubra and Ophiopogonis Radix	Shock, coronary heart disease, viral myocarditis, chronic tuberculosis disease, granulocytopenia.	Occasional allergic reactions, such as palpitations, shortness of breath, tightness in the chest, redness of the face, etc. Sometimes anaphylactic shock, shortness of breath, and heart failure.	Immunosuppression: 250 ml glucose injection + 100 ml Shenmai injection twice a day

However, the authors point out that the clinical use of the above-mentioned medicines of traditional Chinese medicine requires special attention to contraindications to medicines (Pan et al., 2020).

Discussion

Next, we think, it necessary to consider the effectiveness and results of clinical trials of some of the drugs presented above. 1. Lopinavir / ritonavir. Initially, this drug was mainly used for the treatment of human immunodeficiency virus (HIV) infection in adults and children over 2 years of age. In vitro studies have shown that lopinavir and ritonavir can reduce SARS-CoV and MERS-CoV levels (Li et al., 2020). Based on the results of significant clinical benefits of lopinavir and ritonavir in patients with SARS-CoV infection, scientists have suggested that this drug may be effective in patients with SARS-CoV-2 infection (Li et al., 2020). The team from Zhongshan University built a structural model of two new coronavirus proteases-coronavirus endopeptidase C30 and papain-like protein using homology modeling and docked lopinavir / ritonavir with protease models, respectively. The results showed that lopinavir and ritonavir are more easily combined with coronavirus endopeptidase C30 compared to pa-pain-like enzymes that exhibit excellent effects against SARS-CoV-2 (Coperchini et al., 2020). However, after using lopinavir / ritonavir tablets, 40 patients diagnosed with COVID-19 in 29 cases experienced adverse reactions associated with lopinavir / ritonavir, such as increased triglyceride levels, nausea, and diarrhea (Russell et al., 2020). Therefore, larger clinical trials of this drug should focus on its safety.

2. Ribavirin. It is a broad-spectrum antiviral drug that can be phosphorylated in red blood cells to form ribavirin monophosphate, diphosphate, and triphosphate. Ribavirin monophosphate is a strong inhibitor of inosinemonophosphatedehydrogenase, which can inhibit the synthesis of guanylatephosphate in cells, reduce the level of guanylate triphosphate in cells, and block the synthesis of viral nucleic acids. Ribavirin triphosphate inhibits influenza virus RNA-polymerase, thereby preventing virus replication (Zhang et al., 2020). Ribavirin has been shown to inhibit SARS-CoV replication in five different cell types obtained from animals or humans in therapeutically achievable concentrations (Zhang et al., 2020). However, when using ribavirin, some side effects should be noted. For example, 61% of patients developed hemolytic anemia, 58% hypocalcemia, and 46% hypomagnesemia in 110 SARS patients treated with ribavirin [14]. Taking into account the effectiveness of ribavirin in the treatment of diseases caused by SARS-CoV and MERS-CoV, it is expected to be an effective drug for the treatment of COVID-19. However, the effectiveness of ribavirin for the treatment of COVID-19 is still controversial, which are needed for further confirmation in clinical trials.

3. Chloroquine. Chloroquine is an anti-malarial and anti-inflammatory agent that has been widely used in the treatment of malaria and rheumatoid arthritis for more than 70 years. The antimalarial effect of chloroquine can interfere with replication and transcription of Plasmodium schizonta DNA or interfere with its endocytosis, which leads to the death of the parasite due to amino acid deficiency. Chloroquine also has an immunomodulatory activity that can synergistically enhance antiviral effects (McGonagle et al., 2020). Several consecutive clinical trials have now been announced. The results of an open non-randomized clinical study showed that hydroxychloroquine

is significantly associated with a decrease or disappearance of the viral load in patients with COVID-19 (Ulhaq, 2020). Similarly, another randomized clinical trial also confirmed the effectiveness of hydroxychloroquine against COVID-19, which is shown to reduce the recovery time of body temperature and the time of remission from cough in patients with COVID-19 (Ulhaq, 2020).

Preliminary data from a multicenter prospective observational study showed that the average time to undetectable viral RNA was shorter for chloroquine than for non-chloroquine, and no serious adverse reactions were observed in the chloroquine group (Levi et al., 2020). In contrast, the results of some clinical studies have shown negative results of treatment WITH covid-19 with chloroquine or hydroxychloroquine. For example, an open randomized controlled trial showed that hydroxychloroquine did not lead to a higher probability of negative conversion than applying a single standard of treatment in patients with mild to moderate COVID-19, and side effects, especially diarrhea, were higher after taking hydroxychloroquine (Zhang et al., 2020).

4. Arbidol. Arbidol inhibits the fusion between the viral envelope and the cell membrane of target cells, thereby preventing the virus from entering target cells (Snijder et al., 2006). Arbidol is often used to counter flu viruses in Russia and China, which is not yet approved for sale in other countries. In vitro and in vivo studies have shown that Arbidol has antiviral activity against influenza virus, RSV, rhinovirus, Coxsackie virus, Coxsackie B5 virus, and adenovirus (Snijder et al., 2006).

Previous research has shown that Arbidol can inhibit RNA viruses and filoviruses such as SARS-CoV and MERS-CoV. Chinese scientists have found that Arbidol can effectively suppress the pathological effects of SARS-CoV-2 at a concentration of 10 ~ 30 μmol / l with a 60-fold viral load in vitro by screening various antiviral drugs. Currently, two RCCT have been initiated to evaluate the efficacy and safety of Arbidol in the treatment of COVID-19 in China.

5. Favipiravir. Favipiravir is a viral RNA polymerase inhibitor that action can be mediated by its metabolite ribofuranosyl-5' - triphosphate (RTP), which inhibits the activity of influenza virus RNA polymerase. Favipiravir was urgently used, which demonstrated a good inhibitory effect on the Ebola virus in 2014 (Senanayake, 2020). Despite its relatively modest antiviral activity, favipiravir can completely inhibit the replication of mouse norovirus (MNV) at a concentration of 100 micrograms / ml with or without minor side effects on cells (cell survival> 80%) [20]. Favipiravir was officially approved by the Chinese medical products administration for marketing and officially launched into production in China. Favipiravir is the first approved drug with a potential therapeutic effect for COVID-19 in China, which will play an important role in the prevention and control of SARS-CoV-2 infection (Senanayake, 2020).

6. Remdesivir. It has a strong antiphilovirus effect in vitro and a certain anti-coronavirus effect due to the inhibition of RNA-dependent RNA synthetase in experiments on animals. Subsequent studies have shown that remdesivir is not only effective against Ebola virus, but also suppresses respiratory syncytial virus, coronavirus, Nipah virus, and Hendra virus (Devaux et al., 2020).

Researchers reported that the first patient with COVID-19 in the United States recovered after treatment with remesivir (Devaux et al., 2020). In November 2019, the results of a phase II clinical trial showed that 175 out of 681 Ebola patients were treated with remdesivir after 29 serious adverse reactions, only one of which was associated with remdesivir (Schlagenhauf et al., 2020).

Preliminary results of a clinical study conducted by the National Institute of Allergy and Infectious diseases (NIAID) in the United States showed that patients treated with remdesivir had a 31% faster recovery time than patients treated with placebo, indicating a significant positive effect of remdesivir on reducing the recovery time of patients with COVID-19 (Schlagenhauf et al., 2020). However, a randomized double-blind placebo-controlled multicenter clinical trial conducted by Chinese scientists showed that remdesivir does not accelerate recovery and does not reduce mortality in patients with severe COVID-19 compared to the placebo group. The rate of early discontinuation due to side effects, including nausea, vomiting, and cardiopulmonary failure, was higher in the remdesivir group than in the placebo group (11.6% vs. 5.1%). Although this is the first quality clinical trial of remdesivir in the treatment of COVID-19, only 237 samples are included in the clinical

trial. Consequently, the antiviral efficacy and safety of remdesivir still need to be confirmed by higher-quality clinical trials with larger samples (Levi et al., 2020).

7. Rapamycin. This drug is one of the new drugs offered for the treatment of COVID-19 today is rapamycin (Kalra et al., 2020). It is a macrolide immunosuppressant that inhibits mTOR. MTOR is a serine / threonine protein kinase that exists in the form of two protein complexes (mTORC1 and mTORC2) with different protein components and substrates (Kalra et al., 2020). MTORC1 is sensitive to rapamycin, as well as to environmental stimuli including amino acids, glucose, and oxygen, and is also known as a rapamycin-sensitive complex. MTORC2 acts below PI3K and is best described as an insulin / IGF-1 (insulin-like growth factor-1) signal effector (Husain & Byrareddy, 2020) and is known as a rapamycin-insensitive complex. MTORC1 controls protein synthesis, autophagy, and many other cellular processes by phosphorylating the ribosomal protein S6, p70S6K, and 4E-BP1, whereas mTORC2 is necessary for maximum activation of many kinases, including AKT (protein kinase B) (Husain & Byrareddy, 2020).

Target proteins, mTOR, and related rapamycin pathways are widely expressed in almost all eukaryotic organisms, and also regulate proliferation, transcription, autophagy, metabolism, and programmed cell death (Pandey et al., 2020). Based on scientific evidence and due to the involvement of mTOR in the regulation of pathways related to cellular metabolism, proliferation, aging, and immune regulation, here we describe the potential for drug reprofiling that may allow us to consider rapamycin as a drug candidate for the treatment of COVID-19 (Liu et al., 2020).

Traditional Chinese medicine products should also, in our opinion, receive more extensive study due to their ability to resist COVID-19. Chinese herbal recipes refer to a recipe consisting of two or more components for the treatment of a relatively specific disease and syndrome, which has a relatively prescribed treatment method and method of use. Each herb in the Chinese herbal compound recipe has a specific medicinal effect that interacts with each other to enhance the therapeutic effect or reduce toxicity and side effects. Recipes of Chinese herbal mixtures are widely used in clinical practice, which in general has a complex effect on the broad-spectrum antibacterial, antiviral and immune functions.

Conclusion

In a relatively short period of time, a significant amount of research has been conducted to better understand the structure of SARS-CoV-2 and the impact of this virus on human health in order to develop effective countermeasures. Using information about viral proteins, several research groups are developing vaccines and medicines. Some of these therapeutic and prophylactic drugs are currently undergoing clinical trials. It is expected that vaccines and medicines will be found that will reduce the global damage to public health caused by this virus (https://www.fda.gov).

China has some experience in the prevention and treatment of SARS-CoV-2 infection using the above-mentioned medicines, including chemicals, traditional Chinese medications and biological products. Although these drugs are expected to be specific medicines for the treatment of COVID-19, caution should be exercised when taking these drugs without sufficient evidence of their effectiveness and safety. These potential medications are currently being used to treat COVID-19 in many countries and regions due to the COVID-19 outbreak. The main characteristics of these drugs, including pharmacological effects, indications, and adverse reactions, and especially progress in the treatment of COVID-19, should be understood in order to promote reasonable medications and guide further basic research and clinical trials.

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