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REVIEW

Safety and Efficacy of Antiviral Drugs for the Treatment of COVID-19: A Systematic Review

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Objective: To investigate the efficacy and safety of antiviral drugs in the treatment of coronavirus disease 2019 (COVID-19).

Methods: All clinical trials of antiviral drug treatment for COVID-19 from December 2019 to December 2021 in CNKI, PubMed, Embase, Wanfang and VIP databases were searched by computer, and the results were systematically reviewed.

Results: A total of 21 studies were included, including 5 randomized controlled studies, 5 non-randomized controlled studies, 3 retrospective cohort studies, 6 retrospective case series studies, and 2 observational studies, with a total of 2118 patients. The evaluated drugs included Ridzevir, Lopinavir/Ritonavir, Jingluwa, Fapiravi, Abidor, Danorivir, and interferon α. The evaluated antiviral drugs did not show superior efficacy for COVID-19 in clinical trials. In terms of safety, particular attention needs to be paid to the gastrointestinal side effects of lopinavir/ritonavir and the serious side effects of redsivir.

Conclusion: There is no specific drug. Antiviral drugs have a greater therapeutic benefit for mild and usual patients, and in severe patients, lopinavir/ritonavir may not be effective. For critically ill patients, adefovir or more than two antiviral drugs can be used early. Antiviral drugs combined with traditional Chinese medicine treatment is effective. In view of the safety of the drug, it is necessary to consider the increase of serum uric acid caused by fapravi, the increase of bilirubin caused by abidol, and the gastrointestinal reactions of pitavir. In addition, other adverse reactions should also be noted.

Keywords: COVID-19, safety, antiviral drugs

Introduction

Coronavirus Disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread in many countries and regions around the world since 2019. At present, more than 250 million people have been infected and millions have died. Although vaccination and isolation of patients have been implemented in various countries, more than 100,000 new patients are added daily. Previous studies have shown that about 19% of COVID-19 patients develop into severe or critical diseases,[1] and the mortality rate is more than 15%.[2] In addition to severe lung injury and functional changes, patients will also lead to complications such as liver, nervous system and gastrointestinal tract. Single drug may not achieve therapeutic effect. At the same time, the combined use of multiple drugs will increase the risk of drug interactions, resulting in reduced or increased drug exposure, affecting the efficacy and safety of treatment. Therefore, drug selection and diagnosis and treatment plan determination have great challenges.[3] Treatment of COVID-19 has not yet been defined. Early antiviral therapy is based on the experience of fighting SARS and MARS, and a large number of clinical trials are carried out to verify the efficacy of drugs.[4] China National Health Commission has issued eight editions of new coronavirus pneumonia diagnosis and treatment programs. Interferon, lopinavir/ritonavir, ribavirin, chloroch and abidol are among the recommended drugs for the treatment programme.[5] Currently, according to various versions of our pneumonia treatment protocols and studies for novel coronavirus infections,[6] antiviral drugs such as ribavirin, abirater and lopinavir are included in the treatment of COVID-19 in China. Redsivir is currently in clinical trials and has not been put into use on its own, but only as an

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adjuvant drug in conjunction with it. NIH guidelines indicate that the antiviral drugs currently available as therapeutic agents in the US are Redsivir, Paxlovid and Monupivir. Meanwhile, after two years of clinical research and practice, more relevant results have been published. Although there are many reviews that have done the same work we have done, searching for and summarising the effectiveness and safety of antiviral drugs, the main drugs analysed and the focus of each review varies and does not provide a detailed summary of the effectiveness and safety of all drugs, and over time, new characteristics of the physicochemical properties of some drugs are identified. In order to obtain a more comprehensive and higher level of research evidence, this article systematically evaluates the efficacy and safety of antiviral drugs for the treatment of COVID-19 based on published clinical findings. This review adds to certain aspects of drugs and medications not summarised in other reviews and is helpful in how antiviral drugs are used to treat neocrown pneumonia.

Research Materials and Methods

Literature Retrieval Strategy

All the research literatures on antiviral drug treatment COVID-19 from December 2019 to December 2021 in CNKI, PubMed, Embase, Wanfang and VIP databases were searched by computer. Chinese search terms include: novel coronavirus, novel coronavirus pneumonia, novel coronavirus, novel coronavirus pneumonia, COVID-19, antiviral, antiviral therapy, treatment, research, trials, clinical trials. Keywords: COVID-19 (Mesh), 2019-nCo V, SARS-CoV-2, treatment, treatment, clinical observation, antiviral therapy, antiviral.

Standards for Inclusion and Exclusion of Literature

Inclusion criteria: (1) Confirmed cases according to the ninth edition of the Guidelines for the Diagnosis and Treatment of New Coronavirus Pneumonia: suspected cases also have one of the following etiological or serological basis: 1) positive nucleic acid detection of new coronavirus; 2) positive specific IgM antibody and IgG antibody of new coronavirus in those who are not vaccinated with new coronavirus vaccine.

(2) Use antiviral therapy, and describe the clinical outcome; (3) A complete description of the treatment plan with major efficacy or safety outcomes; (4) It is a prospective or retrospective Chinese or English study published in public. The research types include randomized controlled trials (RCT), non-randomized controlled trials (N-RCT), case-control studies, and cohort studies.

Exclusion criteria: (1) Traditional Chinese medicine, immunotherapy as the main treatment; (2) Summary, case report; (3) Patients are diagnosed as suspected cases; (4) Selective reporting results; (5) Studies describing clinical features.

Literature Evaluation

The literature retrieved by two researchers independently read and evaluated, and the literature was screened according to the inclusion and exclusion criteria, such as the controversial introduction of the third researcher to discuss and decide.

Information Extraction

Extract the final information included in the literature. The contents included: (1) Basic information: research area, time, author; (2) Baseline special diagnosis of the subjects: age, disease type, number of cases, number of shedding cases; (3) Research program: research type, research program, course of treatment; (4) Outcome indicators: treatment efficacy, death, adverse reactions.

Results

Literature Retrieval Results

A total of 1508 articles were retrieved, 273 articles with similar contents were excluded, 1059 articles were excluded after reading topics and abstracts, and 155 articles were excluded after further reading. A total of 21 articles were included.[7–25] The results of literature retrieval included 12 Chinese and 9 English, including 5 randomized controlled

studies (RCT), 5 non-randomized controlled studies (N-RCT), 3 retrospective cohort studies, 6 retrospective case series studies, 2 observational studies, and a total of 2118 cases. The results are shown in Table 1.

Effectiveness of Antiviral Therapy

Lopinavir/Ritonavir

Two RCTs evaluated the efficacy of lopinavir/ritonavir on COVID-19 with inconsistent results.[7,8] Both lopinavir/ritonavir and control were administered at 400mg/100mg, po, bid. Lopinavir/ritonavir did not show obvious advantages in severe patients, and the median clinical improvement time was similar to that in the conventional treatment group (16d vs 16d, $P>0.05$). The 28d mortality rate was 5.8% lower than that in the conventional treatment group.[7] However, RCTs conducted in ordinary patients showed that the addition of Lopinavir/ritonavir on the basis of interferon-α and lianhuaqingwen capsule could improve the treatment efficiency (76.67% vs 46.67%, $P< 0.05$), but the sample size of this study was small.[8] Another N-RCT compared the efficacy of lopinavir/ritonavir versus fapiravir in the treatment of mild and common COVID-19. There were 35 patients in the FPV group and 45 patients in the control group, and the drug was administered as falopir 1600 mg, po, bid on day 1, 600 mg, po, bid on day 2–14, and lopinavir/ritonavir 400 mg/100 mg, po, bid. Changes in chest computed tomography (CT), viral clearance and drug safety were compared between the two groups, with 32 in the FPV group and 28 in the control group. Fapiravir was superior to lopinavir/ritonavir in median virus clearance time (4d vs 11d, $P<0.001$) and lung CT improvement at 14d (91.43% vs 62.22%, $P=0.004$).[9] Lopinavir/ritonavir was used in four case series studies.[10–12] There were 83 cases in total. No patient died, only 1 case developed into severe disease, and 3 cases were transferred to hospital.

Hydroxychloroquine

In one RCT, subjects were treated with 1200 mg/d for 1 to 3 days followed by 800 mg/d for 2–3 weeks. The RCT showed that there was no significant difference in virus negative conversion rate between hydroxychloroquine group and standard nursing group on day 28 (85.4% vs 81.30%, $P=0.314$), but the use of hydroxychloroquine could significantly improve clinical symptoms such as fever and cough.[13] The efficacy of hydroxychloroquine for COVID-19 in a small sample of N-RCT at 400 mg, po, qd, was similar to that in the conventional treatment group, and the median time of virus negative conversion was longer than that in the control group (4d vs 2d, $P>0.05$). One case in the hydroxychloroquine group developed into severe disease.[12] Another N-RCT compared the clinical outcomes of patients with COVID-19 who were treated with hydroxychloroquine plus azithromycin, hydroxychloroquine alone and untreated. Hydroxychloroquine is administered as 200 mg, po, bid, with azithromycin added as clinically indicated, 500 mg on day 1 and 250 mg daily for the next 4 days, with virus negative conversion rates of the three groups on the sixth day were 100%, 57.1% and 12.5%, respectively ($P<0.001$). The use of azithromycin could significantly improve the clearance effect of hydroxychloroquine on viruses, and the two had synergistic effects.[12] In view of the results of this study, another retrospective cohort study based on the data of the U.S. Veterans Health Management Center included 368 patients with COVID-19, and also compared the mortality and mechanical ventilation ratio of patients with COVID-19 who were treated with azithromycin, with or without hydroxychloroquine. The results showed that hydroxychloroquine did not reduce the mechanical ventilation ratio (6.9% vs 13.3% vs 14.10%, $P=0.547$), but increased the mortality (22.1% vs 27.8% vs 11.40%, $P=0.03$).[14] The use of azithromycin can reduce the proportion of mechanical ventilation and mortality.

Arbidol

In an RCT comparing the efficacy of abirater and lopinavir/ritonavir in the treatment of mild to moderate COVID-19, lopinavir/ritonavir was administered at 400mg/100mg, po, bid and abirater at 0.2g, po, tid. The RCT showed no significant difference in viral clearance time and viral clearance rates on days 7 and 14.[15] A small sample retrospective cohort study showed that the virus clearance rate on the 7 th and 14 th day and chest CT performance on the 7 th day were significantly improved in the combination of Abidol and Lopinavir/Litonavir compared with Lopinavir or Litonavir alone ($P<0.05$).[16] Another RCT compared the efficacy of abidol with that of fapravi. A total of 240 patients were randomly assigned in a 1:1 ratio to receive treatment. In the trial, fapravi was administered at 1600 mg, po, bid on day 1 and 600 mg, po, bid on day 2–10, while abidol was administered at 0.2 g, po, tid. There was no difference in the recovery

Table 1 Characteristics of the Included Studies

Reference	Region	Research Type	Age of Patients	Disease Classification	Number of Cases in Trial/ Control	Number of Deaths	Treatment	Course
[6]	China	RCT	58±10	Severe	199 (99 vs 100)	44	Test group: lopinavir/ritonavir 400mg/100mg, po, bid; control group: conventional treatment.	14
[7]	China	RCT	28~69 vs 29~68	Moderate	60 (30 vs 30)	0	Test group: α-interferon 5 million IU aerosol inhalation, bid + Lianhua Qingwen capsule 4 tablets, po, tid + lopinavir/ritonavir 2 tablets, po, bid; control group: no use of lopinavir/ritonavir, other with experimental group.	7~10
[8]	China	N-RCT		Mild and Moderate	80 (35 vs 45)	0	Test group: fapiravir 1600 mg, po, bid on day 1, 600 mg, po, bid on day 2–14; control group: lopinavir/ritonavir 400 mg/100 mg, po, bid.	14
[12]	China	N-RCT	8.0±14.1 vs 44.1±15.0	Mild and Moderate	150 (75 vs 75)	0	Test group: hydroxychloroquine 1200 mg/d on 1~3 days, then 800 mg/d, 2–3 weeks of treatment; control group: standard nursing	14~21
[11]	China	N-RCT	50.5±3.8 vs 46.7±3.6	Moderate	30 (15 vs 15)	0	Test group: hydroxychloroquine 400 mg, po, qd; control group: conventional treatment.	5
[14]	France	N-RCT	5.1±22.0	Non classification	42 (26 vs 16)	1	Test group: hydroxychloroquine 200 mg, po, tid (6 patients also received azithromycin: 500 mg, po, qd on day 1; 250 mg, po, qd on day 2–5); control group: no treatment or no use of the above treatment regimen.	10
[13]	USA	Retrospective cohort	68 (59~74) vs 70 (60~75) vs 69 (59~75)	Non classification	368 (113 vs 97 vs 158)	70	Group 1: hydroxychloroquine + azithromycin; group 2: hydroxychloroquine; Group 3: no use of hydroxychloroquine (50 of them used azithromycin).	-
[15]	China	N-RCT	49.4 (19 ~ 79)	Mild and Moderate	86 (34 vs 35 vs 17)	0	Group A: lopinavir/ritonavir 400mg/100mg, po, bid; group B: Abidol 0.2g, po, tid; group C: no antiviral drugs.	7~14
[16]	China	Retrospective cohort	4.56±15.7	Mild	33 (16 vs 17)	0	Test group: abidol 0.2 g, po, q8h + lopinavir/ritonavir 400 mg/100 mg, po, q12h; control group: lopinavir/ritonavir 400 mg/100 mg, po, q12 h; treatment to PCR for 3 consecutive negatives.	5~21
[17]	China	RCT	70.3% < 65 years	Moderate 88.6%, Severe and Critical 11.4%	240 (120 vs 120)	0	Test group: fapiravir 1600 mg, po, bid on day 1, 600 mg, po, bid on day 2–10; control group: Abidol 0.2g, po, tid	10

[18]	China	Retrospective cohort	46.3 (2~18)	Mild 15 cases, Moderate 178 cases, Severe 15 cases, Critica 15 cases	224 (38 vs 137 vs 34 vs 7 vs 3 vs3 vs 1 vs 1)	0	Group 1: INFα+ ribavirin; group 2: INFα+ lopinavir/ritonavir; group 3: INFα+ lopinavir/ritonavir + ribavirin; group 4: INFα; group 5: INFα+ arbidol; group 6: Darunavir cobicistat + arbidol; group 7: INFα+ darunavir cobicistat; group 8: Arbidol + ribavirin	5~21
[19]	China	RCT	45.12±2.15 vs 51.32 ±5.29	Mild 4 cases, Moderate 26 cases, Severe 7 cases, Critica 6 cases	62 (43 vs 19)	0	Control group: interferon α-2b, 5 million U, atomizing inhalation, twice a day; abidol, 200 mg/time, 3 times/d, orally; ribavirin, 500 mg/time, 1time/d, intravenous infusion; lianhuaqingwen capsule, 4 grains/time, 4 times/d, orally. Treatment group: Patients were treated with lopinavir/ritonavir on the basis of routine treatment in the control group. The specifications were 200 mg/50 mg, 2 tablets/time, twice daily, orally, for 7 days.	-
[20]	China	Retrospective case series	44 (34, 53) vs 47.43 ±16.26	Non classification	294 (147 vs 147)	0	Treatment group: FPV 1600 mg, twice a day, then 600 mg, twice a day, for 9 days; control group: Chinese medicine, nutritional support, oxygen inhalation, etc.	22~44
[21]	China	Observational studies	44 (18~66)	Moderate	11	0	Danovavir 100 mg, po, bid + ritonavir 100 mg, po, bid (6 patients also received IFN-α, 5 million IU aerosol inhalation, bid)	4~12
[22]	China	RCT	66 (57~73) vs 64 (53~70)	Severe	237 (158 vs 79)	32	Test group: Redsivir 200 mg, ivgtt, qd on day 1, 100 mg, ivgtt, qd on day 2–10; control group: same dose of placebo	10
[23]	Multi-national	Observational studies	64 (48~ 71)	Severe and Critical	61	7	Redsivir 200 mg, ivgtt, qd, day 1, 100 mg, ivgtt, qd, days 2–10	10

rate and time to viral regression in the Arbidol group, with 71 recoveries out of 116 in the Favipiravir group and 62 recoveries out of 120 in the Arbidol group, but fapravi had obvious advantages in relieving clinical symptoms such as fever and cough, and the improvement time was 1.7 days shorter than that of abidol ($P<0.001$).[17]

Interferon-α

A retrospective analysis of 224 patients with COVID-19 showed that there were no significant differences in the negative conversion time of viral nucleic acids in respiratory tract specimens, the negative conversion rate of viral nucleic acids within 14 days, the proportion of progression to severe disease after admission and the overall incidence of adverse reactions between multiple treatment regimens (interferon-α alone, interferon-α + lopinavir/ritonavir, interferon-α + ribavirin, interferon-α + lopinavir/ritonavir + ribavirin, other solutions) ($P>0.05$).[18] A N-RCT study included 62 patients with COVID-19, and the results showed that there was no significant difference in fever clearance time, symptom relief time, nucleic acid negative conversion time and hospitalization time between the treatment group and the control group ($P>0.05$). In the severe group, the nucleic acid negative conversion time in the treatment group was significantly longer than that in the control group [(23.62 ± 2.12)d vs (9.25 ± 0.95)d], and the difference was statistically significant ($P<0.05$).[19]

Faviraway

A retrospective analysis examined the efficacy of favipiravir (FPV) in the treatment of COVID-19.[20] Experimental group was famipiravir at 1600 mg, twice a day, then 600 mg, twice a day, for 9 days and control group was herbal medicine, nutrition and oxygenation. The results showed that there was no significant difference in hospitalization time between the treatment group (29 (24, 39)d) and the control group (32 (22, 44)d)(=0.575). The median time of novel coronavirus nucleic acid negative conversion was 25 (18, 33) d in the treatment group and 25 (13, 40) d in the control group ($P=0.982$). The incidence of severe disease in the treatment group was significantly lower than that in the control group (6.12% vs 21.77%), and the difference was statistically significant ($P=0.000$). The chest CT remission time of the treatment group (9.38 ± 4.94) d was shorter than that of the control group (13.44 ± 4.67)d, and the difference between the two groups was statistically significant ($P= 0.033$).

Danorevir

An observational study that included only 11 patients with COVID-19 common type showed that the combination of danorrvir and ritonavir had better curative effect.[21] The median time of virus negative conversion was 2 days, and the median time of lung CT obvious absorption was 3 days. All 11 patients were cured and discharged.

Redsieve

In a national multicentre randomised double-blind placebo-controlled trial, patients were randomly allocated in a 2:1 ratio to either intravenous raltegravir (200 mg on day 1, followed by 100 mg on days 2–10 as a single daily infusion) or the same volume of placebo for 10 days. A total of 237 patients were enrolled, 158 receiving raltegravir and 79 receiving placebo. The results showed that there was no significant difference in the clinical improvement time of patients with severe diseases between Redsivir and placebo, which were 21 d and 23 d, respectively. The mortality rates of the two groups were also close, which were 14% and 13%,[22] respectively. Another observational study of international multi-center patients with severe COVID-19 sympathizing with the use of Redsivir showed that 68% of 53 patients had clinical improvements, 57% had extubation, 47% were discharged and 13% died.[23]

Safety of Antiviral Therapy

Thirteen studies described adverse events.[7,11–13,15–19,22–24] Among the three RCTs, the incidence of adverse events in the lopinavir/ritonavir group was 35.3%, 48.4% and 55.56%,[6,15,24] respectively, mainly gastrointestinal reactions. Another retrospective cohort study using lopinavir/ritonavir also reported gastrointestinal dysfunction in 43.7% of patients.[16] Severe gastrointestinal adverse reactions caused by lopinavir/ritonavir led to withdrawal of 13% of patients in one study. In a case series of only 10 patients, 30% of patients stopped taking lopinavir because of gastrointestinal discomfort.[11]

There was no significant difference in the overall incidence of adverse reactions among different antiviral regimens in the comparison of one antiviral treatment for COVID-19 (P=0.080), but there was significant difference in the incidence of nausea/vomiting, diarrhea and dyslipidemia among different regimens ($P < 0.05$).[18] The incidence of gastrointestinal adverse reactions and dyslipidemia in patients receiving three antiviral drugs were significantly higher than those receiving 1–2 antiviral drugs (P<0.05). Another study also showed that Lopinavir/Rituximab combined with interferon-α antiviral therapy could cause higher incidence of diarrhea.[19]

In addition to Lopinavir/Ritalinavir, the safety of Redsivir needs to be paid attention to. The total incidence of adverse events in the two studies was 66% and 60%, respectively, and the incidence of severe adverse events was 18% and 12%, respectively, including multiple organ dysfunction, septic shock, acute kidney injury and hypotension, which led to the withdrawal of 18 patients (12%) and 4 patients (7.5%),[22,23] respectively. Other reported adverse events included nausea caused by light chlorine chirp (one patient was discontinued), diarrhea, and elevation of transaminase, elevation of serum uric acid caused by fapravi, and elevation of bilirubin caused by abidol.

Discussion

At present, the epidemic of COVID-19 is globalized, but there is no evidence-based medical evidence to support antiviral drugs for new coronaviruses. Therefore, it is extremely important to explore effective treatment regimens as soon as possible to control the epidemic.

Lopinavir/ritonavir is one of the earliest recommended antiviral drugs. Multiple controlled trials showed that the clinical efficacy of lopinavir/ritonavir on COVID-19 was poor, but it caused serious gastrointestinal adverse reactions, so the proportion of withdrawal could reach 13%. The adverse reactions of lopinavir/ritonavir mostly occurred in the early stage of medication, and the recommended course of treatment for COVID-19 was 10 days. The risk of adverse reactions at this stage was high, and medication safety should be closely monitored. Ritonavir is a potent CYP3A4 inhibitor and also inhibits P-glycoprotein transporters. Lopinavir is also a substrate of CYP3A and P-glycoprotein, which can interact with many drugs and cause adverse reactions.[9] For COVID-19 patients with more complications, drug interactions should be examined before starting the use of lopinavir/ritonavir to avoid serious adverse reactions.

Chloroquine is also used in the treatment of COVID-19 as an old antimalarial drug. In addition to the recommended treatment plan in China, the FDA also approved that chloroquine and hydroxychloroquine can be used in adult and adolescent COVID-19 inpatients with body weight greater than 50 kg in emergency situations.[25] Based on published research data, whether chloroquine or light chloroquine has curative effect on COVID-19 and whether use increases mortality remains unclear. The synergistic effect of azithromycin and hydroxychloroquine also needs further clinical trials to verify. The American Society of Infectious Diseases recommended the application of chloroquine and hydroxychloroquine in clinical trials in the COVID-19 Guidelines for Treatment and Management, while the addition of azithromycin can only be used in clinical trials, and it is not recommended as a conventional treatment.[26] The safety of chloroquine and hydroxychloroquine in clinical use is also concerned, which can often cause gastrointestinal reactions, skin allergy, and serious liver and kidney function and cardiac dysfunction. Conditional medical institutions can monitor the plasma concentration. When the plasma trough concentration is greater than 0.8 μg/mL, the risk of adverse reactions increases, and it is recommended to reduce the dose. Clinical trial data showed that hydroxychloroquine 600 mg daily, taken three times, the plasma concentration was (0.46 ± 0.2) μg/mL, the dose was relatively safe.[12]

The rapid recovery of the first confirmed patient in the United States was benefited from the treatment of adefovir, making adefovir one of the most concerned drugs that may have special effects on COVID-19. However, the randomized double-blind placebo-controlled trial in critically ill patients in China did not find that Ridzevir had a stronger scavenging effect on SARS-CoV-2 than placebo.[22] The curative effect was more obvious after taking adefovir within 10 days of diagnosis, and the average clearance time of the virus was 5 days shorter than that of the placebo group. The results suggested that adefovir was suitable for early viral infection. If the diagnosis had been confirmed for more than 10 days, it would not only benefit little, but also face the high risk of serious adverse reactions and further aggravate the disease. Due to the effective control of the epidemic in China, the study failed to include the target number of subjects, reducing the statistical effectiveness of the data to some extent. The existing evidence can be supplemented when the results of randomized controlled trials (RCTs) ofvir abroad are published.

Based on the limited clinical trial results, the efficacy of fapravi, abidol and danorrvir on COVID-19 is not clear, and it needs to be further verified by high-quality, large-sample randomized controlled trials. In addition, when the three antiviral drugs are used in combination, they are most prominent in nausea, vomiting, diarrhea and other aspects. Considering that they are related to the combination of the three antiviral drugs, according to the "new coronavirus pneumonia diagnosis and treatment plan (eighth edition)" promulgated by the National Health and Health Commission of China, it is not recommended to use the three drugs in combination, and the more drugs are, the heavier the gastrointestinal burden is. The proportion of dyslipidemia in patients with interferon-α + lopinavir/ritonavir treatment was higher, which was considered to be related to the adverse reactions of lopinavir/ritonavir.[24] It is worth noting that there are many drugs in the treatment of (critically) severe patients, so the adverse reactions need to be considered due to other drugs except antiviral drugs, and the incidence of adverse reactions may be higher. However, some studies have found that compared with Mild and Moderate patients, the incidence of adverse reactions in (critically) severe patients has no significant increase, indicating that most of the adverse reactions may come from antiviral drugs.[18] Fortunately, most patients had mild clinical manifestations of adverse reactions.

The drugs discussed in this paper, such as abidol, pitavir, chloroquine, lopinavir/ritonavir, and interferon, have been marketed in China and approved for the treatment of new coronary pneumonia, and the currently carried out clinical trial for the treatment of COVID-19 is its new indication.[26] Abidol has currently registered five clinical trials of Abidol for the treatment of COVID-19 in five hospitals including the Second Affiliated Hospital of Chongqing Medical University.[27] The trial status of efaprevir is that the "Clinical Study on the Safety and Efficacy of Faprevir in the Treatment of Patients with CO V1D-19" currently cooperated by the National Emergency Prevention and Control Drug Engineering Technology Research Center and the Third People's Hospital of Shenzhen has been completed, and Hisun Pharmaceutical has obtained the marketing approval letter of efaprevir tablets approved by the China Food and Drug Administration based on the results of this clinical trial. A Phase II clinical study to explore the dose of fapiravir tablets in patients with usual COVID- 1 9 has been completed, but results have not been published.[26] Hydroxychloroquine At present, 19 clinical trials of chloroquine/hydroxychloroquine for the treatment of COVID-19 have been registered in 14 hospitals including Peking University First Hospital and the Second Affiliated Hospital of Chongqing Medical University. Lopinavir/ritonavir has been registered in 11 clinical trials using lopinavir/ritonavir for the treatment of COVID-19 in 9 hospitals including the Second Affiliated Hospital of Chongqing Medical University and the Fifth Affiliated Hospital, Sun Yat-sen University. At present, West China Hospital of Sichuan University and Wuhan Jinyintan Hospital have registered two clinical trials of interferon-alpha for the treatment of COVID-19 in the Chinese Clinical Trial Registry.[27] Ruidexivir has been marketed and used in the United States, European Union, Japan and other places, but in China, it is still in clinical trials. At present, Wuhan Jinyintan Hospital and China-Japan Friendship Hospital have registered two clinical trials on the use of repaglinide for the treatment of COVID-19.[27] Danorevir is mainly used for the treatment of hepatitis C. The highest study phase of the trial of danorevir in the treatment of new crowns is now the fourth phase,[28] and the Department of Infectious Diseases of the Ninth Hospital of Nanchang published a clinical study on the medRxiv preprint platform to investigate the therapeutic effect of danorevir combined with ritonavir in the treatment of COVID-19 pneumonia.[29]

In summary, there is no specific drug for COVID-19. Patients with mild and common types have greater benefits in treatment, and antiviral drugs combined with Chinese patent medicine have better curative effect and prognosis. The treatment of severe patients is difficult, and lopinavir/ritonavir may be ineffective. Ridzevir shows initial effect in the early stage of infection, but it still needs higher quality clinical trials to provide evidence. Fapiravir can significantly improve the clinical symptoms of mild to moderate patients such as fever and cough, which can further investigate the curative effect of severe patients.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

An ethics statement was not required for this study type, no human or animal subjects or materials were used.

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Disclosure

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