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**Title : Clinical trial analysis of 2019-nCoV therapy
registered in China**

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Accepted Article

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Abstract

So far, there is a lack of effective drugs for the new coronavirus pneumonia. With more and more patients diagnosed, China has carried out more than one hundred clinical studies of new coronavirus infection, including antiviral drugs, antimalarial drugs, glucocorticoids, plasma therapy, virus vaccine and other western drugs, while Chinese medicine researches accounted for half of studies. Most of the trials were initiated by investigators and the study period would last for one to eleven months. The primary endpoints included symptom improvement and virus nucleic acid turning negative, but the optimal endpoint has not been determined. Although the final results of studies will take a long time to complete, the interim research data may provide some help for the current urgent demand for drug treatment. Compared with that of during SARS period in 2003, China have the stronger capability to carry out clinical trials of new drugs in emergency period.

Keywords: new coronavirus pneumonia, China, new drugs, clinical trial

INTRODUCTION

Since the outbreak of the novel coronavirus (2019-nCoV), also known as novel coronary pneumonia (NCP) in January 2020, a number of clinical trials for treatment have been registered in China. Although the time span of study registration was less than two weeks (January 30, 2020 to February 12, 2020), subtle changes in the classification of registered trials could be seen from the development of the epidemic, including that the proportion of studies targeting critically ill patients had gradually increased in the latter period, and patients' physical and psychological rehabilitation had also received attention. Based on the current registered trials, together with

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epidemic situation in China and published literatures of 2019-nCoV, we made a preliminary assessment on the prospects of therapy for 2019-nCoV and the availability of drugs in the short term.

REVIEW OF CLINICAL STUDIES AND PUBLICATIONS

We used "novel coronavirus" to search in the Chinese Clinical Trial Register and "2019-nCoV" in clinicaltrials.gov. A total one hundred and seven clinical trials had been registered by Chinese researchers, of which ninety were registered in the Chinese Clinical Trial Register and seventeen in clinicaltrials.gov by February 14, 2020. Almost all trials were investigator-initiated. Most of trials involved clinical therapy and a small part of pathogenesis research. And eighty-seven trials were related to drug interventions. More than twenty trial were conducted in Wuhan, the most-severely-affected area (**FIGURE 1**). Most of them were short-term clinical trials, with the planned study period of one to eleven months, and about a quarter of them were within six months.

We used "novel coronavirus AND China" to search on Pubmed website by February 14, 2020, and a total of eighty-one literatures for 2019-nCoV were retrieved after excluding the results like news and comments. Most of the literatures were focusing on the description of epidemiology and clinical characteristics of 2019-nCoV, while studies of diagnosis (imaging, nucleic acid detection) and treatment were limited. In terms of diagnosis, seven literatures were published in Radiology to conduct Computed Tomography analysis for more than eighty patients to summarize the imaging characteristics of NCP¹. In addition, there were two literatures on nucleic acid detection of 2019-nCoV². It should be noted that no shortage of institutions for nucleic acid

detection and even a few of them had been approved by the government, however, the data to prove the sensitivity and consistency were still lacking. And the New England Journal published the first clinical evidence of tumor patients in the outbreak of 2019-nCoV, supporting that tumor patients may be more susceptible to infection due to the influence of malignant tumor, chemoradiotherapy, surgery and other factors on immune status³. In terms of treatment, no successful randomized controlled trial (RCT) had been published, which also reflected the bottleneck of current treatment. In general, finding effective targeted drugs remains an urgent work.

At Sever Acute Respiratory Syndrome (SARS) period seventeen years ago, our capacity to conduct clinical trial on drugs was still relatively weak in China, and there was also a lack of awareness and registration conditions for clinical trials. We attempted to retrieve the registered trials during SARS period from the first patient infected SARS-CoV in November 2002 to the complete end of the epidemic in July 2003, but failed. Therefore, only incomplete statistics based on literatures for SARS-CoV could be obtained. A total of fifty-four literatures of drug studies were retrieved⁴, of which 83% were retrospectively analyzed, with few prospective studies. The selection of the study drugs was similar to that of 2019-nCoV, with ribavirin, lopinavir, interferon and glucocorticoids as the main drugs. Vaccine studies were also launched; , however, the follow-up data were not reported.

Compared with that of in the SARS period, the ability and consciousness of carrying out clinical trials in China during the period of 2019-nCoV were significantly improved. Meanwhile,

the quality of clinical trials and the level of evidence will provide important evidence-based data for the clinical diagnosis and treatment for 2019-nCoV.

CLASSIFICATION OF EXPERIMENTAL DRUGS

The experimental drugs included western medicine, including antiviral drugs, antimalarial drugs, and biotherapy (interferon, stem cell therapy and immune regulation therapy, ect.), and traditional Chinese medicine, and studies of glucocorticoids and plasma also accounted for small proportion (**FIGURE 2 , TABLE 1**). The number of trials on traditional Chinese medicine was much huger than that of on the treatment of previous diseases, which meant that western medicine still lacked effectiveness in antiviral therapy. Almost all drugs were old, and most of them had already been brought to the market for other indications, and some drugs were in phase II clinical trials for infectious diseases caused by other viruses.

Prospective multicenter controlled studies for traditional Chinese medicine, like ShuangHuangLian and Lianhua Qingwen, have been conducted. At the same time, the trials of combining traditional Chinese and western medicine occupied a high proportion. Considering that 2019-nCoV might cause cytokine release syndrome (CRS), patients in the studies of traditional Chinese medicine could also receive western medicine which was very important therapy for them.

Antiviral drugs still drew the most of attention^{5,6}, including Remdesivir, ASC09, Lopinavir/Ritonavir, Arbidol, as well as the traditional biological agents such as interferon-alpha and thymosin alpha-1. At the same time, three studies for glucocorticoids were launched, and two

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of them recruited the patients with severe pneumonia. In addition, the traditional antimalarial drugs—Chloroquine and Hydroxychloroquine—were also widely studying.

It was encouraging that two important drugs registered clinical studies for NCP. As more and more evidence showed that the mechanism of severe pneumonia may be associated with CRS caused by virus infection, Tocilizumab, which was the most effective way to inhibit CRS in the Chimeric Antigen Receptor T-cell therapy, has been on the focus of recent academic discussion. A multicenter RCT for the efficacy and safety of Tocilizumab in the treatment of NCP has been registered at February 14, 2020. Simultaneously, the Wuhan Jinyintan hospital registered a trial to explore the efficacy of PD-1 inhibitor (Carrizumab)—a new drug for tumor treatment—for severe NCP with lymphocytopenia, and this was the first immune checkpoint inhibitor used in the study of NCP. The results of the two studies were very worthy of attention.

The studies for effects of plasma from recovered patients are ongoing, which is promising. Besides, vaccines are an effective way to prevent and reduce the harm of viruses⁷, and a number of pharmaceutical institutions around the world have started the researches for 2019-nCoV mRNA vaccine, which could enter clinical phase as early as April 2020.

In general, compared with that of in SARS period, there are more options for the treatment of 2019-nCoV, including more antiviral drugs, such as Remdesivir, ASC09 and Arbidol. Although previous studies had shown that Chloroquine could inhibit SARS-COV⁸, the conclusion remained at the cellular level study and have not entered the clinical stage. Besides, Tocilizumab and Carrizumab mentioned above might provide patients with more opportunities for treatment.

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THE AVAILABILITY OF DRUGS IN THE SHORT TERM FROM THE TIME OF CLINICAL TRIAL

Most of the trials will spend over a period of about one year (**TABLE 1**), which means that the results of these studies are likely to be of limited help in the current epidemic, with more value for prevention and treatment in the future. However, the epidemic situation is urgent and the number of patients is huge with a certain critically ill proportion. Therefore, the availability of effective experimental drugs in the short-term may be the most concerned. According to the retrieved data, more than twenty studies would be completed within six months, and some important drugs like Remdesivir, ASC09, Lopinavir, Ritonavir, Chloroquine and glucocorticoids might be completed within four months. The RCT of Remdesivir for Severe NCP and the mild to moderate NCP carried out by China-Japan Friendship Hospital respectively, were expected to be completed by the end of April or early May 2020 (**TABLE 1**).

If these trials could be completed on schedule or ahead of schedule with the endpoint achieved, significant impact would be made on the control and prognosis of 2019-nCoV. The First Affiliated Hospital of Zhejiang University School of Medicine carried out two open-label, multicenter RCT to evaluate and compare the safety and efficiency of ASC09/Ritonavir versus Lopinavir/Ritonavir and Baloxavir Marboxil versus Favipiravir versus Lopinavir-Ritonavir for confirmed cases of NCP respectively (**TABLE 1**). And the studies were expected to be completed with June 03, 2020 and May 31, 2020, respectively. Although the epidemic may be coming to an end at that time, the drugs could be approved for treatment in advance with the preliminary

effective results of the interim research (optimistic forecast at March 2020). At the same time, researchers have also carried out the trials for traditional Chinese medicine with a short study period, which might also provide preliminary efficacy and safety data and providing important options for clinical treatment.

Besides, it has been reported that Remdesivir, Chloroquine Phosphate and Farpiravir showed preliminary efficacy in clinical studies⁹, which is encouraging for medical staff and patients who are still in the critical stage of the epidemic.

DIFFERENCES IN OPTIMAL STUDY ENDPOINTS

There were significant differences in the primary endpoint selected in the retrieved studies, including improvement in clinical symptoms, negative nucleic acid detection, and survival, with no clear conclusion for which one of them was most appropriate. The two major concerns of antiviral therapy are certainly: one is prognosis of treatment: for mild to moderate patients, reducing critical illness rate is the primary objective; and for severe or critical illness patients, reducing mortality or improving recovery of pulmonary function matters more, which are indicators of efficacy that can be evaluated in the near future. The other is the rate and time for virus to turn to negative, which is related to patient's speed of recovery and prevention of the virus transmission. Therefore, improvement of clinical symptoms is more important to reduce the incidence of severe illness and mortality, and the detection of virus nucleic acid has a longer-term significance for reducing transmission. However, there were several cases reported that patients with turning negative virus nucleic acid detection after treatment became positive again. Therefore,

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the frequency and time interval of detection after turning negative need to be further discussed. If the frequency of detection is increased or the interval is prolonged, combined with the improvement of clinical symptoms, the disease progression could be more accurately estimated, and whether the patient still carries the virus and is infectious could be further determined.

In addition, in a public health emergency, the race against the epidemic forces us to consider an earlier effective endpoint of as a surrogate endpoint for mortality to accelerate the process of clinical trials. For example, two studies of Remdesivir (NCT04252664, NCT 04257656) used time to clinical recovery (TTCR) and time to clinical improvement (TTCI) as primary endpoint, respectively, instead of virus nucleic acid detection or survival status of sever patients. The former is based on the patient's body temperature, breathing rate, oxygen saturation, and the improvement of clinical symptoms; the latter is based on the time for improvement of the clinical status. And given the relatively low mortality rate of about 2% for NCP at present, the choices of endpoint were based more on recommendations for influenza drug researches, in which mortality is not the primary endpoint in most studies. Besides, TTCR or TTCI as a surrogate endpoint required smaller sample sizes than the other dichotomous endpoints (such as disease control rate). And it should be emphasized that the choice should be dependent on the opinions and decision of the clinical medicine.

Based on the analysis of the current situation of the epidemic in China, effective quarantine measures have been carried out throughout the country, however, a large number of patients are in urgent need of treatment with a significant proportion of critically ill patients. We support that

improvement of clinical symptoms and prognosis of disease should be used as the most important indicators to evaluate the short-term efficacy of experimental drugs. And once supported by interim research data, the drugs should be applied early.

Besides, the current severe illness rate is estimated to be about 15%. And it is unclear whether some of these patients will have long-term recovery problems such as impaired lung function or other organic functional injuries, which should be noticed and launch the trial to demonstrate.

To carry out a large number of clinical trials so rapidly is also worrying. Due to the urgency, the theoretical bases of some trials were needed to be discussed more comprehensively, and the designs might not be reasonable enough. Whether these factors will increase the risk of the patients is also a matter which should be treated with caution in the research.

Compared with the SARS epidemic period seventeen years ago, China had stronger ability to conduct new drug clinical trials independently in an emergency event. However, there is still no effective therapy for virus infection. When expecting that these studies can provide effective treatment for NCP in China, we need to carry out these trials carefully to ensure the safety of the patients.

CONFLICT OF INTEREST:

The authors have declared that no conflict of interest exists.

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AUTHOR CONTRIBUTION:

All the authors have contributed for this article.

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Table 1. Description of Studies within 2019-nCoV Patients.

Classification	Register number ^a	Study design	Enrollment	Drug of interest	Combinations	Disease condition	Study time	Primary endpoint
Antiviral drugs	ChiCTR200029308	RCT	160	LPV/r	Standard treatment	NCP	2020-01-10 To 2021-01-10	Clinical improvement
	ChiCTR200029539	RCT	328	LPV/r	Standard treatment	mild NCP	2020-02-03 To 2021-02-02	Adverse outcome
	ChiCTR200029496	RCT	200	LPV/r	Novaferon	NCP	2020-01-29 To 2021-01-29	RNA negativity
	ChiCTR200029539	RCT	328	LPV/r	Standard treatment	NCP	2020-02-03 To 2021-02-02	Adverse outcome
	NCT04252664	RCT	308	Remdesivir	...	Mild/moderate NCP	2020-02-05 To 2020-04-27	TTCR

NCT042576 56	RCT	452	Remdesivir	...	sever NCP	2020-02-06 To 2020-05-01	TTCI
ChiCTR200 0029600	Non-R CT	120	Favipiravir	Interferon-a lpha	NCP	2020-01-30 To 2020-04-29	RNA Negative, rate of liver or kidney damage
ChiCTR200 0029621	RCT	380	Arbidol	Basic treatment	NCP	2020-01-01 To 2020-12-31	RNA negativity
ChiCTR200 0029603	RCT	160	ASC09F	...	NCP	2020-02-06 To 2020-05-31	Adverse outcome
ChiCTR200 0029580	RCT	70	Ruxolitinib	MSC	Sever NCP	2020-01-31 To 2020-12-31	Safety
ChiCTR200 0029541	RCT	100	Darunavir/co bicista	Thymosin α 1	NCP	2020-02-01 To 2020-12-	RNA negativity

							01	
ChiCTR200029759	RCT	60	ASC09F, Arbidol	...	Mild/normal NCP	2020-02-15 To 2020-05-01	Clinical improvement	
NCT04261270	RCT	60	ASC09F, Ritonavir	Oseltamivir	NCP	2020-02-01 To 2020-07-01	Adverse outcome	
ChiCTR200029548	RCT	30	Favipiravir, Baloxavir Marboxil	...	NCP	2020-02-04 To 2020-06-03	RNA negativity, clinical improvement	
ChiCTR200029387	RCT	36	LPV/r+Ribavirin	Interferon alpha-1b	Mild/moderate NCP	2020-01-25 To 2021-01-25	RNA negativity	
ChiCTR200029468	Non-RCT	120	LPV/r+FTC/ TAF	LPV/r	NCP	2020-02-01 To 2020-06-30	Survival rate	
ChiCTR200029573	RCT	600	LPV/r+Arbidol	Novaferon	NCP	2020-02-05 To 2020-06-	RNA negativity	

Antimalar ial drugs	ChiCTR200 0029542	Non-R CT	20	Chloroquine	Standard treatment	NCP	2020-02- 03 To 2020-07- 30	RNA negativity, mortality
	ChiCTR200 0029826	RCT	45	Chloroquine	...	Serious/cri tically ill NCP	2020-02- 17 To 2020-03- 17	Mortality rate
	ChiCTR200 0029741	RCT	112	Chloroquine	LPV/r	Mild/norm al NCP	2020-02- 12 To 2020-12- 31	Length of stay and severe, oxygen index, mortality
	ChiCTR200 0029762	RCT	60	Hydroxychlo roquine	...	Sever NCP	2020-02- 12 To unknow	RNA negativity unknow
	ChiCTR200 0029559	RCT	300	Hydroxychlo roquine	...	NCP	2020-01- 31 To 2020-02- 29	RNA negativity, T cell recovery time
	ChiCTR200	RCT	320	Hydroxychlo	Arbidol	NCP	2020-02- 15To	...

	0029803			roquine			2022-02-15	
	ChiCTR200029760	RCT	240	Hydroxychloroquine	LPV/r	Mild/moderate NCP	2020-02-12 To 2020-08-11	Time to clinical recovery
	ChiCTR200029740	RCT	200	Hydroxychloroquine	Standard treatment	NCP	2020-02-11 To 2020-02-29	Oxygen index, maximum respiratory rate, lung CT
	ChiCTR200029761	RCT	240	Hydroxychloroquine	Standard treatment	Normal NCP	2020-02-13 To 2020-04-30	RNA negativity
Glucocorticoids	ChiCTR200029386	RCT	40	Glucocorticoid	LPV/r+Interferon- α	Severe NCP	2020-01-29 To 2021-01-29	Mortality, Clinical improvement
	ChiCTR200029656	RCT	100	Low-dose Glucocorticoid	Standard treatment	NCP	2020-02-14 To 2020-04-14	ECG, CT, Complications, vital signs
	NCT042445	RCT	80	Glucocorticoid	Standard	Sever	2020-01-26 To	Lung injury

				id	treatment	NCP	2020-12-25	score
Other therapies	ChiCTR2000029806	RCT	120	Camrelizumab, Thymosin, Conventional treatment	...	Severe NCP with lymphocytopenia	2020-01-01 To 2021-01-31	Lung injury score
	ChiCTR2000029765	RCT	188	Tocilizumab	...	Severe NCP	2020-02-10 To 2020-05-10	Cure rate
	ChiCTR2000029757	RCT	300	Convalescent plasma	Standard treatment	Severe NCP	2020-02-14 To 2021-02-05	Clinical improvement
	NCT04269525	Single arm	10	DMSC	...	Severe NCP	2020-02-06 To 2020-09-30	Oxygen index
	NCT04261426	RCT	80	Immunoglobulin	Standard treatment	Severe NCP	2020-02-10 To 2020-06-30	Clinical improvement
TCM	ChiCTR2000029806	Prospective	400	Xuebijing	...	NCP	2020-01-01 To	Pneumonia severity

0029381	ctive					2020-12-31	index
ChiCTR20029432	Single arm	72	Tanreqing	...	NCP	2020-02-01 To 2020-04-30	Temperatu re
ChiCTR20029605	RCT	400	Shuang-Hua ng-Lian	...	NCP	2020-02-05 To 2021-02-05	Disease recovery
ChiCTR20029418	RCT	42	TCM	Western medicine	Severe NCP	2020-02-03 To 2020-08-31	Critically ill rate
ChiCTR20029400	Non-R CT	20	TCM	LPV/r	NCP	2020-01-29 To 2020-12-31	Remission

^a Searching in <http://www.chictr.org.cn/> and <https://clinicaltrials.gov/>

Abbreviations: RCT, randomized controlled trial; LPV/r, Ritonavir/Lopinavir; NCP, novel coronavirus pneumonia; TTCR, time to clinical recovery; TTCl, time to clinical improvement; ASC09F, ASC09/Ritonavir; FTC/TAF, Emtricitabine/Tenofovir alafenamide Fumarate; CT,

computed tomography; ECG, electrocardiogram; MSC, mesenchymal stem cell; DMSC, derived mesenchymal stem cell; TCM, traditional Chinese medicine;

FIGURE 1. The location distribution for clinical trial of 2019-nCoV.

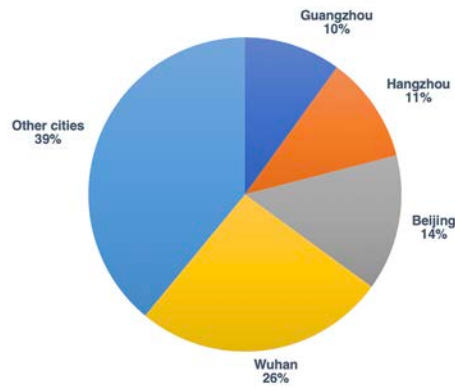


FIGURE 2. The classification of experimental drugs for 2019-nCoV.

