COVID-19, SARS, MERS and Ebola: a comparative analysis registration of intervention clinical trials

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Research

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Abstract

Background

COVID-19 is a novel and highly virulent virus, which caused a rapid and massive onset of clinical trials in a short period of time. With the aim to obtain suggestions in the guidance on performing emergency clinical trials, and control this virus in China and other countries and for the prevention of the onset of other infectious viruses in the future.

Methods

COVID-19, SARS, MERS and Ebola clinical trials registered in the Chinese clinical trial registry and clinical trials.gov were collected and analyzed and intervention protocols were compared, focusing on the analysis and comparison of the drug used. The search period ended on February 24, 2020.

Results

The number of the registered COVID-19 clinical trials was 295. Among 203 intervention trials, 78.3% (159) were drug clinical trials, in which 46.3% (94) used chemical drugs and biological agents, 32.0% (65) were performed using Traditional Chinese Medicine (TCM) and integrated traditional Chinese and western medicine.

The 159 COVID-19 trials were designed and analyzed with the highest proportion of blank randomized controls [45.9% (73)], and placebo randomized trials [14.5% (23)]. The drug mostly used was Lopinavir/Ritonavir (15.1%). The sample size ranged from 10 to 100 in 52.8% (84) trials. The number of the registered SARS was 6, MERS 15, and Ebola 97. Among 3 MERS and 19 Ebola drug intervention clinical trials, MERS and Ebola were randomized, blind, and placebo-controlled drug clinical trials accounting for 100% (3) and 31.6% (6), respectively, while SARS were vaccine trials, without drug intervention clinical trials registered.

Conclusions

Compared with the SARS in 2003, the awareness and capability of clinical research in China greatly improved. However, some of the COVID-19 clinical trials and drug selection performed are somewhat disordered, requiring greater attention to the needs, science assumptions, ethics and quality management of the clinical research. Thus, during the epidemic period, the country should deliver guidance on how to perform appropriate emergency clinical trials, design a scientifically based clinical trial program and focus on researching drugs or vaccines that have great potential.

Introduction

An outbreak of pneumonia occurred in Wuhan, China, on Dec 2019. A novel coronavirus isolated from the bronchoalveolar lavage fluid of a patient was identified as the cause of the outbreak [1]. On Jan 30, 2020,

the WHO (World Health Organization) declared the Corona Virus Disease 2019 (COVID-19) epidemic as a Public Health Emergency of International Concern [2] and now it became a global pandemic. As of March 23, 2020, WHO reported 294,110 confirmed cases worldwide, including 12,944 deaths in 187 countries, areas or territories, and assessed the risk of COVID-19 at a very high level [3]. COVID-19 is the cause of a sudden outbreak, has a high transmission rate, is an infectious disease with a high mortality rate, and so far, no therapeutic drugs are available [4]. Severe acute respiratory syndrome (SARS) suddenly appeared in 2002 in the Guangdong province, China. By July 2003 and after a total of 8,096 reported cases, including 774 deaths in 27 countries, the death rate was 9.6% [5]. Middle East Respiratory Syndrome (MERS) was found in patients in Saudi Arabia in September 2012, and caused severe respiratory diseases and kidney failure [6]. As of November 2020, WHO reported 2494 confirmed cases of MERS and up to 858 (34.4%) deaths [7]. Ebola first occurred in Africa, with an average mortality rate of 50% in previous outbreaks [8].

The above data show that these viruses have a high transmission capacity and mortality, which raised global concern and seriously affected public health safety. However, the treatment methods are often unknown and lagging, thus, it is necessary to urgently launch clinical trials to explore effective treatment protocols. Under the emergency, a large number of COVID-19 clinical trials have been registered. Therefore, the clinical trial data of three viruses with similar emergency background, such as SARS, MERS, and Ebola, were systematically analyzed and compared with COVID-19 clinical trials, with the aim to obtain suggestions on performing appropriate emergency clinical trials to control this virus and prevent the onset of other infectious viruses in the future.

Methods

COVID-19, SARS, MERS and Ebola clinical trials registered in the Chinese clinical trials registry and clinical trials.gov were collected until February 24, 2020. Only one copy of the duplicate projects present in the two websites was considered. The research type, research distribution, research design, and intervention program were analyzed. The protocol design used in clinical research to manage the infection of the four viruses was analyzed, and the clinical results were published through the search of the registration number.

Results

1. Total number and research type

As of Feb 24, 2020, 51 COVID-19, 8 SARS, 17 MERS, and 94 Ebola clinical trials were registered on clinical trials.gov. Among the 247 protocols associated to COVID-19 registered in the Chinese clinical trial registry, 3 Ebola protocols were collected, while no SARS and MERS were found. Only one copy of the three duplicate projects present in both the two registration sites was excluded. 2 duplicate studies of SARS and MERS, which were mainly observational studies on a variety of respiratory viruses were excluded. Thus, the total number of the registered clinical trials considered was 295 COVID-19, 6 SARS, 15 MERS

and 97 Ebola. The time span and research type of the trials are shown in table 1, and the first registered protocol is shown in table 2.

2. Regional distribution

Of the 295 COVID-19 clinical trials, 1 was registered in US NIAID, 2 in France Institut National DE la Sante Et DE la Recherche Medicale, France, and the other 292 were registered in China (including 1 in Hong Kong). Among them, 83 (28.1%) were registered in the Hubei province, where most protocols were started. Subsequently, 36 (12.2%) were registered in the Guangdong Province, 35 (11.9%) in Beijing City and 26 (8.8%) in the Zhejiang Province of China (Fig 1). The top three initiated organizations are 20 (6.7%) Tongji Hospital Affiliated to Huazhong University of Science and Technology, 14 (4.7%) Union Hospital Affiliated to Huazhong University of Science and Technology and 11 (3.7%) Zhongnan Hospital of Wuhan University (Fig 2).

Four of the 6 clinical trials of SARS were performed in the United States, 1 in Beijing and 1 in Taiwan. Four of the 6 SARS clinical trials were distributed in the United States, 1 in Beijing City, China and 1 in Taiwan Province, China. Fifteen MERS clinical trials were distributed in four regions, 4 in Saudi Arabia, 3 in the United States, 3 in South Korea, 2 in Germany and 2 in Russia, and 1 in the United Kingdom.

Ninety seven Ebola clinical trials were distributed in 10 countries, with the top 3 represented by the United States [the highest one with 56 (57.7%) clinical trials], United Kingdom, and China (Fig 3). The top three sponsors were the National Institute of Allergy and Infectious Diseases (NIAID), Janssen Vaccines & Prevention B.V. and the University of Oxford, accounting for 24 (24.7%), 9 (9.3%) and 6 (6.2%) , respectively (Fig 4).

3. Clinical trial intervention types

According to the intervention classification of COVID-19, SARS, MERS and Ebola, the interventional studies regarding COVID-19 were mainly drug clinical trials, in which chemical drugs and biological agents accounted for 46.3%, TCM and integrated Chinese and western medicine accounted for 32.0%. Two SARS intervention studies were all about vaccines. The majority of the interventional clinical trials regarding MERS and Ebola were also about vaccines, accounting for 61.5% and 72.9%, respectively, followed by chemical drugs and biologic agents, accounting for 23.1% and 22.4%, respectively. COVID-19, MERS and Ebola carried out a small number of clinical studies about plasma therapy. Cell therapy was only applied in COVID-19, accounting for 8.9%. (Table 3)

4. Drug clinical trial design

4.1 COVID-19 drug clinical trials

4.1.1 Overall design of COVID-19 clinical trials

Of the 203 intervention trials, 78.3% (159) were drug clinical trials. Of the 159 clinical trials analyzed, 79.9% (127) were designed using randomized controlled trials. According to the different types of control used in Randomized Clinical T, the control group was divided into blank control group (both the experimental group and the control group were subjected to standard treatments or the same drug treatment as the basis), placebo control group, positive drug control group, and standard treatment group (the experimental group was directly compared with standard treatment). Among 159 drug clinical trials, 45.9% (73) in the blank control group, 14.5% (23) in the placebo control group, 10.7% (17) in the positive drug control group, and 8.8% (14) in the standard treatment control group. (Table 4)

The cumulative sample size of the 203 intervention trials was 30,601, and among them, 26146 subjects were involved in the 159 drug intervention trials. Among the 159 trials, the sample size ranged from 10 to 1000 (including both ends). There is 117 samples with the sample size between 10 and 100 among 203 intervention trials, accounting for 57.6%; 84 samples among 159 drug intervention trials have a sample size between 10 and 100, accounting for 52.8%. The largest sample size of 1000 patients was in the "single-arm study of Chinese medicine in the prevention and treatment of novel coronavirus pneumonia (COVID-19)".

4.1.2 Major drugs used in COVID-19 clinical trials

The 159 COVID-19 clinical trials with drug intervention were analyzed. A total of 50 types of chemical and biological agents and nearly 30 types of TCM were used. Most of the chemical drugs and biological preparations are on the market except for the unlisted drugs such as Remdesivir, Azvudine tablets, ASC09/ritonavir tablets, and GD31. The top three used chemical drugs were anti-HIV drugs, antimalarial drugs, and anti-influenza drugs, and among them Lopinavir/Ritonavir, Hydroxychloroquine, Hloroquine, and Abidor were used on 15.1% (24), 13.8% (22) and 5.0% (8), respectively. The biological products used were mainly interferon, with a frequency of 8.2%. Other monoclonal drugs such as Carrilizumab, Adamumab, Meplazumab, and Bevacizumab were also used.

4.1.3 Clinical trial design using Remdesivir in China and the United States

Two randomized, blinded, placebo-controlled clinical trials used Remdesivir have been performed in China. One was about mild to moderated sick patients with a sample size of 308, and the other one was about severe patients with a sample size of 452. The Remdesivir clinical study was also registered in the United States on February 21, 2020, using an adaptive, randomized, blinded, placebo-controlled study with a sample size of 453. The main efficacy evaluation indexes used are different between the Chinese and American schemes. China adopted Time to Clinical Recovery by Day 28, while the US adopted the percentage of subjects reporting each severity rating on the 7-point ordinal scale by Day 15. Other subtle differences are present in the exclusion criteria and course of the treatment.

4.2 Research design of MERS drug clinical trial

Only 3 MERS drug clinical trials were registered, accounting for 23.1% of the intervention trials, and all were RCT. One protocol was a patient-based evaluation of Lopinavir/Ritonavir and interferon phase III, the first patients of this trial was enrolled in November 2016. Although only 194 patients were plan to be recruited, the recruitment process progressed slowly and they are still in the recruitment phase [9]. The other two were phase I clinical trials with healthy subjects. One of these was the first human trial using two monoclonal antibodies, REGN3048 and REGN3051 [10] to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of the combined use of these two antibodies. The study involving 48 healthy adult subjects was completed but the results of the clinical trials have not been announced. The other, using a biological product such as fully human polyclonal IgG antibody (sab-301), completed a placebo-controlled study regarding the safety, tolerability, and pharmacokinetics of 38 healthy adults [11] (Table 5).

4.3 Research design of Ebola drug clinical trials

A total of 19 Ebola drug intervention clinical trials were available, 84.2% (16) were in phase I or II, 11 (57.9%) were RCT, 6 were double-blind RCT and placebo-controlled, accounting for 31.6% of the drug trials. Six specific chemicals were tested in the Ebola clinical trials, including Remdesivir, Favipiravir, Brincidofovir, Avi-7537, TKM and BCX4430, and four antibodies, including REGN-EB3, MAb114, ZMAPP, and GamEMab. However, 8 of the 19 trials were interrupted or withdrawn, accounting for 42.1% (Table 5, Table 6).

Discussion

A total of 292 COVID-19 clinical trials were registered in China in one month. The current awareness and capability of the clinical trials in China significantly improved compared with those related to the SARS period in 2003. Most of the trials were carried out in Guangdong, Beijing, Zhejiang and other regions, and they were not only related to the number of infected cases in these regions but also related to the resources and capacity of the clinical trials accumulated in these regions over the years in China. In addition, the number of clinical trials registered and the speed they were performed in one month in China are surprising, compared with the registration protocol number, speed of implementation, and region of registration of MERS and Ebola, demonstrating the enthusiasm of the Chinese research and determination to defeat COVID-19. However, there are several problems that need to be analyzed and summarized, including an appropriate scientific design of the study and clinical trials management.

The types of intervention protocols were analyzed. Currently, COVID-19 clinical trials were mainly registered with the use of marketed drugs. In a period of sudden outbreak, it is necessary to select the most suitable marketed products to control the spread of the virus as soon as possible and provide timely treatments to patients. The most represented clinical trial registrations regarding SARS, MERS and Ebola used vaccines. The results of the safety and immunogenicity tests of MERS GLS - 5300 coronavirus vaccine clinical trials were completed to support the next step of the efficacy study[16], After nearly 16 years of work, the Ebola vaccine has been a milestone success. One VSVΔG - ZEBOV- GP of Ebola

vaccine efficiency reached the 97.5%, and it was successively approved on the market by the European Medicines Agency (EMA), World Health Organization (WHO) and four countries in the African region [17-21]. at the date of Feb 24, 2020, COVID-19 has registered a vaccine clinical trial with the name of LV-DC vaccine in just one month.. It is possible that the proportion of COVID-19 vaccine research will increase at a later stage. The successful experience of the Ebola vaccine is a useful example to learn from, but a long time is needed to complete multiple clinical trials to answer the questions of vaccine safety, efficacy and duration of immune antibody *in vivo*, and finally meet the National Medical Products Administration (NMPA) or WHO standards.

Van Griensven J et al reported that 84 subjects received plasma from Ebola survivors with an unknown neutralizing antibody levels, and no serious adverse reactions were observed, but the survival rate of the experimental group was not significantly improved [22]. This may be related to the lack of moderate antibody levels, and further research is needed to evaluate the effectiveness of antibodies at a high level [23]. The use of plasma may be an option for critically ill patients, but there are many problems and risks, including epidemiological, virological, immunological, and ethical ones [24]. COVID-19 registered 7 clinical trials regarding plasma therapy and 18 clinical trials regarding cell therapy and also focused on carrying psychological intervention studies for medical staff and patients [25-26]. TCM and integrated Chinese and western medicine also accounted for a large proportion of the treatment plan, making a huge contribution during the SARS period [27]. In terms of intervention methods, COVID-19 used more types of interventions, but to establish which one it is effective or not requires the support of more data.

We focused our analysis on the interventional drug clinical trial design, since COVID-19 is mainly an exploratory trial of marketed drugs, with the purpose of obtaining effective data. Most of the trials registered to solve MERS and Ebola were designed using drugs for drug development, requiring phase validation of safety and efficacy. In the absence of a clear and effective treatment regimen for COVID-19, the blank control group and the control group with basic treatment were the most used, which was consistent with the clinical trial design of MERS and Ebola [9,14]. Although we have positive drug controls in the COVID-19 group, neither a standard, nor a recognized effective treatment regimen was obtained, just an exploration of different interventions. The proportion of COVID-19 placebo-controlled trials (14.5%) was lower than that of MERS (100%) and Ebola (31.6%). Although the cumulative sample size of COVID-19 was large, it is mainly distributed in the range of 10 to 100, which is still small, thus resulting in a waste of research resource (for example human subjects) and in a failure to achieve the expected results and meet the statistical requirements. Nature reported that if China's COVID-19 trials are not designed with strict standards on study parameters, such as control groups, randomization and the measures of clinical outcomes, the efforts will be in vain. [28].

The drugs used in 159 COVID-19 drug clinical trials were analyzed, and showed that a wide variety of drugs were used. Many trials, such as the ones using Lopinavir/Ritonavir, Hydroxychloroquine, Chloroquine, and Abidor, were repeated and resulting in a waste of resources. A retrospective study reported by Chen jun et al. did not find that Lopinavir/Ritonavir and Abidor had the ability of improving symptoms or shortening the time of negative transformation of the respiratory virus nucleic acid [29]. A

recently RCT open-label study showed that in hospitalized adult patients with severe COVID-19, no benefit was observed using the Lopinavir–Ritonavir treatment beyond the standard care [30]. Currently, only Chloroquine, Remdesivir, Famivir and Abidol resulted effective against COVID-19 *in vitro* [31-32]. Many other drugs may be used directly on patients without *in vitro* experiments, with a consequent risk for many patients to receive ineffective or even adverse treatments. A total of 42.1% of the 19 clinical trials on Ebola drugs were concluded or withdrawn, and so far no drugs have been approved for the market. Thus, it is foreseeable that a large proportion of clinical trials on COVID-19 may not produce satisfactory results.

Gilead's Remdesivir nucleoside analog received the highest level of attention in ongoing clinical trials. Remdesivir is a broad spectrum antiviral drug, Remdesivir proved on SARS - CoV, and MERS - CoV showed an inhibiting effect *in vitro* and in animal models [5]. Compared with the effect of biological antibody drugs in the other two groups (MAb114 is 35.1% 33.5%, REGN EB3) [15], tentative analyzes revealed that the 28-day mortality of the Remdesivir group was 53.1%, which did not show any advantage nor significantly reduced the average mortality rate of Ebola disease (about 50%) [8]. However, in N Engl J Med, Michelle I. et al. reported that the first confirmed COVID-19 patient's symptoms were improved after 1 day of using Remdesivir under emergency conditions, and no drug-related adverse reactions were found [33]. The Remdesivir protocol in the United States is designed with an adaptive approach and a data safety oversight board. This flexible trial design and data management is important for subject protection and risk management and has been used in several trial designs for the Ebola and MERS. Many of the Ebola and MERS trials were conducted by national research institutions such as the NIAID or by large pharmaceutical companies, which can pool resources and maintain uniform standards. Therefore, China should learn from these good designs and management experiences in conducting clinical trials on COVID-19.

The ethics of clinical trials and the quality of research during outbreaks are also representing a concern. The spread of the virus created panic in some subjects, and the review of the ethics committee and the subject's knowledge raise sufficient concern in these trials. Some procedures can be simplified to initiate clinical trials during specific periods of virus outbreaks, but the standards of clinical trial ethics and research quality cannot be lowered because of the outbreak [34]. The research team of the joint prevention and control mechanism of new coronavirus pneumonia under the state council of China issued "the notice on standardizing medical institutions to carry out clinical research on drug treatment of new coronavirus pneumonia" [35]. WHO also evaluated many COVID-19 clinical trials, and suggested that experts from other countries together with Chinese experts draft the COVID-19 clinical trial protocols [28], to regulate COVID-19 clinical trials in an appropriate manner.

Conclusions

The clinical trials on COVID-19 demonstrated the improvement in the awareness and capability of clinical research in China. However, COVID-19 clinical trials are somewhat disordered, with lack of unified standard, study design, drug screening, sufficient pre-clinical or clinical data, repetition of a large number

of intervention methods in clinical trials, and scattered resources. Therefore, it is necessary to pay attention on the needs, scientific assumptions, ethics and quality management of the clinical research. The clinical trials on COVID-19 should summarize the research and management experience of SARS, MERS and Ebola. It is of utmost importance to carry out clinical trials efficiently through a international or national protocol design and screening of potential drugs. Therefore, during the epidemic period, the country should deliver a guidance on emergency clinical trials, design a scientifically based clinical trial program and focus on researching drugs or vaccines that have great potential. In addition, when the COVID-19 pandemic is over, all the case information should be collected to perform a big data analysis, to summarize the experience and lessons, and to analyze and compare the benefits and risks of various treatment schemes. However, the retrieval time is up to February 24, 2020, the subsequent updated registration data are not present in the article. In addition, there are only 2 databases we could use in the world, which may not be complete.

Abbreviations

MERS: Middle East Respiratory Syndrome; SARS: Severe Acute Respiratory Syndrome; WHO: World Health Organization; TCM: Traditional Chinese Medicine; NIAID: National Institute of Allergy and Infectious Diseases; RCTs: Randomized Clinical Trials; NMPA: National Medical Products Administration

Declarations

Acknowledgements

Not applicable.

Authors' contributions(There is no need to polish this section)

Yang G, Wang X contributed to the study concept and design. Xiang Y was responsible for the search design, literature search, data analysis, interpretation of data, and preparation of the first draft of the manuscript, figures, and tables. Zhang Z , Hu Z and Huang Z were responsible for the literature review. Zeng C and Liu Y, Chen W were responsible for the data extraction and acquisition of data. Yang. G and Wang X substantively revised the manuscript for significant content and provided translation and editing for English language. All authors critically revised the manuscript for relevant intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets generated and/or analyzed during the current study are available in Chinese clinical trial registry and clinical trials.gov.

Ethics approval and consent to participate

All data were publicly available, no patient contact was established, **no patient identification was necessary** and no individual identifiers were required. Therefore, ethical approval for this study was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Total number and research type of COVID-19, SARS, MERS, and Ebola virus registered.

Study Type	COVID-19 ^a	SARS ^b	MERS ^a	Ebola
Time span (month)	23 Jan 2020 -24 Feb 2020	6 Aug 2003 -22 Feb 2018	15 Jul 2014 - 20 Nov 2019	5 Nov 2003-13 Feb 2020
Total	N=295	N=6	N=15	N=97
Interventional study, %	68.8 (N=203)	33.3 (N=2)	86.7 (N=13)	87.6 (N=85)
Observational study, %	31.2 (N=92)	66.7 (N=4)	13.3 (N=2)	12.4 (N=12)

^aNCT04260594, NCT04261907, and NCT04275388 were not included, which were also found at the Chinese Clinical Trials Registry.

^bNCT01056185 and NCT01056354 were not included, since they were not specifically referred to SARS and MERS.

Table 2. First clinical trial for COVID-19, SARS, MERS, and Ebola

	Study Title	First registration Posted/ date	Sponsor
COVID-19	A randomized, open-label, blank-controlled trial for the efficacy and safety of lopinavir-ritonavir and interferon-alpha 2b in hospitalization patients with novel coronavirus pneumonia (COVID-19)	January 23, 2020	Wuhan Jinyintan Hospital
SARS	Investigating Severe Acute Respiratory Syndrome (SARS)	August 6, 2003	National Institute of Allergy and Infectious Diseases (NIAID)
MERS	Anti-MERS-CoV Convalescent Plasma Therapy	July 15, 2014	King Abdullah International Medical Research Center
Ebola	VRC 204 A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiple Strain Ebola DNA Plasmid Vaccine, VRC-EBODNA012-00-VP, in Adult Volunteers	November 5, 2003	National Institute of Allergy and Infectious Diseases (NIAID)

Table 3. Intervention type used in SARS, MERS, Ebola and COVID-19 clinical trials

Intervention type	COVID-19	SARS	MERS	Ebola
Vaccine, %	0.5 (N=1)	100 (N=2)	61.5 (N=8)	72.9 (N=62)
Chemical drugs and biological products,%	46.3 (N=94)	0 (N=0)	23.1 (N=3)	22.4 (N=19)
Chinese medicine or integrative Medicine therapy, %	32.0 (N=65)	0 (N=0)	0 (N=0)	0 (N=0)
Cell therapy, %	8.9 (N=18)	0 (N=0)	0 (N=0)	0 (N=0)
Plasma therapy, %	3.4 (N=7)	0 (N=0)	7.7 (N=1)	3.5 (N=3)
Medical devices, %	2.5 (N=5)	0 (N=0)	7.7 (N=1)	0 (N=0)
^a others, %	6.4 (N=13)	0 (N=0)	0 (N=0)	1.2 (N=1)
total	N=203	N=2	N=13	N=85

^a Mainly behavioral interventions and psychological interventions.

Table 4. Sample size distribution of 203 COVID-19 intervention trials and 159 COVID-19 drug intervention trials in subgroups

Sample size range	203 interventional clinical trials	Subgroup -159 drug intervention trials
10≤sample size≤100,%	57.6 (117)	52.8 (84)
100≤sample size≤200,%	21.7 (44)	23.3 (37)
200≤sample size≤300,%	7.4 (5)	8.2 (13)
300≤sample size≤400,%	7.4 (15)	8.8 (14)
400≤sample size≤500,%	2.5 (5)	2.5 (4)
500≤sample size≤600,%	2.5 (5)	3.1 (5)
600≤sample size≤1000,%	1.0 (2)	1.3 (2)

Table 5. Research design and results of 3 MERS drug clinical trials

NCT	test group	control group	study design	phase	sample size	primary outcome measures	results/ status
^a NCT02845843	Combination of Lopinavir /Ritonavir and Interferon Beta-1b	Placebo	recursive two-stage group sequential multicenter double-blind randomized controlled trial	II/III	194	90-day mortality	Recruiting [9]
NCT03301090	REGN3048 and REGN3051	Placebo	first-in-human (FIH), double-blind randomized controlled trial	I	48	safety and tolerability	completed but the results were not released
NCT02788188	SAB-301	Placebo	double-blind randomized controlled trial	I	38	safety and tolerability	Single infusions of SAB-301 up to 50 mg/kg appear to be safe and well tolerated in healthy participants [11]

^aboth groups received standard supportive care.

Table 6. Research design of Ebola chemical drug clinical trials

NCT	test group	control group	study design	sample size	phase	primary outcome measures	results/status
NCT02818582	Remdesivir	placebo	double-blind randomized controlled trial	38	II	Assay Negativity Rate (ANR) over days 4, 8, 11, 16, 24, and 28	completed but the results were not released
NCT02319772	BCX4430	placebo	double-blind randomized controlled trial	94	I	safety and tolerability	completed but the results were not released
aNCT02662855	Favipiravir Plus WHO-recommended therapies	WHO-recommended therapies	open-label randomized controlled trial	77	II	Case fatality rate by Day 14	completed but the results were not released
bNCT02329054	Favipiravir plus standardized care		Single Group Assignment	126	II	mortality by Day 14	111 were analyzed and sixty participants died. RNA viral load values and mortality were not significantly different between adults starting favipiravir within <72 h of symptoms compared to others [12]

^aAll patients received standard care and were randomly assigned in a 1:1:1:1 ratio to REGN-EB3, Remdesivir, MAb114, and Zmapp.

Table 7. Ebola virus clinical trial design and results after using biologic agents

NCT	test group	control group	study design	sample size	phase	primary outcome measures	results/ status
NCT03478891	MAb114		Open Label Dose-Escalation Study	19	I	safety and tolerability	mAb114 was well tolerated, showed linear pharmacokinetics [13]
NCT03428347	GamEMab		Open Label Dose-Escalation Study	25	I	safety and tolerability	completed but the results were not released
NCT02363322	ZMAPP Plus Current Standard of Care	Current Standard of Care Alone	open-label randomized controlled trial	72	I&II	mortality by Day 28	although the estimated effect of ZMapp appeared to be beneficial, the result did not meet the pre-specified statistical threshold for efficacy [14]
^a NCT03719586	REGN-EB3 Remdesivir MAb114	Zmapp	open-label randomized controlled trial	1500	II&III	mortality by Day 28	Both MAb114 and REGN-EB3 were superior to ZMapp in reducing mortality from Ebola Virus Disease[15]

Figures

Figure 1

Regional distribution of 292 COVID-19 clinical trials in China

Figure 2

Organizations that registered ≥ 4 protocols among 295 COVID-19 clinical trials

Figure 3

Regional distribution of 97 Ebola clinical trials. "Other" represents the NCT02307591, with the Emergency NGO Onlus sponsor

Figure 4

Organizations that registered ≥ 3 protocols among 97 Ebola clinical trials

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