Review Article

Compilation of registered clinical trials for the treatment of COVID-19 infection

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ABSTRACT

The Wuhan city, the capital of Hubei province in China became the focal point for origin of virulent disease which later named as COVID-19. This paper aims to analyze the on-going clinical trials for drugs/interventions used for treatment of COVID-19 infection in open domain. The data on ongoing clinical trials on COVID-19 was retrieved from database clinicaltrials.gov. The data extracted includes national clinical trial registry number, title of study, recruitment status, results availability, intervention, outcome measure, sponsorship, study types, study design, start and completion dates, and location. All the extracted data was analyzed. As on 10th August 2020, a total of 2935 trials were registered in different countries. Of which 1115 trials are being conducted in Europe and 640 in United States of America (USA). Majority of COVID-19 clinical trials (95%) were enrolling all age groups including children and older adults. Similarly, majority of trials were including both genders (97%). Among all these clinical trials ongoing on COVID-19, 1645 were interventional, 1266 were observational studies. In interventional study 876 trials used drug intervention. Among all these trials 390 different drug interventions are being tried. Among these hydroxychloroquine, antiretrovirals and angiotensin converting enzyme (ACE) inhibitors were top three drug groups. The conduct of clinical trials in time of pandemic have so many tenacious issues that need to be addressed. It is very important to utilize the resources efficiently such as following a standard protocol then one can easily pool the data of various trials conducted at various places. Given the smaller sample sizes, long completion period, high risk of bias and imprecise information, it will take quite a long time to obtain high quality clinical evidence for the treatment of COVID-19 infection.

Keywords: COVID-19, Clinical trials, Medicines, Novel coronavirus, Coronavirus infection

INTRODUCTION

The Wuhan city, the capital of Hubei province in China became the focal point for origin of virulent disease which later named as COVID-19.[1] Patients with COVID-19 have presented with different respiratory tract infection symptoms such as fever, cough, pneumonia and even death.[2] The reported mortality ranges from 2 to 5% which appear to be lower than SARS-CoV (10%) and MERS CoV (35%).[3] However, current reports of risk factors for poor outcomes include age, ischaemic heart disease, hypertension, diabetes mellitus and chronic lung disease.[4] By 27 November 2020, 83,809,734 people have been infected around the world and 1,825,780 people have died because of infection.[5] This has been declared public health emergency of international concern by World Health Organization (WHO)-Director General.[6] Furthermore, human to human transmission has been continued despite of various measures such as wearing facial mask, social distancing and lock-down in various countries. The impact on worldwide economy has been estimated as US$3.5 trillion and is still rising.[6]

At present, there are no approved therapies for the treatment of COVID-19. Various national and international groups are working collaboratively on a variety of preventive and therapeutic interventions. Various avenues are being explored such as vaccine development, convalescent plasma, interferon-based therapies, cell based therapies and monoclonal antibodies.[7]

Given the time required for new drug development, a considerable attention is towards repurposing existing drugs and expediting the developments of antivirals, treatment such as those used for influenza, hepatitis B and C.[7] As prophylaxis vaccination for COVID-19 has been started in various countries including India. The focus of this paper is on the drug treatment for COVID-19 infection.

This paper aims to evaluate the on-going clinical trials for drugs/interventions used for treatment of COVID-19 infection in open domain. It is anticipated that this will clarify the current investigational advances and guide potential future strategies.

METHODS

The data on ongoing clinical trials on COVID-19 was retrieved from database clinicaltrials.gov. There was no language limit for the search and the search deadline was 10th August 2020. The keywords were as following-novel coronavirus, COVID-19, new coronavirus and coronavirus infection.

The inclusion criteria for this study- patient with COVID-19, clinical trials with details such as diagnosis, prevention and treatment of COVID-19, have clear and specific end points and outcomes, any type of study design.

Data extraction and analysis

The data extracted includes national clinical trial registry number, title of study, recruitment status, results availability, intervention, outcome measure, sponsorship, study types, study design, start and completion dates, and location. All the extracted data was analyzed.

RESULTS

The online registries of trial on COVID-19 available in clinicaltrials.gov was collected. All the therapeutic and preventive intervention under clinical investigation of COVID-19 has been collated.

As on 10th August 2020, a total of 2935 trials were registered in different countries. Of which 1115 trials are being conducted in Europe and 640 in USA.

At this time there are no approved therapies for treatment or prevention of COVID-19. Many international agencies are working collaboratively on various therapies for treatment and prevention of COVID-19. A steep rise in number of clinical trials has been observed in first four months of initiation of the pandemic. Figure 2 shows the number of clinical trials being registered in a month.
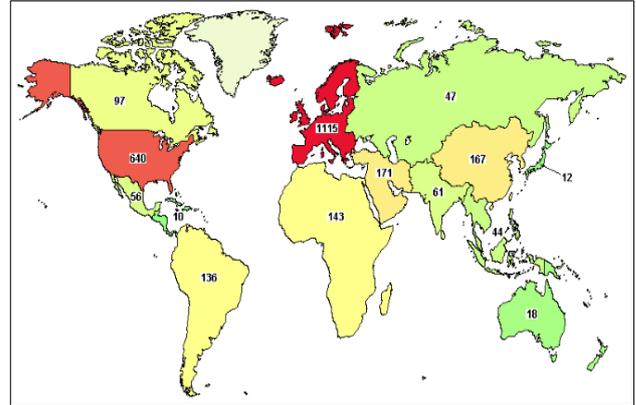

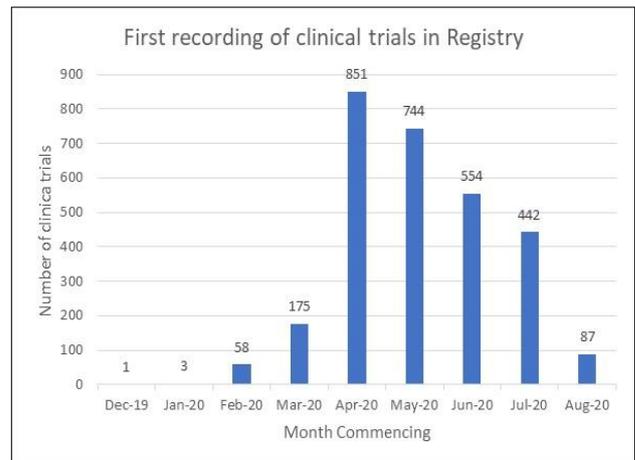**Figure 1: Number of clinical trials on COVID-19 infection being conducted worldwide.[8]**

Figure 2: First recording of clinical trials in registry.

Majority of COVID-19 clinical trials (95%) were enrolling all age groups including children and older adults. Similarly, majority of trials were including both genders (97%). Most of the studies conducted only in females, were on pregnant females (73%) and aims to evaluate maternal fetal transmission, postnatal depression during COVID-19, anxiety and depression in COVID-19 positive pregnant females and birth outcomes.

Few trials (n=21) were conducted in male only, evaluating presence of virus in semen, effect on sexual and ejaculation functions, sperm motility and survival in COVID-19 positive men.

Only 2 clinical trials have been completed and results were available for them and remaining 2933 trials no results were available. One of these two studies have been using povidone-iodine versus essential oils versus water for gargling in COVID patients and other second study was using methylprednisolone as the interventions.

Majority of these trails are still recruiting (n=1519) and 827 has not yet started recruitment and only 269 has completed the recruitment process.

Fifty three trials are not recruiting either terminated or withdrawn because of certain reasons. Among all the registered clinical trials 16% trials (no. 484) are sponsored by the pharmaceutical industry and only 2% trials are funded by National Institute of Health (NIH) and US federal. Majority of trials are sponsored by teaching and research institutes through various grants.

Interventions and comparison

Among all these clinical trials ongoing on COVID-19, 1645 were interventional, 1266 were observational studies. Various types of intervention were used in clinical trials such as behavioral therapy, biological products, drugs, devices, dietary supplements and many more.

Table 2 shows various types of interventions applied in clinical trials.

Majority of clinical trials used various drugs as intervention for treatment of COVID-19. In interventional study 876 trials used drug intervention.

Among all these trials 390 different drug interventions are being tried. Table 3 summarizes top ten ranked drug intervention used in COVID-19 trials.

Table 1: General characteristics of COVID-19 trials.

General characteristics	Number
Age	
Only children (birth-17 years)	40
Child, adult, older adult	2808
Only older adults (65 years+)	85
Gender	
Female	64
Male	21
Both genders included	2848
Study design	
Interventional	1645
Observational	1266
Expanded access	24
Funding for trials	
Industry	484
NIH	53
U.S. federal	9
Others	2389
Phase of trial (interventional studies)	
Early phase 1	28
Phase 1	99
Phase1/phase 2	93
Phase 2	428
Phase 2/phase 3	125
Phase 3	257
Phase 4	77
Not applicable	538

Table 2: Various types of interventions used in COVID-19 clinical trials.

Sl no.	Type of intervention	All trials	Study design: interventional	Study design: observational
1	Behavioural	138	95	43
2	Biological	270	242	16
3	Combination product	18	16	2
4	Device	149	98	50
5	Diagnostic test	251	57	194
6	Dietary supplement	42	37	5
7	Drug	933	876	47
8	Genetic	1	1	X
9	Procedure	71	38	33
10	Radiation	13	13	0
11	Others like wearing face mask, web based survey	582	172	409
12	None	467	X	467

Table 3: Top ten drug interventions used in COVID-19 clinical trials.

Rank	Drugs	No. of trials
1	Hydroxychloroquine and combinations	130
2	Favipiravir and combinations	25
3	ACE inhibitor	22
3	Colchicine	14
3	Nitric oxide	14
4	Enoxaparin	13

Rank	Drugs	No. of trials
4	Lopinavir/ritonavir treatment	13
4	Convalescent plasma and combinations	13
5	Nitazoxanide	12
6	Remdesivir	11
6	Ruxolitinib	11
7	Anakinra and combinations	10
7	Methylprednisolone	10
8	Baricitinib	9
9	Dexamethsone	8
10	Povidone-iodine	7
10	Interferon beta 1a	7
10	Sarilumab	7

DISCUSSION

Over 37% of the clinical trials for prevention/treatment of COVID-19 are registered in Europe. Almost 22% trials are being conducted in USA. At present only 6% trials which registered within 1month of COVID-19 identification were in China. In initial three months of COVID-19 outbreak, out of 62 trials 58 trials were conducted in China, which is not surprise as the country saw the outbreak of disease first. The global community has reacted subsequently as the epicentre of disease shifted from China to Europe to USA, hence the registration of trials also increased in these countries over the time period. Now, India is as one of the epicentre of pandemic.[9]

At present numerous clinical trials are being conducted for COVID-19 infections. These trials are testing various interventions which would help in over-coming this pandemic. The types of interventions are not only limited to usage of drugs for treatment/prevention of COVID infections rather large number of trials are being conducted for testing various diagnostic procedures to be followed for detection of COVID-19 positive patients. Currently, there are no approved therapies for either the treatment or prevention of COVID-19. At present several national and international research groups are working collaboratively on a variety of preventive and therapeutic interventions.[10] Various types of strategies are used in clinical trials such as behavioral, biological, dietary supplement, procedures, using protection measure and web based surveys. Among behavioral interventions almost half (47%) studies analyzed strategies to cope with stress and anxiety in patients with COVID-19.

Coronavirus has genetic proximity to SARS-CoV and MERS-CoV, therefore, the agents previously used to SARS and MERS were potential candidates for treatment of COVID-19. However, the meta-analysis of SARS and MERS treatment studies found no clear benefit of any specific regimen.[11,12] There are 933 on-going clinical trials which are assessing various drugs for prevention and treatment of COVID-19. There is no evidence from randomized clinical trials regarding any potential therapy which can improve outcomes in patients with COVID-19 infection. There aren't any US-FDA, EMA or the other regulatory approved drugs specifically for the treatment of patients with COVID-19.

The Indian Council of Medical Research (ICMR) bulletin dated March 21,2020 recommended the employment of Hydroxychloroquine as prophylaxis for asymptomatic health care workers and asymptomatic household contacts of laboratory confirmed cases of COVID-19.[13] Further, the FDA and WHO have not found adequate evidence to recommend Chloroquine Phosphate or Hydroxychloroquine Sulphate for treatment of COVID-19.[13] Currently, 130 trials are being conducted on evaluating the use of HCQ for treatment/prevention of COVID-19. The combinations of HCQ with macrolide-azithromycin, antiretroviral-ritonavir and dietary supplements like vitamin C and Zinc are also being evaluated. Till now no high quality evidence exist for the chlorquine/hydroxychloroquine treatment. One study conducted in China reported that chloroquine successfully treated more than 100 COVID cases but no clinical trial design or outcomes data has been published.[14] Another French study conducted on 36 patients in open-label randomized trial showed that hydroxychloroquine improved virologic clearance. This study has major limitations such as small sample size and variable baseline viral loads.[15]

Almost 50 clinical trials are on-going use of antiretroviral in treatment of COVID-19. The inconclusive efficacy data with antiretrovirals and their substantial toxicity suggest that it has limited value for treatment of COVID-19. Remdesivir, a newer agent was considered promising potential for the treatment of COVID-19 infection because of its broad-spectrum potency.[16] The first clinical use of Remdesivir was for the treatment of Ebola, however now 11 clinical trials are being conducted to evaluate efficacy of Remdesivir for treatment of COVID-19. COVID-19 virus is a single-stranded RNA-enveloped virus which targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE 2) receptor. Based on this, various discussions started whether ACE inhibitors and/or angiotensin receptor blockers may potentially treat COVID-19 or conversely worsen disease.[17] These drugs upregulate ACE 2 receptors, which could theoretically lead to worse out-comes if viral

entry is enhanced. In contrast, angiotensin receptor blockers could theoretically provide clinical benefit via blockade of ACE2 receptors.[18] There are 22 on-going clinical trials to assess the effect of ACE inhibitors in COVID-19 patients. Till further research outcomes practice guidelines have recommended continuing therapy for patients already taking these drugs.

There is evidence that a hyperinflammatory responses significantly contributes to mortality in COVID-19 infections. The use of corticosteroids is debated as the direct evidence of use in COVID-19 remains limited however the observational studies in patients with SARS ad MERS showed no association of corticosteroid use and improved survival.[19] A meta-analysis conducted in 2019 including 6548 patients showed that corticosteroid when used in influenza pneumonia patients led to increased mortality (RR 1.75 (95% CI 1.3-2.4); p<0.001) and two times increased risk of secondary infections (RR 1.98 (95% CI 1.0-3.8); p=0.04).[20] A recent study conducted in China on COVID-19 patients (n=201) showed that the decreased risk of death and author noted that bias and residual confounding between those who did not receive steroids may exist in this observational study. However, it is one of the adjunct treatment which is given to COVID-19 patients.[21] There are 10 ongoing clinical trials to assess the effect of methylprednisolone in COVID-19 patients.

Nitazoxanide is an antihelminthic agent, which has broad activity antiviral profile and favorable safety profile. There are 12 clinical trials ongoing testing efficacy in treatment of COVID-19. The antiviral profile, immunomodulatory effects and safety profile of nitozoxanide has been used for investigating its use in treatment of COVID-19 infection.[23]

Ruxolitinib a Janus-assoicated kinase (JAK) inhibitor approved by the US FDA and EMA for the treatment of polycythemia vera and myelofibrosis. It was hypothesized that the ruxolitinib might be effective against the consequences of the elevated levels of cytokines in patients with COVID-19.[24] At present there are 11 clinical trials are on-going testing the efficacy of ruxolitinib in the treatment of COVID-19 infections.

The strategies to treat COVID-19 infection is using repurposed drugs and revisiting older strategies.[25] The convalescent plasma was used in past for passive immunizations. In the pre-vaccine era, convalescent plasma was used to treat viral diseases such as poliomyelitits, measles, mumps and influenza and recently, it has been used to treat viral diseases such as Ebola and SARS with varying degree of success.[26] It has been shown than convalescent plasma collected from COVID-19 survivors have specific antibodies with potent antiviral activity. The effect depends on effective titres of antiviral neutralizing antibodies, optimal timing of convalescent plasma treatment, optimal timing of plasma donation, and severity class of patients who are likely to benefit.[27] Various observational studies reporting association between convalescent plasma and reduced

mortality, hospital stay and viral load in patients has been published. But so far three randomized clinical trials have been published. Two of these studies were prematurely terminated – one conducted in China due to inadequate patient enrolment and second the Dutch study because interim findings suggested re-design of the trail.[28] Third clinical trial conducted in India including 464 adult patients showed that the progression to all-cause mortality was not statistically different (p=0.078) in both control (n=41) and intervention (n=44). Further studies are required to find the effectiveness of convalescent plasma and also finding a suitable patient and suitable donor is additional challenge.[27]

The conduct of clinical trials in time of pandemic have so many tenacious issues that need to be addressed. It is very important to utilize the resources efficiently such as following a standard protocol then one can easily pool the data of various trials conducted at various places. Ethical consideration is always a challenge in emerging infectious diseases. For instance, in the design of remdesivir trials (NCT04252664 and NCT 04257656), the placebo was used with the exclusion of any other experimental treatment. The inclusion in placebo group can cause harm to the patients under study for sacrificing the potential best patient care.[27] It is difficult to have a research team specifically designated to conduct and collect data, monitoring research process as well as examining the outcomes specifically in times of pandemic like COVID-19. Timely dissemination of information and positive outcomes of clinical trials and their translation into the clinical practice is also very important.[30]

In this scenario, the tremendous volume and fast pace of published literature on the treatment of COVID-19 indicates the research findings and the recommendations are constantly evolving as new evidence. Hence, author has tries to include the information as far as available from clinicaltrials.gov. All the published literature in this is derived from various studies conducted on smaller groups and mostly observational. The chances of higher risk of bias and imprecision could be there.

CONCLUSION

This study provides information ongoing clinical trials. The pace and volume of clinical trials launched to investigate potential therapies for COVID-19 treatment emphasizes both the need and capability to produce a high-quality evidence even the times of pandemic. Given the smaller sample sizes, long completion period, high risk of bias and imprecise information, it will take quite a long time to obtain high quality clinical evidence for the treatment of COVID-19 infection. The information obtained from the clinical trials should be carefully implemented into the practice taking into the consideration the limitations of the ongoing trials. Till now, no therapies have been approved for the treatment of COVID-19 till date and also it is too early to comment on the outcomes of the vaccination.

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