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Review Article

Current updates on the European and WHO registered clinical trials of coronavirus disease 2019 (COVID-19)

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a major public health concern currently. To date, there are no approved antiviral drugs or vaccines against this transmissible disease. This report sheds light on available information for a better understanding of clinical trials and pharmacotherapy related to COVID-19. MEDLINE, PubMed, EMBASE, Scopus databases, Web of Science, WHO, and EU clinical trial sites were used to perform comparative analysis. Information was collected on the use of therapeutic agents for human therapy in patients with COVID-19 up to May 2020. We have extracted data from 60 clinical trials. Amongst these trials, 34 were from the European Union database of clinical trials and 26 from the National Institute of Health. The data selection procedure includes active, completed, and recruitment in progress status. Most of the clinical trials are ongoing and hence, there is a lack of precise results for the treatment.There is a lack of high-quality clinical evidence. The protocol to be developed requires large randomized clinical trials with a combination of available drugs and prospective therapies. We propose the usage of a large number of cases and different statistical analyses to conduct systematic clinical trials. This could provide comprehensive information about the clinical trial and potential therapeutic progress.

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COVID-19 is a pneumonia-like disease, which is caused by a novel coronavirus [1]. Coronavirus belongs to Orthocoronavirinae subfamily of the Coronaviridae family within the order Nidovirales. COVID-19 is the defining global health crisis that has spread over 205 countries including USA, Italy, Russia, Spain, Japan, Korea, Iran, and Germany [2,3]. By the end of December 2019, a serious pneumonia like cluster of cases with unknown source expanded globally from Wuhan, China [4]. Various reports suggest that the novel coronavirus is 96.2% identical to a bat CoV RaTG13 [5,6]. Evolutionary analysis of virus genome has suspected bat as a natural host of the virus origin that could have been transmitted from an unknown intermediate host to the humans [7]. The infection poses a significant risk to patients with COVID-19 due to the high frequency of pneumonia, fever, and dry cough. Additionally, patients suffer from the potential damage of vital organs, especially the lungs, heart, liver, and kidneys [8–10]. As per the latest reports from China, the mortality rate of COVID-19 disease is approximately 3–4% [11]. The latest data obtained on 30 June 2020 describes that COVID-19 has infected more than Ten million people worldwide. Amongst these cases, 5.6 million have been successfully treated and 5,08,422 has died. The number of infected people is increasing every day by one thousand worldwide.

Recently, severity model based analysis has showed that the fatality ratio for China is 0·66%, on the Diamond Princess ship is 2.3%, and the large meta-analysis of 36 European countries showed the case-fatality rate of COVID-19 range of 4%–4.5% with an increasing profile with age [12–14]. Furthermore, in current scenario, India is ranked as the fourth highest country with positive cases and a case-fatality rate of 1.9–3.6% [15]. In the current situation, a second wave of coronavirus has hit the major cities of European countries including Sao Paulo and Rio de Janeiro, which is the centre for pandemic. Till date, more than 1.3 million positive cases have been identified in Brazil [16]. In Russia, more than 687,862 cases and 10,296 deaths due to COVID-19 infection has been reported [17].

In order to treat COVID-19, the only available treatment currently available is the retroviral therapy. Further, it was proven that convalescent plasma transfusion (CPT) is useful against COVID-19 [18,19]. At this crucial moment, in-depth research is essential to treat and prevent the disease. Several researchers have promptly carried out clinical research aimed towards the diagnosis, treatment, and prevention of COVID-19 [20]. However, globally there is limited information available to analyze and summarize the registered clinical trials. The purpose of this review is to summaries existing COVID-19 clinical trial data that would aid in selecting the most appropriate COVID-19 treatment.

Search Strategy And Selection Criteria

Using various keywords related to COVID-19 including comorbidities, clinical characteristics, epidemiological, immunotherapy, vaccine, and SARS CoV-2 clinical trial data were obtained from different electronic databases. Some of these databases were European union clinical trials database, Clinical Trial Registry, Clinicatrial.gov, International Clinical Trials Registry Platform (WHO ICTRP), Chinese Biomedical Literature Database, and the Wanfang Database. Pubmed, the National Library of Medicine (NLM), and EMBASE database were also used to identify ongoing trials.

Literature Inclusion And Exclusion Criteria

All investigators have selected only the most appropriate and suitable studies. Inclusion criteria encompasses the following: (1) studies of COVID-19 patients' clinical trials, (2) detailed protocol of clinical trials, (3) data mining, (4) the original design type (Interventional or observational), (5) reports that involved the treatment of COVID-19. The exclusion criteria includes the following: (1) studies having duplicate data and (2) vague theoretical research and unregistered clinical trials.

Quality Assessment

Quality of clinical data and extracted data from the literature were assessed by rigorous information cross-check. Discrepancy between the investigators was resolved and the final decisions were decided without any conflicts. Relevant data was summarized in a narrative manner and the treatment strategy was grouped. Each table was categorized according to the drug usage. Results were classified based on the type of study, country, dose, duration of administration, an indication of medication, and the number of patients included in the study.

Results

Trial search outcomes

34 clinical trials from the European Union clinical trial database and 26 clinical trials from the National Institute of Health (NIH) clinical trial database were retrieved and presented in the flow chart [Fig. 1]. A total of 60 clinical trials of COVID-19 were classified as either active, completed, or recruiting. 8 patients used hydroxyquinone alone or in combination with other drugs, 6 used remdesivir, 5 used Tocilizumab, Lopinavir/ritonavir either single or combined, 4 used Interferon alpha and beta, and 4 patients used Plaquenil. All other remaining cases used different types of molecules or interventions [Table 1 and Table 2]. Above all, most of the trials have cleared the ethical approval. Some of the case studies are still in the recruitment phase, whereas 20 trials have begun recruiting patients. Amongst them, only 4 trials are in active phase and in the next few days, patient recruitment will begin. 2 clinical trials are still incomplete.

The first randomized controlled clinical pathways were sponsored by Dongzhimen Hospital of the Beijing University of Traditional Chinese Medicine (medical aspects of traditional knowledge that developed over generations). Those drugs were registered as "Chinese Severe Pneumonia Medicine with Severe Coronavirus Pneumonia" on 3 January 2020. In this review, we have included 60 trials in terms of clinical trial phases. Amongst them, 43 trials are in the preliminary experimental phase, 7 are in the middle phase, 8 are in phase 3

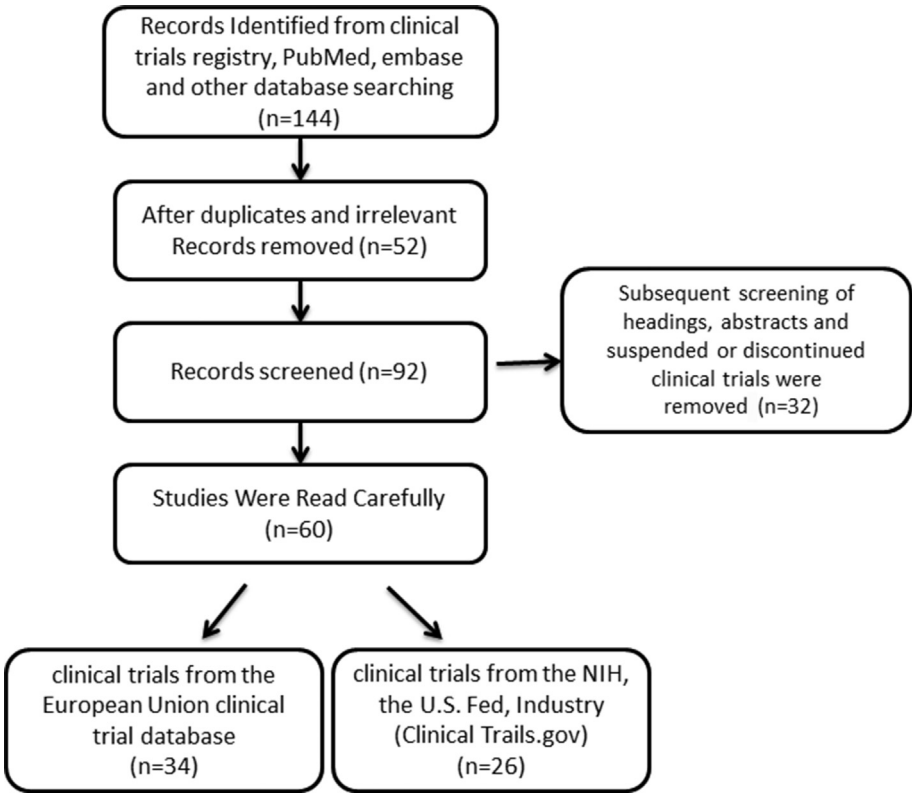

Fig. 1 Flowchart of study selection for the present study.

and extended for validation. 1 trial is completed with Ganovo+ritonavir ± Interferon nebulization drugs and ready for sale as the same diagnostic kit (Quest Diagnostics, Bill and Melinda).

Intervention and evaluation

The leading intervention strategy of registered clinical trials consists of traditional Chinese medicine, western medicine, and conventional integrated treatment. Especially, the outcome of therapy includes treatment time, patient immunity, frequency of use of ventilation, mortality, number of complications, and virological detection indicators. Current duration of the medication is more than 10 days. Medicinal approaches include oral, injection, and inhalation. The control subject was treated regularly with a placebo. At present, 24 western medicinal treatments are registered in clinical trials. On the other hand, single or combination of biological agents such as hydroxychloroquine, camostat mesilate, sargramostim, colchicine, tocilizumab, remdesivir, Itraconazole, IFX-1, Imatinib mesilate, Interferon beta-1a (IFN-β1a), Sarilumab, Budesonide, and Nitric Oxide 0.5%/Nitrogen 99.5% Gas for Inhalation, Recombinant human angiotensin-converting enzyme 2, Plaquenil, lopinavir/ritonavir, RoActemra, Chloroquine phosphate, Hydrocortisone, Levofloxacin, Emapalumab, Anakinra, Sarilumab, Danoprevir+ritonavir ± Interferon, Emtricitabine/tenofovir are listed as intervention methods.

Two clinical trials include biological agents product mRNA, blood stem cells, cord blood mononuclear cells, mesenchymal stem cell (MSC), recombinant cytokine gene-derived vector, and immunoglobulin (IgM, IgG).

Discussion

Since the impact of COVID-19 is extremely severe, the development of an effective treatment strategy against the infection is very critical and concerning throughout the world. Although the molecular diagnosis, treatment, and international public health has improved after experiencing the 2003 SARS (CoV-I) epidemic, due to the new mutant form of the COVID virus, it is difficult to diagnose and treat the infection. Moreover, there is no proven or recognized licensed therapy against COVID-19. This sudden event has caused a high mortality rate in China and other countries around the world, mainly the European regions. The current situation leads us to carry out a systematic review to summarize the on-going clinical trials and possible therapeutic options against COVID-19 [1,11,21]. Intensive clinical trials are being conducted by many researchers to eradicate this disease.

Most of the reports demonstrate the intervention of western medicine and a combination of traditional medicine to treat COVID-19 infection. Most of the studies are still in the preliminary experimental phase of the clinical trail. There are 43 extended (Phase 1) trial studies that show the utilization of drugs (Hydroxychloroquine, Camostat mesilate, Sargramostim, Colchicine, Tocilizumab, Remdesivir, Itraconazole, IFX-1, Imatinib mesilate, Interferon beta-1a (IFN-β1a), Kevzara, Budesonide, Lopinavir/ritonavir, RoActemra,

Table 1 List of various combination strategies used in current WHO clinical trials in the treatment of COVID-19.

NOs	NCT Number	Title	Status	Interventions	Sponsor	Age	Phases	Enrollment	Study Type	Start Date	Completion
1.	NCT04333420	Open label, randomized phase ii/iii study of ifx-1 in patients with severe covid-19 pneumonia	Recruiting	Best supportive Care (BSC) + IFX-1|	InflaRx GmbH	18 Years and older	Phase 2 Phase 3	130	Interventional	31-Mar-20	31-Dec-20
2.	NCT04306497	Clinical Trial on Regularity of TCM Syndrome and Differentiation Treatment of COVID-19.	Recruiting	TCM prescriptions	Jiangsu Famous Medical Technology Co., Ltd.	18 Years–75 Years	NA	340	Observational	02-Mar-20	May-20
3.	NCT04292899	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734„¢) in Participants With Severe Coronavirus Disease (COVID-19)	Recruiting	Remdesivir	Gilead Sciences	18 Years and older	Phase 3	400	Interventional	06-Mar-20	May-20
4.	NCT04292730	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734„¢) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	Recruiting	Remdesivir	Gilead Sciences	18 Years and older	Phase 3	600	Interventional	15-Mar-20	May-20
5.	NCT04324489	DAS181 for Severe COVID-19: Compassionate Use	Recruiting	DAS181	Renmin Hospital of Wuhan University|Ansun Biopharma, Inc.	18 Years–70 Years	NA	4	Interventional	06-Mar-20	30-Apr-20
6.	NCT04330690	Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial	Active, not recruiting	Lopinavir/ritonavir	Sunnybrook Health Sciences Centre|AbbVie	6 Months and older	Phase 2	440	Interventional	18-Mar-20	NA
7.	NCT04324021	Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection.	Recruiting	Emapalumab, Anakinra	Swedish Orphan Biovitrum	30 Years–79 Years	Phase 2 Phase 3	54	Interventional	Apr-20	Sep-20
8.	NCT04327388	Sarilumab COVID-19	Recruiting	Sarilumab	Sanofi|Regeneron Pharmaceuticals	18 Years and older	Phase 2| Phase 3	300	Interventional	28-Mar-20	Jun-21
9.	NCT04334954	SARS-COV2 Pandemic Serosurvey and Blood Sampling	Recruiting	NA	National Institute of Allergy and Infectious Diseases (NIAID)	18 Years and older	NA	1000	Observational	09-Apr-20	31-Mar-22
10.	NCT04325646	Sero-epidemiological Study of the SARS-CoV-2 Virus in France: Constitution of a Collection of Human Biological Samples	Recruiting	Human Biological samples	Institut Pasteur	5 Years and older	NA	1000	Observational	13-Mar-20	28-Feb-23
11.	NCT04328129	Household Transmission Investigation Study for COVID-19 in French Guiana	Recruiting	Human biological samples	Institut Pasteur	5 Years and older	NA	450	Interventional	23-Mar-20	23-Mar-22
12.	NCT04280705	Adaptive COVID-19 Treatment Trial (ACTT)	Recruiting	Remdesivir	National Institute of Allergy and Infectious Diseases (NIAID)	18 Years–99 Years	Phase 3	440	Interventional	21-Feb-20	01-Apr-23
13.	NCT04313127	A Phase I Clinical Trial in 18–60 Adults	Active, not recruiting	Adenovirus Type 5 Vector	CanSino Biologics Inc.|Institute of Biotechnology, Academy of Military Medical Sciences. PLA of China|Jiangsu Province Centers for Disease Control and Prevention|Hubei Provincial Center for Disease Control and Prevention|Tongji Hospital	18 Years–60 Years	Phase 1	108	Interventional	16-Mar-20	20-Dec-22
14.	NCT04321811	Behavior, Environment And Treatments for Covid-19	Recruiting	Human Biological samples	xCures|Genetic Alliance|LunaDNA|Cancer Commons|REDCap Cloud	18 Years and older	NA	100000	Observational	21-Mar-20	20-Mar-22
15.	NCT04333654	Hydroxychloroquine in Outpatient, Adults With COVID-19	Recruiting	Hydroxychloroquine	Sanofi	18 Years and older	Phase 1	210	Interventional	31-Mar-20	May-20
16.	NCT03808922	Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects (Substudy: DAS181 for COVID-19): RCT Study	Recruiting	DAS181	Ansun Biopharma, Inc.	5 Years and older	Phase 3	250	Interventional	23-May-19	28-Dec-21
17.	NCT04291729	Evaluation of GanovòDanoprevir Combined With Ritonavir in the Treatment of Novel Coronavirus Infection	Completed	Ganovo+ritonavir ± Interferon nebulization	The Ninth Hospital of Nanchang|Ascletis Pharmaceuticals Co., Ltd.	18 Years–75 Years	Phase 4	11	Interventional	17-Feb-20	19-Mar-20
18.	NCT04334928	Clinical Trial for the Prevention of SARS-CoV-2Infection in Healthcare Personnel (EPICOS)	Active, not recruiting	Emtricitabine/tenofovir disoproxil|Hydroxychloroquine	Plan Nacional sobre el Sida (PNS)|Effice Servicios Para la Investigation S.L.	18 Years–65 Years	Phase 3	4000	Interventional	01-Apr-20	31-Jul-20
19.	NCT04321369	Impact of Swab Site and Sample Collector on Testing Sensitivity for SARS-CoV-2 Virus in Symptomatic Individuals	Completed	Diagnostic tests	Dr. Deneen Vojta|Quest Diagnostics|Bill and Melinda Gates Foundation|UnitedHealth Group	5 Years and older	NA	533	Observational	09-Mar-20	23-Mar-20

(*continued on next page*)

Table 1 – (continued)

NOs	NCT Number	Title	Status	Interventions	Sponsor	Age	Phases	Enrollment	Study Type	Start Date	Completion
20.	NCT04327804	A Longitudinal Study of SARS-CoV-2 Positive Patients Testing Nasal Swabs and Collecting Blood Samples for Research	Recruiting	Diagnostic Test	Dr. Deneen Vojta|PATH|Mayo Clinic|Bill and Melinda Gates Foundation	5 Years and older	NA	120	Observational	25-Mar-20	10-Apr-20
21.	NCT04283461	Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis SARS CoV-2 Infection	Recruiting	mRNA-1273	National Institute of Allergy and Infectious Diseases (NIAID)	18 Years–55 Years	Phase 1	45	Interventional	03-Mar-20	01-Jun-21
22.	NCT03331445	Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections	Active, not recruiting	Nitric Oxide 0.5%/Nitrogen 99.5% Gas for Inhalation	University of British Columbia|Mallinckrodt	14 Years and older	Phase 2	20	Interventional	24-Oct-17	31-Mar-21
23.	NCT04331171	Epidemiological Observation From a Smartphone Self-monitoring Application for Suspected COVID-19 Patients' Triage	Recruiting	Device	Weprom|Institut Pasteur|Assistance Publique - HÃ³pitaux de Paris|DOCAPOST|Direction GÃ©nÃ©rale de l'Offre de Soins	18 Years and older	NA	3000000	Observational	17-Mar-20	31-Jul-20
24.	NCT04321278	Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition Covid-19 Brasil II)	Recruiting	Hydroxychloroquine + azithromycin	Hospital Israelita Albert Einstein|EMS|Hospital do Coracao|Hospital Sirio-Libanes|Brazilian Research In Intensive Care Network|CristÃ¡lia Produtos QuÃmicos FarmacÃªuticos Ltda.	18 Years and older	Phase 3	440	Interventional	28-Mar-20	30-Aug-20
25.	NCT04326309	Audio Data Collection for Identification and Classification of Coughing	Recruiting	NA	HealthMode Inc.	18 Years and older	NA	1000	Observational	25-Mar-20	25-Sep-22

Chloroquine phosphate, Hydrocortisone, Levofloxacin, Emapalumab, Anakinra, Sarilumab). According to the population size used in the clinical trial, 18 interventional clinical trials were carried out, which included 4 to 4000 candidates/trials and 8 observational studies, that included around 1000 to 3000000 candidates. Most of the trials are on-going; thus, the confirmation level and the clinical significance is limited [Table 1].

The alternative strategy to fight against COVID-19 is mainly based on boosting immune responses and to prevent the disease complications. This strategy improves patient immunity by predominating self-immune damage to the cytokine storm (modulating the post-infection immune response) and symptomatic treatment [22]. Although some Chinese herbs have shown both antiviral and high immune effects, current situations prove that the antiviral effect of western drugs is superior and tolerable in comparison to the traditional ayurvedic, Unani, or homeopathic medicines [23,24]. The combination of Qingfeipaidutang and hydroxychloroquine phosphate might be a potential therapeutic strategy for the treatment and management of COVID-19 [25,26]. Recently, an open-label, randomized clinical trial of standard medical treatment or colchicine (1.5-mg loading dose by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily) in 105 patients showed that event-free survival time was 20.7 days in the colchicine group and 18.6 days in the control group and a significantly improved time to clinical deterioration [27]. Another multicenter, open-label randomized controlled trial in 160 patients with Shenhuang granule (50 g of *Panax ginseng* C. A. Mey, 40 g of *Rheum palmatum* L. stem, 30 g of *Sargentodoxa cuneata* stem, 30 g of *Taraxacum mongolicum*, 50 g of Aconiti Lateralis Radix Praeparata, and 6 g of Whitmania pigra Whitman) twice a day for 14 days is underway and the trail results are awaiting [28].

Still, there is a lack of high-grade substantiation evidence that demands further clinical clarification and verification. Several clinical researchers have used biological products for the treatment of COVID-19. In order to treat COVID-19 infection, Steroid-based therapy has been implemented and the result availability is limited for trials [13,29]. The most commonly used drug is chloroquine (anti-malaria) and ribavirin with a broad-spectrum antiviral combination of Remdesivir and IFN-α2b. An interventional study based in Spain was registered at ClinicalTrials.gov on 1 April 2020 (ID: NCT04334928). Currently, this is the only clinical trial underway with Emtricitabine/tenofovir disoproxil/hydroxychloroquine against COVID-19 infection. Due to minimal interaction, the combination of baricitinib and lopinavir/ritonavir/remdeviate antivirals was used to treat the infection COVID-19 during the pandemic. The combination of baricitinib and above-mentioned drugs may reduce viral replication, infectivity, and aberrant host inflammatory response [30].

Future perspective

In most trials, inclusion and exclusion criteria has eliminated children under 18 years, pregnant women, and comorbidities like liver, heart, and kidney disease. This may result in a lack of substantial clinical evidence. The quality of clinical

Table 2 Characteristics of ongoing European Union Clinical Trials studying the efficacy and safety of Chloroquine, Tocilizumab, Lopinavir/ritonaviror other related formulation for patients with novel coronavirus pneumonia (COVID-19).

S.No	Sponsor Name	Protocol No	Study Title	Start Date	Ongoing/ Completed	Population Age	No. of Subject	Medical Condition	Active Substances	Level	Rout	Country/National Competent Authority
1	Akershus University Hospital	Ahus–NO–COVID-19	Norwegian coronavirus disease 2019 (no covid-19) study: an open labeled randomized controlled pragmatic trial to evaluate the antiviral effect of chloroquine in adult patients with sars-cov-2 infection	2020-03-23	Ongoing	Adults, Elderly (18–64)	200	SARS-COV-2 infection	hydroxychloroquine sulfate 200 mg	LLT	Oral	Norway
2	University of Oxford/Clinical Trials and Research Governance	PRINCIPLE	Platform Randomised trial of interventions against COVID-19 In older people	2020-03-26	Ongoing	Adults, Elderly (18–64)	3000	Suspected COVID-19	Hydroxychloroquine Sulfate 200 mg	PT	Oral	UK - MHRA
3	Department of Infectious Diseases, Aarhus University Hospital	CamoCO-19-001	The Impact of Camostat Mesilate on COVID-19 Infection: An investigator-initiated randomized, placebo-controlled, phase iia trial	2020-03-30	Ongoing	Adults, Elderly (18–64)	180	2019-nCoV acute respiratory disease	Camostat mesilate 100 mg	LLT	Oral	Denmark - DHMA
4	University Hospital Ghent	SARPAC	A prospective, randomized, open-label, interventional study to investigate the efficacy of sargramostim (Leukine®) in improving oxygenation and short- and long-term outcome of COVID-19 patients wit …	2020-03-24	Ongoing	Adults, Elderly (18–64)	80	Acute hypoxic respiratory failure of COVID-19 patients	Sargramostim 250ug	LLT	Intravenous	Belgium - FPS Health-DGM
5	Hellenic Society of Rhythmology	GRECCO-19	The Greek study in the Effects of Colchicine in Covid-19 complications prevention	2020-04-01	Ongoing	Adults, Elderly (18–64)	180	myocardial necrosis and pneumonia development in the context of COVID-19	Colchicine	PT	Intravenous	Greece - EOF
6	Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia	RCT-TCZ-COVID-19	Uno studio randomizzato multicentrico in aperto per valutare l'efficacia della somministrazione precoce del Tocilizumab (TCZ) in pazienti affetti da polmonite da COVID-19	2020-03-27	Ongoing	Adults, Elderly (18–64)	398	COVID-19 infection	Tocilizumab 20 mg/ml	PT	Intravenous	Italy - Italian Medicines Agency
7	CHU Angers	49RC20_0071	HYCOVID - Hydroxychloroquine versus placebo chez les patients ayant une infection COVID-19 à risque d'aggravation secondaire: étude prospective multicentrique randomisée en double aveugle	2020-03-31	Ongoing	Adults, Elderly (18–64)	1300	Covid-19	Hydroxychloroquine 200 mg	LLT	Oral	France - ANSM
8	F. Hoffmann-La Roche Ltd	WA42380	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of tocilizumab in patients with severe covid-19 pneumonia.	31-03-20	Ongoing	Adults, Elderly (18–64)	50	COVID-19 pneumonia	Tocilizumab 20 mg/ml	PT	Intravenous	France - ANSM
9	Regents of the University of Minnesota	10	A Multicenter, Adaptive, Randomised, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults - Version for European U …	25-03-20	Ongoing	Adults, Elderly (18–64)	100, 50, 40	Influenza COVID-19	Remdesivir 100/200 mg	HLT	Intravenous	Denmark - DHMA & UK - MHRA
10	UZLeuven	S63874	Covid-19: A randomized, open-label, adaptive, proof-of- concept clinical trial of new antiviral drug candidates against SARS-cov-2.	26-03-20	Ongoing	Adults, Elderly (18–64)	200	COVID-19	itraconazole	LLT	Intravenous	Belgium - FPS Health-DGM
11	Sanofi-aventis recherche & développement	EFC16858	An adaptive Phase 2/3, randomized, open-label study assessing efficacy and safety of hydroxychloroquine for hospitalized patients with moderate to severe COVID-19	2020-04-02	Ongoing	Adults, Elderly (18–64)	40, 50	Coronavirus infection	Plaquenil 200 mg	PT	Oral	UK – MHRA, France - ANSM

(*continued on next page*)

Table 2 – (*continued*)

S.No	Sponsor Name	Protocol No	Study Title	Start Date	Ongoing/ Completed	Population Age	No. of Subject	Medical Condition	Active Substances	Level	Rout	Country/National Competent Authority
12	InflaRx GmbH	IFX-1-P.2.9	A pragmatic adaptive open label, randomized Phase II/III multicenter study of IFX-1 in Patients with severe COVID-19 Pneumonia - "PANAMO"	2020-03-29	Ongoing	Adults, Elderly (18–64)	47	Severe pneumonia in context of COVID-19	IFX-1	PT	Intravenous	Netherlands - Competent Authority
13	GUSTAVE ROUSSY	2020/3078	COVID-19 - Epidemiology of SARS-CoV-2 and Mortality to Covid19 Disease upon Hydroxychloroquine and Azithromycin Therapy in French Cancer patients	2020-04-03	Ongoing	Adults, Elderly (18–64)	1000	Patients eligible for, or under, or recently treated by chemotherapy (CT) and/or immune-checkpoint blockade (ICB) for the treatment of solid tumors or hematological malignancies.	hydroxychloroquine	LTT	Oral	France - ANSM
14	Amsterdam UMC	COVID-19	COUNTER-COVID - Oral imatinib to prevent pulmonary vascular leak in COVID-19 – a randomized, single-blind, placebo controlled, clinical trial in patients with severe COVID-19 disease	2020-03-31	Ongoing	Adults, Elderly (18–64)	304	Covid19 is characterized by hypoxemic respiratory failure, caused by extensive vascular leak and pulmonary edema early in the course of disease.	Imatinib mesilate	NA	Oral	Netherlands - Competent Authority
15	ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI - FONDAZIONE "G. PASCALE"	TOCIVID-19	Multicenter study on the efficacy and tolerability of tocilizumab in the treatment of patients with COVID-19 pneumonia	2020-03-18	Ongoing	Adults, Elderly (18–64)	330	COVID-19	Tocilizumab 20 mg/ml	PT	Intravenous	Italy - Italian Medicines Agency
16	Synairgen Research Limited	SG016	A randomised double-blind placebo-controlled trial to determine the safety and efficacy of inhaled SNG001 (ifnβ-1a for nebulisation) for the treatment of patients with confirmed SARS-cov-2 infectio …	2020-03-17	Ongoing	Adults, Elderly (18–64)	200	COVID-19	Interferon beat-1a (IFN-β1a)	LLT	Intravenous	UK - MHRA
17	Assistance Publique - Hôpitaux de Paris	APHP200375	Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients	2020-03-25	Ongoing	Adults, Elderly (18–64)	1000	COVID-19	Kevzara	LLT,	Intravenous	France - ANSM
18	DRCI APHP	APHP200394	Protective role of inhaled steroids for COVID-19 infection	2020-04-05	Ongoing	Adults, Elderly (18–64)	Not announced	COVID-19	Budesonide	NA	Inhalation	France - ANSM
19	Gilead Sciences, Inc.	GS-US-540-5774	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment	2020-03-18	Ongoing	Adults, Elderly (18–64)	35, 35, 35,40,50,100	COVID-19	Remdesivir 100 mg	LLT	Intravenous	Germany - BfArM, Spain - AEMPS, France - ANSM, France - ANSM, Netherlands - Authority, UK - MHRA, Sweden - MPA
20	Gilead Sciences, Inc.	GS-US-540-5773	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19	2020-03-18	Ongoing	Adolescents, Under 18, Adults, Elderly	200, 20, 20, 45, 40, 100, 100	Coronavirus disease 2019 (COVID-19)	Remdesivir 100 mg	LLT	Intravenous	Germany - BfArM, Spain - AEMPS, France - ANSM, France - ANSM, Netherlands - Competent Authority, UK - MHRA, Sweden - MPA
21	APEIRON Respiratory Therapies GmbH	APN01-01-COVID19	Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treat-ment for patients with COVID-19	2020-04-03	Ongoing	Adults, Elderly (18–64)	50	Severe COVID-19 POSITIVE hospitalized male or female, between 35 and ≤80 years of age	Recombinant human angiotensin-converting enzyme 2	NA	Intravenous	Denmark - DHMA
22	Oslo University Hospital	WHO-NOR-COVID-19	The NOR Solidarity multicenter trial on the efficacy of different anti-viral drugs in SARS-cov-2 infected patients (COVID-19)	2020-03-26	Ongoing	Adults, Elderly (18–64)	443	SARS-COV-2 infection	Plaquenil	LLT	Oral	Norway - NOMA

23	CHU de Saint Etienne	20CH065	Evaluation of the concentration/viral effect relationship of hydroxychloroquine in COVID-19 patients in the intensive care unit.	2020-03-30	Ongoing	Adults, Elderly (18–64)	50	covid-19	Hydroxychloroquine sulfate 400–800 mg	LLT, PT	Oral	France - ANSM
24	University of Oxford	NDPHRECOVERY	Randomised Evaluation of COVID-19 Therapy (RECOVERY)	2020-03-17	Ongoing	Adults, Elderly (18–64)	Not announced	COVID-19 (infection with SARS-CoV-2 virus)	Lopinavir/ritonavir 200 mg	PT, PT	Oral	UK - MHRA
25	Fondation Méditerranée Infection (FMI) - IHU Méditerranée Infection	202002102	Treatment of Coronavirus SARS-Cov2 Respiratory Infections with Hydroxychloroquine	2020-03-05	Ongoing	Adolescents, (12–17), Adults, Elderly (18–64)	25	Patients with documented respiratory infection with coronavirus SARS COV 2	Plaquenil 200 mg	LLT,	Oral	France - ANSM
26	University Hospital Ghent	COV-AID	A prospective, randomized, factorial design, interventional study to compare the safety and efficacy of combinations of blockade of interleukin-6 pathway and interleukin-1 pathway to best standard ...	2020-04-03	Ongoing	Adults, Elderly (18–64)	342	COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome.	RoActemra		Intravenous	Belgium - FPS Health-DGM
27	INSERM	C20-15	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	2020-03-09	Ongoing	Adults, Elderly (18–64)	1000	COVID-19 -	Plaquenil 200 mg	LTT	Oral	France - ANSM
28	Universitätsklinikum Tübingen	COV-HCQ	Randomized controlled trial of hydroxychloroquine versus placebo for the treatment of adult patients with acute coronavirus disease 2019 – COVID-19	2020-03-25	Ongoing	Elderly (>65)	220	Acute coronavirus disease 2019	Chloroquine phosphate 200 mg	PT	Oral	Germany - BfArM
29	Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.	UNIKINON-01/HOPE	CHROLOQUINE PHOSPHATE AGAINST INFECTION BY THE NOVEL CORONAVIRUS SARS-cov-2 (COVID-19): THE HOPE OPEN-LABEL, NON-RANDOMIZED CLINICAL TRIAL	2020-04-02	Ongoing	Adults, Elderly (18–64)	60	pneumonia from SARS-CoV-2 in patients staying home and improving symptoms of SARS-CoV-2 pneumonia in patients treated in hospital	Tocilizumab	LLT	Intravenous	Greece - EOF
30	Sanofi-aventis Recherche et Développement	EFC16844	An adaptive phase 2/3, randomized, double-blind, placebo-controlled, study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19	2020-03-26	Ongoing	Adults, Elderly (18–64)	25, 40, 25	Corona virus infection	Hydrocortisone	PT	Intravenous	Germany - BfArM, France - ANSM, Italy - Italian Medicines Agency
31	University Medical Center	73249	Reducing health care workers absenteeism in SARS-cov-2 pandemic by enhanced trained immune responses through Bacillus Calmette-Guérin vaccination, a randomized controlled trial (COVID-19).	2020-03-17	Ongoing	Adults, Elderly (18–64)	1000	SARS-CoV-2 infection	BCG-CORONA	HLT	Intravenous	Netherlands - Competent Authority
32	Hellenic institute for the study of sepsis	ESCAPE	Efficiency in management of organ dysfunction associated with infection by the novel sars-cov-2 virus (covid-19) through a personalized immunotherapy approach: the escape clinical trial	2020-04-01	Ongoing	Adults, Elderly (18–64)	20	Organ dysfunction by the novel SARS-Cov-2 virus	Tocilizumab 400 mg	LLT	Intravenous	Greece - EOF
33	The Parker Institute, Bispebjerg and Frederiksberg Hospital,	APPI2-CV-2020-01	Effectiveness of Interleukin-6 Receptor Inhibitors in the Management of Patients with Severe SARS-CoV-2 Pneumonia: An Open-Label Multicenter Sequential Randomized Controlled Trial	2020-04-3	Ongoing	Adults, Elderly (18–64)	200	SARS-CoV-2 infection	Tocilizumab 400 mg	LLT	Intravenous	Denmark - DHMA
34	University Medical Center Utrecht	REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP)	2015-09-16	Ongoing	Adults, Elderly (18–64)	600,600, 40, 800, 200, 270, 600,30, 60, 152	Severe Community Acquired Pneumonia	Levofloxacin	LLT	Intravenous	Netherlands, Ireland, Portugal, UK- MHRA, Hungary, Belgium, Germany, Croatia, Spain, FRance

LLT: Lowest Level Terms, PT: Preferred Terms, HLT: High-Level Terms, NA: Not Available.

research needs to improve drastically. Registered clinical trials must follow Observatory/Interventional Clinical Trial Guidelines. Clinical trials must not be registered without accurate drug testing. Safety guidelines for *in vitro* experiments during clinical trials are a major concern. Thus, The National Science Research Administration (NASR) should consider improving the health risks assessment, good research practice, and coordination of fewer promising drugs i.e.; Remdesivir. Moreover, a major limitation of the registered clinical studies is that most of them follow a traditional conservative approach without considering the timeline.

Conclusion

Due to the lack of intensive and high-quality clinical evidence, there is no final consent to the ideal therapy for COVID-19. It is difficult to obtain reliable data even with a small sample size and prolonged study periods. There is a undoubted need for protocol development that can be used for large randomized clinical trials. In order to establish such clinical trials, prospective therapies must be designed. The NASR must improve the good clinical practice in research and coordination along as well as aid in improving the efficacy and quality of the study that could deal with current health emergencies. Besides, during clinical trials, the implementation of a variety of study designs with a large number of cases and different statistical analyses is crucial. Further; we must recognize the ancient history report of previous infectious diseases in order to implement novel conceptual health-related policies.

Conflicts of Interest

The authors have declared that there are no conflicts of interest.

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