Clinical Trials for COVID-19 – An Urgent Response

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In this article, we listed databases, guidance, protocols, guidelines, and similar resources that have been produced to help in the tracking and identification of trials and studies about COVID-19. We focused the clinical trials with antiviral drugs, inflammatory cascade (cytokine storm) / target-receptors / blokers, antibiotics, complement system, antibodies, breathing support, testing methods, healthcare workers, impact on other conditions, and vaccines. We used four database to reproduce the clinical trials and to present some of the most promising therapeutic approaches from March to May, 2020: clinicaltrials.gov (clincial trials around the word and in the USA – 1,833 clinical trials in May 30, 2020), the data from Brazil (Rebec), EU Clinical Trials Register (European Union – 37,503 clinical trials with a EudraCT protocol), and the list of the International Clinical Trials Registry Platform (ICTRP) from World Health Organization (WHO). We also prepared an Appendix with the main promise clinical trials evidences against COVID-19 until May 10, 2020.
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Introduction

Since COVID-19 spread to over 190 countries, it has become the greatest challenge worldwide. There have been pandemics before in the history of human race, yet this specific pandemic has reached not only individuals but all of society as a whole, becoming not only a health issue but an economic and social problem. Henceforth, fast development and approval of effective and safe treatments is essential to minimize losses of lives during the pandemic. The world teamed up to identify effective strategies, drugs, therapies, and vaccines that are effective and safe to combat COVID-19. There has been exceptional progress, with multiple agents in late-stage clinical trials [1]. We used three databases to reproduce the clinical trials and to present some of the most promising therapeutic approaches. We used the site clinicaltrials.gov (clinical trials around the word and in the USA – 1833 clinical trials in May 30, 2020), the data from Brazil (Rebec), EU Clinical Trials Register (European Union – 37,503 clinical trials with a EudraCT protocol, of which 6,153 are clinical trials conducted with subjects less than 18 years old, and information on 18,700 older pediatric trials – in scope of Article 45 of the Pediatric Regulation (EC) No 1901/2006), and a list from International Clinical Trials Registry Platform (ICTRP) from World Health Organization (WHO) that does not include those from clinicaltrials.gov [1-3]. In order to track the ever growing number of clinical trials (with information and findings emerging at an unprecedented pace), the Global Coronavirus COVID-19 Clinical Trial Tracker has been created, gathering and classifying all trials in order to avoid waste of time and efforts [5].

This article aims to present the clinical trials database and the main promising clinical trials evidences in the treatment for COVID-19 (Appenix 1 – The appendix was listed on May 10,2020).

Promising Clinical Trials

Antiviral Drugs

There were no promising results in the first trials with traditional antiviral drugs [6, 7]. Nevertheless, due to the possibility that multiple small trials might not generate enough evidence to determine the effectiveness of treatments, WHO

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put together the international SOLIDARITY study. The purpose was to compare untested treatments for COVID-19, and it is made up of over dozens of countries studying four possible treatments: a combination of HIV protease inhibitors ritonavir and lopinavir, the RNA polymerase inhibitor remdesivir, and lopinavir associated with ritonavir in combination with the immunomodulatory agent interferon beta-1ª [8][4].

The RECOVERY trial (UK) is ordering together similar selections of possible treatments at several hospitals. Because of the adaptive nature of its design, new treatments are being joined to the trial as evidence emerges. As of the month of May of 2020, RECOVERY is currently the world's biggest trial of drugs to treat COVID-19 patients [9]. Another clinical trial that appears to be encouraging is the antiviral agent ribavirin (Virazole®, Bausch Health Companies Inc., Laval, Canada) - a nucleoside that restrains syncytial virus (RSV) replication, approved in several countries for the treatment of infants and young children with severe lower respiratory tract infections. So, this trial is evaluating the safety and efficacy of hospitalized adult patients with COVID-19 with critical respiratory distress [10]. A similar antiviral drug, favipiravir (Avigan®, FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan), is currently in phase II development (NCT04358549) [11].

Currently, there are many clinical trials about ribavirin, its dose and the effectiveness of the drug. Ribavirin was approved by FDA to be used in severe patients with COVID-19 in intensive care units (ICU) due to the efficacy of the drug in reducing petients'time in ventilators and in reducing mortality.

Antibiotics

The preclinical and clinical data infers that the antibiotic azithromycin (Zithromax®, Pfizer Inc., New York, NY, USA) has antiviral characteristics and this is being investigated in patients with COVID-19 [12].

Inflammatory Cascade (Cytokine Storm) / Target-Receptors / Blockers

Recent data propose that patients with COVID-19 have high serum levels of pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which drive a cytokine storm [13]. So, other proposals include targeting the inflammatory response to the virus. The same study, carried out by a group of several Chinese medical institutions, shows that infiltration of immune cells in COVID-19 patients' lungs due to the aggravated immune response leads to lung damage, which results in acute respiratory distress syndrome (ARDS). "Preventing the cytokine storm has therefore become an important investigational strategy in the development of COVID-19 therapeutics", says medical writer Katrina Mountfort.

One of the over expressed cytokines produced by activated macrophages in COVID-19 infections is Interleukin (IL)-6[14]. That is why some of the first agents to be assessed in patients with COVID-19 infection are antibodies such as sarilumab (Kevzara®, Sanofi, New York, NY, USA and Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) and tocilizumab (Actemra/RoActemra®, F. Hochmann-La Roche AG, Basel, Switzerland), which are effective in blocking IL-6 signal transduction.

Phase II of the investigation regarding sarilumab, in Sanofi's trial (NCT04327388), revealed fast lowering of C-reactive protein, a key marker of inflammation[4]. Sarilumab showed no evidence of benefits when combining the severe and critical groups *versus* placebo, but the clinical trial has been amended, and enrollment to receive treatment became solely for critical patients. It occurs because negative outcomes were reported for most of those in the "severe" group, while there were positive inclinations for outcomes in the critical group [15].

Studies with tocilizumab seem to have more promising results, although the Roche global,

randomized, double-blind, placebo-controlled phase II COVACTA trial (NCT04320615) will be sure to provide a more definitive answer [16]. In the interim, Novartis released plans for phase III the clinical trial that studies Canakinumab, an IL-1β blocker, in COVID-19 patients that developed pneumonia, after evidence of elevated levels of IL-1β in COVID-19 patients [17].

Other conclusions by Dr. Mountfort concerning current clinical trials for COVID-19 treatments involve the possible therapeutic approach in the regulation of overactive signaling through the janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway during a cytokine storm. Ruxolitinib (Jakafi®, Incyte Corporation, Wilmington, DE, USA) is a JAK1/JAK2 inhibitor approved for polycythaemia vera, myelofibrosis and graft-versus-host disease. A global phase III study, RUX-COVID (NCT04331665), is evaluating the safety and efficacy of ruxolitinib, together with the current standard of care for COVID-19 [18]. Also, Barcitinib JAK1/JAK2 inhibitor) (Olumiant®, Eli Lilly and Company, Indianapolis, IN, USA), approved in many countries as a treatment for adults with moderately-to severely-active rheumatoid arthritis, has been studied as a treatment possible in the National Institute of Allergy and Infectious Diseases (NIAID) against COVID-19 (NCT04280705) [19]. Tofacitinib (Xeljanz®, Pfizer Inc., New York, NY, USA), another JAK1/JAK3 inhibitor, used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, is also being reviewed in a phase II study (NCT04332042). Still, specialists have revealed safety concerns around the proposition, since the antiviral effects of interferons are largely mediated by the JAK–STAT signaling pathway [4, 20].

After the results that evidence the performance of BTK pathway in the production of inflammatory cytokines and promoting early clinical data, Astrazeneca is looking to placate the inflammatory cascade with an extremely selective Bruton's tyrosine kinase (BTK) inhibitor currently used to treat chronic lymphocytic leukemia, the Acalabrutinib (Calquence®, AstraZeneca, Cambridge, UK), which is in the phase II CALAVI trial (NCT04346199) [21]. Furthermore, Medicinova is studying ibudilast (MN-166, Medicinova, Inc., La Jolla, CA, USA), a small-molecule inhibitor of macrophage migration inhibitory factor (MIF) and phosphodiesterase (PDE) -4 and -10, which is recognized to suppress the production of pro-inflammatory cytokines and promote neurotrophic factors [22].

Tradipitant (Vanda Pharmaceuticals Inc., Washington, DC, USA), an investigative neurokinin-1 receptor (NK-1R - the principal receptor for substance P, a pivotal component of the neuroinflammatory processes that guides to significant lung injury following a viral infection) antagonist in development for gastroparesis, motion sickness, and atopic dermatitis treatment, has also entered the ODYSSEY phase III clinical trial (NCT04326426) to attest how effective and safe it can be for critical cases of COVID-19 pneumonia [23].

Complement System

The activation of pro-inflammatory responses is connected to the complement system, which is another essential part of the natural immune response to viruses. There is evidence that suggests that complement inhibition might improve lung injury caused by COVID-19 infection, and it stems from animal models of viral pneumonia [24]. Such data and promising findings from compassionate-use cases, Alexion launched a global phase III trial to investigate the use of ravulizumab-cwvz (Ultomiris®, Alexion Pharmaceuticals, Boston, MA, USA) [25]. Alexion are also planning to further investigate a related drug, ecilizumab (Soliris®, Alexion Pharmaceuticals, Boston, MA, USA), in COVID-19.

Antibodies

Antibody-based therapies may also be a hopeful approach to COVID-19 treatment. An

introductory study on 10 Chinese patients infers that immunotherapy with neutralizing antibodies existing in convalescent plasma improved clinical symptoms, higher levels of blood oxygen and lymphocytes, lower C-reactive protein levels, and undetected viral loads; two patients were removed from ventilators. Treatment was particularly successful if the plasma was delivered within 14 days of symptom onset and no adverse effects were observed [4, 9]. This finding needs investigation in larger studies.

Kiniksa Pharmaceuticals (Bermuda) recently published introductory data of treatment response with mavrilimumab, an investigational fully-human monoclonal antibody that targets granulocyte-macrophage colony-stimulating factor receptor alpha (GM-CSFRα), in patients with severe pneumonia and hyperinflammation by COVID-19 infection (all patients presented an early resolution of fever and improvement in oxygenation within 1-3 days; none of these patients have advanced to require mechanical ventilation). However, the N of the study is low (six) and further studies are being started [4, 9].

Eli Lilly and Company initiated a phase II study (A study of LY3127804 in participants with COVID-19; NCT04342897) with LY3127804, a monoclonal antibody against angiopoietin 2 (Ang2), in hospitalized patients with COVID-19 pneumonia, who are at a higher risk of progressing to ARDS. Ang2 levels are known to be elevated in the alveolar components of patients with ARDS. It is hoped that inhibition of Ang2 will decrease the progression to ARDS or the necessity for mechanical ventilation in patients with COVID-19 [19].

Breathing Support

The RECOVERY Respiratory Support (Recovery-RS) study is testing treatments that intend to prevent people to go on a ventilator. They randomized patients and designated to receive oxygen either through a tight-fitting mask (continuous positive airway pressure [CPAP]) or blown up their nose by a machine (high-flow nasal oxygen [HFNO]), or through a normal oxygen mask. Both CPAP and HFNO are already used routinely in the National Health Service (UK) for other conditions [9].

Testing

A rapid bedside test's results for COVID-19 may concede doctors to distinguish infected patients more quickly and stop the virus from circulating in hospitals. Therefore, the CoV-19POC study aims to update the tests already existing and find out whether using a new rapid test for COVID-19 to an earlier decision to better management of the sick patients [9].

Healthcare Workers

The HEROs' study taking place at five hospitals in Canada intends to find out whether taking hydroxychloroquine before and during exposure to patients decreases their risk of COVID-19 infection. The COVVA study in Spain is looking at the effects on healthcare workers wearing personal protective equipment (PPE), such as N95 respirators and FFP2 face masks, to examine whether their working conditions can be improved. The healthcare workers are required about the presence of problems such as headaches and skin lesions after working in isolation areas [9].

Impact on Other Conditions

The COVER study is an international study intending to collect information on how the COVID-19 pandemic is affecting the medical care of patients with artery and vein (vascular) conditions. Also, UKOSS's study is collecting information about all pregnant women admitted to the hospital with COVID-19 in UK to study the effects of the infection and treatments on the mother and baby [9].

Vaccines

Despite all described clinical trials above, the vaccines are the principal target to clinical

trials currently, and the most cost-effective way of controlling outbreaks such as COVID-19. The COV001 and COV002 studies based in Oxford (UK) are testing a new vaccine on healthy volunteers to check if they can be protected from COVID-19. The first results attested to the safety of the vaccine and its capacity to generate good immune responses against the virus. Phase II was initiated in the last week (May 21) [4, 9].

Another promised vaccine is developing in China, which confers promise after early study in 100 people. The vaccine seemed safe and capable to generate an immune response after an early trial in more than 100 people, according to the new study. The Ad5 vectored COVID-19 vaccine, called Ad5-nCoV, being developed by the Chinese company CanSino Biologics, is tolerable and immunogenic at 28 days post-vaccination (almost all participants had developed antibodies that bound to SARS-CoV-2). The vaccine uses a weakened version of adenovírus, a common cold virus, which infects human cells but doesn't cause disease, to deliver a fragment of genetic material from SARS-CoV-2. This genetic material carries instructions for making the "spike protein" on the surface of SARS-CoV-2, leading a humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses from day 14 post-vaccination, The Ad5 vectored COVID-19 vaccine is now in Phae II (500 participants). warrants further investigation [26].

Several other coronavirus vaccine candidates published promising developments this week. On Monday (May 18), Biotech company Moderna announced that 45 volunteers who received doses of its vaccine candidate, called mRNA-1273, developed antibodies within 15 days and that the level of antibodies observed in their blood was similar to that seen in people who have recovered from COVID-19 [26].

Ongoing Trials

In Table 1, based on TranspariMED [33], we listed databases, trial trackers, and similar sources that have been developed to help in the tracking and identification of trials and studies involving COVID-19.

Discussion and Conclusion

There is an imperative demand for strategies, drugs, and vaccines against COVID-19. Since new clinical trials appear by the minute due to the battles to fight COVID-19, this review cannot present a comprehensive account of all the potential therapeutics in clinical development, considering the speed of progress and the gaps that exist in our knowledge of the immunopathology of COVID-19. We do have to be mindful of the safety of patients. The hydroxychloroquine and chloroquine case is a good example of the pitfalls of small and uncontrolled trials [27]. The early studies *in vitro* suggested that the drugs might be effective against SARS-CoV-2 [28], so clinical trials were launched around the world. But as there are many trials, the researchers did not have a clear answer to whether the drugs work against COVID-19 in people.

Despite this — and despite their known effects on the heart — the drugs entered the treatment protocol against Covid all over the world. Currently, the REMAP-CAP study (include participants from more than 160 sites across 14 countries), and several larger and controlled studies [29-32] have demonstrated that hydroxychloroquine and chloroquine, as they were being used, are not benefic for patients and they have no efficacy against COVID-19. In spite of this, novel studies are in course.

A pandemic emergency is a reason to work quicker, but the clinicians and researchers must not lose sight of the fact that experimental interventions carry an inherent risk to the patient. To consider this risk, clinical trials must be as robustly produced as possible. For this purpose, collaborative trials and collaborative efforts between pharmaceutical companies are important because they are the ones with a greater chance of showing what really works. Nevertheless, every

Table 1. Databases, trial trackers and similar resources that have been develped to aid in the tracking and identification of trials and studies concerning COVID-19 [33].

Resource	Description
Cytel COVID-19 Clinical Trial Tracker	Cytel has developed this COVID-19 trial dashboard to identify registered trials investigating the use of interventional strategies for the treatment of COVID-19, or COVID-19 related symptoms. Trials can be filtered by location, trial status and intervention, amongst other identifiers. The dashboard uses data from WHO International Clinical Trials Registry Platform, the European Clinical Trials Registry, clinicaltrials.gov, the Chinese Clinical Trial Registry, the German Clinical Trials registry, the Japan Primary Registries Network, the Iranian Clinical Trial Registry, and the Australian New Zealand Clinical Trials Registry.
COVID-19 TrialsTracker	Developed as part of TrialsTracker.net project run by The DataLab at the University of Oxford, the 'COVID-19 TrialsTracker' brings together structured, cleaned data from clinical trial registries on studies of COVID-19, and tracks the availability of their results.The tracker uses data from the ICTRP and may collect additional information directly from certain registries over time.
COVID-19 Vaccine Development Pipeline	This tracker, developed by the Vaccine Centre at the London School of Hygiene & Tropical Medicine, follows COVID-19 vaccine candidates as they progress through the development pipeline. The tracker is updated weekly. Users can filter developmental COVID-19 vaccines according to stage of development and vaccine type. An overview of the different vaccine types as well as the phases of clinical development is provided in the Summary tab.
GloPID-R/UKCDR COVID-19 Research Project Tracker	UKCDR and GloPID-R are maintaining a live database of funded research projects across the world related to the current COVID-19 pandemic. The database aims to support funders and researchers in delivering a more effective and coherent global research response to the pandemic by providing an overview of research projects mapped against the priorities identified in the WHO Coordinated Global Research Roadmap: 2019 Novel Coronavirus.It includes: new research projects funded to date from the dataset sources; heatmap of these projects against the research priorities set out in the WHO Coordinated Global Research Roadmap: 2019 Novel Coronavirus, March 2020; supporting information on funding calls; links to other sources of information.
GHTC COVID-19 R&D Tracker	The Global Health and Technologies Coalition (GHTC) is tracking research and development (R&D) efforts to combat SARS-CoV-2. Here they summarise the latest updates on: US government-supported R&D for SARS-CoV-2; efforts led by multilateral institutions; R&D being led by GHTC members; other efforts by GHTC members to respond to the pandemic
Milken Institute COVID-19 Treatment and Vaccine Tracker	This document, compiled by The Milken Institute, aims to list all treatments and vaccines currently in development for COVD-19. It contains an aggregation of publicly-available information from validated sources.
WHO International Clinical Trials Registry Platform	The main aim of the WHO ICTRP is to facilitate the prospective registration of the WHO Trial Registration Data Set on all clinical trials, and the public accessibility of that information. Users can download all COVID-19 trials from the ICTRP database.
ClinicalTrials.gov	ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. Users can See listed clinical studies related to the coronavirus disease (COVID-19). Alternatively, users can search 'COVID-19' or related terms.
EU Clinical Trials Register - COVID-19 Trials	The European Union Clinical Trials Register allows users to search for protocol and results information on: interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA); clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development. This link shows the results for COVID-19 clinical trials from the EU Clinical Trials Register.

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Resource	Description
COVID-evidence Database	COVID-evidence, a non-profit initiative of the Department of Clinical Research at University of Basel and the Meta-Research Innovation Center at Stanford, are maintaining this database of available trial evidence on benefits and harms of interventions for COVID-19. As well as trial information, the database provides links to original sources such as study protocol documents, registry entries, and publications. In addition, COVID-evidence also aims to provide reliably extracted key trial information that would otherwise only be accessible by reading every manuscript in detail.
Cochrane COVID-19 Study Register	Cochrane's COVID-19 Study Register is a freely-available, continually-updated, annotated reference collection of human studies on COVID-19, including interventional, observational, diagnostic, prognostic, epidemiological, and economic designs. Please note: the register will not include in vitro study references. The three primary data sources for Cochrane's COVID-19 Study Register are ClinicalTrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) and PubMed
EPPI-Centre COVID-19: Living Map of the Evidence	EPPI-Centre (Evidence for Policy and Practice Information and Co-ordinating Centre) are maintaining an up-to-date map of the current evidence surrounding COVID-19 that is partitioned into broad domains for easy exploration. The map is updated weekly and consists of studies on COVID-19, identified in MEDLINE and Embase, and published in 2019 or later.
RAPS COVID-19 Vaccine Tracker	Compiled by the Regulatory Affairs Professionals Society (RAPS), this tracker lists the major vaccine candidates in development for prevention of COVID-19. The tracker is updated weekly.

possible effort must be made to halt the epidemic as soon as possible respecting all phases and ethics of clinical research to bring efficacy, tolerability, and security in the treatments against COVID-19.

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