

COVID-19 Clinical trials: Quality matters more than quantity

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Abstract

Despite the ferment aroused in the scientific community by the COVID-19 outbreak and the over 11,000 papers listed in PubMed, published evidence on safe and effective drugs has not progressed yet at the same speed of the pandemic. However, clinical research is rapidly progressing, as shown by the hundreds of registered clinical trials on candidate drugs for COVID-19. Unfortunately, information on protocols of individual studies differs from registry to registry. Furthermore, study designs, criteria for stratification of patients and choice of outcomes are quite heterogeneous. All this makes data sharing and secondary analysis difficult. At last, small single centre studies and the use of drugs on a compassionate basis should be replaced by highly powered, multi-centre, multi-arm clinical trials, in order to provide the required evidence of safety and efficacy of novel or repurposed candidate drugs. Hopefully, the efforts of clinical researchers in the fight against the SARS Cov-2 will result into the identification of effective treatments. To make this possible, clinical research should be oriented by guidelines for more harmonized high-quality studies and by a united commitment of the scientific community to share personal knowledge and data. Allergists and clinical immunologists should have a leading role in this unprecedented challenge.

KEYWORDS

biologics, infections, inflammation, lung diseases other than asthma and COPD, pharmacology and pharmacogenomics

1 | INTRODUCTION

COVID-19 has aroused an unprecedented scientific ferment to tackle this deadly pandemic. The most important scientific journals, including *Allergy*, have created a specific section on COVID-19. As of May 12, day of submission, a PubMed search for COVID-19 shows 11 336 papers published in 2020 (almost 10 every working hour). However, this number increases as rapidly as the number of worldwide infected people and deaths reported daily by the WHO and the national authorities. Through this emerging literature, much has been learned on the mechanisms of SARS-CoV-2 infection,^{1,2} modes of transmission, incubation period, clinical features, incidence, and lethality of the disease.^{3,4}

Following initial discordant strategies in different countries,⁵ there has also been general agreement on the efficacy of the lockdown in China and the strict public health measures firstly implemented in Europe by the Italian government to suppress COVID-19 diffusion (isolation of areas with a high number of positive cases, closure of non-essential public places, schools and universities, cancellation of congresses, and mass gathering events). Recommendations made by governments for a lockdown—although implemented at different times—appear to be fully justified and supported by accurate modelling on their potential effect on the mitigation or suppression of the infection.⁶

On the other hand, the search for an effective therapy of COVID-19 is still a work in progress, which demands a harmonized approach

of the scientific community. This article aims to provide a critical overview of the clinical trials exploring candidate drugs for potential treatment of COVID-19. The several ongoing clinical trials on SARS-CoV-2 vaccines do not fall within the scope of this article.

2 | THE LEADING ROLE OF ALLERGISTS AND CLINICAL IMMUNOLOGISTS IN THE FIGHT AGAINST SARS-COV-2

There is no doubt that allergists and clinical immunologists should be on the front line in the fight against SARS-CoV-2, since their expertise is required for a better understanding of COVID-19 pathophysiology and its management. First, the host immune response is the main mechanism to block the viral infection and attenuate or prevent symptoms.⁷ Second, there is a wide consensus that the progression of the disease to the most severe life-threatening forms is associated with an intense inflammatory process and a cytokine storm.⁷ Third, beyond plasma-based therapy and vaccines, several candidate drugs against SARS-CoV-2 are part of the current therapeutic armamentarium of the clinical immunologist and require the expertise of our specialty.⁸

In fact, 39 clinical trials explore the efficacy of tocilizumab, an anti-IL-6R (sIL-6R and mIL-6R) monoclonal antibody widely used by allergists and clinical immunologists for the treatment of rheumatoid arthritis, giant cell arteritis, and the CAR-T-induced cytokine release syndrome.⁹ Some other candidate monoclonal antibodies for COVID-19 clinical trials—targeting IL-1, IL-17A, growth factors, and complement factors—are listed in Table 1.

Beside monoclonal antibodies, several other immunosuppressants and immunomodulators are under investigation.⁹ Interferon beta-1a—both intravenously and in an inhaled formulation—interferon alfa-2a, and peginterferon lambda-1a are object of 31 clinical studies. Immunoglobulin and convalescent plasma-based therapy are investigated in 60 trials.

Twenty-three registered studies⁹ are evaluating the use of systemic corticosteroids in COVID-19. Despite concern about possible detrimental effects,^{10,11} there is yet no evidence for or against their use in COVID-19 patients. There is rational to speculate that their safety and efficacy may be different in the early viral phase compared to the late inflammatory phase. Conversely, there is no evidence to withdraw an ongoing treatment with inhaled steroids in subjects with asthma and rhinitis.^{12,13}

Other immunomodulatory/immunosuppressive drugs and the effect of cytokine filtration devices are also under investigation, particularly in COVID-19 subjects with pneumonia and a severe inflammatory disease.⁸

More studies on anti-TNF drugs have been recommended.¹⁴ Among cell-based therapies, 24 studies plan to investigate the immunomodulatory role of mesenchymal stem cells.⁸

However, despite this intense clinical research and 236 papers (including 4 systematic reviews) on COVID-19 treatment listed by PubMed, evidence available for safe and effective drugs has not progressed at the same speed of the pandemic.¹⁵ In fact, to our knowledge only very few clinical trials have been published.

The randomized, open-label trial with lopinavir/ritonavir in 199 patients with severe COVID-19 failed to meet the primary end-point (time to clinical improvement).¹⁶ However, 70 additional studies are

TABLE 1 Candidate monoclonal antibodies in COVID-19-related clinical trials

Intervention	No. of Trials	Target	Size	Comparator	Phase	Randomized/blinded
Adalimumab ^a	1	TNF alfa	60	Standard of care	2/3	Yes/No
Meplazumab	1	CD-147	20	Single arm	½	No/No
Sarilumab	14	IL-6R	400	Placebo	2/3	Yes/Yes
Eculizumab	3	C5	120	Standard of care	2	Yes/No
Ixekizumab + AV	1	IL-17A	40	AV	2	Yes/Yes
Nivolumab	1	PD-1	15	Standard of care	2	No/No
Siltuximab	1	IL-6	100	Corticosteroids	2	Yes/No
Bevacizumab	4	VEGF	130	Standard of care	2	Yes/No
Gimsilumab	1	GM-CSF	270	Placebo	3	Yes/Yes
IFX-1	1	C5a	130	Best supportive care	2/3	Yes/No
Leronlimab	1	CCR5	390	Placebo	2b/3	Yes/Yes
Lenzilumab	1	CSF- GM-CSF	238	Placebo	3	Yes/Yes
Canakinumab	2	IL-1beta	450	Placebo	3	Yes/Yes
Clazakizumab	2	IL-6	90	Placebo	2	Yes/Yes

Note: For monoclonal antibodies under investigation in more than one clinical trial, only one study has been mentioned. For a complete listing, see Ref. 9 and 46.

^aIn association with tocilizumab.

TABLE 2 Other nonimmunologic candidate drugs for COVID-19

Chloroquine/Hydroxychloroquine (147)
Anti-viral drugs
Lopinavir/Ritonavir (70)
Favipiravir (24)
Umifenovir (15)
Remdesivir (11)
Sofosbuvir (1)
Darunavir (1)
Ritonavir (1)
Oseltamivir (1)
Protein kinase inhibitors
Ruxolitinib (13)
Baricitinib (5)
Imatinib (2)
Anti-infective agents
Azytromycin (55)
Anticoagulants
Enoxaparin (5)
Anti-inflammatory drugs

Note: In brackets No. of ongoing trials. Data from Ref. 9 to 46.

investigating the efficacy of lopinavir/ritonavir in various severity stages of the disease.⁹

Following the more promising results of a cohort study of patients treated with remdesivir on a compassionate use,¹⁷ both FDA and EMA have permitted the use of this drug in COVID-19 clinical trials. While a randomized double-blind placebo-controlled trial could not confirm a significant benefit of remdesivir in a cohort of 236 patients—possibly because of the failure to recruit its target of 453 patients¹⁸—it has been recently anticipated that a larger multi-center trial in over 1000 subjects showed a high significant (<0.001) effect on the primary outcome of the study (ie, time to recovery, which was reduced from 15 to 11 days).¹⁹ Eleven more trials on remdesivir are still ongoing.⁹ A few additional published studies with hydroxychloroquine vs best supportive care, favipiravir vs umifenovir, and lopinavir/ritonavir vs umifenovir are reported by Thorlund and co-workers.²⁰

3 | COVID-19 REGISTRIES AND DRUG PIPELINE

However, clinical research is rapidly expanding and hundreds of clinical trials have been registered including, beside immunologic drugs, antiviral drugs, protein kinase inhibitors, anti-inflammatory drugs, or drugs aimed at facing the most severe symptoms of COVID-19, such as anti-coagulants, anti-infective drugs, and drugs for the cardiovascular, respiratory, and nervous systems (Table 2).

The WHO registry²¹(ICTRP) included, at April 29, 1524 studies, whose details are not easily accessible. The registry, due to the

heavy traffic generated by the COVID-19 outbreak, is temporarily not accessible from outside the WHO.

US NIH ClinicalTrials.gov²² lists 1409 trials, including 830 interventional studies; only 20 of these trials have been completed, but results have not been published yet.

Eudra CT²³ includes 175 clinical trials, all still ongoing.

Cytel, a Global Coronavirus COVID-19 clinical trials tracker, funded, in part, by the Bill & Melinda Gates Foundation,⁹ lists 1029 clinical trials, 340 from China and 51 dealing with traditional Chinese medicinal products. Most interventional studies evaluate the effects of hydroxychloroquine or chloroquine (218 studies), lopinavir/ritonavir (70 studies), plasma-based therapy (60 studies), and tocilizumab (39 studies). Only 8 studies are already completed with results (7 from China and 1 from France), but only one has a randomized double-blind study design.

The comparative review of registries allows some critical considerations.

There is a substantial discrepancy in the number of studies reported in different registries, and it is quite difficult to identify duplicates among registries or studies listed in some registries but not in others.

Furthermore, the available information for individual studies differs from registry to registry and is not easily extractable. At last, protocols of studies are not accessible in most registries. Thus, it is highly appreciable the initiative of tracking and collating clinical trials in a single registry, also using artificial intelligence-based methods for data search and aggregator services.²⁰ This approach will allow easier data sharing among investigators and analysis of pooled data.

Data sharing and secondary analysis represent valuable tools to advance knowledge and help regulatory decisions. Transparency policies have been recently adopted in Europe by the European Medicines Agency (EMA)²⁴ in line with the new EU Clinical Trial Regulation.²⁵ Data sharing is also recommended by several international institutions²⁶ and by the International Committee of Medical Journal Editors.²⁷ Data sharing appears fundamental in health emergencies, such as COVID-19 outbreak, to implement rapid and effective responses. Several platforms are available for data storage and analysis also offering protocol assistance and free anonymization of data from subjects with COVID-19.²⁸

4 | THE NEED FOR A STANDARDIZED APPROACH IN COVID-19 CLINICAL RESEARCH

However, in order to make feasible secondary analysis of individual studies, these should follow guidelines for standard protocols and minimal requirements for outcome measures such as the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT)²⁹ and the Core Outcome Measures in Effectiveness Trials (COMET) initiative.³⁰

In fact, the major criticism emerging from a review of the ongoing trials is the heterogeneity of protocols. Following the decision

of both FDA and EMA, respectively, to allow the use of chloroquine or hydroxychloroquine and remdesivir for clinical trials in COVID-19,^{31,32} several small trials have started using these drugs on a compassionate basis. The EMA has expressed concern for these small studies and the compassionate-use programs across Europe, as they are unlikely to produce the required level of evidence of efficacy and safety of investigational drugs. On the contrary, the EMA strongly recommends that a more coordinated approach and efforts are put in place to prioritize large multi-country randomized trials and multi-arm clinical trials investigating different agents simultaneously.³³ In order to generate robust evidence on efficacy and safety of drugs and vaccines for COVID-19, EMA offers free scientific advice on the best methods and designs to be used in clinical trials.³⁴

Unarguably, high-quality clinical trials cannot be easily performed in the setting of an outbreak, when investigators are often asked to make patients' care a priority. Nonetheless, even if adapted to this challenging context, high-quality research is still needed.³⁵ Accordingly, a more standardized approach to clinical research on COVID-19 should be warranted, including a rigorous but realistic

study design, a well-characterized study population stratified on the basis of age and severity of the disease, a rationale behind the use of the investigational drug and the choice of comparator, and optimal minimal primary outcome(s).

With regard to the study design, while masking might be difficult in studies of COVID-19, randomization should be mandatory. Multi-center trials are highly advisable provided that standard operational procedures are set out. Adaptive designs might be considered, and the setting should be specified. Rules for informed consent must adapt to the chosen population. Centralized Ethics Committees or IRBs might favor a more rapid start of the trial. Investigators should be encouraged to publish the study protocol to be drafted according to the SPIRIT²⁹ and COS-STAP statement.³⁶

Age, gender, ethnicity, previous diseases, and undergoing treatments of the selected population have been reported to influence the incidence of COVID-19.^{3,4,37-39} Demographic and history data should be obtained, possibly through a standard questionnaire, along with other patients' characteristics such as social status and environmental exposure.

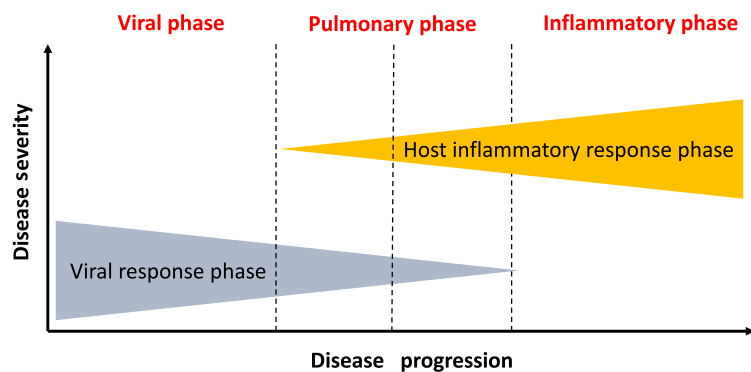


FIGURE 1 Staging of COVID-19. Clinical features, management, and candidate therapeutic options. Modified from Ref. 40 and 47. Legend: ABG, arterial blood gas; ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; CBC, complete blood count; CRP, C-reactive protein; HFNC, high-flow nasal cannula; ICU, intensive care unit; LFTs, liver function tests; LMWH, low molecular weight heparins; MOF, multi-organ failure; MSC, mesenchymal stem cells; NIPPV, noninvasive positive pressure ventilation; PaO₂/FiO₂, ratio of arterial oxygen partial pressure (PaO₂, in mm Hg) to fractional inspired oxygen (FiO₂, expressed as a fraction); PCR, polymerase chain reaction; RR, respiratory rate; SatO₂, oxygen saturation

	<i>Mild</i> (60%-80%)	<i>Moderate</i> (10%-20%)	<i>Severe</i> (10%-20%)	<i>Critical</i> (5%-10%)
Setting	Home	Hospital		ICU
Symptoms & signs	Fever Dry cough Malaise Headache Diarrhea Muscle pain Anosmia Dysgeusia	Fever Dyspnea Chest pain Sat O ₂ ≥93% Normal Lung	Severe Dyspnea RR>30/min Sat O ₂ <93% (PaO ₂ /FiO ₂) <300 Interstitial pneumonia	ARDS Septic shock MOF Cytokine storm
Diagnostics	Viral detection (PCR on nasal oropharyngeal swabs) Routine laboratory tests	Lung imaging ECG ABG CBC (Lymphopenia) CRP (↑)	LDH (↑) D-Dimer (↑) Coagulation Renal function LFTs	Intensive Care Monitoring
Treatment	Self-isolation Antipyretics Risk factors Identification	O ₂ Antibiotics	HFNC O ₂ NIPPV Antibiotics for CAP LMWH	Intubation Mechanical Ventilation Intensive Care
Candidate COVID-19 drugs	Chloroquine/hydroxychloroquine, antiviral drugs, IFNs	Corticosteroids(?), Convalescent plasma Anti-IL6 and other MoAbs, JAK-inhibitors, LMWH Cytokines filtration		

While waiting for a consensus on criteria for the diagnosis of COVID-19 and a classification of the disease, patients should be stratified on the basis of the study setting, severity, and the predominant pathophysiological abnormality in different phases of the disease (viral, pulmonary, and inflammatory; Figure 1).⁴⁰

Several research groups are working on a variety of preventive and therapeutic interventions. However, despite the accelerated development pathways adopted by many regulatory bodies,⁴¹ the marketing authorization pathway for new drugs is a long process, with a high attrition rate. Therefore, there has been considerable interest in repurposing existing drugs—such as antiviral and immunosuppressant agents—for use in COVID-19.⁸ Studies with these drugs should keep in consideration the putative mechanisms of action of the investigational drug in relation to the different phases of COVID-19. Antiviral agents, for example, should be used during the early viral phase of the disease while immunosuppressant may be promising candidate drugs in the severe inflammatory phase (while they might dampen the immune response if used early on¹⁵). Combination or sequential treatment might also be considered.

An interesting alternative strategy for drugs repurposing in COVID-19 is represented by a structural analysis of available medicines with potential inhibitory effects on molecules involved in SARS-CoV-2 infection and replication.^{1,2} In an in silico molecular modelling, screening of 2000 FDA-approved drugs for potential inhibitory effect on SARS-CoV-2 main protease enzyme (Mpro), the top hits bound to the central site of Mpro substrate-binding pocket included antiviral drugs such as darunavir, nelfinavir, and saquinavir. Interestingly, the top hits bound to the terminal site of Mpro substrate-binding pocket included montelukast and fexofenadine.⁴² Independently from the practical impact of the above observation, this strategy appears promising in repositioning available drugs, until novel targeted treatments for COVID-19 are available.

Standard of care seems to be a more realistic comparator than placebo, in view of the emergency nature of the epidemic.

Collaborative trials and multi-arm studies comparing different drugs should also be considered. A commendable example of this kind of approach is represented by the Solidarity clinical trial launched by the WHO.⁴³ The Solidarity trial is a randomized multi-countries open-label trial which compares the efficacy of four treatment options (remdesivir, lopinavir/ritonavir, interferon beta-1a, and chloroquine or hydroxychloroquine) against standard of care in hospitalized adult patients with COVID-19. Underlying conditions are recorded and severity of illness at entry is determined by a reduced set of end-points that can be recorded even in overwhelmed hospitals. Clinically relevant outcomes undergo an interim analysis by an independent Global Data and Safety Monitoring Committee. The simplicity of the trial is balanced by the thousands of patients that are expected to be recruited in more than 70 countries. Preliminary results of this trial are expected by June 2020.

In more rigorous study designs, primary outcome measures should be chosen in relation to the phase of the disease and the drug under investigation. While SARS-CoV-2 RNA clearance and the

effects on the progression of the disease may represent significant outcome measures for antivirals in the mild forms of the disease, hard end-points such survival/death are advisable in the most severe forms. However, a core outcome standard set is urgently needed to define a minimal set of outcome measures relevant to patients, investigators, and regulators.⁴⁴

5 | CONCLUSIONS

Hopefully, the efforts of clinical researchers in the fight against the SARS-CoV-2 will result into the identification of effective treatments. This would largely counterbalance the delaying effects of COVID-19 on ongoing trials for other diseases.⁴⁵ However, these efforts might be negatively affected in the absence of guidelines for a more harmonized clinical research and a united commitment of the scientific community to share personal knowledge and data. Allergists and clinical immunologists should have a leading role in this unprecedented challenge.

CONFLICT OF INTEREST

The authors have nothing to disclose.

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