COVID-19 Clinical trials: quality matters more than quantity

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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 April 28, PubMed listed 7442 papers published in 2020 (almost eight every working hour), but this number is increasing 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[I], 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 appear to be fully justified and supported by accurate modelling on their potential effect on the mitigation or suppression of the infection[5].

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 on the clinical trials exploring potential treatment for COVID-19.

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, for different reasons. First, the host immune response is the main mechanism to block the viral infection and attenuate or prevent symptoms[6]. 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[5]. 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[7].

So far, 26 clinical trials explore the efficacy of Tocilizumab, an anti-IL-6R (sIL-6R and mIL-6R) monoclonal approved for rheumatoid arthritis, giant cell arteritis and the CAR-T induced Cytokine Release Syndrome [II-V]. Some other monoclonal antibodies targeting IL-1, IL-17A, growth factors, complement factors are listed in Table I.

Beside monoclonal antibodies, several other immunosuppressants and immunomodulators are under investigation. Interferon beta 1a – both intravenously and in an inhaled formulation -, interferon alfa 2a and peginterferon lamda 1A are object of 31 clinical studies. Immunoglobulin and convalescent plasma-based therapy are investigated in 35 trials.

Fifteen registered studies[V] are evaluating the use of systemic corticosteroids in COVID-19. Despite concern about possible detrimental effects[8,9], 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[10,11].

Other non-steroid anti-inflammatory drugs and the effect of cytokine filtration devices are also under investigation, particularly in COVID-19 subjects with pneumonia and a severe inflammatory disease[7].

More studies on anti-TNF drugs have also been recommended[12]. Among cell-based therapies, 24 studies plan to investigate the immunomodulatory role of mesenchymal stem cells[7]. 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 include 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[13]. 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.

However, despite this intense clinical research and 177 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[14.] 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)[15]. However, 53 additional studies are investigating the efficacy of Lopinavir/Ritonavir in various severity stages of the disease[V].

Following the more promising results of a cohort study of patients treated with Redemsivir on a compassionate-use[16], both FDA and EMA have permitted the use of this drug in COVID-19. While a randomized double-blind placebo-controlled trial could not confirm a significant benefit of Redemsivir in a cohort of 236 patients – possibly because of the failure to recruit its target of 453 patients[17] -, Anthony Fauci 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 (i.e. time to recovery, which was reduced from 15 to 11 days)[VI]. Eleven more trials on Redemsivir are still ongoing[V]. A few additional published studies with hydroxichloroquine vs best supportive care, favipiravir vs umifenovir, and lopinavir/ritonavir vs umifenovir are reported by Thorlund and co-workers[18].

COVID-19 registries and drugs pipeline

However, clinical research is rapidly expanding and hundreds of clinical trials have been registered including, beside immunologic drugs, anti-viral 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, drugs for the cardiovascular, respiratory and nervous systems (Table 2).

The WHO registry[II] (ICTRP) includes 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.gov[III] lists 997 trials, including 617 interventional studies; only 14 of these trials have been completed, and the results have not been published yet.

EudraCT[IV] includes 131 clinical trials, which are still ongoing.

Cytel, Bill& Melinda Gates' registry[V] lists 665 clinical trials, 322 from China and 102 dealing with traditional Chinese medicinal products. Most interventional studies evaluate the effects of hydroxychloroquine or chloroquine (147 studies), lopinavir/ritonavir (53 studies), plasma based therapy (35), and tocilizumab (26 studies). Only 7 of the 12 studies already completed with results (11 from China and 1 from France) have a randomized study design.

The conclusion of the registry for the two drugs more frequently investigated is that current data do not support the use of hydroxychloroquine/chloroquine for prophylaxis and treatment of COVID-19 and do not provide strong evidence about the efficacy of lopinavir/ritonavir in SARS CoV-2 infection.

In other registries the number of clinical trials ranges from 1480[VII] to 598[IX].

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[18]. This approach will make 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)[19] in line with the new EU Clinical Trial Regulation[20]. Data sharing is also recommended by several international institutions[21] and by the International Committee of Medical Journal Editors[22]. 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[IX].

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)[X] and the Core Outcome Measures in Effectiveness Trials (COMET) initiative[XI].

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 hydroxichloroquine and remdesivir in COVID-19[23,XII], 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 programmes 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[XIII].

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[24]. 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-centres 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 adapted to the chosen population. Centralized Ethics Committees or IRBs might favour a more rapid start of the trial. Investigators should be encouraged to publish the study protocol to be drafted according to the SPIRIT and COS-STAP statement[25].

Age, gender, ethnicity, previous diseases and undergoing treatments have been reported to influence the incidence of COVID[3,26-28]. Demographic and history data should be obtained, possibly through a standard questionnaire, along with other patients' characteristics such as social status and environmental exposure.

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, inflammatory; Fig.1)[29].

Several research groups are working on a variety of preventive and therapeutic interventions. However, despite the accelerated development pathways adopted by many regulatory bodies[XIV], 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[22]. 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 on[14]). Combination or sequential treatment might also be considered.

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[XV]. 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 end-points 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[30].

Conclusions

Hopefully, the unprecedent 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- on ongoing trials for other diseases. 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 unprecedent challenge.

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Resources

I.*https://www.covid19healthsystem.org/mainpage.aspx*

II. https://www.who.int/ictrp/en/

III. https://clinicaltrials.gov/ct2/results?cond=COVID&term=&cntry=&state=&city=&dist=

IV.http://clinicaltrialregister.eu/ctr-search/search?query=COVID-19

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XII. https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19

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