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Editorial

The Rise and Fall in Therapeutic Candidates for COVID-19

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), an RNA virus from the betacoronavirus genus, has caused a serious worldwide turmoil recently. Since the first report of this virus in China in Dec. 2019, several research fields were rapidly opened globally. Virus characterization led to the identification of its similarities with two other known deadly coronaviruses, SARS-CoV (with the highest nucleotide identity of 79.7%) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[1] Its pathogenesis is still one of the hot topics. The methods of viral transfection, epidemiology, and related subjects, have also been in focus to help in suggesting preventives strategies. The key issue of treating the infected patients is also one of the most investigated areas in parallel. Considering the urgency and importance of this subject, many drugs that were already approved or tested for other diseases were proposed to help patients at risk,[2] some of which sooner or later were announced to be unworthy and dropped out of the list.

Many clinical trials are ongoing in different countries to examine the suggested drugs. As of today (3 July 2020), 3,733 COVID-19 clinical trials are recorded on https://covid19.trialstracker.net/. However, most of them cover a small number of patients and have generated contradictory data. Moreover, due to their minor population and some other limitations, they might not provide the required strong evidence for determining the efficacy of potential treatments. Therefore, WHO has launched "Solidarity", a large international randomized clinical trial, with 5500 patients recruited in 21 countries till now. Four treatment arms were designed in this study against standard of care, to compare their relative therapeutic effectiveness against COVID-19, including 1) hydroxychloroquine or chloroquine, 2) remdesivir, 3) lopinavir-ritonavir, and 4) lopinavir-ritonavir plus interferon-beta. The arm receiving hydroxychloroquine, a formerly promising candidate, which was approved for the emergency use in COVID-19 patients by the FDA, was stopped on 17 June 2020 based on some internal and external evidence failing to reduce the mortalities.

The efficacy of several other candidates is also to be verified. Remdesivir, an RNA polymerase inhibitor that has displayed *in vitro* inhibition of SARS-CoV-2, showed a superiority over placebo in reducing the time to recovery in COVID-19 hospitalized adults in a multi-centric randomized clinical trial.[3] FDA and very recently EU have granted emergency use authorization for remdesivir. Despite great hopes in remdesivir, the underway data could clarify its advantage. Lopinavir-ritonavir, a candidate combination medication for COVID-19, which was also under investigation in the RECOVERY and "Solidarity" trilas, is discontinued in "Solidarity" trial very recently. The reason, as announced by WHO, is the lack or low impact of the drug on mortality reduction similar to hydroxychloroquine in the interim analysis results of the study. Favipiravir, another antiviral drug, has also been subject to controversies.

Dexamethasone, with low-dose, was the first drug that showed survival improvement in the hospitalized COVID-19 patients compared to standard care in a large randomized, controlled trial, named RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial. The maximum benefit of dexamethasone therapy was observed in critically-ill patients on ventilators followed by those receiving oxygen only as one-third and one-fifth reduction in the mortality rate, respectively. No advantage was noted in patients who did not require respiratory support.[4] This inexpensive steroid would help in suppressing the hyperactivated inflammatory responses, referred as cytokine storm, which is induced in the advanced stages of COVID-19 disease, leading to serious harm in the lung and some other organs and probably death. Previously, Tocilizumab was also suggested for similar conditions, which is presently under evaluation in the RECOVERY trial.

Interferon-beta also has shown benefit in COVID-19 patients in terms of discharge and mortality rates in some small studies.[5] Further data mainly from the "Solidarity" trial as well as some other ongoing studies could confirm its effect. Interferon-beta is believed to compensate for the downregulation of interferon response by SARS-CoV-2 at the beginning of the disease and also suppress the over-secretion of IL-6 and IL-8 during the cytokine storm, and seems as a promising candidate.

Generally, a trend of rising hopes that were dashed by the results of clinical studies have been seen during this crisis. Which other drugs will fail in these tests? And will a successor be found in this list? Will a vaccine be developed soon enough to end the pandemic? Or herd immunity will be the mere key for the wane of this virus? Only time would help to find the answer to these questions.

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