EDITORIAL

Research in the Context of a Pandemic

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The current literature on the treatment of coronavirus disease 2019 (Covid-19) is filled with anecdotal reports of therapeutic successes in clinical trials with small numbers of patients and observational cohort studies claiming efficacy with little regard to the effect of unrecognized confounders. For the field to move forward and for patients' outcomes to improve, there will need to be fewer small or inconclusive studies and more studies such as the dexamethasone trial now reported by the RECOVERY Collaborative Group[1] in the *Journal*.

In the RECOVERY trial, the benefit of the glucocorticoid dexamethasone for patients with Covid-19 who were receiving mechanical ventilation at the time of randomization was clearly shown. A 28-day mortality of 29.3% was reported for patients in the dexamethasone group as compared with 41.4% in the usual care group. In contrast, no benefit for dexamethasone was seen in patients not requiring oxygen at the time of randomization, with 28-day mortality of 17.8% and 14.0% for the dexamethasone group and the usual care group, respectively. For the heterogeneous group of patients receiving oxygen without invasive mechanical ventilation, mortality was 23.3% in the dexamethasone group and 26.2% in the usual care group. These findings, while limited to patients with Covid-19, provides clarity to an area of therapeutic controversy and probably will result in many lives saved. The use of dexamethasone already has been endorsed by several treatment-guideline panels, including that convened by the U.S. National Institutes of Health.[2]

The RECOVERY trial and the recently published randomized, controlled trial of remdesivir[3] provide clear guidance on therapeutic strategies for Covid-19 along with insights into the pathogenesis of the disease. Remdesivir, a directly acting antiviral drug, has its most favorable effect in hospitalized patients with Covid-19 who have modest pulmonary disease. This effect probably correlates to a time in the infection when viral replication is driving the pathogenic process. In contrast, the antiinflammatory and immunosuppressive dexamethasone has its greatest therapeutic effect in patients who have more advanced disease, a time during which pathogenic effects may be driven by the immune and inflammatory responses.

The RECOVERY trial takes an approach to clinical research popularized in the field of cardiovascular disease by enrolling large numbers of patients into a simple trial as opposed to smaller numbers of patients into a more complex, rigid, and granular study.[4] Both approaches have strengths and weaknesses. Large simple trials are especially useful for addressing questions such as whether a repurposed drug or standard procedure is of value, whereas the latter approach is more suited to the study of novel agents whose mechanisms of therapeutic effect may be unclear. In addition, the RECOVERY trial is using a platform or master-protocol approach in which agents can be added or subtracted from the randomization as data emerge from the trial or as new agents become available. In addition to the current report of efficacy of dexamethasone, RECOVERY investigators have reported a lack of efficacy for hydroxychloroquine and for lopinavir–ritonavir and continue to study the role of dexamethasone in children, as well as the roles of azithromycin, tocilizumab, and convalescent plasma.[1] The key to the success of the RECOVERY

trial has been its pace of enrollment. The ability to rapidly enroll thousands of patients into the trial no doubt was facilitated by the National Health Service in the United Kingdom and the fact that the trial was available to essentially the entire patient population of the country. As noted by the authors, 15% of all the patients who were hospitalized with Covid-19 in the United Kingdom were enrolled in the trial.

It was once widely held that the setting of an outbreak is not an appropriate venue for conducting rigorous clinical research because when people are dying, any and all possible therapies should be "given a chance," rather than studied in rigorous ways. Such was the case during the 2014–2016 Ebola outbreak in West Africa, when many small studies were launched and few, if any, provided conclusive results. A thorough review of that situation by the U.S. National Academies of Sciences, Engineering, and Medicine concluded that "randomized, controlled trials are the most reliable way to identify the relative benefits and risks of investigational products, and . . . every effort should be made to implement them during epidemics."[5] These findings were endorsed by the global research community and led to an adequately powered randomized, controlled trial during the 2018–2020 Ebola outbreak in the Democratic Republic of the Congo that clearly identified two effective therapies.[6]

Despite the decreases in death and complications that are likely to result from appropriate treatment of patients with remdesivir and dexamethasone, far too many people with Covid-19 will die. It is our responsibility in the global medical research community to rapidly design, implement, and complete studies of the most promising therapeutic agents and vaccines against this disease. These agents include monoclonal antibodies, more selective immunosuppressive agents, and vaccines built on platforms ranging from nucleic acids to proteins to recombinant viruses. Such efforts will benefit from national and global coordination and public–private partnerships, including Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) in the United States,[7] the ACCORD (Accelerating Covid-19 Research and Development) platform in the United Kingdom,[8] and the SOLIDARITY effort by the World Health Organization.[9] Scientifically robust and ethically sound clinical research remains the quickest and most efficient pathway to effective treatment and prevention strategies for patients with Covid-19.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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