EDITORIALS

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 this issue of the *Journal*.

In the RECOVERY trial, a benefit was shown for the glucocorticoid dexamethasone in patients with Covid-19 who were receiving mechanical ventilation at the time of randomization. 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, provide clarity to an area of therapeutic controversy and probably will result in many lives saved.

As a cautionary note, there was evidence of harm for patients who were not receiving supplemental oxygen, so it is important for clinicians to think carefully before prescribing glucocorticoids to this group of patients. Since the preliminary findings of this trial were published, dexamethasone has become the standard of care for patients with advanced Covid-19 and is recommended by virtually all treatment guidelines, including those of the National Institutes of Health.[2] However, the same guidelines recommend against its use in patients who are not receiving supplemental oxygen at baseline.

In addition to the RECOVERY trial of dexamethasone, other trials that have provided guidance regarding therapeutic strategies for Covid-19 and insights into the pathogenesis of the disease include the randomized SOLIDARITY trial[3] and the randomized, placebo-controlled Adaptive Covid-19 Treatment Trial 1 (ACTT-1) of remdesivir.[4] Remdesivir, a directly acting antiviral drug, appears to have 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. Although the SOLIDARITY trial showed that remdesivir had no overall effect on 28-day mortality, the subgroup and meta-analyses suggested benefit to hospitalized patients who were not receiving mechanical ventilation. In contrast, the antiinflammatory and immunosuppressive dexamethasone has its greatest therapeutic effect in patients who have more advanced disease, during which pathogenic effects may be driven by immune and inflammatory responses.

At this point, it is clear that SARS-CoV-2 infection leads to a spectrum of clinical manifestations that range from asymptomatic to multiorgan failure. Being able to better identify the subgroups of patients who are most likely to benefit from different therapeutic strategies will greatly accelerate the development of improved

therapies with greater degrees of specificity according to the clinical status of the patient. In this regard, biomarkers of viral replication and of inflammation or immune activation that can reliably predict the clinical course and serve as laboratory surrogates for clinical end points are greatly needed.

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 enrolling smaller numbers of patients into a more complex, rigid, and granular trial.[5] 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 with mechanisms of therapeutic effect that may be unclear. In addition, the RECOVERY trial is using a platform or master-protocol approach in which agents can be added to or subtracted from the randomization process 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, lopinavir–ritonavir, azithromycin, and convalescent plasma, and they have recently completed randomization to tocilizumab, with a pending analysis of the results. The investigators continue to evaluate dexamethasone in children, as well as the roles of colchicine, aspirin, REGN-COV2 (a combination of the monoclonal antibodies casirivimab and imdevimab), and baricitinib, as compared with usual care, in adults and children.[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, 10% of all the patients who were hospitalized with Covid-19 in the United Kingdom during this phase of RECOVERY 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."[6] 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 Congo that clearly identified two effective therapies.[7]

Despite the decreases in death and complications that are likely to result from appropriate treatment of patients with 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 (alone and in combination) against this disease. These agents include targeted small molecules such as RNA polymerase and protease inhibitors, monoclonal antibodies, more selective immunosuppressive agents, and repurposed medicines showing promise in preliminary clinical trials. Such efforts will benefit from national and global coordination and public–private partnerships, including the ACTT trials and the family of Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) trials in the United States,[8] the ACCORD (Accelerating Covid-19 Research and Development) platform in the United Kingdom,[9] and the SOLIDARITY effort by the World Health Organization.[3] 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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A preliminary version of this editorial was published on July 17, 2020, at NEJM.org.

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DOI: 10.1056/NEJMe2024638

The RECOVERY Platform

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In a platform trial, patients with a single disease are randomly assigned to a group of different therapies on the basis of a decision algorithm to determine whether any therapy has benefit.[1] The principle underpinning such trials allows for the execution of efficient, less expensive designs by enrolling populations quickly and collecting minimal data to answer more than one question. These are sensible principles and, when successful, result in trials that provide clear answers to several questions in a timely and efficient way.

In using this approach, investigators designed the RECOVERY trial involving hospitalized patients with coronavirus disease 2019 (Covid-19) in the United Kingdom to assess the efficacy of various treatments, using a single end point: mortality within 28 days after randomization; the results are reported in this issue of the *Journal*.[2] A total of 11,303 patients were randomly assigned to one of four treatment groups (dexamethasone, hydroxychloroquine, lopinavir–ritonavir, or azithromycin) or to usual care. Patients could undergo further randomization to receive either no additional treatment or convalescent plasma, and those with progressive Covid-19 could be randomly assigned to receive no additional treatment or tocilizumab.

What lessons do we take from the outcomes of the 6425 patients who were assigned to receive dexamethasone or usual care in the RECOVERY trial? First, broad populations of patients with Covid-19, along with multiple hospitals and trial coordinators, can be rapidly deployed in a trial. No doubt the swift enrollment in the RECOVERY trial was due to the nature of the pandemic, but the rapidity of trial design, logistics, coordination, and execution are the work of the investigators. Second, minimal data collection with the use of a single online follow-up form as well as routine health care data and national registry data can provide meaningful outcomes. A well-established public health care system probably played a large role in the data availability. Third, dexamethasone showed promise for reducing short-term mortality relative to usual care. Fourth, the benefits of dexamethasone may be restricted to the sickest of Covid-19 patients, those who were receiving ventilatory support at the time of randomization.

Are the findings from the RECOVERY trial clinically directive? In the total sample, the age-adjusted rate ratio of mortality for dexamethasone relative to usual care was 0.83 (95% confidence interval [CI], 0.75 to 0.93; P<0.001), with an absolute mortality benefit for dexamethasone of 2.8 percentage points. However, the adjusted rate ratio of mortality benefit among patients who were receiving mechanical ventilation was 0.64 (95% CI, 0.51 to 0.81), an absolute mortality reduction of 12.1 percentage points. Although there were no standardized criteria regarding who received mechanical ventilation, this finding is probably robust and may be helpful in guiding clinical care.

The platform design for RECOVERY has some limitations. Decisions that were made on removing or adding therapies are difficult in the best