ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

METHODS

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (Covid-19), emerged in China in late 2019 from a zoonotic source.[1] The majority of Covid-19 cases either are asymptomatic or result in only mild disease. However, in a substantial percentage of patients, a respiratory illness requiring hospital care develops,[2] and such infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support.[3-6] Among patients with Covid-19 who have been admitted to hospitals in the United Kingdom, the case fatality rate has been approximately 26%, a percentage that has increased to more than 37% among patients who were undergoing invasive mechanical ventilation.[7] Although remdesivir has been shown to shorten the time until recovery in hospitalized patients,[8] no therapeutic agents have been shown to reduce mortality.

The pathophysiological features of severe Covid-19 are dominated by an acute pneumonic process with extensive radiologic opacity and, on autopsy, diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis.[9] In other severe viral pneumonias, such as highly pathogenic avian influenza,[10] SARS,[11] and pandemic and seasonal influenza,[12] the host immune response is thought to play a key role in the pathophysiological effects of organ failure. Inflammatory organ injury may occur in severe Covid-19, with a subgroup of patients having markedly elevated levels of inflammatory markers, including C-reactive protein, ferritin, interleukin-1, and interleukin-6.[6,13,14] Several therapeutic interventions have been proposed to mitigate inflammatory organ injury in viral pneumonia, but the value of glucocorticoids has been widely debated.[15,16]

Although one small trial has reported improved clinical outcomes in patients with Covid-19 who were given methylprednisolone,[17] the absence of reliable evidence from large-scale randomized clinical trials means there is uncertainty about the effectiveness of glucocorticoids in patients with Covid-19. Many guidelines for the treatment of such patients have stated that glucocorticoids were either contraindicated or not recommended,[18] although in China, glucocorticoids have been recommended for severe cases.[19] However, practice has varied widely across the world: in some series, as many as 50% of patients have been treated with glucocorticoids.[20,21] Here, we report the preliminary results of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial of dexamethasone in patients hospitalized with Covid-19.

METHODS

TRIAL DESIGN AND OVERSIGHT

The RECOVERY trial was designed to evaluate the effects of potential treatments in patients hospitalized with Covid-19 at 176 National Health Service organizations in the United Kingdom and was supported by the National Institute for Health Research Clinical Research Network. (Details regarding this trial are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The trial is being coordinated by the Nuffield Department of Population Health at the University of Oxford, the trial sponsor. Although the randomization of patients to receive dexamethasone, hydroxychloroquine, or lopinavir–ritonavir has now been stopped, the trial continues randomization to groups receiving azithromycin, tocilizumab, or convalescent plasma.

Hospitalized patients were eligible for the trial if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial. Initially, recruitment was limited to patients who were at least 18 years of age, but the age limit was removed starting on May 9, 2020. Pregnant or breast-feeding women were eligible.

Written informed consent was obtained from all the patients or from a legal representative if they were unable to provide consent. The trial was conducted in accordance with the principles of the Good Clinical Practice guidelines of the International Conference on Harmonisation and was approved by the U.K. Medicines and Healthcare Products Regulatory Agency and the Cambridge East Research Ethics Committee. The protocol with its statistical analysis plan is available at NEJM.org and on the trial website at www.recoverytrial.net.

The initial version of the manuscript was drafted by the first and last authors, developed by the writing committee, and approved by all members of the trial steering committee. The funders had no role in the analysis of the data, in the preparation or approval of the manuscript, or in the decision to submit the manuscript for publication. The first and last members of the writing committee vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

RANDOMIZATION

We collected baseline data using a Web-based case-report form that included demographic data, the level of respiratory support, major coexisting illnesses, suitability of the trial treatment for a particular patient, and treatment availability at the trial site. Randomization was performed with the use of a Web-based system with concealment of the trial-group assignment. Eligible and consenting patients were assigned in a 2:1 ratio to receive either the usual standard of care alone or the usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days (or until hospital discharge if sooner) or to receive one of the other suitable and available treatments that were being evaluated in the trial.

For some patients, dexamethasone was unavailable at the hospital at the time of enrollment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. These patients were excluded from entry in the randomized comparison between dexamethasone and usual care and hence were not included in this report. The randomly assigned treatment was prescribed by the treating clinician. Patients and local members of the trial staff were aware of the assigned treatments.

PROCEDURES

A single online follow-up form was to be completed when the patients were discharged or had died or at 28 days after randomization, whichever occurred first. Information was recorded regarding the patients' adherence to the assigned treatment, receipt of other trial treatments, duration of admission, receipt of respiratory support (with duration and type), receipt of renal support, and vital status (including the cause of death). In addition, we obtained routine health care and registry data, including information on vital status (with date and cause of death), discharge from the hospital, and respiratory and renal support therapy.

OUTCOME MEASURES

The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months. Secondary outcomes were the time until discharge from the hospital and, among patients not receiving invasive mechanical ventilation at the time of randomization, subsequent receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Other prespecified clinical outcomes included cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subgroup), and receipt and duration of ventilation.

STATISTICAL ANALYSIS

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the Covid-19 pandemic. As the trial progressed, the trial steering committee, whose members were unaware of the results of the trial comparisons, determined that if 28-day mortality was 20%, then the enrollment of at least 2000 patients in the dexamethasone group and 4000 in the usual care group would provide a power of at least 90% at a two-sided P value of 0.01 to detect a clinically relevant proportional reduction of 20% (an absolute difference of 4 percentage points) between the two groups. Consequently, on June 8, 2020, the steering committee closed recruitment to the dexamethasone group, since enrollment had exceeded 2000 patients.

For the primary outcome of 28-day mortality, the hazard ratio from Cox regression was used to estimate the mortality rate ratio. Among the few patients (0.1%) who had not been followed for 28 days by the time of the data cutoff on July 6, 2020, data were censored either on that date or on day 29 if the patient had already been discharged. That is, in the absence of any information to the contrary, these patients were assumed to have survived for 28 days. Kaplan–Meier survival curves were constructed to show cumulative mortality over the 28-day period. Cox regression was used to analyze the secondary outcome of hospital discharge within 28 days, with censoring of data on day 29 for patients who had died during hospitalization. For the prespecified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among patients who were not receiving invasive mechanical ventilation at randomization), the precise date of invasive mechanical ventilation was not available, so a log-binomial regression model was used to estimate the risk ratio.

Through the play of chance in the unstratified randomization, the mean age was 1.1 years older among patients in the dexamethasone group than among those in the usual care group (Table 1). To account for this imbalance in an important prognostic factor, estimates of rate ratios were adjusted for the baseline age in three categories (<70 years, 70 to 79 years, and ≥80 years). This adjustment was not specified in the first version of the statistical analysis plan but was added once the imbalance in age became apparent. Results without age adjustment (corresponding to the first version of the analysis plan) are provided in the Supplementary Appendix.

Prespecified analyses of the primary outcome were performed in five subgroups, as defined by characteristics at randomization: age, sex, level of respiratory support, days since symptom onset, and predicted 28-day mortality risk. (One further prespecified subgroup analysis regarding race will be conducted once the data collection has been completed.) In prespecified subgroups, we estimated rate ratios (or risk ratios in some analyses) and their confidence intervals using regression models that included an interaction term between the treatment assignment and the subgroup of interest. Chi-square tests for linear trend across the subgroup-specific log estimates were then performed in accordance with the prespecified plan.

All P values are two-sided and are shown without adjustment for multiple testing. All analyses were performed according to the intention-to-treat principle. The full database is held by the trial team, which collected the data from trial sites and performed the analyses at the Nuffield Department of Population Health, University of Oxford.

RESULTS

PATIENTS

Of the 11,303 patients who underwent randomization from March 19 to June 8, 2020, a total of 9355 patients (83%) were eligible to receive dexamethasone (i.e., the drug was available in the hospital at the time and the patient had no known indication for or contraindication to dexamethasone). Of these patients, 6425 underwent randomization to receive either dexamethasone (2104 patients) or usual care alone (4321 patients) (Fig. 1). The remaining patients were randomly assigned to one of the other treatment groups being evaluated in the trial.

The mean (±SD) age of the patients in this comparison was 66.1±15.7 years, and 36% of the patients were female (Table 1). A history of diabetes was present in 24% of the patients, heart disease in 27%, and chronic lung disease in 21%, with 56% having at least one major coexisting illness recorded. In this analysis, 89% of the patients had laboratory-confirmed SARS-CoV-2 infection, and 0.4% were currently awaiting the result. At randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither.

Follow-up information for the primary outcome was complete for 6418 patients (99.9%) who had undergone randomization. In the dexamethasone group, 95% of the patients received at least one dose of the drug (Table S1). The median duration of treatment was 7 days (interquartile range, 3 to 10). In the usual care group, 8% of the patients received dexamethasone as part of their clinical care. The use of azithromycin during the follow-up period was similar in the dexamethasone group and the usual care group (24% vs. 25%), and 0 to 3% of patients received hydroxychloroquine, lopinavir–ritonavir, or interleukin-6 antagonists during follow-up (Table S1 in the Supplementary Appendix). After remdesivir became available in the United Kingdom on May 26, 2020, the drug was administered to 3 patients in the dexamethasone group and 2 patients in the usual care group.

PRIMARY OUTCOME

Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001) (Fig. 2A). In a prespecified analysis according to

Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

* Plus–minus values are means ±SD. HIV denotes human immunodeficiency virus, IQR interquartile range, NA not applicable, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† There was a significant (P=0.01) difference in the mean age between patients in the dexamethasone group and those in the usual care group, but there were no significant differences between the groups in any other baseline characteristic.
‡ Included in this category were 6 pregnant women.
§ Data regarding the number of days since symptom onset were missing for 4 patients in the dexamethasone group and 13 patients in the usual care group; these patients were excluded from estimates of the median number of days since onset.
¶ Severe liver disease was defined as requiring ongoing specialist care.
‖ Severe kidney impairment was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2.

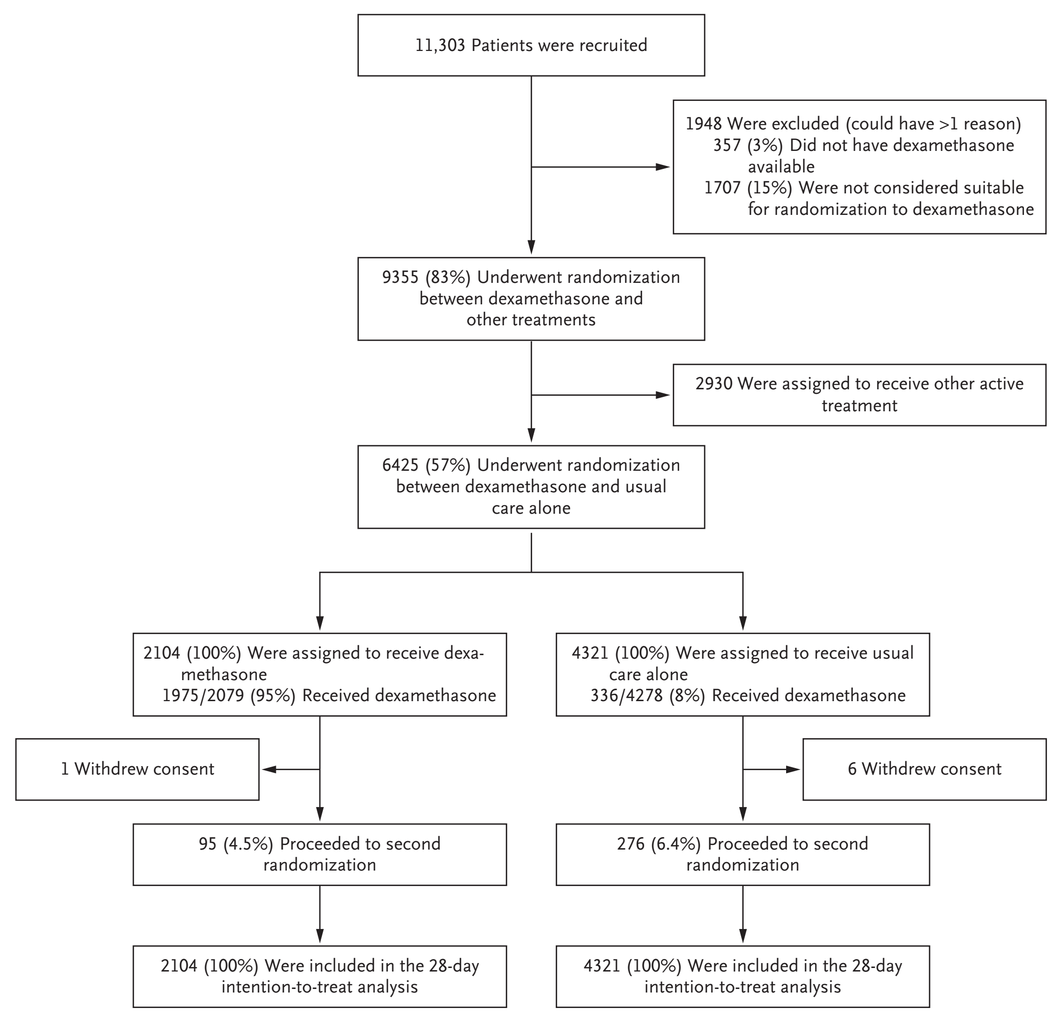

Figure 1. Enrollment, Randomization, and Inclusion in the Primary Analysis.

At the time of this analysis, completed follow-up forms were available for 2079 of 2104 patients (98.8%) in the dexamethasone group and 4278 of 4321 patients (99.0%) in the usual care group. The subgroup of patients who later underwent a second randomization to tocilizumab versus usual care in the RECOVERY trial included 95 of 2104 patients (4.5%) in the dexamethasone group and 276 of 4321 patients (6.4%) in the usual care group. In addition, 13 patients were randomly assigned to receive either convalescent plasma or usual care alone.

the level of respiratory support that the patients were receiving at randomization, there was a trend showing the greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation (11.5 by chi-square test for trend) (Fig. 3). In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) (Fig. 2B and 2C). However, there was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55) (Fig. 2D). The results were similar in a post hoc exploratory analysis restricted to the 5698 patients (89%) with a positive SARS-CoV-2 test result. Likewise, sensitivity analyses without adjustment for age resulted in similar findings (Table S2).

Patients who were receiving invasive mechan-

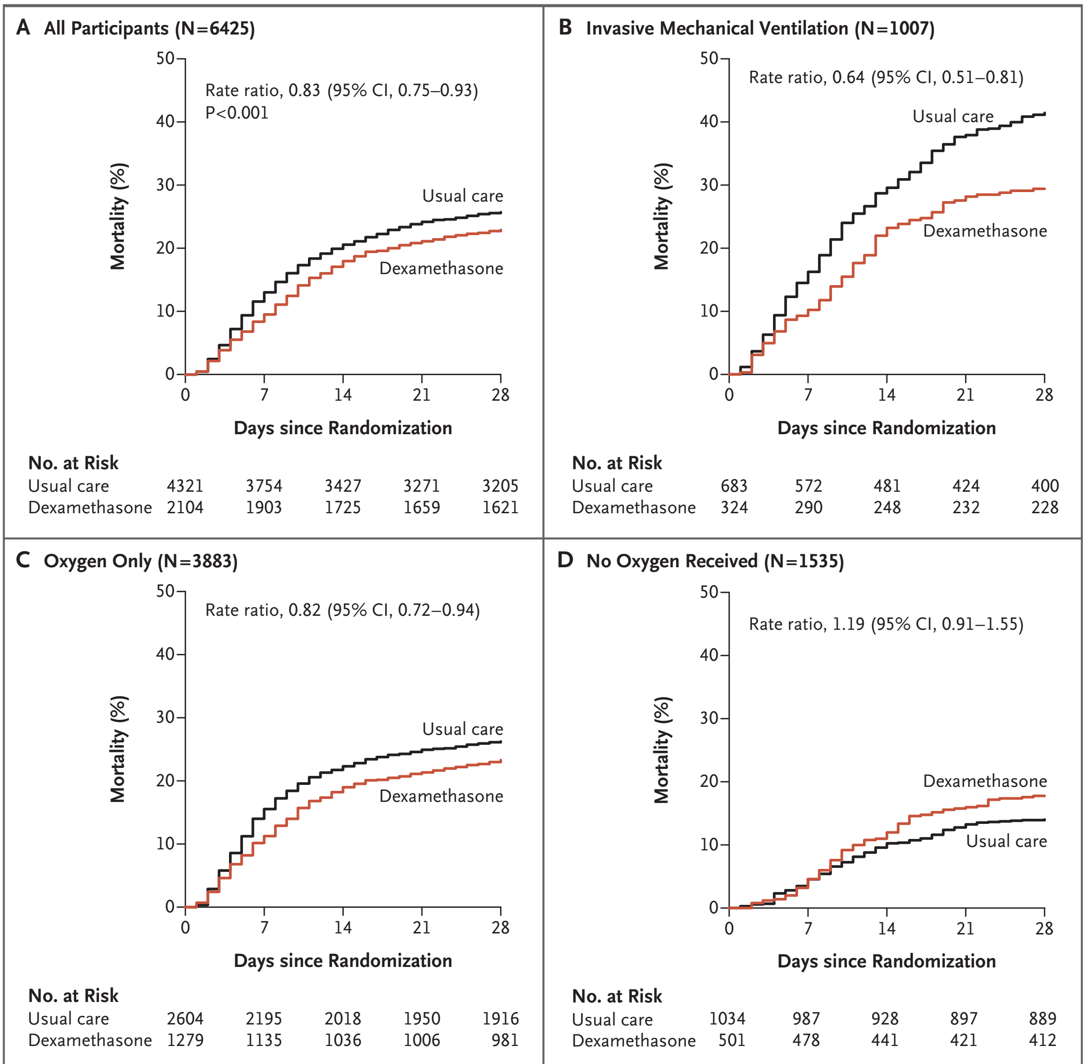

Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

ical ventilation at randomization were on average 10 years younger than those not receiving any respiratory support and had a history of symptoms before randomization for an average of 7 days longer (Table 1 and Table S3). The age-adjusted absolute reductions in 28-day mortality associated with the use of dexamethasone were 12.3 percentage points (95% CI, 6.3 to 17.6) among the patients who were receiving invasive mechanical ventilation and 4.2 percentage points (95% CI, 1.4 to 6.7) among those receiving oxygen only.

Patients with a longer duration of symptoms (who were more likely to have been receiving invasive mechanical ventilation at randomization) had a greater mortality benefit in response to treatment with dexamethasone. The receipt of

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)** **P<0.001**

Chi-square trend across three categories: 11.5

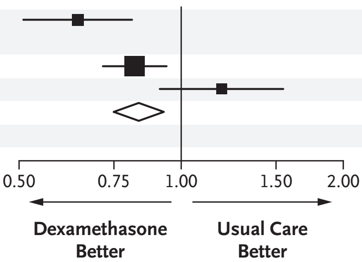

Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.
Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with a more recent symptom onset (12.3 by chi-square test for trend) (Fig. S1).

SECONDARY OUTCOMES

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days vs. 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17) (Table 2). The greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (11.5 by chi-square test for trend) (Fig. S2A).

Among the patients who were not receiving invasive mechanical ventilation at randomization, the number of patients who progressed to the prespecified composite secondary outcome of invasive mechanical ventilation or death was lower in the dexamethasone group than in the usual care group (risk ratio, 0.92; 95% CI, 0.84 to 1.01) (Table 2). This effect was greater among the patients who were receiving oxygen at randomization (6.2 by chi-square test for trend) (Fig. S2B).

OTHER PRESPECIFIED CLINICAL OUTCOMES

The risk of progression to invasive mechanical ventilation was lower in the dexamethasone group than in the usual care group (risk ratio, 0.77; 95% CI, 0.62 to 0.95) (Table 2). Analyses are ongoing regarding cause-specific mortality, the need for renal dialysis or hemofiltration, and the duration of ventilation.

DISCUSSION

Our preliminary results show that among hospitalized patients with Covid-19, the use of dexamethasone for up to 10 days resulted in lower 28-day mortality than usual care in patients who were receiving invasive mechanical ventilation at randomization (by 12.3 age-adjusted percentage points, a proportional reduction of approximately one third) and those who were receiving oxygen without invasive mechanical ventilation (by 4.1 age-adjusted percentage points, a proportional reduction of approximately one fifth). However, there was no evidence that dexamethasone provided any benefit among patients who were not receiving respiratory support at randomization, and the results were consistent with possible harm in this subgroup. The benefit was also clear in patients who were being treated more than 7 days after symptom onset, when inflammatory lung damage is likely to have been more common. In a recent trial involving patients with acute respiratory distress syndrome who were undergoing mechanical ventilation, mortality at 60 days was 15 percentage points lower among those receiving dexamethasone than among those receiving usual care, a finding that was consistent with our results.[22]

The RECOVERY trial was designed to provide

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

a rapid and robust assessment of the effect of readily available potential treatments for Covid-19 on 28-day mortality. Approximately 15% of all hospitalized patients with Covid-19 in the United Kingdom were enrolled in the trial, and mortality in the usual care group was consistent with the overall case fatality rate for hospitalized patients with Covid-19 in the United Kingdom.[7] Only essential data were collected at hospital sites, with additional information (including longer-term mortality) ascertained through linkage with routine data sources. We did not collect information on physiologic, laboratory, or virologic measures. The protocol combines the methods that were used in large, simple trials of treatments for acute myocardial infarction in the 1980s with the opportunities provided by digital health care in the 2020s.[23-25] The trial has progressed rapidly, as is essential for studies during epidemics.[26] These preliminary results for dexamethasone were announced on June 16, 2020, nearly 100 days after the protocol was first drafted, and were adopted into U.K. practice later the same day.[27]

Glucocorticoids have been widely used in syndromes closely related to Covid-19, including SARS, Middle East respiratory syndrome (MERS), severe influenza, and community-acquired pneumonia. However, the evidence to support or discourage the use of glucocorticoids under these conditions has been weak owing to the lack of data from sufficiently powered randomized, controlled trials.[28-31] In addition, the evidence base has suffered from heterogeneity in glucocorticoid doses, medical conditions, and disease severity. It is likely that the beneficial effect of glucocorticoids in severe viral respiratory infections is dependent on a selection of the right dose, at the right time, in the right patient. High doses may be more harmful than helpful, as may such treatment given at a time when control of viral replication is paramount and inflammation is minimal. Slower clearance of viral RNA has been observed in patients with SARS, MERS, and influenza who were treated with systemic glucocorticoids, but the clinical significance of these findings is unknown.[29,32,33] Unlike with SARS, in which viral replication peaks in the second week of illness,[34] viral shedding in SARS-CoV-2 appears to be higher early in the illness and declines thereafter.[35-38] The greater mortality benefit of dexamethasone in patients with Covid-19 who are receiving respiratory support and among those recruited after the first week of their illness suggests that at that stage the disease may be dominated by immunopathological elements, with active viral replication playing a secondary role. This hypothesis would caution against extrapolation of the effect of dexamethasone in patients with Covid-19 to patients with other viral respiratory diseases with a different natural history.

The RECOVERY trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with Covid-19 who are receiving respiratory support. We found no benefit (and the possibility of harm) among patients who did not require oxygen. Before the completion of the trial, many Covid-19 treatment guidelines stated that the use of glucocorticoids was either contraindicated or not recommended.[18] Dexamethasone is on the list of essential medicines of the World Health Organization and is readily available worldwide at low cost. Guidelines issued by the U.K. chief medical officers and by the National Institutes of Health in the United States have already been updated to recommend the use of glucocorticoids in patients hospitalized with Covid-19.[27,39]

The views expressed in this article are those of the authors and do not necessarily reflect those of the National Health Service, the National Institute for Health Research, or the Department of Health and Social Care.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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