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Natalia G. Vallianou, MD, Msc, PhD
First Department of Internal Medicine "Evangelismos" General Hospital of Athens, Greece

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. *N Engl J Med* 2020; Jul 17:NEJMoa2021436. doi: 10.1056/NEJMoa2021436

Coronavirus disease 2019 (Covid-19) is widely known to be related to diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and reduce the rates of progression to respiratory failure and death. In this controlled study, comparing a range of potential treatments in patients who were hospitalized with Covid-19, researchers 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 standard care alone. A total of 2104 patients received dexamethasone and 4321 received standard care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the standard care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval, 0.75 to 0.93; P<0.001). The between-group differences in mortality varied substantially depending on 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 standard care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% Confidence Interval, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% Confidence Interval 0.72 to 0.94), but not among those who were receiving no respiratory support at randomization. In conclusion, among patients hospitalized with Covid-19, the use of dexamethasone resulted in a lower 28-day mortality amongst those who were receiving either invasive mechanical ventilation or oxygen alone at randomization, but not among those receiving no respiratory support.

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK; BACC Bay Tocilizumab Trial Investigators. *N Engl J Med* 2020; Oct 21. doi: 10.1056/NEJMoa2028836

The efficacy of interleukin-6 receptor blockade with Tocilizumab in hospitalized patients with Covid-19 who are not receiving mechanical ventilation remains in doubt. Stone et al performed a randomized, double-blind, placebo-controlled trial involving patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states, and at least two of the following: fever >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. Patients were randomly assigned to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo. They enrolled 243 patients; 141 (58%) were men, and 102 (42%) were women. The median age was 59.8 years (range, 21.7 to 85.4), and 45% of the patients were Hispanic or Latino. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval, 0.38 to 1.81; P=0.64), and the hazard ratio for disease worsening was 1.11 (95% Confidence Interval, 0.59 to 2.10; P=0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had worsening of their disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% Confidence Interval, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% Confidence

Interval, 3.8 to 7.8) in the placebo group (P=0.69). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Interestingly, patients on tocilizumab had fewer serious infections than patients who received placebo. Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Nevertheless, some benefit or harm cannot be ruled out as the confidence intervals for efficacy comparisons were wide.

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse T, Felton T, Williams J, Faccenda J, Underwood J, Baillie JK, Chappell LC, Faust SN, Jaki T, Jeffery K, Lim WS, Montgomery A, Rowan K, Tarning J, Watson JA, White NJ, Juszczak E, Haynes R, Landray MJ. *N Engl J Med*; 2020 Oct 8:NEJMoa2022926. doi: 10.1056/NEJMoa2022926

Hydroxychloroquine and chloroquine have been suggested as potential treatments for Covid-19 on the basis of their in vitro activity and data from some uncontrolled studies. In this randomized, controlled, study comparing a range of possible treatments with standard care in patients hospitalized with Covid-19, researchers randomly assigned 1561 patients to receive hydroxychloroquine and 3155 to receive standard care. Death within 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval, 0.97 to 1.23; P=0.15). The results suggest that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% Confidence Interval, 0.83 to 0.98). Among the patients who were not undergoing mechanical ventilation at baseline, those in the hydroxychloroquine group had a higher frequency of invasive mechanical ventilation or death (30.7% vs. 26.9%; risk ratio, 1.14; 95% Confidence Interval 1.03 to 1.27). There was a small numerical excess in cardiac deaths, but no difference in the incidence of new major cardiac arrhythmia among patients who were treated with hydroxychloroquine. To sum up, among patients hospitalized with Covid-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received standard care.

Remdesivir for the Treatment of Covid-19 - Final Report

Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. *N Engl J Med* 2020; Oct 8:NEJMoa2007764. doi: 10.1056/NEJMoa2007764

Beigel et al conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. A total of 1062 patients were included in the study (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval, 9 to 11), as compared with 15 days (95% Confidence interval, 13 to 18) among those who received placebo. The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29. Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%). These data advocate that the use of remdesivir was superior to placebo in terms of shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.