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INFECTIOUS DISEASES CORNER

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Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

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Severe coronavirus disease 2019 (Covid-19), which is attributed to SARS-CoV-2, is related to an hyper-inflammation syndrome. Baricitinib, a dual Janus activated Kinase 1 and 2 (JAK 1 and 2) inhibitor, which is orally administered, is known to inhibit the intracellular signalling pathway implicated in severe COVID-19, such as the production of IL-1, IL-6, IL-10 and interferon-γ. Remdesivir, a pro-drug administered intravenously, is a ribonucleotide analogue inhibitor of viral RNA polymerase, which was initially used to treat hepatitis C and afterwards showed promise in Embola and Marburg viruses, before being investigated in SARS-CoV-2. The effects of combination treatment with baricitinib plus remdesivir were investigated in this double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir among hospitalized patients with COVID-19. A total of 1033 patients were enrolled in this study. Patients receiving baricitinib had a median time to recovery of 7 days (95% CI, 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control and a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Notably, patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment, whereas in the control group -receiving only remdesivir- 18 days. The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). Serious adverse events were less frequent in the combination group than in the control group. To conclude, baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The recommended dose of baricitinib is 4mg daily, while for remdesivir is 200mg intravenously at day 1, followed by 100 intravenously for at least a total duration of treatment of 5 days and no more than 10 days.

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

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Molnupiravir is an oral, small-molecule, nucleoside analogue, antiviral pro-drug, which, although initially developed to combat influenza, is reported to have activity against SARS-CoV-2. Researchers conducted a Phase 3, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of treatment with molnupiravir started within 5 days after the onset of signs or symptoms among non-hospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed COVID-19 and at least one risk factor for severe COVID-19. Participants in the trial were randomly assigned to receive 800 mg of molnupiravir or placebo twice daily for 5 days. The primary efficacy end point was the incidence of hospitalization or death by day 29. In particular, a total of 1433 participants were enrolled in this study, among

whom 716 received molnupiravir and 717 received placebo. The risk of hospitalization for any cause or death by day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]), P=0.001). In the analysis of all participants who had undergone randomization, the percentage of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709 patients] vs. 9.7% [68 of 699 patients]). One death was reported in the molnupiravir group and 9 were reported in the placebo group by day 29. Adverse events were reported in 216 of 710 participants (30.4%) in the molnupiravir group and 231 of 701 (33.0%) in the group having received placebo. To conclude, early treatment with molnupiravir reduced the risk of hospitalizations or death in at-risk, unvaccinated adults with COVID-19.

REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19

DM Weinreich, S Sivapalasingam, T Norton, S Ali, H Gao, R Bhore, J Xiao, AT Hooper, JD Hamilton, BJ Musser, D Rofail, M Hussein, J Im, DY Atmodjo, C Perry, C Pan, A Mahmood, R Hosain, JD Davis, KC Turner, A Baum, CA Kyratsous, Y Kim, A Cook, W Kampman, L Roque-Guerrero, G Acloque, H Aazami, K Cannon, JA Simón-Campos, JA Bocchini, B Kowal, AT DiCioccio, Y Soo, GP Geba, N Stahl, L Lipsich, N Braunstein, G Herman, and GD Yancopoulos, for the Trial Investigators. *N Engl J Med* 2021;385:e81. Doi: 10.1056/NEJMoa2108163

In a Phase 1/2 study, REGEN-COV, which is a combination of the monoclonal antibodies casirivimab and imdevimab, reduced the viral load and number of medical visits among patients with COVID-19. This combinations has been suggested to possess in vitro activity SARS-CoV-2 variants of concern, but seemingly not of O variant. In a Phase 3 study, researchers randomly assigned outpatients with COVID-19 and risk factors for severe disease intravenous REGEN-COV or placebo. Patients were followed through day 29. COVID-19-related hospitalization or death from any cause occurred in 18 of 1355 patients in the REGEN-COV 2400-mg group (1.3%) and in 62 of 1341 patients in the placebo group (P<0.001). The median time to resolution of symptoms was 4 days shorter with REGEN-COV than with placebo (10 days vs. 14 days; P<0.001). Serious adverse events occurred more frequently in the placebo group (4.0%) than in the 2400-mg group (1.3%); infusion-related reactions of grade 2 or higher occurred in less than 0.3% of the patients in all groups. To sum up, REGEN-COV reduced the risk of COVID-19-related hospitalizations or death from any cause, and it resolved symptoms, while reducing the SARS-CoV-2 viral load more rapidly than placebo.

Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19

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In this Phase 3 study, researchers randomly assigned, in a 1:1 ratio, a cohort of ambulatory patients with mild or moderate COVID-19, who were at high risk for progression to severe disease to receive a single intravenous infusion of either a neutralizing monoclonal-antibody combination agent (2800 mg of bamlanivimab and 2800 mg of etesevimab, administered together) or placebo within 3 days after a laboratory diagnosis of SARS-CoV-2 infection. The primary outcome was the overall clinical status of the patients, defined as COVID-19-related hospitalizations or death from any cause by day 29. A total of 1035 patients were enrolled in this study and received an infusion of a combination of bamlanivimab-etesevimab or placebo. By day 29, a total of 11 of 518 patients (2.1%) in the bamlanivimab–etesevimab group had a COVID-19- related hospitalization or death from any cause, as compared with 36 of 517 patients (7.0%) in the placebo group (P<0.001). No deaths occurred in the bamlanivimab–etesevimab group; in the placebo group, 10 deaths occurred, 9 of which were attributed as related to COVID-19. At day 7, a greater reduction from baseline in the log viral load was observed among patients who received the combination treatment of bamlanivimab plus etesevimab than among those who received placebo (P<0.001). In conclusion, in high-risk patients, bamlanivimab plus etesevimab led to a lower incidence of COVID-19-related hospitalizations and death than did placebo and reduced the SARS-CoV-2 viral load more rapidly than placebo.