Nearly 2 years after the global outbreak of COVID-19, knowledge about drug treatment for the disease continues to accumulate. Pharmacological treatment for COVID-19 can be broadly divided into antivirals, immunosuppressants and anticoagulants, each with a different mechanism of action and effective timing of medication, depending on the severity of the disease.

The main pathogenesis of COVID-19 is thought to be viral replication in the first few days after onset, and an inflammatory response by host immunity after about 7 days. Therefore, it is important to administer antivirals early in the course of the disease and anti-inflammatory drugs in moderate and severe disease after about 7 days of onset.

Several clinical trials by the WHO are underway around the world to evaluate COVID-19 antiviral treatment. This editorial describes a trial of a new drug therapy for COVID-19, which was presented as late-breaking science at the European Society of Cardiology Congress 2021 (ESC 2021), held on 29 August 2021.

**Colchicine: ECLA PHRI COLCOVID Trial**

The anti-inflammatory effect of colchicine on the cytokine storm made it a promising candidate for the treatment of COVID-19, and the drug is known to be safe and well tolerated. Randomised controlled trials (RCTs) in hospitalised patients have reported limited clinical benefits of colchicine, such as increased time to clinical deterioration (mean [SD] event-free survival time was 18.6 [0.83] days in the control group versus 20.7 [0.31] in the colchicine group, log-rank p=0.03) and reduced duration of oxygen supplementation therapy and hospitalisation.

The ECLA PHRI COLCOVID trial (NCT04328480) was an RCT to evaluate the effect of colchicine in patients hospitalised with severe COVID-19 disease, with the aim of reducing mortality; its findings were presented by Dr Rafael Diaz at ESC 2021. In this trial, 1,279 patients aged 18 years and older admitted with COVID-19 were randomly assigned to the control (n=639) or colchicine (n=640) treatment group.

Among the secondary outcomes, there was a significant reduction in deaths due to new intubation or respiratory failure in the colchicine group (20.1%) compared with 24.9% in the control group (p<0.05), suggesting colchicine had a beneficial effect in hospitalised patients. On the other hand, the co-primary outcome of death or ventilator use was not significantly different (25.0% in the colchicine group compared with 28.8% in the control group; p=0.08). In addition, death (the co-primary outcome) was also not significantly different at 20.5% in the colchicine group compared with 22.2% in the control group (p=0.05). The use of colchicine was associated with a significant increase in severe diarrhoea (control group: 4.5%, colchicine group: 11.3%; p<0.05).

After the presentation of the trial at ESC 2021, a systematic review and meta-analysis published at the end of November 2021 showed that colchicine did not improve outcomes for all the established endpoints (mortality, ventilator support, intensive care unit admission and length of stay) and that adverse events were significantly increased.

In conclusion, the efficacy of colchicine in the treatment of COVID-19 is limited and its administration is not recommended.

**Icosapent Ethyl: PREPARE-IT-1 and PREPARE-IT-2**

The anti-inflammatory effect of icosapent ethyl (EPA), a highly purified omega-3 fatty acid that is a safe and well-tolerated oral therapy, makes it a promising therapy for COVID-19.

In an RCT reported from Canada in August 2021, 100 symptomatic COVID-19 positive outpatients were enrolled and assigned to the EPA group (8 g EPA/day for 3 days, followed by 4 g EPA/day for 11 days) or to treatment as usual. The results showed that the main biomarker endpoint – high-sensitivity C-reactive protein (hs-CRP) – was significantly reduced by 25% in the EPA group (−0.5 mg/l; interquartile range [IQR] −6.9, 0.4; within-group p=0.011), but not in the usual care group, which saw a decrease of 5.6% (−0.1 mg/l; IQR −3.2, 1.7; within-group p=0.51). Furthermore, there was a significant improvement in symptoms as measured by the patient-reported FLU-PRO score. This trial suggests that EPA may ameliorate early inflammation and symptoms in symptomatic outpatients with COVID-19.

**PREPARE-IT 1 (NCT04460651)** is a trial that tested whether EPA use reduces the rate of coronavirus infection in unvaccinated, COVID-19-uninfected
healthy participants. It was presented by Diaz at ESC 2021. A total of 4,244 people were screened in the trial, with a total enrolment of 1,712; the mean age was 40.5 years, and 55% were women. Participants were randomised at a ratio of 11 to receive either: EPA (4 g orally twice a day for 3 days, then 2 g twice a day for days 4–60; n=850), or a matching placebo (n=862). Results showed that EPA treatment did not reduce infection rates, and there were no significant differences between EPA and placebo in adverse events, such as AF or bleeding. The trial is significant in that it demonstrated the excellent safety and tolerability of high doses of EPA (8 g/day).

After the PREPARE-IT 1 trial was presented at ESC 2021, the results of the PREPARE-IT 2 trial (NCT04460653), an RCT examining the efficacy of EPA in reducing the severity of disease, was presented by Diaz at the American Heart Association Annual Scientific Sessions on 15 November. Patients in the PREPARE-IT 2 trial were COVID-19-positive patients aged ≥40 years, and had had symptoms of infection (e.g. fever, cough, sore throat, shortness of breath or myalgia) within the previous 7 days, but without an obvious indication for hospitalisation. These participants were randomised at a ratio of 1:1 to receive either EPA (4 g orally twice a day for 3 days, then 2 g twice a day for 4–28 days; n=1,010) or the corresponding placebo (n=1,042).

Results showed that the primary endpoint of COVID-19-related hospitalisations was not significantly different between EPA and placebo groups at 12% versus 13% (HR 0.84; 95% CI [0.65–1.08]; p=0.17). In the secondary analyses, there were no significant differences in new ventilator inductions (p=0.65) or total events (non-fatal MI or stroke, and death; p=0.12). The trial did not show efficacy. Further investigation regarding EPA is awaiting.

Rivaroxaban: The MICHELLE Trial

COVID-19 has a higher tendency to lead to thrombosis than other infections, and thrombotic complications (arterial and venous) are independent predictors of poor outcome.74 For patients hospitalised with non-severe COVID-19, therapeutic doses of heparin appear to be beneficial, reducing the need for organ support and intubation at high rate, and increasing survival rates, regardless of D-dimer results.75 However, for critically ill patients, therapeutic doses of heparin do not improve outcomes, and it has been suggested that they may be harmful.76

The results of the MICHELLE trial, which examined the role of rivaroxaban in extending the duration of post-discharge care, were presented at ESC 2021 and reported in The Lancet.77 In the MICHELLE trial, the mean age was 571 years, 127 (40%) were women and 191 (60%) were men, and the mean BMI was 29.7 kg/m². Patients received standard heparin thromboprophylaxis during hospitalisation and were randomly assigned at a ratio of 11 to receive low-dose rivaroxaban (10 mg once daily for 35 days) or no anticoagulation after discharge. Eligibility criteria included only patients at high risk of venous thromboembolism (VTE), with a total modified IMPROVE VTE risk score ≥24, or total modified IMPROVE VTE risk score ≥2 and D-dimer >500 ng/ml.

The primary efficacy outcome was a composite of symptomatic or fatal VTE, asymptomatic VTE (assessed by screening bilateral lower extremity venous ultrasound and CT pulmonary angiography), symptomatic arterial thromboembolism and cardiovascular death at day 35. In the results, the primary endpoint occurred in five out of 159 (3.14%) patients in the rivaroxaban group and in 15 out of 159 (9.43%) patients in the no-anticoagulation group (RR 0.3; 95% CI [0.12–0.90]; p=0.0293). There were no major bleeding events in either group, and the same was true for the incidence of clinically relevant non-major bleeding. This therefore suggests that thromboprophylaxis with rivaroxaban for 35 days improves clinical outcomes without increasing bleeding compared with no anticoagulation after hospital discharge.

These results are promising and results are awaited of trials evaluating post-discharge thromboprophylaxis including HEAL-COVID (NCT04801940), ACTIV-4C (NCT04650087), XACT (NCT04640181) and Effect of the Use of Anticoagulant Therapy During Hospitalization and Discharge in Patients with COVID-19 Infection (NCT04508439).

Conclusion

In general, viruses mutate gradually through repeated replication and epidemics, and it is thought that severe acute respiratory syndrome coronavirus 2 mutations at a rate of about one a fortnight. At present, mutant strains of B.1.1.529 (omicron strains) are rampant in many parts of the world. The omicron strain has about 30 mutations in the projections on the surface of the virus and is attracting attention because of its high infectivity.

Specific antibody drugs against COVID-19 have been reported to be less effective against omicron strains and, given the possibility of further viral mutations, it would be useful to consider the pathogenesis of the infection. Close attention must be paid to assessing whether candidate drugs against COVID-19 and drugs under development are effective against new mutant strains.

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