Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19: ACT trials for colchicine and antithrombotic therapies

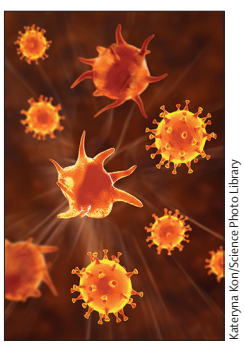
The COVID-19 pandemic destabilised health-care systems and led to millions of excess deaths worldwide.[1] Disproportionate inflammatory response and thromboembolic events denoted the clinical spectrum of patients with severe disease phenotypes and poor outcomes. In early 2020, when SARS-CoV-2 vaccines and antivirals such as nirmatrelvir–ritonavir were not yet available, approved immunomodulatory, immunosuppressive, and antithrombotic agents seemed inexpensive and safe options to treat patients in the community and hospital settings. For physicians to be informed on optimal clinical management, unprecedented efforts permitted the swift initiation of large multinational studies, such as the Anti-Coronavirus Therapies (ACT) trials.

In *The Lancet Respiratory Medicine*, John Eikelboom and the ACT investigators report on the results of two open-label, factorial, randomised controlled trials on colchicine and antithrombotics in patients who were ambulatory (ACT outpatient)[2] and patients who were hospitalised (ACT inpatient).[3] After the COVID-19 outbreak, published guidelines recommended various pharmacological strategies for COVID-19 on the basis of preliminary evidence and hypotheses generated from wet-laboratory research. The ACT investigators deserve recognition for having done these landmark studies, which contribute important information to the management of the disease. The clinical implications are direct.

In the ACT trials, no clinical benefit was shown for either colchicine or for two different antithrombotic regiments. The ACT outpatient trial[2] enrolled 3881 outpatients with symptomatic COVID-19 and additional risk factors. The 45-day incidence of hospitalisation or death in patients treated with colchicine was low and almost identical to that in controls (3·4% *vs* 3·3%, respectively; hazard ratio [HR] 1·02, 95% CI 0·72–1·43; p=0·93). Major thrombosis, hospitalisation, or death occurred in 3·0% of outpatients who received aspirin (*vs* 3·8% in controls) for a HR of 0·80 (0·57–1·13; p=0·21). The ACT inpatient trial[3] enrolled more than 2000 patients recently hospitalised with COVID-19 or with a worsening clinical situation if already hospitalised. Colchicine did not prevent the requirement for high flow oxygen, mechanical ventilation, or death (28·2% *vs* 27·2% in controls; HR 1·04, 95% CI 0·90–1·21; p=0·58); neither did the combination of low-dose rivaroxaban twice daily plus aspirin (26·4% *vs* 28·4% in controls; HR 0·92, 0·78–1·09; p=0·32) for a similar composite outcome also including major thrombotic events.

Despite a broad range of immunomodulatory effects and efficacy in other cardiovascular settings, routine use of colchicine for COVID-19 is not supported by the existing evidence, even if one pools the ACT results together with previous evidence from randomised trials. In both ACT trials, patients were enrolled over a period of about 18 months, over which the authors observed a progressive reduction of the outcome rate. This resulted in figures that could not confirm their hypotheses under the initial statistical assumptions, despite an increase in sample size and a change in the composition of the primary outcome done during the course of both studies.[4] The landscape for COVID-19 treatment has been affected by vaccination campaigns, evolving standards of care, including other immunomodulatory and immunosuppressive agents, and onset of novel virus strains. The case fatality rate dropped worldwide.[5] In ACT, the final treatment effects that have been obtained are the average of many different ones in overlapping (and at the moment lower risk) populations. Temporal changes in population characteristics often occur in large randomised trials, as well as the rationale for a specific intervention and what is considered ethical. For the aforementioned reasons, these changes might have been more extreme for COVID-19 and partly explain some heterogeneity across published trials.

Today, the future of colchicine for COVID-19 is different from what it used to be. Other immunomodulatory and anti-inflammatory treatments, including dexamethasone,[6] janus kinase inhibitors (JAK) inhibitors,[7] and interleukin-6 blocking antibody tocilizumab[8] showed promise in improving survival and accelerating clinical improvement among severely affected patients who were hospitalised. To that end, colchicine has gained considerable attention in the secondary prevention of cardiovascular disease.[9] As at least some studies suggest an increased risk of cardiac events following SARS-CoV-2



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infection, the question is whether it is too early to give up on colchicine in the setting of preventing COVID-19-related vascular events, but without the aim of preventing COVID-19 progression and death. Given its advantage of being cheap and readily available globally, studies targeting high-risk patient groups within this setting might be imperative.

Since the outbreak, the literature on COVID-19 has been filled with observational reports claiming the efficacy of antithrombotic therapy given early in the timeline of infection, possibly before the onset of respiratory complications.[10] Solid data for aspirin was lacking until the ACT trials.[11] The ACT studies could not establish superiority for either aspirin versus standard of care in the community setting or for aspirin plus low-dose rivaroxaban versus standard of care in inpatients. As a cautionary note, the low rate of events and consequent imprecision of risk estimates prevent us from drawing firm conclusions. A marginal benefit, especially for aspirin in community patients, could not be confirmed. On a population level, however, even a small decrease in hard clinical outcomes might have translated into a large number of hospitalisations and death being prevented, and lower societal costs, such as those for hospitalisation and post-discharge care. Coagulation activation represented a key feature of COVID-19 and pulmonary embolism-related mortality has been increasing primarily due to the pandemic.[12] It does not come as a surprise that anticoagulants have been investigated possibly more than antiplatelet agents. Intermediate or therapeutic anticoagulation appears to reduce thromboembolic events and disease progression in moderately ill patients who are hospitalised.[13] In patients requiring intensive care, a clinical benefit of this regimen is much less clear.[13] In the community setting, data from randomised trials does not support the routine use of thromboprophylaxis to reduce hospitalisations and death in patients who are high risk, who nevertheless appear to be characterised by a lower-than-anticipated rate of complications.[11,14,15]

Although the prognosis of patients with COVID-19 enrolled in ACT improved over time or was better than had been postulated when the studies were conceived, a substantial proportion in both ambulatory and hospital settings had either thrombosis or developed a severe complication, at least when compared with historical data from before the outbreak. Observational studies indicate that COVID-19 persists and continues to cause deaths globally, especially in individuals who are not vaccinated. In this scenario, the use of drugs with a strong theoretical rationale for use but without clinical evidence must be discouraged.

We declare no competing interests.

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