and are affordable, they lend themselves to use in low-income and middle-income countries. Baricitinib has few drug–drug interactions, is excreted largely unchanged, and can be used in older adults with comorbidities, such as a decreased glomerular filtration rate.

During the COVID-19 pandemic so far, only a few clinical trials have been done with the highest scientific rigour[12] (placebo-controlled, double-blind, and with randomisation stratified by disease severity and site location), such as the ACTT[5,11] and COV-BARRIER trials. The clinical benefits and significant reduction in mortality, as well as the absence of safety concerns found by both the COV-BARRIER and ACTT-2 studies, place baricitinib among the few proven treatments of choice for hospitalised patients with COVID-19.

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1   Kalil AC, Johnson DW, Lisco SJ, Sun J. Early goal-directed therapy for sepsis: a novel solution for discordant survival outcomes in clinical trials. *Crit Care Med* 2017; **45:** 607–14.
2   Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315:** 801–10.
3   Kalil AC, Syed A, Rupp ME, et al. Is bacteremic sepsis associated with higher mortality in transplant recipients than in nontransplant patients? A matched case-control propensity-adjusted study. *Clin Infect Dis* 2015; **60:** 216–22.
4   Donnelly JP, Locke JE, MacLennan PA, et al. Inpatient mortality among solid organ transplant recipients hospitalized for sepsis and severe sepsis. *Clin Infect Dis* 2016; **63:** 186–94.
5   Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med* 2020; **383:** 1813–26.
6   Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; **384:** 693–704.
7   Stebbing J, Krishnan V, de Bono S, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. *EMBO Mol Med* 2020; **12:** e12697.
8   Smolen JS, Genovese MC, Takeuchi T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. *J Rheumatol* 2019; **46:** 7–18.
9   Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021; published online Sept 1. https://doi.org/10.1016/S2213-2600(21)00331-3.
10   RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.
11   Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med* 2021; **384:** 795–807.
12   Kalil AC. Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA* 2020; **323:** 1897–98.

Colchicine treatment in COVID-19: the remaining unsolved question

Colchicine has been used to treat diverse pathologies in different areas of medicine, including rheumatology and cardiology. During the COVID-19 pandemic, colchicine has been considered a good therapeutic option because of its effects on the parts of the immune system involved in SARS-CoV-2 infection and acute respiratory distress syndrome (ARDS), including its effects on the chemotaxis of inflammatory cells, such as neutrophils and monocytes, and the intracellular transportation of vesicles. Colchicine also inhibits the inflammasome, expression of different molecules involved in leukocytes binding to endothelial cells, and the recruitment of mononuclear cells and neutrophils to inflamed tissue.[1] Therefore, different clinical trials were initiated to test the hypothesis of its benefit in COVID-19. 11 studies enrolling 17 205 patients with COVID-19, most of whom were male, were included in a meta-analysis, published in 2021.[2] Patients who received colchicine had a significantly lower risk of mortality (odds ratio 0·57 [95% CI 0·38–0·87]; I^2 72%; p<0·01) and a non-significantly lower rate of mechanical ventilation (odds ratio 0·67 [95% CI 0·39–1·15]; I^2 67%; p<0·01). Of note, the subgroup analysis involving randomised controlled trials showed no statistically significant difference in mortality between patients who received colchicine and those who did not. The COLCORONA trial,[3] a study of more than 4000 non-hospitalised patients, was included in the meta-analysis, but this trial was stopped before the scheduled sample size had been fully enrolled due to logistical reasons and the result was not statistically significant.

In *The Lancet Respiratory Medicine*, the RECOVERY Collaborative Group report the results of a streamlined,
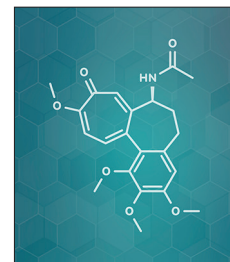
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randomised, controlled, open-label, platform trial,[4] in which adult patients were randomly assigned (1:1) to receive either usual standard of care alone or usual standard of care plus colchicine. The primary outcome was all-cause mortality assessed at day 28. The study suggests that colchicine was not associated with reductions in 28-day mortality (rate ratio 1·01 [95% CI 0·93 to 1·10]; p=0·77), duration of hospital stay (10 days [IQR 5 to >28] in both groups), or risk of progressing to invasive mechanical ventilation or death (risk ratio 1·02 [95% CI 0·96 to 1·09]; p=0·47).

However, the study has important limitations. The maximum duration of colchicine was set at 10 days and in several patients the cause of premature discontinuation was not collected. The authors mention that a longer duration of therapy might have provided benefit, but most participants had stopped colchicine before day 10 either because of death, discharge from hospital, or at the discretion of the treating clinician. Moreover, information regarding the number of patients who received the treatment through a nasogastric tube and the number of patients whose dose frequency was halved because they were also receiving a moderate CYP3A4 was not collected. Additionally, information regarding chest radiographical findings was not gathered appearances was not collected. Furthermore, stratification based on disease severity or autoinflammatory markers was not done. Because of the study's design, it was not possible to know the outcome within the subgroup of patients that received colchicine plus steroids compared with those who received usual care plus steroids without receiving other available treatments. All this information should be considered when deciding the clinical context in which patients with COVID-19 should receive colchicine. Moreover, these factors should be considered when deciding whether new clinical studies are initiated, especially given the low costs and relative ease of administration of colchicine.

The outcome of the RECOVERY trial led us to analyse the difficulties that clinical trials have had, especially the need for a rapid but valid trial development in search of solutions for COVID-19. This situation has tested the question other researchers have asked:[5] can we increase the rate of discovery while staying faithful to scientific method? There are already hundreds of COVID-19 trials registered worldwide, with numbers increasing daily. Several studies have already been reported during the COVID-19 pandemic, often as preprints to publish results quickly. Many of the randomised trials are flawed because of the many challenges associated with research during a pandemic,[6] including ethical concerns.[7] Furthermore, predefined platform trials, such as RECOVERY and SOLIDARITY, have been recognised as an efficient approach to knowledge acquisition, but the randomisation methods of these trials have been considered suboptimal for matching the studied groups based on disease severity in critically ill patients hospitalised with COVID-19—a population with high mortality rates.[8]

Acknowledging the suboptimal randomisation strategies, the results of the RECOVERY trial regarding the use of colchicine in patients hospitalised with COVID-19 should only be applied to patients with very similar characteristics. However, previous published results from the RECOVERY trial showed three alternative effective options to reduce mortality: dexamethasone[9] and tocilizumab[10] in patients who were critically ill and those requiring oxygen therapy and the combination of monoclonal antibodies[11] (casirivimab and imdevimab) for patients without detectable antibodies (seronegative). Questions remain to be resolved regarding the benefit of colchicine in different populations of patients with COVID-19, especially in outpatients with early stage disease.

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1   Parra-Medina R, Sarmiento-Monroy JC, Rojas-Villarraga A, Garavito E, Montealegre-Gómez G, Gómez-López A. Colchicine as a possible therapeutic option in COVID-19 infection. *Clin Rheumatol* 2020; **39:** 2485–86.

2   Lien C, Lee M, Weng S, et al. Repurposing colchicine in treating patients with COVID-19: a systematic review and meta-analysis. *Life* 2021; **11:** 864.

3   Tardif J-C, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med* 2021; **9:** 924–32.

4   RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Respir Med* 2021; published online Oct 18. https://doi.org/10.1016/S2213-2600(21)00435-5.

5   Scott I. COVID-19 pandemic and the tension between the need to act and the need to know. *Intern Med J* 2020; **50:** 904–09.

6   Mitchell EJ, Ahmed K, Breeman S, et al. It is unprecedented: trial management during the COVID-19 pandemic and beyond. *Trials* 2020; **21:** 784.

7   Bierer B, White S, Brnes J, Gelinas L. Ethical challenges in clinical research during the COVID-19 pandemic. *Bioethical Inq* 2020; **17:** 717–22.

8   Emani VR, Goswami S, Nandanoor D, Emani SR. Randomised controlled trials for COVID-19: evaluation of optimal randomisation methodologies—need for data validation of the completed trials and to improve ongoing and future randomised trial designs. *Int J Antimicrob Agents* 2021; **57:** 106222.

9   RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; **384:** 693–704.

10   RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.

11   Horby PW, Mafham M, Peto L, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv* 2021; published online June 16. https://doi.org/10.1101/2021.06.15.21258542 (preprint).

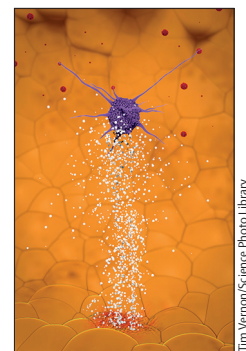# The course of action for effective anti-cytokine treatment in COVID-19

Even in the aftermath of global anti-SARS-CoV-2 vaccination campaigns, safe and effective treatments to inhibit inflammation and reduce mortality continue to be needed for the substantial proportion of unvaccinated individuals at risk of developing severe COVID-19. The COV-AID trial, the results of which were reported by Jozefien Declercq and colleagues in *The Lancet Respiratory Medicine*, was a factorial, randomised controlled trial investigating interleukin (IL)-1 blockade (anakinra) and IL-6 blockade (tocilizumab or siltuximab) in patients with COVID-19, respiratory failure, and cytokine release syndrome.[1] This trial was done between April 4 and Dec 6, 2020 in 16 Belgian hospitals and enrolled 342 patients. The primary outcome was time to clinical improvement (increase in 2 points from baseline status on a 6-point ordinal scale). Patients were randomly assigned in a 1:2 ratio to anakinra or standard-of-care treatment, and then 1:1:1 to siltuximab, tocilizumab, or standard of care. The trial showed near-identical times to clinical improvements across groups, indicating marginal or no added benefit for cytokine blockade in this setting.

The use of a factorial design adds complexity to the interpretation of this data. The advantages of this design are the possibility to test multiple treatments simultaneously, while minimising the number of patients exclusively receiving standard of care. However, the dual randomisation strategy resulted in four treatment groups (no cytokine inhibitors; IL-1 inhibition, IL-6 inhibition; IL-1 and IL-6 inhibition combined) with disparities in allocation: notably, only 34 patients received anakinra alone, compared with 129 patients receiving IL-6 inhibitors alone. In addition, the power of

factorial designs is influenced by potential interactions between treatments: it is increased by synergistic interaction and decreased by detrimental interaction.[2] The authors assumed a priori no interaction between IL-1 and IL-6 blockade; however, whether there is no interaction is debatable from a biologic standpoint as IL-1 is found upstream of IL-6 in inflammatory cascades: inhibiting IL-1 results in IL-6 inhibition, hence the two treatments are partially redundant.[3] In addition, co-administration of anticytokine treatments is typically avoided on the basis of safety concerns. It is interesting to note that co-administration of IL-1 and IL-6 inhibitors was not associated with increased adverse events in COV-AID. However, it is possible that a safety signal did not emerge owing to the relatively small sample size, and the rationale for co-administration of IL-1 and IL-6 inhibitors remains a questionable one.

The results of the COV-AID trial are partially at odds with available evidence. Previously, only observational studies had compared IL-1 and IL-6 inhibition in COVID-19 and found that anakinra was more effective.[4] Two controlled trials evaluated anakinra. The CORIMUNO trial enrolled patients with relatively mild disease and was prematurely interrupted because of assumed futility.[5,6] Conversely, the large SAVE-MORE trial enrolled patients on the basis of biomarker profiling: using soluble urokinase plasminogen activator receptor (suPAR) as a proxy for IL-1 bioactivity, the investigators selected patients at high risk for clinical deterioration and observed dramatic reductions in mortality in patients receiving anakinra in addition to the standard of care (including dexamethasone).[7] In contrast, IL-6 inhibition received much more

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