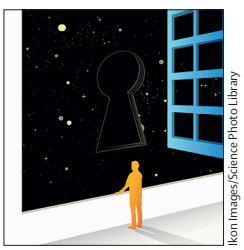
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Exploiting an early immunological window of opportunity in COVID-19



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See Articles page 924

Substantial advances in COVID-19 therapeutics have been made over the past year. Highly effective vaccines now exist to reduce a vaccinated person's risk of developing symptomatic disease and progressing to require hospital admission. For patients who are being treated in hospital and require supplemental oxygen, dexamethasone improves survival,[1] with an additional benefit from tocilizumab if systemic inflammation is present.[2] However, there remains an unmet need for therapeutic interventions that inhibit disease progression in symptomatic people in the community and prevent hospital admission.

Observational immunology data suggest this type of intervention should be possible. Clear differences exist in the inflammatory profiles of people admitted to hospital with COVID-19 compared with people in the community who do not progress to require hospital admission.[3] The inflammatory response remains distinct even when outpatients are compared with hospitalised patients with the least severe disease (eg, requiring no respiratory support or only supplemental oxygen). These differences include markers of endothelial injury and thrombosis, interleukin (IL)-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and the inflammasome product IL-1b. These observations were made using samples obtained at similar timepoints after symptom onset (7 days for both outpatients and patients treated in hospital but not requiring respiratory support), suggesting that progression to requiring hospital admission is the result of a distinct inflammatory trajectory. Although downstream markers of organ injury (including D-dimer and EN-RAGE) increase with illness duration in people admitted to hospital, more proximal signalling mediators do not (eg, IL-6 and GM-CSF), suggesting the inflammatory trajectory is already programmed at the time of hospital admission. Considering the benefit of anti-inflammatory therapy initiated after this point in hospital, it is reasonable to hope earlier anti-inflammatory interventions will inhibit the inflammatory response before it results in lung injury requiring respiratory support in hospital.

In the COLCORONA trial,[4] Jean-Claude Tardif and colleagues sought to exploit this putative window of opportunity with an impressive double-blind randomised controlled trial of colchicine for 4488 outpatients with symptomatic COVID-19 (not requiring PCR confirmation), recruited an average of 5·3 days after symptom onset. A composite endpoint of death or hospital admission was used. Colchicine is an inflammasome inhibitor and reduces caspase-1 activation and IL-1b secretion.[5] Circulating IL-1b is associated with disease severity, and analysis of lung tissue from people who died from COVID-19 confirms NLR-family pyrin domain-containing 3 (NLRP3) inflammasome activation.[6] In COLCORONA,[4] colchicine was dosed at 0·5 mg twice per day for 3 days then once per day for 27 days. This dosage is slightly lower than that used in the treatment of familial Mediterranean fever, an inherited autoinflammatory disease associated with pyrin inflammasome activation, in which 1–1·5 mg per day is recommended, escalated up to 3 mg per day in adults if needed.[7]

The investigators recruited people older than 40 years with additional high-risk criteria (≥70 years, BMI ≥30kg/m^2, diabetes, or other cardiorespiratory comorbidities). Although these criteria did select for people at increased risk of hospital admission, the median age in the treatment group was 53 years and 55.4% were women. Given that increasing age and male sex have the largest effect sizes for risk of mortality in people who are admitted to hospital,[8] the cohort studied in the COLCORONA trial[4] cannot be considered to be in the highest-risk category. The authors found no difference in the primary endpoint between the two treatment groups. However, in a subgroup analysis restricted to patients with PCR-confirmed SARS-CoV-2 infection (4159 [92·7%] of 4488 participants) colchicine was associated with a reduction in hospital admission and death (4·6 *vs* 6·0%, odds ratio 0·75, 95% CI 0·57–0·99), with a number needed to treat of 70 (95% CI 36–1842).

The COLCORONA trial[4] is a valuable addition to the clinical investigation of COVID-19. Is colchicine likely to become a first-line treatment for community management of early COVID-19? The answer is probably not. The effect size was small and the NNT large,

although further investigation in a higher-risk cohort might be warranted, aiming to recruit patients closer to symptom onset and possibly dosing colchicine closer to the recommendations for familial Mediterranean fever. This trial does however add proof of principle of two important therapeutic concepts—progression of COVID-19 lung injury can be inhibited to prevent hospital admission and anti-inflammatory therapy can achieve this. The STOIC trial[9] (167 outpatients with mild COVID-19) also suggested that early anti-inflammatory therapy might be beneficial; when compared with usual care, inhaled budesonide resulted in a reduction in the need for urgent medical care.[9]

Trials of anti-viral therapies in patients that were admitted to hospital have been disappointing, with neither intravenous remdesivir nor subcutaneous interferon (IFN) b-1a improving survival.[10] However, the evidence for a defective IFN response leading to severe disease is compelling; neutralising auto-antibodies against IFN-a2 and IFN-ω are over-represented in severe COVID-19 (compared with asymptomatic infection or healthy controls)[11] and variation in the *IFNAR2* gene, associated with low expression, is associated with COVID-19 critical illness.[12] Evaluation of IFN therapy in outpatients will be valuable, including in combination with anti-inflammatory therapies.

There is observational evidence that an early window of opportunity exists in which to modify the inflammatory trajectory in COVID-19 with the aim of preventing hospital admission. Encouragingly, these findings are now supported by emerging evidence from outpatient clinical trials. As has been the case in trials with patients admitted to hospital, evaluation of multiple agents will probably be required before highly efficacious outpatient therapy is identified. COLCORONA represents the beginning of this important process.

I declare no competing interests.

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Recovery after prolonged ICU treatment in patients with COVID-19

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With millions of individuals contracting COVID-19 worldwide, an unprecedented number of intensive care unit (ICU) survivors are now in recovery.[1] There is an urgent need to understand more fully the consequences of COVID-19 critical illness to prioritise patient-centred and family-centred interventions to meet their post-ICU physical and mental health needs. However, achieving advances in understanding to provide optimum care after acute disease remains challenging, with a paucity of post-COVID-19 long-term outcome data, and little understanding of the intersection between the direct consequences of COVID-19 (currently identified under the term post-COVID-19 condition) and the complex consequences of critical illness (post-intensive care syndrome or PICS). Although lessons certainly can be learned from previous studies of acute respiratory