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.

large randomised trials. However, as has been shown previously with the combination of ipilimumab and nivolumab,[15] it is very feasible to recruit large numbers of patients to an appealing clinical trial, if the funding is available. The MiST1 trial has provided proof of concept for molecular stratification in a mesothelioma trial, which is an important contribution; these trials can be done, but perhaps we need better targets. The NVALT19 trial provides us with an option of switch-maintenance gemcitabine without sufficient evidence for FDA approval, at a time when our first-line management for this disease is changing. Chemotherapy will still be an option in mesothelioma treatment, but it might move into the second line of therapy for some patients. I have no doubt that some clinicians will consider adding gemcitabine, a safe and relatively low-cost drug, to their patient management, particularly when progression would have major consequences for symptom burden. This new information from the NVALT19 trial could provide an opportunity for the mesothelioma community to consider novel clinical trial designs that can rapidly and inexpensively evaluate readily available treatments, such as registry clinical trials.

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Immunotherapy in COVID-19: why, who, and when?

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Nearly 1·5 years into the global COVID-19 pandemic, immense progress has been made against SARS-CoV-2 in health care, most prominently in vaccine development. However, why some people infected with SARS-CoV-2 rapidly develop fulminant respiratory failure, while others have mild, self-limited, or even asymptomatic disease, is not fully understood. In the absence of highly effective antiviral therapy, treatment has focused on modulating the host immune response to SARS-CoV-2. Unsurprisingly, given human genetic variation and the burgeoning genetic variance of the virus itself, evidence for the efficacy of many interventions is unclear. Mortality rates approaching 50% among mechanically ventilated patients in the recent RECOVERY trial of tocilizumab,[1] in both study arms, are a sobering reminder of the limitations of such treatments.

Leigh Wells/Ikon Images/ Science Photo Library

Although available evidence points to a benefit from selected immunomodulatory therapies, it is likely that beneficial effects are contingent on treating the right patient at the right time. In the midst of the pandemic, many factors could lead to differential treatment responses, including heterogeneity of trial design, concomitant therapies trialled in parallel or in series, biological variance in the host response to SARS-CoV-2, intermittent stresses of pandemic surge capacity, local clinical practices, or viral variants. How are practising clinicians to interpret conflicting results and incorporate a nuanced understanding of this heterogeneity into their treatment of patients with COVID-19?

In a Series in *The Lancet Respiratory Medicine*, three papers begin to address these issues in severe COVID-19 by reviewing, in turn, key aspects of the host immune response, the complex roles of interleukin-6 (IL-6) in pathogen clearance and inflammation, and recent clinical trial data on IL-6 receptor (IL-6R) blockade. Marcin Osuchowski and colleagues[2] provide a comprehensive review of the pathophysiology of COVID-19 with a focus on the host immune response. Two overarching themes emerge: first, the pathophysiology of COVID-19 is distinct from that of other severe respiratory infections; and second, considerable pathophysiological heterogeneity exists within COVID-19. The authors describe a disease that begins with epithelial injury and readily progresses to localised endothelial injury with a widespread coagulopathy. The severity of endotheliopathy and coagulopathy, in particular, distinguish COVID-19 from influenza and other viral pneumonitides. The paper highlights the obvious, but frequently disregarded, concept that viral cytotoxicity is central to the pathogenesis of severe COVID-19 and insufficient source control is the major challenge in the management of patients. The authors conclude that although systemic inflammation is clearly important, available data do not indicate that a so-called cytokine storm is the central pathological abnormality in COVID-19.

In the second Series paper, Oliver McElvaney and colleagues[3] provide a detailed review of IL-6 activity in health, disease, and COVID-19, including the salubrious effects of IL-6 as part of an effective host response to infection. They emphasise the relatively low concentrations of circulating IL-6 in those with COVID-19 compared with other critically ill patients, but with elevated C-reactive protein (CRP). These findings are perplexing because IL-6 is a key inducer of CRP production, perhaps highlighting our rudimentary understanding of cytokine responses in COVID-19. How do we reconcile the biological finding of a relatively modest systemic inflammatory response with treatment benefit from IL-6 inhibition observed in the two most recent trials: REMAP-CAP and RECOVERY?[1,4]

To address this question, Federico Angriman and colleagues[5] review the evidence from ten large randomised controlled trials (RCTs) that tested the efficacy of IL-6R blockade with monoclonal antibodies in COVID-19. They conclude that patients with severe COVID-19—those requiring either high-flow nasal oxygen, or non-invasive or invasive ventilation—are likely to benefit from these therapies, whereas patients with non-severe COVID-19 or those at high risk of secondary infections might be at risk of harm. The authors acknowledge the uncertainty of these recommendations and highlight several factors that might explain the discordant results of clinical trials, including severity of illness and timing of therapy, as well as variance in the use of corticosteroids between trials. Other contributing factors might relate to trial design, such as the use of non-contemporaneous patients in the control arm in REMAP-CAP[6] or the absence of block randomisation in RECOVERY,[7] or might be agnostic to trial design, such as the pathogenicity of viral variants[8] or differences in regional approaches to patient management and workflow. Outcomes in severe COVID-19 vary depending on hospital-level or regional factors and the pressure under which the health-care system is operating.[9] REMAP-CAP and RECOVERY,[1,4] the main trials with positive findings for IL-6R antagonists, were both open-label platform RCTs conducted primarily in the UK in the context of pandemic surges. Mortality in mechanically ventilated patients in these trials was quite high. How should the findings be applied in settings where mortality among mechanically ventilated patients with COVID-19 is already well below that observed in the treatment arms of REMAP-CAP (in-hospital mortality 41%) and RECOVERY (28-day mortality 49%)?[1,4]

A possible contributor to conflicting results in immunomodulatory trials is variable derangement in the balance of a well controlled versus a dysregulated immune response.[2,3] Several investigators have proposed an immunosuppressive phenotype of severe COVID-19 that is associated with attenuated interferon responses leading to unchecked viral replication.[10,11] In the context of the competing pathophysiological processes of immunosuppression and hyperinflammatory host response, the effects of immunosuppressive therapies might depend on which

process is dominant in a given patient at a given time. Corticosteroids can have a deleterious effect in the context of immunosuppression by promoting viral replication and prolonging viral infections.[12] In contrast, a recent study suggested that corticosteroids might be beneficial only in patients with severe COVID-19 and a hyperinflammatory response.[13] Likewise, a glaring absence in many conceptual immunobiological frameworks is the consistent and robust association of COVID-19 severity with older age. Although the reasons for this association remain incompletely understood, the immense protection from severe COVID-19 afforded by youth might imply that immunosenescence plays a crucial part in the host response, which is responsible for viral clearance in severe COVID-19.[14] Analysis of data that are able to distill these many competing factors at an individual level might be needed to fully realise the potential of immunotherapies in COVID-19.

Taken together, the first three papers in this Series[2,3,5] suggest that a precision-based approach to treatment might be needed, which is one of the central challenges facing the field. Phenotypes based on a systemic inflammatory response or an immunosuppressive state, or on biological markers of coagulopathy and endothelial dysfunction, might help to identify treatment-responsive subgroups of patients. COVID-19 phenotypes based on the temporal kinetics of immunological markers or disease trajectories are also of interest, and might be key to unlocking the optimum timing and type of immunomodulatory therapy. The role of different SARS-CoV-2 variants and the resulting host response also warrant further evaluation. Finally, studying host immune responses in the lungs will be important, although this comes with its own technical challenges. Future clinical practice is likely to involve targeted therapies based on biological, genetic, or functional immunophenotyping. Until such a time, researchers and clinicians must continue to carry out careful and well planned RCTs, acknowledge the complexity of the challenge we face, and assiduously collect biological specimens to better understand host immune responses to pathogens and their implications for the treatment of patients.

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Vascular mechanisms and manifestations of COVID-19

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Severe COVID-19 is dominated by a multifaceted severe respiratory infection. The pathophysiology of acute disease is the focus of a Series of four papers in *The Lancet Respiratory Medicine*. Dennis McGonagle and colleagues[1] propose that COVID-19 simultaneously affects three compartments of the lungs, thereby leading to disruption of oxygenation: inflammation of the alveolar space, immunothrombosis of the juxtaposed pulmonary vascular compartment, and thrombotic obstruction of the pulmonary and bronchial circulation. Apart from the respiratory features of COVID-19, many extrapulmonary manifestations can occur as