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.

problematic.[5] With amplification of underpowering from trial termination, exclusions of patients with the worst outcomes provide data that are difficult to interpret.

Underpowering aside, the unexpectedly large amount of imputation required because of trial termination must inevitably raise questions as to whether the positive result might have been an artefact of the chosen imputation model. Crucially, the RELIEF investigators[4] re-examined trial efficacy using alternative imputation models as well as evaluating FVC trends without imputation; in all cases, efficacy trends remained significant. The use of multiple imputation models is not normal practice but based on the underlying logic, well illustrated in the RELIEF trial, a strong case can be made for this approach to be applied more widely in future.

Taking these caveats into account, how should the data from the two pirfenidone trials[3,4] be processed by clinicians? It is important to stress that past comparative nintedanib and pirfenidone IPF data are highly relevant to this question. For IPF, there is a striking similarity in efficacy between the two agents and a highly similar level of toxicity.[6,7] Considered in isolation, on the basis of the two trials,[3,4] pirfenidone efficacy appears highly likely in patients with the progressive fibrotic phenotype who do not have IPF, but cannot, perhaps, be considered proven (although opinions on the level of proof might differ). But the more incisive question, relevant to clinical practice, relates to the multiple IPF and non-IPF trials: is there any reason to suspect that these two agents, so similarly efficacious in IPF,[6,7] are at all likely to differ materially in their efficacy in non-IPF fibrotic lung diseases? It is difficult to argue from existing data that differences in efficacy are likely. However, some clinicians will be uneasy about basing their practice on extrapolations of this sort, given the flaws in both pirfenidone studies.

Expert groups independent of the pharmaceutical industry now have a key role in making recommendations or providing informal guidance on the use of pirfenidone and nintedanib in ILDs other than IPF with the progressive fibrotic phenotype, based on existing data, clinical reasoning, and common sense. This is not a situation in which there is insufficient evidence to allow guideline and other groups to help clinicians, for whom the use or non-use of pirfenidone is equally a management decision. Expert group recommendations, whether made formally or as a statement of usual practice of expert group members, are most helpful when evidence is marginal but highly suggestive. This is when clinicians most need guidance in routine practice.

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IL-6 blockade for COVID-19: a global scientific call to arms

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We are more than 1 year into the COVID-19 pandemic and the need for better treatments for patients admitted to hospital with COVID-19 remains great. Despite clear improvements in care, mortality for severely ill patients remains unacceptably high. Thus far, the only agents that have consistently been shown to reduce mortality in hypoxaemic patients are systemic corticosteroids (mainly dexamethasone).[1] Yet, since early in the pandemic, modulating the immune response beyond steroids has been the source of a great deal of scientific attention, with the role of repurposed IL-6-blocking agents reported in a number

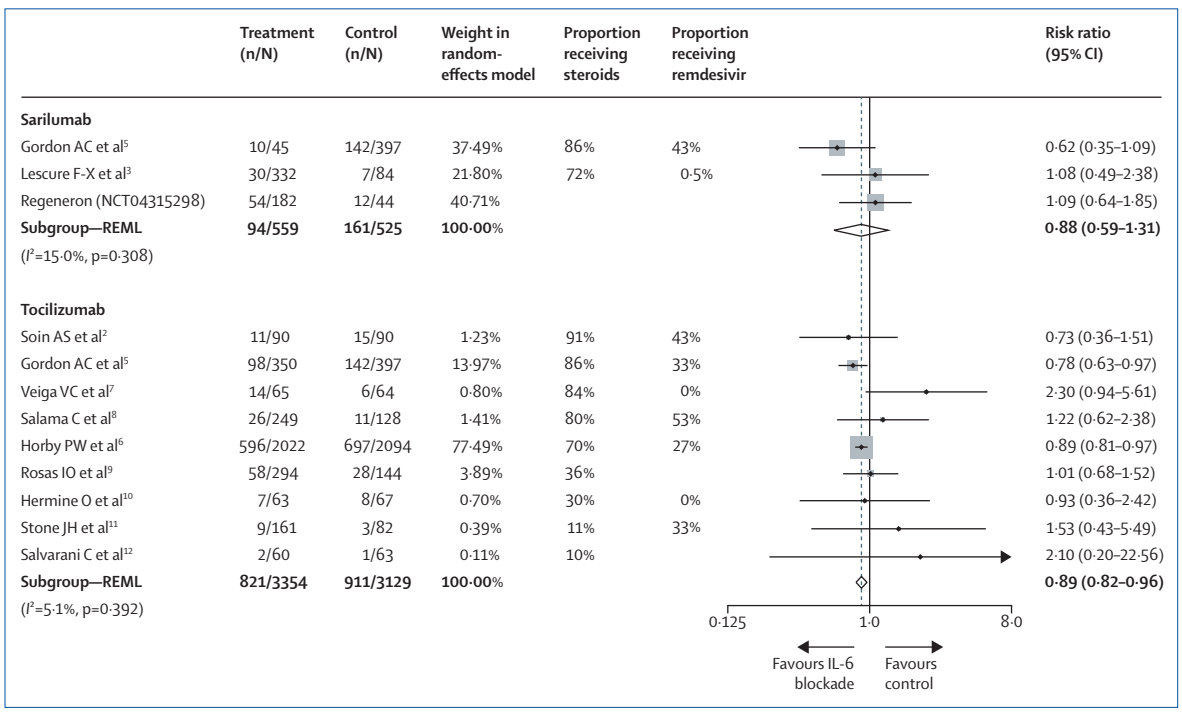

Figure: **Mortality risk in patients admitted to hospital with COVID-19 and treated with IL-6 inhibitors (tocilizumab or sarilumab) or a control**
Heterogeneity between groups p=0·976. Studies are weighted in terms of their contribution to the overall estimate. Weights are taken from the random effects model using REML. The vertical dotted line shows the point estimate of the combined effect for reference to the null line (solid) and the point estimates of the individual studies. REML=restricted maximum likelihood.

of observational studies and randomised controlled trials.

In *The Lancet Respiratory Medicine*, two additional randomised controlled trials report results from IL-6 blockade in patients admitted to hospital with COVID-19: one using tocilizumab in India between May and August, 2020,[2] and the other using sarilumab in 11 countries between March and July, 2020.[3] Arvinder Soin and colleagues randomly assigned 180 patients to receive either tocilizumab plus standard care or standard care alone. François-Xavier Lescure and colleagues randomly assigned 420 patients to receive either sarilumab or placebo. Neither study achieved its primary outcome of either progression of disease up to day 14 for the tocilizumab study or time to clinical improvement in the sarilumab study (defined as an improvement of at least two points on a seven point ordinal scale). Neither study was powered for mortality. Yet, both make a useful contribution to our growing understanding of the role of IL-6 blockade in COVID-19.

First, having trials conducted in settings outside of western Europe and North America is fundamental for generalisability. Both trials were done in settings outside of regions where the bulk of the other IL-6 data is emerging. Second, given impending supply-chain shortages for tocilizumab, more data on sarilumab is required. Indeed, establishing whether there is a class effect or dose effect of IL-6 blockade on improving mortality is a crucial question to answer. Third, both trials add important safety data to the literature, bolstering estimates of the relative short-term safety of these agents in diverse settings and diverse populations.

Given the speed with which these trials were set up and implemented, some concerns are inevitable. The significance of a transition from a moderate to severe state in the study by Soin and colleagues is of questionable clinical significance in an open-label trial where the outcome could be achieved by a difference in oxygen saturation of a few percentage points. The use of a second dose for "clinician concern" in both trials, as with many of the IL-6 trials, is difficult to interpret as a post-randomisation event, and particularly so in the open-label context. The predominance of men in both trials reflects the burden of patients admitted to hospital (>80% in the tocilizumab study); the need for a better understanding of potential sex differences in

treatment effect is underappreciated and could be the focus of targeted investigations in future.

One of the challenges in interpreting the COVID-19 literature is that the standard of care has been rapidly evolving. Changes in supportive care, coupled with evolving therapeutic evidence, mean that trials that began earlier in the pandemic could have markedly different standards of care. For example, treatment with steroids has now become standard for patients with hypoxaemia and treatment with hydroxychloroquine, which was often used earlier in the pandemic, has stopped in most regions.[1,4] These differences can be seen in these two studies, with steroid use more common in the tocilizumab study (91%) than in the sarilumab study (42% concomitant use at baseline, with a peak of 70% at 13 weeks). In REMAP-CAP[5] and RECOVERY,[6] the two largest clinical trials of IL-6 blockade and the only trials to show a mortality reduction, the benefit seemed predominantly in patients who received steroids. Hence, the contribution of negative studies that examined IL-6 blockade in the absence of routine administration of steroids is very useful, but more challenging to interpret at this stage.

By including all trials based on individual publications,[2,3,5] industry data, or the analysis presented in the RECOVERY manuscript,[6] a conservative random-effects meta-analysis for patients admitted to hospital with COVID-19 (figure) yields a risk ratio for mortality of 0·88 (95% CI 0·59–1·31) for sarilumab and 0·89 (0·82–0·96) for tocilizumab. Although the point estimates are very similar, the smaller sample size for sarilumab leaves room to question whether the effect of IL-6 blockade is a class effect, or whether specific agents have a differential benefit. Further data is expected on sarilumab (NCT04315298) but the total sample size will remain well below that for tocilizumab.

Accepting that IL-6 blockade reduces mortality in patients like those in REMAP-CAP[5] or RECOVERY,[6] the question will inevitably become which populations are most likely to benefit. The absolute risk reduction (and corresponding number needed to treat) could vary considerably depending on the baseline risk of death. Given the worldwide burden of COVID-19, a dramatic upswing in prescribing will almost certainly challenge supply chains and health system budgets. It is not hard to imagine low-income and middle-income countries being disproportionately affected in both regards, and solutions to both steward and increase the available supply must be rapidly considered.

For informing these decisions, it is vital that all trial teams urgently participate in a carefully planned meta-analysis, incorporating analyses for heterogeneous treatment effects and standardised subgroups, and focusing on the important clinical outcome of mortality.

Definitions of treatment strategies for COVID-19 have improved greatly over the past 14 months. These two reports add more pieces to the puzzle, and they need to be integrated with all the evidence available to establish the best strategies for patients around the world.

SM is a co-investigator of REMAP-CAP and is the co-chair of the WHO Clinical Characterization and Management research committee for COVID-19.
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