EDITORIAL

Time for tocilizumab in COVID-19?

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Host immune dysregulation is thought to contribute to much of the harm associated with coronavirus disease 2019 (COVID-19) [1, 2]. Accordingly, significant focus has been directed toward finding immunomodulatory therapies to offset this host-mediated damage, leading to the beneficial effects of corticosteroids being demonstrated [3].

As elevated concentrations of interleukin-6 (IL-6) have been found to be an important prognostic factor in COVID-19 [4], attention has also focussed on targeted IL-6 receptor antagonism. Tocilizumab, a recombinant humanised monoclonal antibody, is one such agent. Early observational studies suggested potential benefit with tocilizumab [5, 6], though subsequent randomised control trials (RCTs) demonstrated conflicting results [7–11].

In this rapidly evolving area, much has changed since these initial trials were published. In particular, the landmark RECOVERY [12] and REMAP-CAP [13] platform trials have demonstrated benefit of tocilizumab.

In this issue of *Intensive Care Medicine*, Snow et al. present a timely and methodologically robust systematic review and meta-analysis of RCTs analysing the effects of tocilizumab in patients with COVID-19 [14], including data from REMAP-CAP [13] and the pre-print of the RECOVERY trial [15], which has since been published in full [12].

The authors included nine RCTs (6493 patients) in the meta-analysis of their primary outcome (mortality at 28–30 days) and found reduced odds of mortality in patients treated with tocilizumab compared to standard care or placebo, but the compatibility interval could not

exclude the possibility of no difference or a small adverse effect at the 5% significance level (OR 0.87 [95% compatibility interval (CI) 0.74–1.01]; moderate quality of evidence). The number of patients progressing to the need for mechanical ventilation was also found to be lower in those who received tocilizumab (OR 0.70 [95% CI 0.54–0.89]; very low quality of evidence).

This review raises several important points, some of which are discussed below.

Snow et al. present results for their primary analysis using an odds ratio with random effects with sensitivity analyses using alternate methods (Table 1).

What are we to make of their findings? First, if we look beyond the dichotomisation of p-values, we can see that the data is both consistent and far more compatible with benefit than with harm, regardless of the underlying statistical assumptions made. Second, the results of the trial sequential analysis (TSA) of the primary outcome cross the ‘futility boundary’ (an estimated threshold below which an intervention is unlikely to have an important effect) suggesting enrolling further patients is ‘futile’. Of note, this reflects the current parameters of the TSA (i.e., a relative risk reduction (RRR) of 15.7%, with a large type-II error rate of 20%). It is plausible that a smaller benefit exists (e.g. RRR 5–10%) which is still clinically important, however, the required information size (the number of patients needing to be included to detect an anticipated intervention effect with sufficient power) would be significantly larger than currently presented.

In the RECOVERY trial [14], mortality was lower for the subset of patients who received both tocilizumab and corticosteroids (OR 0.79, 95% CI 0.70–0.89). However, in patients who received tocilizumab without corticosteroids, there was a wide range of possible effects (OR 1.16, 95% CI 0.91–1.48), though the data is more compatible with harm. Similarly, in the REMAP-CAP trial [13] (>90% receiving corticosteroids), a mortality benefit was reported with tocilizumab *in addition* to corticosteroids (OR 0.70 [95% CI 0.52–0.96]). While these trials would

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Table 1 Results of the meta-analysis by Snow et al. with sensitivity analyses for the primary outcome (mortality at 28–30 days)

Statistical analysis of primary outcome (mortality at 28–30 days)	Effect size	95% Compatibility interval
Odds ratio (random effects)*	OR 0.87	0.74–1.01
Odds ratio (fixed effects)	OR 0.85	0.76–0.96
Relative risk (random effects)	RR 0.89	0.82–0.96
Relative risk (fixed effects)	RR 0.89	0.83–0.97

*Authors' primary analysis

seem to indicate an interaction between the two drugs, this was not explored via subgroup analyses or meta-regression in the review by Snow et al. [14]. It would also be prudent to note that the smaller TOCIBRAS trial [11] had a similar level of corticosteroid use as REMAP-CAP [13] and RECOVERY [15], but was stopped early for possible harm.

Consideration must also be taken of the study populations. The REMAP-CAP [13] and RECOVERY [15] trials enrolled predominately white men from western European and North American regions, with the RECOVERY trial [15] signalling subgroup effects for gender and ethnicity. While the TOCIBRAS trial [11] was stopped early for possible harm in a Brazilian cohort, the EMPACTA [8] trial reported reduced likelihood of progression to mechanical ventilation in underserved and racial and ethnic minority populations. Additionally, the meta-regression by Snow et al. also suggests some association of illness severity with tocilizumab, although the treatment effect is not reported in subgroups of patients receiving different levels of respiratory support. It is important to note that these subgroup analyses exploring possible heterogeneity of treatment effect have low power, are prone to false positives and should generally be considered exploratory. Moreover, six trials included in the meta-analysis were open-label raising the possibility of added bias.

It is evident that the evidence of benefit on mortality and progression to need for mechanical ventilation with tocilizumab reported by Snow et al. needs to be interpreted with caution. Tocilizumab appears to improve these outcomes when combined with corticosteroids. However, the magnitude of this effect and the subgroups of patients who will benefit most remains to be fully clarified. Moreover, in the RECOVERY trial [15], almost two-thirds of the patients not mechanically ventilated at randomisation, who subsequently died, did not receive mechanical ventilation, clouding the interpretation of this secondary endpoint.

Whether tocilizumab is beneficial in the absence of corticosteroids is also unclear. However, given the convincing evidence for corticosteroids already, which now constitutes 'standard care', an adequately powered trial investigating this is unlikely to occur.

Whilst there was no strong evidence for increased serious adverse events across the included trials, the RECOVERY trial [15], which contributes the bulk of available data, did not routinely report on the adverse effects of tocilizumab.

Other unanswered questions include the optimal timing and dose of tocilizumab, and whether therapy should be guided by biomarkers (e.g., IL-6 or c-reactive protein concentrations). Additionally, there is not enough data for other IL-6 receptor antagonists, such as Sarilumab, to determine whether the benefit seen with tocilizumab is a specific drug or a class effect.

While further high-quality trials would be useful to clarify these points, carefully planned individual patient data meta-analyses may offer a cost-effective way of reducing this uncertainty and potentially exploring subgroups who would benefit most [16].

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Conflicts of interest

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