

CORRESPONDENCE



“L’histoire se répète”, one size does not fit all. Author’s reply

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We thank the authors for their interest in our meta-analysis; indeed, their concerns reflect many we articulated [1, 2]. We used the published literature to conclude ‘*there is some evidence that tocilizumab use may be associated with a short-term mortality benefit in patients with COVID-19*’. This uncertainty has been extended by the recent WHO meta-analysis [3] which incorporated as yet unpublished trials as well as longer-term outcomes provided by some of the triallists to include nearly 11,000 patients. The overall conclusion of this meta-analysis was stronger as the odds ratio for 28-day mortality did not cross the line of identity. However, the subgroup analyses presented within this paper further reinforce our concerns. Outcome benefit is restricted only to males and, at randomisation, only to subgroups receiving corticosteroids, oxygen or non-invasive ventilation, or with mid-range CRP values (75–149 mcg/ml). Of note, 28-day mortality benefit was only seen in open-label studies and not in placebo-controlled studies, and no survival benefit was seen in either of these subgroups at 90 days. Our meta-analysis demonstrates lack of benefit seen with trials with low risk of bias. With a number of trials being open labelled, and crossover of patients between treatment and control groups, the overall quality of evidence was low.

To challenge the argument made by Dr Kuindersma and Dr Spronk [4], do we simply ignore these sizeable subgroups or use them to generate hypotheses and conduct prospective studies to better understand the science underlying both COVID-19 pathophysiology and individual responses to any intervention? We would disagree with them on the prognostic utility of the baseline CRP value. Indeed, we [5, 6] and many others have reported that CRP is a good

prognosticator of both the need for invasive ventilation and mortality in COVID-19 disease. With respect to IL-6 blockade, the WHO meta-analysis reflects no benefit both in those on invasive ventilation [OR 0.95; 95% CI (0.78–1.16)] and with CRP values ≥ 150 mcg/l [OR 0.96; 95% CI (0.83–1.11)]; these findings are internally consistent and suggest less/no benefit in the sickest cohort of patients.

We are very sympathetic to the notion that ferritin, IL-6 or other biomarkers, or combinations thereof, may be superior tools to identify which patients are likely to benefit from IL-6 blockade. Unfortunately, this too remains hypothetical. The randomised studies performed to date have not provided any data to offer a clear steer in this regard. Obviously, any putative theranostic would need to be prospectively validated. As the editorial accompanying our article notes [7], whether this will happen is doubtful. The possibility of harm associated with tocilizumab use in a subset of patients with COVID-19 is of concern, with some trials showing no overall benefit and others being terminated early due to harm [8]. We are therefore completely in agreement that the ultimate goal should be an individualised treatment approach underpinned by sound scientific understanding.

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Declarations

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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