

## Allocated but not treated: the silent 16%

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The RECOVERY Collaborative Group has provided timely, robust evidence for managing hospitalised patients with COVID-19, including their randomised controlled trial supporting the use of tocilizumab.<sup>1</sup> However, results from other smaller randomised controlled trials of tocilizumab (and sarilumab), particularly those with a placebo control group, did not show a mortality benefit of interleukin-6 inhibition versus control. In seeking to understand the totality of the data, results of any meta-analysis will be heavily weighted by RECOVERY trials, the largest population studied. A complete and nuanced understanding of the trial results is thus crucial for accurate interpretation.

Although an intention-to-treat analysis is important to preserve the prognostic balance that is reached through randomisation, in the open-label RECOVERY trial, one in six (317 [16%] of 1964) allocated patients did not receive tocilizumab. A further 3% were missing data on whether or not they received tocilizumab. The authors wrote that “the size of the effects of tocilizumab reported in this paper are therefore an underestimate of the true effects”, an assertion that was echoed in Shruti Gupta and David E Leaf’s Comment.<sup>2</sup> This interpretation assumes that people who were allocated to but not treated with tocilizumab were as or more likely to die than those who received the drug and, furthermore, that there is no possible harm from treatment. However, if mortality in the 16% of patients who did not receive tocilizumab was lower than in the control group or the patients who were treated with tocilizumab, then the result could be biased away from the null. Fortunately, given that the data exist, we do not need to pursue the academic exercise of debating bias towards or away from the null. We respectfully request the authors to contrast the demographics, baseline clinical status, and outcomes of patients allocated to but not treated with tocilizumab with those who did receive treatment.

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See “Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial” in Lancet, volume 397 on page 1837.

See “Allocated but not treated: the silent 16% - Authors’ reply.” in Lancet, volume 399 on page 1775.

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