Correspondence on 'Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study'

We have read with great interest the study conducted by Ramiro *et al*[1] entitled 'Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study'. This study was among the first publications showing benefit of tocilizumab administration in patients with severe COVID-19-associated cytokine storm syndrome, in July 2020.[1] In the same way, we observed a benefit of tocilizumab administration in a cohort of 206 patients during the first wave of the pandemic, in June 2020.[2]

We have now more 'evidence-based medicine' to discuss tocilizumab's place in COVID-19. Thus, nine randomised clinical trials (RCTs)[3–11] have been published about tocilizumab administration in COVID-19; however, the effects on mortality remain heterogeneous in these trials.[12] We recently made a review of these RCTs[13] and concluded that heterogeneity results seen in overall RCTs are due to the heterogeneous population and that tocilizumab is effective in severe COVID-19. Based on this conclusion, we performed a subgroup meta-analysis on tocilizumab RCTs (in severe COVID-19 and non-severe COVID-19). We selected by a systematic search on PubMed and the preprint server MedRχiv (until 27 April 2021) all RCTs that compared the outcome of patients with COVID-19 treated with tocilizumab versus standard of care or placebo (our endpoint was the mortality of 28–30 days). Due to the heterogeneous description about respiratory support at baseline (different scales or clinical descriptions were used in the RCTs), we cannot divide severe COVID-19 and non-severe COVID-19. However, in these RCTs, the mortality increases in correlation with the severity of respiratory support at baseline[13] ; furthermore, clinical severity at baseline is among the main risk factors associated with mortality in COVID-19 pneumonia.[14] So, we chose to use the mortality in control group to divide the RCTs in two groups: severe COVID-19 group (high mortality in control group) and non-severe COVID-19 group (low mortality in control group). Most of these RCTs included patients in the beginning of the pandemic in wealthy countries (especially North America and Europe), so we chose a mortality proportion of 17% which corresponds to the in-hospital mortality in the beginning of the pandemic among hospitalised adults with COVID-19 in the USA.[15] Our analysis RCTs were divided in two groups: severe COVID-19 group (mortality proportion in control group ≥17%) and non-severe COVID-19 group (mortality proportion in control group <17%). Overall, there were 24.5% (821 of 3357) deaths in the tocilizumab group and 29.1% (908 of 3125) in the control group at days 28–30 (pooled OR, 0.85; 95% CI, 0.76 to 0.96; p=0.006). Considering the subgroup analysis, this benefit was confirmed and amplified in the severe COVID-19 group (pooled OR, 0.82; 95% CI, 0.73 to 0.93; p=0.001) but not in the non-severe COVID-19 group (pooled OR, 1.46; 95% CI, 0.91 to 2.34; p=0.12) (figure 1).

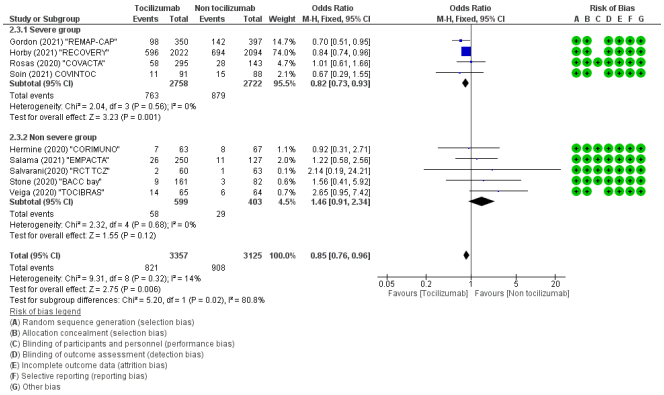

Figure 1 Forest plot for the effect of tocilizumab on mortality at days 28–30 in randomised trials in severity event subgroup.

Based on these results, we conclude that tocilizumab is an effective treatment in severe COVID-19 pneumonia by improving survival. Subgroup analyses are needed in tocilizumab RCTs to determine more accurately tocilizumab's place in COVID-19.

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