# Tocilizumab in COVID-19: Give it time!

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Dear Editor,

We read with interest the article by Malgie *et al*. [1]. Even if we agree with Tleyjeh *et al*, who discuss the methodology of this article, we believe that the title "a rapid systematic review and meta-analysis" announced clearly an exploratory analysis. Contrariwise, we think that the correspondence by Huang *et al*. [7], in which the meta-analysis of five randomized controlled trials (RCTs) [2–6] did not show a better survival in COVID-19 patients treated by tocilizumab (TCZ), should be more nuanced. Indeed, a superficial analysis could misinform practicians in their therapeutic choice concerning tocilizumab. Here we want to pinpoint the impact of tocilizumab on mortality rate in COVID-19.

First, the study by Huang *et al*. must be considered only as an exploratory analysis. Indeed, Huang *et al*. included only 1310 patients, whereas Tleyjeh *et al*. estimated that the necessary patients number to conclude for mortality was 4506 patients (2553 in each arm) [8]. Moreover, this number was calculated from the mortality rate (10.3%) observed in metanalysis control group from the five RCTs performed by Tleyjeh *et al*. [8]. Thus, it should be necessary for Salvarani *et al*. or Stone *et al*. to include more than 4506 patients, according to their inclusion criteria, because the mortality rate in these latest studies were respectively 1.6 % and 4.9% [5,6].

Second, talking about the impact of TCZ on mortality must not overshadow results from retrospective studies when their methodologies are strong. In the metanalysis of 18 cohorts at moderate risk of bias, including 9850 patients, the corrected pooled adjusted RR for mortality was 0.77 (95% CI 0.63-0.95, $I^2$=41%), and this association was found in all stage of severity of the disease [8].

Third, more precise analysis is necessary concerning the results from RCTs because of heterogenous population. For example, in COVACTA sub group of patients who had oxygen, the risk of ventilation or death was significantly reduced (29% *vs* 42 %) with HR 0.61 (CI 95% : 0.40-0.94 ; p=0.03) [3]. Moreover, in EMPACTA, which included homogenized population who had oxygen, the risk of ventilation or death was significantly reduced by 44 % (12.2% *vs* 19.3%), HR 0.56 (CI 95% : 0.32 – 0.97 ; p=0.035) [2]. In addition, most of the studies evaluate mortality at day 28, and the reduction of the rate of mechanical ventilation may translate in an improvement of mortality after day 28.

Fourth, in the pandemic era, where the number of free hospital beds is crucial, other outcomes than mortality are also important. Thus, the metanalysis of RCTs show a diminution of the risk of ventilation RR 0.71 (CI95% : 0.52-0.96 ; $I^2$=0%) and of poor prognostic RR 0.71 (CI 95% : 0.56-0.89 ; $I^2$=0%) [8]. Moreover, in RCT by Stone *et al*., the use of invasive mechanical ventilation was shorter in the TCZ group (15d [12.6-NR] *vs* 28d [16.3-NR]) [6]. Finally, in COVACTA the duration of hospitalization was significatively shorter in TCZ group (20d [17-27] *vs* 28d [20-NE] ; p=0.04)[3].

TCZ is not a magic bullet but in our case, where antiviral drugs seems to have little or no effect, it is important to let time to TCZ, which is, as Huang *et al*. recalls, well tolerated [7,9].

**Conflicts of Interest:**

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