

It is time to determine Tocilizumab place in COVID-19

Timothée Klopfenstein¹, Aurélie Gerazime², Marc Puyraveau², N'dri Juliette Kadiane-Oussou¹, Vincent Gendrin¹, Souheil Zayet¹, For the HNF Hospital tocilizumab multidisciplinary team

¹Infectious Disease Department, *Nord Franche-Comté Hospital*, France

²Methodology unit, clinical investigation center INSERM 1431, *Jean-Minjoz University Hospital*, Besançon, France

Corresponding author:

Timothée Klopfenstein

Department of Infectious Disease, Nord Franche-Comté Hospital, 90400 Trevenans, France

E-mail: timothee.klopfenstein@hnfc.fr

TO THE EDITOR –

We have read with great interest the meta-analysis by Huang et al. (1). Huang et al. made a meta-analysis on the first 5 randomized clinical trials (RCTs) and concluded that tocilizumab does not provide mortality benefit for severe COVID-19 patients. Since the meta-analysis by Huang et al. three new RCTs (2–4) have been published or are at a pre-published state. Veiga et al. trial was stopped early in July 2020 after an increase in deaths (2) in opposition to REMAP-CAP and RECOVERY results (3,4) which showed a positive benefit of tocilizumab on mortality. We think that an updated meta-analysis and discussion are necessary. In this context we aimed to perform a meta-analysis on these 8 RCTs (2–9) about the impact of tocilizumab administration on mortality. We selected by a systematic search on PubMed and the preprint server MedRxiv (until March, 03rd, 2021) all RCTs that compared the clinical outcome of COVID-19 patients treated with tocilizumab versus standard of care or placebo. Our primary endpoint was the 28-day mortality. Secondary endpoints were mechanical ventilation incidence and safety endpoints (adverse events and serious infections).

We included 8 RCTs. A total of 6303 patients were included: 3266 randomized to tocilizumab and 3037 to placebo (Figure 1). Overall, there were 810 (24.8%) deaths at day 28 in the TCZ group and 893 (29.4%) deaths in the placebo group (pooled odds ratio [OR], 0.86; 95% CI, 0.76 to 0.96; $p = 0.008$). Mechanical ventilation incidence had a pooled OR (0.72; 95% CI, 0.62 to 0.84; $p < 0.001$) in favor of tocilizumab. There were 88/705 (12.5%) serious infections in the tocilizumab group and 60/353 (17%) serious infections in the placebo group (pooled OR, 0.67; 95% CI, 0.47 to 0.97; $p = 0.03$) and no significant differences about adverse events (Figure 1).

A few assumptions can be discussed to explain this contradiction on mortality effect in these RCTs results.

Firstly, a lack of statistical power seems manifest in some RCTs. For example, Stone et al. and Salvarini et al. (6,7) had a mortality rate $< 5\%$ in their population and the required number of patients to conclude for mortality wasn't reached; Veiga et al. (2) results must be taken with caution

due to the sample size of the trial and considering that there were no significant differences on mortality at day 28.

Secondly, we only have the results of short-term mortality. For example, in COVACTA (5), at day 28, 72% (83/115) of the patients who were still hospitalized required high level of oxygen support: 17% (50/294) in the tocilizumab arm versus 23% (33/144) in the placebo arm; we can possibly expect a lower number of deaths in the tocilizumab arm in long-term mortality.

Thirdly, these RCTs included heterogenous populations which may explain heterogeneity of results (10). We have recently defined the optimal group which is susceptible to have the greatest benefit from tocilizumab as severe/critical COVID-19 (except patients after some time of mechanical ventilation) (10). For example, in COVACTA (5) if we choose this population, the category 4 and 5 of the 7-category ordinal scale (high-flow oxygen or noninvasive ventilation or mechanical ventilation at an early stage) the number of deaths is clearly lower for tocilizumab than placebo (17% [24/139] versus 28% [15/54]). A mortality rate at 17% is extremely low in this ICU population and is in contrast to the 17% global in-hospital mortality rate in the United States (11).

To conclude, tocilizumab reduces mortality in severe/critical COVID-19 pneumonia. Due to heterogenous population in RCTs, secondary analyses on subgroups are needed and would be helpful to define the optimal group and timing for tocilizumab benefit. Nevertheless, a deep analysis of RCTs results is needed in order to not misinform the medical community. Finding the optimal group of patients who are susceptible to have the greatest benefit has now become the main challenge.

Conflicts of Interest

All authors declare no competing interests.

References

1. Huang Y-T, Chao C-M, Lai C-C. The impact of tocilizumab on the mortality of patients with COVID-19. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 17 nov 2020;
2. Veiga VC, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ*. 20 janv 2021;372:n84.
3. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med*. 25 févr 2021;
4. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial | medRxiv [Internet]. [cité 11 mars 2021]. Disponible sur: <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1>
5. Rosas I, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. *medRxiv*. 12 sept 2020;2020.08.27.20183442.
6. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med*. 10 déc 2020;383(24):2333-44.
7. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*. 1 janv 2021;181(1):24-31.
8. Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med*. 1 janv 2021;181(1):32-40.
9. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med*. 7 janv 2021;384(1):20-30.
10. Klopfenstein T, Conrozier T, Kadiane-Oussou NJ, Gendrin V, Zayet S, For the HNF Hospital Tocilizumab multidisciplinary team. Is there still a place for tocilizumab in COVID-19? *Open Forum Infect Dis* [Internet]. 12 janv 2021 [cité 29 janv 2021];(ofab013). Disponible sur: <https://doi.org/10.1093/ofid/ofab013>
11. Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis* [Internet]. 16 juill 2020 [cité 9 févr 2021];(ciaa1012). Disponible sur: <https://doi.org/10.1093/cid/ciaa1012>

Figure Legends:

Figure 1.A. Forest plot for the effect of tocilizumab on mortality at days 28-30 in randomized trials

Figure 1.B. Forest plot for the effect of tocilizumab on mechanical ventilation incidence in randomized trials

Figure 1.C. Forest plot for relative risk of adverse events for tocilizumab versus control in randomized trials

Figure 1.D. Forest plot for serious infections for tocilizumab versus control in randomized trials

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Figure 1.C. Forest plot for relative risk of adverse events for tocilizumab versus control in randomized trials

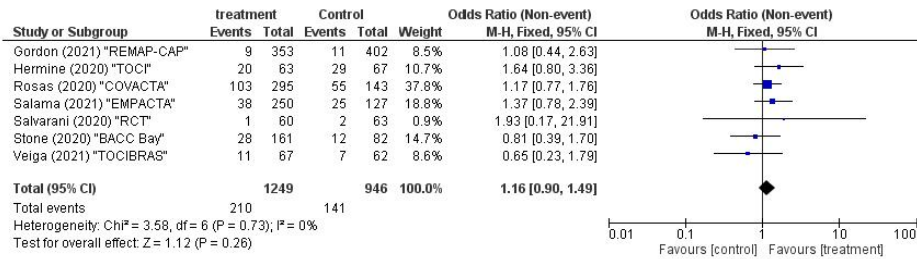


Figure 1.D. Forest plot for serious infections for tocilizumab versus control in randomized trials

