



Tocilizumab in COVID-19 therapy: who benefits, and how?

Avidan Neumann, Mehmet Goekkaya, Karim Dorgham, Claudia Traidl-Hoffmann, Guy Gorochov

► To cite this version:

Avidan Neumann, Mehmet Goekkaya, Karim Dorgham, Claudia Traidl-Hoffmann, Guy Gorochov. Tocilizumab in COVID-19 therapy: who benefits, and how?. The Lancet, 2021, 398 (10297), pp.299-300. 10.1016/S0140-6736(21)01427-6 . hal-03349752

HAL Id: hal-03349752

<https://hal.science/hal-03349752>

Submitted on 26 Sep 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Tocilizumab in COVID-19 therapy: who benefits, and how?

Avidan U Neumann,^{a,b} Mehmet Goekkaya,^{a,c} Karim Dorgham,^d Claudia Traidl-Hoffmann,^{a,b,c} and Guy Gorochovd,^e

^aDepartment of Environmental Medicine, Faculty of Medicine, Universitätsklinikum Augsburg, Augsburg, Germany

^bInstitute of Environmental Medicine, Helmholtz Center Munich, Augsburg, Germany

^cEnvironmental Medicine, Technical University Munich, Munich, Germany

^dSorbonne Université, INSERM, Centre d'Immunologie et des Maladies Infectieuses, Paris, France

^eDépartement d'Immunologie, Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France

The RECOVERY Collaborative Group reported statistically significant improvement in survival of patients with COVID-19 who were receiving tocilizumab interleukin (IL)-6 inhibitor, albeit with very modest reduction of mortality (31% vs 35% with usual care, $p=0.0028$).¹ This result adds to a number of studies with tocilizumab and other IL-6 antagonists, such as sarilumab, which showed only minor, or no, reduction in mortality.² Given that IL-6 is associated with COVID-19 severity and mortality,³ the question arises as to why IL-6 antagonist therapy does not substantially improve survival.

In April, 2021, we showed that IL-6 serum concentrations are indeed associated with COVID-19 severity (appendix); however, a better classification of severity is obtained when IL-6 is combined with other cytokine concentrations.⁴ Moreover, within each respiratory severity group, IL-6 is not significantly associated with mortality (appendix). It is rather distinct combinations of interferon α , inteferon β , IL-10, and tumour necrosis factor α that are better predictors of mortality in different severity groups.⁴

Nevertheless, mortality in the low IL-6 group of patients is significantly lower than in the high IL-6 group of patients (appendix), suggesting that IL-6 inhibitors should be given only to patients with high IL-6. Indeed, a retrospective analysis of tocilizumab therapy as a function of baseline IL-6 concentrations showed a large reduction in mortality (from 36% to 16%) in patients with high-baseline IL-6, but no reduction in mortality in low-baseline IL-6 patients.⁵

In conclusion, clinical trials of IL-6 antagonist therapy, such as RECOVERY¹ and sarilumab COVID-19 global studies,² should consider reanalysis of their results as a function of IL-6 baseline concentrations. More generally, clinical trials of personalised precision medicine, based on cytokine profiling, are needed for optimisation of COVID-19 therapy.

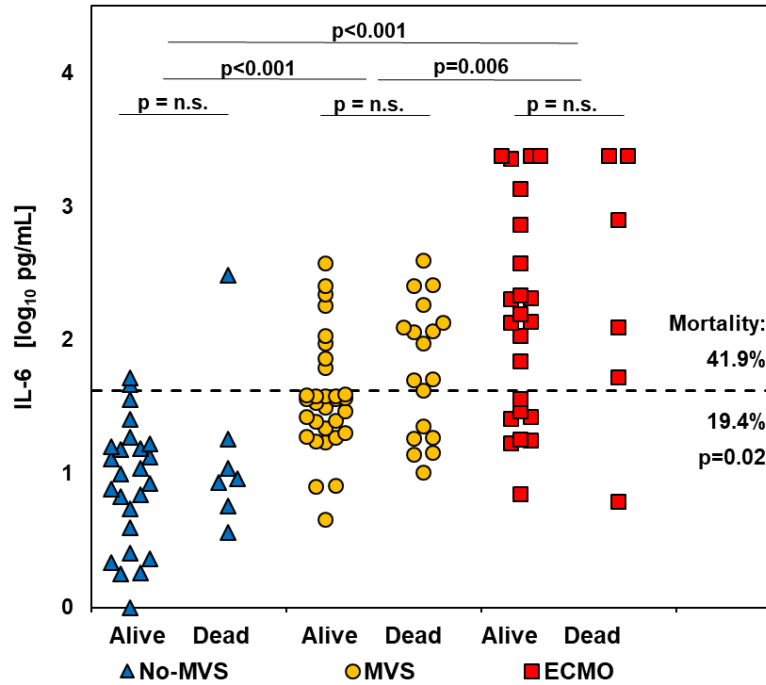
We declare no competing interests.

References

1. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397:1637–1645.
2. Lescure FX, Honda H, Fowler RA. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9:522–532.
3. Del Valle DM, Kim-Schulze S, Huang HH. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020;26:1636–1643.
4. Dorgham K, Quentric P, Goekkaya M. Distinct cytokine profiles associated with COVID-19 severity and mortality. *J Allergy Clin Immunol*. 2021;147:2098–2107.
5. Galvan-Roman JM, Rodriguez-Garcia SC, Roy-Vallejo E. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: an observational study. *J Allergy Clin Immunol*. 2020;147:72–80.

Supplementary appendix:

A



B

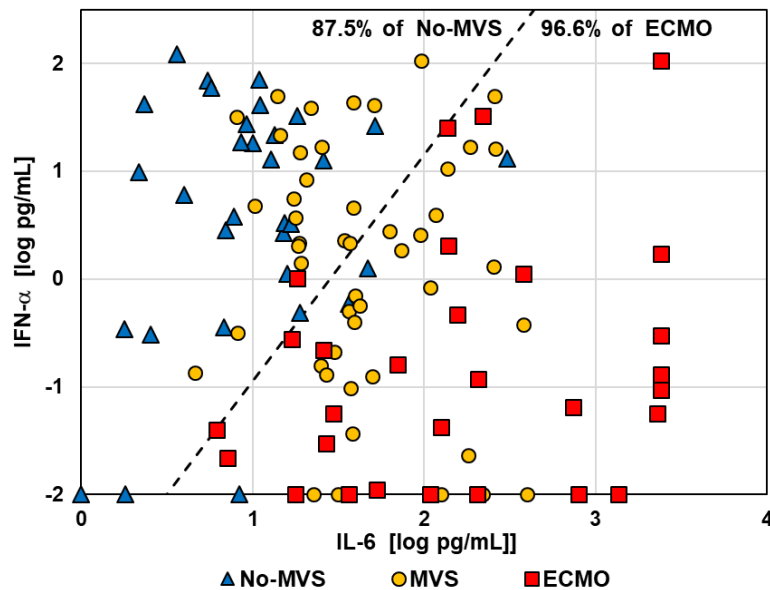


Figure 1: IL-6 association with COVID-19 severity and mortality. IL-6 serum concentrations at day of hospitalization of COVID-19 patients (N=110) are significantly associated with respiratory severity (A), but better classification of severity is obtained by comparison of IL-6 and IFN- α concentrations (B) and even better by the combination of IL-6, IL-8, IL-10, and TNF- α concentrations in comparison to IFN- α and IFN- β .⁴ Mortality one month after admission is significantly higher if IL-6 admission concentrations are above the mean (40 pg/mL, dashed line in A), but within each respiratory severity group mortality is not significantly associated with IL-6 (A).

Study design, methods, patients' characteristics and ethical approval are given in Dorgham et al.⁴

MVS and No-MVS: Patients requiring mechanical ventilatory support or not. ECMO: Patients requiring extracorporeal membrane oxygenation. n.s.: not statistically significant.