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

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 RECOVERY[1] 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.

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4 Dorgham K, Quentric P, Goekkaya M, et al. Distinct cytokine profiles associated with COVID-19 severity and mortality. *J Allergy Clin Immunol* 2021; **147:** 2098–107.

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