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Cytokine Blockade in Coronavirus Disease 2019: Keeping an Open Mind

To the Editor:

We have read the recent review on the ambiguous results of blocking the cytokine pathway published in *Critical Care Explorations* by Rizvi and Gallo De Moraes (1) with great interest. The authors made a compelling argument that blocking the single cascade of cytokine response was not successful in diverse conditions such as bacterial sepsis and acute respiratory distress syndrome (ARDS). We agree that the currently available evidence does not support the use of anticytokine therapy or cytokine removal in these settings (2). However, there is mounting evidence from both observational studies, including some published in *Critical Care Explorations*, and multicentre randomized clinical trials that interleukin (IL)-6 receptor inhibition could indeed significantly reduce mortality in a single agent caused viral sepsis, such as coronavirus disease 2019 (COVID-19) (3–6). There is significant biological plausibility for manipulating the IL-6 pathway as multiple observational studies have shown that IL-6 levels are associated with mortality and morbidity, and it was recently demonstrated that genetic variants in the IL-6 pathway are associated with life-threatening disease in critically ill COVID-19 patients (7–9). Since the publication of their review, several other well-conducted clinical trials have reported their results using tocilizumab or sarilumab in COVID-19 (6–11). By summarizing these published studies, and the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trials results from a preprint, a fixed-effects meta-analysis yields an odds ratio for mortality of 0.86 (95% CI, 0.77–0.96) for IL-6-receptor inhibition versus standard care (**Fig. 1**) (12). The included trials were generally at low risk of bias, and we did not detect significant heterogeneity. Among the trials with data available in the public domain, only the two largest, publicly funded studies have shown benefit.

In addition to reduction in mortality, the Randomised, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial has found significant reduction in organ support needs and reduction in length of ICU stay in the IL-6 receptor blockade arms, while the RECOVERY trial reported significantly less progression to mechanical ventilation or death in those patients who only needed supplemental oxygen on randomization (6, 12). This is especially important as these data could inform further modeling of healthcare resource needs during the pandemic, where stretched ICU capacity has been linked to adverse outcomes (13, 14).

What could be the mechanism for this significant mortality reduction, when our own data also suggest that true hyperinflammation and "cytokine storm" is a rare phenomenon in severe COVID-19 (15)? IL-6 has several diverse functions and effects, apart from being a potent proinflammatory cytokine. It has been shown to inhibit Human Leukocyte Antigen – DR isotype (HLA-DR) expression on monocytes and decrease interferon-gamma production by CD4

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Study or Subgroup	IL-6 receptor inhibitor Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Salvarani et al.	2	60	1	63	0.1%	2.14 [0.19, 24.21]
Stone et al.	9	161	3	82	0.6%	1.56 [0.41, 5.92]
Veiga et al.	14	65	6	64	0.7%	2.65 [0.95, 7.42]
Hermine et al.	7	64	8	67	1.1%	0.91 [0.31, 2.66]
Lescure et al.	30	332	7	84	1.5%	1.09 [0.46, 2.58]
Salama et al.	26	249	11	128	2.0%	1.24 [0.59, 2.60]
Soin et al.	11	91	15	88	2.0%	0.67 [0.29, 1.55]
Rosas et al.	58	294	28	144	4.6%	1.02 [0.62, 1.68]
REMAP-CAP	98	353	142	402	14.5%	0.70 [0.52, 0.96]
Horby et al.	596	2022	694	2094	72.9%	0.84 [0.74, 0.96]
Total (95% CI)		**3691**		**3216**	**100.0%**	**0.86 [0.77, 0.96]**
Total events	851		915			

Heterogeneity: Chi² = 9.64, df = 9 (P = 0.38); I² = 7%
Test for overall effect: Z = 2.67 (P = 0.008)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
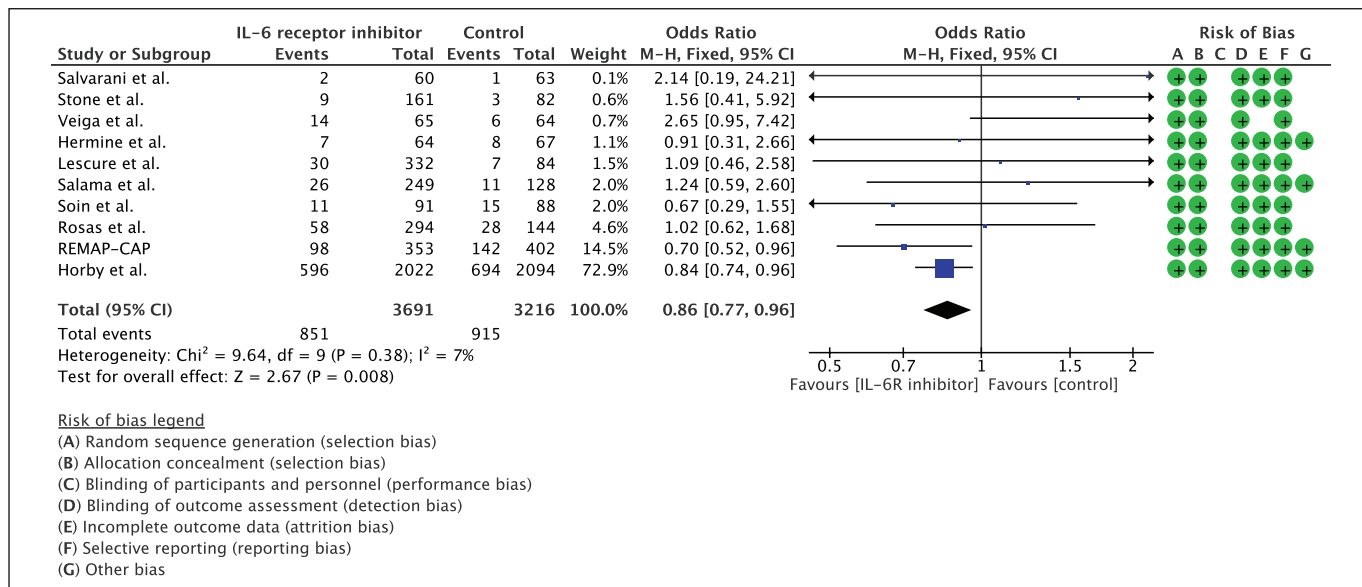(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 1. Twenty-eight-day mortality risk in patients admitted to hospital with coronavirus disease 2019 and treated with interleukin (IL)-6 receptor inhibitors or usual standard care. For statistical analysis, Mantel-Haenszel (M-H) statistics with fixed-effect model was used. *df* = degrees of freedom, REMAP-CAP = Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia.

cells, contributing to the immune paralysis seen in sepsis (16). IL-6 receptor inhibitors may rescue the HLA-DR expression on monocytes, increase the absolute lymphocyte count and in turn increase the host's ability to produce interferon-gamma, which has significant antiviral effects (17). It is possible that the IL-6-receptor blockade is indeed not inhibiting the runaway inflammatory response in COVID-19 but that it helps to reinvigorate the normal antiviral response in a host shackled with immune paralysis.

Importantly, the trials that produced significant results recruited patients whose clinical condition was at least on the moderate to severe state on the World Health Organization scale and, in these studies, the majority of patients have received concurrent corticosteroids (6, 12). The patients in both studies had symptoms well over a week and were hospitalized for 2 days and, hence, were likely over the peak of the viral load and displaying signs of dysregulated host response (18). The median C-reactive protein levels on randomization were in the same range (130–150 mg/dL) in both studies, indicating ongoing inflammation and imbalance of the host response tilting toward persistent inflammation and immunosuppression (17, 18). These are the patients where IL-6 receptor blockade may promote restoration of normal function, rather than further dampening the proinflammatory response.

We share several of the concerns raised by the authors in their well-written review on cytokine pathway blockade in bacterial and viral sepsis. It is likely that widespread and indiscriminate use of potent immunomodulators could result in significant harm, as has been shown in previous sepsis trials that have enrolled patients with different stages of their disease. Based on our meta-analysis, it is clear that the two largest studies, which had similar inclusion criteria and were primarily performed in the same uniform healthcare setting, swing the pendulum toward benefit. Early use of IL-6 receptor blockade without concomitant steroid treatment has shown no benefit in several industry-sponsored studies conducted at the beginning of the pandemic. It is also possible that genetic heterogeneity may play a role in the efficacy of the intervention, as evidenced by the negative studies conducted in Brazil and India. We agree with the authors that there is an even greater need to understand which patient population may benefit most from these interventions. It is unclear whether, with the widespread usage of IL-6 receptor blockade (adopted in the U.K. National Health Service using the REMAP-CAP and RECOVERY study criteria), the feared increase in bacterial and fungal superinfection will manifest with worsening outcomes or frequent reinfections and rehospitalization in survivors. There is an ongoing need for well-conducted observational trials to detect any harmful signal, and

furthermore, IL-6 receptor blockade should be evaluated in more precisely described patient populations in different healthcare settings across the globe.

Beyond IL-6 receptor blockade, there are other potential ways to manipulate the inflammatory response (19). Anakinra has been used to modulate the IL-1 pathway, however, to date randomized controlled trials failed to show any significant benefit in COVID-19 (19). Notably, based on previous studies in sepsis, this intervention is likely to be successful if the patients have features of significant hyperinflammation (19). In this setting, population enrichment using multiple biomarkers is likely to lead to better results as prevalence of the hyperinflammatory phenotype of COVID-19 ARDS is a lower than initially thought (15).

Another modality, which has promise with a positive signal from a randomized controlled trial, is blocking the intracellular pathway of the janus kinase 1 (JAK1) and JAK2 signaling using baricitinib (19). The RECOVERY trial currently evaluates if adding this to the current U.K. standard of care would provide additional benefit. Combining cytokine modulation approaches could result in additional benefit; however, we agree with the authors that this could also lead to harm and should only be evaluated in clinical trials with robust safety reporting mechanisms.

Although the critical care literature is littered with negative studies in this arena, the COVID-19 pandemic is one of the first opportunities to investigate these potential therapies based on a single agent model, on the global scale. Some of the most recent results are encouraging, and we would like to highlight the need to keep an open mind, when evaluating cytokine modulation in COVID-19.

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