Cytokine inhibitors in COVID-19: looking back to move forward

Cytokine inhibitors in COVID-19

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In this issue of the Journal, Monti et al. describes their experiences of using immunomodulatory agents at the beginning of the COVID-19 pandemic in early 2020 [1]. Their retrospective, single centre study showed that anakinra, an interleukin-1 receptor (IL-1R) inhibitor was associated with benefit, however tocilizumab, an IL-6 receptor (IL-6-R) antagonist was potentially associated with harm. They have very carefully analysed their dataset (n=61) and used appropriate Bayesian methods to try to understand if any of the treatment options could be beneficial for their patients, who were all mechanically ventilated and all had viral infection induced ARDS. Some of their observations seem to stand the test of time, whilst others, especially the hint for worse outcome using tocilizumab in the critically ill patients, seems to be counterintuitive, especially after reading the positive results of tocilizumab treatment in the two largest randomised controlled trials (RCT) on this topic [23].

Their analysis provides an opportunity to consider several questions, which have emerged during the pandemic, including data analysis methods, differences in standard of care during the course of the pandemic and the usefulness of relatively small datasets.

The Bayesian method used for analysis might look unfamiliar to clinicians, as it uses a fundamentally different approach to draw statistical conclusions from data, compared to the more conventional frequentist methods. However, it is used by the influential REMAP-CAP trial and also has been proven useful for re-analysis of otherwise "negative" trials [245]. Based on the Bayes theorem, they incorporated prior knowledge to try to answer the question: what is the probability of the treatment, in this case cytokine blockade, has benefit in changing the clinical state at day 28?[6] Calculating the probability of benefit is something clinicians do intuitively at the bedside, when they evaluate information from multiple sources and timepoints before they decide on treatment options. It also must be noted, that the familiarity with frequentist methods might be a false reassurance, as their drawbacks have been laid bare recently[7].

One of the key findings of the study by Monti et al. was, that tocilizumab treatment did not confer mortality advantage and in the secondary analyses there was a signal for harm[1]. This finding should be put into the context of any concomitant treatments and the timing of the intervention. During the early period of the pandemic, which this study is originating from, there was no data on the safety and efficacy of corticosteroids. Previous meta-analyses pointed towards harm if they were used in viral pneumonia, so it is understandable, that Monti et al. did not use steroids in any of their patients [89]. Their

results, pointing toward no effect or even possible harm are in line with the RCTs reporting data from similar time of the pandemic, with patients rarely receiving corticosteroids [10][11]. At the beginning of the pandemic, there was also a genuine concern, that cytokine release syndrome might play an important role in the pathophysiology of the new disease and that it might need to be dampened by cytokine inhibitors, such as tocilizumab [12]. It is now clearer, that the so called hyperinflammatory phenotype of ARDS appears at similar frequency in COVID-19 compared to other ARDS aetiologies and that the inflammatory response to the viral illness is not too dissimilar to previous reports of ARDS from infectious origin[13][14][15]. The important contribution of Monti et al. is the independent confirmation, that tocilizumab should not be used on it's own in critically ill patients, regardless of their perceived inflammatory status. Based on observational studies conducted later during the pandemic and especially analysing the substantial datasets from the REMAP-CAP and RECOVERY trials, it is clear that there appears to be an important synergism between corticosteroid use and the beneficial effect of IL-6R inhibition[2][3][16][17]. It is therefore important that clinicians put the results of the study by Monti et al. in this context, when deciding on the most appropriate treatment strategy for their patients. Furthermore, both recent multi-centre RCTs showed that tocilizumab can significantly reduce the progression of COVID-19 disease and may reduce the need for mechanical ventilation and other organ support [2][3]. Although Monti et al. reports relatively early use of tocilizumab on the ICU, it is still possible, that the sweet-spot of administration has passed by then and this has contributed to their negative findings [1].

The authors also observed, that the administration of anakinra, an IL-1 receptor antagonist was associated with higher probability of clinical improvement by day 28 and this was marked in the most severely ill group of patients [1]. A recent meta-analysis of the observational studies available on the topic by the same group of authors concluded that the use of anakinra is associated with better outcomes, with no increased risk of adverse events [18]. Including the data presented by Monti et al. further strengthens this argument and moves the risk ratio to 0.36 95%CI (0.21-0.59) for mortality using a fixed effect model (Fig 1.). Although the only published RCT on the use of anakinra was stopped for futility, it must be noted that the CORIMMUNO-ANA-1 trial recruited patients with mild to moderate disease severity who also did not have any corticosteroid treatment[19]. The patients in the present study had significantly higher risk of death and could have been benefited from the anti-cytokine therapy, whereas the CORIMMUNO-ANA-1 patients

could have been more prone to the side-effects. Only on the 3rd of May 2021, the results of the SAVE-MORE RCT were announced via a press release, hinting a beneficial effect of anakinra in the most severely ill patient population[20]. We are eagerly waiting for the full publication of the results, which could help us to place this piece of jigsaw in the treatment puzzle of COVID-19.

In conclusion, while we are waiting for more definitive evidence to emerge from well conducted and appropriately powered RCTs, single centre retrospective trials like the one published by Monti et al. can still help us evaluating treatment options, if we put them in the right context of this fast paced pandemic science.

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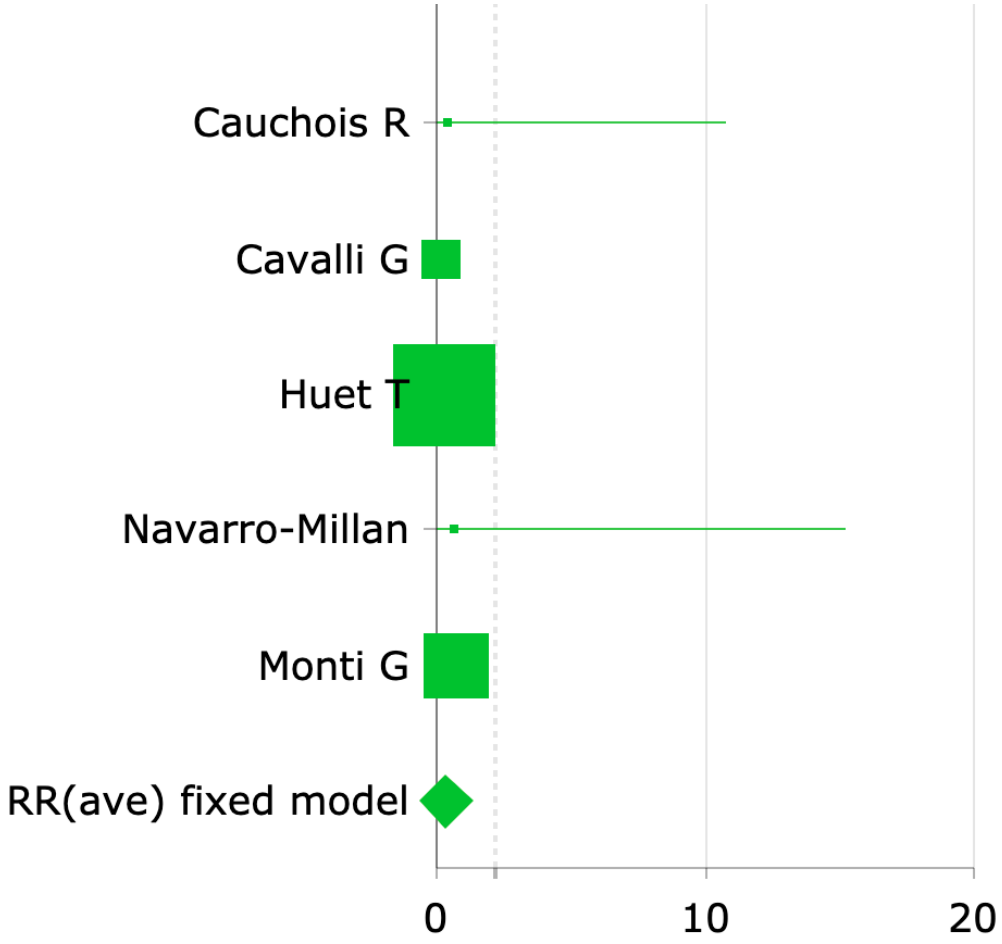
TITLES OF FIGURES

Figure 1.— Forrest plot for mortality in retrospective studies comparing anakinra versus standard of care.



For statistical analysis Mantel-Haenszen methods with fixed effects model was used. Size of boxes depict relative weight of the study. Each box represents the risk ratio and the whiskers incorporate the 95%CI on a logarithmic scale. I^2= 19%.