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Safety and efficacy of interleukin-1 antagonists in hospitalized patients with COVID-19.

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Running head: IL-1 antagonists for COVID-19.

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Dear Editor,

the ongoing pandemic of coronavirus disease-2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection still represents a major public health concern. Severe COVID-19 is characterized by systemic hyper-inflammation, cytokine storm and rapid progression to respiratory failure and acute respiratory distress syndrome (ARDS).[1] Major inflammatory cytokines, such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and IL-1, have been shown to be predictors of disease severity and mortality, therefore, it was relatively early proposed that they should represent both prognostic biomarkers, but also treatment targets in COVID-19. Therefore, there has been a vivid and ongoing discussion regarding the role of antirheumatic drugs targeting various stages of the inflammatory cascade in COVID-19. Concerning the role of IL-1 blockers, former meta-analyses of observational studies resulted in enthusiasm about the promising role of anakinra, for the reduction of COVID-19 related mortality,[2,3] while data concerning the role of canakinumab was limited. Thus, we sought to perform an updated systematic review and meta-analysis of relevant randomized controlled trials, in order to evaluate the safety and efficacy of IL-1 blockers in patients with severe COVID-19.

The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our protocol has been registered at the PROSPERO database (CRD42022324746). We searched PubMed, Cochrane Library, clinicaltrials.gov, European Union (EU) Clinical Trials Register and medrxiv.gov databases from inception to 1st April 2022 for randomized controlled trials (RCTs) enrolling hospitalized adult subjects with documented SARS-CoV-2 infection, assigned either to an IL-1 antagonist (either anakinra or canakinumab) or control (placebo or active comparator). Our exclusion criteria were a. observational studies, b. case series or case reports and c. studies performed in the pediatric population. Complete search strategy is provided in supplementary appendix (supplementary table 1).

We set as primary efficacy outcome the death in the context of SARS-CoV-2 infection. We set as secondary efficacy outcome the need for invasive mechanical ventilation (IMV) or initiation of extracorporeal membrane oxygenation (ECMO) and the composite of non-invasive mechanical ventilation or initiation of high-flow oxygen (HFO). We also assessed major safety outcomes, with emphasis on secondary bacterial infections (bacterial sepsis and septic shock), neutropenia and transaminasemia.

After de-duplication and assessment of eligible studies at title and abstract level for potential inclusion in our systematic review, two independent reviewers (A.D. and D.P.) extracted the data of interest from the eligible report.

Differences were calculated with the use of risk ratio (RR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel (M-H) random effects formula. Statistical heterogeneity among studies was assessed by using I^2 statistics. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software. Two independent reviewers (A.D. and D.P.) assessed the quality of the included RCTs, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary efficacy outcome. Discrepancies between reviewers were solved by discussion, consensus, or arbitration by a third senior reviewer (D.M).

Study selection process is depicted in the corresponding flow diagram (online supplementary material). Seven RCTs were finally included in the present systematic review and meta-analysis.[4-10] Two trials assessed the efficacy and safety of canakinumab,[4,5] while the rest five evaluated the efficacy and safety of anakinra, compared to control or active comparator, in patients with COVID-19.[6-10]

Therefore, we pooled data from seven trials in a total of 2,120 enrolled subjects. A detailed description of enrolled trials is provided in the online supplementary material.

Administration of IL-1 antagonists failed to produce a decrease in the risk for COVID-19 death (RR = 0.93, 95% CI; 0.70 – 1.22, I^2 = 28%, p = 0.22), for COVID-19 related IMV (RR = 1.05, 95% CI; 0.77 – 1.42, I^2 = 41%, p = 0.13) and for the composite outcome of non-invasive mechanical ventilation or HFO initiation (RR = 1.03, 95% CI; 0.65 – 1.62, I^2 = 0%, p = 0.9). No significant difference between the two treatment options was documented for all three comparisons. Data are shown in figure 1 (panels A-C).

Regarding safety outcomes of interest, IL-1 blockers did not result in an increase in the risk for bacterial sepsis (RR = 1.82, 95% CI; 0.83 – 3.99, I^2 = 0%, p = 0.14), for bacterial septic shock (RR = 1.27, 95% CI; 0.29 – 5.45, I^2 = 65%, p = 0.75), for neutropenia (RR = 4.58, 95% CI; 0.83 – 25.39, I^2 = 0%, p = 0.08), for anemia (RR = 0.75, 95% CI; 0.53 – 1.06, I^2 = 0%, p = 0.11), for thrombocytopenia (RR = 0.91, 95% CI; 0.30 – 2.71, I^2 = 0%, p = 0.86), for transaminasemia (RR = 2.64, 95% CI; 0.22 – 31.16, I^2 = 70%, p = 0.44) and for acute kidney injury or acute renal failure (RR = 0.71, 95% CI; 0.38 – 1.34, I^2 = 0%, p = 0.3) [online supplementary material]. Overall risk of bias across the selected trials is considered as low.

In the present updated meta-analysis of relevant RCTs we demonstrated that IL-1 antagonists do not exert any significant effect on "hard" outcomes in COVID-19, such as in-hospital mortality, need for invasive mechanical ventilation and requirement for non-invasive mechanical ventilation. Of note, neither anakinra nor canakinumab provide any significant effect on the above-mentioned surrogate endpoints. However, utilization of IL-1 antagonists in hospitalized patients with severe COVID-19 seems to be relatively safe, across a number of

safety endpoints, including bacterial sepsis and septic shock, cytopenia, acute kidney injury and transaminasemia.

The results of our meta-analysis are opposite to those of relevant meta-analyses of observational studies,[2,3] strongly supporting the use of anakinra in patients with severe COVID-19. In specific, Kyriazopoulou et al.[2] have formerly shown that anakinra led to an impressive reduction in the odds for COVID-19 related death by 68%, regardless of comorbidities, ferritin concentrations, or the baseline PaO_2/FiO_2 ratio. However, authors documented the synergistic effect of anakinra and dexamethasone on mortality benefit,[2] while, no significant effect was shown when anakinra was administered without dexamethasone. Similar results were generated by Barkas et al.[3], who showed in their meta-analysis of observational studies that anakinra decreased the odds for mortality by 68% and the odds for IMV by 62%, compared to standard of care, while, no significant increase in the odds for major adverse events, such as secondary bacteremia or liver dysfunction, was documented.[3]

We consider as major strengths of our meta-analysis the fact that included only RCTs, which are considered as the highest level of evidence, after a thorough and meticulous searching in medical databases and grey literature sources. However, we recognize as main limitation of the present meta-analysis the lack of access to individual participant data, which could permit us to conduct subgroup analyses for the assessed outcomes, according to baseline characteristics of specific interest, such as co-morbidities, pharmacotherapy, or status of prior vaccination. In addition, the results of the present meta-analysis cannot be generalized to newer SARS-CoV-2 variants, such as the omicron variant.

To sum up, in the present updated meta-analysis of relevant RCTs, we failed to document any treatment benefit with IL-1 blockers in hospitalized patients with COVID-19, as added to standard of care, despite being a safe treatment option. Current evidence does not support their administration in patients with severe COVID-19.

Authors contributions

Athina Dimosiari and Demosthenes Makris conceived and designed the study. Athina Dimosiari and Dimitrios Patoulias performed literature searching and data extraction. Athina Dimosiari and Dimitrios Patoulias performed the analyses of retrieved data. Athina Dimosiari, Dimitrios Patoulias and Ioannis Pantazopoulos wrote the first draft. Epaminondas Zakynthinos and Demosthenes Makris critically revised the manuscript. All authors agree to its submission for publication.

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Figure legends

Figure 1 Effect of IL-1 antagonists compared to control on the risk for: a) COVID-19 death,
b) invasive mechanical ventilation due to COVID-19 and c) non-invasive mechanical
ventilation or initiation of HFO due to COVID-19.

Panel A

Panel B

Panel C