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Letter to the Editors-in-Chief

Reduction of venous thromboembolic events in COVID-19 patients: Which role for IL-6 antagonists?

To the Editor,

Recent analyses have demonstrated that COVID-19 patients are at higher risk of venous thromboembolic (VTE) events which increase the mortality risk and need of intensive care admission in the short-term period. In this regard, it has been suggested that prophylactic anti-coagulation was associated with lower in-hospital mortality among SARS-CoV-2 patients, modifying the standard of care of these subjects [1]. Notably, IL-1 and 6, which constitute a relevant part of the cytokine storm triggered by the SARS-CoV-2 infection, promote thrombosis by activating platelets, endothelium, monocytes, and the tissue factor VIIa pathway; moreover, they inhibit fibrinolysis and natural anticoagulants, including protein C and S [2–4].

However, the potential "protective" effect of IL-6 antagonists towards the onset of VTE has not yet been adequately investigated. To elucidate this aspect we performed, accordingly to the PRISMA guidelines (Supplementary file 1), a review of the literature searching for published randomised controlled trials (RCTs) comparing the administration of IL-6 antagonists with usual care or placebo.

For this purpose, RCTs were identified through systematic searches of ClinicalTrials.gov, the EU Clinical Trials Register, and the WHO International Clinical Trials Registry Platform from October 2020 to June 2021. The selection of studies to be included in our analysis was independently conducted by 2 authors (MZ, GZ) in a blinded fashion. Any discrepancies in study selection were resolved consulting a third author (LR).

The search terms used were random* AND COVID in the title or abstract, along with terms for common IL-6 antagonists and interleukin 6. Moreover, we separately search also the available IL-6 antagonists using the term tocizilumab and sarilumab, respectively.

Searches were restricted to completed and published trial status in English language. RCTs were included if: they present data on the use of IL-6 antagonists in patients with confirmed diagnosis of COVID-19 infection, were in English language and compare the use of Tocizilumab against the standard of care. RCTs comparing the use of IL-6 against steroids or antiviral drugs were excluded. References from the included studies were screened to potentially identify other investigations meeting the inclusion criteria. For each trial, the risk of bias (low risk, some concerns, or high risk) was assessed using version 2 of the

Cochrane Risk of Bias Assessment Tool [5]. Risk of bias assessments was done independently by 3 of the investigators (M.Z., L.R., G.R.) (Supplementary file 2) with disagreements resolved through discussion. Ethical approval and informed consent were not required as the study did not directly enroll human subjects. The primary outcome of the study was to compare the VTE risk, in terms of odd ratio (OR), between COVID-19 patients treated with IL-6 antagonist and those treated with standard care.

VTE events risk data were pooled using the Mantel–Haenszel random effects models with OR as the effect measure with 95% CI. Heterogeneity among studies was assessed using Higgins and Thomson I^2. The presence of potential publication bias was verified by visual inspection of the funnel plot. Due to the low number of the included studies ($<$10), small-study bias was not examined as our analysis was underpowered to detect such bias. The meta-analysis was conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA).

A total of 76 potentially eligible trials were identified. After screening these investigations, 47 were excluded due to the absence of inclusion criteria and two studies since they compared the use of IL-6 antagonists with corticosteroids ($n = 2$). Among the remaining 29 eligible trials, only 9 were published (enrolling 6.893 COVID-19 patients, mean age 59.6 years, 4.462 males) and among these 4 reported data on the occurrence of VTE events [6–9].

Overall, 681 patients (mean age 58.8 years, 469 males) with SARS-CoV-2 infection were included into the analysis (Table 1) [6–9]. VTE events were reported as a complication of the treatment or potential adverse effect in 2.3% of cases ($n = 16/681$). More precisely, the incidence of thromboembolic events in patients treated with tocilizumab or sarilumab and controls were 1.5% ($n = 6/380$) [6–8] and 3.3% ($n = 10/301$) [9], respectively.

On pooled analysis, the potential protective effect against of IL-6 antagonists towards VTE events did not reach the statistical significance (OR: 0.48, 95% CI: 0.17–1.37, $p = 0,17$ $I^2 = 0\%$) (Fig. 1). The relative forest plot is presented in Supplementary file 3.

Despite the potential pathophysiological link between IL-6 and VTE events, our brief analysis failed in demonstrating a lower risk of VTE events in COVID-19 patients treated with IL-6 antagonists. However, our results must be considered cautiously and as preliminary. Indeed, among

Table 1

General characteristics of the published trials comparing anti IL-6 drugs versus standard care (control) in the treatment of COVID-19 patients. T: Treatment group; C: Control group: CS: Corticosteroids; NR: Not reported.

Author	Trial N[a]	N[a] of pts	Tocilizumab N	Sarilumab N	Control N	Mean age (years)	Males N, (%)	VTE events	Anticoagulation	CS N (%)
Hermine et al. [6]	NCT04331808	130	63	–	67	64.0 [57.1–74.3][b] 63.3 [57.1–72.3][d]	88 (67.6)	T: 0/63 C:3/67	NR	T: 18 (11.0) C:5 (6.0)
Stone et al. [7]	NCT04356937	243	161	–	82	59.8 [45.3–69.4]	141 (58)	T: 2/161 DVT; 1/161 PE C: 2/82 DVT: 2/82 PE	NR	T: 23 (11.0) C: 5 (6%)
Veiga et al. [8]	NCT04403685	129	65	–	64	57.4 (15.7)[b] 57.5 (13.5)[d]	88 (68.2)	T: 2/65 DVT C: 3/64 PE	Heparin (Prophylactic) T: 50 (94.0) C: 3 (6.0) Heparin (Therapeutic) T: 48 (89.0) C: 6 (11.0)	T: 45 (69.2) C: 47 (73.4)
Soin et al. [9]	CTRI/2020/05/025369	179	91	88		56 [47–63][c] 54 [43–63][d]	152 (84.9)	S:1/91 PE C:0/88 PE	NR	T: 83 (91.0) C:80 (91.0)

[a] Also cause of death.
[b] Referred to Tocilizumab group.
[c] Referred to Sarilumab group.
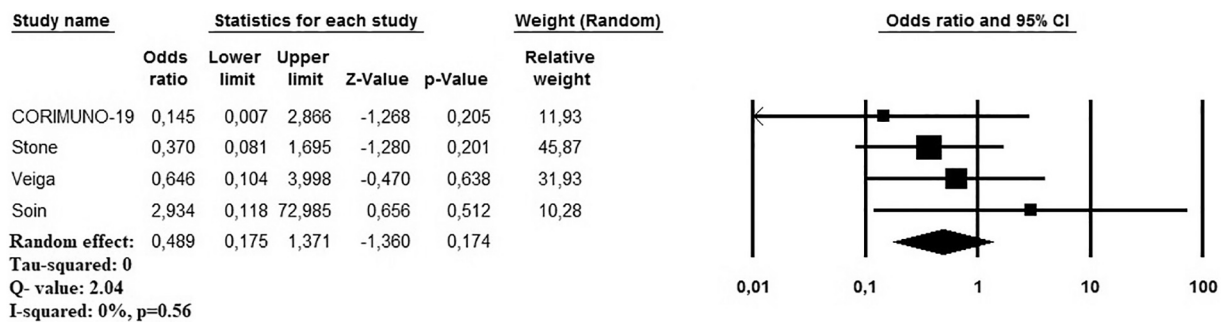[d] Referred to control group.

Fig. 1. Forrest plot investigating the risk of venous thromboembolic events in COVID-19 patients treated with IL-6 antagonists or standard of care.

the RCTs revised, none of the investigations reviewed assessed the risk of VTE events as an outcome of the study. Moreover, the sample analysed was very small and the potential pre-existing risk factors for thromboembolic events cannot be considered as confounding factors, potential distorting our results. Similarly, due to the scant data regarding the administration of anticoagulant treatments we cannot performed a meta-regression considering the use of these drugs as moderators; indeed, different anticoagulant regimens might have influenced the distribution of VTE events. However, the heterogeneity observed was low, providing relative robust statistical evidence of our findings. Notably, IL-6 antagonists have been frequently co-administered with glucocorticoids in the effort to obtain a synergistic effect as for example also in the REMAP- trial [10]; this aspect may represent another potential confounding factor that must be adequately considered in our analysis and adequately evaluated in future RCTs. In the near future, some important results will emerge from ongoing trials such as the HEPMAB (N° Trial NCT04600141) but in the meantime, whether IL-6 antagonists may reduce the risk of VTE events in COVID-19 patients when administered simultaneously with standard prophylactic anticoagulation urgently require larger and dedicated studies, also to identify potential adverse events related to the use of such cytokine inhibitor.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.11.008.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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