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Cytokine adsorption and ECMO in patients with COVID-19

Author's reply

We thank Andrey Rybalko, Pasquale Nardelli, and their colleagues for critically discussing the results from our CYCOV trial[1] and raising valid points.

We agree that randomisation cannot prevent differences between groups in baseline parameters. However, we do not share the concern that the patients in the cytokine adsorption group were particularly sicker at baseline. The number of patients with known comorbidities (12 [71%] of 17 in the cytokine adsorption group *vs* ten [59%] of 17 in the control group) did not differ relevantly. The same was true for the duration of invasive ventilation before initiation of extracorporeal membrane oxygenation (ECMO) with or without cytokine adsorption (5 days *vs* 4 days).

Median partial pressure of arterial oxygen (PaO_2) and the median of the ratio of partial pressure of arterial oxygen and the fraction of inspired oxygen (PaO_2/FiO_2 ratio) were lower at baseline in the cytokine adsorption group. We did extensive post-hoc analyses to detect a potential effect of these random imbalances on survival. In logistic regression analyses and in single and multiple Cox regression analyses, both PaO_2 and PaO_2/FiO_2 ratio at baseline did not show a significant effect on survival. Similarly, norepinephrine support at baseline and the change of norepinephrine support from baseline to 72 h and the cumulative fluid balance from baseline to 72 h did not have a significant effect on survival. Similar observations were made for inflammation parameters (interleukin-6, C-reactive protein, procalcitonin, ferritin) and coagulation parameters (D-dimers, Willebrand factor). Taken together, minor differences in baseline parameters did not explain the survival differences observed between the groups.

In our centre, during the ongoing COVID-19 pandemic, ECMO capacity was never saturated or even overwhelmed. We therefore continuously applied conventional selection criteria for ECMO unchanged from criteria used before the COVID-19 pandemic.[2,3] We agree that patients receiving ECMO support have worse outcomes the longer they are mechanically ventilated before initiation of ECMO. In our centre, in line with Extracorporeal Life Support Organization recommendations, prolonged mechanical ventilation is considered a relative contraindication for ECMO (>7 days), but we do not consider a specific time on mechanical ventilation as an absolute contraindication.[4] Data suggest that selected patients can benefit from ECMO even after prolonged periods of mechanical ventilation.[5]

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	Cytokine adsorption group (n=17)	Control group (n=17)
Cannulation strategy		
Dual-lumen catheter, jugular	6 (35%)	13 (76%)
Femoral–femoral	8 (47%)	3 (18%)
Femoral–jugular	3 (18%)	1 (6%)
Drainage cannula		
Dual-lumen catheter, 32 Fr	1 (6%)	1 (6%)
Dual-lumen catheter, 31 Fr	3 (18%)	9 (53%)
Dual-lumen catheter, 30 Fr	1 (6%)	0
Dual-lumen catheter, 27 Fr	1 (6%)	3 (18%)
23 Fr	10 (59%)	4 (24%)
21 Fr	1 (6%)	0
Return cannula		
Dual-lumen catheter, 32 Fr	1 (6%)	1 (6%)
Dual-lumen catheter, 31 Fr	3 (18%)	9 (53%)
Dual-lumen catheter, 30 Fr	1 (6%)	0
Dual-lumen catheter, 27 Fr	1 (6%)	3 (18%)
23 Fr	2 (12%)	2 (12%)
21 Fr	6 (35%)	1 (6%)
19 Fr	1 (6%)	0 (0%)
17 Fr	2 (12%)	1 (6%)
Type of ECMO system		
Maquet CardioHelp*	1 (6%)	4 (24%)
Sorin SCPC†	11 (65%)	12 (71%)
CARL‡	4 (24%)	0
CentriMag§	1 (6%)	1 (6%)
ECMO settings at 24 h after initiation		
Blood flow, L/min	4·1 (3·6–4·6)	3·9 (3·4–4·4)
Sweep gas flow, L/min	4·0 (2·5–4·8)	3·5 (2·8–6·0)
aPTT during the first 72 h after initiation of ECMO		
aPTT at 24 h, s	65·0 (55·5–75·5)	48·0 (43·0–56·5)
aPTT at 48 h, s	66·0 (62·0–73·5)¶	44·0 (41·5–57·0)
aPTT at 72 h, s	59·5 (51·5–67·3)¶	52·0 (42·3–62·8)¶

Data are n (%) or median (IQR). aPTT=activated prothrombin time. ECMO=extracorporeal membrane oxygenation. *Maquet GmbH, Rastatt, Germany. †LivaNova PLC, London, UK. ‡Resuscitec GmbH, Freiburg, Germany. §Thoratec, Zürich, Switzerland. ¶n=16.

Table: **Cannulation strategies, ECMO systems and settings, and aPTT during the first 72 h after initiation of ECMO**

During the CYCOV trial,[1] four different ECMO systems and three different cannulation strategies were used (table). The secondary endpoint, number of days on ECMO, was reported in the appendix of the Article.[1]

We enrolled patients in the CYCOV trial from March 29, to Dec 29, 2020. During this time, groundbreaking clinical trials were conducted and published at an unprecedented pace and treatment standards had to be revised within a short period of time. For ethical reasons, we could not adhere to a fixed treatment regimen but had to consider these changes and adapt our treatment standards. These developments, however, cannot explain the observed survival differences between the two study groups. Regarding its effect on survival, the most important change was undoubtedly the introduction of methylprednisolone.[6] In the CYCOV trial, the number of patients receiving methylprednisolone in both groups was well balanced.

Anticoagulation treatment in all patients was given according to our pre-existing internal treatment standards for ECMO and CytoSorb. Patients on venovenous ECMO received anticoagulation treatment with unfractionated heparin or argatroban, aiming for an activated prothrombin time (aPTT) of 40–50 s. In patients with bleeding complications, a lower aPTT was accepted (40 s, if acceptable with regard to the bleeding complications); in case of signs of ECMO circuit thrombosis (not requiring immediate or timely system exchange), an aPTT range of 50–60 s was aimed for. During treatment with CytoSorb, the aPTT target was 60–80 s. The same target range was applied in case of patient thromboembolism (eg, pulmonary embolism or deep vein thrombosis; table).

We agree that evaluation of the efficacy of cytokine adsorption should not be based on a single parameter, such as interleukin (IL)-6. However, to better understand the pathophysiological effects and explain potential benefits or harms of cytokine adsorption, we also need to assess the influence of cytokine adsorption on cytokines, including interleukins.[7]

Nardelli and colleagues state that outcomes in patients on ECMO rarely benefit from or are harmed by a single treatment but are rather the result of a comprehensive intensive management. In the CYCOV trial, we have not claimed otherwise. However, randomised controlled trials (RCTs) are the gold standard for the assessment of the effect of a specific treatment option, drug, or medical device. We consider the results of the CYCOV trial an important contribution to the existing body of evidence.

We agree that IL-6 concentrations in our study cohort were lower than in other forms of acute respiratory distress syndrome.[8] The rationale for cytokine adsorption in the CYCOV trial was based on two reasons. First, we postulated that elevated cytokines in patients with severe COVID-19 were associated with poor outcomes.[9] Second, previous evidence suggested immune activation and cytokine release in response to ECMO itself.[10] Based on these considerations we hypothesised a benefit of cytokine adsorption in this patient cohort. The results from our study made us to reject our hypothesis. So far, no conclusive evidence exists to guide initiation or duration of cytokine adsorption with respect to specific clinical or laboratory parameters. Specifically, there is no compelling data supporting the use of cytokine adsorption dependent on a cutoff threshold for IL-6 greater than 500 pg/mL.

The CYCOV trial was designed for the assessment of the benefit of cytokine adsorption in COVID-19 patients supported with venovenous ECMO. The trial was not designed to find out about the optimal timing of cytokine adsorption with respect to disease stages or progression in COVID-19; therefore, based on our data, we cannot make any assumptions about initiation of cytokine adsorption in COVID-19 before initiation of ECMO.

It is reasonable and standard practice in RCTs to assess a broad range of secondary endpoints to cover efficacy, safety, and pathophysiological aspects of a therapeutic intervention. Although we assessed several parameters during the first 72 h, among the secondary endpoints considered in CYCOV, mortality is the most patient relevant.

We agree that the assessment of 30-day survival might be a rather short period in patients with COVID-19 treated with ECMO, who often require prolonged in-hospital treatment. However, the trial was designed and initiated in early 2020 when there was little evidence on the disease. Assessing 90-day survival in the study cohort, the results did not change substantially (3 [18%] of 17 in the cytokine adsorption group *vs* 11 [65%] of 17 in the control group, hazard ratio 3·70 [95% CI 1·51–9·11]; log-rank [Mantel-cox] p=0·0029).

Finally, we agree with Nardelli and colleagues that one single RCT should not steward worldwide clinical practice. This is not what we suggested or implied. One single RCT cannot provide sufficient evidence to inform all treatment decisions for or against cytokine adsorption in COVID-19. Nevertheless, the safety concerns raised by the results from the CYCOV trial must not be neglected.

To date, there is no conclusive evidence from clinical trials showing a clear treatment benefit or even a survival benefit for CytoSorb in COVID-19 or for other indications. Data from small, retrospective registry studies alone should not set treatment standards and guide general treatment decisions.[11,12] Therefore, it is reasonable, as concluded in the CYCOV trial, to urge against uncritical use of cytokine adsorption outside of clinical trials—this is true for COVID-19 and for other indications.

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