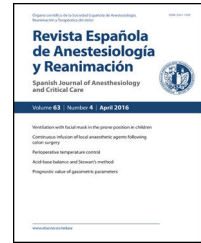




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LETTER TO THE DIRECTOR

Immunomodulation using CONVEHY® for COVID-19: from the storm to the cytokine anticyclone*



Inmunomodulación mediante CONVEHY® para COVID-19: de la tormenta al anticiclón de citoquinas

To the Editor,

The cause of the COVID-19 pandemic is severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Severe forms of the disease occur predominantly in older adults or in individuals with underlying medical comorbidities, such as cardiovascular disease, hypertension, diabetes mellitus, chronic lung disease, and chronic kidney disease. The reason for the fatality of COVID-19 is viral sepsis. This host organ dysfunction is caused by a life-threatening, dysregulated inflammatory response (DIR) that initially has severe pulmonary complications.^{1,2} Therefore, there is generalized endothelial dysfunction leading to multiple organ dysfunction syndrome.

Emerging evidence suggests that some patients may respond to COVID-19 with a disproportionate “cytokine storm,” called secondary hemophagocytic lymphohistiocytosis (HLH).^{3,4} This, however, is not merely a quantitative problem, and dysregulated inflammatory response, which is a functional problem not just a particular cytokine threshold is a better term to describe this phenomenon. This response must be associated with an organ dysfunction to be considered pathological.⁵ Currently, although there are some promising data, there is insufficient evidence to support the recommendation for a specific, effective treatment for patients with COVID-19.⁶ While numerous antiviral treatments are under investigation, their exclusive use may not be sufficient to control the aforementioned dysregulated inflammatory response. Therefore, there is growing interest in identifying alternatives with immunomodulatory action that can eliminate or reduce the formation of cytokines, thereby reducing both inflammatory tissue damage, particularly lung damage,⁷ and mortality. An optimal blood purification technique could play a key role in this context.⁸

The CONVEHY® protocol (online supplements 1, 2, 3) was developed by the Hyperfiltration Research Group to control DIR and the cytokine storm through immunomodulation in patients with septic shock.⁹ The DIR can be triggered by various events, including viral infections such as COVID-19, and can have different systemic effects on endothelial glycocalyx, such as vasodilation, fluid extravasation, and platelet micro-aggregation, in addition to kidney injury. Immunomodulation strategies that involve the elimination of inflammatory mediators should be considered in patients with poor response to treatments.¹⁰

The oXiris® membrane⁵ (BaxterTM, Illinois, USA) is hollow fibre acrylonitrile and methanesulfonate (AN69ST) membrane with a surface treated with polyethyleneimine (PEI) and anchored heparin (AN69-ST-anchored heparin). It is a haemofilter that can eliminate interleukins (IL), tumour necrosis factor alpha (TNF-α), migration inhibitory factor (MIF), interleukin-1 receptor antagonist (IL1-ra), high mobility group box 1 protein (HMGB-1), lipopolysaccharides (LPS), fibroblast growth factors (FGF21, FGF23), complement factors (C3a, C5a), and plasminogen activator inhibitor 1 (PAI-1), in addition to endotoxins. Its ability to remove molecules is related to its electrical charge, and therefore its isoelectric point. Although clinical experience in COVID-19 is limited,^{11–13} in a single-centre, randomized, double-blind clinical trial, oXiris® proved effective in purifying blood and reducing the need for vasoactive agents in bacterial sepsis.¹⁴ The Prismaflex system™ (BaxterTM, Illinois, USA) is used in conjunction with oXiris®. CONVEHY® uses a dose of citrate in a specific stage of the process, in this case specifically adapted to COVID-19. Adsorption capacity decreases over time due to membrane saturation, and membrane replacements are scheduled every six hours, at the discretion of the physician. The membrane can also be used solely for hemofiltration if only renal support is required at that time. The preliminary results of the use of the CONVEHY® protocol comparing outcomes before and after the inclusion of citrate have recently been published.⁹

The SARS-CoV-2 receptor binding domain spike (S) binds to the ACE2 receptor through a remarkable network of hydrophilic interactions. Multiple bonds and two salt bridges can be found at the interface of this complex, with multiple tyrosine residues forming hydrogen-bonding interactions with the polar hydroxyl group.^{15,16} The aforementioned hydrophilic and hydrophobic characteristics of the SARS-CoV-2 virus allows it to adhere to the oXiris® membrane.^{17,18} Similar adsorption-based removal by lectin affinity plasmapheresis has been studied in other RNA viruses such as hepatitis c and Ebola virus.¹⁹

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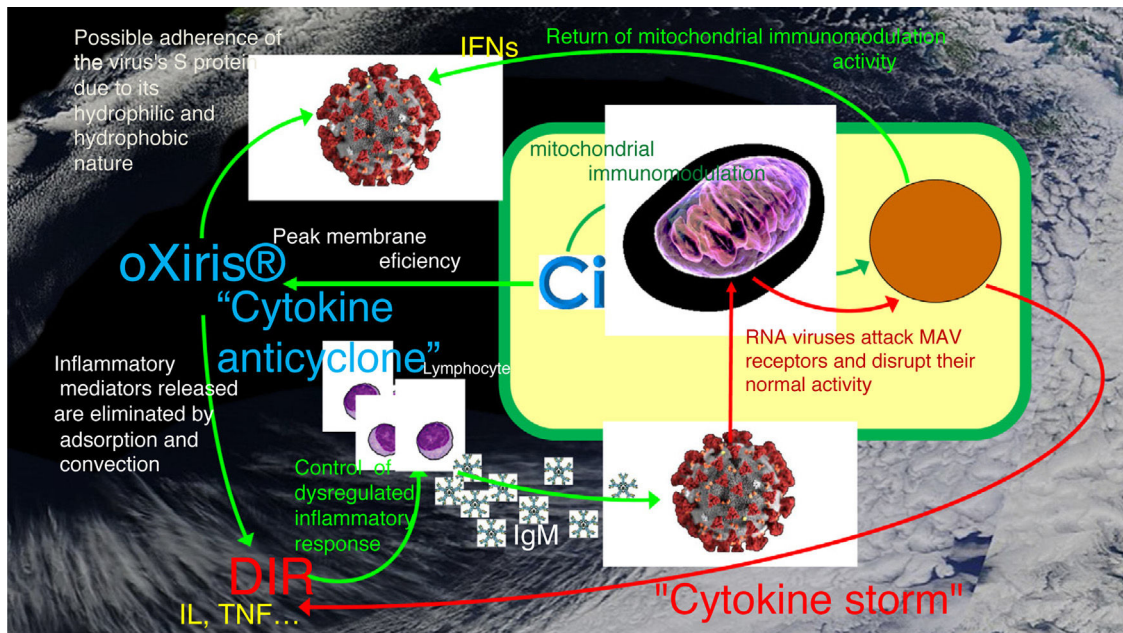


Figure 1 Combined immunomodulation strategy of the CONVEHY® protocol. oXiris®: trademark of the acrylonitrile 69-surface-treated heparin-anchored membrane; Ci: citrate; RNA: ribonucleic acid; DIR: dysregulated inflammatory response; IFNs: interferon; IL: interleukin; TNF: tissue necrotic factor; IgM: immunoglobulin M; curved red arrow: reduction or deterioration; curved green arrow: activation or enhancement.

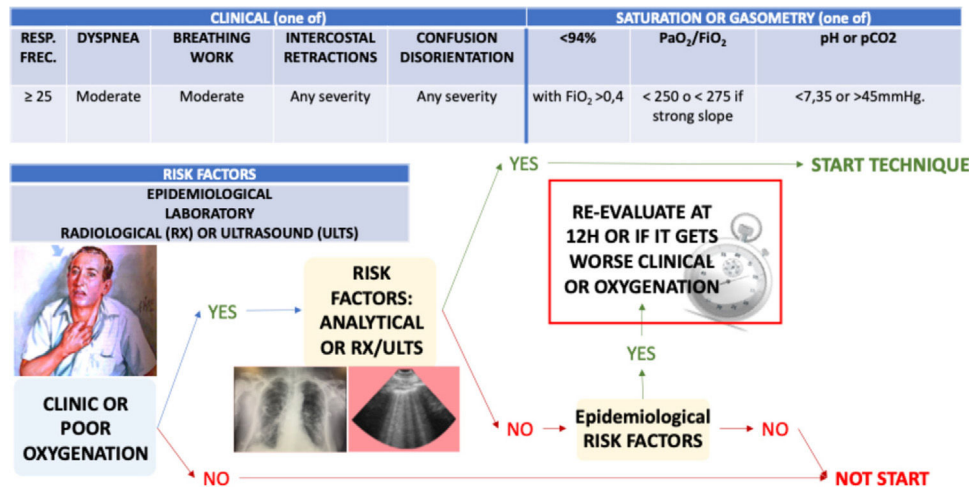


Figure 2 Indication for the early immunomodulation technique for COVID-19 (EIT-C19): patients with manifest symptoms or poor oxygenation who have signs of COVID-19 either on X-ray, pulmonary ultrasound and/or laboratory tests. Particular focus on the subgroup with epidemiological risk factors. See decision tree.

The oXiris® membrane was given an emergency use authorization (EUA) by the United States Food and Drug Administration (FDA) to treat patients with confirmed COVID-19. This technique can be used to reduce pro-inflammatory cytokine levels in adult patients presenting any of the following conditions:

- Early acute lung injury/early ARDS.
- Serious disease
- Life-threatening disease, defined as:
 - Respiratory insufficiency
 - Septic shock and/or

- Multiple organ dysfunction or failure.

Being an RNA (ribonucleic acid) virus, SARS-CoV-2 directly affects the immunomodulatory function of the mitochondria by modifying the mitochondrial antiviral signalling (MAV) receptors, thereby preventing interferon synthesis by the innate immune response. Other interleukins can also be modulated in the same way.²⁰

If the inflammatory response can be controlled in time, the immune system may be able to produce antibodies and overcome the infection.²¹ The same strategy is used by our group in bacterial shock, although in this case we facilitate

Table 1 Risk factors for severe disease.

Symptoms (1 parameter)						O ₂ saturation or blood gas (1 parameter)			
Resp. rate	Heart rate	Dyspnoea	Work of breathing	Respiratory distress	Confusion/disorientation	SatO ₂ % baseline	<94% With FiO ₂ >0.4	PaO ₂ /FiO ₂ SpFiO ₂	pH or PaCO ₂
≥25 rpm	>125 bpm	Moderate	Moderate	Any severity	Any severity	<91%	With FiO ₂ >0.4	<300 or SpFiO ₂ < 315 or if abrupt descent	<7.35 or >45 mmHg
Epidemiological				Laboratory		Radiological or ultrasound			
>65 years				D-dimer > 1000 ng/mL		Multilobular infiltrates.			
History of lung disease				CPK > twice baseline		Completely diffuses, widely spaced B lines ("Berticals") (moving with pleura) Waterfall sign. "White" lung.			
Mod-sev CKD				CRP > 100 mg/L		Pleura thickened, irregular.			
DM HbA1c > 7.6% poorly controlled				LDH > 500 U/L		Healthy and diseased lung patches.			
Uncontrolled HT				Elevated troponin		Subpleural consolidation.			
Cardiovascular disease				Ferritin > 1000 µg/L					
Transplantation or other immunosuppression				Lymphopenia < 500/mm ³					
HIV with CD4 < 500/mm ³									

Resp. rate: respiratory rate; rpm: respirations per minute; Heart rate: heart rate; bpm: beats per minute; FiO₂: fraction of inspired O₂; PaO₂/FiO₂: ratio of arterial oxygen partial pressure to fractional inspired oxygen; SpO₂/FiO₂: ratio of peripheral oxygen saturation to percentage of inspired oxygen; PaCO₂: partial pressure of carbon dioxide in arterial blood.
 CPK: creatine phosphokinase; mod-sev CKD: moderate–severe chronic kidney disease; CRP: C-reactive protein; DM HbA1c: glycated haemoglobin in patients with diabetes mellitus; LDH: lactate dehydrogenase; HT: arterial hypertension; HIV: human immunodeficiency virus; CD4: CD4 lymphocytes or T4 lymphocytes.

and allow time for antibiotics to act, and also determine whether the root cause can be controlled or an invasive treatment is needed. The use of high doses of citrate may be more beneficial than heparin with the oXiris® membrane due to:

1. Greater membrane efficiency – there is less activation of leukocytes and platelets and therefore less saturation²² and greater durability at peak performance.
2. The PEI surface treatment is not completely saturated with the initial sodium heparin flushing solution – more PEI is available for adsorption;
3. The unpredictable negative effect of heparin in patients with septic shock and ischaemia–reperfusion injury, which could cause inflammation and microthrombi in the microcirculation²³ and have disastrous effects on COVID-19 patients. Microthrombus involvement in the microcirculation has been described in autopsies of these patients²⁴;
4. Citrate, being a substrate of the respiratory cycle, can act at the mitochondrial level to improve metabolic alterations and keep respiratory complexes active, thus avoiding apoptosis²⁵;
5. Citrate can revive mitochondria and their respiratory and immunomodulatory function.²⁰

We believe that combining an effective adsorptive cleaning strategy with oXiris®, with controlled convection that

helps eliminate inflammatory molecules, together with the effect of citrate on the mitochondria can result in faster and better recovery. This opinion contrasts with other solely renal support approaches (Fig. 1). In patients with COVID-19 timing the start of the technique can be decisive, and for now we have to rely on epidemiological and clinical risk factors for this purpose (Fig. 2 and Table 1).

CONVEHY® COVID-19 is intended as an early use protocol or rescue technique. It is designed to act as an anticyclone for the cytokine storm, thus restoring proper immune function. Its effectiveness could make it suitable for use in dialysis centres and critical care units, where it can treat as many patients as possible.

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Conflict of interests

Rafael García-Hernández has carried out consulting and conference work in hospitals funded by Baxter SL.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at [doi:10.1016/j.redar.2020.08.001](https://doi.org/10.1016/j.redar.2020.08.001).

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The «new cerebral autoregulation curve», let's take a step further to keep learning[☆]



La «nueva curva de autorregulación cerebral», demos un paso más para seguir aprendiendo

Dear Editor,

The editorial by García-Orellana et al.¹ brings to mind Claude Bernard words: "It is what we think we know already that often prevents us from learning". The classic cerebral autoregulation curve described in the 1950s by Lassen is physiologically inaccurate and prevents us from correctly interpreting what happens in clinical practice. Perhaps the

time has come to go beyond this model and deal more effectively with changes in cerebral blood flow.

Although the incidence of perioperative adverse cardiac events has decreased in recent years, there is evidence of an increase in the incidence of stroke. This is why maintaining cerebral perfusion is a problem that transcends neurosurgery or cardiac surgery. The ageing of the surgical population in the western world has raised awareness of the need to prevent perioperative neurocognitive disorders, which are related to other complications, prolong hospital length of stay, consume resources, and affect the quality of life of patients and their families.

Cerebral perfusion is a more complex process than that shown in the classic curve. In 2012, Tan² developed a new brain autoregulation curve. This author's investigations showed major intra- and interindividual variability in the shape of the curve, and revealed three things: first, that the autoregulation plateau is not always horizontal and is usually shorter than represented in the classic model – in some cases it may be reduced to a range of only 10 mmHg. Second, cerebral blood flow (CBF) adapts better to an increase in mean arterial pressure (MAP) than to a decrease in this pressure. And finally, the faster the MAP

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