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Diagnostic and therapeutic recommendations for the Thrombotic Immune Response Associated to COVID-19 (RITAC)

Recomendaciones diagnósticas y terapéuticas ante la Respuesta Inmune Trombótica Asociada a COVID-19 (RITAC)

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ARTICLE INFORMATION

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The authors declare no competing interests

Abbreviation
MAS: macrophage activation syndrome
MTX: methotrexate
RITAC: abbreviation in Spanish of Thrombotic Immune Response Associated to COVID-19
TNFα: tumor necrosis factor α

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Editor's Note
This work is part of a research project waiting for the approval to be tested in Argentina. On the other hand, in Brazil there is a trial with methotrexate, with no published results so far.

The sudden emergence of COVID-19, with its ability of becoming a pandemic in such a few weeks, has challenged not only the health care systems but also many former concepts of medicine. This has forced us to act as quick as possible, not only to try to stop the progress of infections, but also to develop acting protocols which can reduce mortality.

Our colleagues from Spain and Italy were not warned about the situation they were about to face, but along these weeks, they have been passing to us their experiences, with their ups and downs, but always with the objective of preventing us from suffering the same they have. In Argentina, we had the blessing of a quick implementation of the compulsory quarantine and the possibility of preparing the health care system in the best possible way. Some of us could even sat to quietly read and analyze the information that our colleagues were sending us from the battlefield in Europe.

The following protocol is aimed to decrease the need of using mechanical ventilators as well as to reduce the mortality in the seriously ill patients. Bellow we explain the pathophysiology of the Thrombotic Immune Response Associated to COVID-19 (RITAC, by its abbreviation in Spanish),

as we have decided to call it (**Figure**). When this pandemic ends, we will have the necessary time to gather and analyze the information that we will continue receiving in the next weeks.

The usage of antiviral nucleotide analogues drugs like the remdesivir, or monoclonal antibodies anti IL-6, like the tocilizumab, will be difficult due to their high price and the supply shortage. Knowing the essential medicines' characteristics of the World Health Organization (WHO), we suggest using effective, safe and available drugs as well as the cheapest possible.

PATHOPHYSIOLOGY OF THE RITAC

Why do we say immune?

During February and March 2020, it could be observed that the patients infected with COVID-19, who quickly worsen, presented clinical and laboratory data compatible with the macrophage activation syndrome (MAS). Many of these patients were young or young adults apparently healthy; nevertheless, they had a fatal outcome. This situation cannot be explained by a state of immunodeficiency, on the contrary, they seem to have had an exaggerated immune response being responsible for that end (**Video in external supplementary material**, property of the authors).

In the pathophysiology of the MAS are observed (**Figure**):

- Uncontrolled proliferation of the T cells.
- Excessive macrophage activation.
- Hypersecretion of proinflamatory cytokines, interleukin (IL) IL-1β, IL-6, interferon and tumor necrosis factor α (TNFα)[1].

All these alterations in many patients affected by severe forms of infection with COVID-19 were described by our colleagues, that is why we think that an early diagnosis is essential to reduce mortality. Among the laboratory parameters we consider the hyperferritinemia as the best indicator of the presence of this exaggerated immune response[2], that is why we propose to measure it in all patients corresponding to the scenario Nº 2 established by the Ministry of Health of Argentina (**Table**)[3].

Why thrombotic?

In these patients we find, accompanying the uncontrolled macrophagic response, a pathological activation of thrombin; therefore, multiple thrombotic events are observed, which go from peripheral ischemia, pulmonary thromboembolism, to dissemi-

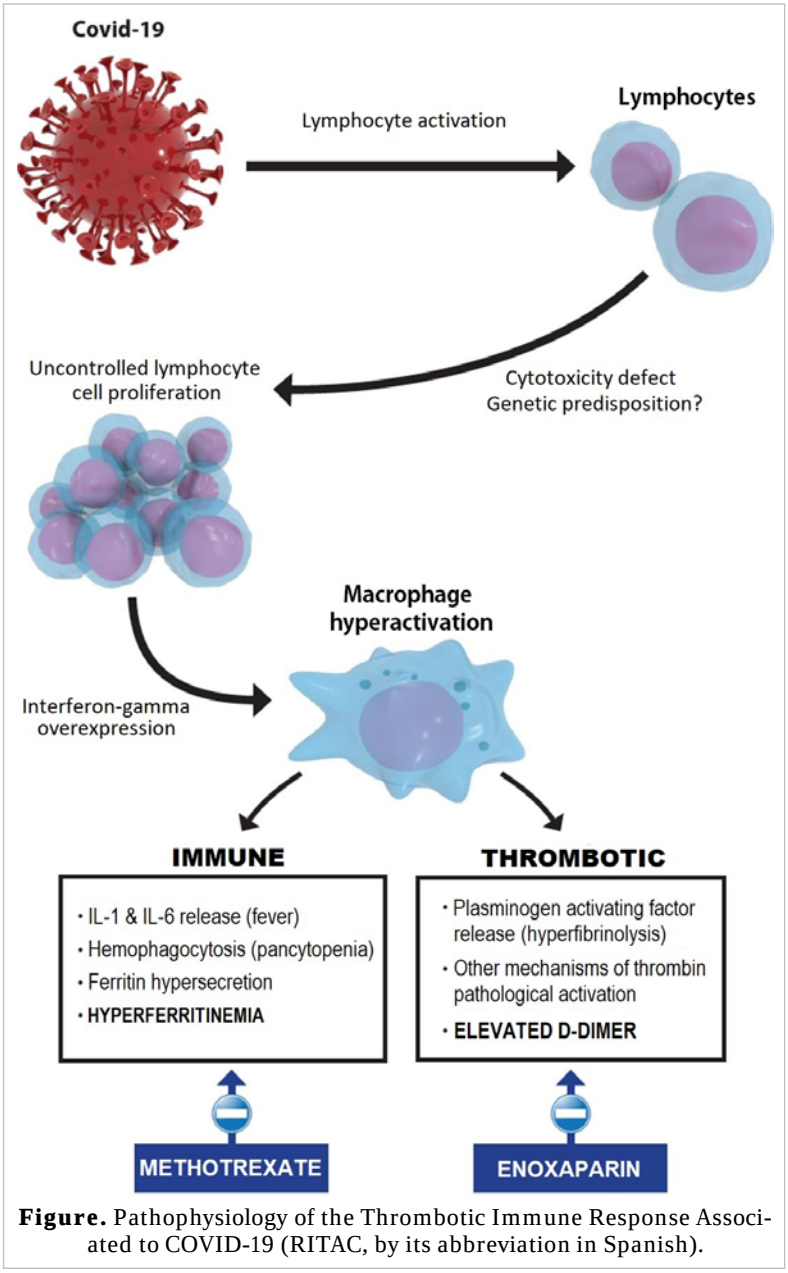

Figure. Pathophysiology of the Thrombotic Immune Response Associated to COVID-19 (RITAC, by its abbreviation in Spanish).

Table. Recommendations from the Ministry of Health of Argentina[3] for the treatment of patients in the different scenarios of COVID-19.

Scenario	Recommendation
1. Severe pneumonia in a patient defined as a suspect or confirmed case of COVID-19; it includes pneumonia plus any of the following: • Breathing rate > 30 per minute • O_2 saturation < 93% (room air) • Requirement of mechanical ventilation support • Increase in the infiltrates > 50% in the next 24 to 48 hours • Deterioration of the sensory • Hemodynamic instability • CURB-65 > 2 points • Requirement for closed unit	1) Support treatment **+** 2) Regular antimicrobial treatment for the severe pneumonia **+** 3) LPV/r 400/100 mg every 12 hours (if oral administration is not well tolerated: LPV/r 80/20 mg/ml, 5 ml every 12 hours through NG tube during 10 days **+/-** 4) HCQ (loading dose: 400 mg every 12 hours during the first 24 hours, sustained: 200 mg every 12 hours) during 10 days *In case of contraindication for HCQ use only LPV/r. Evaluate drug interactions.*
2. Pneumonia without severeness criteria in patients confirmed with COVID-19 and presenting some of the following conditions: • Age ≥ 60 years old • Diabetes • Cardiovascular disease • Chronic kidney disease • Chronic obstructive pulmonary disease • Structural lung diseases • Immunocompromise **Look for RITAC criteria in this group**	1) Support treatment **+** 2) Regular antimicrobial treatment for pneumonia **+** 3) HCQ (loading dose: 800 mg every 12 hours during the first 24 hours, sustained: 400 mg every 12 hours) during 10 days, **or** 4) LPV/r 400/100 mg every 12 hours (if oral administration is not well tolerated: LPV/r 80/20 mg/ml, 5 ml every 12 hours through NG tube during 10 days *The choice of HCQ or LPV/r should be made based on the availability and the individual assessment of the case (including comorbidities and interactions).*
3. Pneumonia without criteria of severeness established in the scenario Nº 2	1) Symptomatic treatment **+** 2) Regular antimicrobial treatment for pneumonia
4. Mild forms with normal chest X-ray with or without comorbidities	1) Symptomatic treatment

CURB-65, scale for prediction of mortality in patients with community-acquired pneumonia; HCQ, hydroxychloroquine; LPV/r, Lopinavir/ritonavir; NG tube, nasogastric tube; RITAC, abbreviation in Spanish of Thrombotic Immune Response Associated to COVID-19.

nated intravascular coagulation (DIC). These complications were the cause of death in many of these patients. The most appropriate laboratory parameter to recognize this thrombophilic estate are the high levels of D-dimer[4]. That is why we propose to measure it in all patients corresponding to the scenario Nº 2, established by the Ministry of Health (**Table**)[3].

DIAGNOSTIC CRITERIA FOR RITAC

Patients with confirmed COVID-19 infection with respiratory symptoms presenting one or more of the following criteria:

1. D-dimer > 1000 ng/mL
2. Ferritin > 500 ng/mL
3. Dyspnea of rapid progression
4. Refractory hypoxemia
5. Thrombotic phenomena
6. Shock

We recommend that, these patients with RITAC criteria, together with the rest of the treatment proposed by the health authorities of our country,

should also be given methotrexate + low-molecular-weight heparin with the aim of stopping the associated immune-thrombotic response to the COVID-19, in order to reduce in this way, the mortality of this disease.

JUSTIFICATION OF THE CHOSEN DRUGS

Methotrexate (MTX)

- Patients with diagnosis criteria of TIRAC will quickly worsen. Faced with the impossibility of using monoclonal antibodies due to their high price, we think the methotrexate is an excellent alternative due to its effectiveness, availability, low price and the wide experience using it in the rheumatoid arthritis[2,5].
- At low doses, it blocks the JAK/STAT pathway. This intracellular pathway is actively involved in the information transduction generated by diverse cytokines and controls immune and inflammatory responses[2].
- The MTX's capacity of limiting the pro-inflammatory response of macrophages was proven when the release of interleukins and TNFα was reduced [5].

Low-molecular-weight heparin (LMWH)

It increases the activity of the antithrombin III, thus, blocking the pathological activation of the thrombin. In this way we can avoid or reduce the above-mentioned thrombotic phenomena that would have worsen the patients' state.

RECOMMENDED DOSES

- Methotrexate (MTX): 1 mg/kg intramuscular dose administered every other day (1, 3, 5, 7). Accompanying this treatment with folic acid and regular hematological and hepatic controls. If there was any situation preventing the MTX administration, corticoids at high doses can be used (1-2 mg/kg/day of prednisone or its equivalent).
- LMWH: 100 UI/kg of enoxaparin subcutaneously administered every 24 hours until the patient is recovered, or alternatively, the LMWH available at the moment can be used.

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