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Short Communication

Use of Therapeutic Plasmapheresis with Itolizumab, a Novel Treatment Perspective for COVID-19 in Cuba

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ABSTRACT

Therapeutic Plasmapheresis (PT) is the process of separation and elimination of plasma from the blood and is considered as a complementary treatment strategy for the causative agent in the management of respiratory viral pandemics. This article reviews the possible benefits of therapeutic plasmapheresis as adjunctive treatment in critical cases of patients with COVID-19 in combination with the monoclonal antibody Itolizumab.

Keywords: COVID-19, Therapeutic plasmapheresis, Itolizumab

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INTRODUCTION

The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020 and has become a public health emergency at the global level. The variability of the clinical picture ranges from asymptomatic carriers, patients who develop very mild symptoms to a severe respiratory condition with multiple organ failure and death. Risk factors associated with COVID-19 have been identified, such as age (older adults), presence of comorbidities (mainly coronary heart disease, diabetes and hypertension), as well as social and socioeconomic factors, physiological and genetic factors, among others. The viral presence triggers an aggressive inflammatory response, leading to airway damage; therefore, the severity of the disease is not exclusively due to the presence of the virus in the body, but also to the uncontrolled response of the host. The host's immune response has been closely related to the cytokine storm in its body. During the progression of SARS-CoV-2 pneumonia, the presence of lymphopenia as a marker of severity in the development of the disease is well known, with a markedly decreased number of CD4 T lymphocytes, CD8 T cells, B cells and NK cells, also showing an increase in the absolute number of neutrophils during the severe phase of the disease. The increase in the number of neutrophils explains the high production of pro-inflammatory cytokines such as IL-6, IL-1, TNF α, and IL-8 and the reduced lymphocyte count leads to the decrease in the natural control of the viral disease due to the disability cytolytic T cells to lyse infected cells. Activation of the IL-6 pathway through its two signaling pathways, Cis and Trans, generates positive feedback from the NLRP3 inflammosome system, a multiprotein complex that converts procaspase 1 into active caspase 1, which in turn converts the pro IL-1B in IL-1B activates, thus prolonging the inflammatory cascade that perpetuates the cytokine storm in the development of moderate-severe disease, this condition being one of the main causes of death in patients with COVID-19 disease. We apply the pathophysiological consequences of cytokine storm, endothelial activation and hypercoagulability disorder as targets in plasma exchange therapy and therapeutic plasmapheresis, the procedure being applied as complementary treatment, with the aim of reducing inflammatory burden and viral, thus minimizing target organ damage. Therapeutic plasmapheresis combined with Itolizumab, a humanized monoclonal antibody, is a therapy that achieved very good results in these patients with confirmed RT-CRP in a moderate, high-risk clinical state.

METHODOLOGY

Two patients are presented, one 53-year-old male, with a history of Arterial Hypertension and a 67-year-old female patient with a history of Arterial Hypertension and Diabetes Mellitus, confirmed case contacts, who are admitted to the Military Hospital Manuel Fajardo Rivero from Santa Clara Villa Clara, with positive PCR-RT, with symptoms such as decay, fever of 38°C, in the case of the female patient she suffered from cough and images of inflammatory lesions were verified through radiological examination of the chest in both lung fields. Laboratory tests are indicated on the first day of hospitalization *(Tables 1 and 2)*. In addition to the protocol established in the process of this disease. Treatment was started with the first dose of the humanized monoclonal antibody Itoliumab, with the subsequent assessment of the markers, and it was decided to indicate therapeutic plasmapheresis 72 hours after the first dose of the monoclonal, fulfilling the inclusion criteria in both patients.

Table 1: The 53-year-old male patient PCR-TR confirmed

Laboratory tests	Hospitalization		After plasmapheresis	
	Units	First day	At	At
			24 hours	48 hours
Hemogram				
Hemoglobin	g/L	122	-	114
Hematocrit	L/L	36	-	38
Leukocytes Total	10^9/L	13.6	-	7
Neutrophils	%	73	-	80
Lymphocytes	%	5	-	11
Platelets	%	208	-	250

LNR	-	14	-	7
Ferritin	ng/ml	928	552	530
LDH	(U/L)	1482	1317	1270
TGP	(U/L)	59	44	38
TGO	(U/L)	51	44	25
GGT	(U/L)	114	107	86
Creatine	µmol/L	182	145	80
C-Reactive Protein	Qualitative	Positive	Positive	Negative
RT PCR	Qualitative	Positive	-	Negative
Note: LDH: Lactate Dehydrogenase; GGT: Gamma Glutamyl Transferase; INR: International Normalized Ratio; TGO: Glutamic-Oxaloacetic Transaminase; TGP: Glutamic Pyruvic Transaminase				

Table 2: The 67-year-old female patient PCR-TR confirmed

Laboratory tests	Positive Units	Positive First day	Positive At 24 hours	Positive At 48 hours
Hemogram				
Hemoglobin	g/L	109	100	111
Hematocrit	L/L	35	32	36
Leukocytes Total	10^9/L	6,2	10.7	8.4
Neutrophils	%	78,4	53	83.5
Lymphocytes	%	18	42	11
Platelets	%	159	153	200
INR	-	7	4	1
Ferritin	ng/ml	860	810	798
LDH	(U/L)	650	630	526
TGP	(U/L)	14	59	43
TGO	(U/L)	25	53	50
GGT	(U/L)	45	92	66
Creatine	µmol/L	143	87	79
C-Reactive Protein	Qualitative	Positive	Positive	Negative
RT PCR	Qualitative	Positive	-	Negative

RESULTS AND DISCUSSION

The analysis carried out by the medical team of both patients took into account how experts recommend that all patients with COVID-19 should be examined for hyperinflammation using laboratory measurements (for example, the NLR index (ratio of neutrophils and lymphocytes) decreased platelet count, increased ferritin, LDH, liver enzymes, the presence of C-reactive protein, among others, in order to identify the group of patients in whom immunosuppression could reduce mortality. As therapeutic options, two types of strategies for the use of anti-CD6 antibodies in the clinic include referenced in the literature, which have followed one another over time: First, antibodies that eliminated T and B cells that express CD6 were used, such as The case of T12 mAb; while the most recent strategies use mAb (monoclonal antibody) aimed at desensitizing these same cells, as is the case of l itolizumab, its mechanism of action reveals that it reduces the expression of intracellular proteins involved in activation and inhibits T cell proliferation. As one of the strategies for disease management in COVID-19, the therapeutic plasmapheresis procedure was performed in both patients to achieve a decrease in inflammatory mediators, antifibrinolytics and the viral RNA that induces the cytokine response, with the following administration of a dose of itolizumab in patients. The laboratory results confirmed the improvement of these markers in both patients *(Tables 1 and 2)* after plasmapheresis was performed at 24 hours and at 48 hours; there was no need for other sessions of plasmapheresis and doses of itolizumab in the patients.

Within the limitations of the cases, no other laboratory tests were carried out to evaluate other inflammatory markers because there was not the necessary input for said tests, due to the same health crisis that occurred due to the COVID-19 pandemic. However, it is important to mention that having been in patients with comorbidity such as Arterial Hypertension, Diabetes Mellitus, it did not prevent the procedure of therapeutic plasmapheresis and treatment with itolizumab, a hospital stay of 6 days and 7 days respectively was achieved.

CONCLUSION

It is concluded, having reported the cases of confirmed positive patients for COVID-19, classified as moderate with high risk, they responded favorably to the therapeutic plasmapheresis procedure and to treatment with itolizumab. With this article we would like to highlight that plasmapheresis, although it is an unproven strategy in COVID-19 in our country, could be a useful approach due to the mechanism of alleviating the cytokine storm and reducing viral load.

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