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Reprofiling the anti-CD6 antibody for the treatment of patients with COVID-19

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Keywords

itolizumab; COVID-19; SARS-CoV-2; cytokine release syndrome; CD6; monoclonal antibody

ABSTRACT

Introduction: COVID-19 can lead to a hyper-inflammatory state. CD6 is a glycoprotein expressed on mature T-lymphocytes, which is a crucial regulator of the T-cell activation. Itolizumab is an antibody targeting CD6. Clinical data in autoimmune diseases indicate that it lowers multiple cytokines primarily involving the Th1/Th17 pathway. Objective: to preliminarily assess the safety and impact of itolizumab on interleukin-6, pulmonary function and mortality of COVID-19 patients. **Methods:** Sixty-eight moderate, severe and critical patients were included in an expanded access trial in Cuba. Itolizumab was administered together with other therapies included in the national protocol for SARS-CoV-2. **Results:** All patients completed the first infusion and 41 received 2 doses. Median age was 68 and 94 % had comorbidities. Itolizumab improved the pulmonary function and was well tolerated; 3 subjects had serious adverse related events. Interleukin-6 decreased in individuals with high levels and did not change in those with lower concentration. 14-day lethality rate was 4 % and 18 % for moderate and severe patients. Although this was not a randomized study, preliminary data suggest that itolizumab reduced the death probability in comparison to controls. The treatment time, neurological manifestations, biomarkers like NLR, neutrophil count and interleukin-6 were

significantly associated with higher lethality. Conclusions. Itolizumab can disrupt the inflammatory cascade and might prevent the morbidity and mortality associated with COVID-19.

Reposicionamiento del anticuerpo monoclonal humanizado anti-CD6 itolizumab en el tratamiento de pacientes con COVID-19

RESUMEN

Introducción: La neumonía COVID-19 puede conducir a un estado hiperinflamatorio. El CD6 es una glicoproteína expresada en linfocitos T maduros que constituye un regulador crucial de la activación de las células T. El itolizumab es un anticuerpo monoclonal que reconoce el CD6. Los datos clínicos en enfermedades autoinmunes indican que reduce múltiples citocinas proinflamatorias. Objetivo: evaluar la seguridad y el impacto de itolizumab sobre la interleucina-6, la función pulmonar y la mortalidad de los pacientes con COVID-19. **Métodos:** Se incluyeron 68 pacientes moderados, severos y críticos en un ensayo de acceso expandido en Cuba. El itolizumab se administró junto con otras terapias incluidas en el protocolo nacional para el SARS-CoV-2. **Resultados:** Todos los pacientes completaron la primera infusión y 41, recibieron 2 dosis. La mediana de edad fue de 68 años y el 94% era portador de comorbilidades. El itolizumab mejoró la función pulmonar y fue bien tolerado; 3 sujetos tuvieron eventos adversos graves relacionados. La interleucina-6 disminuyó en individuos con niveles altos y no se incrementó en aquellos pacientes con concentraciones más bajas. La tasa de letalidad a los 14 días fue del 4 % y del 18% para los pacientes moderados y graves. Aunque este estudio no fue aleatorizado, los datos preliminares sugieren que itolizumab redujo la probabilidad de muerte en comparación con los controles. El tiempo de tratamiento, las manifestaciones neurológicas y los biomarcadores como la razón entre neutrófilos y linfocitos, recuento de neutrófilos y la interleucina-6 se asociaron significativamente con mayor letalidad. Conclusiones. El itolizumab puede interrumpir la cascada inflamatoria y prevenir la morbilidad y mortalidad asociada al COVID-19.

Palabras clave

itolizumab; COVID-19; SARS-CoV-2; síndrome de liberación de citocinas; CD6; anticuerpo monoclonal

INTRODUCTION

COVID-19 is an acute respiratory disease caused by SARS-CoV-2, a highly pathogenic coronavirus. The disease varies from a minimum number of symptoms to severe hypoxia including extra-pulmonary damage, which can be lethal. [1] The viral infection can lead to a hyper-inflammatory state known as cytokine release syndrome.[1]

In the COVID-19 autopsies, lymphomonocytic infiltrates have been found, T CD3 + cells prevailing over monocytes.[2] Ackerman and cols. described the lungs of deceased patients with COVID-19 or influenza with high infiltration of T lymphocytes.[3]

CD6 is a glycoprotein appearing on the surface of mature T cells, B-1 lymphocytes, and immature B cells. CD6 is very important for the immunological synapsis between the cells presenting the antigen and the activated T lymphocytes.[4] The interaction between CD6 and its main ligand, ALCAM (CD166), triggers cellular proliferation and the secretion of pro-inflammatory cytokines.[5]

Although the exact mechanisms causing the disproportionate response against SARS-CoV-2 are still partially unknown,[6] our hypothesis was that inhibiting the activation of T lymphocytes with a CD6-antagonist antibody could control the systemic inflammation and reduce the morbidity and mortality related to the disease.

Itolizumab is a humanized monoclonal antibody (McA) that recognizes the domain 1 of human CD6, obtained at the Center of Molecular Immunology. [7] This McA prevents the activation and proliferation of T cells. This inhibition leads to a considerable reduction of pro-inflammatory cytokines, which involve pathways Th17 and Th1, including interleukin (IL), 17A, TNF- α, IL6, interferon (IFN)- γ and IL-2.[8] It has been widely used in patients with rheumatoid arthritis and psoriasis, significantly reducing the serum levels of IL-6, TNF- α and IFN-γ. [9,10]

In a phase III clinical trial in patients with moderate-to-severe psoriasis carried out in India, McA itolizumab was efficient and well assimilated.[11]

Given the powerful immunomodulatory effect of itolizumab, an expanded access protocol was approved in Cuba. In this paper, we present the results concerning safety and clinical evolution of the first 68 moderate, severe and critical COVID-19 patients treated with itolizumab in 10 hospitals.

The main objective was to evaluate the impact of itolizumab on halting the decay of pulmonary function, measured as the ratio of patients not requiring an increase of the fraction of inspired oxygen (FiO_2) to keep the saturation and the proportion of patients in which the PaO_2/FiO_2 ratio improved, 3 days after the infusion of itolizumab. The secondary objectives were the following: rate of patients that needed mechanical ventilation, duration of ventilation, and the mortality rate 14 days after the administration of the antibody.

METHODS

It was an expanded access open trial in which SARS-CoV-2-positive Cuban patients, in the moderate, severe or critical stage of the disease, were given itolizumab combined with other therapies included in the COVID-19 national protocol. The diagnosis was confirmed by means of reverse transcription polymerase chain reaction (RT-PCR). Additionally, the patients received other therapies such as lopinavir / ritonavir, chloroquine and IFNα2b. The inclusion criteria were the following: age ≥ 18 years, multifocal interstitial pneumonia, need for oxygen therapy to keep the oxygen saturation (SaO_2) > 93% and aggravation of the pulmonary compromise. Alternatively, it was prescribed to patients with one of the following conditions: high-pitched wheezes or irregular talking, respiratory frequency above 22 inspirations/minute, (oxygen pressure) PaO_2<65 mm Hg, a persistent fever ≥ 38ºC, triglycerides > 3 mmol/L, increase in ferritin, amino-aspartate transferases (AST) ≥ 30 UI/L, increase in D dimer, fibrinogen < 2,5 g/L or the occurrence of neurological signs.

The protocol was approved by the Ethics Committee of the Institute of Tropical Medicine "Pedro Kourí" and by the Cuban Regulatory Agency. The entire research was carried out in compliance with the Helsinki Declaration. The informed consent of all fully aware patients was obtained before the treatment with itolizumab. A legal guardian granted the consent of patients with cognitive disorders. The protocol was registered in the National Registry of Clinical Trials (http://rpcec.sld.cu/trials/RPCEC00000311-En).

Critical patients were defined as those who require mechanical ventilation or those who have respiratory insufficiency (partial oxygen pressure/inspired fraction of oxygen, PaO_2/FiO_2< 200), septic shock or systemic dysfunction. Severe patients were those whose respiratory frequency > 30 inspirations/minute, SaO_2 ≤ 93%, PaO_2/FiO_2< 300 or pulmonary infiltrates > 50%. Moderate patients showed either clinical or imaging evidence of lower respiratory infection and SaO_2> 93%. Only moderate patients with high risk of aggravation of their condition were included in the trial. The aggravation risk factors were age ≥ 65 and the comorbidities linked to COVID-19 mortality: hypertension, cardiovascular disease, diabetes mellitus, chronic renal disease, cancer, chronic obstructive pulmonary disorder (COPD), obesity, and nutritional deficit.

In order to preliminarily evaluate the effect of itolizumab on survival, a control group was selected among the Cuban COVID-19 patients; they were treated with the rest of the pharmaceuticals included in the national protocol, but not immunomodulatory agents, according the national base of June 2020. Concerning severe and critical patients, the selection included all the patients taken care of in the Intensive Care Unit (ICU), without biological therapies (n=51). Concerning moderate patients, the selection included patients showing evidence of lower respiratory disease and at least one of the conditions considered to be of adverse prognosis regarding COVID-19 (n=78). The death odds ratio (OR) of the control patients was estimated compared with the patients treated with itolizumab. Besides, the risk of admission to the ICU was estimated for moderate patients with 2 comorbidities.

The adverse events were classified according to the Common Toxicity Criteria, version 5. The full blood count was carried out at the beginning of the study and daily afterwards, up to 168 h after the administration of itolizumab. Other biochemical parameters were evaluated, such as reactive protein C, triglycerides, fibrinogen, ferritin, AST and D dimer. In 30 patients, IL-6 was measured in serum before and 48 h after the administration of itolizumab. The concentration of IL-6 was measured by means of a *Quantikine* ELISA kit *(R&D Systems, Minneapolis*, USA). The treatment consisted of an intravenous infusion of 200 mg of itolizumab diluted in 200 ml of sodium chloride. The patients could receive a second dose of the antibody, if they still showed signs of respiratory difficulty. The duration of the infusion was of at least 2h. The research product was stored at 2ºC to 8ºC.

The demographic and clinical characteristics were analyzed according to the severity groups of the disease. The discriminative power of several biomarkers with respect to the severity and mortality of the disease was evaluated through the analysis of receiver operating curves (ROC). The mortality probability ratio for several independent variables was estimated. They included demographic data, comorbidities, and laboratory parameters. The analyses were conducted with software SPSS, version 25 and R.

RESULTS

Sixty-eight (68) patients confirmed with SARS-CoV-2 (30 men and 38 women), with a moderate, severe or critical condition, were included in the expanded access trial with itolizumab, in 10 Cuban hospitals from April 4 to May 13, 2020.

The severe and critical patients were treated with itolizumab in the Intensive Care Unit (ICU). Out of the 45 severe or critical patients, 25 received mechanical ventilation at the moment of the treatment. The moderate individuals with high risk were treated in the general ward of the hospital.

Table 1 shows the demographic data and the comorbidities of the population selected. In general, the age median was 68 years (29-100) and 94% of subjects had a comorbidity at least (Table 1). The most frequent concomitant conditions were hypertension (66.2 %), cardiovascular disease (33.8 %) and diabetes mellitus (32.4 %). Most moderate patients with high risk (82.6 %) were included in the study after a local transmission event in a nursing home. This elderly population was characterized by a high prevalence of dementia and nutritional deficit. Most patients were treated with lopinavir / ritonavir, chloroquine and IFNα2b before being included in the trial. Only 66 % of patients in the ICU were treated with anticoagulants and 55 % of critical patients kept receiving IFNα2b, despite the aggravation of the disease.

The lapse between the first symptoms and itolizumab was 10 days for critical patients, 7.5 days for the severe ones and 1 day for the moderate patients. All patients completed the first infusion of itolizumab, 41 (60.3 %) received 2 doses, while 3 patients (4.4 %) were given 3 doses of McA. After 72 h, 83.3 % of the severe patients and 63.6 % of critical patients did no need an increase in the fraction of oxygen inspired (FiO_2) to keep the oxygen saturation. Besides, the PaO_2/FiO_2 ratio of 83.3 % of severe patients and 55% of the critical ones improved significantly. Figure 1 shows the thorax X-rays of 2 representative patients showing swift X-ray recovery after the administration of the McA.

Only 8 patients in the 43 ones not ventilated at the moment of admission into the trial required additional mechanical ventilation. After the treatment with itolizumab, the ventilation duration median was 8 days for critical cases and 1 day for severe ones. Only 4 in the 23 moderate patients of high risk needed admission to the ICU after the administration of itolizumab. Three in these four individuals recovered successfully.

In total, 24 patients (1 moderate one, 3 severe ones and 20 critical ones) passed away. The lethality rate after 14 days was 4.3%, 18.7% and 69% for moderate, severe and critical individuals. The mortality risk of control patients with the same degree of severity, but who did not receive immunomodulatory pharmaceuticals, was compared with the series of patients treated with itolizumab. Both groups were homogenous in terms of demography and significant comorbidities, except nutritional deficit and obesity, which were more frequent in individuals treated with itolizumab. In the case of subjects moderately ill, treated patients were compared with control ones having at least 2 comorbidities considered to be factors of poor prognosis for COVID-19.

Moderately ill control patients not treated with itolizumab had a 3.2-fold higher risk of being admitted to the ICU (OR 3,2; 95% IC: 0,9; 11,4) and a 6.9-fold higher risk of death (OR 6,9; 95%IC: 0,8; 50) than those treated with itolizumab. The death risk of severe control patients was 3.85 times higher than those treated with itolizumab (OR 3,85; 95% IC: 1,02; 14,3). In the case of critical patients, the death risk was 1.8 times higher than control patients who did not receive itolizumab (OR 1,8; 95% CI: 0,4; 8,3). Because IFNα2b could have exacerbated the cytokine storm, a separate analysis was conducted of critical patients who halted this treatment when their condition was aggravated. Critical control patients had a 6.2-fold higher death risk than critical individuals treated with itolizumab: (OR 6,2; 95% IC: 0,9; 38,5).

In the case of 30 patients, their serum concentration of interleukin 6 (IL-6) was determined when admitted to the trial. The level of IL-6 was significantly higher in critical patients in comparison with severe or moderate patients. The average concentration of IL-6 was 478,5 pg/mL in critical patients, 31,6 pg/mL in severe ones and 19,1 pg/mL in moderate individuals facing a high risk of aggravation. A ROC curve was plotted to evaluate the predictive value of IL-6 on severity. In our set of data, the IL-6 concentration linked to severity was 27,4 pg/mL. An evaluation of IL-6 concentration was carried out before and 48 h after the administration of itolizumab in 23 patients with samples. Patients were grouped considering the borderline preestablished for the severity of the disease: the level in 13 patients was over 27,4 pg/mL while the level of IL-6 was lower in 10 patients. The median of patients above the borderline was 116,3pg/mL and 78,8 pg/mL, before and after the administration of itolizumab, respectively. The concentration of IL-6 in this "severely inflamed" subset decreased significantly (Wilcoxon P = 0,028) after treatment with the anti-CD6 McA. By contrast, the median of IL-6 concentration in subjects under the borderline was 13,8 pg/mL. The median of post-treatment IL-6 in the "low-inflammation" group was 15,9 pg/mL. The levels of IL-6 before and after the administration of itolizumab were not significantly different. We conclude that the levels of IL-6 decreased after the administration of itolizumab in patients with high concentrations, whereas they did not increase in patients with low initial levels. The antibody was well assimilated.

Table 1. Demographic characteristics and concomitant diseases according to the severity groups

Characteristics		Critical		Severe		Moderate		Total	
		No.	%	No.	%	No.	%	No.	%
		29	100	16	100	25	100	70	100
Sex	Female	11	37,9	12	75,0	16	64,0	39	55,7
	Male	18	62,1	4	25,0	9	36,0	31	44,3
Skin color	White	19	65,5	9	56,3	15	60,0	43	61,4
	Mixed	9	31,0	4	25,0	3	12,0	16	22,9
	Black	1	3,4	3	18,8	4	16,0	8	11,4
	NA					3	12,0	3	4,3
Age	Average ± SD	67,4 ± 14,0		66,9 ± 22,5		71,2 ± 17,7		68,7 ± 17,4	
	Median ± IQR	66,0 ± 26,0		81,5 ± 39,0		75,0 ± 23,0		68,0 ± 30,0	
	min; max	(44; 92)		(29; 90)		(28; 100)		(28; 100)	
Patients with 1 comorbidity		29	100,0	16	100,0	21	84,0	66	94,3
Hypertension		20	69,0	10	62,5	16	64,0	46	65,7
Dementia		5	17,2	8	50,0	11	44,0	24	34,3
Cardiovascular disease		11	37,9	4	25,0	8	32,0	23	32,9
Diabetes mellitus		12	41,4	4	25,0	6	24,0	22	31,4
Bronchial asthma		8	27,6	4	25,0	2	8,0	14	20,0
Malnutrition		1	3,4	1	6,3	10	40,0	12	17,1
Kidney failure		6	20,7	3	18,8	0	0,0	9	12,9
COPD		4	13,8	--	--	5	20,0	9	12,9
Obesity		4	13,8	2	12,5	1	4,0	7	10,0
Smoking		1	3,4	3	18,8	2	8,0	6	8,6
Thyroid failure		3	10,3	1	6,3	--	--	4	5,7
Cancer		4	13,8	--	--	--	--	4	5,7

Globally, 22 in 68 patients (31.4%) underwent adverse events (related or not), while only 10 patients (14.3%) underwent adverse related events. Twenty-six (26) adverse events in 84 (31%) were classified as possibly or probably related to itolizumab. The most frequent adverse related events, either mild or moderate, consisted of chills, hypotension, fever, tachycardia and hypoxia. Three patients (4.3%) underwent severe adverse related events. The severe events consisted of hyperreactivity of the respiratory tract, fever, hypotension, anthema, chills, hypoxia, shock and cyanosis, and were classified as possibly related to itolizumab. Hypoxia and shock caused the death of one patient, whereas the rest of the events were controlled after reducing the infusion speed or with antihistamines. The 3 patients with severe events were being ventilated and receiving lopinavir/ritonavir, chloroquine and IFNα2b.

The count of neutrophils, lymphocytes and platelets was evaluated before the administration of itolizumab and daily afterwards over a week. At the moment of inclusion, the count of neutrophils was correlated with the severity: moderate patients (3,7 x 10^9/L), severe ones (5,4 x 10^9/L) and critical ones (10,8 x 10^9/L). The counts of neutrophils did not increase significantly over the next 7 days. At the moment of admission into the trial, the rate of patients with grade I lymphopenia was 13% in moderate and severe patients, while it was 43% in critical patients. A week after the administration of itolizumab, the proportion of subjects with grade II lymphopenia was 0.11% and 20% in moderate, severe and critical individuals. The count of platelets was within the normal range in all patients. The ROC analysis was used to define borderlines predicting the severity and mortality of several laboratory biomarkers. Table 2 shows the predictive value of triglycerides, AST, D dimer, IL-6, absolute leucocyte count (ALC), neutrophils, neutrophils to lymphocytes ratio (NLR) and platelets to lymphocytes ratio (PLR) in cases of COVID-19 severity or mortality.

Besides, the death probability ratio was estimated for several independent variables, including the demographic characteristics, important comorbidities and the laboratory parameters (Table 3). In the univariate logistic regression analysis, the interval between the symptoms and the administration of itolizumab, the beginning of the neurological manifestations, AST, D dimer, neutrophil count, NLR, PLR and IL-6 were significantly associated with a higher death probability. The only

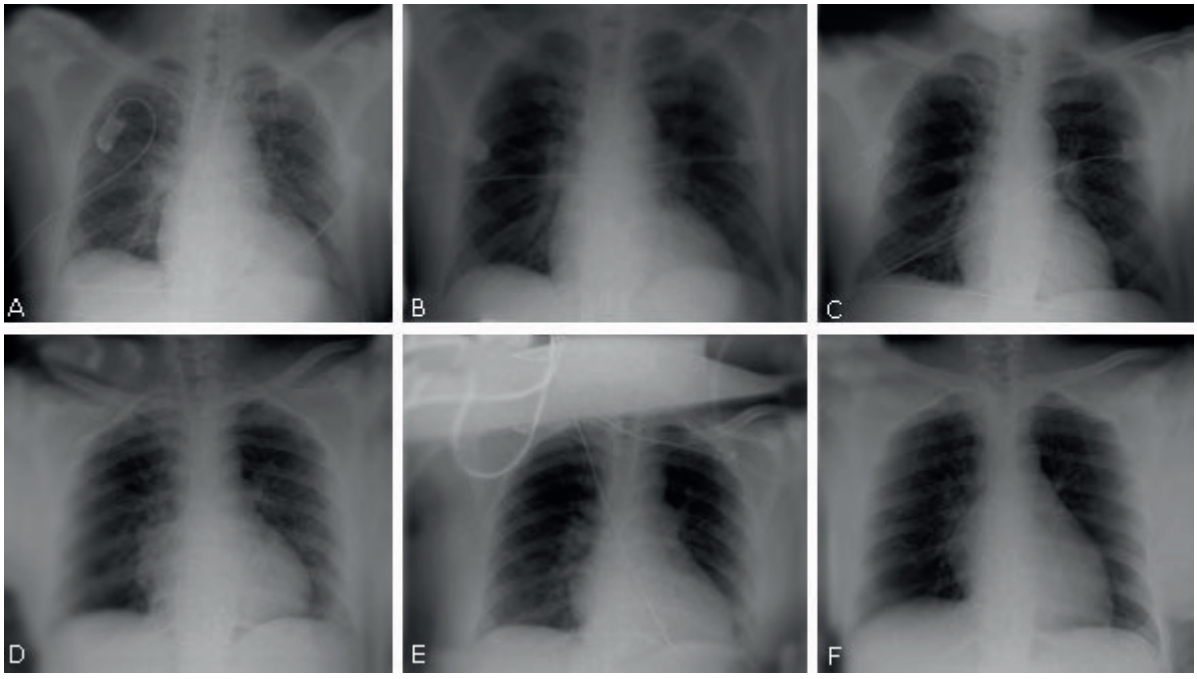

Fig.1. The serial thorax X-rays show a significant recovery of two patients with COVID-19 after a treatment with itolizumab.

Table 2. Predictive values of COVID-19 severity or mortality according to ROC curves of triglycerides, *amino-aspartate transferases* (AST), D dimer, interleukin 6 (IL-6), absolute leucocyte count (ALC), neutrophils, neutrophils to lymphocytes ratio (NLR) and platelets to lymphocytes ratio (PLR).

	Severity						
	Area	**Sig.**	**95% CI**		**Sensitivity**	**Specificity**	**Borderline**
Triglycerides	0,756	0,003	0,617	0,896	78,6 %	65,0 %	1,24 mmol/L
AST	0,858	0,000	0,749	0,966	82,8 %	85,0 %	20,5 IU/L
D Dimer	0,783	0,009	0.603	0,964	80,0 %	78,6 %	1,35 µg/ml
IL6	0,828	0,002	0,683	0,973	71,4 %	73,9 %	27,4 pg/mL
ALC	0,838	0,000	0,740	0,936	82,9 %	70,8 %	6,55 x10^9/L
Neutrophils	0,840	0,000	0,735	0,945	94,7 %	70,8 %	4,34 x10^9/L
NLR	0,799	0,000	0,685	0,913	70,6 %	82,6 %	4,91
PLR	0,673	0,029	0,524	0,823	75,8 %	69,6 %	135,0
	Mortality						
	Area	**Sig.**	**95% CI**		**Sensitivity**	**Especificity**	**Borderline**
AST	0,802	0,000	0,667	0,937	83,3 %	71,0 %	22,1 IU/L
D Dimer	0,742	0,035	0,515	0,969	80,0 %	63,2 %	1,35 µg/mL
IL6	0,770	0,033	0,527	1,000	71,4 %	73,9 %	53,4 pg/mL
ALC	0,727	0,003	0,592	0,863	72,7 %	65,1%	7,60 x 10^9/L
Neutrophils	0,765	0,001	0,636	0,895	81,0 %	65,9 %	5,57 x 10^9/L
NLR	0,894	0,000	0,804	0,984	82,4 %	85,0 %	8,85
PLR	0,711	0,014	0,556	0,866	81,3 %	60,0 %	146,2

comorbidity linked to a significantly higher death probability was the chronic renal disease. The biomarker associated with the highest death risk was NLR.

DISCUSSION

The cytokine release syndromes include a group of disorders with various etiologies resulting in an acute inflammation, multiple-organ dysfunction or even death. [12]

The role of T cells activated in the COVID-19 pathogeny is not fully understood. After the activation, T lymphocytes secrete cytokines such as IL-6, IFNγ, IL-21, and IL-17, which stimulate the innate and adaptive immune response against the virus. [13]

CD6 is a key regulator of the T cell activation. [14] Itolizumab is a non-depleting antibody that recognizes CD6. [8] The clinical data indicate that the antibody acts directly on T cells and reduces multiple cytokines and transduction factors that mostly involve Th1 and Th17 pathways. [8] Our working hypothesis was that the use of an anti-CD6 antibody could reduce the concentration of several pro-inflammatory cytokines, which is an advantage compared with antibodies blocking only one cytokine. The administration of itolizumab can also favor a regulator phenotype instead of an effector one.

Itolizumab was administered to 68 COVID-19 patients, combined with other pharmaceuticals included in the Cuban protocol. Our series had a very unfavorable prognosis: 37% of them were over 80 years old and all of them, except four, suffered from conditions contributing to a poor prognosis. Comorbidities and age exacerbate the manifestations of the disease, which increases susceptibility to endothelial damage and deregulation of the metabolic syndrome. [17] Itolizumab was well assimilated and severe related events took place in only 4.2% of patients. Important changes in the lymphocyte counts were not observed beyond the natural course of the disease. [18] The most common adverse events were similar to those previously found in autoimmune diseases. [8, 11]

IL-6 is the main cytokine responsible for COVID-19 hyper-inflammatory syndrome. [1, 19] McA itolizumab reduced this cytokine in individuals with very high concentrations and it prevented the increase of IL-6 in moderate patients facing a high inflammation risk. It is documented that the ablation of IL-6 can reduce the B cell response and delay the antiviral response.[16] In our series, the viral load was negative in all patients clinically recovered, which suggests that itolizumab did not inhibit the adaptive immune response.

The antibody improved the pulmonary function of both severe and critical patients. Although this was not a controlled and randomized study, the preliminary data suggest that itolizumab reduced the probability of death in comparison with controls that did not receive it. The administration of itolizumab to elderly patients with 2 or more comorbidities also prevented their admission to the ICU. [17] In critical individuals, the impact of itolizumab was bigger than that on subjects who stopped receiving IFNα2b at the moment of aggravation. The administration of type I IFN after the tenth day of the symptoms could have further activated the innate immune system, [20, 21] thus countering the anti-inflammatory effect of the antibody. Our series corresponds to the beginning of the epidemic in Cuba. Consequently, only two thirds of the critical patients received anticoagulation. In addition, many critical patients were included after undergoing invasive mechanical ventilation over 72 h. We conclude that it is best to use itolizumab

Table 3. Univariate analysis of death risk for demographic, clinical, and laboratory variables.

		Odds ratio	IC 95 %	
General information	Age (> 65)	1,520	0,539	4,289
	TimeSintT1 (>7)	6,429	2,096	19,718
	Neurological manifestations	6,154	1,345	28,154
Comorbidities	HT	0,587	0,208	1,658
	DM	1,905	0,668	5,433
	Cardiopathy	1,703	0,603	4,811
	COPD	0,905	0,205	3,994
	Cancer	1,909	0,252	14,488
	Chronic renal disease	3,333	0,837	13,277
	Asthma	1,500	0,452	4,981
	Obesity	1,429	0,292	6,987
	Malnutrition	0,309	0,062	1,547
Other treatments	IFN	1,278	0,468	3,489
	EPO	0,702	0,214	2,301
	Steroides	1,905	0,668	5,433
	Fraxiheparine	0,514	0,168	1,578
	Chloroquine	0,333	0,052	2,150
	Vitamines	0,789	0,285	2,188
Initial laboratory values	Triglycerides (>1.35)	1,467	0,444	4,846
	ASAT (>22.1)	11,667	2,696	50,490
	ASAT (>46)	17,500	3,167	96,705
	D Dimer(>1.35)	6,857	1,124	41,827
		5,744	1,826	18,065
	Neutrophils (>5.57)	9,563	2,648	34,532
	NLR (>8.22)	30,800	6,460	146,853
	PLR (>171.6)	3,771	1,085	13,108
	IL-6 (>53.4)	4,504	0,412	50,000

before patients reach a critical condition or at the beginning of it. In this stage of the disease, the consequences of hyper-inflammation, including micro-vascular or macro-vascular thrombosis, the hyaline membrane, and alveolar lesion, can be irreparable. [6] The systemic inflammation could have affected the glomeruli, the heart or liver also irreversibly. [22]

Since opportune immunomodulation is crucial, it is necessary to identify the patients whose risk of reaching a severe stage of the disease is higher. In our study, the biomarkers associated with a higher death probability were the NLR ratio, the amino-aspartate transferases, the count of neutrophils and IL-6. NLR, a well-known systemic inflammatory marker, [23] was associated with the highest lethality.

In order to control the cytokine storm linked to COVID-19, other anti-inflammatory pharmaceuticals have been evaluated. In a big meta-analysis of 7 randomized trials in critical patients, the mortality after 28 days was lower in the case of patients who received corticosteroids compared with those who were tended to with the support treatment or a placebo. [24] The absolute risk of death was 32% with corticosteroids vs. 40% with a placebo or support therapy. Dexamethasone reduced mortality after 28 days in patients with invasive mechanical ventilation or oxygen therapy. [25] However, mortality did not decrease in patients without supplementary oxygen. [26] The strongest effect was observed in ventilated patients. Unlike dexamethasone, the effect of itolizumab was more significant on moderate and severe patients.

On the other hand, the McA tocilizumab, which recognizes the IL-6 receptor, did not reduce the mortality of severe COVID-19 patients during the Phase III registry trial. The results have not been published yet. [27]

Summing up, the antibody itolizumab was well assimilated; it reduced the levels of IL-6 significantly or prevented the excessive secretion of pro-inflammatory cytokines. Most patients' ventilation function improved and they were discharged from the ICU quickly. A randomized trial with 30 moderate and severe COVID-19 patients came to an end in India recently. [15] According to the initial data, all patients in the itolizumab group recovered, while only 70% of the controls did. [28]

Conclusions

The opportune administration of itolizumab guided by biomarkers can interrupt the hyper-inflammatory cascade and prevent the morbidity and mortality related to the cytokine release syndrome.

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Conflict of interests

Nine authors work at the Center of Molecular Immunology, the center that created and patented the monoclonal antibody itolizumab. The rest of the authors do not maintain any commercial or financial relationships whatsoever that could be a potential conflict of interests.

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