Itolizumab in covid-19

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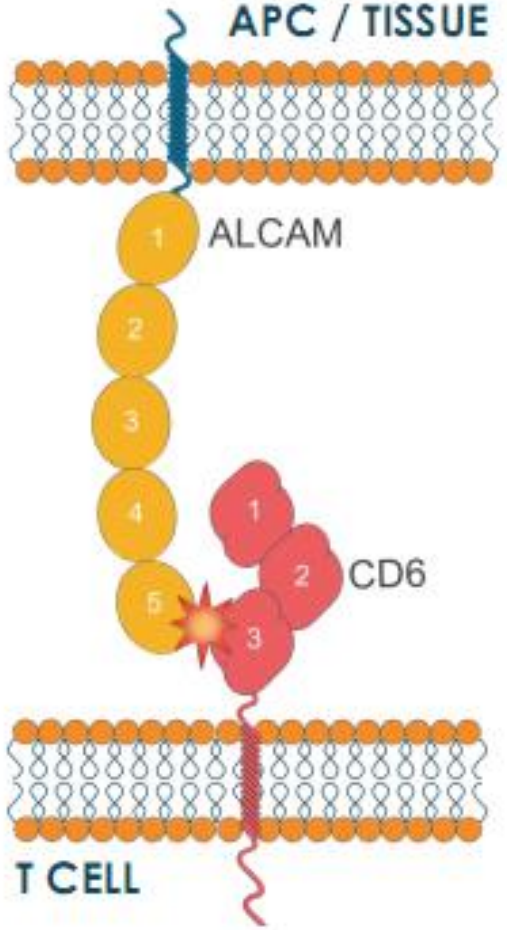
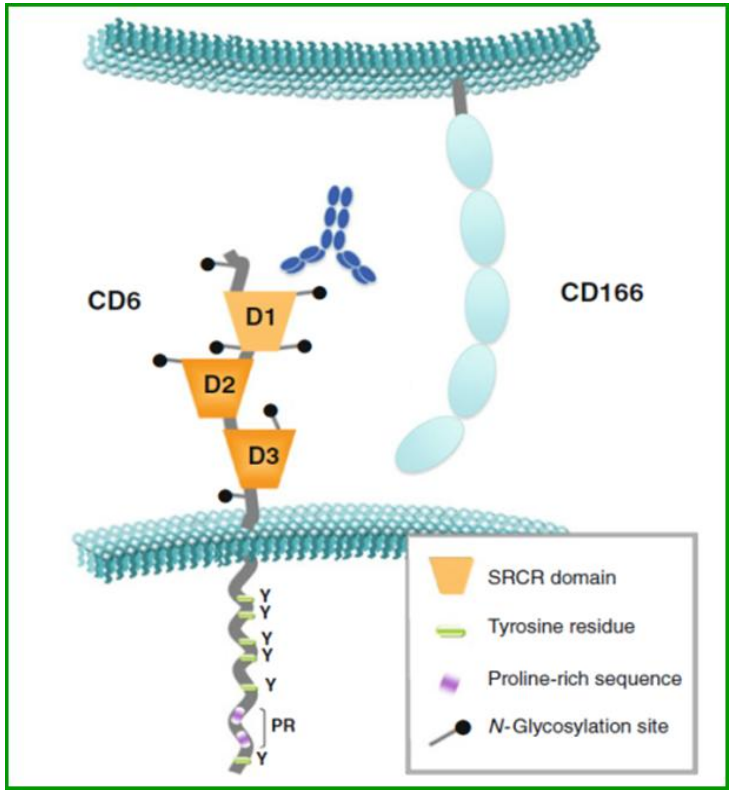
Itolizumab

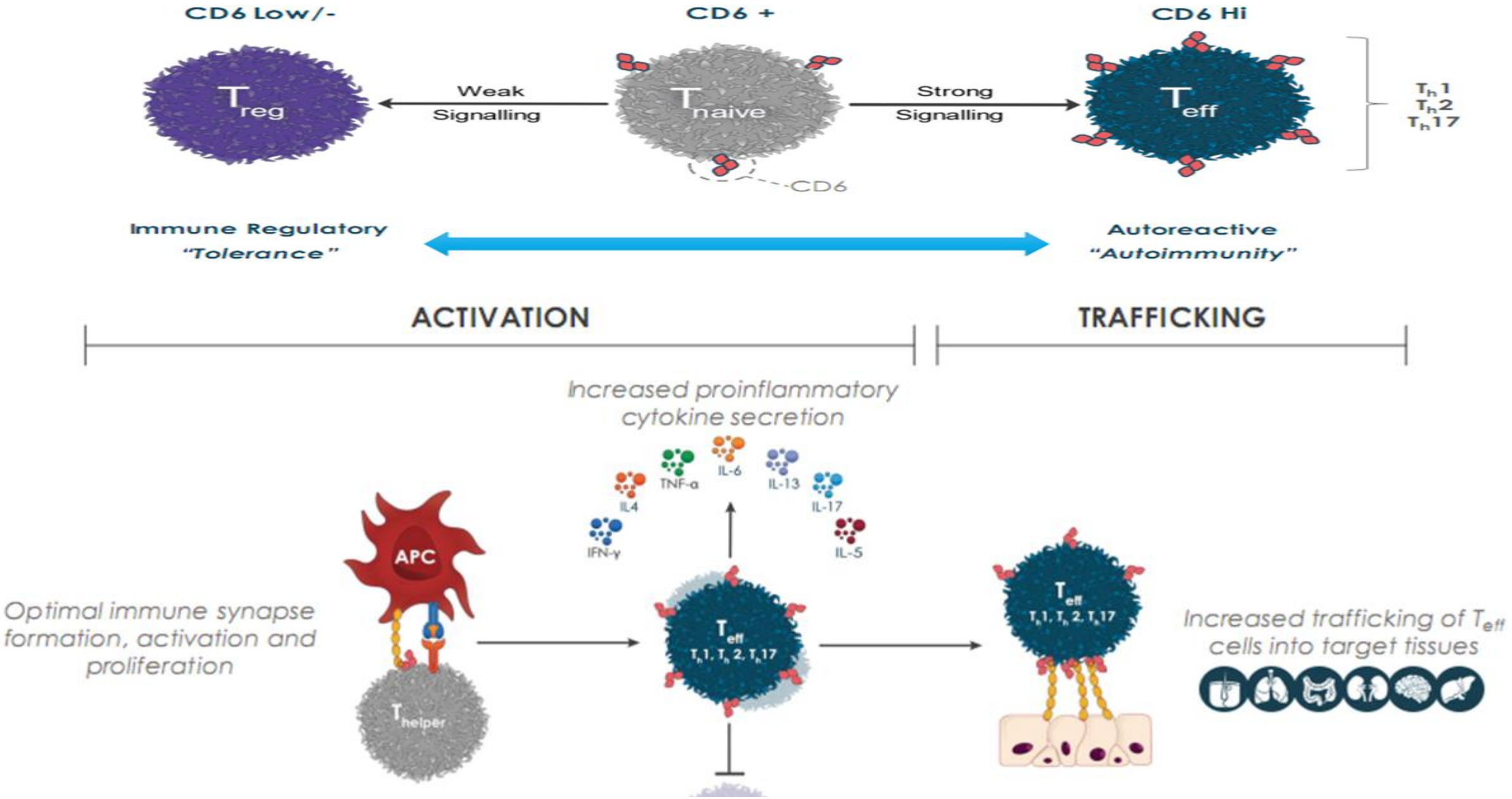


- **CD6 is a glycoprotein expressed on mature T-lymphocytes**
- **Crucial regulator of the T-cell activation**
- **ALCAM: main ligand in immunologic synapsis.**
- **Triple role: adhesion, activation and inflammatory cytokine secretion**



- humanized IgG1 mAb
- binds to the membrane-distal extracellular domain of human and chimpanzee CD6 (domain 1) [Alonso et al 2008, Garner et al, 2018]
- High affinity (KD= 7.8 X 10^{-9} M) [Garner et al, 2018]
- interferes CD6-Ligand (CD166) binding on cells surface [Garner et al, 2018]
- poorly immunogenic in human
- does not induce cell death (non depleting)

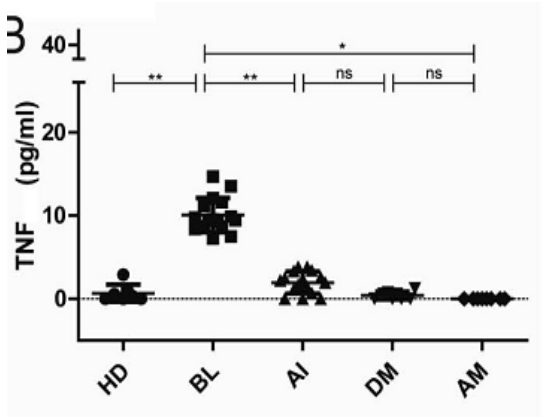
CD6-ALCAM: Rol Central en la Inflamación



Itolizumab


PASI: 22 → PASI: 6


PASI: 10.9 → PASI: 6.3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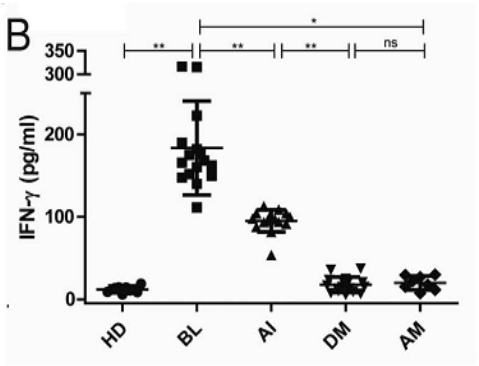
B
IFN-γ (pg/ml)
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300
200
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HD
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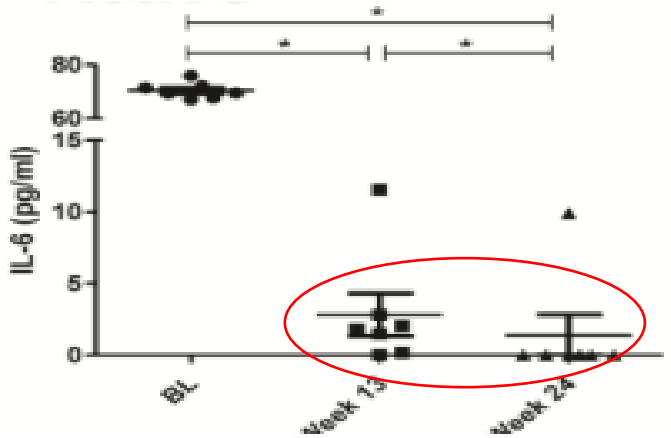

IL-6 (pg/ml)
80
60
15
10
5
0
*
*
*
BL
Week 15
Week 24

Trial Design and inclusion criteria

Open-label, expanded-access trial in which moderate, severe or critical SARS-CoV-2 patients received itolizumab in combination with other therapies included in the national protocol for COVID-19.

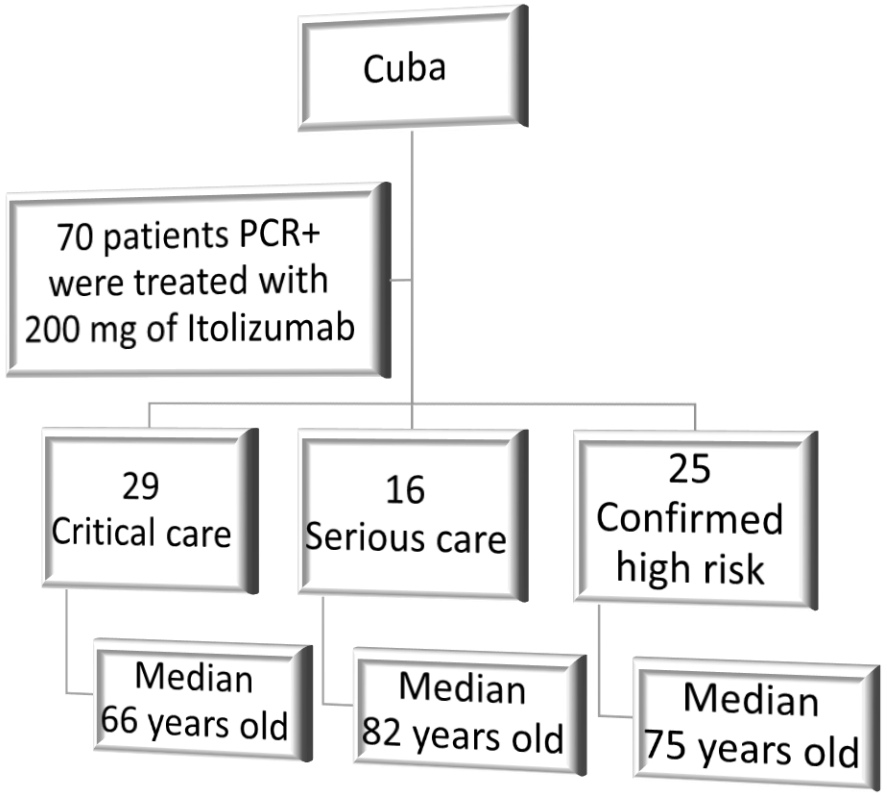
Inclusion criteria

- **age ≥18 years**
- **confirmed multifocal interstitial pneumonia**
- **need for oxygen therapy to maintain saturation (SaO_2)>93%**
- **worsening of lung involvement.**

Other inclusion criteria

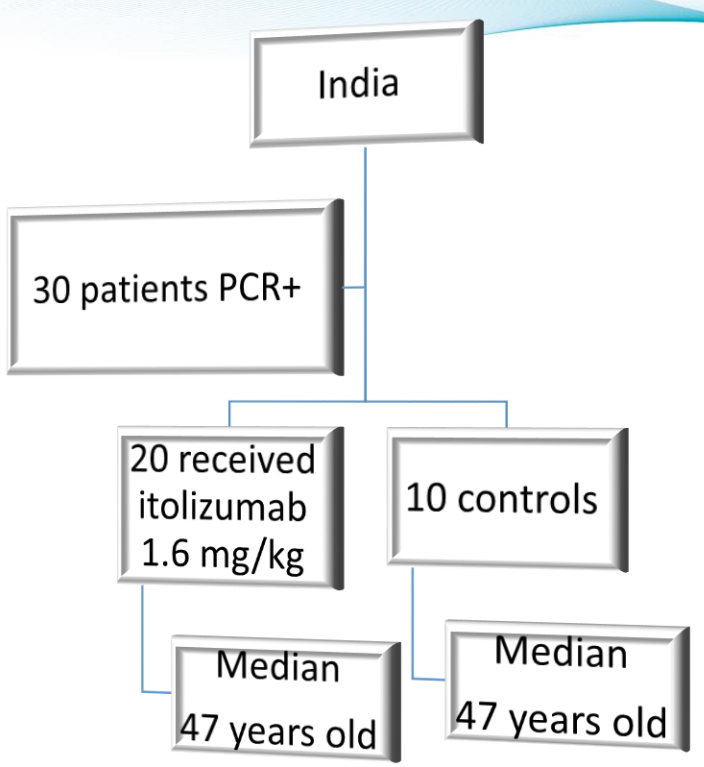
- **wheezing or irregular speech**
- **respiratory frequency greater than 22 breaths/minute**
- **PaO2<65 mm Hg**
- **persistent fever ≥38^{o}C,**
- **decrease of baseline hemoglobin, platelets or leukocytes,**
- **increase in ferritin values or D-Dimer**
- **onset of neurological manifestations**

Patients and Treatment



40 pacientes recibieron 2 dosis
3 pacientes recibieron 3 dosis

2nd and 3rd doses were 200 mg



Moderate
Severe

Itolizumab	Patients (N=20)
At least 1 dose	20
At least 2 doses	14
At least 3 doses	07
At least 4 doses	03

2nd , 3rd and 4th doses were 0.8 mg/kg

Main comorbidities

	Critical		Severe		Moderate		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%
	29	100	16	100	25	100	70	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 diseases	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
Nutrition deficit	1	3.4	1	6.3	10	40.0	12	17.1
CKD	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
Smoker	1	3.4	3	18.8	2	8.0	6	8.6
Hypothyroidism	3	10.3	1	6.3	--	--	4	5.7
Cancer	4	13.8	--	--	--	--	4	5.7

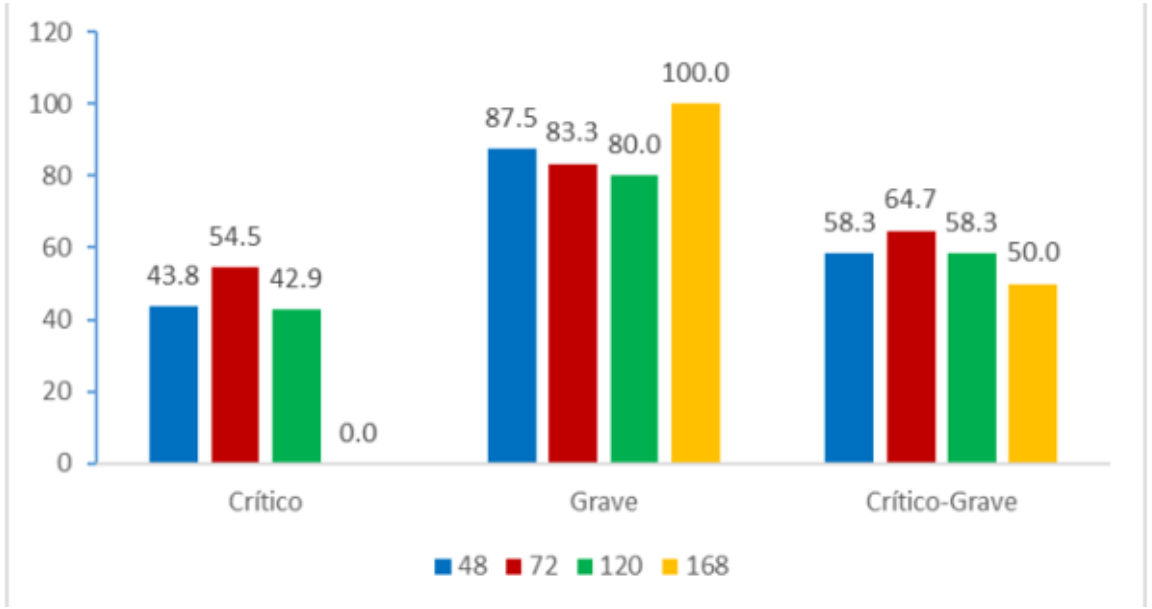
Other concomitant therapies

	Critical ill		Severe ill		Moderate ill		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Lopinavir/ritonavir	29	100.0	16	100.0	23	100.0	68	100.0
Chloroquine	26	89.7	15	93.8	22	95.7	63	92.6
Antibiotics	29	100.0	16	100.0	7	30.4	52	76.5
Fraxiheparin	19	65.5	11	68.8	21	91.3	51	75.0
Interferon α2B	16	55.2	7	43.8	14	60.9	37	54.4

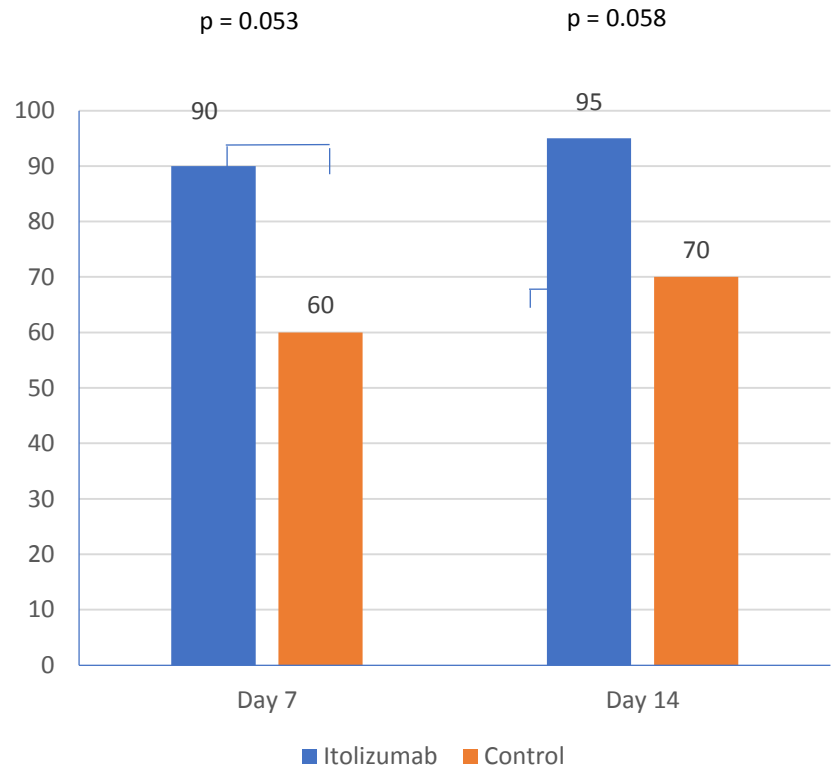
Results

Improvement of ventilatory function

Rate of patients with improvement in PiO2 / FiO2 ratio

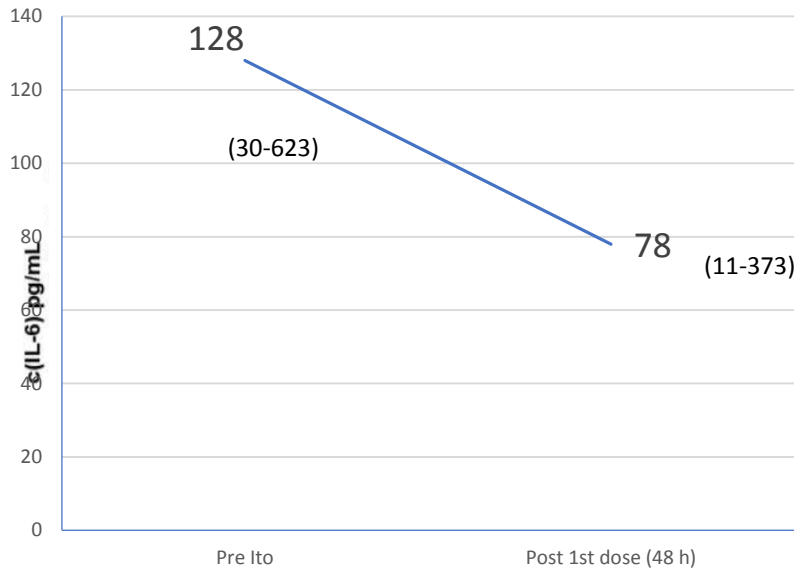


Critical Serious Critical/Serious

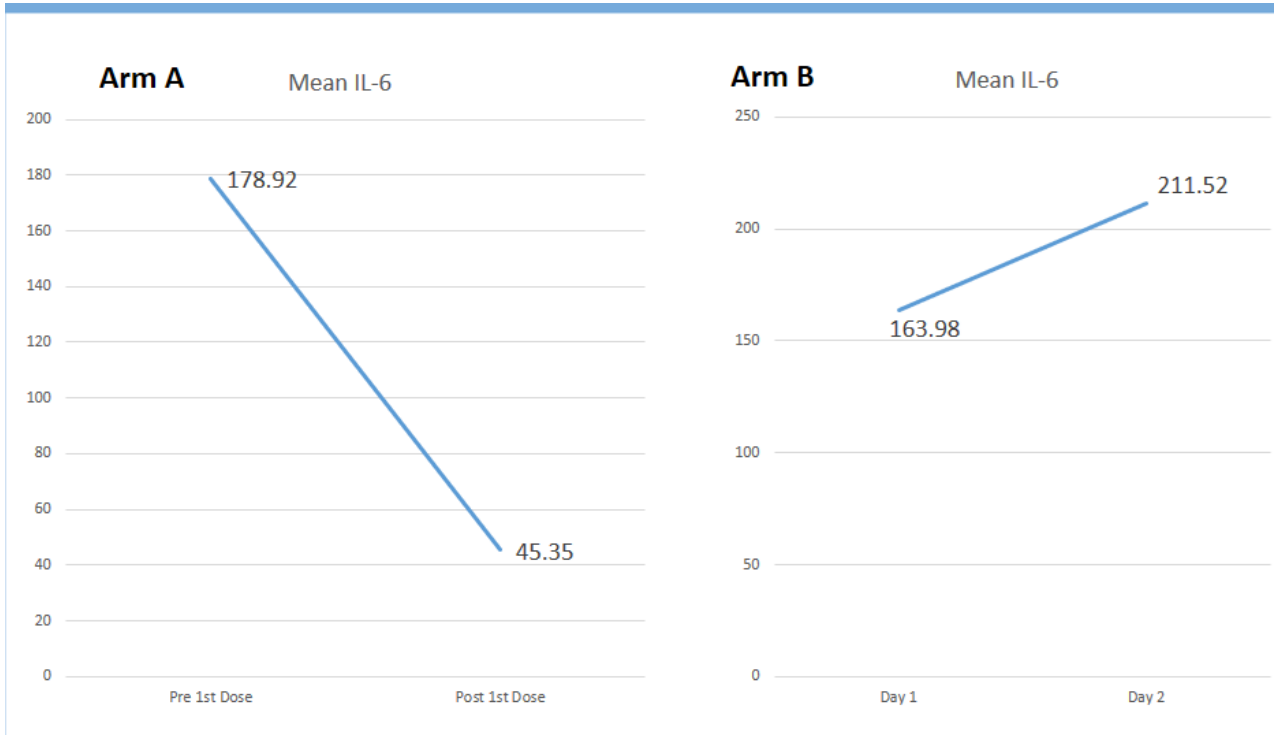


Significant reduction in serum IL-6 concentrations

Cuba



India

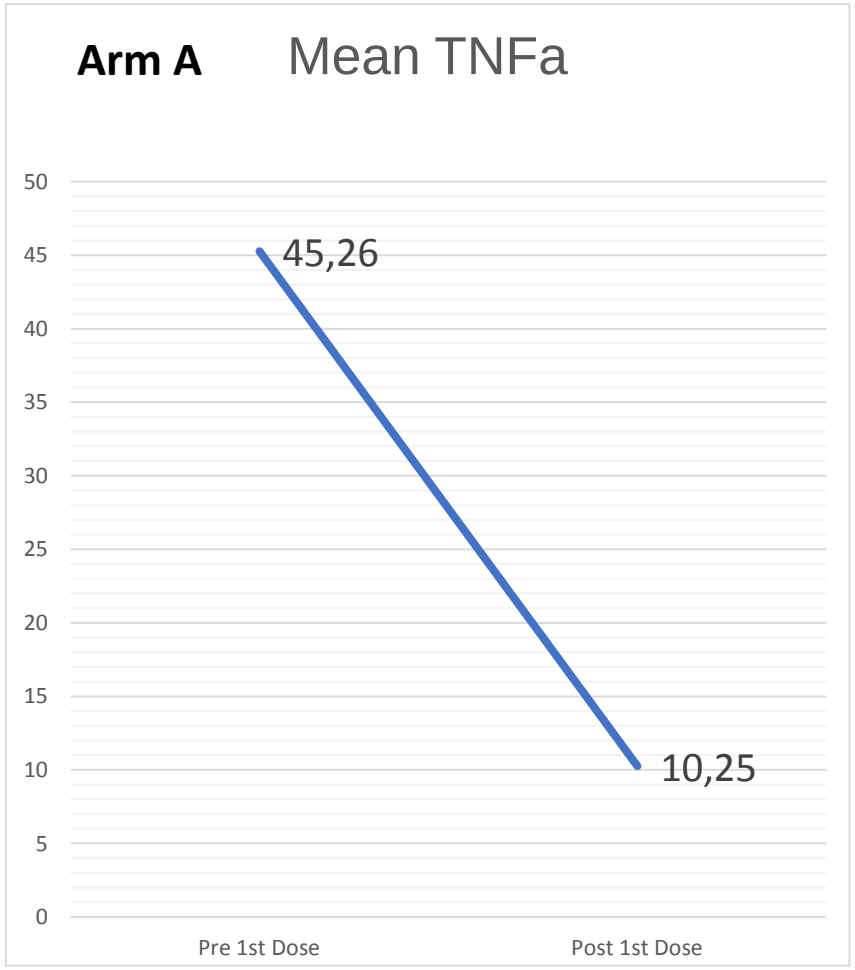


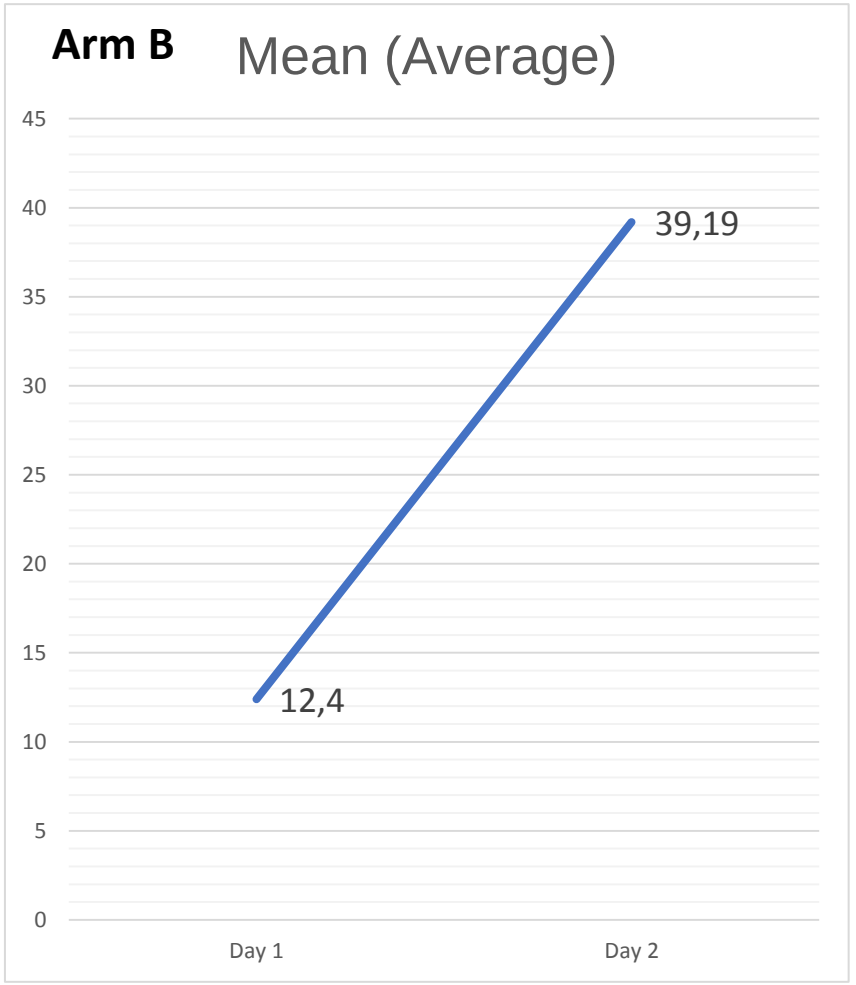
Itolizumab reduces serum IL-6 concentrations in critically and severe ill patients (81.25%) and stabilizes their levels in confirmed high risk patients

IL6 concentrations were significantly reduced in treated patients. In the controls, an increase in the concentration of IL6 was found

TNF-α Levels (pg/mL)

Key marker of Inflammation





Subsequent dose showed similar trends

Greater than 4 fold decline in mean TNF-α levels post infusion seen in Arm A compared to > 3 fold increase in Arm B

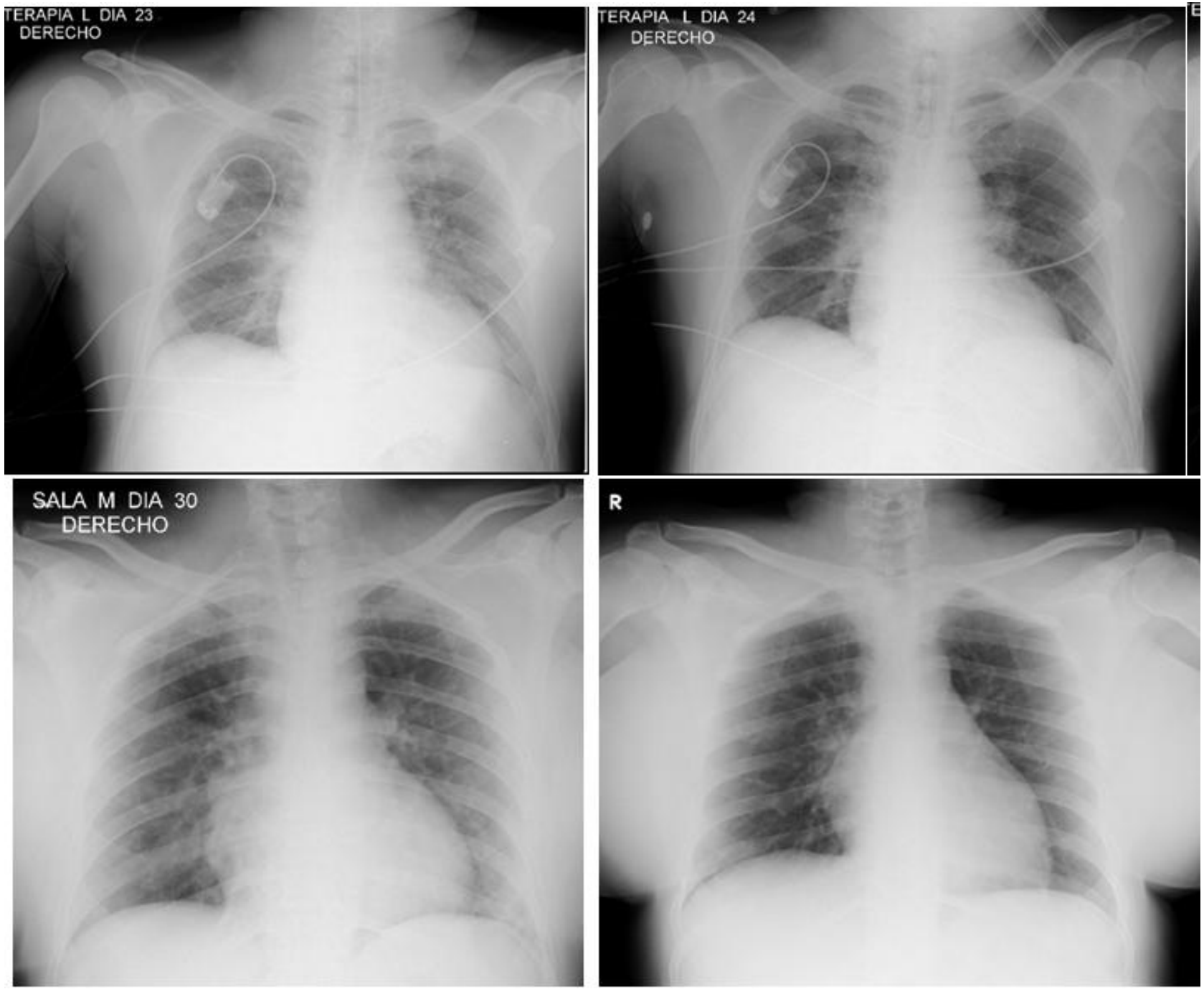
Survival and security data

Survival assessment (14-day survival rate)

- Cuban Severe and moderate patients: 90%
- Indian patients: 100% (Itolizumab) vs 70% (Control)

Safety data

- Cuba: Only 3 patients (4.41%) developed related serious events
- India: Only 1 patient (4.5%) had a serious adverse event related to Itolizumab administration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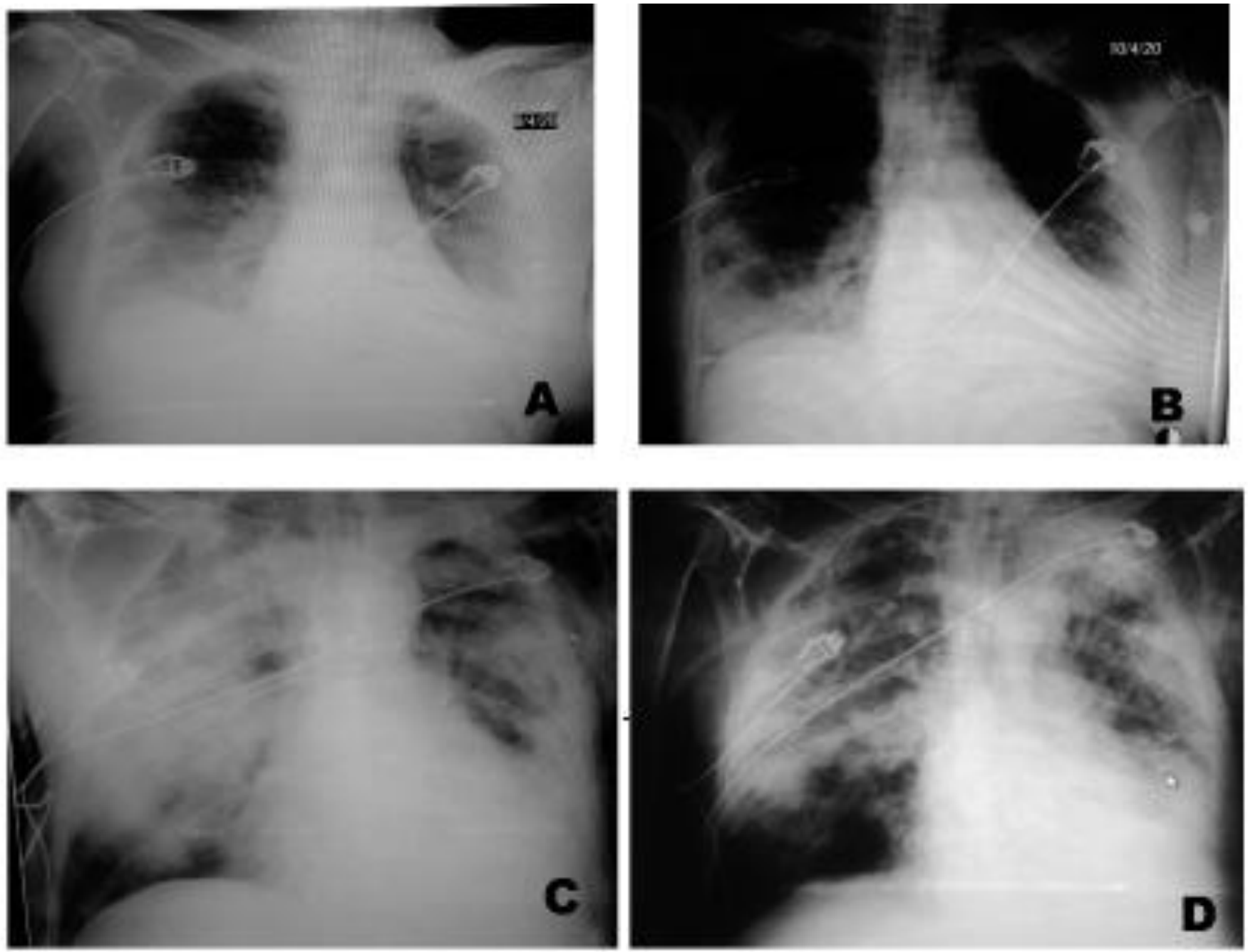

A
B
C
D

Treatment of COVID-19 patients with the anti-CD6 antibody itolizumab

Table 3. Predictive values of triglycerides, aspartate aminotransferase (AST), D-dimer, interleukin 6 (IL-6), absolute leucocyte count (ALC), neutrophils, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) associated with COVID-19 severity or mortality according to ROC analysis

	Area	Sig.	95% CI		Sensitivity	Specificity	Cut-off
Severity							
Triglycerides	0.756	0.003	0.617	0.896	78.6%	65%	1.24 mmol L^{-1}
AST	0.858	0.000	0.749	0.966	82.8%	85%	20.5 IU L^{-1}
D-Dimer	0.783	0.009	0.603	0.964	80%	78.6%	1.35 µg mL^{-1}
IL-6	0.828	0.002	0.683	0.973	71.4%	73.9%	27.4 pg mL^{-1}
ALC	0.838	0.000	0.740	0.936	82.9%	70.8%	6.55 × 10^9 L^{-1}
Neutrophils	0.840	0.000	0.735	0.945	94.7%	70.8%	4.34 × 10^9 L^{-1}
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							
AST	0.802	0.000	0.667	0.937	83.3%	71%	22.1 IU L^{-1}
D-Dimer	0.742	0.035	0.515	0.969	80%	63.2%	1.35 µg mL^{-1}
IL-6	0.770	0.033	0.527	1.000	71.4%	73.9%	53.4 pg mL^{-1}
ALC	0.727	0.003	0.592	0.863	72.7%	65.1%	7.60 × 10^9 L^{-1}
Neutrophils	0.765	0.001	0.636	0.895	81.0%	65.9%	5.57 × 10^9 L^{-1}
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%	146.2

Treatment of COVID-19 patients with the anti-CD6 antibody itolizumab

Table 4. Univariate logistic regression analysis

		Death Odds ratio	IC 95%	
Generals	Age (> 65)	1.680	0.601	4.697
	Time between symptoms and itolizumab (>7)	5.625	1.862	16.989
	Neurological symptoms	4.778	1.076	21.224
Comorbidities	Hypertension	0.613	0.220	1.709
	Diabetes mellitus	2.024	0.712	5.753
	Cardiovascular disease	1.813	0.644	5.102
	COPD	0.952	0.216	4.197
	Cancer	2.000	0.264	15.163
	Chronic renal disease	4.778	1.076	21.224
	Asthma	1.583	0.478	5.246
	Obesity	1.500	0.307	7.326
	Nutrition deficit	0.327	0.066	1.634
Baseline laboratory biomarkers	AST (> 22.1 IU L^{-1})	10.500	2.462	44.78
	D-dimer (> 1.35 μg mL^{-1})	6.857	1.124	41.827
	ALC (> 7.60 × 10^9 L^{-1})	4.978	1.610	15.387
	Neutrophils (> 5.57 × 10^9 L^{-1})	8.196	2.311	29.073
	NLR (> 8.85)	26.444	5.788	120.819
	PLR (> 146.2)	6.500	1.594	26.511
	IL-6 (> 53.4 pg mL^{-1})	7.083	1.075	46.478

The highlighted variables are significantly associated with higher odds of death.

Conclusions

- Itolizumab was safe .
- Itolizumab improved ventilatory function.
- Itolizumab decreased pro-inflammatoty cytokine levels
- Rapid radiological improvement in some patients
- Itolizumab decreased the lethality rate.

Real World Evidence (RWE): Update

RWE Data on hospitalised patients who received Alzumab-L

- Total number of patients treated - 375
- Number of patients recovered/discharged – 349 (93.1%)
- Mortality (number of patients) – 18 (4.8%)
- Estimated recovery rate in published studies for COVID-19 in comparable patient population ~70-80% [1,2]

Data collected as of December 10th 2020

Preliminary RWE data also supports a potential improvement in recovery rate/mortality, with the use of Itolizumab for CRS in ARDS patients due to COVID-19

1. N Engl J Med 2021; 384:20-30 DOI: 10.1056/NEJMoa203034 2. Intensive Care Med (2020) 46:2200–2211 https://doi.org/10.1007/s00134-020-06192-2

Post-authorization use in Cuba

Global recovery rate: 93 %
Recovery rate in severe patients: 85 %
Recovery rate in moderate patients: 97 %

Estudio en sepsis

ATIS Study for the treatment of Sepsis patients

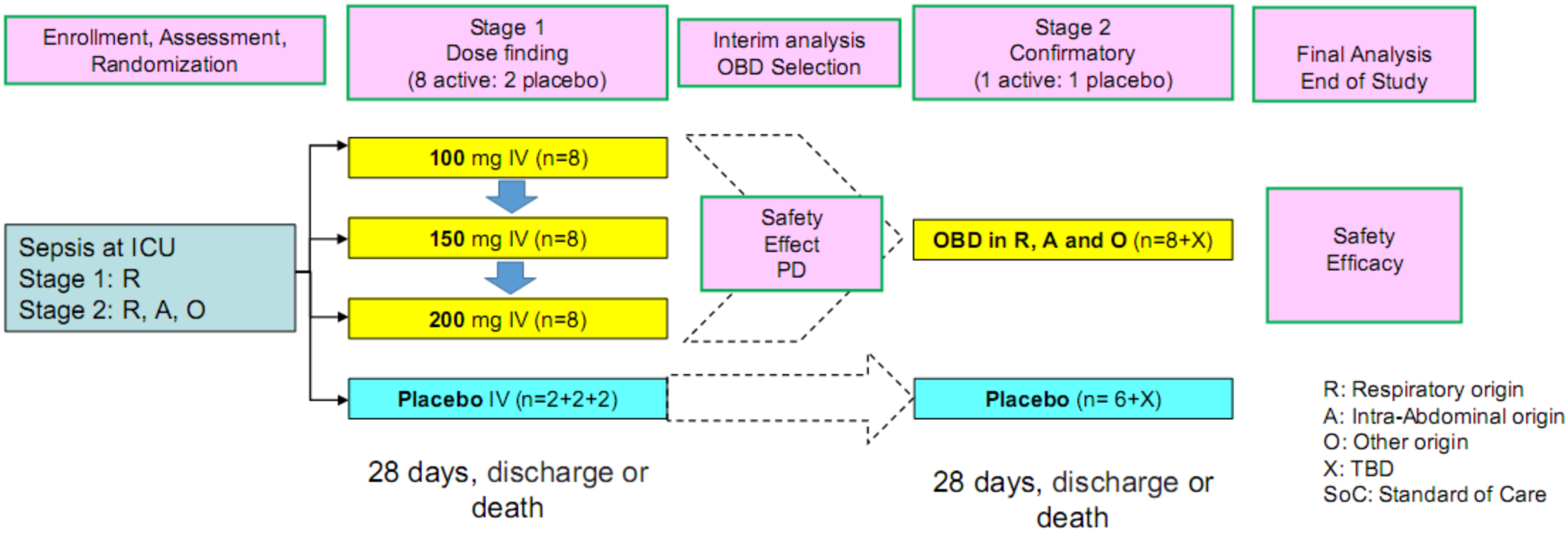
Design: prospective, randomized, double-blind, placebo controlled, 2-stage, Bayesian adaptive Phase I-II study

Stage 1: Phase 1, monocenter, dose-finding, N=30 (sepsis of respiratory origin)

Stage 2: Phase 2, multicenter, N=TBD b/w 80-123 by group (sepsis of any origin)

Treatment: One IV fixed dose (Day 1) and half dose (Day 8, if needed), itolizumab or placebo in addition to SoC per local practice

When N=94 (47 by pb group), a **sample size re-estimation** is planned to adjust the expected mortality (30%-50%)



Objectives

Primary Objectives

- ✓ Assess the safety and efficacy of IV itolizumab in subjects with sepsis

Secondary /Exploratory Objectives (outcomes)

- ✓ Assess the clinical activity of itolizumab on inflammatory biomarkers
- ✓ Assess the clinical efficacy of itolizumab on sepsis improvement:
  - ► Change in SOFA score, time to decrease of SOFA score by 25%, index of organs function and support measurement, progression to septic shock
- ✓ Determine IV fixed optimal biological dose (OBD) of itolizumab in sepsis (**Stage 1**):
  - ► treatment-related-SAE, change of IL-6 blood levels, ΔSOFA>25%
- ✓ Characterize the pharmacodynamics (PD) of itolizumab (**Stage 1**):
  - ► cytokines and CD6 receptor occupancy
- ✓ Assess the clinical efficacy of itolizumab on mortality by sepsis (**Stage 2**):
  - ► 28-day and global mortality rate

Immunity & Ageing

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Saavedra et al. Immunity & Ageing (2020) 17:34
https://doi.org/10.1186/s12979-020-00207-8

Immunity & Ageing

RESEARCH Open Access

An anti-CD6 monoclonal antibody (itolizumab) reduces circulating IL-6 in severe COVID-19 elderly patients

Danay Saavedra[1*], Ana Laura Añé-Kouri[2], Naivy Sánchez[3], Lázaro Manuel Filgueira[4], Julio Betancourt[4], Carlos Herrera[4], Leniel Manso[4], Elibet Chávez[5], Armando Caballero[4], Carlos Hidalgo[3], Geydi Lorenzo[1], Meylan Cepeda[1], Carmen Valenzuela[1], Mayra Ramos[1], Kalet León[1], Zaima Mazorra[1] and Tania Crombet[1]

Case Series

Immunotherapy

An anti-CD6 antibody for the treatment of COVID-19 patients with cytokine-release syndrome: report of three cases

Lázaro Manuel Filgueira[1], Julio Betancourt Cervantes[1], Orlando Adolfo Lovelle[1], Carlos Herrera[2], Carlos Figueredo[1], Jorge Alain Caballero[2], Naivy Sánchez[1], Jorge Berrio[1], Geidy Lorenzo[3], Meylan Cepeda[3], Mayra Ramos[3], Danay Saavedra[3], Ana Laura Añe-Kouri[4], Zaima Mazorra*[,3], Kalet Leon[3], Tania Crombet[3] & Armando Caballero[2]

Clinical & Translational Immunology

Australian and New Zealand Society for Immunology Inc.

Clinical & Translational Immunology 2020; e1218. doi: 10.1002/cti2.1218
www.wileyonlinelibrary.com/journal/cti

ORIGINAL ARTICLE

Treatment of COVID-19 patients with the anti-CD6 antibody itolizumab

Armando Caballero[1], Lázaro M Filgueira[2], Julio Betancourt[2], Naivy Sánchez[2], Carlos Hidalgo[2], Alberto Ramírez[3], Alejandro Martinez[3], Rolando E Despaigne[4], Alberto Escalona[5], Henrry Diaz[6], Elio Meriño[6], Lilia M Ortega[7], Ulises Castillo[8], Mayra Ramos[9], Danay Saavedra[9], Yanelda García[9], Geydi Lorenzo[9], Meylán Cepeda[9], Maylén Arencibia[9], Leticia Cabrera[9], Milagros Domecq[9], Daymys Estévez[9], Carmen Valenzuela[9], Patricia Lorenzo[9], Lizet Sánchez[9], Zaima Mazorra[9], Kalet León[10] & Tania Crombet[9]

Gerontology

SUBMIT MANUSCRIPT

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Use of a Humanized Anti-CD6 Monoclonal Antibody (Itolizumab) in Elderly Patients with Moderate COVID-19

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GRACIAS!!