# Itolizumab in covid-19

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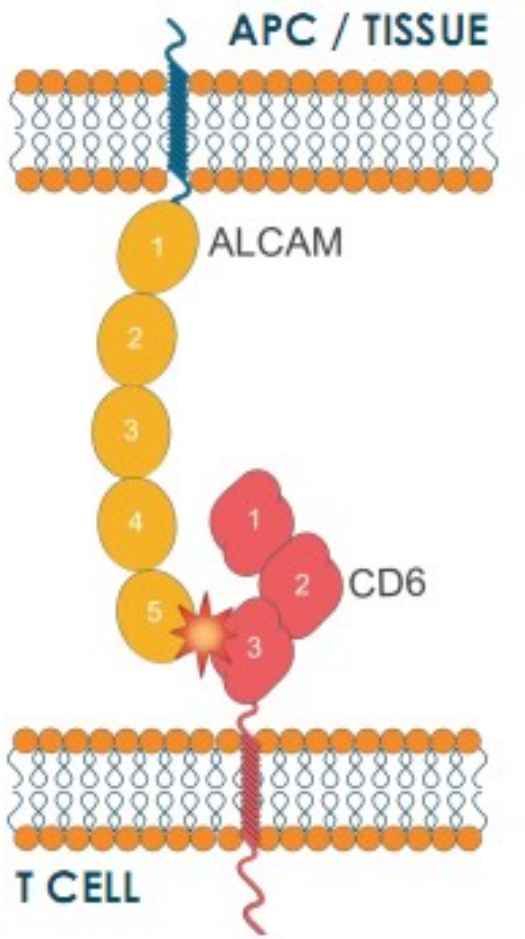
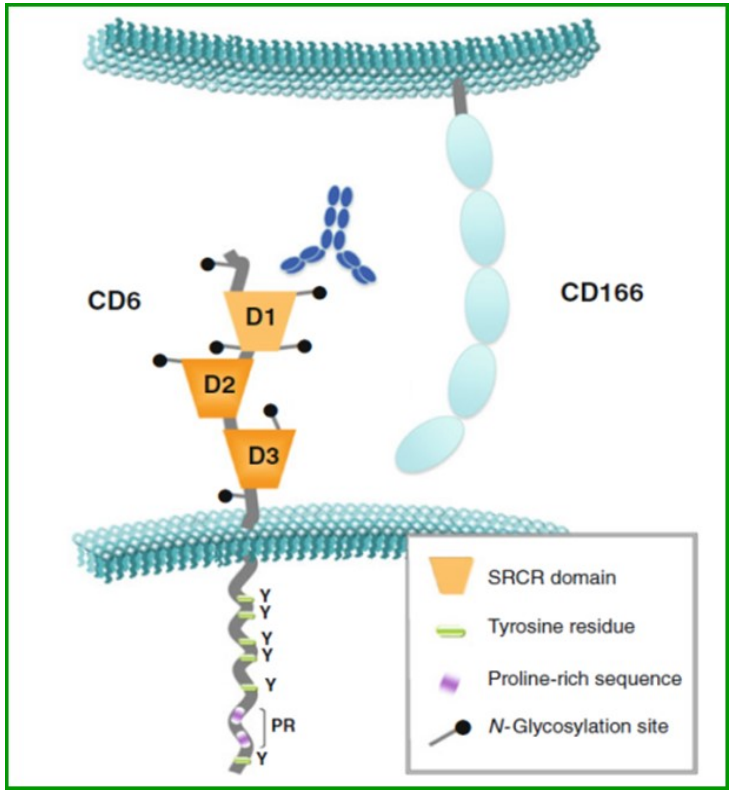
# Itolizumab



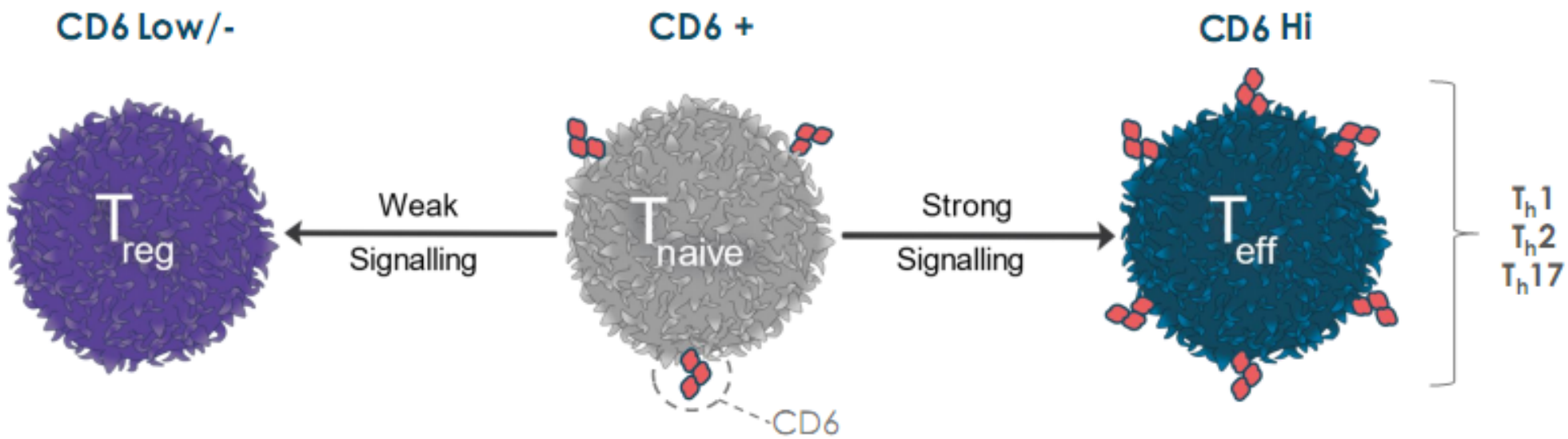

- **CD6 is a glycoprotein expressed on mature T-lymphocytes**
- **Crucial regulator of the T-cell activation**
- **ALCAM: main ligand in immunologic synapsis.**
- **Triple role: adhesion, activation and inflammatory cytokine secretion**




- 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 – Central Role in Effector Cell Development

**Highest levels of CD6 are found on activated T effector cells ($T_{eff}$) and associated with amplification of the auto-reactive cascade**

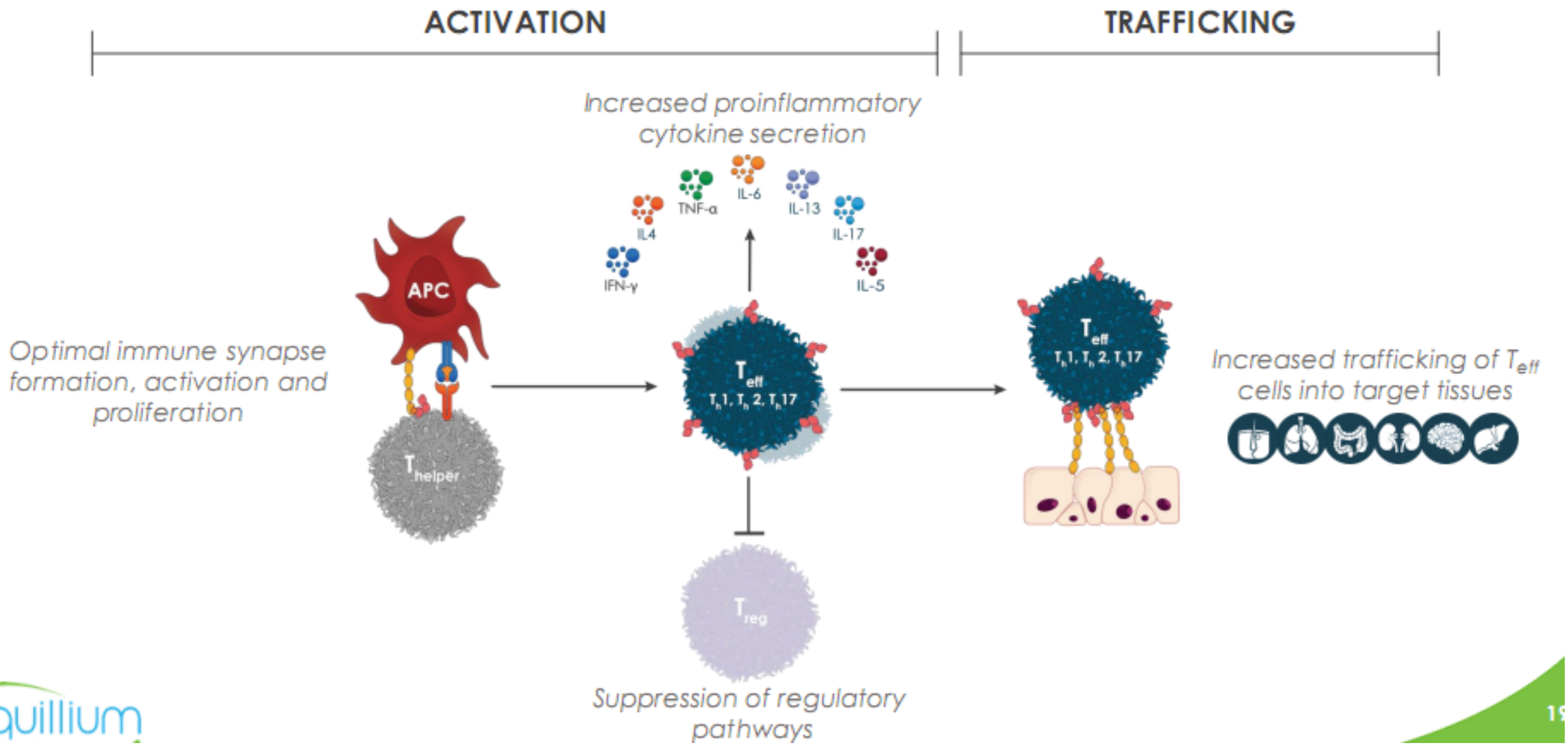



**Immune Regulatory**
***"Tolerance"***

**Autoreactive**
***"Autoimmunity"***

Garcia *et al.*, Cytometry 2014; Bughani *et al.*, PLoS 2017

# CD6-ALCAM Pathway Central to Immuno-inflammation



# 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**

# Trial Design

**Protocol approval**

- The protocol was approved by the Ethics Committee of the Institute of Tropical Medicine "Pedro Kourí" and by the Cuban Regulatory Agency.
- All investigations were conducted in accordance with the Helsinki Declaration

**Treatment administration**

- Treatment consisted in one intravenous infusion of 200 mg of itolizumab diluted in 200 ml of sodium chloride (0.9%).
- Patients could receive a second dose of the antibody, if they still had signs of respiratory distress. Infusion duration was at least 2 hrs.

# Demographic characteristics of the patients

Table 1: Patients demographics and comorbidities at baseline

| Demographic | | Critical | | Severe | | Moderate | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | Freq. | % | Freq. | % | Freq. | % | Freq. | % |
| | | 29 | 100 | 16 | 100 | 25 | 100 | 70 | 100 |
| Gender | Female | 12 | 37.9 | 12 | 75.0 | 16 | 64.0 | 39 | 55.7 |
| | Male | 4 | 62.1 | 4 | 25.0 | 9 | 36.0 | 31 | 44.3 |
| Skin color | White | 9 | 65.5 | 9 | 56.3 | 15 | 60.0 | 43 | 61.4 |
| | Mixed | 4 | 31.0 | 4 | 25.0 | 3 | 12.0 | 16 | 22.9 |
| | Black | 3 | 3.4 | 3 | 18.8 | 4 | 16.0 | 8 | 11.4 |
| | ND | | | | | 3 | 12.0 | 3 | 4.3 |
| Age | Mean ± SD | 67.4 ± 14.0 | | 66.9 ± 22.5 | | 71.2 ± 17.7 | | 68.7 ± 17.4 | |
| | Median ± IR | 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) | |

# 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 |

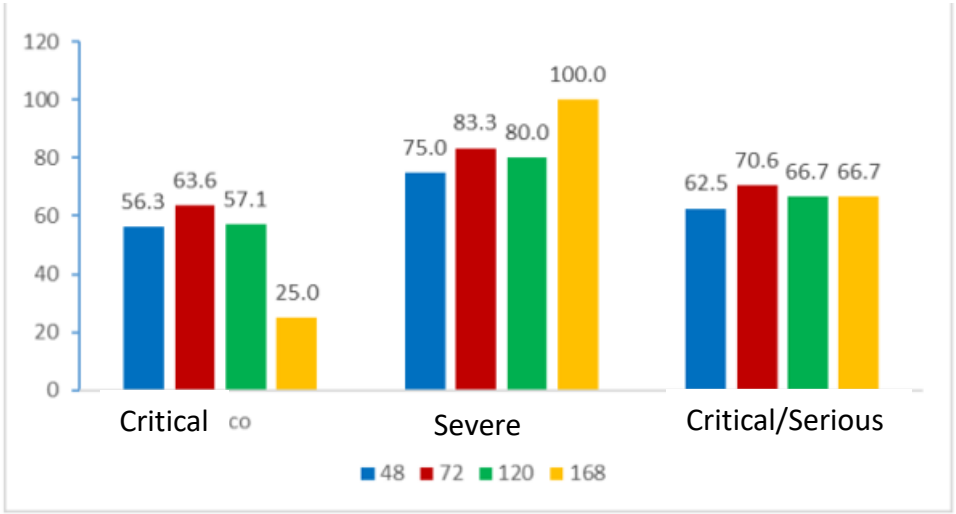
# Itolizumab number of doses

| | | Critically ill | | Severely ill | | Moderately ill | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | No | % | No | % | No | % | No | % |
| | | 29 | 100.0 | 16 | 100.0 | 25 | 100.0 | 70 | 100.0 |
| Itolizumab | 1 dose | 29 | 100.0 | 16 | 100.0 | 25 | 100.0 | 70 | 100.0 |
| | 2 doses | 14 | 48.3 | 8 | 50.0 | 19 | 76.0 | 41 | 58.6 |
| | 3 doses | 3 | 10.3 | -- | -- | -- | -- | 3 | 4.3 |
| P (kruskall-wallis) | | 10.2 ± 5.1 | | 7.9 ± 6.0 | | 2.7 ± 3.7 | | 7.0 ± 5.9 | |
| Time to start itolizumab | Mean ±SD | 10.0 ± 6.5 | | 7.5 ± 5.5 | | 1.0 ± 4.0 | | 7.0 ± 10.0 | |
| | Median ± IR | (0; 22) | | (1; 27) | | (0; 13) | | (0; 27) | |
| | (min; max) | 0.0000 | | 0.016 | | | | | |

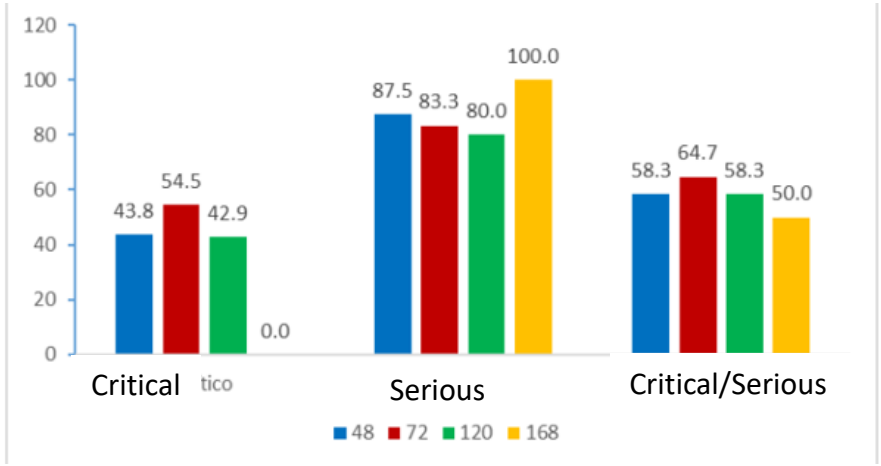
# Results

# Improvement of ventilatory function

Rate of patients without need to increase FiO2 to maintain stable SO2




Rate of patients with improvement in PiO2 / FiO2 ratio



## Safety data

- Itolizumab was safe
- Treatment-related events were recorded in 14.3% of the patients
- Most frequent adverse events were mild to moderate chills, hypotension and fever.
- Only 3 patients (4.41%) developed serious related adverse events

# Survival rate

**Tabla 10. Proporción de pacientes fallecidos a los 14 días siguientes al uso del medicamento-**

| | | Crítico | | Grave | | De cuidado | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| Fallecidos a los 14 días | | Frec. | % | Frec. | % | Frec | % | Frec | % |
| | | 29 | 100.0 | 16 | 100.0 | 23 | 100.0 | 68 | 100.0 |
| Estado a los 14 días | Fallecido | 20 | 69.0 | 3 | 18.8 | 1 | 4.3 | 24 | 35.3 |
| | Vivo | 9 | 31.0 | 13 | 81.3 | 22 | 95.7 | 44 | 64.7 |

**Comparison with Cuban controls**

| | **Crítical** | **Severe** | **Moderately ill (2 or more comorbidities)** |
|---|---|---|---|
| Odds ratio | 1.75 (0.37; 8.33) | 3.85 (1.02-14.28) | 6.67 (0.83-50) |
| Odds ratio (No IFN) | 6.2 (0.9; 38.5) | 3.7 (0.7-18.2) | |

# 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 |

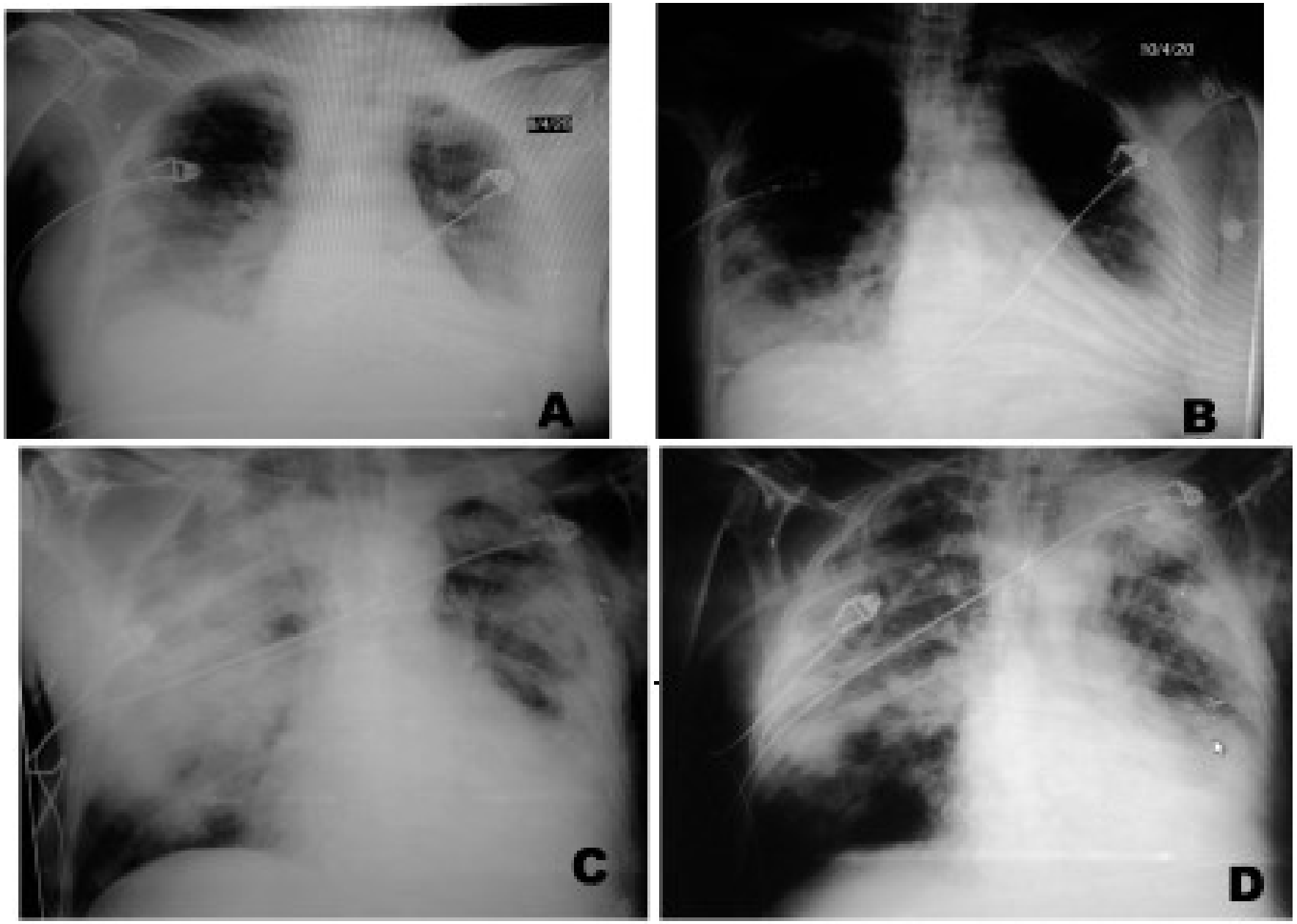
# Treatment of COVID-19 patients with the anti-CD6 antibody itolizumab

**Table 4.** Univariate logistic regression analysis

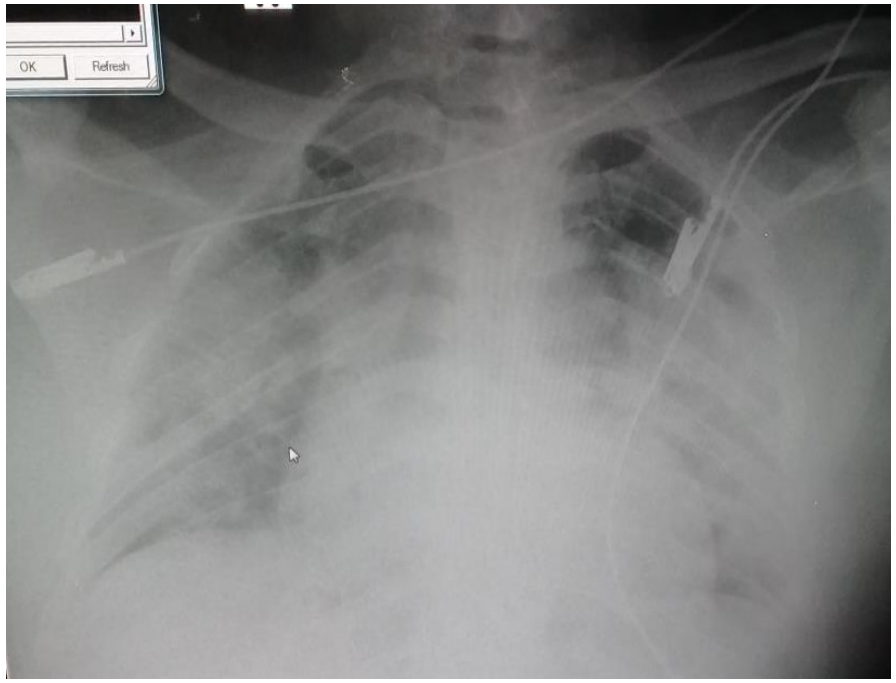
| | | Death Odds ratio | IC 95% | |
|---|---|---|---|---|
| Generals | Age (> 65) | 1.680 | 0.601 | 4.697 |
| | Time between symptoms and itolizumab (>7) | 5.625 | 1.862 | 16.989 |
| | Neurological symptoms | 4.778 | 1.076 | 21.224 |
| Comorbidities | Hypertension | 0.613 | 0.220 | 1.709 |
| | Diabetes 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 |

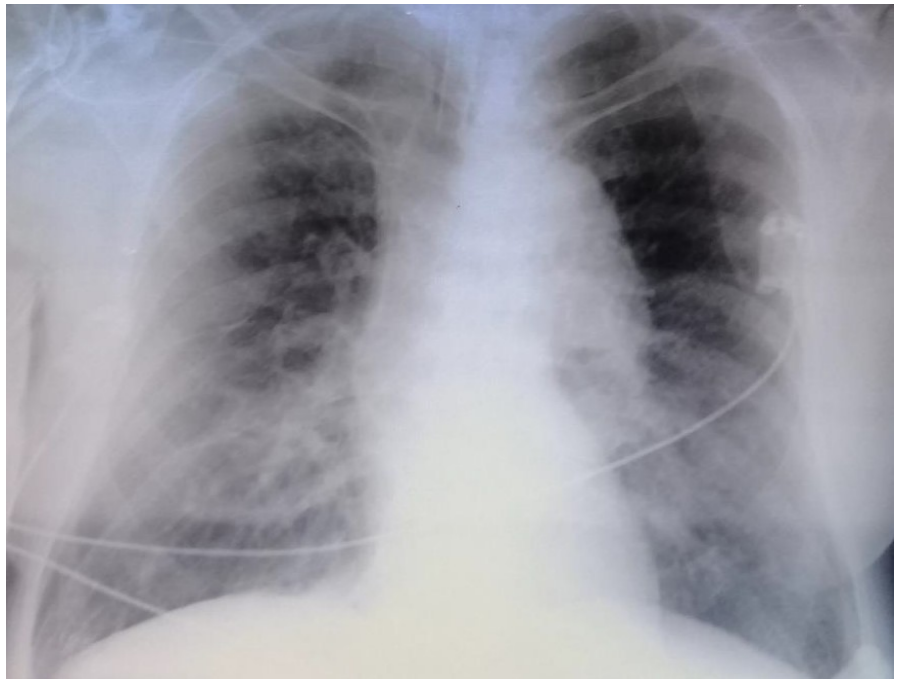
The highlighted variables are significantly associated with higher odds of death.

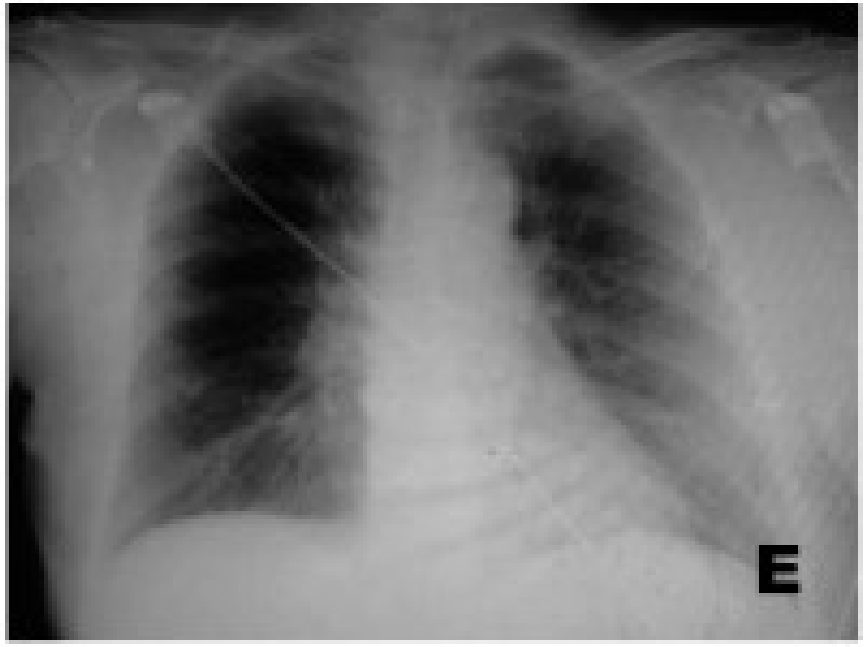
# Representative X Rays

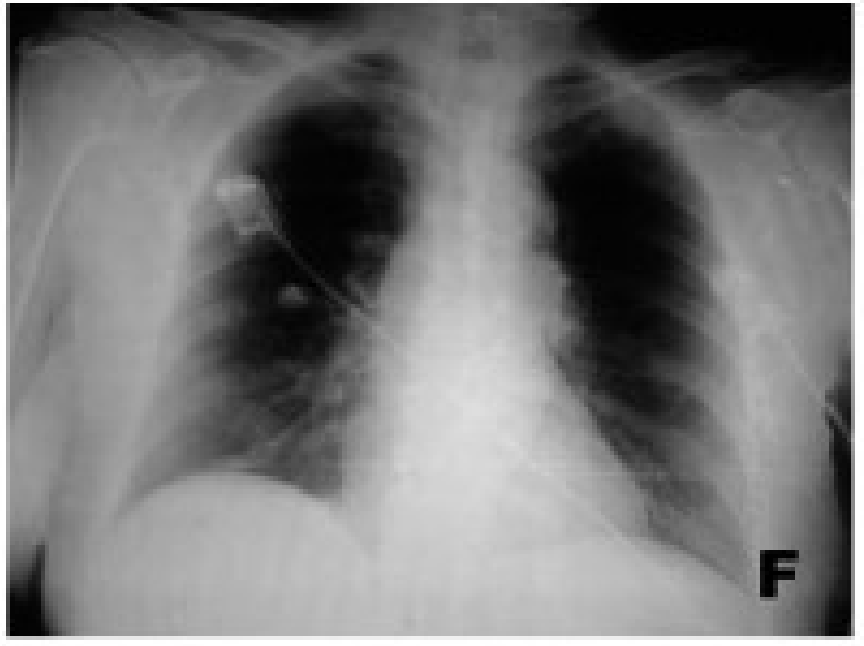


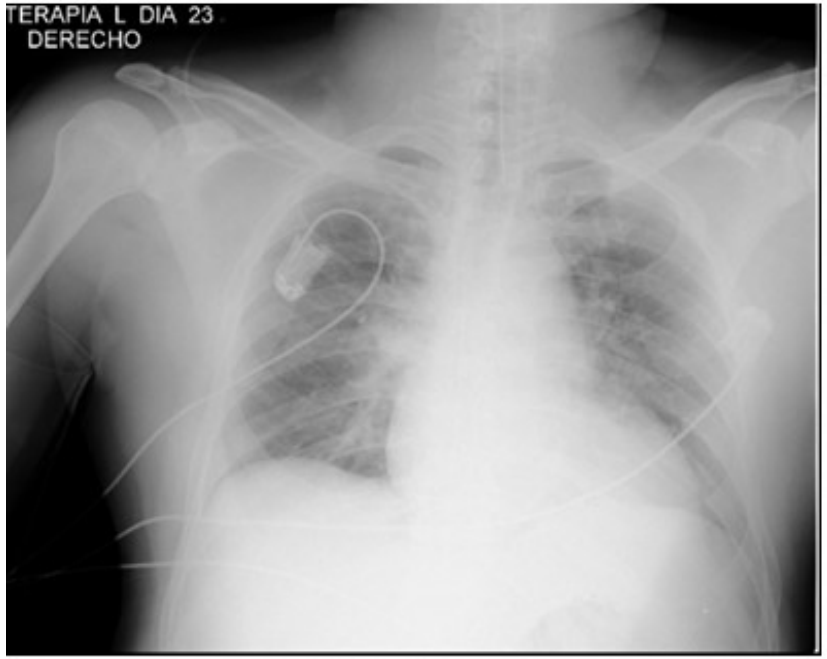
# Representative X Rays



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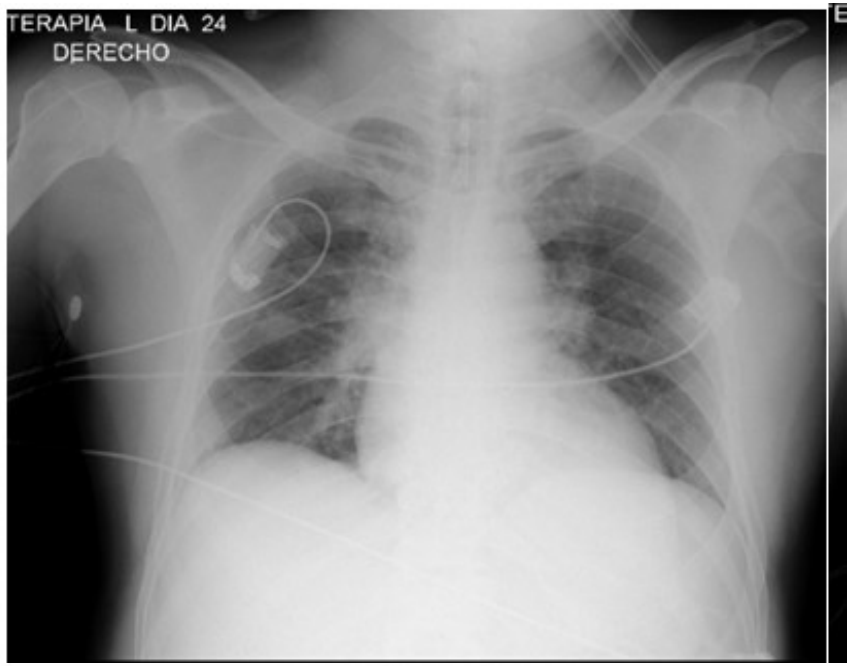
DERECHO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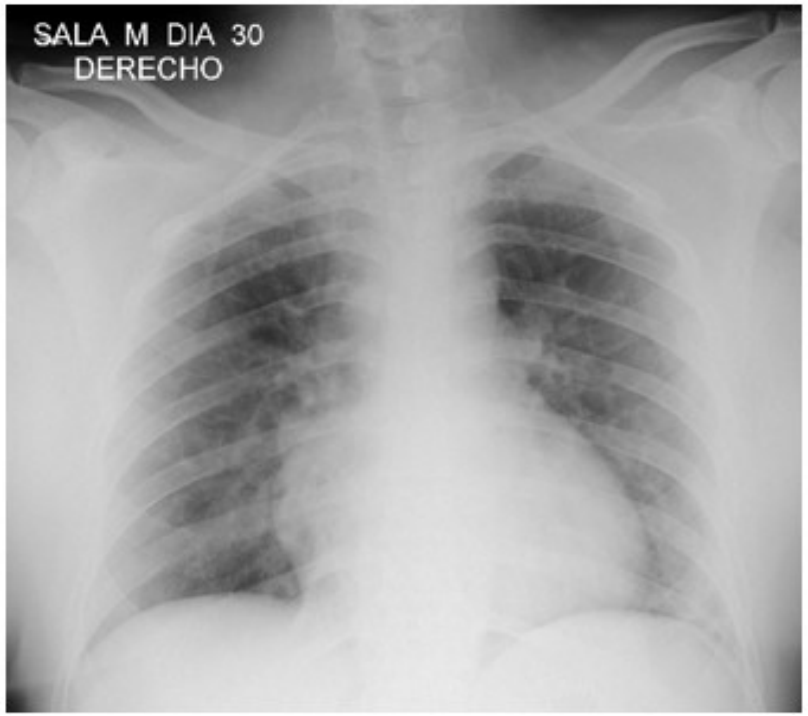
SALA M DIA 30
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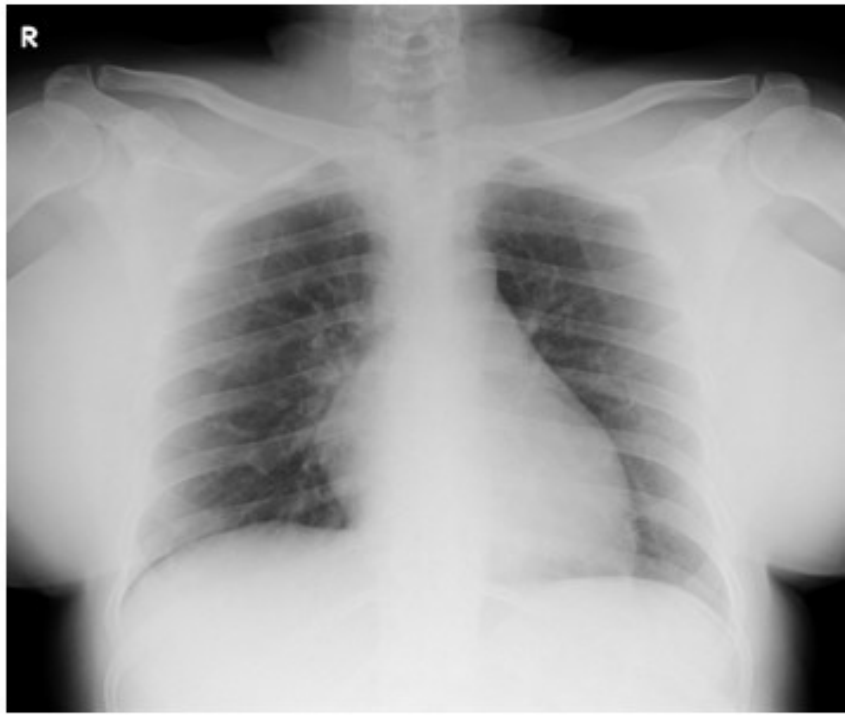
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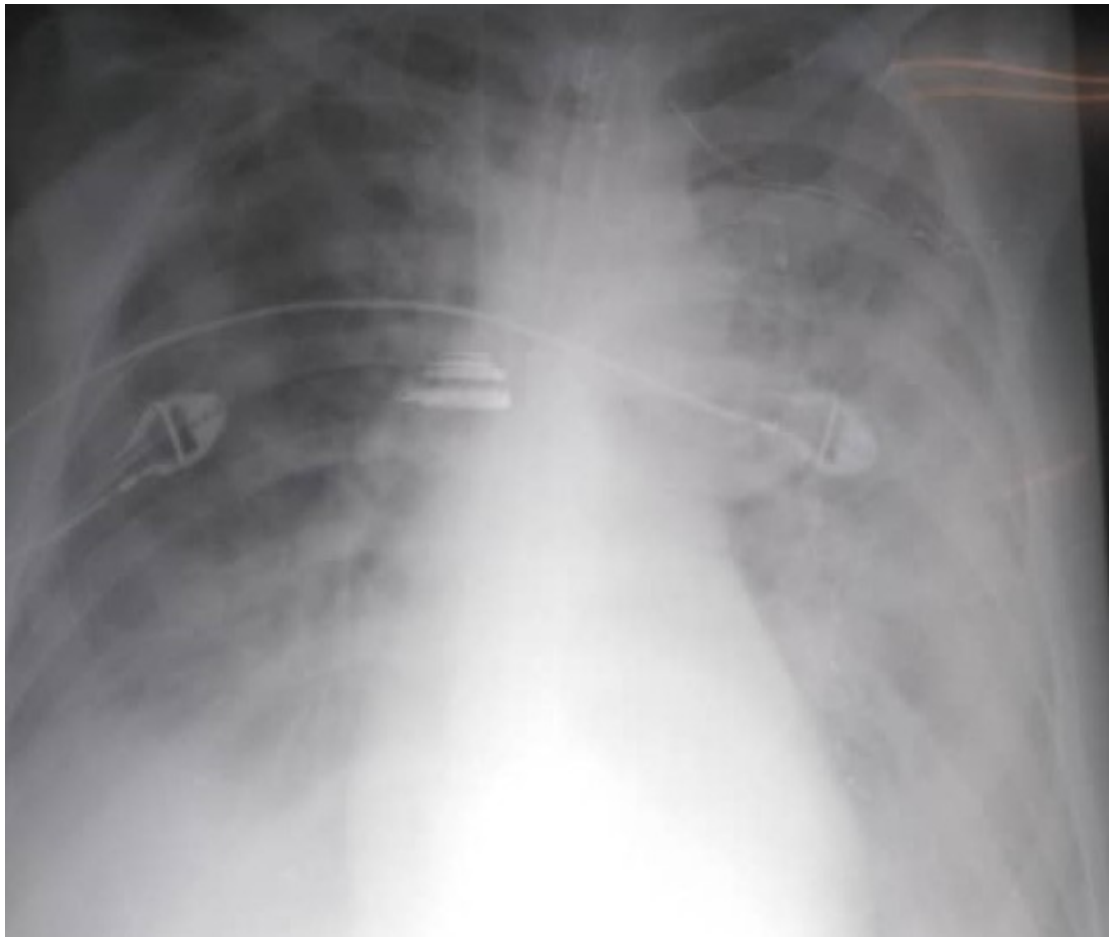
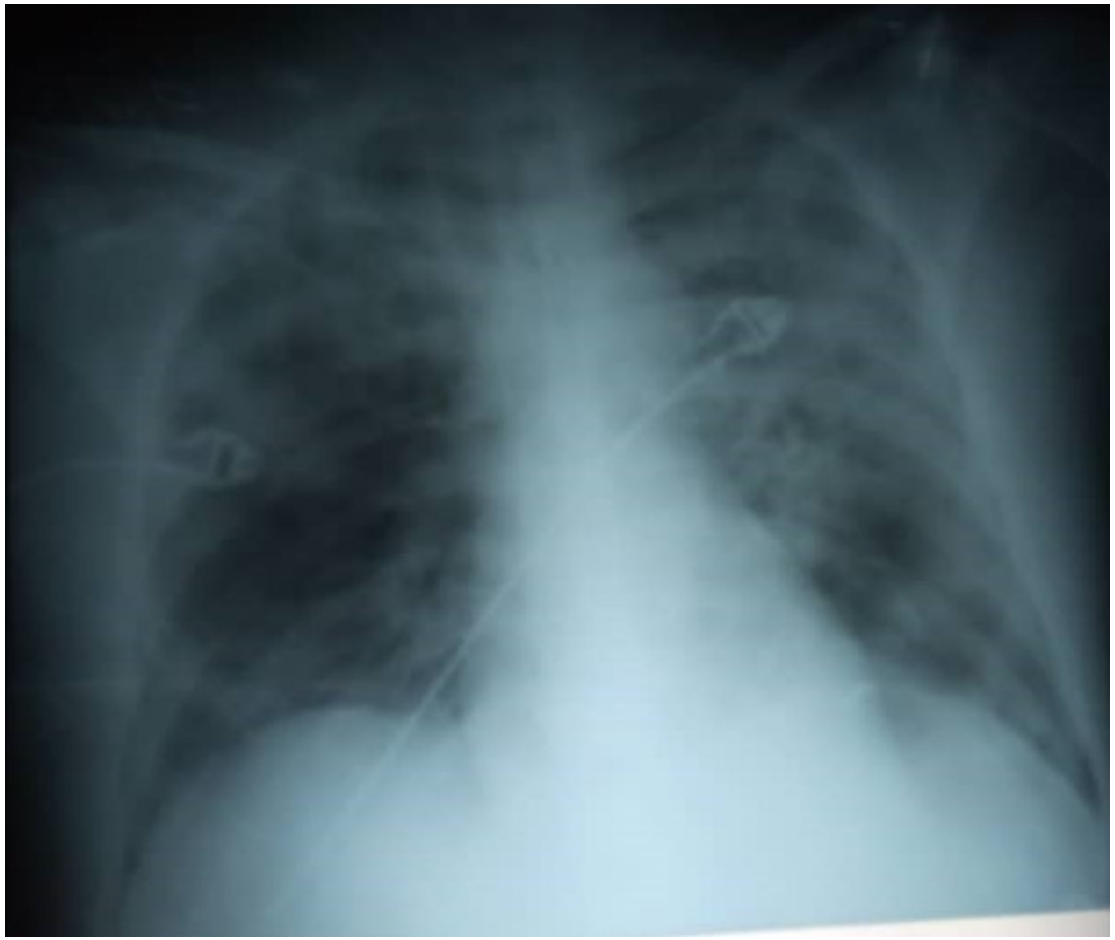
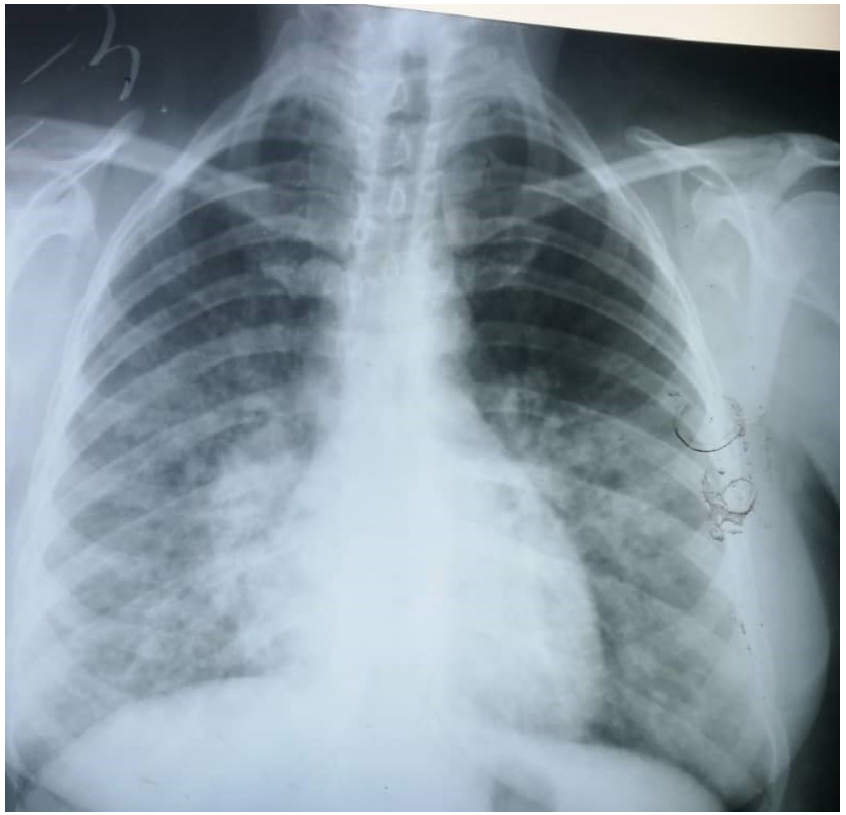
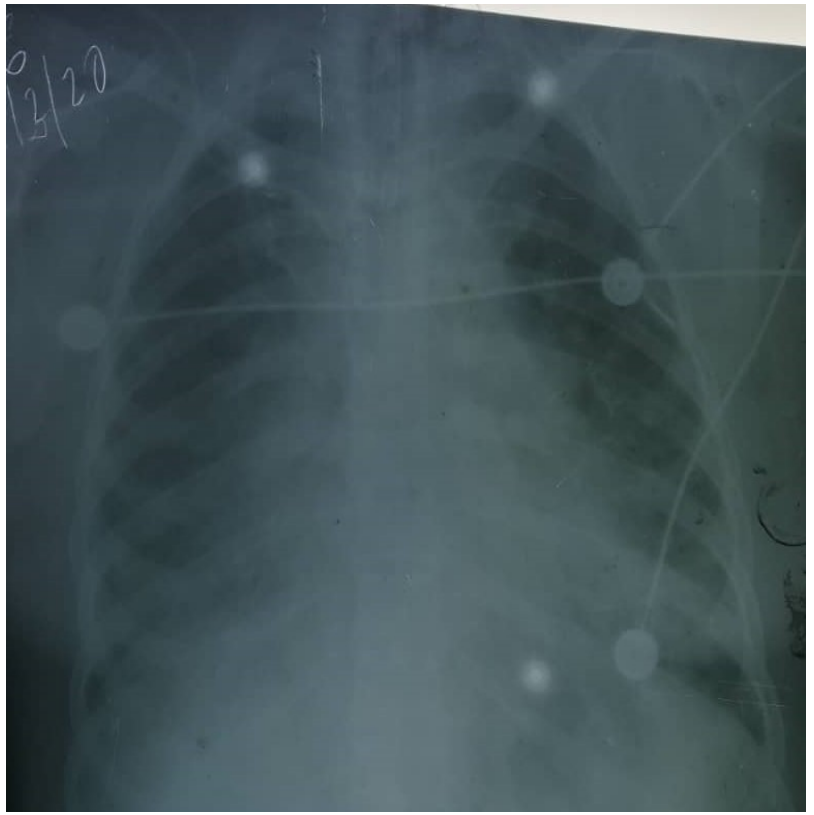
# Pcte CJMQ, Mtzas



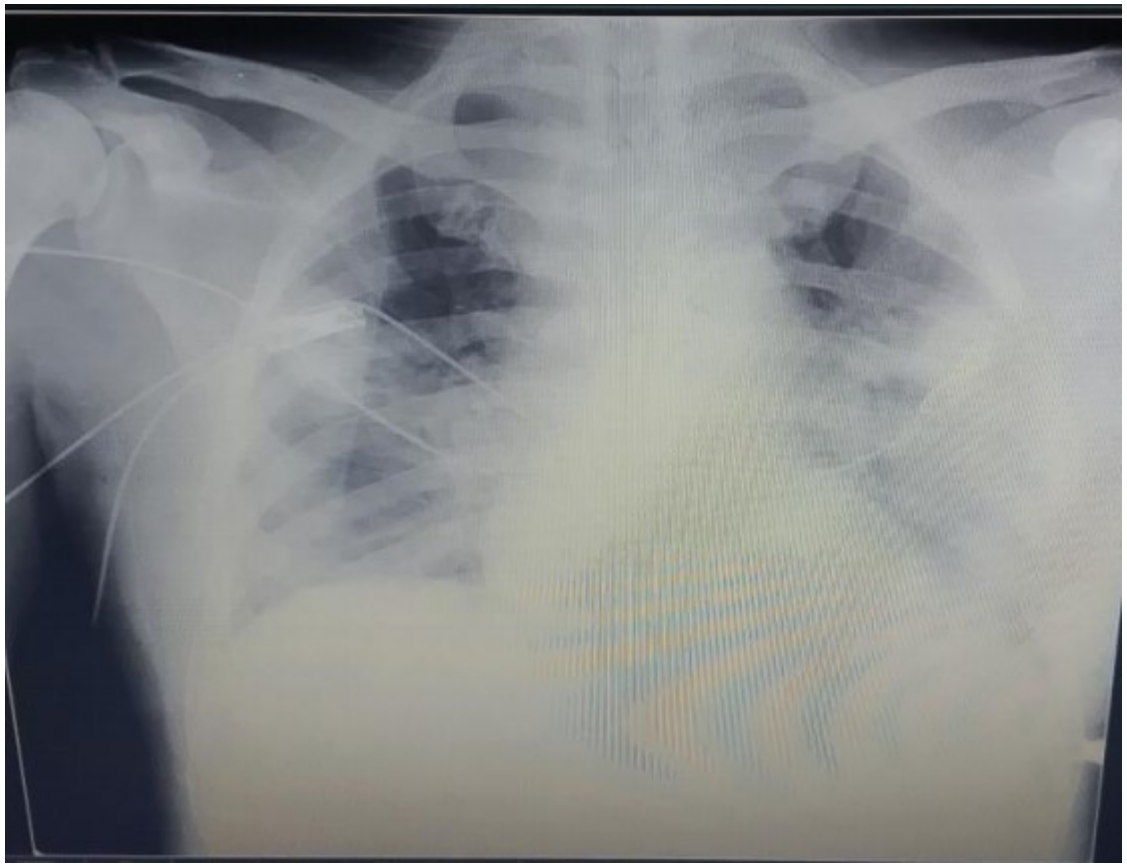


# Paciente YHF, Mtzas

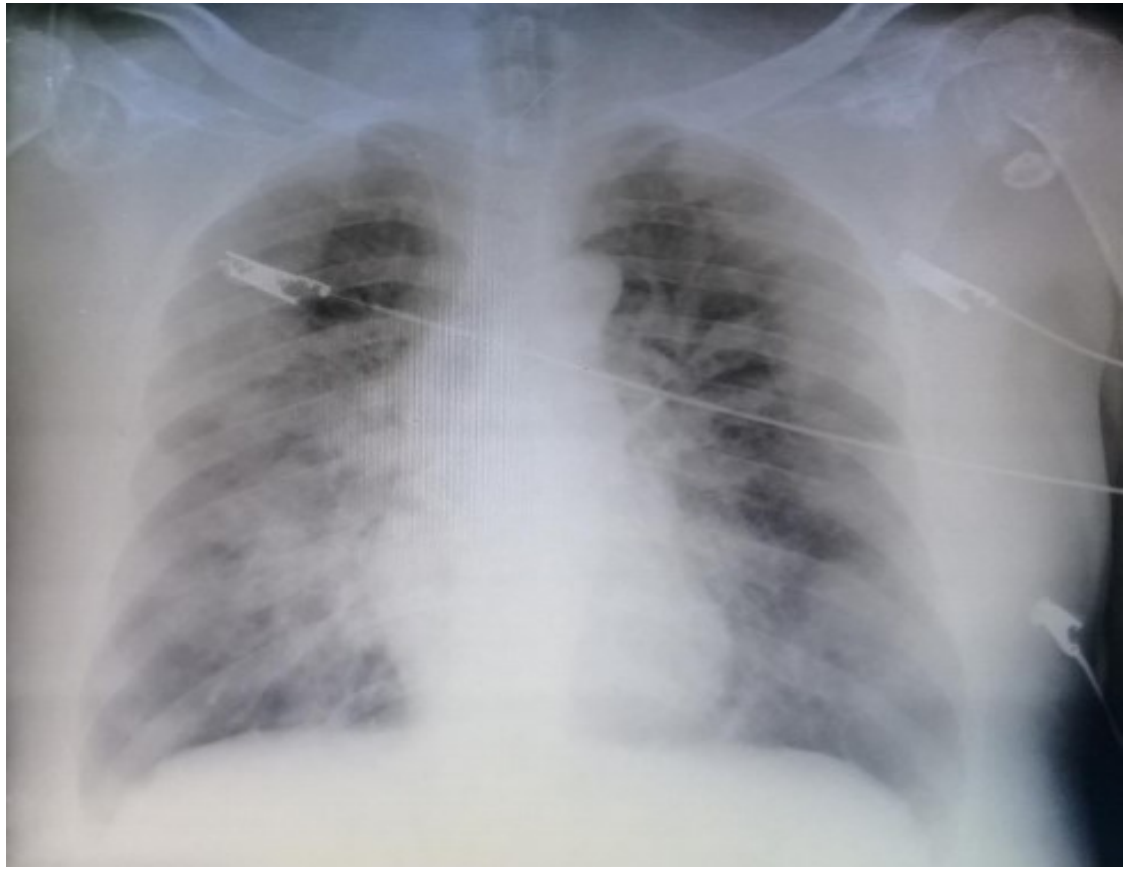




# Paciente SADD (Hospital Salvaor Allende)
# Itolizumab 8 de Abril : Dosis 1



Antes del tratamiento



10 de Abril

# Conclusions

- Itolizumab was safe.
- Itolizumab Improved ventilatory function of the ICU patients.
- Itolizumab successfully reduced interleukin 6, in individuals with very high concentration and did not trigger the cytokine release in low-level patients.
- Reduction of the mortality as compared to Cuban controls. Larger benefit in moderately and severely ill patients