





Nimotuzumab for COVID-19: case series

Anselmo A Abdo Cuza¹ , Jonathan Pi Ávila¹, Rafael Machado Martínez¹, José Jordán González², Guillermo Pérez Aspuro¹, Juan A Gutiérrez Martínez¹, Mayra Ramos Suzarte³, Danay Saavedra Hernández³, Ana L Añé-Kouri³ & Tania Crombet Ramos^{*,3} 

¹Intensive Care Unit. Medical & Surgical Research Center (CIMEQ), Havana, Cuba

²Radiology Department. Medical & Surgical Research Center (CIMEQ), Havana, Cuba

³Clinical Research Direction. Center of Molecular Immunology (CIM), Havana, Cuba

*Author for correspondence: Tel.: +537 2143143; taniac@cim.sld.cu

Background: In COVID-19, EGFR production is upregulated in the alveolar epithelial cells. EGFR overexpression further activates STAT-3 and increases lung pathology. The EGFR pathway is also one of the major nodes in pulmonary fibrosis. **Methods:** Nimotuzumab, a humanized anti-EGFR antibody, was used to treat three patients with severe or moderate COVID-19. The antibody was administered in combination with other drugs included in the national COVID-19 protocol. **Results:** Nimotuzumab was well tolerated. IL-6 decreased from the first antibody infusion. Clinical symptoms significantly improved after nimotuzumab administration, and the CT scans at discharge showed major resolution of the lung lesions and no signs of fibrosis. **Conclusion:** Safe anti-EGFR antibodies like nimotuzumab may modulate COVID-19-associated hyperinflammation and prevent fibrosis.

Clinical Trial Registration: RPCEC00000369 (RPCEC rpcec.sld.cu).

Lay abstract: Background: In COVID-19, the protein EGFR is overactive in the infected lung cells. **Methods:** Nimotuzumab, an anti-EGFR antibody, was used to treat three patients with severe or moderate COVID-19. The antibody was administered in combination with other drugs included in the national COVID-19 protocol. **Results:** Nimotuzumab was safe. The most important inflammatory markers decreased from the first administration. The patients' clinical symptoms and imaging results improved significantly. **Conclusion:** Anti-EGFR antibodies like nimotuzumab may contribute to the recovery of COVID-19 patients without long-term consequences.

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Keywords: COVID-19 • cytokine release syndrome • EGFR • monoclonal antibody • nimotuzumab • SARS-CoV-2

COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2 which has a high rate of morbidity and mortality [1]. Its pathogenicity is started by the SARS-CoV-2 NSP1 and ORF6 proteins, which provoke a dysfunction of STAT1 together with a compensatory activation of STAT3 [2].

EGFR is a 170-kDa protein which is frequently expressed at high levels in epithelial tumors, correlating with cancer progression and poor prognosis [3]. Overall, EGFR overexpression by epithelial cells alters cycle regulation, blocks apoptosis, promotes angiogenesis and increases motility, adhesiveness and invasiveness [4]. In COVID-19, EGFR is also upregulated in the type II alveolar epithelial cells because of the reduced STAT-1 and the acute lung damage [2]. EGFR overexpression further activates STAT-3 and increases lung pathology [2,5–8]. The EGFR pathway is also one of the major nodes in pulmonary fibrosis [9–18], controlling several cascades of cell proliferation, mucus secretion, inflammatory response and tissue repair. A recent viral fibrotic scoring and drug screen uncovered EGFR as a key regulator of COVID-19 fibrosis [19]. EGFR has been classified as one of the most influential receptors in the network involved in COVID-19 [20–25]. **Figure 1** highlights the roles of EGFR in cancer and COVID-19.

Nimotuzumab is a humanized antibody that recognizes EGFR [26]. The antibody blocks the binding of ligands to EGFR and works by inhibiting the receptor's tyrosine kinase activity, interfering with the cell signaling pathway [26]. Preclinical and clinical studies have shown that the antitumor response evoked by nimotuzumab is mediated by antiproliferative, antiangiogenic and proapoptotic mechanisms [27,28]. Clinical trials have demonstrated that the

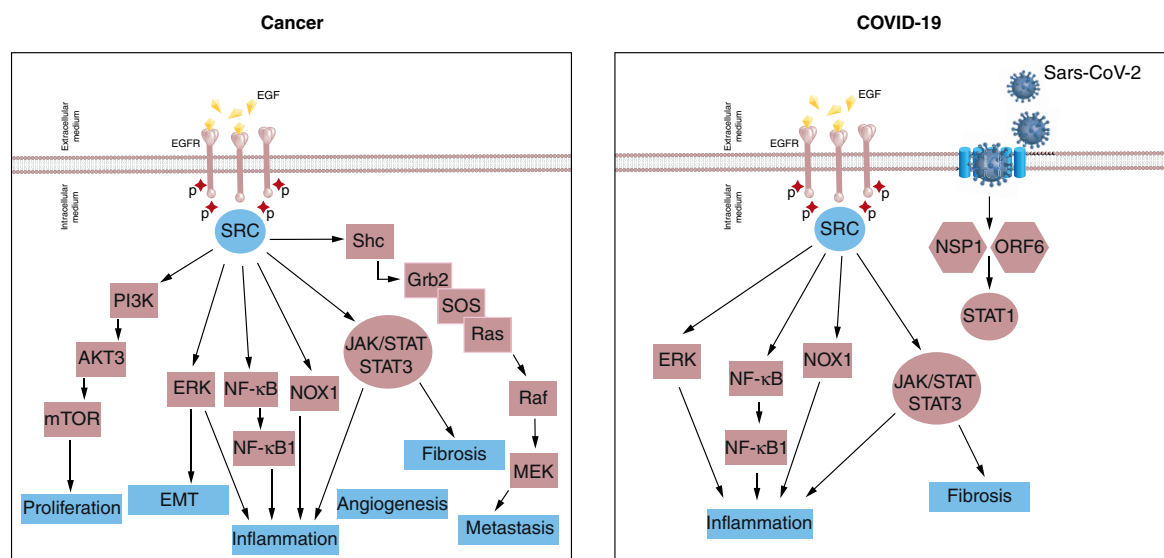


Figure 1. EGFR's role in cancer and COVID-19. In cancer, EGFR increases proliferation, inflammation, angiogenesis, fibrosis, epithelial–mesenchymal transition and metastasis. In COVID-19, EGFR promotes inflammation and fibrosis. (SRC = a non-receptor tyrosine kinase protein)
EMT: Epithelial–mesenchymal transition; P: Protein phosphorylation; SRC: Sarcoma.

antibody, in combination with radiation and chemotherapy, significantly increases the survival and objective response rate of patients with advanced epithelial tumors [29–35].

Nimotuzumab has previously been shown by immunohistochemistry to decrease IL-6 in mice xenografted with pancreatic cell lines overexpressing EGFR. This result was confirmed by western blot and real-time PCR [36].

In view of the well-proven role of EGFR in inflammation [37–50] and fibrosis [9–19], an expanded access protocol for RPCEC0000369 was launched in patients with severe and moderate COVID-19. The study is ongoing and here we describe the outcomes in three patients receiving the antibody at the Center for Medical and Surgical Research.

Patients & methods

A noncontrolled, multicenter clinical trial was carried out to evaluate the preliminary safety and effect of nimotuzumab in patients with confirmed SARS-CoV-2 infection by real-time PCR (RT-PCR). The clinical trial included patients with severe or moderate illness. Severe patients were individuals with an oxygen saturation (SpO_2) <94 % on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 mm Hg, a respiratory rate of 30 breaths/min or lung infiltrates >50%. Moderate patients were those subjects who showed evidence of lower respiratory disease during clinical assessment or imaging and who had $SpO_2 \geq 94\%$ on room air at sea level. The main efficacy variables were: rate of patients recovered 14 days after the first infusion, rate of patients requiring mechanical ventilation after nimotuzumab, and length of stay in the hospital. Inflammatory parameters like CRP, ferritin, LDH and IL-6 were measured over time. Patients were able to receive other treatments included in the national protocol for the management of COVID-19, including steroids, anticoagulants and antibiotics.

Here we report the results in three patients with confirmed SARS-CoV-2 infection classified as severely (patients 1 and 2) or moderately ill (patient 3) who were included in the referred trial. The study was approved by an ethical review board and by the National Regulatory Agency. All patients provided informed consent for the investigational treatment.

Nimotuzumab was administered by the intravenous route at a loading dose of 200 mg diluted in 250 ml of sodium chloride (0.9%). Patients could receive a second or third dose of the monoclonal antibody (100 mg) if they still had laboratory or radiological signs of inflammation. The infusion duration was 2 h. Laboratory exams included routine bloods, leukocyte subsets and the following biochemical parameters: LDH, ferritin, CRP, D-dimer, aspartate aminotransferase, bilirubin, creatinine and procalcitonin. IL-6 levels were measured using a commercially available kit from R&D Systems (MN, USA), the human IL-6 Quantikine ELISA Kit (Cat no. S6050).

Results

Patient descriptions

Patient 1

A 54-year-old female patient with a personal history of Type 2 diabetes mellitus, hypertension and obesity presented at the emergency room with shortness of breath, cough with whitish expectoration and nasal secretion. She had had symptoms for the previous 3 days and had worsening dyspnea. At physical examination, the patient had mild edema in the lower limbs, reduced thoracic expandability, decreased vesicular murmur and a respiratory rate of 27 breaths per minute. Her room-air SpO₂ was 72% and she was admitted to the intensive care unit. She had fever of 38°C and her general performance status was markedly deteriorated. Her condition was classified as severe.

Upon her admission, SARS-CoV-2 infection was confirmed by RT-PCR. At hospital entry, the patient required supplemental oxygen and started treatment with remdesivir (loading dose of 200 mg, then 100 mg for 5 days), dexamethasone (8 mg orally), meropenem (1 g intravenously every 8 h) and low-molecular-weight heparin.

After deterioration of the clinical and inflammatory markers in the first 24 h, the medical team decided to start nimotuzumab administration at a loading dose of 200 mg by the intravenous route. At that moment, the oxygenation index (SpO₂/FiO₂) was 228; then two additional infusions of nimotuzumab at a dose of 100 mg every 3 days were administered. No adverse events were detected after any of the infusions. Overall, the patient had a stable respiratory evolution, requiring supplemental oxygen for 8 days but not mechanical ventilation. Remarkably, after the first nimotuzumab infusion, her IL-6 concentration dropped from 112 pg/ml to levels below 1.5 pg/ml and did not increase after this initial reduction (Table 1). Ferritin and CRP levels significantly decreased after two antibody doses. Table 1 shows the evolution of laboratory markers from baseline to hospital discharge at day 12.

Figure 2 displays comparative images of the axial CT scans performed at admission and every 6 days, showing improvement of the bilateral inflammatory lesions.

Patient 2

A 62-year-old female patient with a personal history of hypertension and overweight was admitted at the hospital after 14 days of marked asthenia and nausea. SARS-CoV-2 positivity was confirmed by RT-PCR. At physical examination, she had crackles in the right lung base and sporadic cough. The room-air SpO₂ was 88%, which rose to 95% with supplemental oxygen at 2 l/min. On the first day of admission, treatment began with oral dexamethasone 6 mg/day, remdesivir (loading dose of 200 mg, then 100 mg/day up to five doses), aspirin, low-molecular-weight heparin and nimotuzumab (200 mg loading dose followed by two 100 mg doses on days 4 and 7). No adverse events occurred after any of the antibody infusions. The evolution of the patient was satisfactory. Within 24 h of the first antibody administration, IL-6 decreased from 120 to 3.97 pg/ml and then to 1.5 pg/ml (Table 1). Ferritin and CRP decreased after the second nimotuzumab dose. Aspartate aminotransferase was elevated at baseline and started to decrease after the initial therapy. Table 1 shows the results of the laboratory markers, while Figure 2 displays the imaging evolution by CT scan. The patient was discharged on day 7 after a marked clinical, laboratory and radiological improvement.

Patient 3

A 55-year-old, overweight male patient presented at the emergency room because he was a contact of a positive SARS-CoV-2 case. He was asymptomatic but the RT-PCR result was positive. The patient was admitted at the hospital and started therapy with favipiravir and azithromycin; 2 days later, he complained of nasal secretion and asthenia. On day 3 of admission, dexamethasone (8 mg/day) was added after the detection of peripheral inflammatory lesions at the CT scan together with IL-6 increase (from 1.5 to 10 pg/ml). On day 4, he complained of headache and fever of 38°C. After 2 days of treatment with dexamethasone, his clinical symptoms continued to worsen and the fever, headache and marked general discomfort persisted. The IL-6 level increased to 25.2 pg/ml and ferritin from 689 to 919 ng/ml, while the CT scan showed worsening of the inflammatory lesions. Considering the deteriorations in clinical symptoms and radiological and inflammatory markers, nimotuzumab was prescribed (200 mg loading dose, followed by 100 mg 72 h later). The antibody was well tolerated. After nimotuzumab, the clinical symptoms improved, IL-6 decreased to 1.5 pg/ml and there was a significant recovery of the radiological lesions. The patient was discharged on day 9 of hospital admission. Figure 2 & Table 1 show the evolution of imaging and laboratory markers, respectively.

Table 1. Laboratory biomarkers of the three patients by day.

Laboratory markers	Patient	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 12
IL-6 (pg/ml)	1	112	<1.50	<1.50	<1.50	<1.50	<1.50	<1.50	<1.50	<1.50	<1.50
	2	120	3.97	<1.50	<1.50	<1.50	<1.50	<1.50	–	–	–
	3	25.2	–	<1.50	<1.50	–	–	–	–	–	–
LDH (mg/dl)	1	708	528	536	392	286	453	374	368	353	315
	2	435	474	310	260	226	224	554	–	–	–
	3	275	–	180	179	–	–	–	–	–	–
Ferritin (ng/ml)	1	1269	1290	–	–	741	741	–	1338	1356	956
	2	2000	2000	2000	2000	1970	1786	–	–	–	–
	3	919	–	1208	–	–	–	–	–	–	–
D-dimer (pg/ml)	1	0.95	1.15	1.00	0.40	0.34	0.34	–	0.28	0.23	0.31
	2	2.18	–	3.37	2.10	2.9	2.19	1.34	–	–	–
	3	0.20	–	–	0.25	–	–	–	–	–	–
CRP (mg/l)	1	77.3	–	–	–	8.46	8.96	–	–	–	2.26
	2	120	120	90	69	50	35	–	–	–	–
	3	46	–	32	–	–	–	–	–	–	–
Procalcitonin (ng/ml)	1	0.194	0.193	0.134	–	–	0.189	–	–	–	0.086
	2	0.17	–	–	–	0.06	–	–	–	–	–
	3	0.079	–	0.033	–	–	–	–	–	–	–
AST (U/l)	1	55	36	37	36	32	55	38	32	29	33
	2	142	95	52	33	25	26	41	–	–	–
	3	31	–	17	22	–	–	–	–	–	–
Bilirubin (mmol/l)	1	–	–	–	–	–	17	–	–	–	12
	2	17	8	7	8	–	–	9	–	–	–
	3	10	–	8	–	–	–	–	–	–	–
Creatinine (mmol/l)	1	111	70	71	48	50	48	–	64	–	68
	2	64	48	59	53	56	54	54	–	–	–
	3	119	–	83	85	–	–	–	–	–	–
NLR	1	4.7	5.1	5.6	6.5	4.8	7.7	6.4	5.4	4.5	2.1
	2	8.2	8.9	13.4	4.6	7.2	6.9	4.1	–	–	–
	3	3.6	–	1.8	2.5	–	–	–	–	–	–

Day 1 corresponds to baseline values, before nimotuzumab administration.

NLR: Neutrophil–lymphocyte ratio.

Discussion

To date, there is no specific treatment for SARS-CoV-2 infection. In general, therapeutic alternatives for patients include the combination of antiviral, anticoagulant and anti-inflammatory drugs [51,52]. Among the latter, in addition to steroids, some immunomodulatory drugs such as tocilizumab, baricitinib and itolizumab, commonly used to treat autoimmune disorders, have been employed in COVID-19 patients [53–56]. These anti-inflammatory drugs are prescribed in combination with steroids to reduce the so-called cytokine release syndrome or cytokine storm that characterize the hyperinflammatory stage of COVID-19 [57]. In a large randomized trial (RECOVERY), 4116 patients were enrolled to receive an anti-IL-6 receptor inhibitor or usual care. Most of the patients also received concomitant steroid therapy. Globally, tocilizumab improved survival of the hospitalized COVID-19 patients with hypoxia and systemic inflammation. There were three serious adverse reactions [54]. Likewise, baricitinib (a small inhibitor of JAK) plus standard of care, including systemic corticosteroids and antivirals, significantly decreased mortality compared with placebo [58].

Here we report the use of a humanized anti-EGFR antibody to treat three patients with severe or moderate COVID-19. The use of an anti-EGFR antibody theoretically offers, in the same drug, the modulation of hyperinflammation [37–50] and the prevention of fibrosis [9–18].

Nimotuzumab was administered in combination with remdesivir or favipiravir, dexamethasone, low-molecular-weight heparin and antibiotics. At hospital admission, all three patients had a poor prognosis in view of their comorbidities. Two patients were severely ill, considering their hypoxemic acute respiratory failure and oxygen

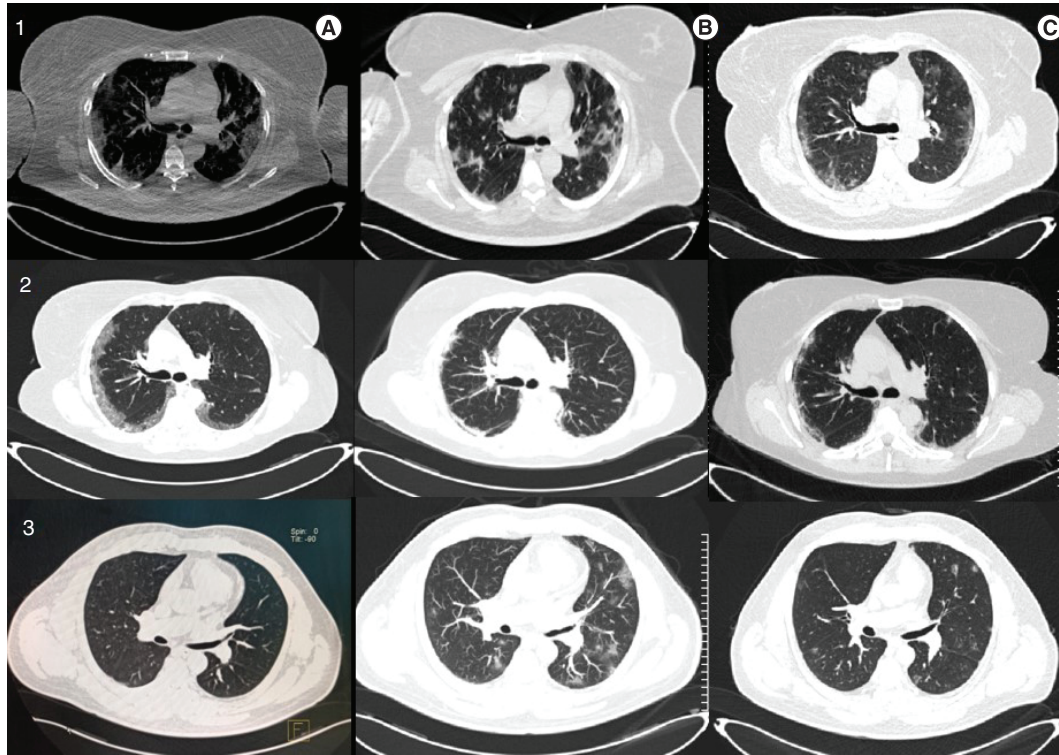


Figure 2. Axial chest computed tomography scan at the level of the parahilar region (patients 1, 2 and 3). Sequential images (A) on admission, (B) on day 6 and (C) on day 12. (A) In patients 1 and 2, bilateral pulmonary condensation lesions of inflammatory type, predominantly at the periphery, were observed at the time of admission. Patient 3 was admitted without CT scan lesions. (B) On day 6 of admission, patients 1 and 2 showed improvement of the lung inflammatory lesions, with lower radiological density and bronchial paths in those of peripheral location. At day 6, patient 3 showed patchy bilateral ground-glass opacities. (C) On day 12 of admission, the three patients showed further resolution of the lung inflammatory lesions and no sign of fibrosis.

requirements. The antibody did not cause any adverse events. In general, nimotuzumab is a very safe drug because it has an intermediate affinity against EGFR which facilitates preferential uptake by tissues with high EGFR expression [27]. Most frequent nimotuzumab-related events in cancer comprise mild or moderate anorexia, chills, headache, fatigue and fever; nimotuzumab does not induce skin rash or hypomagnesemia like other EGFR-targeting drugs [29].

After adding nimotuzumab to the standard of care, IL-6 concentrations decreased to almost undetectable levels in all three subjects. Remarkably, IL-6 was very high (>110 pg/ml) in the two patients with severe disease. Moreover, in patients 1 and 3, the IL-6 concentration was rising despite therapy including steroids, aspirin and anticoagulants. Lactate dehydrogenase also decreased from the first nimotuzumab dose, while ferritin and CRP declined after two antibody infusions. The three patients had a rapid and significant clinical improvement. The CT scans at discharge showed a major resolution of the lung lesions and no signs of fibrosis. Pulmonary function tests, together with lung ultrasound echocardiography and new CT scans, will be done as part of the patients' follow-up.

Conclusion

We hypothesize that safe EGFR antagonists, like nimotuzumab, might reduce the morbidity and mortality associated with SARS-CoV-2 infection. More than 1000 severely or moderately ill patients have already been treated with the antibody in combination with other drugs included in the national protocol for COVID-19. The analysis of the complete series is ongoing.

Future perspective

Safe EGFR-targeting drugs might also be used to treat acute respiratory distress syndrome, associated with acute hypoxemia, pulmonary damage and fibrosis.

Summary points

- In COVID-19, EGFR is upregulated in the type II alveolar epithelial cells after the STAT-1 reduction and the acute lung damage.
- EGFR overexpression further activates STAT-3 and increases lung pathology.
- The EGFR pathway is also one of the major nodes in pulmonary fibrosis.
- Nimotuzumab is a humanized antibody that recognizes EGFR.
- Three severe or moderate COVID-19 patients with multifocal interstitial pneumonia were treated with nimotuzumab in combination with antiviral, anticoagulant and steroid therapy.
- Treatment was safe and no adverse events were detected.
- Nimotuzumab, combined with the standard of care, reduced circulating IL-6 concentrations in the 3 COVID-19 patients.
- Other inflammatory markers (ferritin, LDH, CRP and neutrophil–lymphocyte ratio) also declined after antibody therapy.
- The three patients showed rapid clinical and radiological improvement.
- Safe anti-EGFR antibodies like nimotuzumab may modulate COVID-19 associated hyperinflammation and prevent of fibrosis.

Author contributions

T Crombet, M Ramos Suzarte, D Saavedra Hernández and AL Añé-Kouri designed the clinical trial, informed consent and CRFs of the expanded access trial; AA Abdo, J Pi Ávila, R Machado, J Jordán, G Pérez and JA Gutiérrez administered the experimental drug plus SOC and followed the COVID-19 patients at the hospital intensive care unit; AA Abdo and T Crombet drafted the manuscript. All authors reviewed and approved the final manuscript

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Financial & competing interests disclosure

This study was funded by the Cuban Ministry of Health and the Center of Molecular Immunology. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have followed the principles outlined in the Declaration of Helsinki for human experimental investigations. The study was approved by an ethical review board and by the National Regulatory Agency. All patients provided informed consent for the investigational treatment and for publication.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data on three patients (RPCEC00000369). Individual participant data that underlies the results reported in the article, after de-identification are available along with the study protocol. The data will be available 9 months after article publication and will end 36 months following article publication. The information will be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose and for individual participant data meta-analysis. Proposals may be submitted up to 36 months following article publication. After this date the data will be available in our data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposal and accessing data may be found at <https://rpcec.sld.cu/ensayos/RPCEC0000369-Sp> or <https://rpcec.sld.cu/en/trials/RPCEC00000369-En>.

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