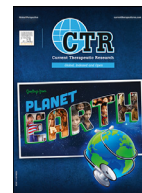




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## Original Research

# The Effects of the Uncontrolled Use of Biomodulina T on the Severity of Severe Acute Respiratory Syndrome-Coronavirus 2 Infection in Older Cuban Adults: An Open Label Evaluation

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## ABSTRACT

**Background:** The ongoing coronavirus disease 2019 (COVID-19) pandemic is a worldwide public health threat. Millions of people are at risk and older adults are more susceptible to developing the most serious manifestations of the disease, in part because of the effects of ageing on the immune system. Biomodulina T is an injectable immune modulator that has been licensed for use in Cuba for many years.

**Objective:** An open-label, uncontrolled trial was conducted to investigate whether or not it might be useful to prevent or modulate the serious effects of severe acute respiratory syndrome coronavirus 2 infections in older Cuban adults before the availability of vaccinations.

**Methods:** From April 12 to August 31, 2021, 1239 adults aged 60 years and older, unvaccinated against COVID-19 were recruited from the José Luis Dubrocq polyclinics, to receive Biomodulina T, 1 intramuscular 3 mL dose weekly for 6 weeks. Each person was visited at home weekly to be administered Biomodulina T. Once daily patients were seen by a medical student to collect information on any possible adverse events related to the medication as well as any symptoms of COVID-19. The possible usefulness of the intervention and its potential adverse events were assessed based on the number of older adults who became infected with COVID-19, and the severity of any symptoms reported or noted both during the 6-week treatment period and during an additional 6-week posttreatment observation period.

**Results:** Sixteen patients were diagnosed with symptomatic COVID-19 during the intervention using a specific reverse transcription polymerase chain reaction test. One patient died because of COVID-19. The most common preexisting diagnoses in treated patients included high blood pressure in 64.8%, diabetes mellitus in 19.85%, and ischemic cardiopathy in 13.88%. Biomodulina T was well tolerated. Only infrequent, mild, transient, and self-limited adverse events were identified. Both the incidence of COVID-19 infections and the overall mortality rate were lower in the treated patients than what was observed in the untreated general population of this Cuban province during the same time period.

**Conclusions:** Although further, confirmatory, double-blind, controlled clinical trials are needed, Biomodulina T injections were well tolerated, and the results of this open, uncontrolled study suggest that it may have been useful to decrease the incidence and severity of symptomatic COVID-19 infection in these older Cuban adults. (*Curr Ther Res Clin Exp.* 2022; 82:XXX-XXX) © 2022 Elsevier HS Journals, Inc

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## Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic is a worldwide public health problem with millions of people at risk of

serious symptoms or death.<sup>1</sup> In an attempt to control or decrease further transmission, Cuba developed multiple strategies in which the biotech industry has been deeply involved.<sup>2,3</sup> As part of these strategies, 23 drugs are in use throughout the country and 5 vaccine candidates are the subject of ongoing research. Three of these vaccines—Abdala, Soberana 02, and Soberana Plus—have now been approved by national authorities for emergency use but were not available when this study was initiated.

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The proportion of the adult population that is aged 60 years or older has steadily increased in Cuba as well as worldwide, and data suggest this increase will continue for many years to come. Because older adults are more likely to experience the most serious manifestations of COVID-19, at least in part the result of the ageing of the immune system, it is especially important to identify methods to either prevent infections or mediate their effects in this population subgroup. Although immunizations have now been proven to be effective in this and younger populations, there were no approved immunizations available in Cuba when the public health intervention described herein was designed and initiated.

Among several Cuban products that was and still is in use for treatment of COVID-19 is Biomodulina T, a biological immunomodulator of natural origin present in polypeptide fractions obtained from the bovine thymus.<sup>4,5</sup> This medication exhibits cellular regeneration and immunomodulatory properties, presumably because it stimulates lymphoblastoid mitosis and thus the differentiation of T lymphocytes. In models of acute inflammation, edema, and chronic inflammation, Biomodulina T has been reported to illicit an anti-inflammatory response associated with the modulation of the induced inflammatory response and inhibition of the release of arachidonic acid by macrophages.<sup>6,7</sup> In a 2000 Cuban study, the authors reported that Biomodulina T permitted the recovery of the thymic mass in children with atrophy or hypoplasia of the gland, with a subsequent increase in the release of hormones by thymic epithelial cells, as well as a decrease in recurrent infections.<sup>8</sup> Another clinical study suggested possible beneficial effects of this medication in patients with relapsing–remitting multiple sclerosis.<sup>9</sup>

Biomodulina T administration temporarily expands naïve CD4+ T-cell production, thymic emigrant cell production, and stem cell-like memory CD 8+ T-cell production.<sup>10</sup> Peripheral production and maintenance of the naïve T-cell repertoire is critical to normal immune system function.<sup>5,10</sup> The biological effects of Biomodulina T and the results of its clinical use suggest that it might be useful to reverse T-cell immunosenescence and restore the immune response in older adults and immunocompromised people, decreasing the risk of the more serious complications of COVID-19 infections.<sup>4</sup> Although Biomodulina T might not prevent COVID-19 infection, it could help stimulate the immune systems of individuals, and thereby modulate symptoms and improve responses to this viral infection.

The aim of this article is to present the results of a government approved, experimental public health intervention involving repeated Biomodulina T injections as a way to potentially ameliorate or prevent symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19 disease, in older adults in an urban area in Matanzas, Cuba.

## Research Design and Methods

The intervention was carried out at 3 downtown medical offices of the José Luis Dubrocq Polyclinics, Matanzas City, Matanzas Province, Cuba, from April 12, 2021, to August 31, 2021. The intervention began during the period of time when the highest numbers of new cases of COVID-19 were being reported in this territory and before the availability of vaccines or other proven treatments.

Older, unvaccinated adults (aged 60 years or older) were recruited to be given Biomodulina T, 1 3-mL intramuscular dose once weekly for 6 weeks followed by an additional 6-week surveillance period. The total intervention lasted 12 weeks. The recruitment was done by the staff of the medical offices responsible for this population along with an intervention team.

- The product: Biomodulina T (Centro Nacional de Biopreparados, Bejucal, Cuba)

- Sanitary registry No.: B-08-038-J05
- Inscription date: May 22, 2008
- Presentation: Box, 25 ampules of 3 mL each

## Enrollment and patient selection

A total of 1295 older adults were assessed for eligibility (Figure 1). Twelve did not meet the inclusion criteria, 38 declined to participate, and 4 were not enrolled because they reported being in contact with a COVID-19–positive person. According to the Cuban National Protocol for COVID-19,<sup>3</sup> contacts of patients testing positive for COVID-19 are isolated in health institutions for confirmation; therefore, contacts of suspected COVID-19 patients could not be included in this intervention study.

Patients were excluded from the intervention for any of the following: a history of sensitivity to Biomodulina T; having received any antibiotic, antiparasitic, or steroid therapy during the preceding 4 weeks; the presence of any chronic noncontrolled diseases; participation in another intervention or clinical trial; or in the case that they were judged by the study staff to be unlikely to attend all required follow-up visits. Eligible patients who had none of the exclusion criteria, and from whom written informed consent was obtained, were enrolled in the intervention.

The general and oral health of each patient were evaluated during the first visit by both a generalist physician and a general odontologist, respectively. The study team visited each patient once weekly at home to administer Biomodulina T and to provide information about how to prevent COVID-19 infection. In addition, a medical student visited each patient daily for the entire study period (6 weeks of injections and during the 6-week postinjection surveillance period) to inquire about any possible adverse events related to the medication or any evidence of infection.

A total of 1241 adults were originally allocated to receive the medication, but 2 died from the complications of a chronic, non-communicable disease (diabetes mellitus). These 2 patients had transient ischemic attacks that led to fatal strokes before receiving the first dose of the medication. Therefore, 1239 patients, 485 men and 754 women, all aged 60 years or older, who were regular patients of medical offices number 8, 15, and 16 of the polyclinic were included, received all 6 once weekly injections, and then completed the additional 6-week follow-up surveillance period (see the Figure 1).

## Ethics approval

The study was approved by both the institutional review board of the José Luis Dubrocq Polyclinics (Code-003, Friday, January 29, 2021) and the institutional review board of the University of Medical Sciences, Matanzas City, Cuba (Code-23, February 19, 2021). The science and technology office of the Cuban Ministry of Public Health provided oversight of the entire study process from its inception. Adult patients were fully informed about the aims and potential risks of the interventions and the medication used, as well as the fact that their participation was optional. Comprehensive oral instructions regarding the intervention were given to each participant by a health professional of on the team. Written informed consent was obtained from all adults before the intervention was begun. Personal medical histories were assessed from the personal medical record of each adult located at the medical offices, as is required by the Cuban Program for Primary Care.

## Evaluation of effectiveness

The effectiveness of the intervention was based on the number of older adults who developed symptomatic COVID-19 infection during the 6-week period receiving the medication or during

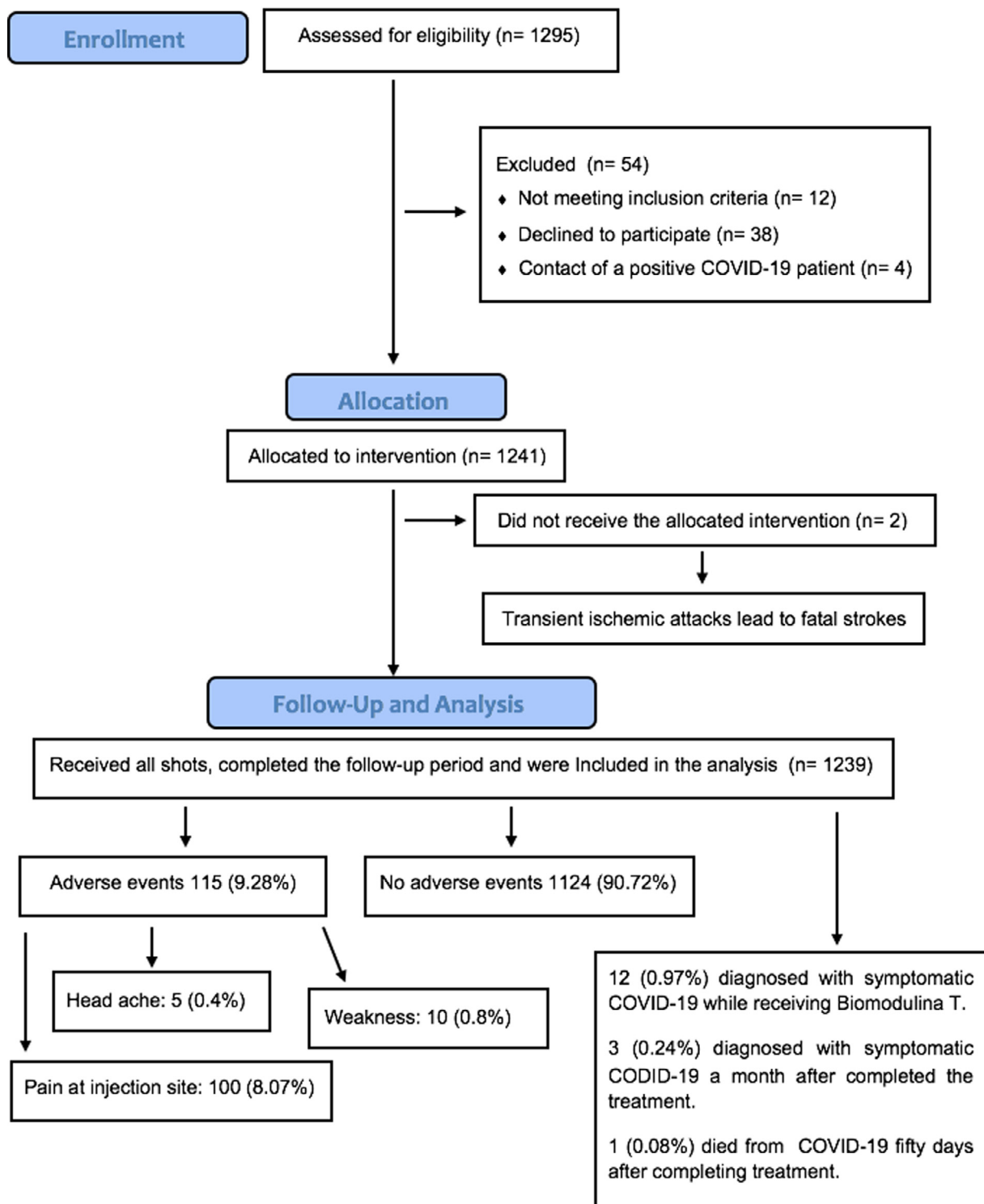


Figure 1. Flow diagram of the intervention.

the 6 weeks after the last injection as well as the outcome of any infections. Infections were confirmed by reverse transcription polymerase chain reaction test and clinical evaluation.

No patients were vaccinated against COVID-19 either before or during the 12-week study period. The number of new positive cases in the study patients was compared with the total number of infections noted in the nonstudy population in the same Matanzas region during the second and third trimester of 2021 as a surrogate marker of efficacy.

Evaluation of the Biomodulina T safety profile

Regardless of their suspected causal relationship to Biomodulina T, details of all clinical adverse events were recorded. Adverse events were defined as the development of any signs or symptoms that did not exist before, or became more serious following the commencement of the treatment. Serious adverse events were defined as death, any life-threatening, disabling, or incapacitating events, or those requiring hospitalization.

**Table 1**  
Demographic characteristics of older adult patients treated with Biomodulina T (N = 1239) at admission as reported on data collection forms.

Variable	Biomodulina T-treated group
Sex*	
Male	485 (39.1)
Female	754 (60.8)
Age† (y)	75.6 (60–104)

\* Values are presented as n (%).

† Values are presented as mean (range).

**Table 2**  
Preexisting diagnoses of older adult patients (N=1239) in the Biomodulina T-treated group.\*

Variable	Biomodulina T-treated group
High blood pressure	799 (64.48)
Diabetes mellitus	246 (19.85)
Ischemic cardiopathy	172 (13.88)
Bronchial asthma	81 (6.53)
Cerebrovascular accident including stroke	16 (1.29)
Cancer	15 (1.21)
Chronic obstructive pulmonary disease	8 (0.64)
Chronic kidney disease	2 (0.16)
Other preexisting diagnoses	143 (11.54)

\* Values are presented as n (%).

### Data management and statistical analysis

Data regarding the intervention and adverse events were recorded on predesigned case report forms filled out by a health professional and double-checked by the person responsible for the intervention. Microsoft Excel for Mac, version 16.16.27 (Redmond, Washington), was used for data entry and analyses.

### Results

From April to August 2021, a total of 1239 older adults; 485 men and 754 women, mean age 75.6 years (range = 60–104 years), from the José Luis Dubrocq polyclinics, were enrolled and treated with Biomodulina T (see the Figure 1 and Table 1). All patients received all 6 doses of Biomodulina T and did not miss any scheduled evaluation appointments.

High blood pressure (n = 799; 64.48%), diabetes mellitus (n = 246; 19.85%), and ischemic cardiopathy (n = 172; 13.88%) were the most common preexisting diagnoses identified in this intervention group (Table 2). Other, less commonly identified preexisting diagnoses are also noted in Table 2.

Only 16 (1.3%) patients developed laboratory confirmed symptomatic COVID-19 during the 12-week study period; 12 during the initial 6 weeks while receiving the shots, another 3 during the first month after completing the injections, and another, single patient who died from a severe COVID-19 infection 50 days after the final dose. All confirmed infected adults were symptomatic and their infections were diagnosed by reverse transcription polymerase chain reaction test. The incidence of COVID-19 observed among the people receiving the medication was equivalent to 1.291 per 100,000 individuals. This is less than the incidence reported in the Matanzas province during the same time period, (9.441 per 100,000 individuals). Similarly, the mortality rate (0.08%) was lower among individuals receiving the intervention than was reported for the general population of the province (0.81%) during this time period. The incidence and mortality data were collected from the daily and weekly reports for the Matanzas Office of the Cuban Ministry of Public Health.

Biomodulina T was well tolerated. Only mild, transient, and self-limited adverse events were notified. One hundred (8.07%) adult patients reported pain at the injection site, 5 (0.4%) reported

a headache, and 10 (0.8%) reported weakness. No unexpected or serious adverse events occurred, and none of the patients needed to discontinue treatment or receive additional drugs to treat an adverse event.

### Discussion

The current COVID-19 pandemic is a major public health problem affecting people of all ages.<sup>5</sup> Despite the existence of national interventional strategies lead by the Cuban Ministry of Public Health, with the support and participation of the Cuban government,<sup>2,3</sup> in provinces throughout Cuba designed to preserve population safety and to reduce the number of hospitalization and deaths.

It is well known that vaccination, wearing a face mask, cleaning hands frequently, and keeping a safe distance from others are effective ways to decrease the number of new infections. However, infections still occur and due to the ageing of the immune system, people older than age 60 years are more likely than younger people to experience the most serious consequence of these COVID-19 infections. These facts led the Public Health System in Matanzas, to begin this open label, uncontrolled health intervention: administration of Biomodulina T to adults, aged 60 years and older, living in the capital city of the province. The intervention was given to 1239 nonvaccinated older adults and was begun at the same time that the most cases of COVID-19 were being identified in the territory.

The only vaccines available in Cuba during the time period of this study were those that were developed in Cuba. Vaccinations using these vaccines began in cluster groups such as public health workers and other first responders in the middle of the postinjection follow-up period of this study. In the municipality where the study population lived, vaccinations began in these clusters by July 2021, but were not available to the older adults included in this study until the second half of August 2021 when only some of these patients were in their surveillance phase. Vaccination was delayed in these patients to allow them to finish the 15 days remaining in their participation. This delay was approved by the local institutional review board.

Biomodulina T is a biological immunomodulator of natural, biologic origin, composed of a specific extract from bovine thymus. The product has been in use in Cuba for more than 15 years with excellent results reported in reducing the frequency of upper respiratory infections, decreasing hospital admissions, and drug intake.<sup>5,8,9,11</sup>

Only 16 treated older adults developed symptomatic COVID-19 during the intervention and only 1 of whom died, suggesting that nonvaccine technologies currently in use to prevent the transmission—face masks, cleaning hands frequently, and keeping a safe distance from others—when complemented by Biomodulina T can be very effective in reducing the incidence of COVID-19.

The open label, uncontrolled design limits the conclusions that can be drawn. In part this is because the injections were not the only intervention provided. The relationship created between the researchers and these older adults during the visits is likely to have influenced the outcomes. The researchers created an environment where information related to the pandemic and other health topics were shared and discussed and adapted to be more understandable to older adults. This relationship is likely to have improved the understanding and perception of these adults about the importance of using masks, cleaning hands frequently, and maintaining physical distancing.

The incidence of COVID-19 among the elderly Cuban population receiving the medication was 1.291 per 100,000 individuals, which is less than the incidence at Matanzas in the same period of time of 9.441 per 100,000 individuals. The mortality rate was also

much lower in the patients given the intervention drug (0.08%) than that reported throughout the province (0.81%), despite being a nonelderly population.

Biomodulina T was well tolerated. Only relatively uncommon pain at the injection site, weakness, and headache were reported. Although Biomodulina T is not an anti-COVID-19 medication, its immunomodulant effects may improve the immunological status of older adults and therefore allow them to better tolerate viruses like SARS-CoV-2. Double-blind, controlled clinical trials are needed to assess whether or not this biological product, when used in addition to vaccines and proven personal protective tools and social practices, can provide a way to reduce new symptomatic COVID-19 infections, hospitalization, or deaths in elderly populations. Such studies might even be ethically possible in vaccine averse populations.

Vaccines have dramatically reduced the opportunity of humans to experience the consequence of some infectious diseases, including smallpox, poliomyelitis, tuberculosis, and yellow fever; however, in older adults, where T-cell immunosenescence naturally occurs, Biomodulina T could act as a vaccine enhancer.<sup>4</sup> Biomodulina T could be also useful in people with medical conditions where vaccination is ineffective, not recommended, or refused on religious or other grounds.

### Conclusions

Although further, confirmatory, controlled clinical trials are needed, Biomodulina T injections were well tolerated safe and the results of this open, uncontrolled study suggests that it may have been useful to prevent decrease the incidence and severity of SARS-CoV-2 in older Cuban adults in Matanzas.

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