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Coronavirus Pandemic

Outpatient treatment of COVID-19: an experience with 552 cases in Mexico

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Abstract

Introduction: The impact of the coronavirus disease 2019 (COVID-19) pandemic has globally challenged health services, especially because when the pandemic first reached Mexico, in February 2020, there was no known effective and safe treatment. A treatment scheme was offered by the Institute for the Integral Development of Health (IDISA) in Mexico City from March 2020 to August 2021 when there were many patients with COVID-19. This report summarizes the experience managing COVID-19 with this scheme.

Materials and Methods: This is a descriptive, retrolective study. The data was obtained from the case files of the patients who attended the IDISA from March 2020 to August 2021 with COVID-19. All the cases were treated with the scheme consisting of nitazoxanide, azithromycin, and prednisone. Various laboratory blood tests and chest computerized tomography scan were done. When indicated, supplementary oxygen, and another specific treatment were used. A standardized clinical recording was conducted for 20 days based on symptoms and systemic symptoms.

Results: Based on the World Health Organization criteria, the patients were classified according to the disease severity: 170 mild, 70 moderate, and 312 severe cases. The outcome was the discharge of 533 patients after their recovery, 16 were excluded from the study, and 6 died.

Conclusions: The use of nitazoxanide, azithromycin, and prednisone proved to be effective as it resulted in improvement of symptoms and in successful outcomes for the management of COVID-19 outpatients.

Key words: COVID-19; treatment; Nitazoxanide; Prednisone; Azithromycin.

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Introduction

The lack of a safe and effective etiologic treatment against coronavirus disease 2019 (COVID-19) has led to the exploration of several alternatives that have shown some benefit against the betacoronavirus severe acute respiratory syndrome coronavirus (SARS-CoV-2), the agent that causes this rapidly spreading disease that is associated with severe forms of respiratory diseases [1].

No medicines were consistently used against this virus since November 2019. The situation demanded the exploration of alternative therapies to prevent the disease progression towards its fatal outcomes [2]. At the beginning of the pandemic, there were no guidelines or World Health Organization (WHO) recommendations. Multiple pharmacological alternatives were proposed and some antimicrobials such as azithromycin were tested. Antiparasitic agents such as ivermectin, hydroxychloroquine, and nitazoxanide that had at least some antiviral activities were used as the main options. In addition, corticosteroids (dexamethasone, hydrocortisone, and others) were also used. The aim was to provide a treatment that could restrict viral replication and the enhanced immunologic-inflammatory response ("cytokine storm") observed in the patients as the result of the infection [1].

Promptness of diagnosis and treatment are critical for a favorable outcome. Decreased viral replication and the dampening of the increased inflammatory response are key steps for preventing COVID-19 progression to more severe forms and rapid recovery. It may also be possible to suppress the onset of functional or structural sequels in patients who had surpassed the acute phase.

Based on the highly proinflammatory profile of COVID-19, several options have been proposed against the disease and its etiological agent. A retrospective study conducted with 201 patients in China showed that methylprednisolone (MP) administration decreased the risk of death in patients with severe acute respiratory syndrome (SARS) [3]. Another preliminary report based on patients admitted in the intensive care unit indicated that low doses of systemic corticosteroids had no effect on mortality. However, it was shown that their use during the first days of the disease's onset they may improve oxygen saturation [4]. A recently published clinical trial with 277 patients affected by moderate to severe SARS reported the administration of dexamethasone 20 mg/day doses for 5 days and subsequently 10 mg/day through days 6 to 10 of the management [5]. This study concluded that a corticosteroid therapy is associated with a considerable decrease of the mechanical ventilation time as well as hospital death rates [6].

Despite being initially developed to treat diseases caused by protozoans, the antiviral properties of nitazoxanide (NTZ) and its metabolite tizoxanide have raised some interest due to their property to act as a broad-spectrum antiviral through diverse mechanisms. The latter may differ depending on the type of virus, although they generally interfere with the pathways regulated by the host, including the interferon or mTORC1 signaling, both involved in viral replication. They also display antiviral mechanisms including the inhibition of RNA or DNA replication, a direct inhibition of viral protein expression, the interference with the host cell metabolism, and the restriction of viral immune evasion mechanisms [7]. NTZ is indicated as an antiviral in some clinical presentations of influenza and in vitro studies have shown potent antiviral effects against MERS-CoV. Other in vitro studies have recently observed that it also has an inhibitory effect against SARS-CoV-2 [8]. Cao *et al* reported that NTZ may inhibit bovine (L9) and murine coronaviruses, mouse hepatitis virus (A59), as well as human enteric coronavirus (4408) cultured in mouse astrocytoma (CBT) and fibroblasts (17Cl-1) with a 0.3 μg/mL inhibitory concentration (IC_{50}). This effect comprises the inhibition of the viral N protein [9-10]. Wang *et al* reported that NTZ may inhibit the SARS-CoV-2 within Vero E6 cells (ATCC-1586) after they were infected with SARS-CoV-2/Wuhan/WIV04/20192 at micromolar concentrations [11].

Azithromycin (AZM) is a macrocyclic lactone macrolide antibiotic that reportedly exhibited activity against the Zika and Ebola viruses. It has also significantly decreased the Rhinovirus-16 load in bronchial epithelial cells, including the expression of type I and III interferons in cells from donors with chronic obstructive disease. Remarkably, only azithromycin has shown increased interferon induced by 1B and 16 rhinoviruses and the mRNA expression of the interferon-stimulated gene as well as protein production. The antibiotic leads to a significantly reduced rhinovirus replication and release in bronchial epithelial cells [12].

Another recent publication reported that AZM in combination with hydroxychloroquine efficiently enhanced SARS-CoV-2 elimination and this led to a faster virologic resolution as demonstrated by a negative nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR) as well as the improvement in patients with COVID-19 [12]. A study conducted by Magagnoli *et al.* suggested an increased overall mortality of patients treated with hydroxychloroquine without AZM, when compared to the standard of care alone. There is no evidence showing that the use of hydroxychloroquine, with or without AZM, decrease the risk of mechanical ventilation in admitted patients with COVID-19 [13].

The first case of COVID-19 in Mexico was confirmed on February 28, 2020, and since then its spread was accelerated, and finally led the country to occupy one of the top places in mortality and sequelae within the global statistics with at least 271,481 deaths and 3,548,398 confirmed cases. By the time this manuscript was prepared (August 30th, 2021), a third outbreak occurred, during the vaccination campaign, and reached parts of the country that were so far unaffected by the pandemic [14].

The Institute for Health Integral Development (IDISA, acronym in Spanish), is an organization with more than 16 years of experience and brings together a group of physicians with diverse specialties for healthcare purposes and to establish disease prevention strategies based on knowledge dissemination, emphasizing on an effective vaccination strategy as the basis for disease prevention.

Since the report of the first COVID-19 case in Mexico (February 28th, 2020), a partial on-site healthcare strategy for COVID-19 diagnosis and outpatient treatment had been established. The aim of this work is to summarize the clinical and therapeutical experience regarding the diagnosis and the integral management of COVID-19 patients during appropriate times for their ambulatory/house management.

Methodology

This is a descriptive, retrolective study in which the data obtained from COVID-19 patient records at the IDISA, Mexico City, were analyzed.

The clinical criteria for COVID-19 established by the WHO was used to include patients who requested medical treatment for COVID-19. We established a model of care for COVID-19 patients and treated them starting in March 2020. This report includes 552 records of patients treated with a therapeutic regimen that consisted of NTZ, prednisone and AZM (Table 1), as well as individualized prescription of some adjuvants.

Clinical model

The medical care team was comprised by five specialized physicians who, right from March 2020, provided care to all attending patients.

Inclusion in this program were based on the symptoms presented in Table 2; anyone who reported at least one symptom from group A + at least one from group B + at least one from group C were included in the program. The recording of each case was established with this information and detailed instructions were provided to the patient and his/her relatives to initiate the treatment. Overall measurements (rest, food, mobility), any medication taken (dose, regime, duration), the recorded clinical data such as temperature per time schedule, oximetry, heart rate and, for diabetic and hypertension patients, capillary glycemia and blood pressure, respectively, were recorded.

The following diagnostic adjuvants were requested: blood biometry, globular sedimentation rate, basic blood chemistry, ferritin, fibrinogen, D dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), and a chest CT scan, to have a complete evaluation and an informed treatment strategy. Furthermore, other information regarding the patients including prescriptions prescribed by other physicians or self-administered was collected and analyzed.

Clinical follow-up was conducted through phone calls made by the physician (at least one per day, based on the progression) or calls made by the patient/relative to the physician right after the detection of some serious symptom such as fever, < 90% oxygen saturation, dyspnea, and heart rate above 120 or less than 50 beats per minute.

In some cases, adjunctive treatment agents were added. Supplementary oxygen through a mask and a reservoir was indicated if the patient showed a ≤ 85% capillary oxygen saturation (response-dependent dose), as well as 4.5 mg formoterol and 160 mg budesonide (two shots every 8 hours) as spray provided with an antistatic spacing chamber support (AerochamberÒ). Rivaroxaban (10 mg/day for 10 days) was included if the serum D dimer levels were above 500 ng/mL and 100 mg benzonatate pearls every 4 hours were indicated in the case of cough crisis that decreased oxygen saturation to < 90%.

Patient discharge occurred when the following criteria were met: decreased symptoms, lack of dyspnea, > 90% oximetry. An on-site appointment was scheduled for the patient at the IDISA facilities to perform an integral clinical assessment, to evaluate the presence of residual symptoms, and to identify data compatible with "prolonged COVID-19" to provide general indications for discharge. The integral clinical assessment was complemented with an interview designed to detect related symptoms the previous day and with a complete physical examination.

The discharge criteria were the following: ≥ 90% oximetry, no pathologic sounds in lung fields, no dyspnea. After this, the patient was discharged and pulmonary rehabilitation was indicated (if needed) and general preventive measures were integrated to their everyday activities.

Ethical aspects

This report includes information contained in the clinical records of patients treated at the IDISA, who voluntarily and freely requested their care. Due to the restrictions imposed by the pandemic in March 2020, contact with IDISA was established by telephone call and the assigned physician explained the care process, specific instructions on medications and follow-up conditions, which were expressly accepted by each patient voluntarily. In addition, it was explained to them

Table 1. Medications, doses, and frequency.

Medication	Dose	Frequency
Nitazoxanide	500 mg	Each 12 h/6 days
Azithromycin	500 mg	Each 24 h/6 days
Prednisone	50 mg	Each 24 h/6 days
	25 mg	Each 24 h/6 days
	12.5 mg	Each 24 h/3 days

Table 2. Symptoms to be admitted in the program.

Group A	Group B	Group C
Fever	Headache	Diaphoresis
Pharyngodynia	Fatigue	Diarrhea
Anosmia and/or dysgeusia	Myalgias and/or arthralgias	Chest pain
Cough		
Dyspnea		
Oximetry < 90%		

that their clinical data would be recorded in an electronic system (clinical record) and that they could be used to generate statistics or specific studies.

As it is a retrolective and descriptive review of clinical records, the protocol was not submitted to an ethics committee.

Data collection

A standardized computerized clinical recording instrument was implemented to be used by the physicians who treated patients within the scope of this model. Every examined case was identified by a unique sequential registration number. When the first phase was concluded, the data from all patients were transferred to a single database to be electronically managed.

Statistics

Data collection and analysis was performed with Microsoft Excel® v16.52 software. Actual and relative frequencies were determined. The percentage of patients observed during the 20-day evolution was recorded as well as their evaluation per symptom classified by the system. 48 symptoms were analyzed. Graphs for several quantitative variables were plotted during the 20 days established by the model. A descriptive analysis of the most common symptoms was performed to evaluate their duration as mean ± standard deviation. Finally, a frequency analysis was performed between initial vs final oximetry for each symptom.

Results

A total of 552 patients were included in the IDISA healthcare program between March 2020 and May 2021. Their general features are presented in Table 3, and their comorbidities are presented in Tables 4-5.

Table 4. Comorbidities.

	N (%)
No comorbidities	241 (43.7)
One	171 (30.9)
Two or more	140 (25.4)

Table 5. Types of comorbidities.

Disease	N (%)
Diabetes mellitus	61 (11.1)
Obesity	153 (27.7)
Systemic arterial hypertension	100 (18.3)
Lung disease	8 (1.4)
Hypothyroidism	23 (4.2)
Heart disease	10 (1.8)
Cancer	4 (0.7)
Asthma	6 (1.1)

Table 3. Patient features.

Characteristics	Value
Gender	
Men	256 (47.3%)
Women	285 (52.7%)
Age	
Mean	47.8 ± 14.6
18-30 years old	13.7%
31-60 years old	67.0%
> 60 years old	19.3%
Mean weight (kg)	76.7 ± 16.7 kg
Mean height (m)	1.7 ± 0.1 m

The discomforts pointed out by the patients were of diverse nature and included general, respiratory, neurological, gastrointestinal, ocular, and cutaneous symptoms. Among these, the most observed were the following: fever, headache, fatigue, myalgias, arthralgias, diaphoresis, pharyngodynia, cough, dyspnea, chest pain, back pain, diarrhea, dysgeusia, and general discomfort (Table 6). Among the 552 attended patients, 170 (30.7%) were classified as a mild case, 70 (12.7%) as a moderate case, and 312 (56.6%) as a severe case based on the WHO criteria [15].

Medication was administered as follows: NTZ and AZM was indicated to all 552 patients (100%) for 6 days, and prednisone was indicated for an average of 13.2 ± 3.2 days. Formoterol and budesonide were prescribed in 136 cases (24.6%), and they were maintained for up to 2 months after the discharge; 143 patients (25.9%) received rivaroxaban for 10 days; supplementary oxygen was provided to 144 (26%) patients by using a mask with a reservoir.

Out of 552 patients, 533 were discharged based on clinical improvement and they were provided with general indications. Pulmonary rehabilitation was prescribed for some of them. Another 16 (2.9%) were excluded from the program as communication with them was lost or they decided to attend to other physicians. Finally, 6 (1%) died. The features of these

Table 6. Symptoms at the time of seeking medical care.

Symptoms	%
Fever	29.2
Headache	42.8
Fatigue	45.7
Myalgias	34.8
Arthralgias	28.3
Diaphoresis	31.9
Pharyngodynia	42.0
Cough	34.8
Dyspnea	15.8
Chest pain	14.3
Back pain	24.3
Diarrhea	13.6
Dysgeusia	19.9
General discomfort	12.1

patients are shown in Table 7, along with the cause of death. In is noteworthy that 5 deaths were caused by the lack of supplementary oxygen as consequence of a supply shortage.

Figures 1-4 show the data for all patients during a 20-day follow-up monitoring their evolution. The beginning of the treatment is indicated as "day 0". Figure 1 shows a high proportion of general symptoms on day 0, its progressive decrease and the clinical resolution of most of them. Fatigue and diaphoresis were persistent in some cases: 3.4% and 1.6%, respectively.

Figure 2 shows the respiratory symptoms: cough, pharyngodynia, dyspnea, and sputum production. Some of these persisted on day 20, such as cough (2.7%), pharyngodynia (0.5%), dyspnea (0.2%), and sputum production (0.9%). They were expressed in a minimal form.

Among the neurological symptoms the following were noteworthy: anosmia, insomnia, and heat sensation. The first two were the most important and persistent (Figure 3). Regarding gastrointestinal symptoms, the presence of diarrhea and abdominal pain were important. These disappeared by day 20 (Figure 4).

Figure 1. General symptoms on day 0 and their evolution at 20 days.

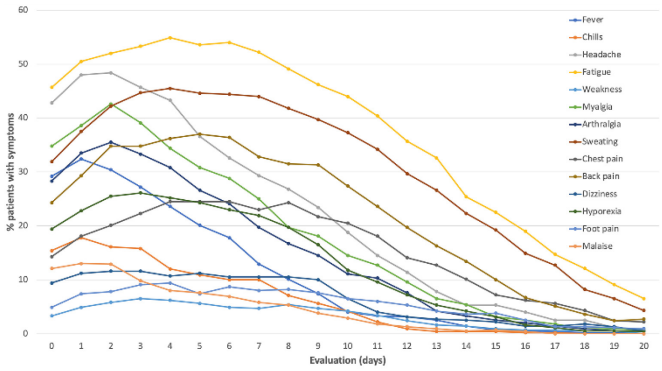

Figure 2. Respiratory symptoms evolution from day 0 to day 20.

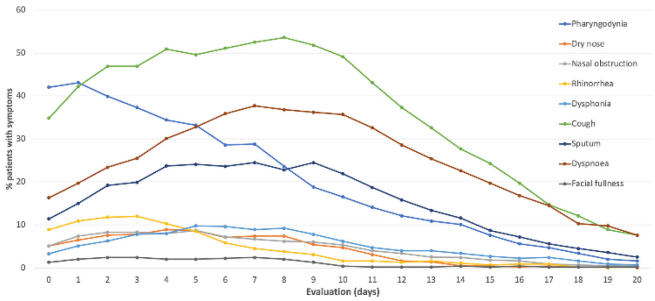

Figure 3. Neurological symptoms evolution from day 0 to day 20.

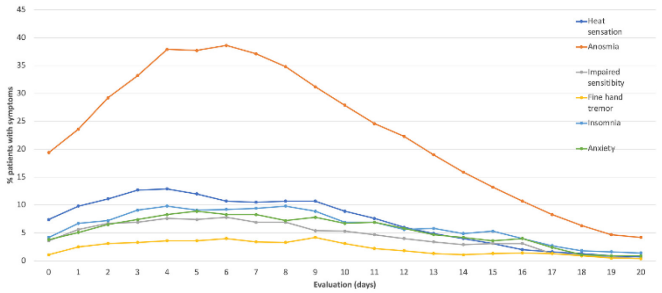

Figure 4. Gastrointestinal symptoms evolution from day 0 to day 20.

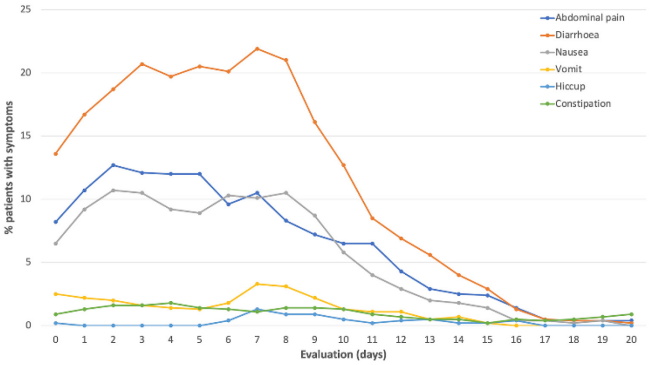

Table 7. Mortality.

Patient registration number	Gender	Age (years)	Comorbidity	Cause of death	Days attended at IDISA
114	Male	60	DM	Desaturation	14
136	Male	54	SAH	Desaturation	28
140	Male	68	No	Desaturation	18
447	Male	51	Ob SAH	Desaturation	14
454	Male	54	No	AMI	23
466	Male	52	Ob	Desaturation	8

DM: Diabetes mellitus; SAH: systemic arterial hypertension; Ob: Obesity; No: none; AMI: acute myocardial infarction.

Discussion

In face of the health crisis caused by the COVID-19 pandemic and based on the medical literature available up to March 2020, we integrated a therapeutic package that included NTZ, AZM, and prednisone. The first two were included because they possess documented antiviral activity, whereas the last one is a corticosteroid with potent anti-inflammatory activity and is easily administered by the oral route. This treatment was applied by using the method described here. Its basic premises and perspectives are:

Inclusive: It considers the patient as the "key" for contact/contagion, including his/her family core based on their need of support and as potentially infected.

Remote during the first days and on-site or virtually for discharge assessment.

Timely, based on clinical data and diagnostic adjuvants, depending on the needs of the individual case.

Instructive for the patient and his/her family.

Integral and multisystem regarding the individual ("key" patient) and the family.

Close to the patients and their relatives with a daily follow-up.

Based on the results obtained, we may state that the treatment provided to the patients at IDISA proved to be effective. A significant number of COVID-19 patients were treated at different clinical stages, from a mild presentation to severe cases, and 1% mortality was observed.

This regime that combines NTZ, AZM, and prednisone was established based on evidence indicating the effectiveness of NTZ [1,2,7]. In fact, some protocols have combined NTZ and AZM [12,16] and optimal results were obtained. It is important to point out that the use of corticosteroids to treat COVID-19 has raised controversy. However, there is evidence supporting its usefulness and advantages [4-6,17]. In our case, while establishing a model of ambulatory care, we decided to include prednisone as it is a drug that can be administered by oral route.

The symptoms of all treated patients improved right from the beginning of the treatment and the evolution was very fast during the following days. As shown in the figures, a trend towards decrease of the initial discomforts is observed in most cases at day 6, when the administration of NTZ and AZM concluded, and they cease from day 7, where the daily dose of prednisone is decreased.

The NTZ dose was established since its plasma levels surpass the EC_{50} for SARS-CoV-2 with a 500 mg dose each 12 hours, especially at the lung level [15]. With such dose and using the indicated combination of drugs, this study obtained optimal results regarding symptom alleviation when compared to the study conducted by Rocco *et al* [18] in which no clinical improvement was observed. Nevertheless, such study showed a decreased viral load. They used 500 mg three times a day for 5 days, although without association with other antiviral or anti-inflammatory medications. The study did demonstrate a decreased viral load, a parameter that was not measured in our study.

Fontanesi *et al.* used a NTZ dose of 600 mg twice for 7 days without being associated with other medication [7]. They observed a clinical improvement from the first days, including an evident improvement of the inflammatory parameters. Our results are very similar to the ones obtained by this study.

Regarding the clinical data, the observed patients did not show fever, whereas cough and fatigue were considerably decreased, although they were still observed as a small percentage. Gastrointestinal and cutaneous symptoms disappeared. Concerning the neurological data, anosmia was persistent in a small percentage of patients. Thus, we consider a satisfactory clinical evolution. Other authors as Fontanesi *et al* [7] have recently demonstrated that the clinical parameters, the mean evolution time, and the hospital discharge were all decreased with NTZ. Mendieta *et al* observed a favorable response measured as the number of hospital admissions after they administered NTZ to COVID-19 patients [19].

It is important to point out that the patients with persistent dyspnea and low saturation levels at day 20 required treatment with high doses of supplementary oxygen and their stabilization was achieved by decreasing oxygen levels. They exhibited extensive lung damage and subsequently they were provided with pulmonary physiotherapy. Among these patients, only three remained with oxygen: a 60-year-old woman who, after 15 months, consumed either 2 liters of oxygen through a concentrating device or one liter of pure oxygen; a 70-year-old male with a heart disease who consumed supplementary oxygen for 3 months after day 20 of our study and up to this date (9 months after) he remains in satisfactory condition), and finally a 60-year-old male who consumed 2 liters of oxygen for a month.

We consider that the results were a consequence of an antiviral effect and possibly an immunomodulation elicited by NTZ and AZM [1,2,8,10,12], besides the potent anti-inflammatory activity of prednisone. To support this statement, we consider several studies, such as the one conducted by Silva *et al.* in which a

significant decrease of the viral load was shown by using NTZ 500 mg BID for 14 days [20]. Chen *et al.* proposed that a higher rate of hospital admissions is proportional to the viral load and, consequently, to the occurrence of most severe disease. They concluded that these medications decrease the viral load as well the disease and hospital admissions [21]. This supports other studies conducted by Pujadas *et al.* and Riediker *et al.* that additionally propose a decreased patient infectivity when the viral load diminishes [22,23]. Fontanesi *et al* reported a decreased acute inflammatory process within a group of patients treated with NTZ [7] as demonstrated by the low values of the serum inflammatory parameters.

We consider that it is important to highlight that NTZ is a medication that has been used for several decades and it has proven to be safe, a fact demonstrated by our study. Other authors support its application to treat COVID-19 and it has been used in pregnant women [7,16,23]. Besides its safety, NTZ is cost-effective and easily available [19]. Thus, it may be a useful medication in the context of the current pandemics. It is also important to point out that Kelleni proposed to use the NTZ + AZM combination to treat COVID-19 since April 2020. After conducting our study, we confirm the usefulness of such combination and we also obtained promising results regarding the ambulatory management of these patients [12].

Evidently, our study would possess more statistical power if a control group was used for comparison. However, considering the results observed on the first cases and because we needed to appropriately treat these patients, we decided that all of them were to be treated with all the medications. This clinical experience produced good results based on a three-medication regime and eventually with some of the adjuvants that showed benefits in other studies. We are not aware of a similar experience regarding either the pharmacological association or the methodology. The latter had to be adapted to a great extent because of the conditions imposed by the COVID-19 pandemic.

Conclusions

More studies are needed to objectively assess the causes of evident improvement shown by the patients. This report describes our experience which was mainly successful, and which may serve as a guide to other groups that also face the current COVID-19 situation. Thus, the healthcare program established at IDISA was successful in treating ambulatory COVID-19 patients.

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