Health and Primary Care

Research Article ISSN: 2515-107X

Efficacy of an experimental phenotype-based treatment for patients with COVID-19

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Abstract

Introduction: Most patients with SARS-Cov2 (COVID-19) improve well; however, a considerable percentage develops acute respiratory distress syndrome (ARDS), require mechanical ventilation and a low rate of patients die. Currently, no effective treatment alternatives have been found. For this purpose, the aim of this study was to evaluate the efficacy of an experimental treatment based on phenotypes to treat patients diagnosed with SARS-Cov2 (COVID-19) hospitalized at the Unión Médica del Norte Clinic.

Materials and methods: A non-randomized controlled before-and-after study design was carried out. The experimental group (n=18) received a medical treatment based on the phenotypic classification of the patients and the control group (n=23) received the treatment as usual (TAU). The use of mechanical ventilation, days of hospitalization and mortality were taken as primary outcomes. As secondary outcomes, we evaluated the presence of acute respiratory distress syndrome (ARDS), D-dimer, platelet count, oxygen saturation (O_2 Sat) and partial pressure by inspired fraction of oxygen (O_2 Pa/Fi).

Results: Primary outcomes: after treatment the experimental group, unlike the control, showed a lower average in the days of hospitalization, patients did not need assisted mechanical ventilation and there were no deaths. Secondary outcomes: after treatment the experimental group had the lowest number of patients with ARDS and showed to be superior to the control in O_2 Pa/Fi.

Conclusions. The experimental treatment by phenotypic classification has shown to be a promising treatment to treat patients diagnosed with SARS-Cov2 (COVID-19). While the results are encouraging, more studies with larger sample sizes are needed.

Introduction

Although research into treatments for the SARS-Cov2 (COVID-19) is prolific, scarce treatment alternatives have been described as clinical efficacious. SARS-Cov2 disease predominantly affects the lower airways and is characterized by dry cough, fever and myalgia or fatigue. Of those with SARS-Cov2, 80% develop asymptomatic-mild disease, approximately 14% require hospitalization and oxygen, and 5% must be admitted to an intensive care unit [1,2]. The condition can become severe and manifest itself as acute respiratory distress syndrome (ARDS) with the presence of sepsis and septic shock, multiorgan failure, including acute renal and cardiac damage [3].

Although the immunopathogenesis of COVID-19 in the immune system is not yet well understood many research have tried to explain it. When the virus enters the body, its receptors encounter respiratory epithelium activating stromal thymic lipoprotein (STL) which triggers the activation of Il-33 and Il-25. These processes are part of the adaptive response mediated by the respiratory sensors of the immune system; the toll like receptors II and IV react by inducing macrophages and neutrophils response to viruses and bacteria. The activation of these receptors depends on T1 lymphocytes, which activate IL-6 and TNF-α. In previous studies that analyzed the extent of this virus at the immune level in critically ill patients in intensive care, in addition to the presence of IL-6, elevated plasma levels of IL-2, IL-7, IL-10, granulocyte colony stimulating factor (G-CSF), interferon-inducible protein-γ (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1-alpha (MIP1A) and TNF-α (1) were found. This inflammatory cascade triggers a series of manifestations, in which the macrophage activation syndrome is involved [4-6]. This syndrome is activated in individuals that exhibited a pleomorphism and immune activity with a predisposition to generate this response. In this inflammatory pathway, the most decisive is cytokine lI6 with great power to induce response in the vascular endothelium due to its inflammatory capacity, generating the induction of microthrombi to different organs causing thromboembolism, mesenteric infarcts, strokes, among others. In histopathological studies of deceased patients, bilateral diffuse alveolar infiltrates with cellular fibromixoid exudates were found, and mononuclear inflammatory lymphocytes were observed in both lungs. These findings support that the inflammatory factors triggered are the product of a cytokine cascade [4-6].

A randomized controlled trial evaluated the treatment efficacy of severely hospitalized patients with SARS-Cov2 (COVID-19) with lopinavir-ritonavir compared to treatment as usual (TAU). The results found no benefit for those patients treated with lopinavir-ritonavir in relation to patients receiving TAU [7]. On the other hand, a review

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Key words: *SARS-Cov2, COVID-19, treatment, phenotype, acute respiratory distress syndrome*

Received: May 14, 2021; **Accepted:** May 21, 2021; **Published:** May 24, 2021

regarding the use of chloroquine and hydroxychloroquine as treatment of patients with SARS-Cov2 showed that both drugs may be plausible to use in efficacy and effectiveness studies due to the *in-vitro* antiviral characteristics observed. These findings support the hypothesis that these drugs could be not only effective but also safe in the treatment of COVID-19 [8-13]. However, in a randomized controlled trial conducted in 150 patients with mild, moderate and severe symptoms, researchers found that the administration of hydroxychloroquine (1200 mg dose for three days and then 800 mg daily for maintenance) compared to usual treatment did not show significant differences in patient recovery [14]. A similar investigation carried out on patients (N= 20) with severe and critical SARS-Cov-2, it was observed that after treatment with tocilizumab, they showed a decrease in the need for oxygen through assisted ventilation, improvements in lung lesions observed in the tomography, body temperature returned to normal and achieved a decrease in blood lymphocytes [15,16]. Moreover in a study conducted with 196 patients treated with tocilizumab and/or with methylprednisolone, it was observed that early treatment with these drugs separately or combined may improve outcomes in non-intubated patients [17]. These findings and the evidence shown by show the usefulness of tocilizumab for the treatment of severe and critical patients infected with COVID-19 [15-17]. Likewise, iron chelators show chelating, antiviral and immunomodulatory effects in vitro and in vivo especially against RNA viruses. These agents may attenuate acute respiratory distress syndrome (ARDS) and help to control SARS-COV-2 (COVID-19). These findings require further studies and randomized controlled designs to fully elucidate the efficacy and safety of iron chelators as therapeutic agents against COVID-19 as an adjunct therapy [18].

Based on the history related to treatment options against SARS-COV-2 and because clinical manifestations in patients with SARS-Cov2 are diverse [19], the option of an empirical categorization of the patients into different phenotypes was considered. This categorization was made based on the interpretation and classification of the symptoms and clinical manifestations of the disease [20,21]. Although there is no previous empirical or theoretical background previously examined of this stratification, it is based on patient's characteristics (based on empirical findings), to adapt the interventions to them according to the stage of the disease and its phenotypic peculiarities leading to an early pharmacological intervention. This strategy would allow an adequate therapeutic approach, either for outpatient management, hospitalization, or intensive care admission; as well as implementing adequate follow-up of patients. The proposed treatment is based on the incorporation and combination of drugs that are promising for intervention in patients infected with SARS-COV-2 due to the clinical manifestations observed by phenotype: chloroquine and/or hydroxychloroquine, lopinavir, ritonavir, tocilizumab, tofacitinib, deferasirox, washed red blood cells, among others.

Therefore, this paper presents the evaluation of a novel intervention for the treatment of SARS-COV-2 (COVID-19). The main objective was to evaluate the efficacy of a protocolized experimental phenotypic treatment for patients diagnosed with SARS-COV-2 (COVID-19) and hospitalized at the Unión Médica del Norte University Clinic.

The hypotheses stablish that after treatment:

1. The mortality rate in the treatment group will be lower than in the control group.
2. The average number of days of hospitalization will be lower in the treatment group.
3. The levels of thrombocytopenia in the patients in the treatment group will be lower.
4. The treatment group will show a greater reduction in D-dimer levels than the control group.
5. The rate of patients with acute respiratory distress syndrome will be higher in the control group.
6. Oxygen saturation levels (O_2 Sat) and partial pressure of oxygen per inspired fraction (O_2 Pa/Fi) will increase more in the treatment group.

Materials and methods

Design

The SARS-COV-2 pandemic has spread rapidly putting national health systems under increasing pressure. In this context, many challenges have emerged in terms of developing and implementing effective and efficacious interventions to address it. According to the Head Medicines Agencies [21], these challenges require pragmatic, flexible and harmonized measures, procedures and methodological designs to find solutions for the high social demands due to the pandemic. In this way and according to the nomenclature proposed by Cochrane, a non-randomized controlled before-and-after study (CBA) was used. Following the Cochrane Effective Practice and Organization of Care Review Group (EPOC) [22] criteria, this design is characterized by involving the evaluation of an intervention in which, through the use of a control group, measures taken contemporaneously of determined outcome variables in comparable groups are tested.

A treatment protocol based on phenotypes was developed and carried out from March 5 to April 24, 2020 to the clinical manifestations and characteristics of the patients; table 1 describes the baseline characteristics relevant to the stratification. Days of hospitalization, use of mechanical ventilation and mortality were taken as primary outcomes. Regarding secondary outcomes, platelet count, D-dimer, oxygen saturation (O_2 Sat), partial pressure of oxygen by inspired fraction (O_2 Pa/Fi) and the presence of acute respiratory distress syndrome (ARDS) were considered.

Participants

The study sample consisted of 41 patients (9 women and 32 men; Mean = 56.93; SD= 15.062) with clinical diagnosis of SARS-COV-2 who voluntarily went to the Unión Médica del Norte University Clinic for outpatient and emergency care (Table 1).

All patients who presented to the clinic with symptoms similar to SARS-COV-2 (COVID-19) were evaluated and included in the study on the dates indicated. After the corresponding tests were performed, both groups, treatment (treatment by phenotypes) and control (TAU), were assigned by a self-conforming non-probabilistic sampling method. It should be noted that both groups of patients were comparable (presented similar characteristics) as can be seen on table 1. Patients who belonged to the treatment group (N=18) were classified, after being accepted to the group, according to the clinical manifestations in six phenotypes depending on age, individual´s pleomorphic characteristics, presence of comorbidities, markers such as ferritin, D dimer, lymphopenia, clinical signs and indicators such as oxygen saturation (O_2 Sat) and tachycardia (Table 2). Patients belonging to the control group (N=23) were not classified according to any criteria.

Procedure

Patients with symptoms compatible with SARS-Cov2 who presented were assigned to the evaluation boxes where clinical examination and

Table 1. Socio-demographic and clinical characteristics of the sample

	Control	Treatment							Total (n= 45)
	Total (n=)	Total (n=18)	Phenotype A (n= 0)	Phenotype B (n= 0)	Phenotype C (n= 5)	Phenotype D (n= 4)	Phenotype E (n= 3)	Phenotype F (n= 6)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Male/Female	21 (77.8)/6 (22.2)	15 (83.3)/3 (16.7)	--	--	4 (80)/1 (20)	3 (75)/1 (25)	2 (66.7)/1 (33.3)	6 (100)/0 (0)	36 (80)/9 (20)
Positive in ARDS	18 (66.7)	14 (77.8)	--	--	3 (60)	3 (75)	2 (66.7)	6 (100)	32 (71.1)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age in years	56.96 (14.76)	56 (16.54)	--	--	40.20 (12.43)	63.25 (8.34)	70.67 (20.03)	57 (13.53)	56.58 (15.32)
Platelets ($x10^9$/L)	211.7 (68.31)	232.72 (140.32)	--	--	326.8 (238.81)	222.75 (84.06)	193 (17.43)	180.83 (62.06)	220.11 (102.34)
D dimer (mg/dl)	1921.55 (3088.85)	2719.72 (4751.41)	--	--	4665.2 (6331.85)	1489 (1846.21)	749.33 (528.75)	2904.17 (5929.61)	2240.82 (3810.08)
O_2Sat (%)	90.44 (8.88)	90.65 (5.31)	--	--	93 (2.3)	95.25 (1.25)	87.67 (7.09)	87.5 (5.24)	90.52 (7.62)
O_2 Pa/Fi (mmHg)	239.89 (142.82)	210.12 (89.92)	--	--	257 (46.02)	225.25 (29.1)	239 (143.44)	154.33 (98.44)	228.39 (124.74)

Table 2. Classification of the treatment group by phenotypes

Phenotype	Characteristics
A	Age between 18-50 years No comorbidities Mild symptoms (anosmia, dry cough, fever, pharyngodynia, odynophagia, nasal congestion) MMRC grade 0. O_2 Sat: > 96 %. Curb-65: < 2 points
B	Age between 18-65 years With or without comorbidities. Respiratory symptoms: mild to moderate and fever 38°C MMRC grade 0-1 dyspnea O_2 Sat: 96-94% CURB 65: < 2 points. Kirbi Index (O_2 Pa/Fi) > 300 mmHg
C	Age >18 years With or without comorbidities. Moderate respiratory symptoms MMRC dyspnea: grade 1-2 O_2 Sat: 93 %. CURB 65: 2 points, Kirbi Index (O_2 Pa/Fi) > 300 mmHg
D	Age >18 years Obesity. Presence or absence of other comorbidities. Moderate to severe respiratory symptoms MMRC dyspnea: 3 O_2 Sat: 92-90% CURB 65: 3-4 points Kirbi Index (O_2 Pa/Fi): 300-200 mmHg
E	Age >18 years Obesity. Presence or absence of other comorbidities Meeting criteria for pneumonia severity MMRC dyspnea: 4 O_2 Sat: < 90% CURB 65: 4-5 points Kirby Index (O_2 Pa/Fi): 200-100 mmHg
F	Age >18 years Obesity. Presence or absence of other comorbidities. Refractory to therapy of previous phenotypes. MMRC dyspnea: 4. O_2 Sat: < 90%. CURB 65: 4-5 points Kirby Index (O_2 Pa/Fi): <100.

corresponding tests were performed: vital signs were monitored, lung evaluation was performed, and then swabbing and screening and follow-up studies were done. Before starting treatment, tests were performed to measure secondary outcomes: D dimer (the sample values and parameters were considered), presence of acute respiratory distress syndrome (ARDS), platelet count (to assess thrombocytopenia), partial pressure of oxygen by inspired fraction (O_2 Pa/Fi) and oxygen saturation (O_2 Sat). To collect the data, the guidelines proposed by EPOC [22] were followed. According to these guidelines, data collection from both groups was carried out at the same time.

After the patients were evaluated through the corresponding tests and before starting the treatment, all of them received an informed consent in which they voluntarily accepted to receive the treatment for COVID-19. In the document provided patients received all the information regarding the treatment to be administered and further details regarding drug´s information (see the Ethical Considerations' section).

After testing, patients were assigned to both groups. In the case of the treatment group, after having classified the patients according to their phenotype, each one of them received the treatment according to their phenotype. In turn, the control group received the TAU adjusted to the clinical and symptomatological manifestations (Table 3).

It should be noted that patients in both groups have in common the treatment of their patients with the medication described for the TAU group. In addition, in the case of the treatment group, the following medication was also administered: tocilizumab (only one 400 mg dose, in the TAU two could be applied), tofacitinib (5 mg every 12 hours), deferasirox (500 mg every 24 hours) and partial exsanguination of 500 ml (washed blood cells) and blood transfusion of 300 ml from a healthy donor.

For both groups, the discharge criteria were: correction of respiratory failure by increasing O_2 Pa/Fi (greater than 300), decreased oxygen supply, decreased D dimer (using the sample´s values), and improved tomographic findings.

For statistical analysis of the data, SPSS 25 for Windows was used. With the aim to determine whether the variables were normally distributed, Shapiro-Wilk and Kolmorogov-Smirnof statistics were estimated with corrections by Lilliefors. No significant differences were found in any of the indices ($p > .01$), accepting the hypothesis of a normal distribution in the studied variables. Moreover, an analysis of q-q plot graphs was performed, which enables linearization of the normal distribution; since most points lay on the diagonal of the graph, the

Table 3. Treatment description of the treatment group and control group

Treatment			**Control (TAU)**
Phenotype	**Treatment**	**Evaluation and monitoring**	**Treatment**
A	Hydration Oral decongestants and Hypertonic nasal solution. 1. Oral azithromycin 500 mg/day for 6 days. 2. Bromhexine: 1 cap. w/ 8 hours for 7-10 days 3. Bronchodilators: Salbutamol and beclomethasone or formoterol, if there is bronchospasm. 4. Oral acetaminophen or paracetamol.	Report and epidemiological surveillance. Revalue in 48 hours. If symptoms persist or increase in dyspnea and persistence of fever, advise the patient accordingfy. Isolation for 7 days, until proof is obtained: - *If positive:* reassess management, remain isolated for 14-21 days and repeat 2 PCR based assays tests. - *If negative:* return to normal activity under respiratory etiquette: mask use and social distancing.	1. Hydroxychloroquine (200 mg every 12 hours). 2. Lopinavir (200 mg every 12 hours) 3. Ritonavir (50 mg every 12 hours) 4. Azithromycin (500 mg every 24 hours) 5. Salumedrol (40 mg every 8 hours) 6. Broad-spectrum antibiotics: ceftriaxone, vancomycin, cefepime and meropenem 7. Tocilizumab (400 mg 1 or 2 doses)
B	Hydration Decongestants Hypertonic solution nose jobs 1. Oral azithromycin 500 mg/day for 6 days 2. Betamethasone or prednisolone and antihistamines, in case of bronchospasm (in non-diabetics). 3. Oral acetaminophen or paracetamol if temperature is over 38ºC. 4. Bronchodilators: salbutamol and beclomethasone or formoterol. 5. Oral N-acetyl cysteine (600 mg): 1 dose per day for 20 days 6. If bacterial co-infection is suspected: oral amoxicillin with clavulanate or oral cefixime. 7. Oral apixaban 2.5 mg every 12 hours for 14 days (if more than D-dimer 1000)	- Reporting and epidemiological surveillance. - Evaluation by Pneumology and Cardiology in emergency, to approach and follow up the QT interval in the electrocardiogram - Outpatient management - Clinical evaluation in 48 hours If symptoms persist or increased dyspnea and persistent fever (advise the patient). Isolation for 7 days, until COVID-19 test is obtained: - *If positive:* reevaluate patients´ management, remain isolated 14-21 days and repeat 2 PCR based assays tests. - *If negative:* return to normal activity: mask use and social distancing	
C	1. Oral hydroxychloroquine 200 mg every 12 hours or oral chloroquine 250 mg every 12 hours for 10 days 2. Oral lopinavir and oral ritonavir (200-50 mg): 1 tab every 12 hours x 10 days 3. Oral azithromycin 500 mg/day EV for 3 days, then 250 mg/day for 3 days (complete 6 days). 4. Bectalamic antibiotic (cefotaxime, ceftriaxone). 5. Oral paracetamol or oral acetaminophen in case of fever. 6. Acetaminophen and codeine: in patients with a persistent cough 7. Methylprednisolone: 1 mg/kg for 3 days, then decrease 0.5 mg/kg, for 3-6 days (do not exceed 2mg/kg weight). 8. Enoxaparin prophylactic dose (0.5mg/kg/day). 9. Intravenous N-acetyl cysteine: 600 mg w/8 hr 10. Oral tofacitinib (5 mg every 12 hr for 14 days) and oral deferasirox (500 mg daily for 10 days). 11. Intravenous pantoprazole 40 mg daily. 12. Oral atorvastatin 20 mg or oral rosuvastatin 10 mg, daily.	1. Management with hospital admission (follow up by a pneumologist and a cardiologist). 2. Repeat the protocol 48 hours after the beginning of the treatment. If symptoms worsen, initialize the treatment as a Phenotype D.	
D	1. Intravenous azithromycin: 500 mg/day for 3 days. Then, oral azithromycin 250 mg/day (complete 6 days). 2. Hydroxychloroquine: 200 mg every 12 hours or Chloroquine 250 mg every 12 hours for 10 days. 3. Lopinavir 200 mg and ritonavir 50 mg every 12 hours for 10 days, both orally. 4. Bectalamic antibiotic (ceftriazone, cefotaxime). Stagger the medication based on positive cultures or extended peripheral blood compatible with an infectious process and/or persistence or ascent of leukocytes and increased pulmonary infiltrates. 5. Oral tofacitinib 5 mg every 12 hours for 14 days and oral deferasirox 500 mg per day for 10 days. If there is no improvement, suspend tofacitinib and start intravenous tocilizumab 400 mg (1 dose). If the patient is obese, calculate 7 mg/kg. 6. Methylprednisolone: 0.5mg/kg per day (suspend it at the 6th day). 7. Acetaminophen and codeine in case of persistent cough. 8. Intravenous pantoprazole 40 mg/day. 9. Oral atorvastatin 20 mg or oral rosuvastatin 10 mg, daily. 10. Anticoagulation dose of enoxaparin (1 mg/kg every 12 hours). 11- Early parenteral nutrition.	1. Multidisciplinary hospitalized management (pneumonology, infectology, cardiology, haematology, intensive care, rheumatology, and gastroenterology). 2. Continuous monitoring of clinical parameters. 3. Serological marker controls and computerized axial tomography of thorax every 48 hours. If the patient worsens, follow the protocol for Phenotype E.	

E	1. Prone position for 12-16 hours. 2. Early parenteral nutrition. 3. Azithromycin 500 mg, intravenous dose for the first 3 days; then 250 mg daily, orally (complete 6 days). 4. Oral hydroxychloroquine 200mg every 12 hours for 10 days or chloroquine 250 mg every 12 hours for 10 days. 5. Oral lopinavir 200 mg and oral ritonavir 50 mg every 12 hours for 10 days. 6. Bectalamic antibiotic (ceftriaxone, cefotaxime): stagger antibiotic therapy based on positive cultures or peripheral blood with compatible data of infectious process and/or persistence or ascent of leukocytes, increased pulmonary infiltrates. 7. Intravenous tocilizumab 400 mg. Twelve hours later evaluate tomographic evolution and administer a second dose. If the patient is obese calculate at 7 mg /kg weight up to 1,200 mg. Oral deferasirox 500 mg daily for 10 days. 8. In case of no clinical improvement after 48 hours, start the administration of oral tofacitinib 5 mg every 12 hours for 10 days and oral deferasirox 500 mg daily for 10 days. 9. Methylprednisolone 0.5mg /kg every 24 hours (suspend its use the 6th day). 10. Acetaminophen and codeine, only if needed. 11. Intravenous pantoprazole 40 mg daily. 12. Oral atorvastatine 20 mg or oral rosuvastatin 10 mg: daily. 13. Anticoagulation dose of enoxaparin (1 mg/kg every 12 hours).	1. Multidisciplinary hospitalized management. 2. Continuous monitoring of clinical parameters and revaluation of progression to phenotype F. 3. Perform serological markers and computerized axial tomography of the thorax every 48 hours. 4. If there is a clinical worsening within the 24 to 48 hours, go to the Phenotype F patient protocol.	
F	1. Continuous decubitus prone for 72 hours, with Fio2 50-100% (high flows). Individualize. 2. Pseudo analgesia: opioids or dexmedetomidine. 3. Early parenteral nutrition (in the first 48 hours). 4. Infusion of loop diuretic (furosemide or bumetanide) and management of complications with acetazolamide. 5. Intravenous tocilizumab 400 mg (from the 7th day of symptoms). If the patient is obese: 7 mg/kg up to 1,200 mg. Intravenous deferasirox 500 mg daily for 10 days. Evaluate in 12 hours tomographic evolution (apply 2nd dose). 6. In case of no improvement at 48 hours, start with oral tofacitinib 5 mg every 12 hours for 10 days and deferasirox. 7. Intravenous immunodfobulin in refractory patients to Tocilizumab: 25 grams for 3 days. Patient is revaluated daily with clinical and analytical markers. 8. Previous 500 ml partial exsanguination and transfusion of 300 ml of healthy donor red blood cells. 9. Methylprednisolone: 0.5mg /kg every 24 hours (up to the 6th day). 10. Enoxaparin anticoagulation dose, 1 mg/kg every 12 hours.	Cardiovascular assessment with transthoracic echocardiography.	

variables were considered to be normally distributed [23]. For statistical analysis of the data, the Student t-test for related samples to assess intra-group mean differences, and the Students t-test for independent samples when evaluating inter-group mean and proportion differences were used. In addition, in order to measure the effect size of significant differences, Cohen's d was used.

Ethical considerations

The study protocol was approved by the Ethics Committee of the institution. Moreover, as it was previously mentioned, all participants received an informed consent in which they voluntarily accepted to receive the treatment for COVID-19. The informed consent form provided details of the treatment to be received, the description of the drugs and interventions that would be administered, as well as the possible adverse effects and drug interactions. Specifically, patients who received the experimental treatment were informed of the experimental nature of this intervention.

Results

Primary outcomes

Days of hospitalization: Statistically significant differences in mean days of hospitalization between the groups (95% CI; t= -1.87; df= 39; p < 0.034) were found, with mean days of hospitalization for the treatment group being 9.33 (SD= 4.1) and for the control group 12.13 (SD = 5.19). The effect size of these differences is small (d= 0.41).

Use of mechanical ventilation: Significant differences were found between the groups in the use of mechanical ventilation (95% CI; t= -2.15; df= 22; p< .0105). The magnitude of the difference found is moderate (d= -0.67). The results indicate that in the treatment group the patients did not require mechanical ventilation (0%; n= 0), and in the control group, 14.4% (n= 4) patients did.

Mortality: Significant differences in patient mortality rate were found between the treatment and control groups (95% CI; t= 2.15; df=

22; p< .021), with these differences being of moderate size (d= 0.67). The results indicate that no patients died in the treatment group, while in the control group, 17.4% (n= 4) of the patients died.

Secondary outcomes

Platelet count: Regarding platelet levels, no significant differences were found between the groups (95% CI; t= 1.207; df= 39; p< .11). However, pre-post-treatment differences were found in both groups. In relation to patients in the treatment group, significant increases in platelet count were found after treatment (= 319.56; SD= 112.67; 95% CI; t= -2.83; df= 17; p< 0.006). The magnitude of this difference is moderate (d= -0.67). On the other hand, in relation to the control group, significant increases in platelet levels after treatment were also found (= 273.22; SD= 128.72; 95% CI; t= -2.507; df= 22; p< .0.01), although the size of this difference is moderate (d= -0.55), it is smaller than that exhibited in the treatment group.

D dimer: No significant differences were observed between the groups in terms of D-dimer levels (95% CI; t= -0.35; df= 38; p< 0.36), nor were there any pre-post treatment differences in the treatment group (95% CI; t= 1.15; df= 16; p< 0.13) or the control group (95% CI; t= -0.93; df= 22; p< 0.18).

Oxygen saturation (O_2 Sat): Regarding this variable, no significant differences were found between groups (95% CI; t= -0.56; df= 38; p< 0.28) nor in the pre-post intervention differences of the treatment group. However, in the control group significant increases in O_2 Sat after treatment were observed (= 95.22; 95% CI; t= -1.86; df= 22; p< 0.038), being this difference of moderate magnitude (d= -0.53).

Oxygen partial pressure by inspired fraction (O_2 Pa/Fi): Significant differences in O_2 Pa/Fi levels were found between the treatment and control groups (95% CI; t= 2.62; df= 38; p< 0.003) with the treatment group showing a greater increase (= 336.12; SD= 141.36) than the control group (= 227.13; SD= 120.32) in Pa/Fi O2 levels. The magnitude of the difference found is large (d= 0.86). On the other hand, in relation to intragroup differences, the treatment group showed a significant increase in O_2 Pa/Fi levels after the intervention (= 336.12; SD= 141.36; 95% CI; t= -4.35; df= 16; p< 0.000), being this difference of magnitude large (d= -0.98). However, no significant differences in O_2 Pa/Fi levels were found for the control group (95% CI; t= 0.073; df= 22; p< 0.47).

Acute Respiratory Distress Syndrome (ARDS): In relation to ARDS, significant differences were observed between the treatment and control groups (95% CI; t= -3.76; df= 22; p< 0.000). In the treatment group, after the intervention, 0% (n= 0) of patients exhibited ARDS, while in the control group 39.1% (n= 9) of patients were positive for ARDS. The size of the difference exhibited in these measures is very large (d= -1.184). However, regarding intra-group differences, the treatment group showed significant reductions in ARDS (95% CI; t= 7.71; df= 17; p< 0.000), this implies that after treatment 94.4% (n= 17) of patients scored negative in ARDS. The magnitude of this difference is very large (d= 2.397). On the other hand, the control group also showed significant reductions in ARDS after treatment (95% CI; t= 3.76; df= 22; p< 0.000): 60.9% (n= 14) scored negative in ARDS. The magnitude of the difference found is large (d= 0.84), although smaller than in the treatment group.

Discussion

The present study aimed to evaluate the efficacy of a phenotype-based treatment in comparison with the TAU in a sample of Dominican patients hospitalized with SARS-Cov2 (COVID-19). From the observed results, the evaluated treatment seems to have efficacy in treating SARS-COV-2 (COVID-19).

Firstly, with regard to the primary outcomes, the group of patients who received treatment based on phenotypic categorization did not require mechanical ventilation. This finding is of importance since in previous studies, the rate of patients infected with COVID-19 requiring ventilatory assistance ranged from 2.3% to 33.1% [24, 25]. Likewise, the zero mortality rate in the sample of the present study is an encouraging result since in studies carried out in the United Kingdom, the United States and Italy the mortality rate of hospitalized patients was between 10.38% and 30.46% [24,26]. In relation to the difference in mean days of hospitalization found is small, the mean for the treatment group (Mean= 9.33; SD= 4.1) is smaller than for the control group (Mean= 12.13; SD= 5.19), and smaller compared to the mean days of hospitalization in the China-based study (13 days for non-severe patients and 18.5 days for severe patients) [25]. In this sense, the proposed treatment is shown to be effective in reducing patient stay in hospital.

On the other hand, in relation to the secondary outcomes, the phenotype-based treatment was superior to the control in improving the levels of partial pressure of oxygen per inspired fraction (Pa/Fi O2) and in reducing the number of patients with acute respiratory distress syndrome (ARDS). According to one study, between 15 and 30% of patients hospitalized with SARS-Cov2 (COVID-19) develop ARDS [25, 27], data consistent with those obtained in our sample. According to the commentary published by Matthay, Aldrich and Gotts in The Lancet Respiratory Medicine, the treatment of ARDS has become a challenge in the treatment of patients infected by COVID-19 [28]. In this study, experimental phenotypic treatment has been shown to be superior to control (with very large effect size) in treating this syndrome: in the treatment group 94.4% of patients scored negative for ARDS after treatment, while in the control, 60.9% scored negative for ARDS. Also, the experimental treatment was shown to be effective, with large effect size, in increasing O_2 Pa/Fi levels, although TAU was superior in increasing O_2 Sat (with medium effect size). Finally, both treatments (treatment and TAU) were shown to be effective in increasing platelet levels.

The proposed treatment has been designed following two main guidelines: to propose an intervention adjusted to the needs of each patient (represented by the phenotypic classification) according to clinical manifestations; and, on the other hand, to incorporate drugs that have been shown to be potentially beneficial for the treatment of COVID-19 [8,18,29,30]. In this sense, the designed treatment introduced a pharmacological management specially thought for each phenotype, trying that each intervention is directed to treat the particularities of each patient according to the proposed classification. It is believed that the differences obtained in the results (primary and secondary outcomes) that show the superiority of the proposed experimental treatment, could be due to: on the one hand, the reduction of the dose of tocilizumab to one; and, on the other hand, the incorporation of tofacitinib, deferasirox, convalescent plasma and washed blood cells. These points define the interventions carried out in each group.

The present study makes novel contributions to the treatment of COVID-19 as no background studies have been found to date that stratify patients according to phenotypes. Although this stratification is based on empirical criteria, it seems to be a useful strategy for adapting the treatment to the characteristics of each patient. Likewise, the design of the treatment and of the pharmacological strategies employed is

novel for the treatment of a disease for which effective and efficacious treatments are not yet well established. On another note, the limitations of the study should be highlighted in order to guide future research. First, the sample size used is small, so future studies require not only expansion but also stratified random allocation to ensure group equivalence. Secondly, the monitoring and systematization, with its consequent reporting, of the side effects of the treatments administered would allow a more extensive understanding of their scope and unwanted consequences.

Although further studies are required, the results obtained in this study are preliminary but promising evidence of a treatment alternative that has been shown to be effective in reducing the need for assisted mechanical ventilation, improving the response to treatment of ARDS and decreasing the death rate in patients diagnosed with SARS-Cov2 (COVID-19).

Conclusions

The experimental treatment by phenotypic classification has shown to be a promising treatment to manage patients diagnosed with COVID-19: after the intervention the treatment group showed a lower mean in terms of hospitalization days, patients did not need assisted mechanical ventilation and there were no deaths. Besides, the treatment group had the lowest number of patients with ARDS and showed to be superior regarding the control of O_2 Pa/Fi. While these results are encouraging, more studies with larger sample sizes are needed.

Acknowledgements

Special thanks are due to the board and all the medical and administrative staff of the Unión Médica del Norte Clinic for supporting this study.

Author contributions

Natalia García contributed to the study concept, treatment design and draft review; Jacdalia Cortes and Francis Fajardo collected the data, reviewed the draft and the literature, and assisted Natalia García during treatment; DR, MS, YP, JC and ET contributed equally in data collection, literature review and draft review; Luciana Sofía Moretti contributed to the conception of the study, its methodology, did the statistical analysis and wrote the draft.

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