Sulodexide in the Treatment of Patients with Early Stages of COVID-19: A Randomized Controlled Trial

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may induce several vascular endothelial-dependent systemic complications, and sulodexide has pleiotropic actions on the vascular endothelium, which may prove beneficial. We aimed to assess the effect of sulodexide when used within 3 days of coronavirus disease 2019 (COVID-19) clinical onset. We conducted a randomized placebo-controlled outpatient trial. To be included, patients must have been at high risk for severe clinical progression. Participants received sulodexide (oral 1,000 LRU/d) or placebo for 21 days. The primary endpoint was the need for hospital care. Also assessed were patients' need for supplemental oxygen as well as D-dimer and C-reactive protein (CRP) levels, thromboembolic events, major bleeding, and mortality. A total of 243 patients were included in the per-protocol analysis from June 5 to August 30, 2020. Of these, 124 received sulodexide and 119 received a placebo. Only 17.7% of the patients in the sulodexide group required hospitalization, compared with 29.4% in the placebo group ($p = 0.03$). This benefit persisted in the intention-to-treat analysis (15% in sulodexide group vs. 24% with placebo [$p = 0.04$]). With sulodexide, fewer patients required supplemental

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oxygen (30 vs. 42% [$p = 0.05$]). After 2 weeks, fewer patients had D-dimer levels >500 ng/dL (22 vs. 47% [$p < 0.01$]), and patients also had lower mean CRP levels (12.5 vs. 17.8 mg/dL [$p < 0.01$]). There were no between-group differences in thromboembolic events, major bleeding, or mortality. Treatment of COVID-19 patients with sulodexide, when provided within 3 days of clinical onset, improved their clinical outcomes. Although the results should be confirmed, sulodexide could be valuable in an outpatient setting.

Introduction

The novel coronavirus disease 2019 (COVID-19) has developed into a pandemic[1] that has changed our way of life to a degree that has yet to be determined. The reported percentage of infected patients who require hospital care is between 15 and 25%.[2,3] However, the virus' high contagiousness has resulted in health care systems worldwide being placed under massive strain due to the vast numbers of patients requiring hospital care. Effective early treatment to prevent the more severe effects of COVID-19 could improve this situation.

The endothelial surface layer in the lungs plays a critical role in the immune response to SARS-CoV-2 infection, both as an effector and as a target organ. There is evidence of viral inclusion[4] in the endothelium and diffuse inflammation (endothelialitis), which trigger a systemic release of inflammatory cytokines.[5] Such conditions diminish the endothelium's protective properties. The resulting proinflammatory and prothrombotic state can cause microvascular thrombosis,[6,7] which might explain the impaired systemic function of various vascular beds and their clinical sequelae in some patients.[8–10] COVID-19-induced endothelialitis may be a particularly relevant concern for vulnerable patients with pre-existing endothelial dysfunction, which is associated with males, old age, and chronic comorbidities—all of which are linked with adverse disease outcomes.[11,12]

Sulodexide is a compound of two glycosaminoglycans (GAGs): a fast-moving heparin fraction (80%) and dermatan sulfate (20%). Although possibly better known for its antithrombotic effect,[13] sulodexide's endothelial-protective properties may contribute a benefit of equal or greater importance in the early stages of COVID-19.[14,15] As a precursor for the synthesis of GAGs, sulodexide can help restore a shredded endothelial glycocalyx and prevent further degradation.[16,17] This improvement restores endothelial barrier function and allows the endothelium to better modulate the generation of key inflammatory molecules, while at the same time downregulating its response to them.[17,18] This can help prevent the aberrant immunothrombosis reaction seen in some patients. Sulodexide's antithrombotic and profibrinolytic effects may still be significant against the procoagulant state caused by SARS-CoV-2. Finally, sulodexide is also associated with a lower bleeding risk than is seen with other oral anticoagulants.[19]

Reports suggest low-molecular-weight heparin (LMWH) is accompanied by a reduction in mortality when used in a hospital setting.[20] It has been hypothesized on this basis that patients on chronic anticoagulation may experience lower incidences of thromboembolic events upon hospitalization for COVID-19; thus, research into its outpatient use in ameliorating the disease's clinical course has been proposed.[21,22] Few outpatient trials for nonanticoagulation and nonvaccine-related studies are ongoing.[23] However, prospective randomized trials on COVID-19 patients are pending and largely overlook the potential of pulmonary endothelial cells as a therapeutic target.[24,25]

With this premise, we decided to evaluate whether sulodexide's pleiotropic properties prevent the SARS-CoV-2-mediated endothelialitis with hypercoagulability and inflammation. This benefit, if found, could improve clinical outcomes and translate into a reduced need for hospital care.

Methods

Study Design

We performed a prospective, randomized placebo-controlled trial with a parallel-group design to assess the effect of sulodexide on clinical outcome in consecutive patients suffering from the early clinical stages of COVID-19, as defined in ►**Table 1**.

The recruiting period ran from June 5 to August 5, 2020, with the follow-up period concluding on August 30, 2020. The study site is located in San Luis Rio Colorado, Sonora, a border port of entry in Mexico's northwestern region. As of August 5, 2020, 28,990 confirmed COVID-19 cases had been reported within a 100-mile radius of this site, including cities in the United States. We conducted this trial in compliance with the Declaration of Helsinki. The trial was board-reviewed by the Universidad Autonoma de Baja California Faculty of Medicine Campus Mexicali at the Department of Ethics and Investigation Committee and has the approval number FMM/CEI/0011/2020–2. Although some participants were U.S. residents, all were under the supervision of physicians and hospitals in Mexico.

Patients

We anticipated difficulties in recruiting eligible patients and consequently utilized social media outreach, as well as contacting primary care physicians in state and private clinics for early referral. We reached out to health care

Table 1 Inclusion, exclusion, and elimination criteria

Inclusion criteria	Exclusion criteria	Elimination criteria
• Age > 40 years • Male or female • Body mass index of 18–35 kg/m^2 • The onset of 3 days or less of suspected COVID-19 symptoms defined as any two of cough, fever, or headache. Plus one of sniff, dyspnea, diarrhea, loss of smell/taste, conjunctivitis, or body/muscle ache. • Sign informed consent • High level risk to develop a severe clinical progression of COVID-19[a]	• A negative RT-PCR SARS-CoV- 2 test result • Known pregnancy • Prolonged anticoagulation in the last 6 months[b] • History of deep vein thrombosis in the previous 6 months • Severe clinical symptoms that warrant immediate hospital care • Chronic use of steroid medication in the previous 6 months • Bed confinement in the last 6 months • Already hospitalized for other reasons. • Previous treatment for COVID-19	• Withdrawal of informed consent • Lost to follow-up • A negative RT-PCR SARS-CoV-2 test result not available

Abbreviations: BMI, body mass index; RT-PCR, reverse-transcriptase polymerase chain reaction.
[a]According to the COVID-19 Health Complication calculator (IMSS, Gobierno de Mexico).
[b]Start of anticoagulation after trial inclusion was not a criterion for exclusion.

workers at hospitals admitting COVID-19 patients and household members known to be hosting COVID-19-positive patients, as they were at high risk of infection and had first-hand knowledge of the symptoms.

Virtual communication was used for patient-eligibility screening, and the inclusion and exclusion criteria are summarized in ►**Table 1**. Key inclusion criteria were the combination of symptoms described above and being deemed at high risk (>50%) of severe clinical disease progression. Risk was assessed according to the percentage risk calculated using the COVID-19 Health Complication (C19HC) calculator (IMSS, Gobierno de Mexico), which considers the importance of various chronic comorbidities (►**Supplementary Table S1** [available in the online version]).[26] Important exclusion criteria included a negative reverse-transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 test result and prolonged anticoagulation treatment. Once the trial was ongoing, the initiation of anticoagulant medication at a prophylactic dose was not considered a criterion for elimination. However, due to the possible risk of bleeding complications, these patients underwent stricter follow-ups. Eligible patients signed informed consent forms and were scheduled the earliest for blood tests and RT-PCR SARS-CoV-2 test.

Study Protocol

Group allocation was performed at the research site through sequential randomization using computer software provided by Castor Electronic Data Capture (EDC; Amsterdam, the Netherlands). The software generated a permuted block randomization sequence in a 1:1 ratio with no underlying strata. The medical team in charge of the patients and treatment regimens was blinded to group allocation.

The indicated treatment dose was 500 LRU (lipase releasing units) twice daily for 3 weeks. On a 7-day schedule, the research site distributed 250 LRU masked capsules of sulodexide (Vessel due F, Alfasigma, Mexico) or masked capsules of placebo. A patient representative would collect the medication at the study site. When this was not possible, a staff member was responsible for its delivery at the patient's home. Although 250 RLU twice daily has been observed to produce effective plasma concentrations in vitro and is regularly prescribed in daily practice,[27] we chose the higher 500 RLU dosing regimen based on the SURVET (Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis) study, in which an antithrombotic effect was safely achieved in a clinical setting.[28] Placebo capsules were prescribed to the control group according to the same regimen. Due to local logistical limitations resulting from the regional pandemic lockdown, which jeopardized the medication's timely distribution, the lead researcher was not blind to group allocation. Apart from being used to provide the study medication and perform follow-ups on study endpoints, the research site was not involved in the disease's primary treatment. Patients were encouraged to continue with the standard care recommended by their health care providers.[29] Some of the researchers were involved in the complementary treatment of patients outside the research site; however, they were blind to group allocation.

Independent authorized laboratories processed the RT-PCR SARS-CoV-2 tests. Since the test result was not reported for several days, participants continued with the follow-up as scheduled. If confirmed positive, the participant continued in the trial. If negative, the medication treatment was suspended and the patient was excluded from the data analysis.

We performed follow-ups to assess the study endpoints via remote communication with participants or household members every 7 days or as deemed necessary during the 3-week participation period. If no virtual form of contact was possible, we scheduled a field visit to the participant's home. New blood tests were scheduled on follow-up day 14 for secondary endpoint assessments. Laboratory staff followed strict safety protocols. If we were unable to contact the participant during the follow-up period and no data were available other than the initial inclusion survey, the patient was excluded from the final analysis once mortality was ruled out as the cause of inability to follow up.

If the patient's symptoms worsened, we recommended the patient undergo an emergency department examination with their health care provider. A visit to the hospital's emergency department was not considered a study endpoint unless it resulted in formal admission to the COVID-19 hospital ward. The in-house protocols for clinical management and admission applied by hospitals included—but were not limited to—respiratory failure (oxygen saturation $< 90\%$, severe hypoxemia [partial pressure of oxygen < 60 mm Hg] or breathing rate > 30 breaths per minute while breathing ambient air); abnormal chest X-ray compatible with COVID-19-associated pneumonia; and relevant clinical changes together with clinically significant laboratory abnormalities.[30] The hospital's admission decision (or, alternatively, the determination of a need for at-home supplemental oxygen) was left to discretion of the emergency department physician, who was blind to group allocation. If the patient required hospital care, we suspended the oral dose of sulodexide or placebo but continued gathering data on the patient's progression and included that data in the final analysis. The research team was not involved in any of the treatment decisions made during hospital care, but in such cases the follow-up was extended beyond the specified 3-week period until we could define an outcome or until the trial ended. Sulodexide was not resumed after discharge from the hospital.

Data Sources

Data were collected using Castor EDC software for validation and monitoring and kept a hard copy on file at the research site.

The data collected from each patient included the following: (1) the patient's general demographics; (2) clinical characteristics and outcomes; (3) serum and RT-PCR SARS-CoV-2 test results; and (4) the duration and dosages of all treatments the participant received, adverse events, and medication adherence.

Study Endpoints

Outcomes were assessed at day 21 after randomization. The primary endpoint was the need for hospital admission for clinical care. Secondary clinical endpoints were the total length of stay (LOS) in the hospital due to COVID-19; the need for and duration of supplemental oxygen at home, in the hospital, or both; the need for mechanical ventilation; the occurrence of a thromboembolic event or major bleeding (define as fatal bleeding or bleeding causing a fall in hemoglobin levels of 20 g L^{-1} or more, or leading to transfusion of 2 or more units of whole blood or red blood cells); and mortality. Serum levels of D-dimer (using a chemiluminescence assay with the reference range of 0–500 ng FEU/mL), C-reactive protein (CRP; using a turbidimetric assay with the reference range of 0–6 mg/L), and creatinine (Cr) were measured as secondary laboratory endpoints.

Statistical Analysis

The need for hospital care was the endpoint used to determine the sample size required for statistical significance. Since the patients included were at high risk of severe COVID-19 clinical progression, we estimated that 40% of the patients would require hospital care. Since there is no precedent for treating COVID-19 patients with sulodexide, we assumed that sulodexide treatment could result in a 25% reduction in hospital admissions based on results from other clinical trials that outlined benefits similar to the one expected with this trial.[31] We calculated a required sample size of 100 patients in each group based on a *t*-test difference between two independent means with an effect size of 0.4, an α error of 0.05, and a power of 80%. The sample size increased to 120 participants per group when factoring in an estimated 20% rate of attrition.

Relative risk (RR) estimates are shown with a 95% confidence interval (CI) and calculated using the MedCalc software (MedCalc Software Ltd., Olsted, Belgium). All *p*-values are two-sided and shown without adjustment for multiple testing. The study team has retained the complete database.

Quantitative variables are expressed as means ($\pm$standard deviation) and qualitative variables are expressed as frequencies and percentages. Differences in means were calculated using the Student's *t*-test, while differences in percentages were assessed using the χ^2-test. Before and after serum levels in the same patients were analyzed using two paired *t*-tests. If the data were not normally distributed, a Wilcoxon test was used. A Kaplan–Meier curve was used to graphically compare time to endpoint for hospital admission and mortality.

Although an intention-to-treat analysis was planned initially, the inclusion of clinically suspected COVID-19 patients and the exclusion of patients who began the treatment before reporting a negative RT-PCR SARS-CoV-2 test result led to a per-protocol data analysis instead. However, an additional intention-to-treat analysis was performed for the primary and secondary endpoints of importance. Data analysis was performed using SPSS software (IBM SPSS Statistics for Windows, version 26, IBM Corp., Armonk, New York, United States). Data were missing for less than 10% of patients; this was compensated for by multiple imputation analysis. However, no primary endpoint result data were imputed. When missing, the last known value was used for analysis. An independent data monitoring committee had access to the accumulating data in general, with safety monitoring as the major purpose.

Results

Of the 656 suspected COVID-19 patients assessed for eligibility, a total of 312 underwent randomization for group allocation. Thirty-one of the 312 patients reported a negative RT-PCR SARS-CoV-2 test result (14 out of 157 [8.9%] in the sulodexide group and 17 out of 155 [10.9%] in the control group). A total of 38 patients were lost to follow-up (19 out of 157 [12.1%] in the sulodexide group and 19 out of 155 [12.2%] in the control group). A total of 243 patients (124 patients in the sulodexide group and 119 in the placebo group) were

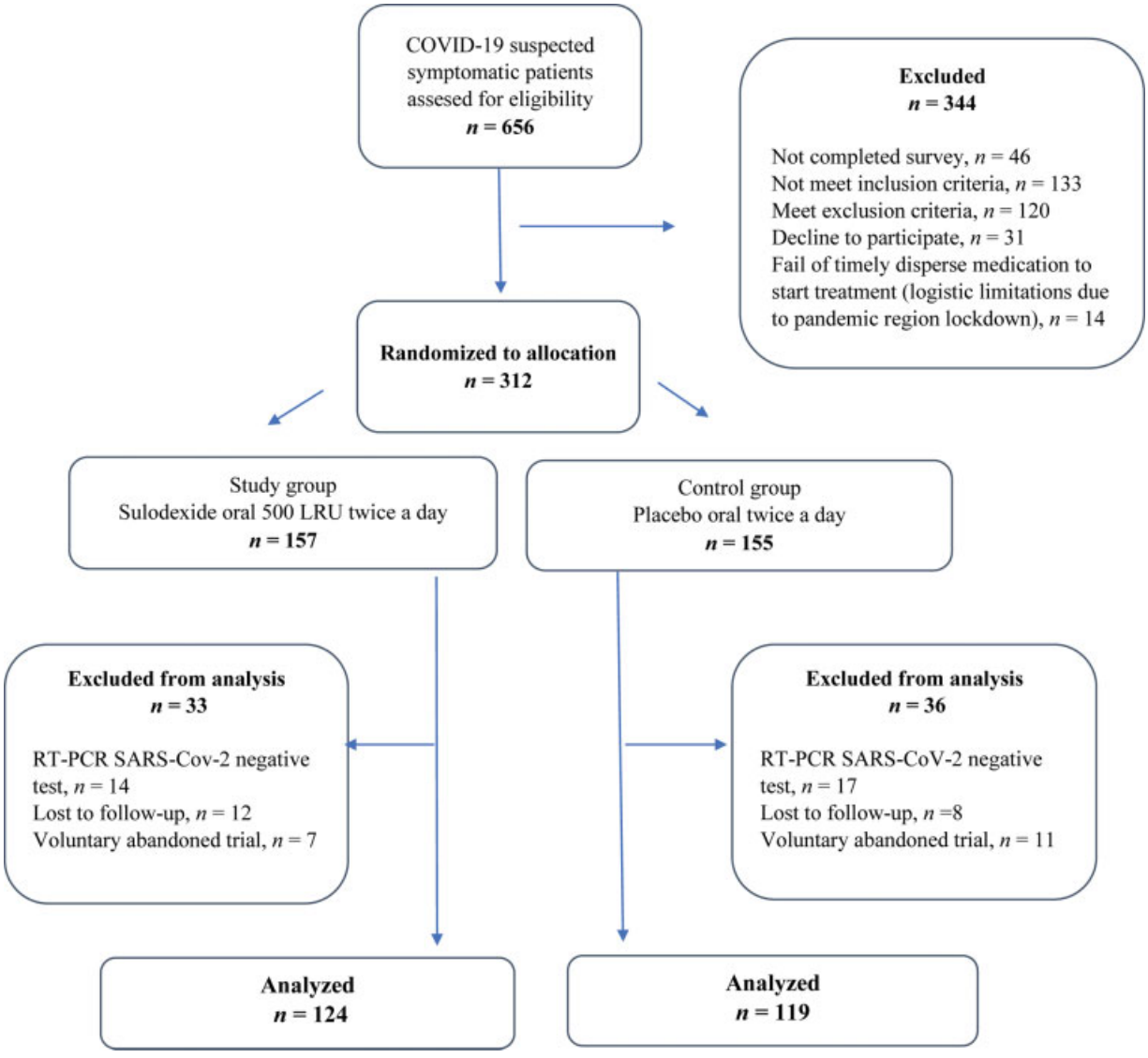


Fig. 1 CONSORT flow diagram.

eligible for final data analysis (►**Fig. 1**). Demographics and clinical characteristics were similar in both groups (see ►**Table 2**).

Primary Endpoint

Overall, 57 of the 243 patients (23.4%) required hospital care during the 21-day follow-up (22 of 124 [17.7%] in the sulodexide group and 35 of 119 [29.4%] in the placebo group, with a RR of 0.6, 95% CI of 0.37–0.96; $p = 0.031$). The estimated number of patients who needed to be treated with sulodexide rather than standard care for one additional patient to benefit was 8.5. When including the 312 randomized patients in the intention-to-treat analysis (►**Supplementary Table S2** [available in the online version]), 23 of 155 patients (14%) in the sulodexide group required hospital care versus 38 of 157 (24%) in the placebo group (RR of 0.6; 95% CI of 0.38–0.97; $p = 0.037$). ►**Fig. 2** shows the Kaplan–Meier curve for time to hospital admission (log rank: $p = 0.05$; Breslow: $p = 0.04$).

Secondary Clinical Endpoints

Secondary endpoint results are summarized in ►**Table 2**. Most importantly, 87 of the 243 patients (35.8%) developed respiratory symptoms requiring supplemental oxygen (37 out of 124 [29.8%] in the sulodexide group vs. 50 out of 119 [42%] in the control group [RR of 0.71; 95% CI of 0.5–1; $p = 0.053$). These results were slightly modified in the intention-to-treat analysis (39 out of 155 in the sulodexide group vs. 56 out of 157 in the placebo group [RR of 0.71; 95% CI of 0.5–0.9; $p = 0.046$]). Patients in the sulodexide group required supplemental oxygen for fewer days than did those in the placebo group ($p = 0.02$). There was no difference between groups regarding mean hospital LOS ($p = 0.21$) or mortality rate (3 out of 124 [2%] vs. 7 out of 119 [6%] with a RR of 0.41; 95% CI of 0.10–1.55; $p = 0.19$). ►**Fig. 2** shows the Kaplan–Meier mortality curve (log rank: $p = 0.16$).

Secondary Laboratory Endpoints

There was no between-group difference in serum levels of either D-dimer or CRP at baseline. Mean D-dimer levels at

Table 2 General demographics, comorbidities, and outcome

	Sulodexide ($n = 124$)	Placebo ($n = 119$)	RR (95% CI)	*p*-Value
Demographics				
Age in years, mean (SD)	55.3 (10.3)	54 (10.9)	–	0.26
Female, *n* (%)	64 (52)	64 (54)	0.95 (0.75–1.21)	0.73
BMI, mean (SD)	29 (4.0)	28.7 (3.2)	–	0.30
Chronic comorbidities, n (%)				
Diabetes mellitus	22 (18)	28 (24)	0.75 (0.45–1.24)	0.26
Hypertension	48 (39)	35 (29)	1.31 (0.92–1.87)	0.13
COPD	30 (24)	26 (22)	1.10 (0.69–1.75)	0.66
Cardiovascular disease	28 (23)	23 (19)	1.16 (0.71–1.90)	0.53
C19HC risk calculator, mean (SD)[a]	68 (14)	66 (14)	–	0.32
Outcome				
Need for hospital care, *n* (%)	22 (18)	35 (29)	0.60 (0.37–0.96)	0.03
Length of hospital care (days), mean (SD)	6.3(4.1)	7.8 (4.5)	–	0.21
Need for supplemental oxygen, *n* (%)[b]	37 (30)	50 (42)	0.71 (0.50–1.00)	0.05
LOD of supplemental oxygen, mean (SD)[b]	9 (7.2)	11.5 (9.6)	–	0.02
Mortality, *n* (%)	3 (2)	7 (6)	0.41 (0.10–1.55)	0.19
Invasive mechanical ventilation, *n* (%)	3 (2)	6 (5)	0.47 (0.12–1.87)	0.29
Hemodialysis, *n* (%)	0	0	–	–
Thromboembolic events, *n* (%)	2 (2)	2 (2)	0.95 (0.13–6.70)	0.96
Laboratory findings				
D-dimer baseline, ng/dL				
Mean (SD)	294 (117)	318 (131)	–	0.12
>500, *n* (%)	14 (11)	21 (18)	0.63 (0.34–1.19)	0.16
D-dimer at week 2				
Mean (SD)	465 (630)	898 (1215)	–	<0.01
>500, *n* (%)	27 (22)	56 (47)	0.46 (0.31–0.67)	<0.01
CRP, mg/dL				
Baseline, mean (SD)	10.6 (6.4)	10.1 (6.9)	–	0.55
Week 2, mean (SD)	12.5 (10.2)	17.8 (11.5)	–	<0.01
Creatinine at week 2, mg/dL				
>1.6	11 (8.8)	12 (10.0)	0.87 (0.40–1.91)	0.74

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; LOD, length of days; *n*, number of patients; RR, relative risk; SD, standard deviation.

[a]Percentage is given by the COVID-19 Health Complication (C19HC) risk calculator (Gobierno de Mexico, IMSS).

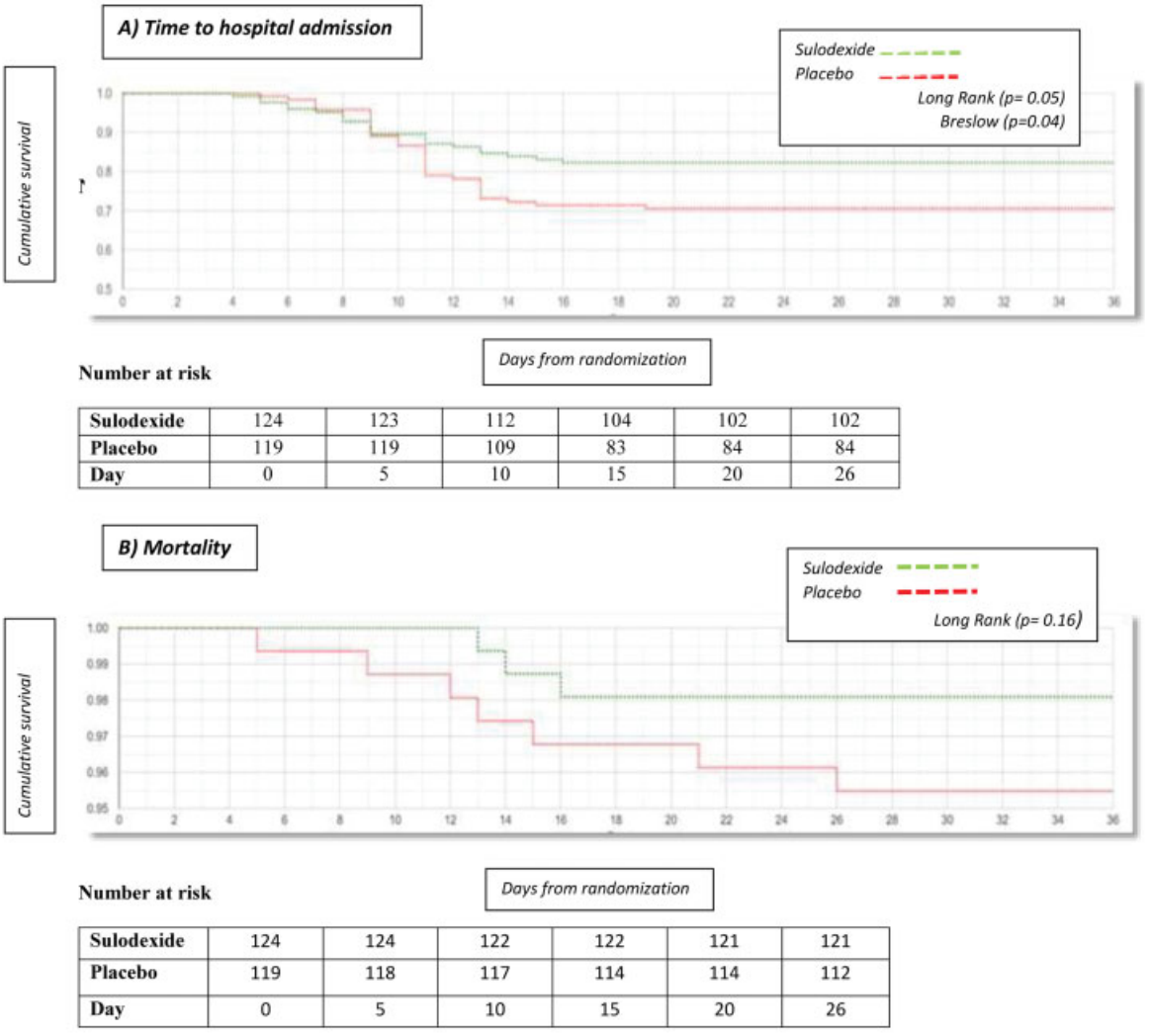
[b]Including the total number of days patients needed supplemental oxygen at home or in hospital. Some patients continued supplemental oxygen at home after hospital care or started supplemental oxygen at home and later required hospital care.

week 2 were significantly higher in the placebo group than in the sulodexide group ($p < 0.01$). A total of 27 of the 124 patients (22%) in the sulodexide group showed a D-dimer value >500 ng/dL, compared with 56 out of 119 (47.05%) in the placebo group (RR of 0.46; 95% CI of 0.31–0.67; $p > 0.01$). Mean CRP levels at week 2 were lower in the sulodexide group than in the placebo group ($p < 0.01$).

Adherence and Safety

Medication adherence was assessed at each follow-up examination and was also verified indirectly by counting the number of capsules left in the medication blisters. The results are summarized in ►**Table 3**. A total of 17 of the 243 patients (13.7%) felt they had clinically recovered, resulting in voluntary premature interruption of medication. This interruption occurred after a minimum of 14 days of treatment in all such patients, none of whom later required hospital care or supplemental oxygen. None of the patients who suspended medication were excluded from the final analysis.

An adverse event was severe enough to cause medication cessation in 14 of the 243 patients (5.7%), with no between-group difference. Gastrointestinal discomfort was the main



Sulodexide	124	123	112	104	102	102
Placebo	119	119	109	83	84	84
Day	0	5	10	15	20	26

Sulodexide	124	124	122	122	121	121
Placebo	119	118	117	114	114	112
Day	0	5	10	15	20	26

Fig. 2 Time to even for hospital admission and mortality in patients with COVID-19. Shown is an expanded axis of the cumulative incidence of events in both groups; from randomization until the end of the 21-day follow-up (with prolonged follow-up until the defined endpoint or the end of the trial period). In panel (**A**), the use of sulodexide shows a statistically significant difference benefit for time to hospital admission (log rank [$p = 0.05$] and Breslow [$p = 0.04$]). Panel (**B**) displays mortality with no significant difference between groups (log rank [$p = 0.16$]). The number of patients at risk over time is shown below each panel.

reason for suspension. A major bleeding event occurred in one patient from the control group; this event occurred in hospital care and eventually proved fatal.

The additional outpatient treatment prescribed to the study population was heterogeneous but evenly distributed between groups. Notably, the use of inhaled bronchodilators was lower in the sulodexide group ($p = 0.01$). A complete list is shown in ►**Table 4** and (►**Supplementary Table S3** [available in the online version]).

Discussion

This study evaluated sulodexide's therapeutic effect for patients in the early stages of COVID-19 in a real-life setting. Sulodexide was effective in decreasing the need for both hospital admission and supplemental oxygen treatment. Sulodexide-treated patients also had lower serum levels of CRP and D-dimer as markers for inflammatory and prothrombotic states.

This trial benefited from the use of the C19HC calculator to identify patients at higher risk of progressing to a severe clinical stage, clustering each patient's age and various chronic comorbidities into a numeric risk value.[26] In many of these patients, the endothelial surface layer may already be dysfunctional,[32] and sulodexide can serve as a precursor for the synthesis of the GAGs needed for glycocalyx restoration. Animal studies show regrowth at 12 hours with recovery of the hemodynamically relevant glycocalyx in 5 to 7 days.[10] The protective effect of sulodexide on vascular glycocalyx is also achieved through reducing the degradation of GAGs.[33,34] The clinical progression of COVID-19 is associated with a severe inflammatory response in which symptoms can rapidly progress to full acute respiratory distress syndrome, which requires treatment with supplemental oxygen and/or hospital care.[35,36] Sulodexide modulates and inhibits the generation of free radicals and critical inflammatory molecules, such as interleukin (IL)-1 β (β),

Table 3 Medication adherence and adverse events

	Sulodexide ($n = 124$)	Placebo ($n = 119$)	RR (95% CI)	*p*-Value
Medication adherence, *n* (%)				
All the time[a]	91 (73)	99 (83)	1.13 (0.99–1.29)	0.06
Most of the time[a]	14 (11)	8 (7)	0.59 (0.25–1.36)	0.22
Medication suspended				
Total	19 (15)	12 (10)	1.81 (0.88–3.74)	0.10
Adverse event[b]	8 (6)	6 (5)	0.78 (0.27–2.18)	0.63
Voluntary[c]	11 (8.8)	6 (5)	0.56 (0.21–1.48)	0.24
Adverse event, *n* (%)				
Total[d]	96 (77)	85 (71)	1.08 (0.93–1.25)	0.28
Abdominal discomfort (gastritis, nausea, vomiting, or diarrhea)	36 (29)	39 (32)	1.12 (0.77–1.64)	0.52
Headache	96 (77)	85 (71)	0.92 (0.79–1.07)	0.28
Major bleeding	0	1 (0.8)	3.12 (0.12–75.96)	0.48
Skin reaction	3 (2.4)	5 (4.2)	1.73 (0.42–7.10)	0.44

Abbreviations: CI, confidence interval; *n*, number patients; RR, relative risk.
Note: Values are up to day 21, the scheduled completion date of the trial. The main reason for the voluntary suspension of medication was an improvement in symptoms.
[a]Patients while in the per-protocol outpatient setting.
[b]Three patients in the control group and five patients in the study group who suspended the medication due to an adverse event required hospital care due to severe clinical disease progression.
[c]No patient who suspended medication voluntarily needed hospital care or supplemental oxygen.
[d]More than one adverse event could occur per patient.

IL-6, IL-8, and tumor necrosis factor-α.[37,38] Although sulodexide's effect in modulating the glycocalyx can take time, its impact on modulating the endothelial response to these molecules (particularly IL6, which is very relevant in COVID-19) can occur in as little as 24 hours.[34] This effect could help explain the reduced need for hospital care and supplemental oxygen observed in the sulodexide group.

Coagulopathy in severe COVID-19 is characterized by increased D-dimer.[39] Although nonspecific, this increase suggests thrombus generation and fibrinolysis possibly attributable to a coagulation cascade activation secondary to systemic inflammatory response syndrome.[40] However, limited data exist regarding their value in the outpatient setting. In the hospital setting, levels of biomarkers such as D-dimer and CRP have been proven to be helpful in identifying clinical severity of the disease,[41] including occurrence of mortality.[42] Lower D-dimer levels are therefore suggestive of a decreased severity of the disease,[43] a relationship that has prompted the use of anticoagulation, though the debate on proper dosing and duration is ongoing.[44,45] Sulodexide has been proposed as an option for targeting thromboembolic risk in COVID-19 patients.[46] The drug's antithrombotic effect is a result of its interaction with antithrombin and heparin cofactor II.[47] Thus, the lower D-dimer and CRP levels observed with sulodexide treatment could result from the drug's effect against the thromboinflammation response and microvascular thrombus formation. Although the number of confirmed thromboembolic events was low in (and similar among) both groups in our study population, we strongly suspected (but could not confirm) additional clinical cases.

In addition, reports on a select group of patients under prolonged anticoagulation who later tested positive for COVID-19 presented better outcomes[48] and D-dimer elevation was common upon hospital admission.[49] We found that almost 15% of the study patients had elevated D-dimer levels at baseline. We also observed that once patients required hospital care, there was no between-group difference in the total number of days of hospital care or the need for mechanical ventilation or hemodialysis, and there was also no between-group difference in mortality. These findings suggest that the severe systemic disease complications may obscure sulodexide's effect once patients become critically ill, highlighting the importance of early action.

Moreover, other anticoagulants are known to have secondary, nonanticoagulant properties that can be beneficial to COVID-19 patients, particularly unfractionated heparin and LMWH[21,46]; however, the risk of bleeding that accompanies these treatments has limited their use in the hospital setting. Sulodexide, in contrast, can be used early in treatment with no significant risk of side effects and no need to monitor blood for dose control.

Several limitations of this study must be acknowledged. Asymptomatic carriers and a lack of widespread diagnostic testing have made it difficult to establish the disease's true incidence. Consequently, the posthoc sample size was relatively small, mortality was underpowered, and the *p*-value for hospitalization was not especially strong. Nonmajor, clinically relevant bleeding was not assessed. At the time of the study, it took an average of 5 days to receive the SARS-

Table 4 Concomitant medication

	Sulodexide group ($n = 124$)	Placebo group ($n = 119$)	RR (95% CI)	*p*-Value
Medication before trial, *n* (%)				
Aspirin	33 (27)	44 (37)	0.71 (0.49–1.04)	0.08
Oral hypoglycemic drugs	19 (15)	27 (23)	0.67 (0.39–1.14)	0.14
Insulin	14 (11)	18 (15)	0.74 (0.38–1.43)	0.37
ACE inhibitors	22 (18)	32 (27)	0.65 (0.40–1.06)	0.09
Other antihypertensive drugs	45 (36)	41 (34)	1.05 (0.74–1.48)	0.76
Statins	14 (11)	16 (13)	0.83 (0.42–1.64)	0.61
Medication added during the trial, *n* (%)				
Paracetamol	78 (63)	82 (69)	0.91 (0.76–1.09)	0.32
LMWHs	12 (10)	16 (13)	0.71 (0.35–1.45)	0.36
NOACs	9 (7)	11 (9)	0.78 (0.33–1.82)	0.57
Ivermectin	54 (44)	59 (50)	0.87 (0.67–1.15)	0.34
Hydroxychloroquine	46 (37)	36 (30)	1.22 (0.85–1.75)	0.26
Corticosteroids	79 (64)	73 (61)	1.17 (0.97–1.40)	0.08
Statins	25 (20)	21 (18)	1.14 (0.67–1.92)	0.61
Vitamins—supplements	95 (77)	101 (85)	0.90 (0.79–1.02)	0.10
Antibiotics	41 (33)	35 (29)	1.12 (0.77–1.63)	0.54
Other NSAIDs	67 (54)	56 (47)	1.14 (0.89–1.47)	0.27
Omeprazole	98 (79)	105 (88)	0.88 (0.78–0.98)	0.03
Antacids	44 (35)	36 (30)	1.17 (0.81–1.68)	0.38
Inhaled bronchodilators	70 (56)	85 (71)	0.79 (0.65–0.95)	0.01
Oseltamivir	33 (27)	28 (24)	1.13 (0.73–1.74)	0.58

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; LMWHs, low-molecular-weight heparins; *n*, number of patients; NOACs, non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants); NSAIDs, nonsteroidal anti-inflammatory drugs; RR, relative risk.
Note: The showed list only includes medications used in the outpatient setting. Patients usually received more than one additional medication.

CoV-2 RT-PCR test results. Consequently, given the time-sensitive nature of sulodexide's expected benefit, patients were included under clinical suspicion alone. We did not foresee some of the logistical limitations that stemmed from the region's pandemic lockdown, resulting in poor access to Doppler ultrasound and computed tomography scans. The lead researcher was not blinded to group allocation. During the outpatient setting, the numbers and types of medications prescribed to the study population were heterogenic. Although these factors were evenly distributed between the groups, one must still consider them when interpreting the results.

In summary, when used in the early stages of COVID-19, the synergistic activity of sulodexide's pleiotropic effects on different biological targets may play an essential role in limiting disease progression, thus resulting in a reduced need for supplemental oxygen and hospital care—as was observed in this trial. These results have promising implications that indicate a contribution toward patients' well-being, making sulodexide a valuable medication in the outpatient treatment of COVID-19. These findings justify further confirmatory multicenter studies.

What is known about this topic?

- The use of low-molecular-weight heparin (LMWH) has reduced mortality in critically ill COVID-19 patients.
- There are insufficient data regarding the benefit of anticoagulation in SARS-COV-2-positive persons with mild to moderate COVID-19.
- Patients' laboratory values during the different clinical stages of COVID-19 are rarely available outside the hospital setting.

What does this paper add?

- Treatment of mildly to moderately diseased COVID-19 patients may be improved by sulodexide's antithrombotic effect without increasing the risk of bleeding.
- The increase in D-dimer and C-reactive protein levels is lower with sulodexide compared with placebo during the outpatient treatment of COVID-19.
- Oral treatment with sulodexide may be an alternative to other oral anticoagulants due to its multiple non-antithrombotic pharmacological actions.

Note

The data analyzed and presented in this study are available from the corresponding author upon reasonable request, providing that the request meets local ethical and research governance criteria. This trial is listed in the ISRCTN registry with the study ID ISRCTN59048638.

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Conflict of Interest

A.G.O. has received speaker fees, honoraria, and travel reimbursement from Alfasigma Mexico for research unrelated to this study. The other authors have no competing interests to declare.

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