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MAJOR ARTICLE

Fostamatinib for the Treatment of Hospitalized Adults With Coronavirus Disease 2019: A Randomized Trial

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Background: Coronavirus disease 2019 (COVID-19) requiring hospitalization is characterized by robust antibody production, dysregulated immune response, and immunothrombosis. Fostamatinib is a novel spleen tyrosine kinase inhibitor that we hypothesize will ameliorate Fc activation and attenuate harmful effects of the anti-COVID-19 immune response.

Methods: We conducted a double-blind, randomized, placebo-controlled trial in hospitalized adults requiring oxygen with COVID-19 where patients receiving standard of care were randomized to receive fostamatinib or placebo. The primary outcome was serious adverse events by day 29.

Results: A total of 59 patients underwent randomization (30 to fostamatinib and 29 to placebo). Serious adverse events occurred in 10.5% of patients in the fostamatinib group compared with 22% in placebo ($P = .2$). Three deaths occurred by day 29, all receiving placebo. The mean change in ordinal score at day 15 was greater in the fostamatinib group (-3.6 ± 0.3 vs -2.6 ± 0.4, $P = .035$) and the median length in the intensive care unit was 3 days in the fostamatinib group vs 7 days in placebo ($P = .07$). Differences in clinical improvement were most evident in patients with severe or critical disease (median days on oxygen, 10 vs 28, $P = .027$). There were trends toward more rapid reductions in C-reactive protein, D-dimer, fibrinogen, and ferritin levels in the fostamatinib group.

Conclusion: For COVID-19 requiring hospitalization, the addition of fostamatinib to standard of care was safe and patients were observed to have improved clinical outcomes compared with placebo. These results warrant further validation in larger confirmatory trials.

Clinical Trials Registration. NCT04579393.

Keywords. COVID-19; immunomodulator; respiratory failure; SARS-CoV-2.

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China in December 2019 and subsequently has led to a global pandemic with significant mortality. Patients with COVID-19 are hospitalized predominately with respiratory failure but may also exhibit other disease manifestations including thromboembolic events, myocardial injury, shock, and renal failure [1]. The underlying pathogenesis of COVID-19 is thought to be a dysregulated immune response resulting in endothelial dysfunction, a hypercoagulable state, and immunothrombosis [2]. Currently, remdesivir is the only antiviral that has proven efficacy in SARS-CoV-2 infection, whereas the broad acting steroid dexamethasone, Janus/kinase (JAK) inhibitor baricitinib, and anti-interleukin-6 (IL-6) receptor inhibitor tocilizumab have shown varying degrees of efficacy as immunomodulators [3-7]. Despite these therapeutic advances, mortality of hospitalized patients with COVID-19 remains high; therefore, there is a need to find more efficacious therapies targeting pathophysiologic pathways implicated in disease severity.

It is hypothesized that exuberant plasmablast and antibody responses result in more severe COVID-19, and transcriptomics have revealed that Fc receptor activation is increased in patients with COVID-19-induced acute respiratory distress syndrome (ARDS) [8-11]. Spleen tyrosine kinase (SYK) is a cytoplasmic tyrosine kinase that associates primarily with immunoreceptor tyrosine-based activation motifs on Fc receptors and B-cell receptors as well as immunoreceptor tyrosine-based activation motif-like sequences on C-type lectin receptors [12]. Fostamatinib is an oral SYK inhibitor that is US Food and Drug Administration-approved for the treatment of chronic idiopathic thrombocytopenic purpura. R406, the active metabolite of fostamatinib, inhibits both the release of proinflammatory

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cytokines (IL-1β, IL-6, IL-8, tumor necrosis factor, and IL-10) from macrophages and platelet-mediated thrombus formation provoked by anti-spike immune complexes (antigen/antibody complexes) predominately in an FcγRIIA-dependent manner [13, 14]. Further, R406 has been shown to abrogate the release of neutrophil extracellular traps (NETs) when healthy neutrophils were stimulated with plasma from patients with COVID-19 [15]. NETs are web-like structures of citrullinated DNA, embedded with antimicrobial proteins such as neutrophil elastase and myeloperoxidase, which promote immunothrombosis and have been found in the lungs of patients who died from COVID-19 [16-18]. NETs levels have been associated with disease severity in COVID-19, and therefore agents that target NETosis are of interest as potential therapeutics to mitigate the disease [19]. In addition to decreasing inflammation and immunothrombosis, R406 has also been shown to inhibit Mucin-1, a pulmonary epithelial transmembrane protein associated with ARDS severity [20].

These preclinical studies and awareness of the upstream role that SYK plays in disease pathogenesis provide a unique therapeutic approach to COVID-19 and led us to hypothesize that SYK inhibition would be therapeutically beneficial by decreasing Fc-mediated immune dysregulation and thrombosis. Therefore, we conducted a phase 2 trial to evaluate the safety of fostamatinib treatment in hospitalized patients with COVID-19 and to assess for early evidence of clinical efficacy.

METHODS

Study Design and Participants

We conducted a randomized, double-blind, placebo-controlled, investigator-initiated trial (clinicaltrials.gov identifier NCT04579393) across 2 centers: Inova Fairfax Hospital (Falls Church, VA) and the National Institutes of Health (NIH) Clinical Center (Bethesda, MD). The protocol was designed by the authors with input from the manufacturer, Rigel Pharmaceuticals, Inc. The study was approved by the NIH institutional review board via a reliance agreement between both sites and was overseen by an independent data and safety monitoring board. Study drug and matching placebo were provided by Rigel Pharmaceuticals, Inc. Written informed consent was obtained from all participants or from the patients' legally authorized representatives in the event a patient was unable to consent.

The study enrolled hospitalized patients age ≥ 18 years with a laboratory confirmed SARS-CoV-2 reverse transcriptase polymerase chain reaction test within 7 days and oxygen saturation ≤ 94% on room air requiring supplemental oxygen via nasal canula, noninvasive mechanical ventilation, mechanical ventilation, or extracorporeal membrane oxygen (5–7 on the 8-point ordinal scale [3, 5]; see Supplementary Table 1). Patients treated with immunomodulators including tocilizumab within 30 days before enrollment were excluded. Full enrollment criteria are provided in Supplementary Methods.

Randomizations and Interventions

Randomization sequence stratified by site and severity of illness was generated by an independent statistician. A permuted block randomization of block size 2 or 4 was used within each stratum. Eligible patients were randomized 1:1 to receive fostamatinib or placebo on day 1 in addition to standard of care. Standard of care was defined by each participating center and consisted primarily of remdesivir and corticosteroids. Fostamatinib or placebo was administered at a dose of 150 mg orally or via gastric tube twice daily for a total of 14 days (or 28 doses) and continued outpatient if the patient was discharged before day 14. Patients discharged on medication received daily phone calls to assess compliance and adverse events. Study drug was held for systolic blood pressure above 180 mmHg and/or diastolic blood pressure over 120 mmHg, increase in aspartate transaminase/alanine aminotransferase by 3 times their baseline level at enrollment, grade 3 diarrhea, or absolute neutrophils count less than 1.0×10^9/L and was restarted at a dose of 100 mg twice daily upon resolution.

Clinical Outcomes

The primary outcome was the cumulative incidence of serious adverse events (SAEs) through day 29. Additional safety endpoints included grade 3 and 4 adverse events (AEs), and proportions of the patients who developed acute renal failure, or deep vein thrombosis and pulmonary embolism. SAE and AE reporting was based on the Common Terminology Criteria for Adverse Events version 5.0.

Prespecified secondary efficacy endpoints, evaluated up to day 29, included 14-day and 28-day mortality; ordinal scale score at day 15 and day 29 (Supplementary Table 1); number of days on supplemental oxygen and days hospitalized in the intensive care unit (ICU) after randomization; time to an ordinal scale score of 3 or less (defined as time to recovery [either discharge from the hospital or hospitalization for infection control reasons only], with the recovery status sustained through day 29); progression to mechanical ventilation among patients not receiving mechanical ventilation at enrollment; and changes in correlative biomarkers. Exploratory endpoints included changes in levels of NETs. All information presented in this report is based on a data cutoff of March 30, 2021, with all patients having completed follow-up through day 29.

Statistical Analysis

A sample size of 60 patients was determined based on feasibility. The double-blind randomized design was used to evaluate safety and early efficacy of fostamatinib compared with placebo. All analyses were performed by the intention-to-treat principle according to the prespecified statistical analysis plan.

The Kaplan-Meier method was used to estimate the rates of SAEs, grade 3 and 4 AEs, and other efficacy outcome events up to day 29. The log-rank test was used to compare the event rates between fostamatinib and placebo groups, and the rate ratio was estimated based on the Cox proportional hazards regression. For all the time-to-event analyses (other than mortality), we considered early death without the specified event as having the least favorable rank through day 29 [21]. For ordinal scores, laboratory measures, and their changes over time, we reported the summary statistics and compared the differences by Wilcoxon rank-sum test between the treatment groups. All *P* values were two-sided with no adjustment for multiple testing. A 2-sided *P* value < .05 was considered statistically significant. Statistical analyses were performed using the R software version 4.0.3 (R Core Team).

RESULTS

Patients

From October 8, 2020, through March 2, 2021, a total of 62 patients hospitalized with moderate to critical COVID-19 disease were assessed for eligibility and consented, with 59 undergoing randomization (Figure 1). Baseline demographic and clinical characteristics were balanced in the 2 treatment groups (Table 1). At baseline, the mean (±SD) age was 55.6 (±13.7) years, 23/59 patients (39%) had moderate disease (ordinal score 5 [oxygen via nasal canula]) and 36/59 (61%) had severe or critical disease (with ordinal score 6 or 7 [oxygen via noninvasive ventilation, high-flow oxygen devices, or mechanical ventilation, respectively]). Across both study groups, 39% of patients were White, 10% were Black or African American, 10% were Asian, and 59% were Hispanic. The median time from symptom onset was 10 days (interquartile range, 8 to 12 days). Standard of care was consistent in both groups with all patients receiving remdesivir and corticosteroids (58/59 received dexamethasone), whereas 42% of patients received convalescent plasma (24 patients) or monoclonal antibodies (1 patient). In the fostamatinib group, patients received a mean of 23 of 28 planned doses, with 28 (93%) receiving at least 7 doses and 20 (67%) receiving the full planned 28 doses. The study drug compliance and modifications are summarized in Supplementary Table 2.

Primary Outcome

The primary outcome of SAEs occurred in 9 patients (Table 2; Supplementary Figure 1). The rates of SAEs were not statistically different between the fostamatinib group and the placebo group (10.5% vs 22.0%, *P* = .2). The most frequent SAE was worsening hypoxia, which occurred in 4 patients. When classifying SAEs as being respiratory-related or death, only 1 patient had an event in the fostamatinib group compared with 5 patients in the placebo group (3.3% vs 18.5%, *P* = .08). Additional information for SAEs and sensitivity analysis (excluding subjects who withdrew) are shown in Supplementary Table 3.

Mortality

A total of 3 deaths occurred, all in the placebo group. Kaplan-Meier estimates of mortality at 28 days after randomization were 11.1% in the placebo group and 0% in the fostamatinib group (*P* = .07; Table 2, Supplementary Figure 1B). There were 4 patients who were on mechanical ventilation at enrollment: 2 received fostamatinib and were extubated (3 and 6 days following enrollment) and discharged from the hospital before

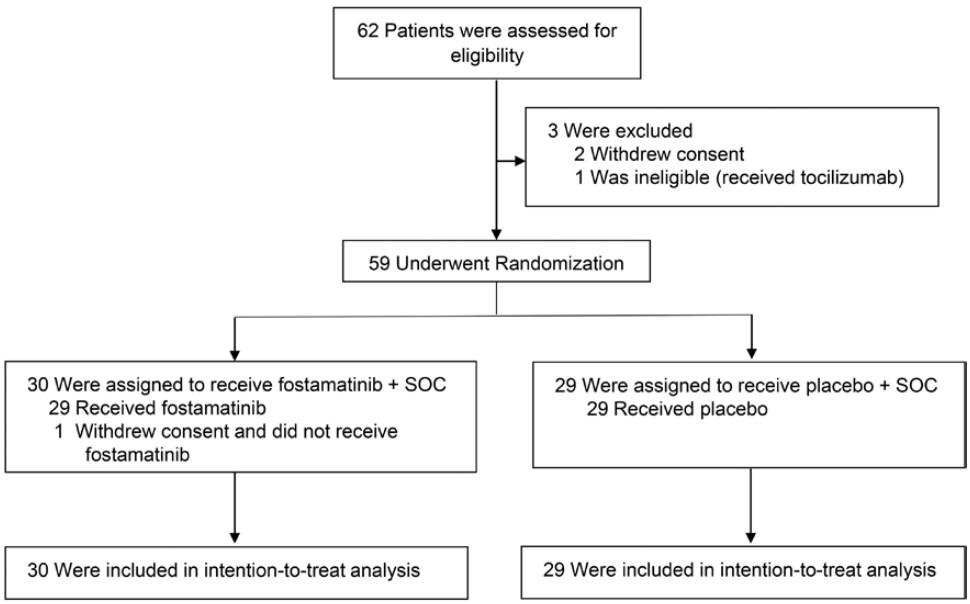

Figure 1. Study flow diagram. Abbreviation: SOC, standard of care.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline

Characteristic	All Patients (N = 59)	Fostamatinib (N = 30)	Placebo (N = 29)
Age, y			
Mean ± SD	55.6 ± 13.7	54.3 ± 13.5	57.0 ± 14.1
Median (range)	57 (26-85)	55 (30- 80)	60 (26-85)
Distribution, no. (%)			
18-39 y	9 (15.3)	5 (16.7)	4 (13.8)
40-64 y	31 (52.5)	17 (56.7)	14 (48.3)
≥65 y	19 (32.2)	8 (26.7)	11 (37.9)
Sex, no. (%)			
Female	12 (20.3)	8 (26.7)	4 (13.8)
Male	47 (79.7)	22 (73.3)	25 (86.2)
Race, no. (%)			
Asian	6 (10.2)	2 (6.7)	4 (13.8)
Black or African American	6 (10.2)	3 (10.0)	3 (10.3)
White	23 (39.0)	12 (40.0)	11 (37.9)
Multiple race or unknown	24 (40.7)	13 (43.3)	11 (37.9)
Ethnic group, no (%)			
Hispanic or Latino	35 (59.3)	18 (60)	17 (58.6)
Not Hispanic or Latino	24 (40.7)	12 (40)	12 (41.4)
Body-mass index (kg/m^2), mean ± SD	32.3 ± 7.7	32.5 ± 7.5	32.1 ± 8.0
Median time (IQR) from symptom onset to randomization (days)	10 (8, 12)	10.5 (9, 12)	10 (6, 12)
Coexisting conditions, no. (%)			
None	11 (18.6)	6 (20)	5 (17.2)
One	15 (25.4)	6 (20)	9 (31.0)
Two or more	33 (55.9)	18(60)	15 (51.7)
Main comorbidities[a], no. (%)			
Obesity (BMI ≥ 30)	34 (57.6)	18 (60)	16 (55.2)
Hypertension	32 (54.2)	15 (50)	17 (58.6)
Type II diabetes	22 (37.3)	12 (40)	10 (34.5)
Coronary artery disease	8 (13.6)	4 (13.3)	4 (13.8)
Asthma	7 (11.9)	4 (13.3)	3 (10.3)
Score on ordinal scale, no. (%)			
5. Requiring supplemental oxygen	23 (39.0)	11 (36.7)	12 (41.4)
6. Noninvasive ventilation or high-flow oxygen devices	32 (54.2)	17 (56.7)	15 (51.7)
7. Invasive mechanical ventilation or extracorporeal membrane oxygen	4 (6.8)	2 (6.7)	2 (6.9)
Medication for COVID-19 other than the study drug, no. (%)			
Remdesivir	59 (100)	30 (100)	29(100)
Dexamethasone or other steroids[b]	59 (100)	30 (100)	29(100)
Convalescent plasma or monoclonal antibodies[c]	25 (42.4)	12 (40)	13 (44.8)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; IQR, interquartile range; SD, standard deviation.

[a]Comorbidities considered include hypertension, obesity, type 1 and 2 diabetes, dementia, peripheral vascular disease, chronic kidney disease, end-stage renal disease (dialysis), chronic liver disease (chronic hepatitis, cirrhosis), chronic respiratory disease, chronic obstructive pulmonary disease, sarcoidosis, asthma, chronic oxygen requirement, coronary artery disease, congestive heart failure, stroke, venous thromboembolism, pulmonary embolism, solid malignancy, leukemia, lymphoma, and immune deficiency (acquired or innate).

[b]1 patient received steroids (methylprednisolone and prednisone) other than dexamethasone.

[c]1 patient received monoclonal antibodies but did not receive convalescent plasma.

day 29, whereas both patients who received placebo died (11 and 20 days following enrollment). There was an additional patient in the placebo group who was enrolled on high-flow oxygen, progressed to mechanical ventilation, and died. Because no deaths occurred in patients with a baseline ordinal score of 5, we performed a subgroup analysis in those enrolled with a baseline ordinal score of 6 or 7, which suggested a trend toward reduced mortality in patients with severe or critical disease in the fostamatinib group compared with those receiving placebo (0% vs 20%, $P = .049$).

Efficacy Outcomes

Several prespecified secondary outcomes are shown in Table 2. For the entire cohort, the mean change in ordinal score at day 15 was greater in the fostamatinib group compared with the placebo group (-3.6 ± 0.3 vs -2.6 ± 0.4; $P = .035$; Figure 2A). This difference was most evident in patients with severe or critical disease ($P < .05$ for days 8, 11, and 15; Figure 2B). Consistent with this, the median time to improvement in ordinal scale by 1 point or greater was 3 days in the fostamatinib group compared with 7 days in the placebo group (rate ratio for improvement, 1.61; 95% confidence interval [CI], 0.92–2.81; $P = .09$). This finding also appeared to be more pronounced in those with severe or critical disease (3 vs 9 days; rate ratio, 2.05; 95% CI, 0.98–4.32; $P = .053$). Among the 40% of patients who required ICU care during the study, the median ICU length was 3 days in the fostamatinib group and 7 days in placebo ($P = .07$). Finally, by day 15, a greater proportion of patients in the fostamatinib group with severe or critical disease no longer required any supplemental oxygen compared with the placebo group (57.9% vs 20%; $P = .016$, Supplementary Figure 2); additionally, the median duration on oxygen through day 29 was shorter in the fostamatinib group than in the placebo group (10 vs 28 days; $P = .027$).

Twenty-seven patients (93.1%) recovered (ordinal score 3 or less by day 29) in the fostamatinib group compared with 22 (81.2%) in the placebo group (rate ratio for recovery, 1.33; 95% CI, 0.75-2.33; $P = .3$). Among patients with severe or critical disease, 89.5% of patients in the fostamatinib group and 73.1% in the placebo group had sustained recovery by day 29 (median time to recovery, 10 vs 13 days; rate ratio, 1.59; 95% CI, 0.74-3.41, $P = .2$; Supplementary Figure 3).

Among patients who were not receiving mechanical ventilation at baseline, 1 patient (3.6%) in the fostamatinib group and 2 patients (8%) in the placebo group progressed to invasive mechanical ventilation by day 29 (Supplementary Table 4). The patient in the fostamatinib group was extubated after 21 days and recovered to discharge, whereas the 2 newly intubated patients in the placebo group either died or remained on mechanical ventilation by the day 29 assessment.

Finally, we performed an analysis to explore the effects of prespecified subgroups such as patient demographics,

Table 2. Summary of Primary and Secondary Outcomes

	All Patients			Patients with Severe or Critical Disease (Ordinal Score 6 to 7)		
	Fostamatinib	Placebo		Fostamatinib	Placebo	
Outcomes	(N = 30)	(N = 29)	*P* Value	(N = 19)	(N = 17)	*P* Value
Primary outcome, no, (%)[a]						
Any SAE by day 29	3 (10.5)	6 (22.0)	.2			
Most frequent SAE: hypoxia	1 (3.3)	3 (11.3)	.3			
Any respiratory SAE or death[b]	1 (3.3)	5 (18.5)	.08			
Secondary outcome						
Mortality						
14-day estimate, no. (%)	0 (0)	1 (3.7)		0 (0)	1 (6.7)	
28-day estimate, no. (%)	0 (0)	3 (11.1)	.07	0 (0)	3 (20.0)	.049
Score on ordinal scale						
Ordinal score at day 15, median (IQR)	1 (1-2)	2 (1-5)		1 (1-5)	2 (2-6)	
Mean change from baseline to day 15[c]	-3.6 ± 0.3	-2.6 ± 0.4	.035	-3.4 ± 0.5	-2.3 ± 0.6	.043
Ordinal score at day 29, median (IQR)	1 (1-2)	1 (1-2)		1 (1-2)	2 (1-5)	
Mean change from baseline to day 29[c]	-4.2 ± 0.2	-3.3 ± 0.4	.12	-4.4 ± 0.3	-3.1 ± 0.7	.15
Improvement by ≥ 1 category on ordinal scale						
Median days (IQR)	3 (3-5)	7 (5-7)		3 (3-5)	9 (6-11)	
Rate ratio (95% CI)	1.61 (0.92-2.81)		.09	2.05 (0.98-4.32)		.053
ICU[d]						
No. admitted to ICU (%)	13 (43.3)	12 (41.4)	>.99	11 (57.9)	10 (58.8)	>.99
Median days in the ICU (IQR)	3 (2-5)	7 (2-10)	.07	3 (2-5)	8 (2-19)	.09
Supplemental oxygen requirement[d]						
No. of patients free of oxygen at day 15 (%)	19 (65.5)	11 (39.9)		11 (57.9)	3 (20.0)	
Rate ratio (95% CI) for data through day 15	1.92 (0.91-4.04)		.08	4.27 (1.19-15.39)		.016
Median days on oxygen through day 29	8 (5-10)	20 (14-27)	.2	10 (5-16)	28 (20-28)	.027
Recovery (ordinal score ≤ 3 or hospital discharge) by day 29[d]						
No. of recoveries (%)	27 (93.1)	22 (81.2)		17 (89.5)	11 (73.1)	
Median days to sustained recovery (IQR)	8 (5-9)	8 (6-12)		10 (6-13)	13 (11-19)	
Rate ratio (95% CI)	1.33 (0.75-2.33)		.3	1.59 (0.74-3.41)		.2

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range, SAE, serious adverse event.

[a]No. is number of patients with at least 1 event. SAE event rates were estimated by the Kaplan-Meier methods and compared with log-rank test between the 2 groups, censoring patients who withdrew from the study after randomization. If a patient had more than 1 SAE, the patient was counted only once and the time to the first SAE was used in the calculation.

[b]Included 5 respiratory-related SAEs (4 hypoxia and 1 post-COVID-19 fibrosis), and 1 COVID-19-related death for a patient with on mechanical ventilation at baseline.

[c]Plus–minus values are means ± SEM (standard error of the mean). The mean changes of ordinal scores were compared by the Wilcoxon rank-sum test between the 2 groups.

[d]Early death without the specified event was considered as having the least favorable rank through day 29: any patient who died before recovery was censored at day 29 for time to recovery; the days of hospitalization was imputed as hospitalized through day 29 (28 days following randomization) for any patient who died before day 29; if the patient died in the ICU (or on oxygen), the length in the ICU (or oxygen) was imputed as if the patient had stayed in the ICU (or on oxygen) through day 29 (28 days after randomization).

convalescent plasma, and symptom duration (Supplementary Table 5). None of the tests for interactions between subgroups and treatment assignment for safety and efficacy outcomes were statistically significant. The observed trends of clinical outcomes for all patients were consistent across the subgroups and remained almost the same when controlling for patients' demographic characteristics univariately.

Correlative Biomarkers

We prospectively evaluated multiple inflammatory biomarkers to inform and better understand the efficacy and mechanistic findings (Supplementary Table 6, Figure 3, and Supplementary Figures 4-5). At enrollment, all were markedly elevated above normal levels, with a similar baseline distribution between the 2 study groups. Following treatment, differences favoring fostamatinib were observed for C-reactive protein (CRP), D-dimer, fibrinogen, and ferritin levels at one or more time points within 2 weeks of therapy initiation. Trends toward improvement in these 4 biomarkers were more pronounced in patients with severe or critical disease; however, fostamatinib treatment did not appear to affect IL-6 levels compared with placebo (Supplementary Figure 5). Additionally, NETs levels were quantified by measuring myeloperoxidase-DNA complexes on days 1, 5, and 11 (Supplemental methods). Baseline levels of circulating NETs were found to correlate with disease severity at enrollment (Supplementary Figure 6). Furthermore, an exploratory analysis of patients with elevated baseline NETs showed a trend toward a greater decline in the mean NETs level at day 5 from baseline in those who received fostamatinib compared with those who received placebo (Supplementary Figure 7).

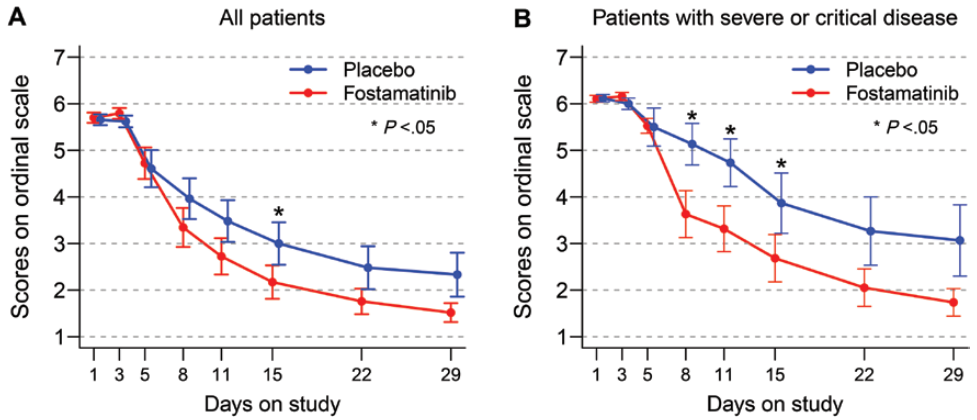

Figure 2. Efficacy outcomes. The mean scores on ordinal scale over the study days for (A) all patients (n = 59) and (B) patients with severe or critical disease (n = 36). *Indicates a *P* value < .05 for comparing the mean changes of ordinal scores from baseline between the 2 treatment groups based on the Wilcoxon rank-sum test.

Additional Safety Outcome and Adverse Events

The rates of any adverse events with at least grade 3 were similar between the 2 treatment groups, occurring in 11 patients (37.9%) in the fostamatinib group and 11 (40.0%) in the placebo group (Supplementary Table 7). The most common nonserious grade 3 or 4 AE was a decrease in lymphocyte count, which occurred more frequently in the placebo group (25.1% in placebo vs 13.9% in fostamatinib). The other grade 3 and 4 AEs that occurred in at least 3 patients were anemia, hypoalbuminemia, and hypokalemia. The percentage of patients with acute kidney injury (10% vs 17.2%) and deep venous thrombosis (6.7% vs 0%) were not statistically significant between the fostamatinib and placebo groups (Supplementary Table 8).

DISCUSSION

This double-blinded, randomized, placebo-controlled trial demonstrated that the addition of fostamatinib to standard of care is safe. Serious adverse events were observed to occur less frequently in the fostamatinib group versus the placebo group (10.5% vs 22.0%, respectively), providing evidence that this agent can be safely used in this patient population. Additionally,

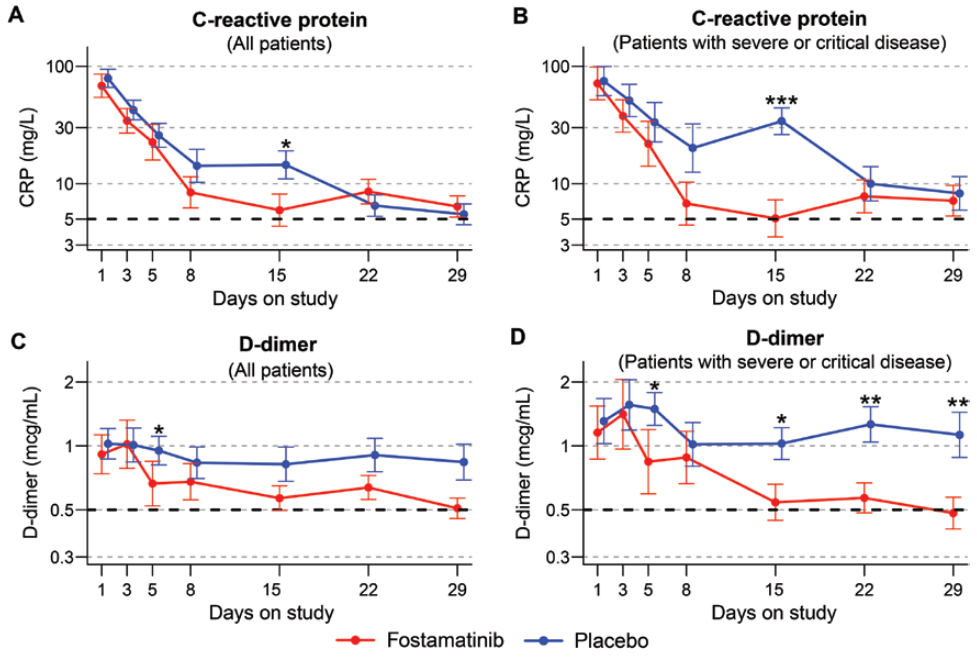

Figure 3. Longitudinal measurements of biomarkers through day 29. Mean levels and standard error of the mean error bars of C-reactive protein for (A) all patients and (B) patients with severe or critical disease as well as D-dimer for (C) all patients and (D) patients with severe or critical disease in the fostamatinib group (in red) and the placebo group (in blue) are shown in log-scale. *$P < .05$, **$P < .01$, ***$P < .001$ for comparing the mean biomarker levels between the 2 treatment groups based on the Wilcoxon rank-sum test (see also Supplementary Table 6). The black dashed line in each plot indicates the upper limit of the normal range for the corresponding biomarker.

the observed differences in SAEs between cohorts were primarily a reflection of more respiratory-related disease progression and death in the placebo group. Although this study was not powered for efficacy, numerous secondary endpoints consistently favored fostamatinib, including 28-day mortality, days on supplemental oxygen, ordinal score at day 15, median time to improvement in ≥ 1 category in ordinal scale, and number of days in the ICU. Importantly, the potential clinical improvements seen in this study occurred in patients who all received remdesivir and corticosteroids.

Fostamatinib was well tolerated, resulting in a similar AE profile as observed with placebo. More patients received the full planned treatment course of 28 doses of fostamatinib compared with those given placebo. Only 1 patient in the fostamatinib group had study drug held because of an elevation in alanine aminotransferase compared with 2 patients in the placebo group. No patients required their study drug to be held for any other predefined side effects known to be associated with fostamatinib (Supplementary Table 2).

Patients developing respiratory failure from COVID-19 are at an increased risk for mortality. All 3 patients in the fostamatinib group requiring mechanical ventilation before day 29 (2 at baseline and 1 after enrollment) survived and were discharged from the hospital. In contrast, the 4 who required mechanical ventilation in the placebo group (2 at baseline and 2 after enrollment) had worse outcomes, with 3 dying and the fourth patient remaining hospitalized at the last study follow-up.

Recent studies have focused on oxygen-free days as a more clinically meaningful outcome than time to recovery [22]. In this context, freedom from oxygen is more reflective of lung function improvement in contrast to the time to recovery (achieving an ordinal score of 3 or hospital discharge), which often includes patients with persistent lung injury that have an ongoing requirement for supplemental oxygen after hospital discharge. In this trial, lung injury appeared to resolve more quickly in those receiving fostamatinib because more patients were discharged home on oxygen and the overall days on oxygen were higher in those in the placebo group.

The observed improvements in clinical outcomes, coupled with robust biomarker data demonstrating more rapid reductions in CRP, D-dimer, fibrinogen, and ferritin, provide strong biological evidence that fostamatinib modulates harmful aspects of host immunity and inflammation beyond that observed with corticosteroids alone. The divergence in these inflammatory biomarkers favoring fostamatinib was observed within a week of study drug initiation and temporally correlated with the onset of clinical improvements in the fostamatinib group. Because elevated levels and worsening trends in CRP and D-dimer have been associated with COVID-19 disease severity and mortality, these biomarker changes provide indirect evidence to support fostamatinib as having a favorable biologic and clinical impact on thromboinflammation [23, 24]. Additionally, our data showed baseline NETs levels correlated with disease severity at enrollment, with a trend toward a greater decline at day 5 from baseline in the levels of NETs observed in those who received fostamatinib compared with placebo. Taken together, the correlative analysis results suggest fostamatinib's unique mechanism of action inhibiting Fc-mediated thromboinflammation may shorten the protracted immune dysregulation that characterizes this viral illness, restoring biological homeostasis and preventing pathophysiologic events that contribute to COVID-19-associated morbidity and mortality.

The trial has several limitations. First and foremost, the trial was limited by the sample size that was chosen to obtain reliable data quickly using a double-blind, placebo-controlled design to evaluate the primary endpoint of safety of fostamatinib in this population with an urgent need for more effective therapies. Second, the trial was underpowered for efficacy outcomes and subgroup analysis. Although there were favorable trends in multiple secondary clinical outcomes in the fostamatinib group, these findings should be viewed with caution and need to be further assessed in a well-powered, larger randomized clinical trial. Third, although the potential clinical improvements associated with fostamatinib treatment coincided with a reduction in NETs and multiple inflammatory biomarkers, additional correlative studies are needed to elucidate the full spectrum of effect for fostamatinib on thromboinflammation.

In conclusion, fostamatinib did not result in more SAEs compared with placebo, when added to standard-of-care remdesivir and corticosteroids in this study of hospitalized patients on oxygen. In addition, patients in the fostamatinib group were observed to have a decrease in the number of days they required supplemental oxygen and a trend toward more rapid improvement in multiple biomarkers compared with placebo. Larger confirmatory trials are needed to further evaluate the efficacy of fostamatinib in COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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