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Early View

Original article

A randomised trial of *Mycobacterium w* in critically ill patients with COVID-19 (ARMY-1)

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A randomized trial of *Mycobacterium w* in critically ill patients with COVID-19 (ARMY-1)

(Running title: immunomodulation in covid-19)

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ABSTRACT

Purpose: We investigate whether *Mycobacterium w* (*Mw*), an immunomodulator, would improve clinical outcomes in coronavirus infectious disease 19 (COVID-19).

Methods: We conducted an exploratory, randomized, double-blind, placebo-controlled trial of hospitalized subjects with severe COVID-19 (pulmonary infiltrates and oxygen saturation ≤94% on room air) conducted at four tertiary care centers in India. Patients were randomized 1:1 to receive either 0.3 mL/day of *Mw* intradermally or a matching placebo for three consecutive days. The primary outcome of the study was the distribution of clinical status assessed on a seven-point ordinal scale ranging from discharged (category 1) to death (category 7) on study days 14, 21, and 28. The co-primary outcome was a change in SOFA score on days 7 and 14 compared to the baseline. The secondary outcomes were 28-day mortality, time to clinical recovery, time to RT-PCR negativity, adverse events, and others

RESULTS: We included 42 subjects (22 *Mw*, 20 placebo). On days 14 (OR, 30.4; 95% CI, 3.3-276.4) and 21 (OR, 14.9; 95% CI, 1.8-128.4), subjects in the *Mw* arm had a better clinical status distribution than placebo. There was no difference in the SOFA score change on days 7 and 14 between the two groups. We did not find any difference in the mortality, or other secondary outcomes. We observed no adverse events related to the use of *Mw*.

CONCLUSIONS: The use of *Mw* results in better clinical status distribution on days 14 and 21 compared to placebo in critically ill patients with COVID-19. [clinicaltrials.gov: NCT04347174]

Keywords: *Mw*; Mycobacterium w; Mycobacterium indicus pranii; COVID; coronavirus

INTRODUCTION

Coronavirus infectious disease 19 (COVID-19) can cause illness ranging from asymptomatic cases to severe disease, including death. The organ damage in severe COVID-19 is believed to be due to a dysregulated host immune response.[1-4] In patients with severe COVID-19, there is a sustained reduction of peripheral lymphocytes, mainly CD4 and CD8 T cells.[5, 6] Also, there is a suppression of type I and type III interferon leading to low viral clearance.[2, 7] The use of immunosuppressive drugs such as systemic corticosteroids and anti-interleukin 6 receptor monoclonal antibodies further suppress the immunity.[8-12] Thus, patients with severe COVID-19 are likely to have a sustained immune-paralytic state after the initial pro-inflammatory state, similar to Gram-negative sepsis.[3] Interestingly, those who recover mount a Th1 predominant response than the historical controls with non-COVID infection.[13]

Mycobacterium w (*Mw*), also known as *Mycobacterium indicus pranii*, is a non-pathogenic, rapidly growing atypical mycobacterium. *Mw* shares T and B cell determinants with *M.leprae* and *M.tuberculosis*. Heat-killed *Mw* administered intradermally is a potent toll-like receptor (TLR)-2 agonist,[14] inhibits TLR-9,[15] and augments the Th1 immune response.[16] *Mw* enhances the expression of IL-1 receptor associated kinase (IRAK)-1 and tumor necrosis factor receptor associated factor (TRAF)-6 that are critical for activation of TLR4 downstream kinases.[17] Mw also upregulates the inhibitor κ kinase (IKK) α and IKKβ.[17] *Mw* has been studied for its immune-modulating properties in patients with pulmonary tuberculosis, tuberculous pericarditis, sepsis, lung cancer, and leprosy.[17-22] Elsewhere, *Mw* alone and in combination with anti-retroviral therapy increased the CD4 T cells count in patients with human

immunodeficiency virus (HIV).[23] Previously, we have demonstrated that *Mw* (at a dose 0.3 mL intradermally for three days) in combination with standard care, reduced the all-cause 28-day mortality (unpublished data), the days spent on mechanical ventilation, and the ICU and hospital length of stay.[19] We hypothesized that *Mw*, by its immunomodulatory mechanism, would result in clinical improvement in severe acute respiratory syndrome (SARS)-CoV-2. Herein, we evaluate the role of *Mw* as adjunctive therapy to standard care in critically ill patients with COVID-19.

METHODS

Study design: We conducted an exploratory, multicenter, randomized, double-blind, two parallel arms, comparative controlled trial (clinicaltrials.gov: NCT04347174), to evaluate the efficacy of *Mw* in combination with standard therapy in critically ill subjects with COVID-19. Each participating center obtained ethical approval from the respective institutional ethics committee. We obtained written informed consent from all subjects or the next of kin. We conducted the trial per the principles of the Declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice guidelines. The protocol is available at www.clinicaltrials.gov (identifier: NCT04347174). No amendments were made to the protocol after commencement of the trial. The subjects were enrolled between 15th June 2020 and 15th July 2020, and the final followup visit was on 15th August 2020. The study product is marketed by Cadila Pharmaceuticals India and is a regulatory trial. The study however, was conducted under a public-private partnership through a grant received from the Council of Scientific and Industrial Research (Government of India) under the New Millennium Indian Technology Leadership Initiative (NMITLI). The Cadila Pharmaceuticals provided the study drug and the matching placebo and was not involved in the data analysis or interpretation of the results.

Setting: The study was conducted in intensive care units (ICU) or high dependency units (HDU) of four tertiary care centers in India.

Patients: We screened consecutive patients aged >18 years who were positive for SARS-CoV-2 RNA on reverse transcription-polymerase chain reaction (RT-PCR). We included subjects with a saturation of ≤94% on ambient air and infiltrates on a chest radiograph. Subjects of childbearing age were included if they agreed to take effective contraception measures during the study

period. We excluded subjects with any of the following: (1) pregnancy or breastfeeding; (2) prior cardiorespiratory arrest; (3) chronic liver disease; (4) hemodialysis dependent chronic kidney disease; (5) enrollment in another trial; (6) active malignancy; and, (7) subjects unwilling to provide consent. The use of other drugs according to the institutional protocol at each participating center was allowed. Briefly, the treatments included systemic glucocorticoids, hydroxychloroquine, convalescent plasma, tocilizumab, and anticoagulation.

Trial monitoring: An independent data safety and monitoring board monitored the trial periodically and evaluated the study data for participant safety, study conduct, and progress. An independent steering committee oversaw the conduct of the entire study.

Randomization: A central team not directly involved in patient care or patient data analysis provided a computer-generated randomization sequence. The randomization was stratified according to the centers. The subjects at each center received either the investigational drug or a matched placebo in individually numbered packs according to the sequential order. The investigators at each participating center and the subjects were blinded to the treatment allocation. Envelopes were provided to each participating center for emergency unmasking.

Sample size: The initial target of the study was 40 subjects. The ARMY-1 trial was designed to assess the feasibility and safety of *Mw* in severe COVID-19. The results were presented to the regulatory body of India, namely the drug controller general of India (DCGI), to seek permission for the next phase of the trial (ARMY-2).

Study procedures: We recorded clinical data for all the subjects on paper case record forms that were entered subsequently into an electronic database and validated by the trial staff at each center. We assessed the respiratory rate, oxygen supplementation device used (nasal

cannula, venturi mask, non-rebreathing mask, high flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation), oxygen saturation, the use of concomitant medications, and adverse events during hospitalization. We performed complete blood count, blood glucose, liver and renal function tests, arterial blood gas analysis each day until day seven, and then on days 14, 21, and 28, if the patient was still hospitalized. We recorded the sequential organ failure assessment (SOFA) score for each day until hospital discharge. We obtained nasopharyngeal or oropharyngeal or endotracheal aspirate for detecting COVID-19 RNA by RT-PCR at days 5, 7, 14, 21, 28, or at the time of hospital discharge.

We evaluated the clinical status of the study participants from day 1 through day 28 or hospital discharge on a seven-point ordinal scale consisting of the following: category 1, not hospitalized with the resumption of normal activities; category 2, not hospitalized but unable to resume normal activities; category 3, hospitalized but not requiring supplemental oxygen; category 4, hospitalized and requiring supplemental oxygen (nasal cannula, venturi mask, or non-rebreathing mask); category 5, hospitalized and requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; category 6, hospitalized and requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); category 7, death. We recorded the worst score for clinical status every day for hospitalized subjects. We made the final assessment on day 28 in person for a hospitalized subject or telephonically for those discharged before day 28.

Study drug: Each dose of 0.1 ml *Mw* contains 0.5×10^9 heat killed *Mycobacterium w*, 0.9% sodium chloride, and 0.01% thimerosal (as preservative). We used a matching placebo (0.9% sodium chloride, 0.01% thiomersal) as control.

Intervention: Subjects were randomized to receive a single daily dose of 0.3 ml of *Mw* or a matching placebo (in aliquots of 0.1 mL at three different sites) intradermally in the deltoid region for three consecutive days. We administered the study drugs within 24 hours of admission to the hospital. We observed the subjects for any adverse effects, local or systemic, that could be associated with the administration of the study drug.

Study outcomes: The **primary outcome** of the study was the distribution of clinical status assessed on the seven-point ordinal scale on days 14, 21, and 28 after randomization. If treatment with *Mw* improved the outcomes, the distribution of the scores among patients who received *Mw* would shift more towards lower values of the scale than the distribution of the scores among patients who received a placebo. The co-primary outcome was a change in SOFA score (delta SOFA) on days 7 and 14 compared to the baseline and the maximum SOFA attained during the hospital stay.

The **secondary outcomes** were 28-day mortality, the proportion of patients with adverse events that occurred on or after the first dose of the study drug for up to 28 days, time to clinical recovery (defined as a reduction by two-points on a seven-point ordinal scale), time to one-point improvement on a seven-point ordinal scale, days on vasopressor drugs, days on mechanical ventilation, time to RT-PCR negativity, and ICU and hospital length of stay.

Statistical analysis: We present the data descriptively as mean and standard deviation (SD), median and interquartile range (IQR), or number and percentage. The difference between the continuous and categorical variables was analyzed using the Mann-Whitney U test (or student's t-test) and chi-square test, respectively. We performed all analyses on an intention-to-treat (ITT) basis. All the subjects who were randomized and received at least one study dose were

assessed for efficacy and safety. If the subject died before day 14, the day 14 category on the ordinal scale was recorded as “died”; if the subject was discharged before day 14, the category on day 14 was recorded as “not hospitalized”. Similarly, if the subject died before day 7 or day 14, we assumed the highest value for the SOFA (SOFA score of 20) or the value just before death on days 7 and 14. We used the proportional odds model for the ordinal scale data, including treatment as the independent variable and the baseline disease severity, and the use of experimental therapies (hydroxychloroquine, convalescent plasma and tocilizumab) as covariates. An odds ratio greater than 1 would suggest treatment with *Mw* to be superior to placebo on days 14, 21, and 28. We assumed statistical significance at a p-value <0.05. We performed all statistical analyses using the Statistical Package for Social Sciences (IBM SPSS Statistics, version 23, IBM Corporation, Armonk, NY).

RESULTS

Baseline characteristics of the study subjects: We randomized 42 (n=22 assigned to *Mw* arm; n=20 assigned to placebo arm) subjects (Figure 1). One patient each in the *Mw* arm and the placebo arm received a single dose and withdrew consent. Both these subjects were included in the primary and safety analysis.

The baseline parameters, the severity of illness, and comorbid illnesses in the two groups are described in Table 1. The study population comprised predominantly of men (69%) with a median (IQR) age of 50 (50-65) years. The median (IQR) time from symptom onset to randomization was 7 (5-10) days and was similar in both the study arms. Fever, new-onset-cough, and dyspnea were frequently reported symptoms. More subjects in the placebo arm presented with dyspnea and a lower platelet count. Any comorbid illness was seen in 57% (n=24) subjects and one-fifth of them had more than one comorbid illness. Diabetes mellitus followed by systemic hypertension were common comorbid illnesses. The median (IQR) Pa_{O2}:Fi_{O2} ratio was 186 (135-234) mmHg and was comparable in the two study arms. The median (IQR) baseline SOFA score was 3 (2-4). The median neutrophil-lymphocyte ratio was 7.5 and was not different between the *Mw* and the placebo arm. The baseline ordinal scale score was also similar in the two groups. Two-third of the study population required oxygen supplementation using a venturi-mask or a non-rebreather mask, while the remaining study subjects needed either HFNC or mechanical ventilation at admission. All the subjects received systemic glucocorticoids and anticoagulation. Eleven subjects received hydroxychloroquine, while five subjects were treated with intravenous tocilizumab.

Primary outcomes: The odds of having a low ordinal scale score was significantly higher with the use of *Mw* on days 14 (OR, 30.4; 95% confidence intervals [CI], 3.3-276.4, p=0.002) and 21 (OR, 14.9; 95% CI, 1.8-128.4, p=0.013), compared to the placebo arm (Table 2). There was no difference in the clinical status between the two arms on day 28. We did not find any difference in the delta SOFA score on days 7 and 14 between the two groups. Also, there was no difference in the maximum SOFA score during hospitalization between the two study arms (Table 2).

Secondary outcomes: One patient in the *Mw* and the placebo arm received a single dose and withdrew consent. Of these two, the subject who received *Mw* died after 48 hours of hospitalization, while the subject in the placebo arm went to another hospital and was presumed to have died. Finally, there were nine deaths (Table 2). We did not find any difference in mortality in the two groups (4 [18%] died in the *Mw* arm vs. 5 [25%] in the placebo arm). We also did not observe any difference in the time to clinical improvement (a two-point improvement on an ordinal scale), days spent on a mechanical ventilator, days on vasopressor therapy, or time to achieve a negative RT-PCR (Table 2). We did not find any difference in the ICU and the hospital length of stay between the two groups (Table 2).

Adverse events: We found no safety concerns associated with the study drug, based on the assessments of organ dysfunction, vital signs, laboratory parameters, and the local site reaction at the site of the injection.

DISCUSSION

We found that *Mycobacterium w* combined with standard care was safe and resulted in better clinical status on days 14 and 21 than those receiving routine care alone in critically ill patients with severe COVID-19. There was, however, no difference in the change in SOFA scores and mortality between the two groups.

Viral infection usually activates the intracellular pattern recognition receptors that result in effective viral clearance by type I and III interferons and leads to an effective adaptive immune response in most individuals.[24] However, COVID-19, like severe acute respiratory syndrome (SARS) evades innate immunity at multiple levels by impeding the production of type I and III interferons.[7] Also, those with the SARS-CoV-2 infection have impaired adaptive immune response manifested as peripheral lymphocytopenia.[2, 4] There is also a reduction in the peripheral CD8 and CD4 T cells in those with severe disease.[5, 6] Further, due to unabated viral replication, there is an activation of alveolar macrophages that causes a hyperinflammatory response in critically ill patients with SARS-CoV-2.[1, 2] Thus, there is both a state of hyper-immune response and an immune-suppressive state in SARS-CoV-2.[3]

Mw has been shown to induce apoptosis of activated macrophages by suppressing IL-β, thus subduing the hyperinflammatory response.[25] This is supported by our observation, where we could demonstrate a fall in inflammatory markers (like C-reactive protein) in patients with moderate-to-severe COVID-19 using *Mw* alone.[26] Also, *Mw* can potentially enhance viral clearance by its action via the MyD88 pathway of TLR-2 and TLR-4 activating Th1 mediated innate immune response.[17, 27, 28] This suggests *Mw* can modulate the immunity by

suppressing the overexpressed inflammatory cytokines while at the same time inducing adaptive immune response for effective clearing of the virus.

We found an early resolution of respiratory failure in the *Mw* group compared to the placebo arm on days 14 and 21 but not day 28. This is because most patients had either improved or died by 28 days, an observation similar to previous trials describing the use of remdesivir.[29-31] However, unlike the remdesivir, the effect size was clinically significant in our study. We did not find any difference in the change in SOFA score or mortality between the two study arms due to the small sample size. Based on the results of this study, we are planning a larger trial. Importantly, similar to the use of *Mw* in severe sepsis, we found no adverse events attributable to *Mw*.[19, 26] The deaths were attributed to the progressive disease course of COVID-19 by investigators at each site.

Finally, our study is not without limitations. The small sample size makes the study underpowered to detect differences in mortality. We did not measure the cytokine levels in our subjects that could have enabled us to understand the mechanism of action of *Mw* in COVID-19. Future studies should also measure the Th1 and Th2 cytokines to elucidate the immune modulation by *Mw* in patients with COVID-19. The study is hypothesis-generating. Based on the study's encouraging results, we have designed a larger study with mortality as the primary outcome.

In conclusion, the use of an immunomodulator *Mycobacterium w* in addition to standard care resulted in early clinical improvement compared to standard care alone. Larger multicenter trials are required to confirm our findings.

LEGENDS TO FIGURES

Figure 1: CONSORT diagram depicting the flow of subjects during the study

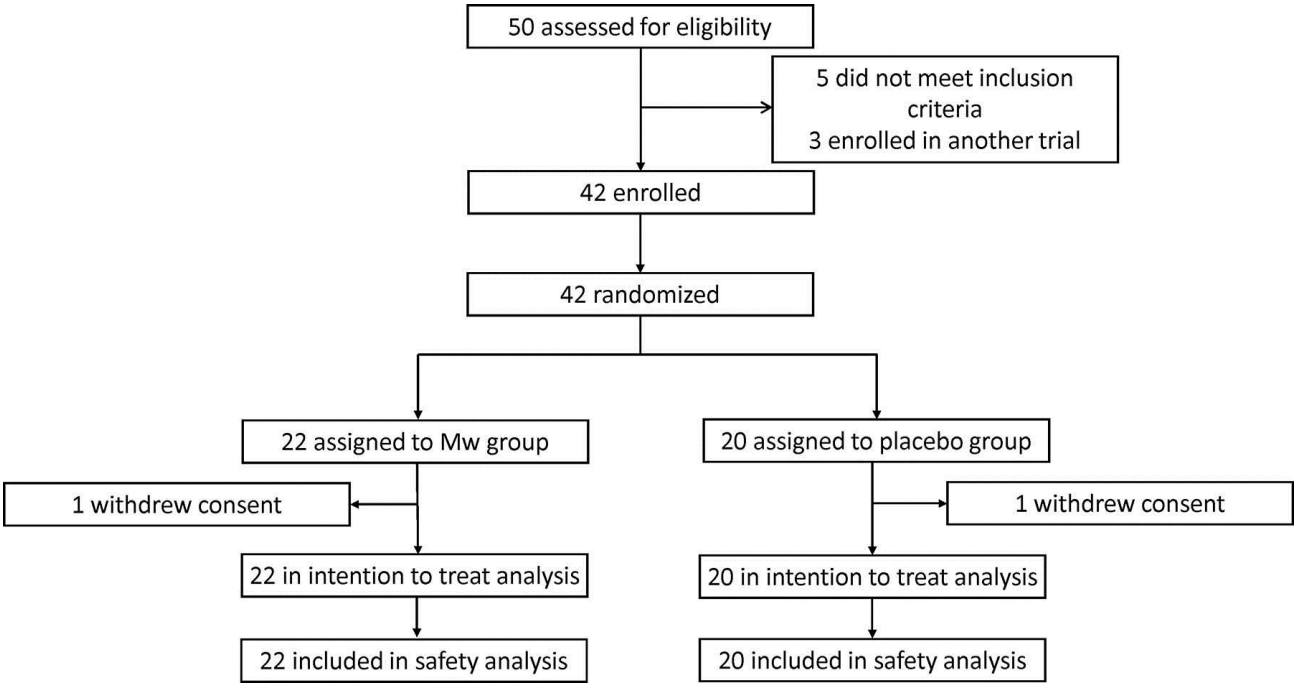

Table 1. Baseline demographics, clinical parameters, laboratory investigations, and disease severity at baseline

Parameter	*Mw* (n=22)	Placebo (n=20)	Total (n=42)	P-value
Demographics				
Age, in years	59 (52-62.5)	51 (45-65)	56 (50-65)	0.16
Male sex, No. (%)	13 (59)	16 (80)	29 (69)	0.19
Clinical parameters				
Median time from symptom onset to randomization, days	9 (5-14)	7 (4-10)	7 (5-10)	0.16
Symptoms at presentation				
Fever	18 (81.8)	18 (90)	36 (85.7)	0.61
Cough	18 (81.8)	14 (70)	32 (76.2)	0.44
Dyspnea	9 (40.9)	15 (75)	24 (57.1)	0.03
Presence of any comorbid illness, n (%)	12 (54.5)	12 (60)	24 (57.1)	0.76
Hypertension	6 (27.3)	7 (35)	13 (31)	0.74
Diabetes mellitus	5 (22.7)	9 (45)	14 (33.3)	0.19
Chronic obstructive pulmonary disease	1 (4.5)	1 (5)	2 (4.8)	1.00
Asthma	1 (4.5)	1 (5)	2 (4.8)	1.00
Two or more comorbid illness, n (%)	2 (4.8)	6 (30)	8 (19)	0.12
Respiratory rate, breaths/minute	26 (26-30)	28 (26-30)	28 (26-30)	0.19
Heart rate, beats/minute	82 (80-94)	83 (78-94)	83 (78-94)	0.85
PaO_2: Fi_{O2} ratio	184 (114-244)	188 (152-225)	186 (135-234)	0.68
Baseline SOFA score	3 (2-4)	3 (2-4)	3 (2-4)	0.85
Investigations				
Hemoglobin, g/dL	12 (11-13)	12 (11-13)	12 (1-13)	0.33
Total leucocyte count, /µL	9570 (7465-13033)	8400 (5090-12215)	8720 (5670-12523)	0.23
Neutrophil/lymphocyte ratio	7.6 (6-13.5)	6.7 (4.7-17.7)	7.5 (5.3-13.7)	0.66
Platelet count, /µL	287 (201-357)	170 (127-309)	226 (156-323)	0.03
Serum creatinine, mg/dL	0.7 (0.6-0.8)	0.9 (0.6-1.1)	0.7 (0.6-1)	0.33
Serum albumin, g/dL	3.5 (3.3-3.7)	3.5 (3.2-3.9)	3.5 (3.2-3.8)	0.61
Serum bilirubin, mg/dL	0.5 (0.4-0.8)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.44
ALT, U/L	39 (29.3-85.3)	42 (26.5-77.7)	39 (28.8-78.5)	0.92
AST, U/L	45 (30.5-61)	46 (37.8-58)	45 (32.8-55.6)	0.61
D-dimer, ng/mL	603 (254-840)	621 (245-1484)	621 (263-1145)	0.58
Score on the ordinal scale at baseline, n (%)				0.49
4- Hospitalized, requiring oxygen supplementation	14 (63.6)	15 (75)	29 (69)	
5- Hospitalized, requiring high-flow oxygen devices or non-invasive ventilation	7 (31.8)	5 (25)	12 (28.6)	
6- Hospitalized, receiving invasive mechanical ventilation or ECMO	1 (4.5)	0	1 (2.4)	
Concomitant medication				
Systemic glucocorticoids	22 (100)	20 (100)	42 (100)	-
Anticoagulation	22 (100)	20 (100)	42 (100)	-
Tocilizumab	3 (13.6)	2 (10)	5 (12)	1.00

Convalescent plasma therapy	2 (9.1)	1 (5)	3 (7)	1.00
Hydroxychloroquine	4 (18.2)	7 (35)	11 (26.2)	0.03
Antibiotics	20 (90.9)	17 (85)	37 (88.1)	0.59

All values are presented as median (interquartile range) unless otherwise mentioned

ALT: alanine transaminase; AST: aspartate transaminase; ECMO: extracorporeal membrane oxygenation; Fi_{O2}: fraction of oxygen in inspired air; PaO_2: partial pressure of oxygen in arterial blood; SOFA: sequential organ failure assessment score

Table 2. Primary and secondary outcomes

Parameter	*Mw* (n=22)	Placebo (n=20)	Total (n=42)	P value
Primary outcome				
Clinical status (7-point scale) on day 14				
1- Not hospitalized with resumption of normal activities	13 (59.1)	8 (40)	21 (50)	
2- Not hospitalized, but unable to resume normal activities	-	-		
3- Hospitalized, not requiring supplemental oxygen	2 (9)	4 (20)	6 (14.2)	
4- Hospitalized, requiring supplemental oxygen	3 (13.6)	3 (15)	6 (14.2)	
5- Hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both	1 (4.5)	0	1 (2.4)	
6- Hospitalized, requiring ECMO (extracorporeal membrane oxygenation), invasive mechanical ventilation, or both	1 (4.5)	1 (5)	2 (5)	
7- Death	2 (9)	4 (20)	6 (14.2)	
Difference in clinical status distribution vs. placebo, odds ratio (95% CI)*	30.4 (3.3-276.4)	Reference		0.002
Clinical status (7-point scale) on day 21				
1- Not hospitalized with resumption of normal activities	16 (72.7)	11 (55)	27 (64.3)	
2- Not hospitalized, but unable to resume normal activities	1 (4.5)	0	1 (2.4)	
3- Hospitalized, not requiring supplemental oxygen	0	3 (15)	3 (7.1)	
4- Hospitalized, requiring supplemental oxygen	1 (4.5)	0	1 (2.4)	
5- Hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both	0	1 (5)	1 (2.4)	
6- Hospitalized, requiring ECMO (extracorporeal membrane oxygenation), invasive mechanical ventilation, or both	2 (9.1)	1 (5)	3 (7.1)	
7- Death	2 (9.1)	4 (20)	4 (14.3)	
Difference in clinical status distribution vs. placebo, odds ratio (95% CI)*	14.9 (1.8-128.4)	Reference		0.013
Clinical status (7-point scale) on day 28				
1- Not hospitalized with resumption of normal activities	16 (72.7)	14 (70)	30 (71.4)	
2- Not hospitalized, but unable to resume normal activities	1 (4.5)	0	1 (2.4)	
3- Hospitalized, not requiring supplemental oxygen	0	1 (5)	1 (2.4)	
4- Hospitalized, requiring supplemental oxygen	1 (4.5)	0	1 (2.4)	
5- Hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both	0	0	0	
6- Hospitalized, requiring ECMO (extracorporeal membrane oxygenation), invasive mechanical ventilation, or both	0	0	0	

7- Death	4 (18.2)	5 (25)	9 (21.4)	
Difference in clinical status distribution vs. placebo, odds ratio (95% CI)[*]	1.1 (0.2-4.5)	Reference		0.95
Delta SOFA score at day 7	1 (0-2.5)	1 (0-4)	1 (0-3)	0.52
Delta SOFA score at day 14	0 (0-0)	0 (0-1)	0 (0-0.8)	0.35
Maximum SOFA score	3 (2-4)	3 (2-5)	3 (2-4)	0.51
Secondary outcomes				
28-day mortality[$]	4 (18.1)	5 (25)	9 (21.4)	0.69
Time to reduction by one-point on seven-point ordinal scale, in days	9 (5-10)	7 (3-10)	7 (4-10)	0.52
Time to reduction by two-point on seven-point ordinal scale, in days	12 (11-14)	11 (8-24)	12 (10-15.3)	0.85
Days on vasopressor drug[#], in days	0.7 (0.6-2.1)	1 (0.4-2.1)	0.8 (0.2-1.7)	0.15
Days on mechanical ventilation[#], in days	2 (2.5-6.5)	4 (1.3-9.3)	3 (1-6.2)	0.83
ICU length of stay, in days	8 (4-11)	8 (4-13)	8 (4-12)	0.84
Hospital length of stay, in days	12 (9.5-16)	12 (9-22)	12 (9.3-17.8)	0.92
Time to PCR negativity, days	9 (7-15.5)	7.5 (5-14)	8.5 (6.3-14)	0.53

[*] the odds ratio and p-value for the *Mycobacterium w* (*Mw*) treatment arm comparison were estimated using the proportional odds assumption after adjustment for baseline disease severity and use of experimental therapies

[$] the 28-mortality is calculated for 42 subjects (one patient in *Mw* arm withdrew consent after the first dose of the study drug and died on day 2, one patient in placebo arm left against medical advice and was assumed to have died)

All values are described as median (interquartile range) or number (percentage) unless specified

[#] mean (95% confidence interval [CI])

CI: confidence interval; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation; SOFA: sequential organ failure assessment score

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