A Randomized Controlled Trial to Evaluate the Safety and Efficacy of a Novel Inhaled Biologic Therapeutic in Adults with Respiratory Distress Secondary to COVID-19 Infection

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ABSTRACT

Introduction: Inhaled therapeutics may act to directly target and attenuate lung inflammation due to COVID-19. An inhalation form of a novel biologic drug, AMP5A, is being developed as an immunomodulatory agent to treat dysregulated immune responses and is being studied in hospitalized patients to treat respiratory complications due to COVID-19.

Methods: A randomized, controlled, phase I trial was conducted to evaluate hospitalized adults with respiratory distress secondary to COVID-19. Patients received the standard care (SOC) for COVID-19, including respiratory therapy, corticosteroids, and antiviral therapies such as remdesivir. Patients were randomized 1:1 to inhalation treatment with AMP5A as an adjunct to SOC or to SOC alone (control). AMP5A was administered via inhalation daily for 5 days via hand-held nebulizer, non-invasive ventilator, or mechanical ventilation. Safety and clinical efficacy endpoints were evaluated.

Results: Forty subjects were enrolled and randomized \( n = 19 \) AMP5A, \( n = 21 \) control. Remdesivir was used in fewer AMP5A subjects (26%) than control (52%), and dexamethasone was administered for most subjects (84% AMP5A, 71% control). The study met its primary endpoint with no AMP5A treatment-related adverse events (AEs), and the incidence and severity of AEs were comparable between groups: 18 AEs for control (8 mild, 1 moderate, 9 severe) and 19 AEs for AMP5A (7 mild, 7 moderate, 5 severe). Notably, subjects treated with AMP5A had fewer deaths (5% vs. 24%), shorter hospital stay (8 days vs. 12 days), fewer ICU admissions (21% vs. 33%), and a greater proportion with improved clinical outcomes than control.

Conclusion: The phase I clinical results indicate inhaled AMP5A is safe, is well tolerated, and could lead to fewer patients experiencing deterioration or death. Based on the treatment effect (i.e., reduced mortality), a phase II trial has been initiated.

Trial Registration: Clinicaltrials.gov identifier: NCT04606784.
Keywords: Efficacy; Safety; COVID-19; Inhalation treatment

Key Summary Points

Why carry out the study?

One of the most common complications of COVID-19 infection is respiratory distress, a condition of impaired respiratory function that causes hypoxia and requires treatment with supplemental oxygen and/or assisted breathing. Because there are few COVID-19 treatment options aimed at respiratory distress, this phase I trial was conducted to investigate whether the biologic drug AMP5A is well tolerated and provides clinical benefit when administered as an inhaled therapeutic for patients hospitalized with COVID-19.

What was learned from the study?

This trial met its primary endpoint, demonstrating that nebulized AMP5A was well tolerated and safe in patients with respiratory distress due to COVID-19. Importantly, there were no treatment-related SAEs for inhaled AMP5A, and there were fewer SAEs resulting in death for patients treated with AMP5A compared to the control group (5% vs. 24% mortality). Additional trials are being conducted to determine if AMP5A has a survival benefit and improves respiratory parameters in patients with moderate and severe COVID-19.

INTRODUCTION

COVID-19 disease is a respiratory illness caused by the novel severe acute respiratory syndrome coronavirus 2 coronavirus (SARS-COV-2). The severity of symptoms varies dramatically from asymptomatic infection to death, with a case fatality rate of 2% that can be as high as 49% in critical cases [1]. Approximately 20% of patients with COVID-19 will progress to severe disease [1].

One of the most common complications of COVID-19 infection is respiratory distress, a condition of impaired respiratory function that causes hypoxia and requires treatment with supplemental oxygen and/or assisted breathing. Treatment for respiratory distress includes supportive interventions designed to improve ventilation and mitigate hypoxemia. The World Health Organization (WHO) recommends early intervention with supplemental oxygen for COVID-19 patients with low blood oxygen saturation (SpO2) beginning with the least invasive modality possible (e.g., hand-held oxygen source) and moving to more invasive modalities (e.g., bilevel positive airway pressure [BiPAP] and/or non-invasive ventilation) [2] as severity increases [3].

Like other viral-induced infections, including influenza, the patient’s immune response is thought to play a key role in the pathophysiology of COVID-19 respiratory distress, organ failure, and death. At the end of the initial viral response phase, the innate immune response initiates localized inflammation in the lung, which can cause difficulties breathing, low oxygen saturation, and the need for respiratory therapy [4]. An imbalance in the immune response may drive a progression to more severe stages of infection marked by migration of the virus into the lower respiratory track and the upregulation of immune mediators, including TNFα, IFNγ, IL-1β, IL-6, IL-12, and CXCL-10, which are indicative of cytokine release syndrome or the “cytokine storm” [5–7]. As the innate inflammatory response may impact the clinical course of COVID-19 in several significant and potentially fatal ways, there is a need for treatments that can interrupt and/or prevent the progression of inflammation.

The FDA has granted emergency use authorization for several treatments for COVID-19 including convalescent plasma, monoclonal antibodies (e.g., tocilizumab, sotrovimab, casirivimab with imdevimab), and baricitinib (a drug for the treatment of rheumatoid arthritis)
in combination with remdesivir [8]. To date, there is only one FDA-approved treatment for COVID-19, the antiretroviral drug remdesivir [9]. Additional off-label treatments often considered for advanced stages of respiratory distress include corticosteroids (e.g., dexamethasone) and neuromuscular blocking agents.

Identifying a treatment for COVID-related respiratory distress which could improve the clinical course would greatly benefit this patient population and may help reduce overall progression to more severe disease, reduce hospital length of stay (LOS) and healthcare burden, and decrease mortality due to COVID-19. There is recent interest in treatments delivered directly to the lungs by inhalation and nebulization, theoretically minimizing systemic adverse events [10]. Inhaled therapeutics may act to directly target and attenuate lung inflammation.

AMP5A is a novel non-steroidal, anti-inflammatory biologic agent containing a cyclized dipeptide and other small molecules with immunomodulatory and anti-inflammatory properties. In vitro experiments in activated immune cells show that AMP5A inhibits the production of inflammatory cytokines, including TNFα, IFNγ, IL-1β, IL-6, IL-12, and CXCL-10, by interfering with the inflammatory transcription factor NF-κB while at the same time activating immunomodulatory transcription factors aryl hydrocarbon receptor (AhR) and peroxisome proliferator activator receptor gamma (PPARγ) [11]. AMP5A is also in clinical development as an anti-inflammatory therapy for osteoarthritis and has been safely administered as an intra-articular injection for the reduction of pain and improvement in function in patients with osteoarthritis of the knee [12, 13]. AMP5A has been formulated for inhalation, which may work to reduce lung inflammation in pulmonary viral infections such as COVID-19. The objective of this phase I randomized controlled trial (RCT) was to evaluate the safety, tolerability, and efficacy of nebulized AMP5A as a treatment for COVID-19.

METHODS

Design, Setting, and Patients

A phase I, randomized, controlled trial of 40 hospitalized patients with respiratory distress due to COVID-19 was conducted to evaluate the safety and efficacy of inhaled AMP5A. All patients were followed for the participation period lasting from index hospitalization to day 90. The trial was performed in accordance with the principles of Good Clinical Practice (GCP) guidelines, received institutional review board (IRB) approval across all sites, and was registered prior to patient recruitment (Clinicaltrials.gov identifier NCT04606784). Patients were enrolled and treated at two sites within the USA between October 2020 and March 2021 with follow-up and study completion through June 2021. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Study inclusion criteria were age ≥ 18 years, diagnosis of COVID-19 (as evaluated by PCR test confirming infection with SARS-CoV-2, or suspected COVID-19 diagnosis based on radiologic clinical findings), and respiratory distress as evidenced by two of the following: radiographic pulmonary infiltrates, SpO2 of ≥ 90% or the patient requires supplemental oxygen to maintain an SpO2 ≥ 90%, requiring supplemental oxygen, or diagnosis of ARDS by Berlin definition [14]. Patients were excluded based on presence of severe COPD (previous determination of stages 3 and 4 from the gold gradation), chronic renal failure (previously known and persistent elevated creatinine and blood urea nitrogen associated with decreased glomerular filtration rate, and patients on dialysis treatment), significant liver abnormality (e.g., cirrhosis or transplant), prolonged QT interval, or use of chronic immunosuppressants. Patients were also excluded for participation in another clinical trial (not including COVID-19 emergency use authorization treatments), known pregnancy or breastfeeding, imminent progression to death within 24 h based on the opinion of the clinical team, or history of allergic reaction to the ingredients in AMP5A.
Blinding and Randomization

Patients were randomized 1:1 to inhaled treatment with AMP5A in addition to standard of care (SOC) or to SOC alone ("control") within 72 h of hospital admission. The randomization scheme was developed and maintained by an independent statistician, and the scheme was stratified by delivery device (hand-held nebulizer, invasive or noninvasive ventilation) to decrease the imbalance between treatment and control groups.

Enrollment was staggered for the first 6 subjects to observe the safety effects of the full 5-day treatment period before enrollment was opened to the remaining patients. Safety was evaluated by the Data Safety Monitoring Board (DSMB). The first three DSMB meetings reviewed safety data from the staggered enrollment. No remarkable safety concerns were observed during the staggered enrollment, and the study advanced to open enrollment in November 2020.

Treatment was administered by unblinded hospital personnel and patients were unblinded to treatment. Clinical efficacy was evaluated by blinded clinicians (co-investigators not involved in patient care).

Treatments

All patients received standard care for respiratory distress, which included oxygen administration to maintain \( \text{SpO}_2 \geq 90\% \); nursing physical that could include review of neurologic, pulmonary, cardiac, gastrointestinal, and urinary assessment at least every 12 h; telemetry monitoring to evaluate heart rhythm and rate; vital signs monitoring (heart rate, blood pressure, temperature, respiratory rate, \( \text{SpO}_2 \)) at least once a day; diet as tolerated to satisfy nutritional needs. Any additional medication was recorded as concomitant medication, tabulated, and compared between arms, including corticosteroids and antiviral therapies such as remdesivir. Oxygen administration for respiratory support included the use of supplemental oxygen, non-invasive ventilation (NIV), and mechanical ventilation. If patients progressed to ARDS, SOC guidelines utilized by the hospitals participating in the study follow the open lung ventilation strategy for ARDS consisting of low tidal volume ventilation, recruitment maneuvers, and subsequent titration of applied positive end expiratory pressure (PEEP) [15]. All COVID-19 precautions were taken to limit exposure of health care personnel to the exhalation of COVID-19, including the following as applicable: use of N95 masks in treatment areas, patients required to wear masks over face/nose to minimized aerosol dispersion, and the use of viral filters that do not obstruct the drug aerosol pathway.

In addition to SOC, patients randomized to the AMP5A arm received nebulized AMP5A inhaled four times daily (quarter in die, q.i.d) for 5 days with treatment sessions lasting approximately 30 min. AMP5A was delivered via an aerosol delivery assembly for inhaled drug administration as clinically indicated, e.g., using a hand-held nebulizer, non-invasive ventilator (NIV), and/or mechanically ventilated circuit. The control arm did not receive inhalation therapy with AMP5A.

Outcomes

The primary endpoint was safety, as assessed by incidence and severity of adverse events (AEs) through day 28. AEs were also evaluated through treatment day 5, at hospital discharge or in-hospital mortality, at day 60 and at day 90. AEs included complications (respiratory failure due to COVID-19, hyperglycemia, atrial flutter, cardiac arrest, thrombocytopenia), change in vital signs (respiratory rate, heart rate, blood pressure), abnormal laboratory results (biochemistry and hematology), and \( \text{SpO}_2 \). As this is a new route of administration for AMP5A, the first three patients receiving AMP5A were monitored for vital signs and \( \text{SpO}_2 \) immediately before and within 30 min from nebulized treatment.

Efficacy was evaluated by all-cause mortality, hospital LOS, ICU admission and ICU LOS, \( \text{SpO}_2 \), oxygen flow rate (l/min), and gas exchange ratio (\( [\text{PaO}_2]/[\text{FiO}_2] \)) (as applicable), and the World Health Organization (WHO)
scale for clinical improvement. This is an 8-point ordinal scale: 0 = uninfected, 1 = ambulatory without limitation of activity; 2 = ambulatory with limitation of activity; 3 = hospitalized mild disease, no oxygen; 4 = hospitalized mild disease, supplemental oxygen; 5 = hospitalized severe disease, non-invasive ventilation or high-flow oxygen; 6 = hospitalized severe disease, intubation and mechanical ventilation; 7 = hospitalized severe disease, ventilation plus additional organ support; 8 = death [16].

Additional covariates collected were demographics (age, sex, race, height, and weight), comorbidities, radiographic findings of the lungs/chest, oxygen therapy (supplementation oxygen mode and intubation status), and concomitant medications including antibiotics (for secondary bacterial infection), antiviral agents, convalescent plasma infusion, corticosteroids, inhaled nitrous oxide, and neuromuscular blockers.

Statistical Analysis

Due to the small sample size, there were no formal statistical tests or level of significance. AEs are tabulated and presented for all randomized patients. Oxygenation parameters (SpO2, oxygen flow rate (l/min), SpO2/FiO2 ratio) were tabulated as the proportion of subjects with stable or improved oxygenation parameters from baseline (day 0). Similarly, the WHO ordinal scale was tabulated as the proportion of subjects with a stable or improved score from baseline (day 0). Baseline was defined as the last assessment prior to randomization.

RESULTS

Baseline Patient Demographics and Clinical Characteristics

Forty subjects were randomized; 19 received nebulized AMP5A and 21 received control (Fig. 1). The mean age was 64 years, 62.5% were male, with a mean hospital LOS of 10 days.

Baseline demographic data are shown in Table 1. There were no clinically meaningful imbalances in demographics between AMP5A and control. Remdesivir was used in 16 (40%) subjects: 5 (26%) of the AMP5A arm and 11 (52%) of the control arm. Dexamethasone was administered for 31 (78%) subjects: 16 (84%) of the AMP5A arm and 15 (71%) of the control arm.

Safety

Adverse events were reported for 15 (37.5%) subjects. Incidence and severity of AEs was comparable between treatment arms (Table 1). A total of 37 AEs were reported in 15 subjects: 18 AEs in the control arm and 19 AEs in the AMP5A arm. There were only three mild AEs that could be possibly related to AMP5A,
including lightheadedness, intermittent headache, and non-productive cough. There were no treatment-related SAEs. There were six SAEs resulting in death due to the worsening of COVID-19, and none were related to treatment: one (5%) death occurred in the AMP5A group, and five (24%) deaths occurred in the control group. There were two additional SAEs not resulting in death in the AMP5A group due to worsening COVID-19.

### Efficacy

Patients treated with AMP5A had an improvement in all-cause mortality rate compared to control with fewer deaths (5% AMP5A vs. 24% control), representing a 78% reduction in mortality with AMP5A treatment (Fig. 2). Patients who received AMP5A required less hospitalization time, with a mean hospital LOS of 8 days for AMP5A vs. 12 days for control, had a lower ICU admission rate (21% for AMP5A vs. 33% for control), and spent fewer days in the ICU (mean ICU LOS 8 days for AMP5A vs. 11 days for control) (Fig. 2 and Table 1).

At treatment day 5, 89% of patients receiving AMP5A were stable or had improvement on a scale of clinical improvement compared to 77% receiving control. This trend in improvement with AMP5A was observed by day 2 and continued to day 5.

A greater proportion of AMP5A-treated subjects had stable or improved oxygenation parameters as measured by FiO₂, oxygen flow rate, and FiO₂ ratio (treatment days 1–5) compared to control (Table 2). SpO₂ was also improved with AMP5A compared to control on treatment days 1, 2, 3, and 5. There was a continued trend toward improved oxygenation parameters with AMP5A versus control after treatment termination (days 6–10), as shown in Table 2.

### DISCUSSION

This phase I trial of patients with respiratory distress secondary to COVID-19 infection met its primary endpoint and showed no remarkable safety concerns for inhalation therapy with AMP5A, supporting the safety and tolerability of this nebulized AMP5A for patients hospitalized with respiratory distress secondary to COVID-19 infection. These results support possible clinical benefits of inhaled AMP5A by reducing oxygen use, improving oxygenation parameters, reducing impact on health care resources with fewer days in the hospital and

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**Table 1** Baseline characteristics and study endpoints, by treatment arm

| Covariate, n (%) | AMP5A (n = 19) | Control (n = 21) |
|-----------------|---------------|-----------------|
| Age, years—mean (SD) | 63 (16) | 65 (14) |
| Male sex | 13 (69%) | 12 (57%) |
| White race | 18 (95%) | 20 (95%) |

**Safety-adverse events (AE)**

| Patients with an AE | 8 (42%) | 7 (33%) |
| Total AEs, n | 19 | 18 |
| Mild | 7 (37%) | 8 (44%) |
| Moderate | 7 (37%) | 1 (6%) |
| Severe | 5 (26%) | 9 (50%) |
| Patients with a TEAE | 7 (37%) | 6 (29%) |
| Patients with a serious AE (SAE) | 3 (16%) | 5 (24%) |
| Patients with SAE resulting in death | 1 (5%) | 5 (24%) |

**Efficacy**

| All-cause mortality | 1 (5%) | 5 (24%) |
| Mean (SD) Hospital LOS, days | 8 (4) | 12 (12) |
| ICU admission | 4 (21%) | 7 (33%) |
| Mean (SD) ICU LOS, days | 8 (5) | 11 (14) |
| Ordinal scale—% responder on treatment days 1, 2, 3, 4, 5 | 100%, 94%, 95%, 84%, 88%, 77%, 77% |

**TEAE** treatment-related AE, **ICU** intensive care unit, **LOS** length of stay
ICU, and leading to fewer patients experiencing deterioration or death.

The overall 28-day mortality rate in the control group was 24%, which is similar to the reported mortality rate of 26% among patients receiving standard of care in a large study of over 4300 patients with COVID-19 and the 26% mortality rate for hospitalized patients in the UK during the first wave in early 2020 [17, 18]. In contrast, the lower mortality rate with AMP5A of 5% is encouraging. Based on the treatment effect and reduced mortality rate, AMP5A is being further evaluated in a phase II, double-blinded, randomized, placebo-controlled study designed to demonstrate a survival benefit among 200 patients hospitalized with COVID-19.

Patients receiving AMP5A were also less likely to receive remdesivir compared to controls (26% vs. 52%). The decision to administer remdesivir was based on the individual clinician and was not related to the study protocol; remdesivir is given routinely to admitted patients with the diagnosis of COVID-19 even if they are several days into the disease course. Synthesized evidence for hospitalized patients

| Covariate            | AMP5A (n = 19) | Control (n = 21) |
|----------------------|---------------|-----------------|
| Oxygen saturation (SpO₂) |               |                 |
| Treatment days 1–5   | 72%, 65%, 56%, 58% | 48%, 42%, 53%, 58% |
| Post-treatment days 6–10 | 86%, 100%, 75%, 64% | 50%, 25%, 67%, 60% |
| Flow rate (l/min)    |               |                 |
| Treatment days 1–5   | 78%, 88%, 94%, 90% | 67%, 79%, 88%, 85% |
| Post-treatment days 6–10 | 71%, 100%, 100%, 98% | 63%, 75%, 50%, 80% |
| FiO₂ (%)              |               |                 |
| Treatment days 1–5   | 78%, 88%, 94%, 92% | 76%, 79%, 82%, 84% |
| Post-treatment days 6–10 | 86%, 75%, 100%, 99% | 63%, 635, 67%, 80% |
with COVID-19 demonstrates remdesivir is safe and efficacious for early clinical improvement, although its effect on reduced mortality is not consistently demonstrated [19–22].

Patients with COVID-19 may see benefit with nebulized AMP5A due to its immunomodulatory and anti-inflammatory properties that have been shown in clinical studies for treatment of osteoarthritis in vivo [12, 13, 23] and in vitro [24–28]. In patients who develop respiratory distress associated with COVID-19, the activation of the innate immune system leads to a dysregulated or ‘hyper-inflammatory’ response, resulting in the excess release of innate pro-inflammatory cytokines by alveolar macrophages and neutrophils as part of a “cytokine storm.” The severity of COVID-19 and related inflammatory complications, such as ARDS, is closely associated with increased serum levels of pro-inflammatory cytokines, including TNFα, IL-1β, IL-6, IL-12, and CXCL-10, and accompanied by a corresponding decrease in anti-inflammatory cytokines [5, 29, 30]. In vitro studies using AMP5A show it can modulate these cytokine levels in various immune cell models; this activity is suggested to decrease inflammation and promote the resolution of the immune response [11, 31, 32], particularly in the treatment of the hyperinflammatory response related to COVID-19 [26].

Study limitations included the open-label design without double blinding of patients and providers; only assessors were blinded to treatment. Second, this phase I study was not powered for the primary endpoint. Third, the trial was conducted at two sites, limiting the study generalizability. Finally, the average length of stay of the index hospitalization for patients with COVID-19 infection was approximately 12 days; evaluations at day 28 and day 90 typically occurred via telephone contact.

CONCLUSIONS

This phase I trial demonstrated that inhalation therapy with AMP5A for respiratory distress due to COVID-19 is safe and may provide clinical benefit. Due to its mechanism of action, AMP5A may be a viable treatment option for those infected with COVID-19 to improve clinical outcomes and decrease the progression and severity of associated COVID-19 inflammatory conditions (e.g., COVID pneumonia, ALI, ARDS, and ultimately mortality). Further study will evaluate whether AMP5A provides an early intervention option for COVID-19 patients in respiratory distress.

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Author contributions. Conceptualization: DB-O, HC, LG; methodology: MR, LL-F, KS; formal analysis and investigation: HC, LG; writing—original draft preparation: KS; writing—critical revisions: MR, LL-F, and DB-O. All authors provided final approval of the submitted manuscript.

Disclosures. Dr. Bar-Or serves as a director on the board of directors of Ampio Pharmaceuticals, owns stock and stock options in the company, and has approximately 80 patents on related matters. Holli Cherevka and Laura Goldberg are employed by Ampio Pharmaceuticals and have stock/stock options in the company. Kristin Salottolo owns stock in the company and reports personal fees from Ampio Pharmaceuticals, Inc. Drs. Roshon and Lemos-Filho report consulting fees paid for their roles as investigators in the clinical study.
Compliance with Ethics Guidelines. The study was approved from the Centura Health Institutional Review Board (IRB approval #1,664,792) and HCA HealthONE IRB (IRB approval #1,676,933) with documentation of informed consent. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES
1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323(13):1239–42.
2. Stringer S, Minica CC, Verweij KJ, Mbarek H, Bernard M, Derringer J, et al. Genome-wide association study of lifetime cannabis use based on a large meta-analytic sample of 32 330 subjects from the International Cannabis Consortium. Transl Psychiatry. 2016;6:e769.
3. World Health Organization. (2020). https://apps.who.int/iris/handle/10665/331736. License: CC BY-NC-SA 3.0 IGO Clinical care for severe acute respiratory infection: toolkit: COVID-19 adaptation. https://apps.who.int/iris/handle/10665/331736. Accessed 27 Sep 2021.
4. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405–7.
5. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 2016;19(2):181–93.
6. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet. 2020;395(10234):1407–9.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
8. Food and Drug administration. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs. Emergency Use Authorization. Accessed 27 Sep 2021.
9. Food and Drug administration. Know Your Treatment Options for COVID-19 https://www.fda.gov/consumers/consumer-updates/know-your-treatment-options-covid-19. Accessed 27 Sep 2021.

10. Artigas A, Camprubi-Rimblas M, Tantinya N, Bringue J, Guillamat-Prats R, Matthy MA. Inhala-
tion therapies in acute respiratory distress syn-
drome. Ann Transl Med. 2017;5(14):293.

11. Thomas G, Frederick E, Thompson L, Bar-Or R, Mulugueta Y, Hausburg M, et al. LMWF5A suppresses cytokine release by modulating select inflammatory transcription factor activity in stimulated PBMC. J Transl Med. 2020;18(1):452.

12. Bar-Or D, Salottolo KM, Loose H, Phillips MJ, McGrath B, Wei N, et al. A randomized clinical trial to evaluate two doses of an intra-articular injection of LMWF-5A in adults with pain due to osteoarthritis of the knee. PLoS ONE. 2014;9(2): e87910.

13. Cole B, McGrath B, Salottolo K, Bar-Or D. LMWF-5A for the treatment of severe osteoarthrosis of the knee: integrated analysis of safety and efficacy. Orthopedics. 2018;41(1):e77–83.

14. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respira-
tory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526–33.

15. Siegel MH, RC. Ventilator management strategies for adults with acute respiratory distress syndrome. In: UpToDate, editor. https://www.uptodate.com/contents/ventilator-management-strategies-for-adults-with-acute-respiratory-distress-syndrome#H252021. Accessed 27 Sep 2021.

16. World Health Organization. R&D blueprint novel coronavirus COVID-19 therapeutic trial synopsis. Geneva: WHO; 2020.

17. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexam-
ethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704.

18. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369: m1985.

19. Angamo MT, Mohammed MA, Peterson GM. Effic-
cacy and safety of remdesivir in hospitalised COVID-19 patients: a systematic review and meta-
analys.

20. Elsawah HK, Elsokary MA, Abdallah MS, ElShafie AH. Efficacy and safety of remdesivir in hospitalized Covid-19 patients: systematic review and meta-
analys.

21. Singh S, Khera D, Chugh A, Khera PS, Chugh VK. Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-
analys.

22. Tasavon Gholamhoseini M, Yazdi-Feyzabadi V, Goudarzi R, Mehrholhassani MH. Safety and efficacy of remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. J Pharm Pharm Sci. 2021;24:237–45.

23. Salottolo K, Cole B, Bar-Or D. Intra-articular injection of the anti-inflammatory compound LMWF-5A in adults with severe osteoarthritis: a double-blind prospective randomized controlled multi-center safety and efficacy trial. Patient Saf Surg. 2018;12: 11.

24. Bar-Or D, Thomas GW, Bar-Or R, Rael LT, Scarborough K, Rao N, et al. Commercial human albumin preparations for clinical use are immunosuppres-
sive in vitro. Crit Care Med. 2006;34(6):1707–12.

25.攻坚合作组，Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexam-
ethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704.

26. Thomas G, Frederick E, Hausburg M, Goldberg L, Hoke M, Roshon M, et al. The novel immunomodulatory biologic LMWF5A for phar-
macological attenuation of the “cytokine storm” in COVID-19 patients: a hypothesis. Patient Saf Surg. 2020;14:21.

27. Thomas GW, Rael LT, Hausburg M, Frederick ED, Brody E, Bar-Or D. The low molecular weight fraction of human serum albumin upregulates COX2, prostaglandin E2, and prostaglandin D2 under inflammatory conditions in osteoarthritic knee synovial fibroblasts. Biochem Biophys Rep. 2016;8: 68–74.

28. Thomas G, Frederick E, Hausburg M, Goldberg L, Hoke M, Roshon M, et al. The novel immunomodulatory biologic LMWF5A for pharmacological attenuation of the “cytokine storm” in COVID-19 patients: a hypothesis. Patient Saf Surg. 2020;14:21.

29. Del Valle DM, Kim-Schulze S, Huang HH, Beck-
mann ND, Nirenberg S, Wang B, et al. An inflam-
matory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10): 1636–43.
30. Yang J. Serum levels of TNF-α, IL-1β, IL-9, and IL-15 in acute respiratory distress syndrome. Int J Clin Exp Pathol. 2017;10(1):781–8.

31. Shimonkevitz R, Thomas G, Slone DS, Craun M, Mains C, Bar-Or D. A diketopiperazine fragment of human serum albumin modulates T-lymphocyte cytokine production through rap1. J Trauma. 2008;64(1):35–41.

32. Thomas GW, Rael LT, Hausburg M, Frederick ED, Mains CW, Slone D, et al. The low molecular weight fraction of human serum albumin upregulates production of 15d-PGJ2 in peripheral blood mononuclear cells. Biochem Biophys Res Commun. 2016;473(4):1328–33.

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