COVID-19 associated chronic ARDS successfully treated with lenzilumab

Authors: Juan D. Pulido, M.D.¹, Rida Rasool, D.O.¹, Gabrielle Chappell², Omar Ahmed, Pharm.D.², Cameron Durrant, M.D. M.B.A.², Dale Chappell, M.D. M.B.A.²

Affiliations:

¹Baptist Medical Center Jacksonville, FL

²Humanigen, Inc, Burlingame, CA

Corresponding Authors

Cameron Durrant, M.D. M.B.A., Chief Executive Officer, Humanigen, Inc., CA USA,
cdurrant@humanigen.com

Or Juan D. Pulido, M.D., Baptist Medical Center Jacksonville, FL USA,
juan.pulido@bmcjax.com

Or Dale Chappell, M.D. M.B.A., Chief Scientific Officer, Humanigen, Inc., CA USA,
dchappell_humanigen.com@pm.me

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ABSTRACT

Background:

Myeloid hyperinflammation leading to T-cell immune suppression and lymphocytopenia is a hallmark of severe COVID-19. Granulocyte macrophage-colony stimulating factor (GM-CSF) neutralization may prevent myeloid driven T-cell suppression leading to increased lymphocyte counts in patients with COVID-19. Given the dual mechanism of action, lenzilumab (anti-human GM-CSF monoclonal antibody) may reduce myeloid driven hyperinflammation and improve CD8+ antiviral T-cell responses directed at SARS-Cov-2 reducing the morbidity, mortality, need for invasive mechanical ventilation (IMV) and duration of hospitalization.

Methods:

Hospitalized subject with confirmed COVID-19 pneumonia and established risk factors for poor outcomes was treated in the ICU for 12 weeks using standard supportive care for chronic acute respiratory distress syndrome (ARDS). An emergency single-use investigational new drug application (IND) was approved for lenzilumab 600 mg, administered intravenously every eight hours for a total of three doses. Patient characteristics, clinical and laboratory outcomes, and adverse events were recorded through duration of hospitalization.

Results:

77-year-old Caucasian male with past medical history of severe chronic obstructive pulmonary disease (COPD) with emphysema, coronary artery disease, type II diabetes, and obstructive sleep apnea admitted to ICU with fever, shortness of breath and confirmed SARS-CoV-2 infection. Patient was treated with standard supportive care including corticosteroids. Over the course of his ICU stay, the patient developed ARDS and on week 13, and after several unsuccessful attempts at oxygen weaning, lenzilumab was administered via emergency single use IND. One-week post lenzulimab therapy, oxygen demands decreased, lymphopenia appeared to improve and sixteen days post lenzulimab therapy, the patient was discharged home on 4L nasal cannula. No infusion-related or systemic side effects were noted.

Conclusion:

In a case of COVID-19 with multiple co-morbidities, refractory to corticosteroids, and deteriorating for several months, GM-CSF neutralization with lenzilumab appeared to reduce oxygen requirements, improve lymphopenia and accelerate time to recovery/discharge in a COVID-19 subject. A randomized, double-blind, placebo-controlled phase 3 clinical trial is ongoing to validate these findings (NCT04351152).

INTRODUCTION

A 77-year-old Caucasian male presented to the emergency department (ED) who complained of difficulty breathing for the prior four days. Associated symptoms included intermittent fever of 102°F (39.9 °C) and chills for the prior seven days. The patient's past medical history included severe chronic obstructive pulmonary disease (COPD) with emphysema, coronary artery disease with coronary artery bypass graft, systolic heart failure, type II diabetes and obstructive sleep apnea. The patient reported wearing his continuous positive airway pressure (CPAP) at night with an increase in his home oxygen use from as needed to 3 liters (L) (per minute) continuous for the past several days. The patient tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was admitted to the ICU on respiratory isolation.

On examination the patient's vital signs were: pulse of 105 bpm, respiratory rate of 20 breaths/min, blood pressure of 98/59 mmHg, oxygen saturation of 89% on 3L of oxygen, and an oral temperature of 98.7°F. He appeared in mild distress with evidence of accessory respiratory muscle use, awake, alert and with normal appearing skin color. Cardiac auscultation noted an irregular heart rate and rhythm with a mild systolic ejection murmur and pulmonary auscultation noted diminished breath sounds at the bases with scant expiratory wheezes throughout. Per the ED workup, the patient had atrial fibrillation on electrocardiogram, evidence of bilateral infiltrates on chest x-ray (Figure 1A), lymphopenia on complete blood count (CBC) and a mild transaminitis on liver function tests.

At the time of admission in March 2020, treatment options for COVID-19 were limited. The patient was started on broad spectrum antibiotics for community acquired pneumonia, steroids, and bronchodilators for possible COPD exacerbation and hydroxychloroquine with zinc for COVID-19. He continued to deteriorate for the next 12 weeks with an increase in oxygen demand from continuous low-flow oxygen to high-flow and eventually intermittent bilevel positive airway pressure (BIPAP). Given his degree of severe hypoxemia, inhaled epoprostenol was added with marginal improvement of his alveolar-arterial gradient. The patient's chest computed tomography scan (CT) was significant for diffuse ground glass opacities predominately at the bases with bilateral upper lob severe emphysematous changes (Figure 1B). Echocardiogram demonstrated left ventricular ejection fraction of 40-45% and mild mitral regurgitation. The initial sputum culture was positive for *Stenotrophomonas maltophilia* for which he was placed on trimethoprim/sulfamethoxazole (TMP/SMX). He eventually underwent flexible bronchoscopy due to persistent hypoxemia which resulted in positive *candida* cultures and fluconazole was initiated. Antimicrobial therapy was tailored for sensitivities and course duration by an infectious disease specialist.

Over the course of his ICU stay, the patient developed acute respiratory distress syndrome (ARDS). On week 11, and after several unsuccessful attempts at oxygen weaning, the patient was considered for lenzilumab (Humaneered® anti-hGM-CSF monoclonal antibody), a novel COVID-19 therapy, given the recent positive case series report from the Mayo Clinic.

An emergency single use IND was approved on week 13 and after the patient was consented, lenzilumab was administered at a dose of 600 mg intravenously every 8 hours, for a total of 3 doses. No infusion-related or systemic side effects were noted.

One-week post lenzilumab therapy, the patient's oxygen demand decreased from high-flow to low-flow nasal cannula and he was able to walk with physical therapy outside of his room (Figure 2A). The patient's lymphopenia, which had been slowly improving, appeared to improve post lenzilumab therapy (Figure 2B). Sixteen days post lenzilumab (week 15), the patient was discharged home on 4L nasal cannula.

DISCUSSION

Advanced age, male sex, COPD, and type II diabetes are all associated risk factors for severe COVID-19. This patient presented with respiratory symptoms and upon examination significant radiographic abnormalities were found. The patient progressed to ARDS that did not resolve with standard therapies including steroids. Recent clinic data suggests that steroids may only be appropriate for patients on invasive mechanical ventilation with high levels of c-reactive protein (CRP) and non-diabetics while those patients with lower CRP levels and diabetes may be harmed by steroid use.¹

The patient's length of hospitalization (15 weeks) is highly unusual as it is currently estimated that 95% of COVID-19 associated hospitalizations last between 1 and 31 days. Extended length of stay coupled with lymphopenia increases the risk of hospital acquired infection, as demonstrated in the patient's susceptibility to bacterial and fungal infection.

Recent immune-profiling studies of patients with severe COVID-19 suggest a myeloid driven hyperinflammatory immune suppression as the underlying pathophysiology wherein immature and dysfunction myeloid cells result in inflammation but also profound suppression of T-cell responses delaying viral clearance and increasing susceptibility to opportunistic infections.² Neutralization of GM-CSF may suppress myeloid hyperinflammation and restore balance to the dysregulated immune response. Lenzilumab is currently being studied in a phase III trial for severe and critical COVID-19 pneumonia (NCT04351152) and in the National Institute of Allergy and Infectious Diseases (NIAID) sponsored Big Effect Trial (BET) in combination with remdesivir.

After deterioration in the hospital for 13 weeks, this patient was administered lenzilumab under an emergency single use IND. Rapid resolution of the patient's hypoxemia was demonstrated by a reduction in oxygen requirements, improved mobility, and accelerated time to discharge. A recent case-control study published by the Mayo Clinic suggests lenzilumab may improve clinical outcomes, oxygenation requirements, and improve lymphocyte counts in patients with severe and critical COVID-19 during the acute hyperinflammatory immune response.³ This case report suggests that lenzilumab may be beneficial to patients who are unable to wean off of supplemental oxygen, have failed multiple rounds of prior therapy, and are outside the initial acute hyperinflammatory window.

REFERENCES

1. Keller MJ, Kitsis EA, Arora S, et al. Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19. *Journal of Hospital Medicine* 2020;15(8):489-493. DOI 10.12788/jhm.3497
2. Bost P, De Sanctis F, Cane S, et al. Deciphering the state of immune silence in fatal COVID-19 patients. doi.org/10.1101/2020.08.10.20170894
3. Breeher L, Boon A, Hainy C, et al. A Framework for Sustainable Contact Tracing and Exposure Investigation for Large Health Systems. *Mayo Clinical Proceedings* 2020; 95. https://els-jbs-prodcdn.jbs.elsevierhealth.com/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_ft95_8_7.pdf

FIGURE 1: Radiographic findings upon initial ED examination. A) Initial chest x-Ray on presentation. B) Initial chest CT scan on presentation.

FIGURE 2: Arrows indicate date of lenzilumab administration A) Supplemental oxygen requirements (liter flow per minute) from presentation to discharge. B) Lymphocytes as a percentage of complete blood count (CBC) from admission to discharge (normal range 18-45%).

A

B