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Case Reports and Series

Recombinant human plasma gelsolin (rhu-pGSN) in a patient hospitalized with critical COVID-19 pneumonia

Julie V. Catteeuw [a,1], Mark J. DiNubile [b,*,1]

[a] Jan Palfijn, Gent, Belgium
[b] BioAegis Therapeutics, North Brunswick, NJ, USA

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ABSTRACT

Life-threatening COVID-19 pneumonia follows an exaggerated immune response to SARS-CoV-2. pGSN levels fall after SARS-CoV-2 infection. Rhu-pGSN improves outcomes in models of inflammation. In an intubated patient with critical COVID-19 pneumonia and progressive hypoxemia despite standard care, improvement became evident during rhu-pGSN infusions with full recovery within a few weeks.

Introduction

Community-acquired pneumonia (CAP) is a common and sometimes fatal infection, usually due to bacteria and viruses alone or in combination; an etiology is often not determined despite extensive evaluation (Jain et al., 2015). The substantial morbidity and mortality associated with severe (s)CAP has not been adequately addressed. Irrespective of microbial etiology, patients with severe CAP are at risk for complications both from ineffectively managed infection and the overzealous inflammatory responses that underlie acute lung injury and sepsis. Pandemic COVID-19 has become a leading cause of life-threatening pneumonia during its later excessively reactive immune stage.

Plasma gelsolin (pGSN), an abundant protein in the blood of healthy individuals, is functionally distinct from its cytoplasmic isoform. Circulating pGSN is consumed in serious infectious and non-infectious conditions such as bacterial sepsis, major trauma, burns, oxygen toxicity, and malaria resulting in extensive tissue injury (DiNubile, 2007). Correlative studies of patients following a diverse spectrum of common insults have established a consistent relationship among the severity of the precipitating insult, the magnitude of resultant pGSN decline, and the subsequent likelihood of death or organ failure. Patients admitted with CAP who have the lowest pGSN levels at presentation have the worst outcomes (Self et al., 2019).

Mechanistically, pGSN leaves the circulation to scavenge intracellular debris leaked from damaged tissues that interfere with host defenses. Concurrently, pGSN enhances bacterial uptake and killing by macrophages at the infected site (Ordija et al., 2017; Yang et al., 2015). Once leaked cytoskeletal actin and nuclear/mitochondrial DNA are cleared, free pGSN can bind proinflammatory lipid and peptide mediators to foster resolution of local injury and prevent spread to distant uninvolved organs (Piktel et al., 2010). Consequently, pGSN boosts the early innate immune response to clear pathogens at the infected site while tempering the injurious consequences of unnecessarily prolonged or distant inflammation.

Excessively zealous inflammatory reactions can occur in a variety of infections (Abers et al., 2021; Messner et al., 2020) like influenza or the recently identified COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During the course of their illness, infected patients may suffer from injurious inflammation +/- cytokine storm in the face of declining viral loads and die from the subsequent hypoxemic respiratory failure. In severe or critical COVID-19, circulating pGSN levels drop (Abers et al., 2021; Messner et al., 2020; Overmyer et al., 2021). Rhu-pGSN repletion may counteract host-mediated lung damage in animal models (Piktel et al., 2010; Yang et al., 2019; DiNubile et al., 2020). Our ultimate goal is to investigate if supplementing depleted levels of pGSN under such circumstances would be beneficial in aborting the pathophysiological events leading to acute respiratory distress syndrome.

Methods

Rhu-pGSN (BioAegis Therapeutics, North Brunswick, NJ) is an

* Corresponding author at: BioAegis Therapeutics Inc., Suite 270, 685 US Highway One, North Brunswick, NJ 08902, USA.
E-mail address: mdinubile@bioaegistx.com (M.J. DiNubile).
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investigational treatment produced and purified from *Escherichia coli*. Under a compassionate-use agreement, rhu-pGSN at a dose of 12 mg/kg based on actual body weight was given intravenously to an intubated patient with critical COVID-19 pneumonia at 0, 12, and 36 h.

Case report

The patient is a 73 year-old, non-obese (wt. 60 kg), active woman with osteoporosis and untreated chronic lymphocytic leukemia (CLL) in generally good health. She had not been immunized against SAR-CoV-2 before her illness. Approximately a week prior to her admission on 23-March-2021, she developed flu-like symptoms with anorexia and progressive myalgias, followed by dyspnea and fever. Her chief complaint at presentation to the hospital was progressive dyspnea, cough, and a decreased O_2 saturation down to 85% by pulse oximetry at home. A BinaxNOW™ COVID-19 Ag Card (Abbott Laboratories, Abbott Park, IL USA) was positive and a decreased O_2 saturation measured by pulse oximetry was 89%. Admission evaluation included abnormal chest imaging with bilateral patchy infiltrates, a C-reactive protein (CRP) of 94 mg/L, an absolute lymphocytosis (attributed to her CLL) which was lower than her baseline counts, modest hyperglycemia, and normal ferritin and D-dimer levels.

She was admitted to a ward bed for nasal O_2 and dexamethasone 6 mg once daily was begun. Nonetheless, her respiratory rate and oxygen requirement [3L, 94%; 6L,92%; 15L, 94%] increased. She had fever with more coughing. On the second hospital day, she exhibited further deterioration and was transferred to the ICU for high flow nasal O_2. Later that night she was intubated and sedated for worsening respiratory distress. Soon thereafter she was started on amoxicillin-clavulanate and anticoagulation with enoxaparin up to 60 mg subcutaneously BID. Her condition further deteriorated and antibiotics were changed to piperacillin-tazobactam. On the fifth hospital day she experienced transient hypotension and a norepinephrine infusion was administered for ~ 36 h until the evening of 29-March. The CRP peaked at 235 mg/L on this day, and chest radiographs revealed increasing infiltrates. The family became alarmed and wanted to start an additional experimental therapy, specifically rhu-pGSN (BioAegis Therapeutics, North Brunswick, NJ, USA) which they knew from investment opportunities. Since not recommended by WHO guidelines at the time, immunomodulators including tocilizumab and Janus kinase inhibitors were not administered.

Three doses of rhu-pGSN were given at 12 mg/kg by slow intravenous push through a 0.2 μm-pore filter over 36 h [30-March PM, 31-March AM (12 h later) and 1-April (24 h after the second injection)]. No infusion reactions or adverse events were recognized. Her blood pressure remained stable without vasopressor support. She noticeably improved while receiving rhu-pGSN. Her recovery continued after completion of the course of rhu-pGSN. On 4-April, she was extubated and antibiotics were discontinued. After 2 weeks in the hospital, she felt progressively better while still in the ICU; her O_2 saturation climbed to 98% on 2 L of nasal oxygen despite little radiological improvement.

She left the ICU on 2 days later with a CRP of 16 mg/L and was eventually discharged from the hospital after approximately 5 weeks following inpatient rehabilitation. Her outpatient recovery 3 weeks after discharge was complete and uneventful, returning to her baseline status. At last follow-up in early August, she reportedly remained in good health with almost complete clearing of her pulmonary infiltrates.

Discussion

Life-threatening COVID-19 pneumonia can be incited by a delayed overexuberant immune response to SARS-CoV-2. Plasma gelsolin (pGSN) levels fall early after SARS-CoV-2 infection in direct relationship to the severity of the ultimate illness (Abers et al., 2021; Messner et al., 2020; Overmyer et al., 2021). Recombinant human (rhu-)pGSN) improves disease outcomes in diverse animal models of infectious and non-infectious inflammation (Piktel et al., 2010; Yang et al., 2019; DiNubile et al., 2020). Under a compassionate-use agreement, rhu-pGSN was given intravenously to an intubated patient with critical COVID-19 pneumonia and progressive hypoxemia despite dexamethasone, antibiotics, high-flow nasal O_2, and ICU care. Improvement was noticed during the rhu-pGSN infusions and continued over the subsequent weeks. No adverse reactions to rhu-pGSN were observed. Rhu-pGSN was well tolerated and possibly efficacious in this critically ill patient intubated for acute respiratory failure following COVID-19 pneumonia. Whether rhu-pGSN administration was in part responsible for the rapid improvement cannot be conclusively determined from a single case. Moving forward, rhu-pGSN should be studied as a potential immunomodulatory therapeutic for advanced COVID-19 pneumonia.

The mortality rate for patients hospitalized in the USA with COVID-19 aged 65–75 years had fallen from 22.8% to 10.3% during 2020 (Finelli et al., 2021). However, certain immunosuppressive conditions can impair response to vaccines and worsen the outcome of infection. Patients with B-cell CLL respond less well to SARS-CoV-2 vaccines and experience poor outcomes after COVID-19 infections even when not being treated with chemotherapy (Mato et al., 2020; Scarfò et al., 2020; Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients, 2021). In a recent report, only 23% of CLL patients given mRNA vaccines developed detectable antibodies despite nearly 70% of these patients not undergoing cancer therapy. Treatment-naïve CLL patients with COVID-19 exhibit similar complications to treated patients with mortality rates > 30%.

Rhu–pGSN is structurally identical to endogenous human pGSN. In a small phase 1 dose-escalation trial (ClinicalTrials.gov Identifier: NCT03466073), once daily intravenous administration of rhu-pGSN at doses of 6, 12, and 24 mg/kg of actual body weight for 3 days to patients hospitalized on general medical wards with modestly severe CAP appeared safe and well tolerated (Tannous et al., 2020). Even with supraphysiological pGSN levels throughout the dosing interval, neither serious nor drug-related adverse events were observed in rhu-pGSN recipients given three consecutive days of therapy.

Our patient was elderly and has CLL, putting her at high risk for a poor outcome after infection with COVID-19. As is typical of the clinical course in hosts with significant comorbidities, the disease can flare in the second week. The patient worsened despite dexamethasone from the day of hospital admission. Her caregivers described her improvement after initiation of rhu-pGSN therapy as remarkable although this timing could have just represented a coincidence.

A double-blinded proof-of-concept trial to confirm the safety and assess the efficacy of rhu-pGSN for severe COVID-19 pneumonia is ongoing (ClinicalTrials.gov Identifier: NCT04358406). The result of this single case cannot establish efficacy despite the temporal association of rhu-pGSN administration with dramatic improvement. Nonetheless, in light of the overall findings to date, rhu-pGSN deserves consideration as a potential immunomodulatory therapeutic for advanced COVID-19 pneumonia.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JVC has no disclosures. MJD is an employee of BioAegis Therapeutics which is developing rhu-pGSN for clinical use and owns stock in the company.

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References

Abers, M.S., Delmonte, O.M., Ricotta, E.E., et al., 2021. An immune-based biomarker signature is associated with mortality in COVID-19 patients. JCI Insight 6 e144455.

DiNubile, M.J., 2007. Plasma gelsolin: in search of its raison d'ètre. Focus on "Modifications of cellular responses to lysophosphatidic acid and platelet-activating factor by plasma gelsolin". Am. J. Physiol.-Cell Physiol. 292 (4), C1240–C1242.

DiNubile, M.J., Levinson, S.L., Stossel, T.P., Lawrenz, M.B., Warawa, J.M., 2020. Recombinant human plasma gelsolin (rhu-pGSN) improves survival and attenuates lung injury in a murine model of multi-drug resistant Pseudomonas aeruginosa pneumonia. Open Forum Infect. Dis. 7 (ofaa236).

Finelli, L., Gupta, V., Petigara, T., Yu, K., Bauer, K.A., Puzniak, L.A., 2021. Mortality among US patients hospitalized with SARS-CoV-2 infection in 2020. JAMA Network Open 4 (4), e216556. https://doi.org/10.1001/jamanetworkopen.2021.6556.

Jain, S., Self, W.H., Wunderink, R.G., Fakhran, S., Balk, R., Bramley, A.M., Reed, C., Grijalva, C.G., Anderson, E.J., Courtney, D.M., Chappell, J.D., Qi, C., Hart, E.M., Carroll, F., Trabue, C., Donnelly, H.K., Williams, D.J., Zhu, Y., Arnold, S.R., Ampofo, K., Waterer, G.W., Levine, M., Lindstrom, S., Winchell, J.M., Katz, J.M., Erdman, D., Schneider, E., Hicks, L.A., McCullers, J.A., Pavia, A.T., Edwards, K.M., Finelli, L., 2015. Community-acquired pneumonia requiring hospitalization among U.S. adults. N. Engl. J. Med. 373 (5), 415–427.

Mato, A.R., Roeker, L.E., Lamanna, N., et al., 2020. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. Blood 136, 1134–1143.

Messner, C.B., Demichev, V., Wendisch, D., Michalick, L., White, M., Freiwald, A., Textoris-Taube, K., Vernardis, S.I., Egger, A.-S., Kreidl, M., Ludwig, D., Kilian, C., Agostini, F., Zelezniak, A., Thibeault, C., Pfeiffer, M., Hippenstiel, S., Hocke, A., von Kalle, C., Campbell, A., Hayward, C., Porteous, D.J., Marioni, R.E., Langenberg, C., Lilley, K.S., Kuebler, W.M., Mülleder, M., Drosten, C., Suttorp, N., Witzenrath, M., Kurth, F., Sander, L.E., Ralser, M., 2020. Ultra-high-throughput clinical proteomics reveals classifiers of COVID-19 infection. Cell Syst. 11 (1), 11–24.e4.

Ordija, C.M., Chiou, T.-Y., Yang, Z., Deloid, G.M., de Oliveira Valdo, M., Wang, Z., Bedugnis, A., Noah, T.L., Jones, S., Koziel, H., Kobzik, L., 2017. Free actin impairs macrophage bacterial defenses via scavenger receptor MARCO interaction with reversal by plasma gelsolin. Am. J. Physiol. Lung Cell. Mol. Physiol. 312 (6), L1018–L1028.

Overmyer, K.A., Shishkova, E., Miller, I.J., Balnis, J., Bernstein, M.N., Peters-Clarke, T. M., Meyer, J.G., Quan, Q., Muehlbauer, L.K., Trujillo, E.A., He, Y., Chopra, A., Chieng, H.C., Tiwari, A., Judson, M.A., Paulson, B., Brademan, D.R., Zhu, Y., Serrano, L.R., Linke, V., Drake, L.A., Adam, A.P., Schwartz, B.S., Singer, H.A., Swanson, S., Mosher, D.F., Stewart, R., Coon, J.J., Jaitovich, A., 2021. Large-scale multi-omic analysis of COVID-19 severity. Cell Syst. 12 (1), 23–40.e7.

Piktel, E., Wnorowska, U., Cieśluk, M., et al., 2010. Recombinant human plasma gelsolin stimulates phagocytosis while diminishing excessive inflammatory responses in mice with Pseudomonas aeruginosa 2epsis. Int. J. Mol. Sci. 21, 2551.

Scarfò, L., Chatzikonstantinou, T., Rigolin, G.M., et al., 2020. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia. Leukemia 34, 2354–2363.

Self, W.H., Wunderink, R.G., DiNubile, M.J., et al., 2018. Low admission plasma gelsolin concentrations identify community-acquired pneumonia patients at high risk for severe outcomes. Clin. Infect. Dis. 69, 1218–1225.

Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. medRxiv preprint accessed April 2021; https://doi.org/10.1101/2021.04.06.21254949.

Tannous, A., Levinson, S.L., Bolognese, J., Opal, S.M., DiNubile, M.J., 2020. Safety and pharmacokinetics of recombinant human plasma gelsolin in patients hospitalized for nonsevere community-acquired pneumonia. Antimicrob. Agents Chemother. 64, e00579–e620.

Yang, Z., Chiou, T.-Y., Stossel, T.P., Kobzik, L., 2015. Plasma gelsolin improves lung host defense against pneumonia by enhancing macrophage NOS3 function. Am. J. Physiol. Lung Cell. Mol. Physiol. 309 (1), L11–L16.

Yang, Z., Bedugnis, A., Levinson, S., DiNubile, M., Stossel, T., Lu, Q., Kobzik, L., 2019. Delayed administration of recombinant plasma gelsolin improves survival in a murine model of severe influenza. F1000Res 8, 1860. https://doi.org/10.12688/f1000research10.12688/f1000research.21082.1.