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Case Series

Early intervention of ARDS using anti-CD6 monoclonal antibody Itolizumab: Case series of clinical evidence

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ABSTRACT

The case series of three patients is an attempt to report the importance of early use of Itolizumab in the treatment of non-COVID 19 acute respiratory distress syndrome (ARDS) admitted to the intensive care unit. Monitoring total counts, oxygen requirements, respiratory capacity, and sepsis biomarkers along with strong clinical history and presentation helped in determining the stage of sepsis, allowing the treating physician to prescribe Itolizumab as the treatment of choice when septic shock and complications such as multiple (greater than or equal to 2) organ system failure MOSF has not set in. The efficacy of Itolizumab in this clinical setting was preventative as it blocked the CD6+ receptors, preventing activation of inflammatory reaction and release of large amounts of pro-inflammatory mediators including IL-1, IL-6, TNF-α, and INF-γ, and salvaged the clinical deterioration observed in early stages of ARDS. When the clinical, biomarker and haematological parameters indicate advanced sepsis with impending MOSF, other rescue measures should be instituted to save the patient from fatal outcome. The three patients received Itolizumab while two patients showed improvements due to early institution of therapy, the third patient, in advanced sepsis led to rapid deterioration of clinical condition and death.

1. Introduction

Acute respiratory distress syndrome (ARDS) in sepsis is a common complication and considered to be fatal with mortality rates up to 40% when not treated.[1] The pathophysiology of ARDS is heterogenous and its pathogenesis is well-mapped, from excessive transepithelial neutrophil migration, pro-inflammatory cytokine release, fibro-proliferation that triggers apoptosis and loss of alveolar-capillary integrity with abnormally active innate immune response coupled with dysfunctional coagulation impacting gas exchange with reduce carbon dioxide excretion and increasing hypoxia, culminating to acute respiratory failure and death of patients.[2,3]

The role of proinflammatory and anti-inflammatory cytokines have taken a prominent role in devising therapeutic strategies including IL-1β, Il-1, IL-6, IL-8, IL10 and sTNFR-1.[4] Release of extensive amounts of proinflammatory cytokines (cytokine storm syndrome) can attack multiple organs and can be a life-threatening catastrophe. ARDS with cytokine storm syndrome was remarkable in conditions such as hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS) and various virus induced ARDS including SARS-CoV-2, MERS- and even recently, the COVID-19.[5] Several cytokines released due to infection or immunotherapy includes IL-1, IL-6, TNF-α, and INF-γ, produced primarily by activation of innate immune cells such as macrophages, neutrophils, monocytes, and natural killer cells, these further leading to activation of CD4+ and CD6+ cells.[6]

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Among all inflammatory cytokines, IL-6 is considered as a major mediator and considered to be a prognostic indicator. Anti-cytokine treatment strategies have been tried for COVID-19 hyperinflammatory state, of which tocilizumab is a selective IL-6 receptor blocker, without any impact on other cytokines such as TNF-α, and INF-γ. Blocking the CD6+ cells can achieve that broader and specific inhibition of cytokine storm before it is set-off, representing a clear advantage over selective cytokine interventions. Itolizumab is the anti-CD6+monoclonal antibody that binds to surface of CD6+ T-Cells and blocks generation of gamut of cytokines and proinflammatory mediator's release. Therefore, when Itolizumab is administered at a stage when IL-6 values are below 200mg/L, it showed prompt improvement in clinical and radiological parameters.[7]

This case series is aimed at describing the clinical outcomes when the anti-CD6 antibody, Itolizumab is administered early in ARDS, where the biomarkers (IL-6, CRP and D-dimer) are lower, compared to, when Itolizumab is administered when these biomarker values were higher.

2. Case Presentation

2.1. Case 1

A seventy-year-old male patient with history of diabetes mellitus, hypertension, coronary artery disease, and decreased urine output presented to hospital with chief complaints of fever, headache, sore throat, diarrhoea, shortness of breath, chest pain, vomiting, tiredness, and weakness. There was no history of coughing, stomach pain, convulsions, altered consciousness/confusion, or throat irritation. His day 1(D1) temperature was 101°F and 99 °F on day 8 (D8). His blood pressures ranged from 160/100 mmHg on day 1 to 140/80 mmHg on day 8. His average arterial blood pressure was from 72 to 70 mmHg on admission D1 & D8 respectively, FiO_2 of 100% (D1) & 40% (D8) and the respiratory rate 32 breaths/min (D1) and 28 breaths/min (D8), SPO_2 of 90% (D1) and 98% (D8). The Glasgow Coma Scale (GCS) score remained 15 throughout the hospitalization.

His blood tests on day 1 and day 8 are as follows: D1 of CRP (20 mg/L) and D8 (10mg/L), D1 of D-Dimer (1096 ng/ml) and D8 (640 ng/ml), D1 ferritin (1100 mg/L), IL-6 (8 mg/L), and PCT (10 ng/ml). On day 1, the lipid profile- AST (100U/L) and D8 was 45 U/L, D1 ALT (90 U/L) and D8 was 60 U/L. There was no significant difference between D1 and D8 for Serum albumin (3.5 g/L), serum creatinine (2.5 mg/dL), bilirubin (1.6 mg/dL), and troponin of 14 ng/ml. The blood counts on day 1 were found to be total counts 24,000/dL, neutrophil 79%, lymphocyte 40%, platelet 1,20,000/dL and on day 8 the total counts were 14,000/dL, neutrophil 69%, lymphocyte 50%, platelet 1,45,000/dL. The patient was diagnosed as ARDS (Acute Respiratory Distress Syndrome), severe sepsis without septic shock along with adenylate kinase deficiency (AK1).

On day one, he was started on Meropenem, Colistin, Enoxaparin, Clarithromycin, and Actrapid insulin, Ecosprin, Telmisartan, Amlodipine, and Itolizumab.

He was on a ventilator on days 1 and 2 due to his high oxygen need and deteriorating breathing. He was then placed on BiPAP from day 3 to day 8. The drug was tolerated by the patient, and he was discharged from the hospital on day 8 (Figure 1).

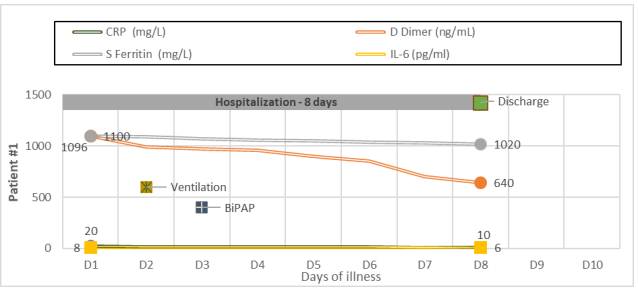

Fig. 1: Patient #1 (70 Years/Male/Diabetes Mellitus, Hypertension, Coronary Artery Disease (CAD)/ARDS (Acute Respiratory Distress Syndrome), severe sepsis without septic shock along with adenylate kinase deficiency (AK1

2.2. Case 2

A 75-year-old female patient weighing 60kgs with comorbidities- diabetes mellitus, hypertension, asthma, multiple heart problems, viz, heart failure, CAD, cardiomyopathy, with history of operated umbilical hernia presented to the hospital with fever, headache, cough, sore throat, shortness of breath, abdominal pain, vomiting, exhaustion, altered consciousness, weakness, lack of appetite, and rashes. There had been no previous reports of chest discomfort, convulsions, throat irritation, or diarrhoea.

Her temperatures on day 1 were 103°F and 102°F, and on day four, they were 99°F and 100°F. From day 1 to day 4, her mean arterial pressure fluctuated between 60- and 50-mm Hg. Her oxygen saturation in room air was 85% on day 1, dropping to 80% on day 4, and her blood pressure was 90/60 mm Hg on day 1, dropping to 70/50 mm Hg on day 4. PaO_2 of 60 mm Hg on day 1 and 50-mm Hg on day 4, with FiO_2 of 100% on all four days. On days 1 and 4, her respiratory rate 28 breaths/min. On day 1, the Glasgow Coma Scale (GCS) score was 14, and by day 3, it dropped to 10.

Her initial blood tests revealed CRP (24 mg/L), D-Dimer (1200 ng/ml), ferritin (640 mg/L), and IL-6 (40 mg/L), as well as Procalcitonin, PCT (10 ng/ml). She was diagnosed as acute respiratory distress syndrome (ARDS), severe sepsis without septic shock, and adenylate kinase

deficiency (AK1).

On day one, Doripenem, Polymyxin B, Teicoplanin, Enoxaparin, Doxofylline, Human actrapid infusion, and Ulinastatin injections were administered, followed by Ecosprin and Rosuvastatin tablets, and Itolizumab injections.

She was placed on invasive mechanical ventilation on day one due to her oxygen need and stayed on it until day four. The patient was unable to tolerate the medicine well due to her high oxygen need and deteriorating respiratory effort. Over the following 48 hours, there was no change in biomarkers or oxygen needs, and she remained on mechanical ventilation. The patient died on the fourth day (Figure 2).

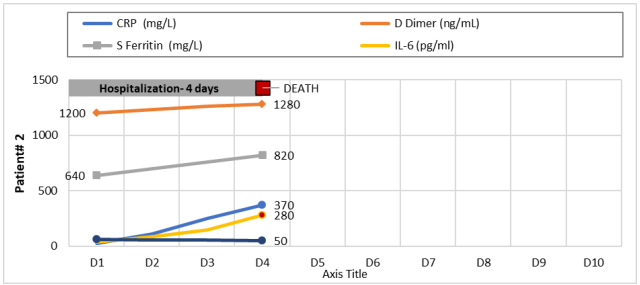

Fig. 2: Patient #2 (75 Years /Female/ Diabetes Mellitus, Hypertension, Asthma, Heart problem (Heart Failure, CAD, Cardiomyopathy)/ARDS (Acute respiratory distress syndrome), severe sepsis without septic shock along with Adenylate Kinase Deficiency (AK1)

2.3. Case 3

A thirty-year-old male patient weighing 60 kgs with no past medical conditions was diagnosed with fever, headache, sore throat, abdominal discomfort, vomiting, exhaustion, weakness, and rashes. There had been no previous history of coughing, diarrhoea, dyspnoea, chest pain, convulsions, altered awareness, throat irritation, or lack of appetite.

On examination, his body temperatures on day 1 were 101°F and 100°F, and on day 8 they were 100°F and 99°F. From day 1 to day 8, his mean arterial pressure was between 70- and 60 mm Hg. His saturation in room air was 90%, increasing to 99% on day 8, and his blood pressures were 100/70 mm Hg on day 1 and day 8. PaO2 of 60mm Hg on day 1 and 68mm Hg on day 8, and FiO2 of 100% on day 1 and 40% on day 8. On days 1 and 8, his respiratory rate was 28 breaths per minute. Throughout the hospital stay, the Glasgow Coma Scale (GCS) score remained at 15.

His initial blood tests revealed C-reactive protein, CRP (10 mg/L), D-Dimer (960 ng/ml), Ferritin (680 mg/L), and IL-6 (92 mg/L) with PCT (2 ng/ml) and a CRP value of 9 mg/L on day 5. On day 1, the liver function test was Aspartate aminotransferase, AST (340 U/L), Alanine transaminase, ALT (175 U/L), Serum albumin (2.8 g/L), Serum creatinine (1.2 mg/dL), and bilirubin (1.9 mg/dL). AST (280 U/L), ALT (150 U/L), S. albumin (2.8 g/L), S. creatinine (1 mg/dL), and bilirubin (1.6 mg/dL) were the readings on day 5.

He was treated with Cefoperazone sulbactam, Ulinastatin, and Doxycycline on day 1 and started on Itolizumab on day 2.

He was on venturi mask on day 1 and changed to rebreathing mask from day 3 till day 8. The patient tolerated the medication well and was discharged after day 8 (Figure 3).

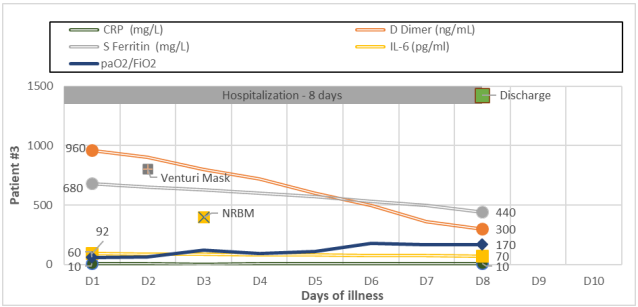

Fig. 3: Patient#3 (30 Years /Male/ No Comorbidities/ ARDS (Acute Respiratory Distress Syndrome, Dengue with septic shock)

3. Discussion

While ARDS presents as approximately 10% of all patients admitted in intensive care unit, the notorious fatality rate of 30-40%[8] is alarming and newer therapeutic interventions are evolving to gain control of this grave situation. Early diagnosis of ARDS before they met Berlin criteria reduced the morality rates to <8.5% compared to 24% when they met the criteria.[9] The pathophysiology of ARDS is such that the majority of patients developed ARDS within 12-48 hours of hospitalization, which lead to the development of predictor scores– Lung Injury Prediction Scores (LIPS) and Early Acute Lung Injury (EALI) scores, more reliable are the biomarkers as potentials ARDS predictive yardsticks such as CRP, D-dimer and IL-6 values. Early intervention either preventative or managing early progression at the stage where patients have incipient acute hypoxemic respiratory failure progressing to ARDS has been the key focus for the treating physicians.[8]

This was an observational, prospective study, conducted in a 350-bedded tertiary care centre (Wockhardt Multi-speciality Hospital, Nashik in Maharashtra, India). Three Acute patients diagnosed with ARDS were admitted in the intensive care unit and all three tested negative for COVID-19 (RT-PCR test) were included in the study. Two of the patients had diabetes and hypertension as comorbid conditions, which is consistence with most ARDS trials where ~33% of patients presented with hypertension and ~20% had diabetes.[10,11] All 3 patients were treated with

antibiotics, and supportive oxygen therapy, based on SpO2 levels, ventilatory support was provided for patients 1 and 2, while patient 3 was on a venturi mask. Patients 1 and 3 were started on Itolizumab before the onset of septic shock, on Day 0 and Day 1 respectively, while patient 2 was also prescribed Itolizumab on admission, by which severe sepsis had set in as indicated by high total counts, CRP, D-dimer and IL-6 values leading to progression of sepsis, falling Glasgow coma scale, increasing demand for oxygen and deteriorating respiratory effort. Itolizumab was effective in preventing progressions of sepsis in patients 1 and 3, while it was not effective in patient 2, when sepsis had already set in resulting in the death of the patient.

4. Conclusions

ARDS is an elusive emergency condition, lung injury progressing to rapid deterioration within 12-48 hours leading to sepsis and multi-organ system failure. Prevention of cytokine storm should be the primary goal in the treatment of ARDS and Itolizumab is an effective therapeutic option to prevent the onset of a sepsis-induced cytokine storm. It may not be the treatment of choice after sepsis has progressed and cytokines such as IL-1, IL-6, TNF-α, and INF-γ are already in circulation, triggering Multiple Organ System Failure (MOSF). It is crucial to begin Itolizumab treatment in when ARDS is diagnosed early to prevent cytokine storm and resulting ARDs related morbidity and mortality.

5. Conflict of Interest

The author(s) certify that they have no conflict of interest in the subject matter or materials discussed in this manuscript. No funding has been received for the conduct of this study. Data supporting this study will be available from the author following a 6-month embargo.

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