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Case Series

Clinical course of critically ill non-COVID 19 ARDS patients using Itolizumab versus conventional treatment: A case series

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ABSTRACT

We tracked the inflammatory mediators and blood gases ratios to evaluate the progress of treatment with Itolizumab administered in 5 critically ill patients against other therapeutic options in COVID 19 negative patients admitted to the ICU with ARDS. All patients had PaO2/FiO2 ratio <200>25mm Hg, while inflammatory markers such as D-Dimer value of > 0.21 g/L and IL-6 values >150 up to 1250 pg/ml at the time of admission. Radiological images were evaluated for improvement, patients requiring ventilator support were intubated and when the patient's PaO2 was within normal range, they were extubated. The prognostic indicators were measured till clinical outcomes in patients were met in all 10 patients of which 5 received Itolizumab on day 2 of hospitalization. All prognostic indicators showed a decline in inflammatory markers, proportionate improvement in PaO2/FiO2 values, and a reduction in PaCo2 values. All patients treated with Itolizumab were recovered and discharged, while one patient died and did not receive Itolizumab.

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1. Introduction

Acute respiratory distress syndrome (ARDS) is a broad entity signifying an acute form of inflammatory lung injury arising from a variety of underlying aetiologies, both pulmonary (infective such as bacterial, viral, and fungal pneumonia and non-infective that happens from aspiration of gastric contents) and non-pulmonary causes such as traumatic injuries, systemic sepsis, etc.). Although the aetiologies are varied, ARDS also is heterogeneous in its clinical and radiological presentations and behaviour thus considered to be elusive in diagnosis and treatment leading to high mortality.[1,2]

Biomarkers in ARDS have paved the way for diagnosis, risk identification, stratification, prognosis, and identification of appropriate therapeutic candidates.[3] Pro-inflammatory cytokines such as IL-β, IL-6, TNF-a, IL-8, IL-18 along with non-specific inflammatory markers such as CRP and thrombolytic markers such as D-dimer and ferritin are also used as yardsticks to monitor the course of ARDS.[4] Current therapies outlines are supportive with Lung protective ventilation, higher-level PEEP, Lung recruitment manoeuvres, and prone positions along with HFO and ECMO in severe cases. Pharmacotherapy includes inhaled NO, neuromuscular blockade, and stem cell treatments. To have a quick response to mortality, ARDS therapy should target arresting the inflammatory mechanisms triggered by immune systems.[4] Interleukin 6 is one of the cytokines that are known to increase the pro-inflammatory cytokines in ARDS and sepsis and agents that inhibit the biological effects of this cytokine before the trigger of pro-inflammatory cytokines can be a promising therapeutic option.[5–7]

Our case series is comprised of patients with moderate to severe ARDS (PaO2/FiO2 <200) and chest X-rays of the 10 patients showed diffuse bilateral peripheral

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infiltrates and these patients were tested negative for COVID 19. All 10 patients were admitted to the intensive care unit necessitating intubation and ventilator support and were monitored for PaO2/FiO2 and PaCO2. Inflammatory biomarkers used to monitor the prognosis of treatment were CRP, D-Dimer, IL-6, and Ferritin. All 10 patients were treated with, anticoagulants, and antibiotics. Five patients received Itolizumab on D2 of admission. Our case series highlights the benefits reaped when Itolizumab is administered early to prevent cytokine storm, improve PaO2/FiO2, and progressive decline in inflammatory markers in line with clinical improvement in these patients.

2. Case Discussions

2.1. Case 1

A 44-year-old male with comorbidities Diabetes Mellitus and Hypertension was diagnosed with ARDS. The baseline day (D) 1 of PaO2/FiO2 was 108 and PaCO2 was 58. The patient was treated with steroids, antibiotics, and anti-coagulants. On D2, the patient was intubated and Itolizumab was introduced. On D3, 5, 7 PaO2/FiO2 values were 140, 168, 172 and PaCO2 values were 43, 42, 38 respectively. Initially the inflammatory markers were raised CRP (41.8mg/L), D-Dimer (0.21ng/mL), IL-6 (41pg/mL), ferritin (185mg/L), and total counts (22380/dL) and they improved at the time of discharge with the values as CRP (11.2mg/L), D-Dimer (0.23ng/mL), IL-6 (24pg/mL), ferritin (117ng/mL), and total count (12710/dL). Radiological improvements were observed on D8 with a PaO2/FiO2 value of 202 and PaCO2 of 35. The patient was extubated and put on NIV with 100% improvement in PaO2/FiO2 value as 288 & PaCO2 value as 37 on D12. The patient recovered and was discharged after 18 days. [Figure 1]

2.2. Case 2

A 58-year-old female with a medical history of Diabetes Mellitus, Hypertension & Hyperthyroidism was admitted to the hospital. The patient was treated with glucocorticoids, antibiotics, and anti-coagulants. On D1 PaO2/FiO2 was 129 and PaCO2 was 28 and the patient was intubated on D2. Itolizumab was introduced on D3 where the PaO2/FiO2 value was 116 and PaCO2 was 36. On D5 and D7, PaO2/FiO2 values were 154 & 198 and PaCO2 values were 36 & 38 respectively. The radiological improvement was observed on D7. The patient was extubated and put on NIV with 100% improvement in PaO2/FiO2 value as 298 & PaCO2 value as 39 on D9. The elevated inflammatory markers receded during the hospital stay and the patient recovered and was discharged on D10 of illness [Figure 1].

2.3. Case 3

A 59-year-old female with comorbidities of Diabetes Mellitus. The baseline (D1) of PaO2/FiO2 was 94 and the patient was intubated on D1. At the time of admission, raised inflammatory markers were observed and the patient was treated with steroids, antibiotics, and anti-coagulants. Itolizumab was introduced on D2 where the PaO2/FiO2 value was 113 and PaCO2 was 31 mm Hg. Tracheostomy was done on D5 with a PaO2/FiO2 value of 196. On D7 & D9, PaO2/FiO2 values were 202 & 248 respectively. The radiological improvement was observed on Day 9. The patient was put on ventilation with a 50% improvement in PaO2/FiO2 value as 298 on D13 when compared to D9. The patient recovered and was discharged after 16 days [Figure 1].

2.4. Case 4

A 69-year-old male with a medical history of hypertension was admitted to the hospital with very high inflammatory markers. The baseline D1 of PaO2/FiO2 was 126 and PaCO2 was 55 mm Hg. The patient was intubated on D1, and the patient was treated with steroids, antibiotics, and anti-coagulants. Itolizumab was introduced on D2 where the PaO2/FiO2 value was 96 and PaCO2 was 45 mm Hg. On D3, D5, and D7 PaO2/FiO2 values were 112, 133, and 155 and PaCO2 values were 44, 46, and 42-mm Hg respectively. Tracheostomy was done on D8 with a PaO2/FiO2 value of 168 and a PaCO2 value of 42 mm Hg. The radiological improvement was observed on D12. The patient was put on ventilation with 100% improvement in PaO2/FiO2 value of 281 and PaCO2 value of 34 mm Hg on D13 when compared to D7. The inflammatory markers receded along with the other parameters and hence the patient was discharged on D16 of illness [Figure 1].

2.5. Case 5

A 75-year-old male with comorbidities such as Diabetes Mellitus & Hypertension. The patient was treated with steroids, antibiotics, and anti-coagulants. On D1 PaO2/FiO2 was 186 and PaCO2 was 27mm Hg. The patient was intubated on D2 and Itolizumab was introduced on the same day. PaO2/FiO2 values for D3 & D5 were 188 & 246 respectively. The patient's inflammatory markers such as CRP, D-Dimer, and IL-6 were found elevated, but the Ferritin value was found to be normal at the time of admission. The radiological improvement was observed on D5. The patient was extubated on D7 with a PaO2/FiO2 value of 300. There is a 54% improvement in D7 when compared to D5. The patient recovered and was discharged after 9 days [Figure 1].

2.6. Case 6

A 54-year-old female with Diabetes Mellitus and hypothyroidism. The patient was treated with steroids, antibiotics, and anti-coagulants. Highly elevated inflammatory markers were observed during the time of admission and the baseline (D1) of PaO2/FiO2 was 108 and PaCO2 was 22 mm Hg. The patient was intubated from D1. On D5 & D8 the PaO2/FiO2 readings were taken in the prone position which were 110 and 101 and PaCO2 was 38 mm Hg for both days respectively. On day 8, the patient had a septic shock. On D9 and D10, the PaO2/FiO2 readings were taken in the supine position 110 and 138 and PaCO2 values were 33- and 38-mm Hg respectively. The patient showed no radiological improvement and died due to septic shock with MODS (Multiple Organ Dysfunction Syndrome) on D14 [Figure 1].

2.7. Case 7

A 71-year-old male with comorbidities such as Diabetes Mellitus & Hypertension. The patient was treated with steroids, antibiotics, and anti-coagulants. On D1, the patient was intubated and PaO2/FiO2 was found to be 148, and PaCO2 was 33. On D3, D5, and D7 PaO2/FiO2 values were 165, 196 and 255, and PaCO2 values were 34-, 42-, and 35-mm Hg respectively. At the date of admission, the inflammatory markers were raised with the values as CRP (28.1mg/L), D-Dimer (0.55ng/mL), IL-6 (158pg/mL), ferritin (373mg/L), and total count (16500/dL) and they improved at the time of discharge with the values as CRP (12.4mg/L), D-Dimer (0.4ng/mL), IL-6 (15.6pg/mL), ferritin (292ng/mL), and total count (10800/ml). Radiological improvements were observed on D5. The patient was extubated and put on NIV on D7. PaO2/FiO2 value of 303 and PaCO2 value of 36 mm Hg were observed on D10, and the patient recovered and was discharged after 11 days [Figure 1].

2.8. Case 8

A 68-year-old male with diabetes mellitus and seizure disorder. The patient was treated with steroids, antibiotics, and anti-coagulants. On D4, the patient was intubated and PaO2/FiO2 was found to be 155, and PaCO2 was 42 mm Hg. On D7 PaO2/FiO2 value was 191 and the PaCO2 value was 38 mm Hg. The patient was extubated and put on High Flow Nasal Cannula (HFNC) on D7. On D9 & D10, PaO2/FiO2 values were found to be 268, 297 and PaCO2 values were 38- and 36-mm Hg respectively. Radiological improvements were observed on Day 9. The elevated inflammatory markers receded during the hospital stay and the patient recovered and was discharged after 16 days [Figure 1].

2.9. Case 9

A 49-year-old male with diabetes mellitus. At the time of admission, raised inflammatory markers were observed and the patient was treated with steroids, antibiotics, and anti-coagulants. The baseline D1 of PaO2/FiO2 was 242 and PaCO2 was 28 mm Hg. On D3, D5, D7, D9 PaO2/FiO2 values

Were 238, 196, 198, 226 and PaCO2 values were 36, 30, 29 and 30 respectively. Radiological improvements were observed on D10 with a PaO2/FiO2 value of 246 and a PaCO2 value of 36 mm Hg. The patient was extubated on D13 with a PaO2/FiO2 value of 314 and a PaCO2 value of 36. The patient recovered and was discharged after 17 days [Figure 1].

2.10. Case 10

A 57-year-old female with a medical history of hypertension was admitted to ICU. On D1, the patient was intubated and PaO2/FiO2 was found to be 236, and PaCO2 was 36 mm Hg. On D3, D5, and D7 PaO2/FiO2 values were 248, 261, and 286, and PaCO2 values were 40, 42, and 40 respectively. Radiological improvements were observed on D8 where PaO2/FiO2 value was 306 and the PaCO2 value was 38. The patient was extubated on D9 with a PaO2/FiO2 value of 312 and a PaCO2 value of 36. The inflammatory markers receded along with the other parameters and were discharged on D12 of illness [Figure 1].

3. Discussion

ARDS is one of the dreaded conditions that are notorious to have very high mortality rates from 30% to 75% mostly attributed to inflammatory reactions culminating in multi-organ failure (MOF) or sepsis rather than respiratory failure.[8–10] The diagnostic work-up for ARDS is primarily to understand the aetiology (pathogens – bacterial, viral, fungal, and parasitic) using microbiological assessment and culture. Chest X ray and clinical findings as per Berlin definition of ARDS[11] and prognostic indicators, as it is well documented that patients with higher levels of TNFα, IL-1β, IL-6, and IL-8 on day 1 of ARDS to have persistent levels had fatal outcomes.[12] Monitoring biomarkers such as IL-6, D-dimer, and ferritin helps manoeuvring therapeutic strategies along with a measure of blood gas analysis for PaO2, FiO2, and PaCO2.

Diagnosis helps triage the patients as per Berlin assessment to mild, moderate, or severe ARDS. The main treatment for severe ARDS is rescue therapy using various standard ventilator management strategies including ECMO, prone position etc. Further treatment is targeted at inflammatory mechanisms that lead to lung-injury and create cytokine storm that leads to MOF for anti-inflammatory properties feature in your standard protocols as early as 1967,[13] IL-6 receptor blocker and IL-6 domain

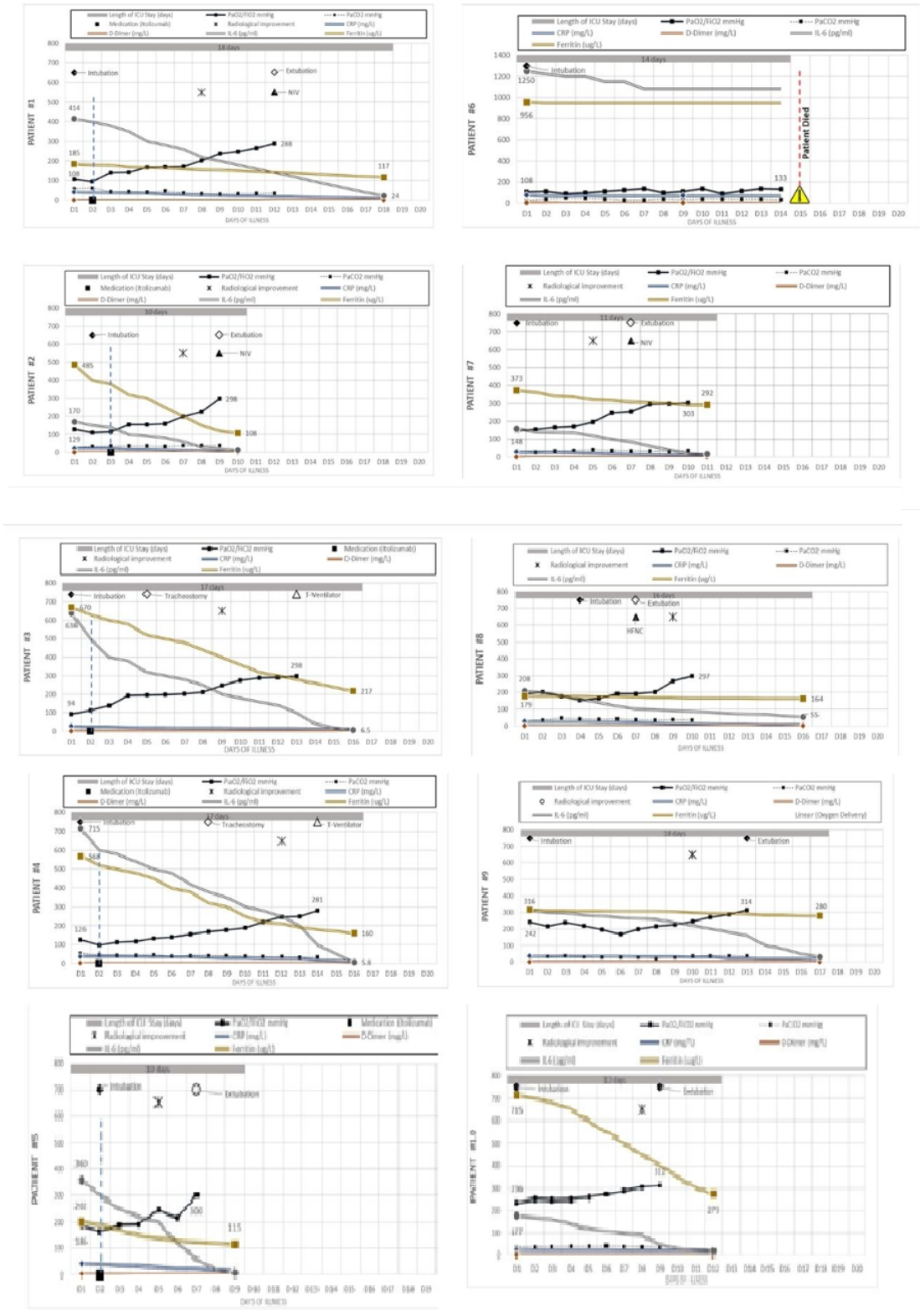

Fig. 1: Profile of patients in the case series, Patients 1-5 received italizumab and 6-10 did not.

in CD6 is blocked by Itolizumab which further prevents a chain reaction in lymphocytes preventing cytokine storm and subsequent development of MOFs.[14]

This was an observational, prospective study, conducted in a 340 bedded tertiary care centre in the south Indian city of Chennai (Vijaya Group of Hospital, Chennai). Adult patients diagnosed with ARDS and tested negative for COVID 19 (RTPCR test) were admitted to the ICU for management. A total of 10 patients between the age range of 40 to 75 with comorbidities such as Diabetes Mellitus, Hypertension, Hypothyroidism, and seizure disorder were enrolled in this observational study and the course of their illness was documented till outcomes were met. For all the patients, clinical characteristics were collected at admission and ICU patients received appropriate treatment with a mix of oxygen therapy and support agents. Among the 10 patients, 5 patients received immunomodulator Itolizumab along with other medications such as, antibiotics, and anticoagulants. While remaining 5 patients did not receive Itolizumab but were treated with other medications as mentioned above. The PaO2/FiO2 ratio was calculated from the first available arterial blood gas analysis performed in the emergency department. PaO2/ FiO2 thresholds to grade the severity of respiratory failure were taken from the acute respiratory distress syndrome (ARDS) Berlin definition as: normal (PaO2/ FiO2 >300 mm Hg); mild (PaO2/FiO2 201–300 mm Hg); moderate (PaO2/FiO2 101–200 mm Hg); severe (PaO2/ FiO2 ≤100 mm Hg).[8,9] The clinical outcomes were defined as recovered and discharged or death.

The shortest ICU stay was case 5 (9 days) with Day1 IL-6 value of 360 which fell to 6 on Day 9 showing drastic and significant improvement as Itolizumab was administered on D2 itself. The longest stay was patient 1 (18 days) with IL-6 value 414 at D1 and improved to 24 on D18. While Patient 6 who did not receive Itolizumab and had an IL-6 value of 1250 on D1, while this was the highest IL-6 values across all 10 cases presented in this series and this was consistent with findings presented by Meduri et al.,[12]

Itolizumab was given restricted emergency use authorization (EUA) by government of India during the COVID 19 pandemic to prevent ARDS and moralities. Due to its CD6 specific activity and its ability to prevent cytokine storm, early use of Itolizumab is promising in preventing severe inflammatory conditions such as sepsis and pancreatitis.

4. Conclusions

As ARDS pathophysiology converges on the inflammatory pathway, the diagnostic, prognostic, and treatment modalities are specific and precise providing a targeted therapeutic intervention for better clinical outcomes. The prognostic markers of inflammation IL-6, D-dimer and Ferritin provide a real view of clinical course, as reflected by improving the PaO2/FiO2 values and reduction in PaCO2 following the use of Itolizumab. This case study highlights the necessity for well-designed clinical studies to investigate the advantages and safety profile of Itolizumab in the treatment of life-threatening IL-6-mediated inflammatory diseases, with prognostic markers serving as a standard for assessing clinical response.

5. Acknowledgments

None.

6. Conflict of Interest

None.

7. Source of Funding

None.

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