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Case Series

Successful management of cytokine storm induced acute respiratory distress syndrome secondary to H1N1 influenza with itolizumab: A case series

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ABSTRACT

Critically ill patients often have a dysregulated immune response to the underlying insult leading to varied clinical features and end-organ dysfunction. One of the dysregulated immune responses termed 'cytokine storm (CS)' secondary to SARS-COV-2 during the recent COVID-19 pandemic was responsible for unacceptably high morbidity and mortality across the world. Cytokine storm is not unique to just COVID-19 but can also occur due to certain other viruses like H1N1 influenza. This phenomenon accelerated not only our understanding of the underlying pathophysiology and the role of the immune system in critically ill patients but also strengthened the concept of the possible need for an immunomodulator incorporated with standard therapy for treating Acute Respiratory Distress Syndrome(ARDS). Itolizumab, a reformulated anti-CD-6 humanized monoclonal antibody, downregulates the synthesis of proinflammatory cytokines leading to reduced interferon-γ (IFNγ), interleukin (IL-6), and tumour necrosis factor-α (TNFα) levels, along with reduced T-cell infiltration at the inflammatory site. Its usage in the management of CS in non-COVID 19 ARDS seems to be an appealing therapeutic approach given its mechanism of action. The current cases highlight an underlying possible hyperimmune response secondary to H1N1 in two patients who were successfully managed using Itolizumab along with standard treatment of ARDS.

1. Introduction

Immune dysfunction is readily recognized in many of the critically ill patients.[1,2] Although the initial insult may be of varied aetiologies (infection, trauma, burns, pancreatitis, etc.), the end result of such an insult is usually determined by a dynamic interplay between proinflammatory and anti-inflammatory immune regulators. The characteristic clinical outcome is either that of a pronounced inflammatory reaction or an injury-related immunosuppression. Such dysregulated immune system, along with infection, inflammation, ischemia, and/or shock are important determinants of both morbidity and mortality in intensive care patients.[3]

1.1. Role of immune regulation in the management of ARDS

Since its initial description, Acute Respiratory Distress Syndrome (ARDS) has been recognized as a syndromic condition arising as a result of a primary insult.[4] The initial insult could be pulmonary (such as damage associated mitochondrial proteins) or extrapulmonary (pathogen associated mitochondrial proteins, sepsis, trauma, burns, pancreatitis, etc.) in nature and are responsible for activating macrophages in the alveoli.[5] The activated macrophages release proinflammatory cytokines such as TNF-α, IL-6, IL-8, etc., which further recruit macrophages and neutrophils. An inflammatory cascade thus sets in which is responsible for not only damage to the alveolar epithelium and endothelium but also result in some of the systemic features

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like fever, increased capillary permeability, and sometime vasoplegia[6].

Such proinflammatory response is also followed by an activation of anti-inflammatory response in the form of release of mediators such as IL-10. These cytokines are responsible for restoring homeostasis, however, in some instances, there can be an exaggerated and concurrent pro and anti-inflammatory response, a condition which is sometimes referred to as 'cytokine storm (CS)'.[7] This pathophysiological phenomenon was very well recognized during the pandemic by SARS-CoV-2 which resulted in acute lung injury, MODS, and high mortality.[8]

Immunomodulation has been shown to be beneficial in a spectrum of critically ill patients including in ARDS.[9–11] In order to achieve optimal clinical benefits, such drugs have to be given at the right time and the right dose, given the dynamic nature of the immune response. Itolizumab, by inhibiting CD6, downregulates the synthesis of proinflammatory cytokines leading to reduced IFNγ, IL-6, and TNFα levels, along with reduced T-cell infiltration at the inflammatory sites. The current case series highlights the importance of recognizing the role of immune-mediated tissue damage, challenges in quantifying cytokine storm, and measures to mitigate the end organs damage in such critical scenario.

2. Case 1

A forty-five-year-old female patient, with no previous comorbidities, presented with fever with chilis for 5 days, cough with expectoration 3 days, and increasing breathlessness for 2 days. There was no history of sore throat, headache, or diarrhea. On examination, her temperature was 38^{o}C, saturations of 85% in room air, heart rate between 110 and 130/min, blood pressure of 110/70 mm of Hg. Her arterial blood gas showed pH of 7.30, $PaCO_2$ of 45mm of Hg, PaO_2 of 81mm of Hg, bicarbonate 33 mmol/L, and lactate of 0.7 mmol/L.

Her initial blood works showed an elevated level of CRP (72 mg/L), LDH (750 U/L), Ferritin (950 ng/ml), D-Dimer(350 ng/ml), and IL-6 (72 mg/L) with normal PCT (0.05 ng/ml). An NT Pro BNP and ECHO were normal indicating normal cardiac functions. A chest X-ray showed bilateral perihilar infiltrates and ground-glass opacities indicating ARDS (Adult Respiratory Distress Syndrome). Nasal swab was positive for H1N1.

She was started on symptomatic treatment along with Cefoperazone/Sulbactam and Methylprednisolone followed by Oseltamivir. Her clinical status remained worse with saturations in the low 80s on a non-rebreathing mask (NRBM). In view of high oxygen requirement and worsening of work of breathing, she was electively intubated 24 hours after her admission.

She was administered Itolizumab (1.6 mg/kg) over a duration of 6 hours after premedication with 100 mg of IV Hydrocortisone, 30 minutes prior to the medication. The patient tolerated the medication well.

There was a steady improvement over the next 48 hours with a downward trend in biomarkers and oxygen requirement (Fig 1). This trend paralleled radiological clearance of perihilar and interstitial shadows. She was extubated to facemask (NRBM) on day 4 and discharged home on day 11 completely weaned off oxygen.

3. Case 2

Twenty-five years old male, previously fit and fine presented with a short history of fever, cough, and breathlessness. There was no history of headache, vomiting, or loss of smell. General examination revealed a body temperature of 38 degrees Centigrade, blood pressure 120/70 mm of Hg, respiratory rate of 28/min, and saturation of 85% on room air. A systemic examination suggested bilateral bronchial breathing but no other significant abnormality.

His nasal and throat swabs were positive for H1N1 influenza. He was started on 15 liter of oxygen through NRBM. His initial lab work-up showed a total count of 11,500/$mm^3$with 86 percent neutrophils, ABG showed a pH of 7.45, $PaCO_2$ of 32 mm of Hg, PaO_2 of 75 mm of Hg, Bicarbonate 21 mmol/l, Lactate 1.2 mmol/L. His inflammatory markers were raised (CRP 30 mg/L, LDH 425 U/L, Ferritin 1250 ng/L,D Dimer 650 ng/ml, IL-6 62pg/L). Procalcitonin was normal (0.09 ng/L), so were his NT Pro BNP. He was started on Cefotaxime, Dexamethasone, and Oseltamivir.

Over the next 24 hours, patient had a steady deterioration with increasing work of breathing and oxygen requirement and hence was started on continuous positive airway pressure (CPAP).

He was administered Itolizumab (1.6 mg/kg) over a duration of 6 hours after premedication with 100 mg of IV Hydrocortisone, 30 minutes prior to the medication. The patient tolerated the medication well.

The response to Itolizumab was evident with gradual improvement in overall clinical condition, reduction in oxygen requirement, and fall in inflammatory biomarkers (Fig 2). He was taken off CPAP by day 6 and discharged on day 10.

4. Discussion

With over 476 million cases worldwide and nearly six million deaths, as of March 2022, COVID-19 resurged as one of the main causes of ARDS with high mortality despite our best efforts.[12] One of the key features of ARDS caused by COVID -19 was excessive cytokine release, the so-called cytokine storm (CS), with the release of mediators like IFNγ, IL-6, and TNFα, leading to systemic inflammatory response syndrome (SIRS) and Multi Organ Dysfunction Syndrome (MODS). However, the role of CS and the

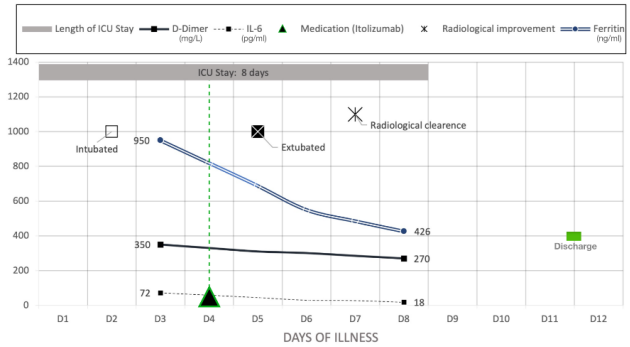

Fig. 1: Patient 1 (45 Years /Female /No co-morbidities /H1N1 influence

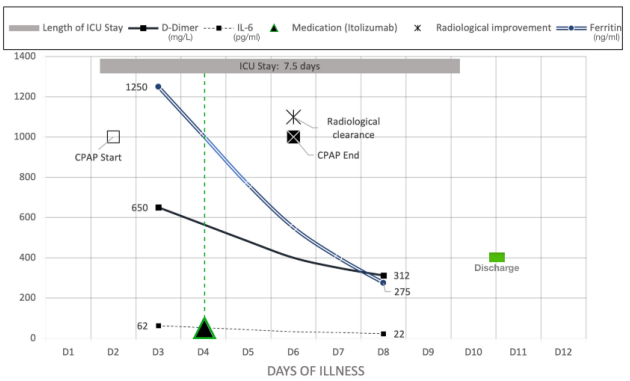

Fig. 2: Patient2 (25 Years /Male /No co-morbidities /H1N1 influence

resultant hypercoagulation, microthrombi, and increased vascular permeability are also known with other viruses like MERS-CoV and H1N1 influenza.[13]

Both the patients in our case series had no comorbidities and both were diagnosed with H1N1 influenza. Repeated RT-PCR for COVID-19 were negative for both the patients. They both had raised inflammatory markers at the time of presentation which was suggestive of initiation of immune mediated inflammatory cascade {Figures 1 and 2}. The author acknowledges the fact that no single test can detect the CS, and the diagnosis of cytokine storm-induced ARDS requires an appropriate correlation of clinical, radiological, and haematological parameters.

Both the patients were started on similar treatment, but they continued to have progression of illness. Based on the blood results and clinical progression along with lack of response to conventional treatment, both were considered for an adjunctive immunomodulator.

Immune dysfunction in critically ill patients remains difficult to quantify and hence the clear lack of consensus on immunomodulators usage in ARDS and sepsis. However, recent expert opinion by Yatin Mehta et al., and colleagues have strongly supported the use of immunomodulators in sepsis, ARDS, and acute pancreatitis provided one is able to identify the hyperactive immune response.[14] Mehta et al., and his team have also emphasized the need for source control and the importance of choosing the right drug and the right dose along with right time of administration.[14]

Both the patients in our setting were administered Itolizumab after due consent. The response to the medication was satisfactory and both of them tolerated the medication well and made a complete recovery. About 25% of H1N1 influenza patients developed bacterial superinfection during the 2009 pandemic and this was associated with a worse prognosis.[15] There was no evidence of secondary bacterial infection in either of our patients and although this could be attributed to pre-existing presence of antibiotics, it is also likely due to the ability of the Itolizumab to preserve the native T-cell function. A unique mechanism of action of Itolizumab is its ability to inhibit inflammatory cascade by inhibiting new receptor formation and internalization of receptors. In vitro studies have shown that Itolizumab does not cause depletion of T cells but inhibits T cell proliferation induced by ALCAM (activated leukocyte cell adhesion molecule).[16] Itolizumab may have a theoretical advantage of preserving native T-cell number and function with possible reduced incidence of secondary bacterial infection but this needs to be investigated urgently in appropriate clinical trials. In both patients, the decreasing trend of inflammatory markers paralleled clinical improvement and radiological clearance after administration of Itolizumab.

Itolizumab has received Restricted Emergency Use Authorization (EUA) in India for the treatment of moderate-to-severe ARDS in patients with COVID-19 infection. To the best of our knowledge, this is the first case series of H1N1 influenza or 'non-COVID-19' ARDS cases successfully managed with Itolizumab. Given its mechanism of action, Itolizumab may have role across spectrum of critical care illness with CS and may be considered in cases like acute pancreatitis and selective cases of sepsis.

5. Conclusions

It is important to understand the dynamic host-virus interaction and identify opportunities at various time points to combat the illness. The role of immunomodulation in a critically ill patient is still not in the mainstream pathway due to a lack of clear consensus and established guidelines. Itolizumab has the potential to treat hyperimmune response in patients with not just COVID-19 but also secondary to H1N1 influenza. More robust and well-designed trials should be undertaken urgently to prove the efficacy of this drug which has a potential role as an immunomodulator in a spectrum of critically ill patients.

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8. Conflicts of Interest

The author declare that they have no conflict of interest

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