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CASE REPORT

A case of severe COVID-19 pneumonia in pregnancy managed with tofacitinib and review of literature

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ABSTRACT

The incidence of coronavirus disease (COVID-19) is increasing each day worldwide and its clinico-pharmacological dynamics of it are also changing with time. Pregnant women do also get infected though mostly mild to moderate in nature. To date, there is no specific drug against the severe acute respiratory syndrome coronavirus disease-2 (SARS-CoV-2), more so its drug management in pregnancy in view of adverse maternal and fetal effects. There are different treatment modalities described in the literature. Here, we present a case of severe COVID-19 pneumonia in second trimester pregnancy managed successfully with "off-label" use of tofacitinib along with steroid pulse therapy in preventing her from going to invasive mechanical ventilation and probable catastrophe due to hyperinflammatory syndrome characterised by a surge of cytokines.

Keywords: COVID-19, cytokine Strome, pneumonia, teratogenicity, tofacitinib.

World Health Organization (WHO) officially declared the COVID-19 outbreak a pandemic on 11 March 2020. It has caused 17,58,47,347 cases and 38,07,276 deaths by 15 June 2021[1]. Physiological and mechanical changes in pregnancy are making pregnant women more susceptible to infections, particularly when the cardiorespiratory system is affected with the possibility of rapid progression to respiratory failure.

Altered immunity and elevated levels of interleukins and cytokines are associated with extensive lung damage followed by increased mortality in COVID-19 patients[2-4]. To date, there is no specific pharmacological agent identified against SARS-CoV-2. The usual approach is to treat symptoms limited by different conditions. Tofacitinib, a non-specific Janus kinase- signal transducer and activators of transcription (JAK-STAT) inhibitors, is a potent immune-modulator approved as second-line therapy for many auto-immune diseases [5].

In this case report, we aimed to access clinical improvement following administration of tofacitinib along with steroids in a rapidly deteriorating pregnant patient in her second trimester with severe COVID-19 pneumonia keeping teratogenic effects in mind.

Case

A 28 years old patient with gravida 3 para 1 living 1 abortion 1 and Rh non-iso-immunized status was admitted at 26 weeks gestation with breathlessness (SpO_2 - 76 % in room air) without recordable fever with a history of fever and cough three days back. On admission, she was maintaining her blood pressure and her fetal heart rate was 156 beats per minute (BPM). Her baseline investigations including reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 were requested and started with injectable 3rd generation cephalosporin, steroid nebulization and oxygen supplementation (5 L/min) on the concentrator. However, on deterioration, high flow oxygen (15 L/min) through a non-rebreathing mask (NRBM) was started to achieve her SpO_2 level above 92%. She was started with dexamethasone for antenatal steroid induction.

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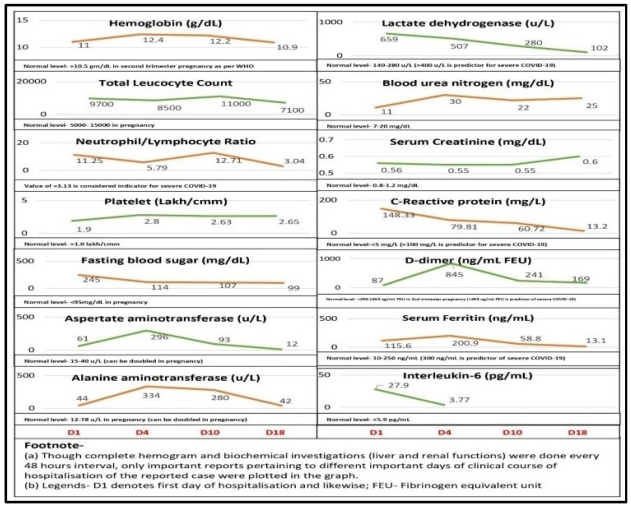

Figure 1: Date-wise investigations during hospitalisation

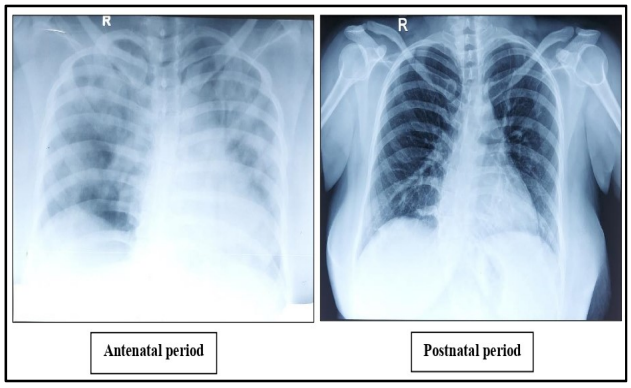

Figure 2: Comparative chest radiograph showing bilateral widespread consolidation/ opacities with severe ARDS (during the antenatal period) and fine fibrotic changes (during the postnatal period).

On the third day early morning, on the occurrence of a severe degree of hypoxic episode (SpO_2 - 54%) even with NRBM, she was immediately shifted to the COVID-19 intensive care unit (ICU) and started on non-invasive ventilation (NIV) with pressure support of 15 cm of H_2O, positive end-expiratory pressure (PEEP) of 8cm of H_2O and fraction of inspired oxygen (FiO_2) of 65% with intermittent NRBM. Injectable remdesivir 200mg followed by 100mg daily for next 4 days and thromboprophylaxis with low molecular weight heparin (LMWH) 40mg twice daily and oral aspirin 75mg daily were also started with a concern of rising D-dimer, C-reactive protein (CRP), serum ferritin, lactate dehydrogenase (LDH) (figure 1). Her chest X-ray was done at this stage with an abdominal lead shield, which showed bilateral widespread extensive consolidation/ opacities suggesting acute respiratory distress syndrome (ARDS) (figure 2). Arterial blood gas analysis (ABG) also showed arterial partial pressure of oxygen (PaO_2)/FiO_2 ratio <100mm of Hg, indicating severe ARDS with 'cytokine storm'.

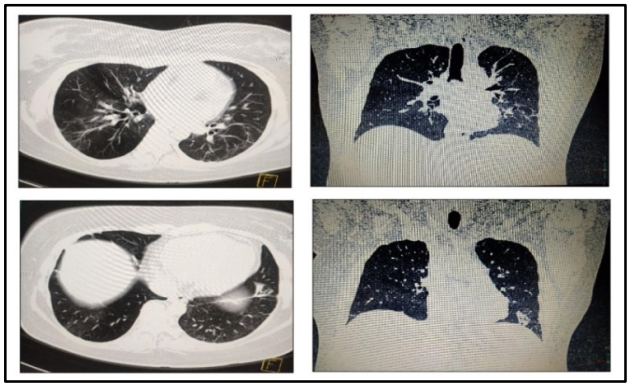

Figure 3: Multi planner high-resolution CT scan of the chest showing fine fibrotic changes with 'air trapping' in both lungs (postnatal period).

Given the above findings, methylprednisolone pulse therapy of 250mg daily for 3 days started in place of dexamethasone. On 24 hours of methylprednisolone pulse therapy, she was requiring NIV with FiO_2 70% to maintain SpO_2 level up to 85% and her liver enzymes levels were also elevated. After counselling of the patient and relatives, immunomodulation with oral tofacitinib 10 mg twice daily was added for five days with ongoing pulse therapy to halt the 'cytokine storm'. Antimicrobial agent upgraded to injectable piperacillin-tazobactam 4.5 gm six hourly and teicoplanin 400 mg daily. Oral ursodeoxycholic acid (UDCA) and L-arginine sachet were also started.

With this treatment, she was showing no further deterioration though the prognosis was guarded given the high flow oxygen requirement. From the tenth day onwards, she started improving in terms of improving PaO2/FiO_2 ratio and decreased FiO_2 on NIV and blood parameters as well. She was gradually weaned out from NIV to NRBM (15 L/min) and then via Hudson mask. Next week she was shifted to nasal prongs oxygen support. She was shifted out of COVID 19 ICU when maintaining a SpO2 level >92% with an oxygen concentrator at 2-3 L/ min. She was also gradually weaned off steroids and antimicrobials and started with a novel antifibrotic agent oral pirfenidone 200mg daily for four weeks.

Throughout her hospital stay, dietary supplementation was done and frequent change of positioning was performed as per COVID awake repositioning/ proning Protocol

(CARP). She was psychologically counselled and explained regarding postcovid precautions with a management plan. Her ophthalmological evaluation was normal and fetal heart rate was maintained between 150- 160 BPM. Her Obstetric ultrasonography was without any congenital malformation, mild degree of fetal growth retardation and normal doppler study. No further chest radiograph or computed tomography (CT scan) was performed to limit teratogenic radiation exposure.

On the twentieth day of admission, she was discharged with oxygen support of 1-2 L/min on a concentrator and thromboprophylaxis. After three weeks of discharge (at 34th week of gestation), she was able to maintain SpO_2 level 90-92% in room air for about two hours at stretch in a sitting position but her feto-maternal evaluation revealed asymmetric fetal growth restriction along with polyhydramnios and advised strict follow-up. At 36 completed weeks of gestation, fetus was in a transverse lie with loops of umbilical cord occupying the lower uterine pole and her dyspnoea level had also increased. Given these findings, she was delivered by elective cesarean section under low dose spinal anaesthesia and maintaining higher PaO_2 levels by O_2 supplementation through NRBM at 15L/min; delivering an alive and healthy newborn baby. The post-operative period was uneventful including blood investigations and was discharged with thromboprophylaxis and O_2 support of 1-2 L/min on the concentrator. Chest X-ray and CT scan were done during the postoperative period for assessment of her lung status, showing features of thin fibrotic bands with air trapping in both lungs (figure 2, 3).

Discussion

Since the onset of a global pandemic of COVID-19, clinicians and medical researchers worldwide are trying to evolve measures for the early recovery of patients and also to ensure every opportunity to rescue severe cases and reduce mortality.

During hypoxaemia, an aberrant autoimmune inflammatory response is the key mechanism for COVID-19 pneumonia and rapid deterioration as per Lucas et al [6]. McGonagle et al not only confirm a direct relationship between COVID-19 disease severity and rising cytokine levels but also supports the clinical approach of early intervention for achieving good outcome [7]. Oxygen saturation level, degree of inflammation (CRP, ferritin, LDH) and hypercoagulability (D-dimer) are well-established markers of severity and also noted in the case reported [8].

As no specific anti-SARS-CoV-2 therapeutic agents are available, symptomatic treatment and pregnancy-specific management of complications such as ARDS comprise the current standard of care. The monitored emergency use of unregistered interventions (MEURI) framework from WHO should guide the ethical use of non-licensed drugs during pregnancy during the pandemic. Interventions aimed at modulating the inflammatory immune response by reducing toxic cytokine levels are key in improving COVID-19 pneumonia outcomes; usage of dexamethasone in hospitalized patients got well-established momentum after the publication of the recovery study [9]. The kinase inhibitors are proposed as a treatment for COVID-19 as they can prevent biochemical changes involved in immune activation and inflammation in response to proinflammatory cytokines and interleukin (IL-6) [10]. Baricitinib, a JAK-STAT inhibitor got emergency use authorization (EUA) by the food and drug administration (FDA) on 19 November 2020, when used in combination with remdesivir for hospitalized adults and children above 2 years of age with COVID-19 requiring supplemental oxygen [11]. However, there was a paucity of data on the usage of JAK-STAT inhibitors in pregnancy. Being a small molecule drug, it can cross the placenta and fetal risk cannot be ruled out [12].

Tofacitinib is a prototypical JAK-STAT inhibitor and is FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis and ulcerative colitis as it decreases IL-6 level [13]. Like dexamethasone, tofacitinib possesses a broad anti-inflammatory effect, though target different inflammatory pathway, contrary to monoclonal antibodies [14]. A study by Hayek ME et al showed that adding tofacitinib-based anti-inflammatory therapy into the treatment regimen with dexamethasone has potential benefit in improving COVID-19 pneumonia and patient survival [15]. Data on pregnancy outcomes on tofacitinib used in pregnancy for other usual conditions are similar to that among the general pregnant population without any statistically significant fetal teratogenicity [16-18].

Conclusion

Pregnant women represent a uniquely vulnerable group to any infectious disease outbreak due to altered physiology and there has been a significant rise in the incidence of severe COVID-19 disease in pregnancy as well. As there was no specific pharmacotherapy evolves till date, different modalities of anti-inflammatory therapy are being used to stem the florid immune response associated with it. Need to safeguard the unborn fetus adds to the ongoing challenge. Survival benefit with the use of tofacitinib is found in the reported case.

It is concluded that a treatment protocol including anticoagulation therapy, antiviral and anti-inflammatory therapy with tofacitinib along with steroid pulse therapy offers a model for management of severe COVID-19 pneumonia and averting mortality when used within 48-72 hours of 'cytokine storm' even in pregnant women.

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