Tofacitinib as a novel therapy in COVID-19 acute respiratory distress syndrome

INTRODUCTION

On March 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) as a pandemic.[1] Coronaviruses causes rapid virus replication with massive inflammatory cell infiltration and elevated proinflammatory cytokine/chemokine responses [e.g. interleukin (IL)-2, IL-6, IL-8, tumor necrosis factor-α, etc.] resulting in cytokine storm syndrome causing dysregulated, hyperimmune response, which is the main cause of acute respiratory distress syndrome. Therefore, immune modulation or suppression of excessive cytokine production becomes necessary in critical disease.

The kinase inhibitors are the new class of drugs for COVID-19 management, which prevent phosphorylation of key proteins involved in the signal transduction that leads to inflammation and activation of transcription proteins that are involved in several cell functions like signalling, growth, and survival.[2]

Tofacitinib is an inhibitor of Janus kinases 1 and 3 (JAK1 and JAK3), with immunomodulatory and anti-inflammatory properties. It prevents the activation of the JAK-signal transducers and activators of transcription (STAT) signalling pathway. This leads to reduction in the production of pro-inflammatory cytokines, and may prevent both an inflammatory response and the intracellular enzymes involved in signalling pathways affecting immunity and inflammation in patients with COVID-19.[3] We present a clinical course of four patients with severe COVID-19 ARDS who were administered oral tofacitinib, in our intensive care unit (ICU).

CASE DESCRIPTION

Four reverse transcription-polymerase chain reaction confirmed COVID-19 positive patients admitted to our ICU had presented in the emergency department with symptoms of fever, cough and severe breathlessness between 1st May 2020 to 30th May 2020. Out of four, three were females in late thirties and mid-forties, without any co-morbidities, and with a history of onset of symptoms 10–15 days ago. There was no history of prior hospitalisation. One 46-year-old male patient, with a history of hypertension, presented after 30 days of symptom onset. On ICU admission, all the patients had oxygen saturation of 88–90% on non-invasive ventilation with 100% fractional inspired oxygen concentration (FiO_2). All patients received injection remdesivir, antibiotics, steroids, and injection enoxaparin as per standard COVID-19 treatment protocol of our institute. In two patients, tablet tofacitinib 10 mg BD was initiated 5 days after ICU admission whereas in the other two, it was started on the seventh and fifteenth days respectively, for a period of 14 days. The criteria for initiation of treatment were worsening or persistently high C-reactive protein (CRP) value, high FiO_2 requirement to maintain oxygen saturation (SpO_2), high neutrophil to lymphocyte ratio (NLR) and low PaO_2/FiO_2 (P/F) ratio. All patients were followed for the period of 14 days after initiation of tofacitinib. In three out of four patients, significant decrease in oxygen requirement, improved NLR and P/F ratio, de-escalation of ventilatory support was observed within 5 days of starting the therapy and the patients were discharged to ward on 24–28% FiO_2. However, one patient did not respond to the treatment, was put on mechanical ventilation and ultimately succumbed to death on the ninth day of ICU admission. The trend of FiO_2 requirement, P/F ratio, NLR and CRP level was noted [Table 1].

DISCUSSION

Tofacitinib is a small synthetic molecule, available in oral formulation with fast bioavailability and elimination rate. Its predictable pharmacokinetics and lack of immunogenicity suggest good efficacy and safety.[4,5]

The interaction of the spike protein of Severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) with angiotensin-converting enzyme II causes activation of metalloprotease 17 and angiotensin-converting enzyme II release from host cells, resulting in increased angiotensin II (Ang II) and hyaluronan (HA) concentrations. Ang II interacts with Ang II receptor-1, which leads to JAK-STAT pathway activation, ultimately culminating in a pro-fibrotic and pro-inflammatory state, resulting in respiratory distress and severe inflammation.[6] Tofacitinib may counteract this pathological process.[7] A retrospective study by Maslennikov *et al.*[5] has shown that mortality and the incidence of admission to ICU were

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Table 1: Clinical, laboratory and respiratory parameters of cases

	Timeline	Case 1	Case 2	Case 3	Case 4
FiO_2 Requirement (%)	Baseline (At the time of ICU admission)	100	100	100	80
	On Day 1 of Tofacitinib administration	100	90	100	90
	On Day 3 of Tofacitinib administration	90	75	100	70
	On Day 5 of Tofacitinib administration	80	50	100	60
	On Day 7 of Tofacitinib administration	50	35	100	50
	On Day 14 of Tofacitinib administration	24	28	-	40
P/F ratio	Baseline (At the time of ICU admission)	80	70	73	67
	On Day 1 of Tofacitinib administration	80	90	67	63
	On Day 3 of Tofacitinib administration	100	100	80	96
	On Day 5 of Tofacitinib administration	110	125	73	103
	On Day 7 of Tofacitinib administration	140	150	53	110
	On Day 14 of Tofacitinib administration	210	180	-	150
N/L ratio	Baseline (At the time of ICU admission)	23	15	24	24
	On Day 1 of Tofacitinib administration	23	19	25	25
	On Day 3 of Tofacitinib administration	15	14	20	16
	On Day 5 of Tofacitinib administration	10	10	22	8
	On Day 7 of Tofacitinib administration	6	5	24	6
	On Day 14 of Tofacitinib administration	3	2.3	-	4
CRP (mg/L)	Baseline (At the time of ICU admission)	210	84.7	220	125
	On Day 1 of Tofacitinib administration	210	99	218	109
	On Day 3 of Tofacitinib administration	90	37.8	180	38
	On Day 5 of Tofacitinib administration	67	16.3	184	11
	On Day 7 of Tofacitinib administration	31	8.3	150	8.7
	On Day 14 of Tofacitinib administration	4.2	6.2	-	5.3
Mode of ventilatory Support	Baseline (At the time of ICU admission)	NIV	NIV	NIV	NIV
	On Day 1 of Tofacitinib administration	NIV	NIV	NIV	NIV
	On Day 3 of Tofacitinib administration	NIV	HFNO	Invasive	NIV
	On Day 5 of Tofacitinib administration	HFNO	HFNO	Invasive	HFNO
	On Day 7 of Tofacitinib administration	NRBM	Venturi mask	Invasive	HFNO
	On Day 14 of Tofacitinib administration	Nasal Prongs	Nasal prongs	-	Venturi mask

ICU: intensive care unit; HFNO: High frequency nasal oxygen; NRBM: Non-rebreathing mask; FiO_2: Fraction of inspired oxygen concentration; N/L: neutrophil to lymphocyte ratio; P/F ratio: PaO_2/FiO_2 ratio; NIV: Non-invasive ventilation; CRP: C-reactive protein

lower in the tofacitinib group than in the control group ($P = 0.009$ and $P = 0.004$). Further, there was a marked improvement in oxygen saturation ($P = 0.012$), decrease in CRP ($P = 0.048$) as well as the number of patients requiring mechanical ventilation ($P = 0.020$) in the tofacitinib group than in the control group, 7–10 days after starting tofacitinib administration. A recently published randomised placebo-controlled trial (STOP-COVID) on hospitalised COVID-19 patients also concluded that tofacitinib administration decreases the risk of death and respiratory failure at 28 days as compared to placebo (18.1% vs 29%).[8]

All our patients required high FiO_2 to maintain SpO_2 on presentation. All patients were of comparable age group and only one patient had hypertension. After administration of tablet tofacitinib, three patients showed marked recovery whereas one case died on the ninth day of ICU admission. The patient who expired was hypertensive and on mechanical ventilation, which are possibly the risk factors for resultant mortality. Adverse effects such as deep vein thrombosis, acute myocardial infarction, ventricular tachycardia and myocarditis are reported with tofacitinib but none of our patients had these complications. Further, there was no evidence of secondary infection in our patients as suggested by negative blood cultures (all cases) and tracheal culture (Case 3). A recent study has shown that the incidence of serious infection is lesser in tofacitinib as compared to placebo group (3.5% vs. 4.2%).[8] Three out of four patients who improved had a duration of onset of symptoms between 10 and 15 days, whereas the patient who died had symptoms for 30 days. Cantini *et al*.[9] suggested that baricitinib therapy when started in an early phase of moderate COVID-19 disease (7 days from symptom onset) may cause low number of ICU admissions and deaths. STOP-COVID trial has provided further evidence that tofacitinib can be used in the management of COVID-19 pneumonia especially in patients who are on non-invasive ventilation with median time from symptom-onset to randomisation of 10 days.[8]

Three patients were followed-up for 14 days, during which markers of disease severity such as CRP, NLR, P/F ratio and FiO2 requirement improved significantly. Cantini *et al*.[9] have showed that all laboratory, clinical and respiratory parameters (P/F ratio, SpO2, CRP, IL6 and lymphocyte count) have significantly improved at 1 and 2 weeks of baricitinib administration.

CONCLUSIONS

In conclusion, JAK inhibitors such as tofacitinib can be used in the treatment of severe COVID-19 disease. Ongoing randomised controlled trials will provide better insight on its efficacy.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Submitted: 02-Sep-2021
Revised: 07-Oct-2021
Accepted: 10-Oct-2021
Published: 28-Oct-2021

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Access this article online	
Quick response code	Website: www.ijaweb.org
	DOI: 10.4103/ija.ija_817_21

How to cite this article: Panda R, Singh P, Kodamanchili S, Anand A. Tofacitinib as a novel therapy in COVID-19 acute respiratory distress syndrome. Indian J Anaesth 2021;65:174-6.