Safety of an immunomodulator *Mycobacterium* w in COVID-19

Sir,

Coronavirus disease 2019 (COVID-19) pandemic is associated with a high mortality, especially in those with severe pneumonia. Patients with COVID requiring intensive care unit (ICU) admission have higher cytokine levels compared to those who do not need ICU care.[1] Even among patients admitted to ICU, those discharged from hospital had lower cytokine levels compared to those who died.[2] An immunomodulator may thus be of potential benefit in managing these critically ill COVID patients. The Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R) and the World Health Organization have identified adjuvant therapy as one of the key areas of research to save lives of patients infected with COVID-19.[3] A heat-killed *Mycobacterium* w (Mw), originally developed as an immunomodulator for leprosy, which acts through the toll-like receptors (TLRs) pathway and enhances the host-T cell responses.[4] We have previously shown the benefit of Mw in patients with severe sepsis.[5] Herein, we describe the safety of Mw in four cases of severe COVID treated with this immunomodulator [Table 1].

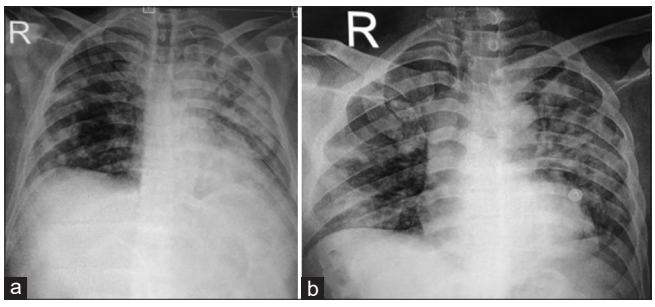

Figure 1: Chest radiograph anteroposterior view of one of our patients demonstrating consolidation and infiltrates in the left upper zone at baseline (a) that improved at day 7 of admission to hospital (b)

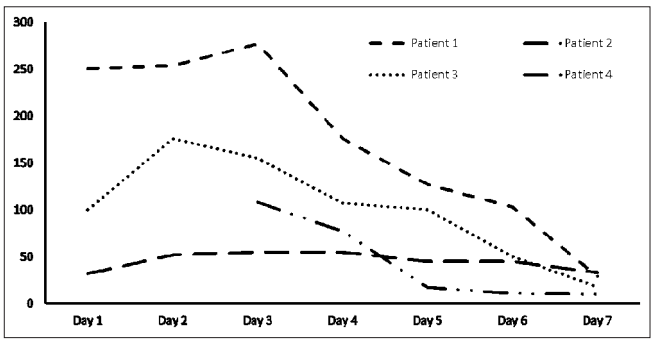

Figure 2: Trend of C-reactive protein during hospital stay

Table 1: Details of patients who received *Mycobacterium* w vaccine along with standard medical care

Days in hospital	Patient 1							Patient 2						Patient 3					Patient 4			
	1	2	3	4	5	6	7	1	2	4	5	6	7	1	2	3	4	7	1	2	3	7
Hemoglobin (g/dL)	13.6	13.2	12.4	12	11.6	11.6	11.8	12.7	12.8	13	13.3	14.5	14.8	12.4	11.8	11.3	10.9	13.3	12.9	13.3	13.4	13
TLC (cells/μL)	15,200	14,800	13,800	14,900	12,900	12,600	8500	14,000	11,500	11,700	12,400	10,700	8600	7000	7500	8900	10,000	6400	4300	6400	5600	4300
Neutrophils (%)	96.6	94.1	95.5	94.9	91.4	91.9	76	90	87.4	80.2	78	79	74	80.6	82.7	82	82	84	80	84.9	81	66
Lymphocytes (%)	2.6	3.7	3.5	3.1	4.3	4.3	13	4	6.2	7.1	7.6	9.7	12	14.6	11.7	14	10.8	10	13.7	10.1	13	24
Eosinophils (%)	0.4	0.3	0.2	0	2.2	1.6	3.2	0.1	1.2	4.7	6.4	5.3	5	0.3	0.9	1.4	2.7	4	0.7	0.7	1.6	2
Platelet count, cells/μL ($\times 10^9$)	510	507	513	528	507	513	532	243	289	381	411	454	537	112	299	247	348	495	189	204	221	289
CRP (mg/L)	251	254	277	176	127	103	29	244		108	77	17.4	10.9	100	176	155	107	18	32	52	55	33
Procalcitonin (ng/mL)	0.02	0.03	-	-	-	-	0.01	0.09	0.07	0.2	-	-	0.04	0.08	0.08	-	-	-	-	0.03	-	0.03
FiO_2	0.6 (RBM)	0.5	0.3	0.28	0.24	0.24	0.21	0.36	0.36	0.28	0.24	0.21	0.21	0.5	0.4	0.28		0.21	0.28	0.24	0.24	0.21
SpO_2	89	94	94	94	95	98	98	93	94	96	94	94	93	85	94	94	94	95	94	94	97	98
PaO_2:FiO_2 ratio	170	200	250	250	280	300	300	220	280	290	300	330	273	200	220	221	250	300	221	250	263	300
RR	40	35	35	35	30	20	18	35	30	22	20	19	25	35	25	20	20	20	32	25	25	20
D-dimer	3619	1799	1795	2033	1586	-	1081	428	422	333	309	690	710	289	249	317	339	126	127	172	550	590
CKMB	35	65	47					71						44					50			
AST (U/L)	207	225	92	110	111	71	76	32	28	27	24	29		36	34	34	43	51	57	43	49	49
ALT (U/L)	236	259	156	156	156	131	125	32	39	34	32	39		26	30	30	36	69	88	54	55	56
SAP (U/L)	97	102	86	100	123	122	115	114	107	96	86	83		82	89	105	125	147	130	43	39	40
S. cr (mg/dL)	1.1	1.2		0.7	0.7	0.7	0.7	0.8	0.7	0.8	0.8	0.8		0.5	0.5	0.5	0.4	0.4	1.2	0.8	0.9	0.9
Albumin (g/dL)	3.2	3.1	2.6	2.6	2.6	2.7	2.7	3.2	3.1	3	2.9	3.22		3.4	3.4	3.3	3	3.3	4	3.8	3.6	3.4
Adverse event due to Mw			Mild erythema at injection site					None								Mild erythema at injection site					None	

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CKMB: Creatine kinase–myocardial band, RBM: rebreathing mask, RR: Respiratory rate, SAP: Serum alkaline phosphatase, S. cr: Serum creatinine, SPO_2: Peripheral capillary oxygen saturation by pulse oximeter, FiO_2: Fraction of oxygen in inspired air, PaO_2: Partial pressure of oxygen in arterial blood, TLC: Total leukocyte count, *Mw: Mycobacterium* w, CRP: C-reactive protein

All the four patients presented with a history of fever, myalgia, and dyspnea and had a history of contact with a patient of COVID-19. At presentation, patients had tachypnea [Table 1] and were hypoxemic at room air. Complete blood count showed neutrophil predominant leukocytosis and lymphocytopenia [Table 1]. The serum D-dimer levels were elevated in all patients at presentation and were >500 ng/mL in one patient. C-reactive protein (CRP) levels were also elevated in all patients, suggesting a hyperinflammatory state. Creatine kinase–myocardial band was elevated in all patients; however, transthoracic echocardiography did not reveal any abnormality. As per our institutional protocol, all patients received standard medical care comprising oral paracetamol (for fever), oral proton-pump inhibitor for stress ulcer prophylaxis (pantoprazole 40 mg/day), and low-molecular-weight heparin for deep venous thrombosis prophylaxis (enoxaparin 1 mg/kg, once daily). Therapeutic anticoagulation (enoxaparin 1 mg/kg, twice daily) was given in patients who had D-dimer levels >500 ng/mL. We used antibiotics (azithromycin or ceftriaxone) if patients had a total leukocyte count of >11,000 cell/μL, procalcitonin >0.5 ng/mL, or if they had hypotension (mean arterial blood pressure <65 mmHg). We did not use hydroxychloroquine in any of these patients. We also used intradermal Mw (0.3 mL/day [0.1 mL contains 0.5 × 10^9 heat-killed Mw] for 3 consecutive days, Immuvac, Cadila Pharmaceuticals, Ahmedabad, India) in addition to standard medical care.

The treatment protocol resulted in clinical and radiological improvement in all the cases [Figure 1]. The CRP levels improved gradually [Figure 2], and all the patients could be successfully managed without the need for mechanical ventilation. Importantly, Mw did not cause any adverse events, similar to our previous experience in patients with severe sepsis.[5]

Based on our preliminary experience, we believe that adjunctive Mw is safe in patients with severe COVID-19 infection. However, the efficacy needs to be evaluated in a future randomized controlled trial (clinicaltrials.gov: NCT04347174).

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Conflicts of interest
There are no conflicts of interest.

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