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Original Research Article

Effect of mycobacterium on clinical and laboratory parameters in COVID-19

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ABSTRACT

Background: Initial wave of COVID-19 created a massive health crisis everywhere including India due to a limited understanding of the disease pathology. Most physicians used sepsis as a prototype to manage COVID-19, as there are similarities. Heat-killed Mycobacterium w (Mw) (inj. sepsivac®) is a known immunomodulator approved for the treatment of gram-negative sepsis. Our purpose of this observation is to evaluate the safety and efficacy of Inj sepsivac in COVID-19 patients along with the standard of care.
Methods: Total 49 patients data with reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed critically ill COVID-19 patients who were admitted at Velocity Hospital, Surat between May 4, 2021, and May 18, 2021 were evaluated. They were evaluated for vital parameters like pulse, blood pressure, respiratory rate and temperature as well as laboratory parameters like ALT, S IL-6, serum creatinine and CRP during three follow-up visits after the administration of Inj sepsivac. Further follow-up was done until the discharge/death of the patient.
Results: There was a statistically significant reduction of mean CRP observed compared to the baseline value during all follow-up visits. The rest of the laboratory parameters as well as clinical assessment did not show any significant change as compared to baseline. Out of 49, two patients died (mortality rate; 4%). Inj. sepsivac was found to be well tolerated without any systemic side effects.
Conclusions: The addition of Mw to the standard of care can improve laboratory parameters like CRP, without any safety concerns. These results should be further substantiated by larger randomised clinical trials.

Keywords: COVID-19, CRP, D-dimer, Mycobacterium w, RT-PCR

INTRODUCTION

On March 11, 2020, WHO declared COVID-19, which posed a significant challenge to human health as a pandemic. The highly contagious nature of the virus spread it rapidly from human to human and aggravated the situation.[1]

SARS-CoV-2 led to the death of close to 69 lacs of people out of 76 crore infections caused worldwide as of July, 2023 (WHO). Clinical manifestations range from fever, dry cough to shortness of breath, acute respiratory failure to death. Because of the need for hospitalization, COVID-19 has become not just a public health issue but also affected the economy.[2]

Majority of the physicians have used sepsis as a prototype to understand severe COVID-19 pathogenesis. This is due to hyper-cytokinemia, associated with severe COVID-19.[3] In addition to that, the early immunological picture of COVID-19 shares many similarities with bacterial sepsis.[4] This allows us to hypothesize the role of

immunomodulation as potential therapeutic approach for COVID-19.

Inj. sepsivac® (heat-killed mycobacterium w (Mw), Cadila Pharmaceuticals Limited, Ahmedabad, Gujarat, India) was developed originally to treat leprosy, non-small cell carcinoma of the lung along with chemotherapy, and gram-negative sepsis. Heat-killed mycobacterium w is proven to modulate T cell responses of the host cells by acting through the toll-like receptors (TLRs) pathway and is a known immunomodulator.[5]

With the present observational study, we have evaluated the safety and effectiveness of Inj sepsivac in COVID-19 patients at our hospital.

METHODS

This retrospective observational cohort study was carried out on the patients diagnosed with COVID-19 by RT-PCR and consecutively admitted to tertiary care centre at Surat (Gujarat) between March 2021 and June 2021. This being a retrospective study, timeframe and sample size were not predetermined. Case files of 49 the patients admitted in the hospital with COVID-19 infection was extracted.

Inclusion criteria

All COVID-19 patients admitted to the hospital, and received Mw along with the standard of care treatment, were included in this study.

Inclusion criteria

Patients who did not receive Inj. sepsivac, pregnant woman, lactating woman and children less than 18 years of age were excluded from the study.

Clinical and laboratory were evaluated at baseline. Levels at the time of admission were considered as baseline and levels at discharge/dead status were considered as last.

Our primary objective was to observe the change in clinical parameters (respiratory rate, SpO^2), and laboratory parameters (CRP, ALT, s. creatinine) of all the patients from baseline to various time points (three follow-ups until discharge/death of the patient) after administration of study drugs.

We evaluated patients for vital signs as well as various laboratory parameters including haematology, ALT, S IL6, s. creatinine and CRP at baseline and during three follow-ups until discharge/death of the patient.

All the patients on admission received standard treatment as per institutional protocol, which included prophylactic antibiotic (azithromycin), antipyretic (paracetamol), zinc, vitamin C supplementation, and corticosteroid (dexamethasone/methylprednisolone). Inj sepsivac was administered as 0.3 ml intradermal, (0.1 ml X 3 injections at three different sites) for 3 consecutive days.

All statistical analyses were performed using Statistical Analysis Software (SAS), version 9.4 or above and MS Excel. Changes from baseline to end-of-study visit values for efficacy variables at various time points were analysed using a two-sample t-test and a p-value of less than 0.05 ($p<0.05$) was considered as statistically significant. Analysis was performed on the data available at different time points.

RESULTS

Data of total 49 patients was collected and analysed series of demographic details. The mean age of all cases was 57.55 years (26-85 years) of which 36 (73.5%) were male and 13 (26.5%) were female (Table 1).

Two out of 49, (2/49) patients died during the course of treatment which shows 4.1% mortality. The laboratory parameters like haemoglobin, total leukocyte count, neutrophil, lymphocyte, platelet count, serum IL6, ALT and Serum Creatinine did not show any significant changes throughout the study. No significant change in the vital signs (pulse, BP, temperature and respiratory rate) was observed (Table 2). N in each table represent number of patient's data available at baseline and at subsequent visits.

Table 1: Demographic details.

	Total cases (N)	49
Age (in years)	Mean	57.55
	SD	14.11
	Range	26.00-85.00
Gender (%)	Male	36 (73.5)
	Female	13 (26.5)

However, there was a statistically significant reduction observed in the value of mean CRP during the entire observation. The mean CRP on admission was 89.86±51.30 that decreased significantly during the study and was found to be 63.27±49.93 at 1st follow-up, 48.66±53.85 at second follow up and 48.11±35.11 at third follow-up visit (Table 3).

This result reveals that, at admission mean CRP levels were 89.86 mg/L, after therapy at the end of First follow up mean CRP showed a significant fall from admission. Same trends were observed till 3rd follow up from admission.

There were no Mw-related adverse effects observed in any of the study patients.

Table 2: Change in laboratory parameters from baseline.

Parameters	Mean values (X±SD)							
	N	On admission	N	1st follow up	N	2nd follow up	N	3rd follow up
Hemoglobin (g/dL)	46	13.04±1.63	27	12.72±2.05	32	13.14±1.78	21	13.01±2.13
TLC (/cmm)	46	10845.22± 18614.06	27	10718.52± 7111.75	32	12493.75± 7400.35	21	15661.90± 6182.35
Neutrophils (%)	43	82.26±7.56	25	78.68±10.14	29	80.76±7.73	20	82.75±7.25
Lymphocytes (%)	43	10.30±5.73	25	13.44±8.78	29	11.34±5.73	20	10.10±4.63
Eosinophils (%)	43	1.35±0.65	25	1.44±0.65	29	1.55±0.78	20	1.35±0.49
Platelet count (/cmm)	45	205911.11± 86028.49	27	249000.00± 129931.34	32	262593.75± 134729.09	21	270714.29± 126108.74
S IL-6	01	0.54±0.00	01	0.46±0.00	01	0.48±0.00	-	-
ALT	39	37.56±23.34	07	49.74±43.91	03	34.68±28.71	-	-
Serum creatinine	37	1.31±0.41	12	1.28±0.38	10	1.66±0.65	07	1.45±0.55

Table 3: Changes in mean CRP levels from baseline.

Duration	N	Mean CRP (mg/L) (X±SD)
On admission	46	89.86±51.30
1st follow up	33	63.27±49.93
2nd follow up	35	48.66±53.85
3rd follow up	26	48.11±35.11
Mean diff. (on admission-1st follow up)	33	*-27.41±47.18
Mean diff. (on admission-2nd follow up)	35	*-41.64±56.84
Mean diff. (on admission-3rd follow up)	26	*-39.56±62.90

By student t test, * Significant

DISCUSSION

This was the retrospective observational study of compassionate usage of Mw in 49 patients for the treatment of COVID-19 patients. Cytokine storm is the umbrella term that includes several immune dysregulation disorders characterized by constitutional symptoms, systemic inflammation, and multi-organ dysfunction and, if not adequately treated, leading to multi-organ failure.[6] The mechanism of "cytokine storm" or "cytokine cascade" apart from COVID-19 is well established in the pathophysiology of bacterial sepsis that very clearly describes that COVID-19 and bacterial sepsis share many similarities in cytokine profiles (Remy KE et al, 2020).[4,7]

Mw which is approved in India to treat gram-negative sepsis is acting through multiple mechanisms and is reported to have immunomodulatory potential.[8] Mw is a potent TLR2 agonist and poly TLR antagonist (4,5,7,9) and also a potent inducer of Th1 response.[8-10] The reduction of dendritic cell function is observed in the COVID-19 infection, and it suggests that strategies that reverse this negative effect might be useful in COVID-19 therapy.[11] Mw activates dendritic cells through TLR2 and increases dendritic cell survival, translating into a reduction in the viral load.[12]

Sehgal IS et al demonstrated the compassionate usage of Mw in COVID-19 patients to stop the progression of the disease and faster recovery. They showed clinical and radiological improvement in all the cases, and Mw did not cause any adverse events.[13]Another retrospective observational study on 117 patients of COVID-19 showed that the usage of Mw was associated with rapid recovery and improvement in patient's condition. CRP and IL-6 levels were also found to decrease in that study.[14] In the present study, we observed that the mean CRP level showed a consistent decline after Mw treatment which was maintained till discharge. This result was consistent with the previous study by Ingale et al, which also showed that inflammatory markers started reducing soon after the single dose of Mw.[14]

Usage of Mw in COVID-19 patients was found to be well tolerated and safe, without any systemic side effects.

Limitations of our study includes absence of comparator arm, small sample size and absence of ethics committee approval as this is retrospective observational study.

CONCLUSION

The majority of mild COVID-19 patients improve within a few days, however, it is of utmost importance to stop the progression to more severe disease. Management of cytokine storm is seemingly an effective way for such patients. Usage of Mw in COVID-19 patients led to significant improvements in CRP without any major safety concerns, which might indicate the efficacy of Mw in COVID-19. These results should be further substantiated by larger randomised clinical trials.

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REFERENCES

1. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science. 2020;368(6490):489-93.
2. Ayati N, Saiyarsarai P, Nikfar S. Short and long term impacts of COVID-19 on the pharmaceutical sector. DARU J Pharmaceut Sci. 2020;1-7.
3. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
4. Remy KE, Brakenridge SC, Francois B, Daix T, Deutschman CS, Monneret G, et al. Immunotherapies for COVID-19: lessons learned from sepsis. Lancet Resp Med. 2020;8(10):946-9.
5. Sepsivac [package insert]. Ahmedabad, India: Cadila Pharmaceuticals Limited; 2019.
6. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transpl. 2019;25(4):625-38.
7. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39:517-28.
8. Desai NM, Khamar BM. Immunotherapy for tuberculous pericarditis. N Engl J Med. 2014;371(26):2531-5.
9. Power CA, Wei G, Bretscher PA. Mycobacterial dose defines the Th1/Th2 nature of the immune response independently of whether immunization is administered by the intravenous, subcutaneous, or intradermal route. Infect Immun. 1998;66(12):5743-50.
10. Kumar P, Tyagi R, Das G, Bhaskar S. Mycobacterium indicus pranii and Mycobacterium bovis BCG lead to differential macrophage activation in Toll-like receptor-dependent manner. Immunol. 2014;143(5):258-68.
11. Campana P, Parisi V, Leosco D, Bencivenga D, Della Ragione F, Borriello A. Dendritic cells and SARS-CoV-2 infection: still an unclarified connection. Cells. 2020;9(9):2046.
12. Kumar P, John V, Marathe S, Das G, Bhaskar S. Mycobacterium indicus pranii induces dendritic cell activation, survival, and Th1/Th17 polarization potential in a TLR-dependent manner. J Leukoc Biol. 2015;97(3):511-20.
13. Sehgal IS, Bhalla A, Puri GD, Yaddanapudi LN, Singh M, Malhotra P, et al. Safety of an immunomodulator Mycobacterium w in COVID-19. Lung India. 2020;37(3):279-81.
14. Ingale A, Ingale F, Kunwar B, Ahmed S, Salvi K, Chavan V, et al. Role of Mycobacterium w for the treatment of COVID-19: an observational study. J Assoc Physicians India. 2021;69(1):19-22.

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