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Systematic Review

A systematic review of reactivation of tuberculosis due to use of corticosteroids for COVID-19 treatment between January 2020 to January 2022

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ABSTRACT

Coronavirus-19 disease became a matter of concern for the whole world and WHO declared it as pandemic on 11 March 2020. Soon a number of clinical trials started to check for the treatment modalities, to compare their efficacy and safety. Out of which corticosteroids in trials showed decrease in mortality in severe COVID-19 patients. However existing diseases such as tuberculosis still remains a leading killer and matter of concern. One out of four individuals are said to be having tuberculosis (mostly in inactive form or latent form) but there remains a threat of reactivation of tuberculosis in presence of risk factors such as corticosteroid administration as it causes immunosuppression. This is a retrospective observational study on reactivation of tuberculosis due to corticosteroids used in COVID-19 treatment. Most commonly given corticosteroid was found to be dexamethasone and the duration of corticosteroid therapy ranged between 5 to 12 days. Majority of patients (5 out of 6) showed reactivation of tuberculosis within 30 days of starting of corticosteroid therapy and most common co-morbidity associated was found to be diabetes mellitus followed by hypertension in such patients. Symptoms of 4 out of 6 patients resolved after starting of anti-tubercular therapy.

Keywords: COVID-19, Tuberculosis, Reactivation, Corticosteroids, Latent tuberculosis

INTRODUCTION

The WHO declared COVID-19 as pandemic on 11 March 2020.[1] About 505,817,953 confirmed cases and about 6,213,876 deaths have been reported worldwide due to COVID-19 infection as of 22 April 2022.[2] The infected person may present with symptoms such as fever, cough, fatigue, dyspnoea, etc. Dyspnoea is a suggestive of severe infection which is often related with cytokine storm.[3] Trials like recovery trial stated reduction in mortality by one-third in ventilated patients (p=0.0003) and by one-fifth in patients on oxygen only (p=0.0021) by low dose corticosteroids (CST) (like dexamethasone) in severe cases. Dexamethasone significantly reduced 28-day mortality and need for mechanical ventilation in severe cases.[4]

Hence, WHO recommended use of CST for severe cases of COVID-19 considering two meta-analyses pooling data from eight randomized trials including recovery trial.[5]

However, the world should not forget about some deadly diseases like tuberculosis (TB) which still remains one of the top infectious killer in the world. About 1.5 million people died from TB in the year 2020 alone and about one-quarter of total world population is infected with the TB bacteria (*Mycobacterium tuberculosis*). However, most of the people does not develop active disease rather the bacteria lives inside body without causing any symptoms.[6] But under certain conditions like immunosuppression there can be reactivation of TB and a number of studies have been done to correlate between immunosuppression by use of CST and reactivation of TB. A similar study

showed significant increase in risk of pulmonary TB with corticosteroid use.[7]

The use of CST in case of severe COVID-19 infection have shown promising results by showing reduction in 28-day mortality and reducing need of mechanical ventilation but at the same time the long-term effects are unclear and CST can predispose the patient to opportunistic infections or even exaggerate existing conditions by their immunosuppressive actions. The aim of the study was to determine the reactivation of TB by CST in COVID-19 era.

METHODS

This was a retrospective observational study. A search was carried out with the keywords 'COVID-19', 'coronavirus', 'SARS-Cov-2', 'TB', 'CST', 'corticosteroid', 'reactivation' arranged in different combinations on the PubMed central (PMC) database with the custom time range of 01 January 2020 to 01 January 2022. The references of relevant reviews and retrieved articles were also screened for potentially eligible articles. A total of 324 records were screened against Title and Abstract and 12 records were selected for full text analysis. Three records were found to be duplicate and were excluded. 6 records were found to be eligible for the study and used in the synthesis of the article.

RESULTS

Following a thorough literature search, we included 6 case reports in our study. The age of the patients ranged between 44 years to 71 years out of which all the six patients were male.

All the six patients tested positive for COVID-19 PCR. 4 out of 6 patients presented with fever as one of the chief complaints. One patient presented with dyspnoea and 85% oxygen saturation at room air. 3 out of 6 patients had significant radiological finding when presented to the hospital. CST were given in all the 6 patients and most commonly given corticosteroid was dexamethasone (administered in 3 patients out of 6) followed by methylprednisolone (administered in 2 patients out of 6) and betamethasone (administered in 1 patient) and prednisolone (administered in 1 patient).

The duration of corticosteroid therapy ranged between 5 days to 12 days. One patient was also started on pulse corticosteroid therapy for 3 days (1000 mg methylprednisolone daily). All the six patients had increased progression or reactivation of TB within 13 days to 3 months after administration of CST. 5 out of 6 patients had reactivation of TB within 30 days of corticosteroid therapy (10 days, 13 days, 22 days, 30 days, 30 days). 2 patients were also administered tocilizumab once during the treatment.

Diabetes was the most common co-morbidity found in 5 patients followed by hypertension in 3 patients. Other co-morbidities included atrial fibrillation, history of stroke, renal failure and dyslipidaemia. 4 patients after testing positive for *Mycobacterium TB* and starting ATT recovered while 1 patient died and outcome of 1 patient is not known (Table 1).

Table 1: Cases of reactivation of tuberculosis due to use of CST for COVID-19 treatment between January 2020 to January 2022.

S no.	Reported by	Age (years) /gender	CSD used	Dose and time	Reactivation of TB	Tocilizumab co-administration	Co-morbidities
1	Garg et al (2020)	44/M	Dexamethasone	20 mg daily for 12 days	Within 22 days after starting CST	800 mg once	Diabetes mellitus, hypertension, atrial fibrillation
2	Sasson et al (2020)	44/M	Dexamethasone and methyl-prednisolone	20 mg dexamethasone for 2 days followed by 10 mg dexamethasone for 6 days and 1 dose of methylprednisolone (40 mg) (Total days= 8)	Within 30 days after starting CST	400 mg once	hypertension, diabetes mellitus, and a previous stroke secondary to a left atrial thrombus
3	Pozdnyakov et al (2021)	64/M	Methyl-prednisolone	40 mg for 5 days and 1000 mg for 3 days with time interval of 26 days	Within 30 days after starting CST	No	Diabetes mellitus, hypertension, dyslipidaemia and acute renal failure

Continued.

S no.	Reported by	Age (years) /gender	CSD used	Dose and time	Reactivation of TB	Tocilizumab co-administration	Co-morbidities
4	Wang-Da Liu et al (2021)	46/M	Betamethasone	6 mg for 10 days	Within 13 days after starting CST	No	Not present
5	Younes et al (2021)	71/M	Dexamethasone	Unknown dose for 10 days	Within 3 months after starting CST	No	Diabetes mellitus
6	Gandotra et al (2021)	47/M	Prednisolone	40 mg for 7 days followed by 10 mg daily. Total days= 10	Within 10 days after starting CST	No	Invasive pulmonary aspergillosis and hemophagocytic lymphohis-tiocytosis with previous history of diabetes

DISCUSSION

Garg et al reported a case of 44-year-old male presenting with cough and fever for 5 days who tested positive for COVID-19 PCR test. The patient had other co-morbidities including hypertension, diabetes mellitus and atrial fibrillation. Chest radiograph showed bilateral patchy ground glass opacities. The patient was treated with anti-malarial drug and other antibiotics. Within 3 days after hospitalization the patient was started on dexamethasone (20 mg IV daily) therapy as patient's condition deteriorated and patient required intubation. Blood investigations revealed high levels of inflammatory markers like CRP for which the patient was administered tocilizumab (800 mg IV) once. Patient's condition improved and was extubated within 15 days of hospitalization. The patient developed fever after 10 days and on radiological investigation showed consolidation in lung with multiple air spaces. The sputum of patient tested positive for acid fast bacilli (AFB) and culture showed *Mycobacterium tuberculosis*. The patient was started on anti-tubercular treatment (ATT) and discharged after 51 days of hospitalization.[8]

Sasson et al reported a case of 44-year-old male presenting with cough and fever for 5 days after being transferred from another hospital. The patient was already intubated and also had co-morbidities including hypertension, diabetes mellitus and history of stroke. Chest radiograph showed patchy ground-glass opacities. The patient tested positive for COVID-19 PCR. The patient was started on antibiotics and anti-malarial drug and was shifted to intensive care unit (ICU) as the condition worsened. Dexamethasone was started and administered for 8 days with a cumulative dose of 100 mg and single dose of methylprednisolone (40 mg) was also administered. The patient was also administered 400 mg of tocilizumab. The patient was started on antibiotics after new bouts of fever and leukocytosis. The radiological investigation by day 35 showed area of consolidation in lung with increased cavitation. Patient's sputum was found to be positive for AFB. The patient was started on ATT.[9]

Pozdnyakov et al reported a case of 64-year-old man with severe COVID-19 symptoms including dyspnea and oxygen saturation of 85% on room air. The patient had other co-morbidities including hypertension, diabetes mellitus and dyslipidemia. The patient tested positive for COVID-19 PCR. The patient was administered 40 mg methylprednisolone for 5 days as patient had respiratory distress. Antibiotics were also administered for ventilator-associated pneumonia. After 21 days of methylprednisolone administration, the patient developed fever and failed to respond to antibiotics and antifungals. A pulse steroid with IV methylprednisolone (1000 mg for 3 days) was administered 5 days after the onset of new bout of fever. The patient failed to respond to pulse steroid therapy. Patient's sputum tested for AFB came out to be positive and was immediately started on ATT. Within 47 days of hospitalization the patient died as the family agreed to treatment withdrawal.[10]

Liu et al reported a case of 46-year-old male presenting with fever, cough, malaise, sore throat and chest tightness. Chest radiograph showed infiltrations in both lungs. The patient tested positive for COVID-19 PCR. The patient was started on antibiotics because of positive result for pneumococcal antigen in urine. Sputum was examined for AFB which came out to be negative. The patient was started on betamethasone (6 mg daily for 10 days) and patient showed improvement of oxygenation and patient was discharged within 18 days of hospitalization. Liu et al patient complained of dyspnea on exertion after discharge and chest radiograph showed increased lung infiltration. The patient was re-admitted and sputum culture reports were positive for *Mycobacterium TB*. The patient was started on ATT and symptoms resolved soon.[11]

Younes et al and colleagues reported a case of 71-year-old male who presented with dyspnea, fever and cough. Chest

radiographs showed diffuse nodular opacities with dense consolidation associated with areas of cavitations in lungs. The patient had diabetes mellitus. The patient was tested positive for COVID-19 3 months back for which he was started on dexamethasone and remdesivir for 10 days. Bronchial washing PCR came out to be positive for *Mycobacterium TB*.[12]

Gandotra et al reported a case of 47-year-old male presented with fever and dry cough for two weeks. The patient tested positive for COVID-19. The patient had other co-morbidities including diabetes (new-onset diabetes after transplant), history of liver transplant, history of recurrence of hepatocellular carcinoma which was managed by microwave ablation (MWA) and doxorubicin drug-eluting bead trans arterial chemoembolization (DEB-TACE).

The patient was on metformin therapy for diabetes and sirolimus therapy for post-transplant immunosuppression. His immunosuppression was shifted from sirolimus to prednisolone (a total of 280 mg orally in 1 week). Within 10 days of the corticosteroid therapy the patient developed shortness of breath along with fever and fatigue. The patient tested negative for COVID-19. Examination and investigations suspected *Hemophagocytic lymphohistiocytosis* which was later confirmed by bone marrow biopsy. Sputum examination revealed presence of AFB on Ziehl-Neelson stain while the sputum culture grew *Aspergillus flavus*. The patient was managed with intravenous immune globulin for HLH, liposomal Amphotericin B and ATT.[13]

CONCLUSION

From the study and the case analysed we found that the cases of reactivation of TB after corticosteroid therapy may present similarly to COVID-19 with common symptoms such as fever and hence becomes very important to diagnose and differentiate both entities correctly and timely. As CST are used in moderate to severe cases of COVID-19, we may see the reactivation of TB from CST more commonly in moderate to severe case or in complicated cases and hence it becomes more important to be prompt in diagnosing and starting the treatment in such cases. For the incidence of reactivation of TB and its association with co-morbidities and medications, further additional clinical studies are required.

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