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Original Research Article

Treatment outcome in new smear positive pulmonary tuberculosis patients with and without immunosuppression on RNTCP regimen: a comparative observational study

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ABSTRACT

Background: Immune status of a patient influences the susceptibility, clinical presentation of tuberculosis and its treatment outcome. Some of the most common conditions associated with immune deficiency includes, human immunodeficiency virus (HIV) infection, diabetes and chronic steroid therapy for any underlying diseases.
Methods: A cohort study, enrolled patients with tuberculosis alone (n=51) and those with tuberculosis and immunosuppressed state (patients with HIV, diabetes and those on steroid therapy, n=97).
Results: All patients received Directly Observed Treatment Short course (DOTS) regimen implemented through RNTCP. Among the immunosuppressed patients, 32 were HIV patients, 45 of them were diabetic and 20 received chronic steroid therapy. All immunocompetent patients (control) were totally cured but 62.5% and 88.9% of HIV and diabetic patients in the immunosuppressed group were cured. Mortality was high in the immunosuppressed group (18.75% in HIV, and 11.11% in diabetic group). The grade of sputum smear had significant influence on the treatment outcome after adjusting for death and default ($p>0.05$). After intensive phase, the smear conversion rate were 86.27% in the control group,37.5% in the HIV patients, 22.22% in diabetics and 55% among chronic steroid use. The mortality and cure rate among those who received treatment for diabetes mellitus is comparable with that of immunocompetent group. Treatment prolongation was required for patients in the immunosuppressed group (62.5% in HIV group, 77.7% in diabetes group and 45% in chronic steroid users group).
Conclusions: Immunosuppression was a risk factor for increased morbidity and mortality among new smear positive pulmonary tuberculosis patients. Prolonged DOTS regimen requires long-term close follow-up of patients who are immunocompromised.

Keywords: Chronic steroid use, DOTS, HIV, Immunocompromised, Immunosuppression, Immune deficiency Tuberculosis

INTRODUCTION

Tuberculosis is one of the most life-threatening infections, which has turned into a global epidemic. According to the World Health Organization (WHO), nearly one-third of the 34 million people living with HIV worldwide have latent tuberculosis. Persons co-infected with tuberculosis and human immunodeficiency virus (HIV) is 21-34 times more likely to develop active tuberculosis disease than those without HIV.[1] Thus, an increasing trend in tuberculosis among HIV patients presents as a massive challenge to global tuberculosis control.[2] Simultaneously, the incidence of diabetes is also turning into an epidemic. The impact of diabetes on

tuberculosis is related to the complex interaction between nutrition, obesity, diabetes, and tuberculosis. Tuberculosis develops most often in those with poor diabetic control. The prevalence of tuberculosis was two-times in those with diabetes when compared to the general population.[3] Nearly 15% of the tuberculosis cases could be attributed to diabetes primarily due to compromise in host defense system. Drugs that depress cellular immunity, such as corticosteroids and cytotoxic agents, also predispose patients to tuberculosis.[4] Clinical manifestations of tuberculosis vary and depend on the degree of immunodeficiency.[5] Diabetes, HIV and other conditions associated with immunosuppression is likely to influence the clinical presentation and severity of tuberculosis as well as the response to therapy. Therefore, we conducted a study to know the treatment outcome and relapse after Revised National Tuberculosis Control Program (RNTCP) treatment in immuno-suppressed and immunocompetent (controls) subjects with new smear positive pulmonary tuberculosis.

In this scenario, the present study was undertaken to compare RNTCP treatment outcome and relapse between new smear positive pulmonary tuberculosis patients on immunosuppression and those without immuno-suppression. Further, any difference in clinical features, response to treatment, and drug side effects in immunosuppressed patients as compared to those without immunosuppression were also measured.

METHODS

Patients on immunosuppression and confirmed smear positive tuberculosis were enrolled in a cohort study. Age- and sex-matched controls were selected from tuberculosis unit and enrolled into the study. Pregnant women and patients with medical conditions that are associated with immunosuppression such as hepatitis B virus infection, malignancies, transplant recipients, patients on immunosuppressant drugs are excluded from the study.

A patient was smear-positive when at least two initial sputum examinations [direct smear microscopy] were positive for acid fast bacilli. On the contrary, a patient who was declared cured or treatment completed by a physician but later returned to hospital and sputum tested positive was regarded as relapse case. Patients were regarded diabetic as per the standard guideline. National AIDS Control Organisation (NACO) protocol was used to confirm human immunodeficiency virus (HIV) positive cases.

Patients were considered to be on prolonged steroid therapy, if they received 10 mg equivalent of prednisolone per day for >2 weeks before being diagnosed with tuberculosis. Patients who remained smear-positive at 5 months or more after starting treatment were regarded as treatment failure cases. A patient is said to default when he does not take anti-tuberculosis drugs consecutively for two months or more, and who is found to be sputum smear-positive.

RESULTS

One hundred and forty eight patients were enrolled into the study, of them 51 were immunocompetent (controls) and 97 were immunosuppressed. Thirty two were HIV patients, 45 of them were diabetic and 20 received chronic steroid therapy. The study population was predominantly men (n=115 and women, n=33). Among men, 39 were in control group, 23 were HIV positive 38 patients were diabetic and 15 were on chronic steroid therapy. Out of the 33 women, 12 were enrolled in controls, 9 were HIV positive, 7 patients were diabetic and 5 were on chronic steroid therapy.

Table 1: Treatment outcome across the study population.

Groups	Cure	Default	Failure	Death
Control	51	0	0	0
HIV positives	20	3	3	6
Diabetes	40	0	0	5
Steroid users	20	0	0	0

The mean body weight was 46.5 kg, 40.4 kg, 44.4 kg, and 47.9 kg in the control, HIV positive, diabetic patients and chronic steroid users, respectively. The clinical response of different categories to treatment was assessed by weight gain at 2nd, 4th and 6th month of treatment. In each of these categories weight gain was noted among the cure group.

The general symptoms of the patients were fever, cough, chest pain, hemoptysis, and breathlessness. Out of 148 patients, 83 patients had chest pain, 118 patients had cough with sputum production and 115 people had low grade fever, especially evening rise of temperature. Patients in the control group (immunocompetent) group were totally cured. However, 62.5% and 88.9% of HIV and diabetic patients were cured. All the patients receiving chronic steroid therapy were cured of tuberculosis (Table 1).

Table 2: Treatment outcome according to the sputum grade.

Sputum grade	Cure	Default	Failure	Death
SCANTY	4	1	0	0
1+	50	1	0	1
2+	23	0	1	1
3+	54	1	2	9

Mortality was high in the immunocompromised group (18.75% in HIV, and 11.11% in diabetic group). Treatment failure was noted in 9.37% of patients in the HIV group. Default rate is also high in HIV group despite being counselled. Of the 11 dead, 9 were alcoholics.

Table 3: Treatment outcome at the end of 2 months in the study cohort.

Sputum grade	Control	HIV positives	Diabetes	Steroid users
Negative	44	12	10	11
Scanty	2	5	10	2
1+	3	7	17	4
2+	1	2	3	3
3+	1	4	3	0
Death	0	1	2	0
Default	0	1	0	0

Significant number of patients with Grade 1+, 2+, and 3+ were cured at the end of 2 months (Table 2). The grade of sputum smear had significant influence on the treatment outcome after adjusting for death and default (p>0.05). After 2 months of intensive treatment phase, sputum smear negativity was attained in 44 patients in control group (86.27%), 12 HIV patients (37.5%), 10 diabetics (22.22%) and 11 people (55%) with chronic steroid use (Table 3). Other patients required prolongation of intense treatment phase. In the control group, 7 (13.73%) patients required treatment prolongation while 62.5% in HIV group, 77.7% in diabetes group and 45% in chronic steroid users group required treatment prolongation.

Table 4: Radiological features in the study group.

Radiology features	Control	HIV positive	Diabetes	Steroid users
Nil	32	3	10	6
Unilateral parenchymal	13	3	12	5
Bilateral parenchymal	3	23	13	3
Cavity	0	0	0	1
Unilateral parenchymal + cavity	0	0	4	2
Bilateral parenchymal + cavity	2	3	6	3
U/L parenchymal + pleural effusion	1	0	0	0

After 2 months of continuous treatment phase, sputum smear was significantly faster in the immunocompetent (control, n=50) group vs. immunosuppressed group (HIV positives (n=18), diabetes (n=36), and chronic steroid users (n=17); p=0.002). At the end of continuation phase cure rate was 100% in control group. Mortality and treatment failures were substantial in immunosuppressed group. Of three failure cases, one patient received category 2 treatment and was cured; one person died immediately and another person was lost to follow-up.

Table 5: Treatment outcome in diabetic and non-diabetic group.

Treatment group	Cure	Default	Failure	Death
Non diabetic	92	3	3	5
Patients on oral hypoglycemic agents	32	0	0	6
Patients on insulin	7	0	0	0

Another important observation is the radiological features wherein bilateral lesions were more common in the immunosuppressed group (Table 4) and mortality rate high among them (p=0.02). Extra pulmonary lesions were noted in four patients, two of whom were cured and two died. The mortality and cure rate among those who received treatment for diabetes mellitus is comparable with that of immunocompetent group (Table 5). There were no reports of relapses during the 6 months of follow-up. However, mortality was higher among subjects who failed to adhere to regular treatment [55.5%] as compared to those who adhered to treatment [4.3%]. CD4 count was less than 100 among the 6 HIV patients who died. No significant drug side-effects were noted among both the study groups during the study period.

DISCUSSION

Immunocompromised patients are more vulnerable to infections including tuberculosis. Immunosuppression has significant influence on the incidence and treatment outcome of tuberculosis. The classic symptoms of tuberculosis may be absent in those who are additionally immunosuppressed. The common clinical presentations of tuberculosis among immunosuppressed patients (patients with HIV or diabetes) included cough with or without sputum, fever and loss of appetite and/or weight.[6] In our study, immunocompetent and immunosuppressed patients presented with fever, cough, chest pain, weight loss, hemoptysis, and breathlessness. Chest pain, cough with sputum production and low-grade fever, was the frequent symptoms. From our data, the trend of TB was significantly higher among males in both groups. There is no clear data on the gender-wise prevalence of tuberculosis in immunocompromised patients; however mortality due to tuberculosis and HIV is high among men

than women.[1]Smoking and alcohol consumption are known to worsen the outcomes in pulmonary tuberculosis.[7,8] However, in our current, we could not see any significant effect of smoking and alcohol consumption. Of note, 9 out of 11 patients who died were alcoholics. Perhaps alcohol intake might have also contributed to added mortality in these subjects by accelerating immunosupression. Treatment outcome showed an increase in mortality rate and treatment failure in the immunosuppressed group when compared to control group. Among HIV-positive patients with tuberculosis, the mortality was higher than in those without HIV.[9] High mortality in HIV-positive patients with tuberculosis was attributed to CD4(+) lymphocyte depletion.[9] In present study also, the CD4 count was <100 in all the six HIV patients who died.

In this study, sputum smear-conversion rate was lower at the end of the study in the immunosuppressed group when compared to immunocompetent. A statistically significant decrease in cure rate was reported as the initial smear grading increased (p=0.01).[10] A similar trend was also observed in present study. A study reported that smear conversion occurred in 58%, 61%, and 62% of patients in control group (only pulmonary tuberculosis), diabetes and HIV, respectively.[11] In present study, the smear conversion rate were 86.27% in the control group, 37.5% in the HIV patients, 22.22% in diabetics and 55% among chronic steroid use. Delayed sputum conversion remains an area of concern because of the possibility of failure or relapse. Of the three failure cases in HIV group, one patient was lost during follow-up, one patient was cured after treatment prolongation and one patient died. The need for prolongation of intensive phase is highly significant for immunosuppressed patients as the sputum smear conversion rates to negative are significantly slower in the immunocompromised group (p=0.0003). In our study, Directly Observed Treatment Short course (DOTS) regimen implemented through RNTCP was successful in treating tuberculosis in immuno-compromised patients. However, longer follow-up and prolonged treatment was required.

CONCLUSION

We found that immunosuppression was a risk factor for increased morbidity and mortality among new smear positive pulmonary tuberculosis patients. All the patients in the study received DOTS regimen only. After 6 months of treatment, weight gain in both immunocompetent and immunosuppressed patients was a sign of clinical improvement. During the 6 month follow-up period, no relapses were reported in either of the treatment groups and therefore confirm the efficacy of DOTS implemented through RNTCP. Prolongation of intensive phase therapy was required among those who were immunosuppressed because the sputum smear conversion rate was slower among the immunosuppressed as compared with immunocompetent in our study. Treatment adherence was associated with positive treatment outcome.

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