Original Article

EVALUATION OF AN INTERMITTENT SIX-MONTH REGIMEN IN NEW PULMONARY TUBERCULOSIS PATIENTS WITH DIABETES MELLITUS

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Summary

Background: The treatment of tuberculosis (TB) with category I regimen of the Revised National Tuberculosis Control Programme (RNTCP) for patients with diabetes mellitus (DM) needs evaluation.

Objective: To assess the cure and relapse rates in 3 years, among the new smear-positive TB patients with Type-2 DM (DMTB) treated with CAT-I regimen ($2E_3H_3R_3Z_3/4R_3H_3$) of RNTCP.

Methodology: TB suspects attending the diabetology units and the TB research centre (TRC) Chennai, were investigated. Eligible DMTB cases were enrolled. Baseline estimation of cardiac, renal, liver function tests and glycosylated-HBA1c were undertaken. All patients received $2E_3H_3R_3Z_3/4R_3H_3$ under supervision at TRC. Clinical and sputum (smear and culture) examinations and monitoring of diabetic status were undertaken every month up to 24 months, then once in 3 months up to 36 months.

Results: Of 100 patients admitted, 7 were excluded for various reasons from analysis. Of 93 patients, 87 (94%) had a favourable response at the end of treatment. Pre and post treatment mean glycosylated-HBA1c were 9.7% and 8.4 %.(>7% poor control). During follow-up period, 6 died and one lost to follow-up. Of the remaining, four relapsed.

Conclusion: Category-I regimen, recommended for all the new smear-positive patients in the Indian TB programme, is effective in the treatment of DMTB patients, despite poor control of diabetes.

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Key words: Treatment of TB patients with diabetes mellitus, Type-2 diabetes mellitus

INTRODUCTION

Prevalence of Diabetes Mellitus (DM) is increasing in epidemic proportions in Asian countries and it is 8% in rural and 13% in urban population in India.[1,2] Pulmonary TB (PTB) has been reported to be five to six times more common among diabetics, compared to non-diabetics and causes a greater mortality.[3,4] Active tuberculosis intensifies Diabetes Mellitus and vice versa; thus the two diseases constitute a dreaded companion.[5] Generally it is felt that TB patients with Diabetes (DMTB) need longer duration of treatment and they have been treated with regimens of longer than 12 months duration, even though short-course chemotherapeutic regimens (SCC) of 6-9 months have been proven to be effective both in pulmonary and extra-pulmonary forms of TB.[6-8].

In India, under Revised National TB Control Programme (RNTCP) Category-I regimen (CAT-I, $2E_3H_3R_3Z_3/4R_3H_3$) an intermittent 6 months regimen is recommended for all the new smear positive patients.[9] Hence it is proposed to assess the cure and relapse rates during a period of 3 years following treatment with CAT-I regimen in DMTB.

METHODS

Study design and objective

A prospective, observational cohort study was undertaken to assess the adequacy of CAT-I regimen in the new smear positive DMTB patients.

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Collaborating institutions

The collaborating Institutions were the Diabetology Units of Government Hospitals, Institute of Thoracic Medicine, and Tuberculosis Research Centre (TRC), Chennai. All diabetics patients suspected to have tuberculosis attending these hospitals were investigated.

Eligibility criteria

A patient was eligible for enrolment, if all the following conditions were satisfied. Known Type-2 diabetics, who were diagnosed as diabetics in the outpatient departments of the hospitals, not insulin dependant, with at least 2 positive sputum smears for AFB, aged ≥30 years, has not had >1 month of previous ATT, living in Chennai or its outskirts, was willing to attend as required for 3 years, willing to have medicaments administered under supervision three times a week during the treatment period and for blood tests and other investigations at periodic intervals.

Exclusion criteria

Patients were not eligible for enrolment, if they were too ill or in moribund condition or with history suggestive of bleeding diathesis or fits or with creatinine levels ≥2 mg/dl or with acetone in urine or patients with end stage complications of DM such as proliferative retinopathy or nephropathy.

Study patients

New sputum smear and culture positive DMTB patients formed the study population.

Sample size

The sample size was calculated on the following basis: The efficacy of a 6-month regimen $2H_3R_3E_3Z_3/4H_2R_2$ investigated at TRC, among the new sputum positive tuberculosis patients, without associated diabetes mellitus was 89%.[10] Anticipating an efficacy of 83% for the current regimen $2H_3R_3E_3Z_3/4H_3R_3$ among diabetic patients, with type-1 error of 0.05, approximate sample size was calculated to be 74. Allowing for a 20% drop-out, for 3 years the sample size was 74+15 or 90 patients.

Assessments and investigations

The list of investigations and assessments undertaken prior to start of treatment is given below: A full plate P.A. view of X-ray chest was taken and the radiological extent of the lesion was classified as per the number of zones or lobes involved and presence or absence of cavity. Four sputum specimens were examined (2 spot and 2 home) by smear and culture for *Mycobacterium Tuberculosis*. If less than two smears were positive two more additional smears were examined. Mantoux test with 1 tuberculin (RT 23 with Tween 80) on the flexor aspect of the left forearm; the greatest diameter of palpable induration was measured and presence or absence of erythema was marked after 72 hours. Urine examination for albumin, sugar, acetone, deposits, bile pigments, acetyl INH and Rifampicin was undertaken. Blood was examined for routine liver function tests, renal function tests, fasting blood sugar, glycosylated haemoglobin and lipid profile. HIV screening was undertaken for all patients. Diabetic status was assessed based on glycosylated haemoglobin percentage; <7% was taken as normal value and ≥7% was considered as abnormal value. History of contact with pulmonary TB patients was enquired. If present, the relationship to the patient was recorded. Presence or absence of family history of Diabetes Mellitus was also recorded. A detailed examination of cardiovascular system including condition of peripheral vessels and ECG was done to ascertain cardiac status. Tests for sensitivity to streptomycin, Isoniazid, Ethambutol and rifampicin on two positive pre-treatment sputum cultures were undertaken. A detailed neurological examination was undertaken to assess the status particularly of peripheral nerves and examination of respiratory system, abdomen, skin, and joint involvement was undertaken. Details of duration of diabetes, treatment of diabetes, and family history of diabetes, including treatment such as oral anti-diabetic drugs and or insulin injection was obtained for all patients. A detailed ophthalmic examination was carried out to assess the status of retina. Any past events like history of gangrene, bronchial asthma, convulsion

or jaundice, bleeding disorders were obtained.

The list of investigations and assessment during and in the follow-up period are listed in Table-1.

Bacteriological procedures

Sputum smears were examined for AFB by fluorescence microscopy. The specimens were processed by modified Petroff's method and cultured on the Lowenstein Jenson medium. The sputum smears were graded according to the number of bacilli visualized per high power field (HPF) and all positive cultures were subjected to identification tests for *Mycobacterium tuberculosis* and to drug susceptibility tests described elsewhere.[11,12]

Treatment regimen for tuberculosis

All patients were given a six-month SCC ($2H_3R_3Z_3E_3/4H_3R_3$) regimen, consisting of 2-months of isoniazid (H) plus Rifampicin (R) plus Ethambutol (E) plus Pyrazinamide (Z) three times a week followed by 4 months of isoniazid plus Rifampicin three times a week. Every dose of treatment was given under supervision. The dosages were as follows: H=600mg, R=450mg, E=1200mg and Z=1500mg.

Defaulter action

If a patient fails to attend on a due date for treatment, prompt retrieval actions were undertaken by a health visitor/social worker/physician.

Management of diabetes

All patients were seen by a diabetologist at TRC once a week and oral anti-diabetic drugs (ADT) were adjusted based on fasting blood sugar levels. Insulin injections were given only after completing ATT.

Management of adverse reactions to ATT

If a patient made a spontaneous complaint, attributable to ATT, was referred to a physician, who recorded the complaints in detail and managed appropriately.

Definitions used for primary treatment outcomes

Favourable response: If all six sputum cultures were negative during the last 2-months of chemotherapy or if one culture was positive during the last 2-months with negative cultures subsequently (without additional chemotherapy).

Table 1: Investigations and assessments during treatment and follow-up period

Clinical examination, recording of adherence to treatment and adverse reactions if reported	Every month upto 24months, once every 3 months upto 36months
Smear and culture examination of three sputum specimens Two sputum specimens	Every month upto 6 months Once every 3 months upto 36 months
Estimation of Fasting blood sugar Glycosylated HBA1c	Every month upto 24 months, then once every 3 months upto 36 months Once every 3 months upto 36 months
Examination by Diabetologist	Every month upto 24 months, Once every 3 months upto 36 months
Renal & liver function tests	0,6,12, 24, 36 months
Chest radiograph	2,6,12,24 & 36 months
Urine examination for acetone, sugar, albumin including deposits	Every month upto 24 months, then once every 3 months upto 36 months
Cardiac, ophthalmological and neurological assessments	0 and 6 months

Unfavourable response: When (a) two or more cultures were positive in last two months of treatment, including at least one in the last month, with at least one culture growing 20 colonies or more, or (b) persistent bacteriological positivity or radiographic and/or clinical deterioration warranting change of chemotherapy, or (c) death due to tuberculosis during the treatment phase or (d) change of treatment for adverse drug reactions.

Bacteriological relapse requiring treatment

Among patients with a favourable response, relapse requiring treatment was defined as a total of two or more cultures positive for *M. Tuberculosis* in any two consecutive months during the follow-up period, at least one with a growth of ≥20 colonies with a positive smear, or persistent radiological deterioration with a positive smear or clinical deterioration during the follow-up period.

Data analysis

Intention-to-treat analysis and analysis of adverse reactions were undertaken. The proportion of patients who became sputum smear negative and or culture negative at the end of intensive phase were also analysed.

This study was done after getting the approval from the Scientific Advisory Committee and the Institutional Ethics Committee of TRC.

RESULTS

Patients' enrolment

A total of 258 patients (January 1998-January 2002) with Type-2 Diabetes Mellitus with suspected tuberculosis were assessed and 87 did not meet the inclusion criteria, 48 refused to participate and 23 were not included for other reasons. The remaining 100 patients were enrolled.

Patients in analysis

Intention to treat analysis included 98 patients, two however, refused treatment. Baseline characteristics of patients and analysis of adverse reactions were undertaken in all 100 patients enrolled.

Baseline characteristics of study population (Table 2)

The median age was 48 years (range 30-70 years), 72% were males and median weight was 51.5kg. Radiological involvement of >2 zones in 61%, bilateral in 50%, lower lobe in 19%, middle lobe in 45% and presence of cavity in 21%. Table 2 describes the initial smear and culture grading. Ninety-six per cent of patients were infected with organisms susceptible to S, H, R and E, 3% resistant to INH and 1% to Rifampicin.

Profile of diabetic status

Duration of diabetes was <6 months in 50% of patients (Table-2). Of them 51% were on oral anti-diabetics (ADT), 18% on insulin and 20% on both insulin and ADT. Median glycosylated HbA1c (good control ≤7%) was 10.1% (range 6.9-14%). The median fasting sugar was 238 (range 78-518) mg per d/l. Initially, 13% had mild non-proliferative retinopathy, maculopathy in 2%, ischemic heart disease in 2%, macroalbuminuria in 5%, distal peripheral sensory neuropathy in 15% and 64% did not have any complications.

Drug regularity

The amount of scheduled anti-TB medication received was ≥75% in 91, 60-65% in 3 and 2 had completed 50-92% of intensive phase only, 2 patients refused treatment after 5th and 6th doses and in two treatment was changed for severe adverse reactions.

Smear conversion during treatment

Of 93 patients in analysis, conversion to smear negativity occurred in 26 (28%) by the first, 57 (61%) by the second, 76 (82%) by the third and 88 (95%) by the 6th month. Conversion to culture negativity occurred in 34 (37%) by the first, 82 (88%) by the second, 90 (97%) by the 3rd and 4th but 89 (96%) by the sixth month.

Profile of diabetes at the end of treatment and follow-up

At the end of treatment the glycosylated HBA1c was 8.4% and the median fasting blood sugar was 184 (86-412) mg/dl. At the 30th month of follow-up the median fasting blood sugar was 214 (78-515) mg/dl.

Management of adverse reactions to Anti-Tuberculosis Treatment (ATT)

Of 100 patients 89 did not have any problems. Adverse reactions attributable to ATT occurred in 11. Two developed severe toxicity to Rifampicin and Pyrazinamide and both drugs were terminated; one developed persistent vomiting with fever, after two-weeks of treatment and the other vasculitis (pruritic rashes with itching) after one-month of treatment. Arthralgia occurred in three, gastro-intestinal symptoms in six and these patients responded to symptomatic management.

Treatment outcome

Intention to treat analysis and relapses in the follow up period of 36 months from enrolment to study (Fig.): Of 100 patients enrolled, intention-to- treat analysis was done for 98 patients (two refused treatment after 5 and 6 doses). Of 98, 92 (94%) had a favourable response and six patients had unfavourable bacteriological response. Of six who had unfavourable response, three patients with initially drug sensitive organisms developed resistance

Table 2: Baseline characteristics of study population (n=100)

Characteristics		Per cent
Sex	Males	72
Age (yrs)	Median	48
	Range	30-70
Weight (Kg)	Median	51.5
	Range	32.6 - 74.7
X-ray chest		
Lung zones involved	>2 Zones	61
Lower lobe involvement		19
Middle lobe involvement		45
Cavity		21
Extent of the disease	Bilateral	50
Initial Smear grading	1+	46
	2+	43
	3+	11
Initial culture grading	<1+	13
	2+	25
	3+	62
Sensitivity pattern	HRES sensitive	96
	Resistant to H	3
	Resistant to R	1
Duration of diabetes	<6 months	50
	6months-2 years	20
	2 -5 years	10
	>5 years	20
Family history of DM		41
History of contact with TB		9

Figure: Flow diagram of patients from eligibility to analysis stage

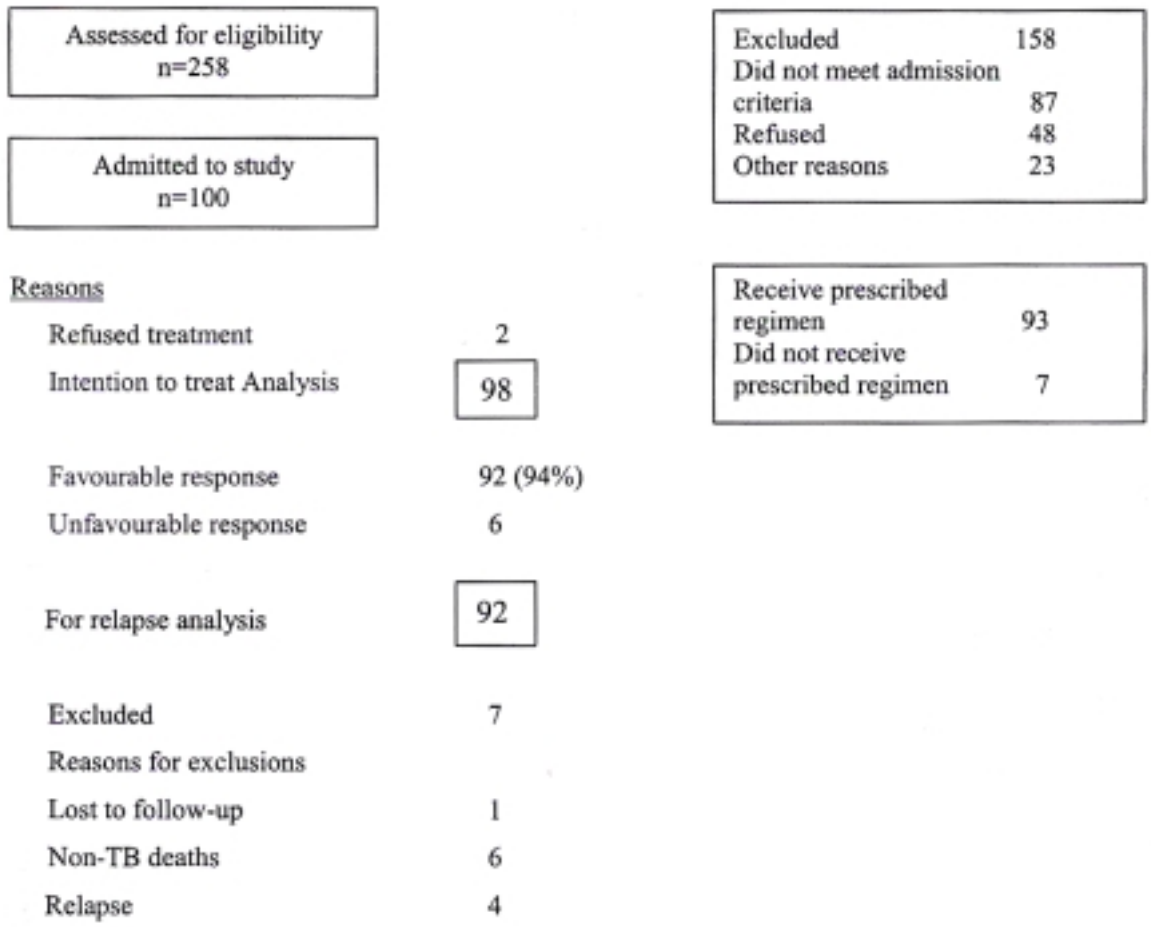

Table 3: Sputum Bacteriology for M. Tuberculosis: Month by month smear for AFB and culture conversion (n=93)

Month	Smear conversion		Culture conversion	
	No	%	No	%
1	26	28	34	37
2	57	61	82	88
3	76	82	90	97
4	83	89	90	97
5	88	95	89	96
6	88	95	89	96

Table 4: Pre and post-treatment radiological assessment

Type of lesion	Pre treatment (n=100)	Post treatment (n=98)
	%	%
Exudative	81	29
Infiltration	76	27
Fibrotic	8	80
Pleural involve	-	1
Cavity	21	2

A patient may have multiple radiological lesions

to isoniazid alone at the 5th month and remained smear and culture positive at the end of treatment and 2 had change of treatment for severe adverse reactions. One other patient with organisms initially resistant to Rifampicin alone, remained smear and culture positive at the end of treatment.

During 30 months of follow-up among 92 patients, 4 (4%) relapsed at the 11th, 12th, 13th and 30th months period; 6 died; 3 due to myocardial infarction, 2 of cardiac failure and one committed suicide.

Pre and post-treatment radiological assessments (Table 4)

Post–treatment, cavity closure was observed in 19 of 21 patients and 80% had fibrotic lesions.

Response related to initial sensitivity pattern

Of 100 patients, 96 had organisms sensitive to Rifampicin, Isoniazid, Streptomycin and Ethambutol. Of 3 patients with resistance to Isoniazid, all had a favourable response. One patient, with initial Rifampicin resistance failed to treatment.

DISCUSSION

This study has shown that CAT-I regimen (intermittent six-month regimen) of RNTCP was adequate in Type-2 DMTB patients, as the treatment success was 94% and 4% relapsed in 30 months of follow-up. The treatment outcomes are comparable to that of non-diabetics. This indicates that association of diabetes did not influence the outcome of TB treatment. This is in contrast to that reported earlier from Japan, where despite treatment with chemotherapeutic regimens of 9-12 months or more the relapse rates in 30 month follow-up period was 10%.[6] Our finding is contrary to that reported earlier that DM was a risk factor for relapses in TB patients and thus can allay the concerns of diabetologists and TB programme managers across the globe, as the relapses were not higher among diabetic patients compared to non-diabetics.[6-8]

It is reported that strict glycaemic equilibrium is essential for the success of ATT among the DMTB patients.[4] But in our series, despite poor diabetic control, majority of our patients had responded to ATT. Even though it is recommended that smear positive DMTB patients should be treated with insulin injections, as a policy, they were treated only with oral anti-diabetic drugs during the period of ATT. It is worth noting that this practice did not result in therapeutic penalty.[13]

Although our patients were on both Rifampicin and oral anti hypoglycemic drugs, adverse reactions to ATT were not a major problem. This finding highlights the suitability of this RNTCP regimen to DMTB patients.

The low smear conversion rates (61%) observed in this series, compared to the National average of 80% is more likely to be due to the use of the fluorescent auramine rhodamine stain, which is known to be more sensitive than the Ziehl Neelsen stain in sputum smear reading for acid fast bacilli.[14,15] Patients (54%) with higher smear grading (2+ and 3+) initially were less likely to convert, compared to patients (46%) with 1+ smear. Similar findings have been reported earlier.[16-18] Initially 87% of our patients had higher culture grading. At the end of intensive phase, culture conversion was 88% and smear conversion was 61%. Culture conversion is a surrogate marker of the sterilising activity of the regimen.[19] This is borne out of by the high proportion of patients with a favourable response (94%) at the end of treatment. These findings are similar to our findings observed among PTB patients with or without HIV infection[20,21]. These findings demonstrate the competence of the RNTCP regimen in the treatment of DMTB.

Majority of our patients (96%) were infected with organisms, sensitive to RHES etc (first line drugs). This probably reflects the drug susceptibility profile, among diabetics attending the diabetic clinics of two of the teaching hospitals of the city. Similar findings have been reported by Singla et al.[22] However this is contrary to a report from an Indian tertiary hospital, where only 51% of the DMTB patients were infected with sensitive organisms.[23] This is possibly

due to the diverse spectrum of cases seen at tertiary hospitals, as complicated cases were more likely to throng specialized hospitals. Another important finding is that all the 3 patients infected with organisms, resistant to isoniazid responded well to the CAT-I regimen, indicating the potency of the CAT-I regimen in isoniazid resistant patients.

None of our patients had Multi-Drug Resistance (MDR), similar to Singla's series[22] This is contrary to earlier reports, where higher proportions (26% from south India and Bellevue) had MDR-TB among DMTB patients.[23,24] Thus there are conflicting reports about incidence of MDR-TB among diabetics and more studies are needed in this area.

In our series, even though the clinical profile was similar to that of PTB, the radiological images were atypical as 45% had middle lobe and 19% had lower lobe involvement, similar to earlier reports.[25-28] Six patients died due to cardiac problems unrelated to tuberculosis. Higher mortality rates due to the diabetic complications is well known.[2-4]

This study is not without limitations. The glycosylated HBA1c was undertaken for all patients enrolled initially but was done only for half of the patients, in the follow up period, as the kit was not available. Therefore, monitoring of the diabetic status was done by estimation of fasting blood sugar.

To conclude, this cohort analysis has proved that DMTB patients have similar clinical presentation as PTB, but atypical radiological presentation, higher bacillary load at the time of diagnosis as shown by higher culture grading, a lower prevalence of anti-tuberculous drug resistance and excellent outcome to ATT. This study lends support to the current practice of treating all the new sputum positive patients with diabetes mellitus with CAT-I regimen under RNTCP.

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