The Professional Medical Journal
www.theprofesional.com

DOI: 10.17957/TPMJ/17.3810

ORIGINAL PROF-3810

TUBERCULOSIS;
RELAPSE IN INTERRUPTED ANTITUBERCULOUS THERAPY

Javed Iqbal[1], **Muzamil Nazir**[2]

1. FCPS
Associate Professor Pulmonology
Quaid e Azam Medical College,
Bahawalpur.
2. MBBS
House Officer

Correspondence Address:
Dr. Javed Iqbal
Associate Professor Pulmonology,
Quaid e Azam Medical College,
Bahawalpur.
jiqb@hotmail.com

Article received on:
07/01/2017
Accepted for publication:
15/05/2017
Received after proof reading:
03/07/2017

ABSTRACT… Objectives: To know the frequency of relapse in patients of tuberculosis who completed the total therapy but in interrupted course. **Study Design:** Prospective Cohort study. **Place and duration of study:** Outpatient and Inpatient units of Chest and TB ward Bahawal-Victoria Hospital Bahawalpur. **Methodology:** Patient showing characteristics according to WHO standard were included in the study i.e. clinical features and radiographic abnormalities consistent with active pulmonary tuberculosis; and no response to a course of broad-spectrum antibiotics regarding signs and symptoms. Also included were those with clinical features consistent with tuberculosis with Mycobacterium smear and culture positive or smear positive or culture positive. Such patients were interviewed and case file/charts were reviewed. Specific things looked were their prior antituberculous therapy, number of days antituberculous therapy interrupted, age, and gender. All others with diabetes mellitus, smokers, alcoholic were excluded from the study. **Results:** There were total 67 patients enrolled in the study and among them 34 (50.7%) males and 33 (49.3%) females. Male age ranges 26-75 years(mean 46.20+ SD 12.46) and female age range 13-70 years (mean 40.42+SD 13.32) Among these relapse cases 6 (9%) patients had interrupted ATT during their prior therapy for a period ranged 2-90 days (P-value <0.001). Among these 5 (83%) were females and 1 was male. **Conclusion:** Interrupted ATT caries significant risk for future relapse of tuberculosis.

Keywords: Recurrence, Antituberculous Agents, Tuberculosis.

Article Citation: Iqbal J, Nazir M. Tuberculosis; relapse in interrupted antituberculous therapy. Professional Med J 2017;24(7):942-946. **DOI:** 10.17957/TPMJ/17.3810

INTRODUCTION

Relapse for tuberculosis refers to the disease pattern in which a patient at some point after declared cured with completion of therapy, either becomes culture positive again or has clinical or radiographic deterioration that is consistent with active tuberculosis. For culture negative patients at least two sputum smear examinations should be negative for acid fast bacillus (AFB) and radiographic abnormalities must be consistent with active pulmonary tuberculosis and no response to a course of broad-spectrum antibiotics given for appropriate time.[1]

This may particularly happens because of interrupted antituberculous therapy.[2] Other remarkable conditions are in severe disease with aggressive clinical course and due to lack of insight into the disease, and lack of importance of compliance in the long course of treatment.[2]

Among other factors are malabsorption of drugs and smoking, advancing age, silicosis.[3] The smoking increases resistance to Mycobacterium tuberculosis due to functional and morphological changes to macrophages in the alveoli.[4]

It has been demonstrated that even after completion of full treatment span some mycobacterium remains alive in dormant stage within the post-tuberculous fibrotic tissues[5] Once the condition for them becomes favorable as patient on steroids therapy, on antineoplastic therapy, acquires diabetes mellitus, becomes malnourished, alcoholism, Human immunodeficiency virus (HIV) infection then it can again erupt into active tuberculosis.[6] Certain regions of world has shown more relapse in HIV positive patients.[7,8]

Another factor that is proposed to be contributing to relapse is body iron over load. The iron loading causes reductions in tumor necrosis

factor-alpha (TNF-A) and nitric acid which are key factor combating mycobacterium. There is a need to devise effective strategies to demarcate the effective level of iron in body in patients with tuberculosis.[9]

Considering interruption of therapy as major threat for not only tuberculosis relapse but also for emergence of drug resistant strain world health organization WHO directed directly observed treatment short course DOTS therapy has proven importance.[10,11] It consists of observation by a health care provider or other responsible individual as patient's takes antituberculous medications. Its importance is further emphasized by the fact that modified treatment strategies has been proposed for strict DOTS compliance by alternate therapy by slight modification of treatment.[12]

Other factor that improves compliance is the patient education about the disease and about better outcome for uninterrupted antituberculous therapy ATT.

Adherence to treatment is not only important to minimize relapse but also for cure of patients, controlling spread and minimizing the emergence of not only multi-drug resistance but also of extensive drug resistance or total drug resistant strain of mycobacterium.[13]

The debate of relapse or reinfection can only be reliably sorted out by the ability to differentiate the strains involved in the first and the second tuberculosis episode by genotyping methods of some of the deoxyribonucleic acid (DNA) insertion elements[14] but this was beyond the scope of our study.

Considering above facts we conducted a study to look into frequency of relapse of tuberculosis in patients whose ATT was interrupted during anytime within previous treatment at Bahawalpur Chest and TB unit.

METHODOLOGY

This analytic retrospective cohort study was conducted at chest and tuberculosis (TB) unit at Bahawalpur. All patients who were treated for tuberculosis in past with four drugs (Isoniazid, Rifampicine, Ethambutol, Pyrazinamide) or five drugs combination therapy (Isoniazid, Rifampicine, Ethambutol, Pyrazinamide, Streptomycine) and completed treatment and declared cured and enjoyed healthy time period after treatment now again started showing signs and symptoms. Patients showing following characteristics according to WHO[1] standard were included in the study.

1. Clinical features and radiographic abnormalities consistent with active pulmonary tuberculosis; and no response to a course of broad-spectrum antibiotics regarding signs and symptoms.
2. Clinical features consistent with tuberculosis with Mycobacterium smear and culture positive or smear positive or culture positive.

All those patients whose comorbids which could have lead to tuberculosis as an isolated factor were excluded from the study i.e. diabetes mellitus, smokers, alcoholics and with malabsorption syndrome.

All patients who gave informed consent files/ case charts/radiology reports were reviewed with patient were asked history by principal researcher. Information was collected on the variables, tuberculosis relapse, patients, age, gender, number of relapses, Antituberculous therapy interruption time in days.

Data was entered and analyzed in Statistical Package for Social Sciences (SPSS) version 11. Frequencies and percentages were calculated for categorical and mean with standard deviation were calculated for numerical variables. Fisher's exact test was applied to check significance of interrupted therapy and P-values less than 0.05 were considered significant. The value < 0.05 strongly determined the significance of the given data variables.

RESULTS

There were total 67 patients enrolled in the study and among them 34 (50.7%) males and 33 (49.3%) females. Male age ranges 26-75 years

(mean 46.20+ SD 12.46) and female age range 13-70 years (mean 40.42+SD 13.32) (Table-I). Sixty five patients took four drug regimen and 2 took five drugs. Among these relapse cases in 6 (9%) of patients ATT was interrupted for four drugs regimen for all drugs during their first therapy for a period ranged 2-90 days (P-value < 0.001) (Table-II). Among these 5 (83%) were females and 1 was male (Table-III). None of the patient took modified ATT during previous therapy at anytime during interrupted time or during therapy.

Age (years)	Frequency of Interruption
13	1
35	1
50	2
60	1
70	1

Table-I. Age of patients Antituberculous therapy (ATT) Interrupted

Days ATT interrupted	Frequency of Interruption
2	1
18	1
30	1
08	1
90	2

Table-II. Days Antituberculous therapy (ATT) Interrupted

Gender	Number of patients Participated in study	Number of patients with interrupted ATT
Male	34	1
Female	33	5
Total	67	6

Table-III. Gender of Patients with Interrupted Antituberculous therapy

DISCUSSION

Although this area of research has been studied in many countries but in tuberculoses endemic country like Pakistan such study had added to the knowledge that what aspects of tuberculosis elimination must be addressed in future with more assurance. The inclusion criteria for patients in our study followed rigorous standards made by WHO that depict better results with the given risk factor.[1] Our study has shown statistically significant role of interrupted therapy as a risk for future relapse of disease (P-Value <0.001).

The tuberculosis incidence for Pakistan is 276 cases per 100,000 though less than previous years.[1] Nine percent patients took irregular treatment in this study thus adding to the existing burden of disease. The importance of regular treatment was emphasized many times in past by different countries because of same threat it imposes everywhere. In one retrospective study in tuberculosis patients in New York City about 50% of them took interrupted treatment, the nonadherent patients not only took longer to convert to negative culture results but were more likely to acquire multidrug resistance and required longer treatment span.[2] In the study cited above the patient groups which were studied were enrolled before the time when their control program was mature and public health department intervention was almost absent though in our study too, it signifies that self administration of therapy by patient himself at any stage must be discouraged.

Our study population included patients who completed their therapy inspite of being interrupted and yet again relapsed is avouched by the results of several randomized control trials (RCTs) conducted in different regions of the world.[15,16] In India during 1997-98 relapse rates at Mumbai was 4.5% in patients who were declared cured after they have completed treatment.[15] However in south India controlled clinical trial with short course antituberculous therapy showed better outcome with 2.7% of relapse in the second phase of study.[16]

None of the patient in our study was declared treatment failure during first antituberculous therapy as inspite of interruption in therapy they showed full clinical recovery with first line drugs.

Similarly 9% relapse results were obtained in one of review in south India on mycobacterium fully drug sensitive individuals.[17] While Mitchison et al. reported a relapse rate of only 4.6% among patients treated initially for full drug sensitive organisms.[18]

It is important to note that among 9% patients who interrupted the therapy mostly were females (83%) this is contrary to what was observed at Thailand.[19] The females in this study at a developing country, Thailand showed more compliance then male patient.[19]

In addition to gender other factors that affect compliance are lack of accessibility, time commitment and lack of social and emotional support by family and friends, taste of medication, duration of therapy, requirement of drug timings and storage.[20] Adding to this list one other major factor identified in our study contributing to interruption was forgetfulness by patient.

We acknowledge that the results in our study are obtained from a highly selected patient population. Careful consideration of all other medical comorbids including smoking is vital when dealing patients in general practice.

Our results have several programme implications as;

1. Interrupted therapy should be considered as a risk factor in any patient with relapse of tuberculosis.
2. Test to check levels of antituberculous drugs in the body must be introduced to make compliance more objective.
3. A comprehensive history and examination Performa to be filled by medical officer, must be made available throughout country TB centers/DOTS center addressing not only points leading to disease diagnosis but also include points to understand any psychological problem or any other medical problem that may interrupt the regularity of treatment.
4. Being an effected area because of tuberculosis we need to develop gene typing laboratories to segregate issues of reinfection and relapse.
5. Educational programs need to be developed to educate healthcare providers about counseling and education of patients.
6. There is a need to develop effective communication strategies with patients and to provide health education materials addressing these issues, so that patients develop insight in this chronic ailment.
7. Further research is needed to develop local strategies to help segregate among reinfection and relapse and emergence of drug resistant strain.
8. Females being the mother of future generation must be taught in groups about importance of treating tuberculosis properly within time, as only healthy mothers can raise a healthy nation.

CONCLUSION

Interrupted ATT caries significant risk for future relapse of tuberculosis.

DISCLOSURE

No potential conflicts of interest exist with any company/organization in this study. No funding was received from any source for this study. Confidentiality of patient has been ensured and only those were included in study who gave consent.

REFERENCES

1. World health organization. **WHO definitions of TB cases used until the end of 2012 (and in 2013 global TB report).** Global TB report 2013 available at-http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf?ua=1.

2. Pablos-M A, Knirsch CA, Barr RG, et al. **Nonadherence in tuberculosis treatment: predictors and consequences in New York City.** Am J Med 1997; 102:164.

3. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. **A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong.** Am Rev Respir Dis 1991; 143: 262–67.

4. Batista JAL, Albuquerque MFPM, Ximenes RAA, and Rodrigues LC. **Smoking increases the risk of relapse after successful tuberculosis treatment.** Int J Epidemiol. 2008 August; 37(4): 841–851.

5. Fox W, Ellard GA, Mitchison DA. **Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications.** Int J Tuberc Lung Dis 1999; 3: S231–79.8.

6. Sonnenberg P, Murray J, Glynn JR, Shearer S,Kambashi B, Godfrey-Faussett P. **HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers.** Lancet 2001; 358: 1687–93.

7. Simon SH, Sara K, Dete H, Warren, Robin, Donald, Peter R et al. **Recurrent Culture-Confirmed Tuberculosis in Human Immunodeficiency Virus-Infected Children.** Pediatr. Infect. Dis. J:2005(24);8-685-691.

8. Murray J, Sonnenberg P,Shearer SC, Faussett PG. **Human Immunodeficiency Virus and the Outcome of Treatment for New and Recurrent Pulmonary Tuberculosis in African Patients.** Am J Respir Crit Care Med: 1999(159); 733–740.

9. Boelaert JR, Vandecasteele SJ, Appelberg R, Gordeuk VR. **The Effect of the Host's Iron Status on Tuberculosis.** J. Infect. Dis 2007; 195:1745–53.

10. DOTS exxpansion. **Pursue high-quality DOTS expansion and enhancement.** available at http://www.who.int/tb/dots/en/-WHO Pursue high-quality DOTS expansion and enhancement.

11. Volmink J, Garner P. Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment. BMJ 1997; 315:1403.

12. American Thoracic Society, CDC, Infectious Diseases Society of America. **Treatment of tuberculosis.** MMWR Recommendation and Report June 20, 2003 / 52(RR11); 1-77.

13. Chaulk CP, Kazandjian VA. **Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel.** JAMA 1998; 279:943.

14. Kremer K, van Soolingen D, Frothingham R, et al. **Comparison of methods based on different molecular epidemiological markers for typing of Mycobacterium tuberculosis complex strains: inter laboratory study of discriminatory power and reproducibility.** J Clin Microbiol 1999; 37: 2607–18.

15. Dholakia Y, Danani U, Desai C. **Relapse following directly observed therapy short course (DOTS)—a follow up study.** Indian J Tuberc 2000; 47: 233–236.

16. **Tuberculosis Research Centre. Study of chemotherapy regimens of 5 and 7 months duration and the role of corticosteroids in the treatment of sputum positive patients with pulmonary tuberculosis in south India.** Tubercle 1983; 64: 73–91.

17. Tuberculosis Research Centre. **Split-drug regimens for the treatment of patients with sputum smear-positive pulmonary tuberculosis—a unique approach.** Trop Med Int Health 2004; 9: 551–558.

18. Mitchison D A, Nunn A J. **Influence of initial drug resistance on the response to treatment of pulmonary tuberculosis.** Am Rev Respir Dis 1986; 133: 423–430.

19. Lertmaharit S, Kamol-Ratankul P, Sawert H, Jittimanee S, Wangmanee S. **Factors associated with compliance among tuberculosis patients in Thailand.** J Med Assoc Thai. 2005 Sep; 88 Suppl 4:S149-56.

20. Jing J , Grant ES, Vernon MSO and Shu CL. **Factors affecting therapeutic compliance: A review from the patient's perspective.** Ther Clin Risk Manag. Feb 2008; 4(1): 269–286.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Javed Iqbal	Data collection	
2	Muzamil Nazir	Data collection	