Clinical Outcomes in Patients with Multi Drug Resistant Pulmonary Tuberculosis after Fixed Dose Combination Therapy of Anti-Tuberculous Drugs

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ABSTRACT

Background and Objective: *Tuberculosis has been an epidemic for humans over ages caused by Mycobacterium Tuberculosis (MTB). First line drugs in fixed dosage are employed for its treatment. Therefore this study was designed to observe the clinical outcomes after two months of initial treatment with antituberculous drugs in patients with pulmonary tuberculosis.*

Methods: *The study was conducted on n = 30 newly diagnosed patients having pulmonary tuberculosis confirmed with acid fast bacilli positive sputum at Gulab Devi Chest Hospital, Lahore. After informed written consent, blood samples were drawn at 02 and 06 hours post dose intervals for anti-tuberculous drugs in fixed dose combination (FDC). Liver and renal enzyme levels in relation with clinical signs and symptoms were assessed and recorded before and during drug therapy on day 1, 14 & 56. Data was entered and analyzed by Statistical Package for Social Sciences (SPSS software, version 20). ANOVA test was used to determine the mean differences in laboratory parameters.*

Results: *Clinical improvement was seen at the end of therapy particularly in fever and weight status. Plasma levels of hepatic enzymes and renal urea and creatinine were raised (P > 0.05) however no renal and hepatic toxicity was reported.*

Conclusion: *Anti-tuberculous drugs as FDC were effective with improved compliance and minimal hazardous effects.*

KEYWORDS*:* *Fixed dose combination, Pulmonary tuberculosis, Liver enzymes, Renal function, Clinical outcomes.*

INTRODUCTION

Pulmonary tuberculosis (TB) is the most common infection among mycobacterial diseases in humans for millennia. *Mycobacterium tuberculosis* (MTB) is the causative agent for this disease. It is an infectious but curable diseasewith 6-24 months treatment. It affects many organs like lungs, kidneys, bones, spines and central nervous system.[1] Pakistan is ranked 5th among high prevalence countries for TB and 6th among countries for highest number of multidrug-resistant tuberculosis (MDR-TB).[2]

It's a droplet infection that spreads by various means like coughing, sniffling and talking of a man with pneumonic or laryngeal tuberculosis. It is more common in people with low socio-economical status and having other co-morbidities like human immunodeficiency virus infection.[3]

Isoniazid (INH) is one of the first line anti-tuberculous drugs for TB treatment. It is used in combination with Rifampicin, Pyrazinamide and Ethambutol as fixed dose combination (FDC).[4] Treatment for MDR-TB needs those drug regimens that are prolonged (18-24 months), more efficacious and less toxic. Patients of pulmonary TB present with high grade fever, cough, night sweats, anorexia, hemoptysis and weight loss. Patients become emaciated, malnourished and immune-compromised with poor clinical outcomes.[5] Treatment of MDR-TB becomes difficult because of resistance to drugs with treatment success of only 50% globally; thereby second-line drugs are used. In Pakistan, poverty, poor literacy rate, less awareness about disease and its consequences, false faiths about drugs being prescribed in TB clinics are the major factors leading to treatment failure.The current study is carried out to determine the clinical outcomes after two months of initial treatment as FDC in sputum positive pulmonary TB patients.

METHODS

It was a descriptive study conducted in the Department of Pharmacology at University of Health Sciences (UHS) and Department of Chest Diseases, Gulab Devi Chest Hospital, Lahore, Pakistan, from

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January 2017 to December 2017 following the approval by both University of Health Sciences and Hospital's Ethical Committee. Newly diagnosed patients with acid fast bacilli positive sputum as diagnostic criteria of pulmonary tuberculosis were admitted to the hospital and enrolled in the study after receiving written informed consent. Both males and non-pregnant females within the age limit of 18 to 65 years and MTB sensitive to 1st line anti-mycobacterial drugs were included. While patients having pregnancy, other debilitating co-morbidities and below 18 years of age were excluded from present study. Fixed dose combination protocol followed in Gulab Devi Chest Hospital, Lahore was adopted. The anti-mycobacterial drugs in FDC combination containing Isoniazid (dose 300 mg) and Rifampicin (dose 450 mg or 600 mg) and single drug products of Pyrazinamide (maximum dose 1500 mg) and Ethambutol (maximum dose 850 mg) were given daily to patients by strict monitoring for 8 weeks, in accordance with the guidelines of the Pakistan National Tuberculosis Program. Standardized meals were served to the subjects during study period. Blood samples were taken at 02 and 06 hours after drug administration on day 1, 14 & 56. Clinical signs and symptoms like fever, night sweats, cough, hemoptysis with renal function tests (RFTs), liver function tests (LFTs) and sputum AFB were recorded before the start of treatment and at the time of blood sampling on day 1, 14 and 56.

STATISTICAL ANALYSIS

Data was entered and analyzed by Statistical Package for Social Sciences (SPSS software, version 20). Mean ± SD was given for quantitative clinical and laboratory parameters. Frequency and percentage was given for qualitative clinical parameters such as cough, night sweats and hemoptysis. Moreover, Chi-square/ Fisher's exact test was used to determine the association of qualitative clinical parameters with days of treatment. Repeated measures ANOVA test was used to determine the mean differences in laboratory parameter. A *P*-value of less than or equal to 0.05 was taken as statistically significant.

RESULTS

Demographic parameters of n=30 newly diagnosed pulmonary TB patients are shown below(Table- 1). The median age of the patients was 44 years with the age ranging from 18 to 65 years.

Table -1: *Demographic parameters of patients taking anti-tuberculous therapy (n = 30).*

Parameters	Present (%)	Absent (%)
Family history	24	76
Contact history	24	76
Immunization history	32	68
Sputum AFB (positive)	100	0
Gender Percentage	*Male* 68%	*Female* 32%

Clinical symptoms of cough, night sweats and hemoptysis were significantly improved during anti-tuberculous drug therapy for 02 months *(P-value < 0.0001)** except for hemoptysis *(P-value > 0.120)* (Table- 2).

Table -2: *Clinical parameters of enrolled patients (n = 30).*

Cough	Days 1	14	56	Mean ± SD	P-value
Absent	4.0%	4.0%	16.0%	08% ± 0.302	
Mild	12.0%	24.0%	64.0%	33.3% ± 0.272	< 0.0001*
Moderate	48.0%	68.0%	20.0%	45.3% ± 0.241	
Severe	36.0%	4.0%	0.0%	13.3% ± 0.197	
Night Sweats					
Absent	20.0%	20.0%	48.0%	29.3% ± 0.161	
Mild	12.0%	32.0%	48.0%	30.7% ± 0.18	< 0.0001*
Moderate	36.0%	44.0%	0.0%	26.7% ± 0.234	
Severe	32.0%	4.0%	4.0%	13.3% ± 0.161	
Hemoptysis					
Absent	60.0%	60.0%	80.0 %	66.7% ± 0.069	
Mild	16.0%	24.0%	20.0%	20.0% ± 0.04	> 0.120
Moderate	16.0%	16.0%	0.0%	10.7% ± 0.092	
Severe	8.0%	0.0%	0.0%	2.7% ± 0.046	

Fisher's Exact Test = 32.486 **Statistically Significant*

Similarly, there was a significant improvement *(P-value<0.001*)* in fever and overall weight status of patients from start till end of drug treatment(Table -3).

Table-3: *Body temperature and weights of patients on various days of study (n = 30).*

	Days	Mean (°F)	Std. Deviation	p-value
Temperature (°F)	1	100.80	1.225	
	14	100.08	0.954	< 0.001*
	56	99.44	0.583	
Weight (Kg)	1	53.40	9.359	
	14	53.92	8.836	< 0.001*
	56	56.92	7.637	

Plasma levels of hepatic enzymes and renal urea and creatinine in the patients taking anti-tuberculous drug were assessed on days 1, 14 and 56 respectively. There was a significant *(P-value < 0.05)* increase in the serum levels of alanine transferase (ALT), bilirubin, serum urea and creatinine levels at the end of treatment. No hepatic or renal toxicity was reported (Table- 4).

Table- 4: *Plasma levels of hepatic enzymes and renal urea and creatinine of patients (n = 30).*

	Days	*Mean*	*Std. Deviation*	*P-value*
ALT (µ/L)	1	23.20	10.697	< 0.001*
	14	24.72	11.742	
	56	27.20	12.312	
AST (µ/L)	1	26.80	11.075	0.099
	14	27.24	11.252	
	56	28.28	11.563	
Alkaline Phosphatase (µ/L)	1	238.32	85.964	0.160
	14	245.68	89.597	
	56	238.84	86.772	
Bilirubin (mg/dl)	1	0.748	0.1851	< 0.008*
	14	0.848	0.2584	
	56	0.840	0.2160	
Urea	1	27.12	8.043	0.018*
	14	28.84	7.598	
	56	28.64	7.879	
Creatinine	1	0.816	0.2211	0.004*
	14	0.888	0.1856	
	56	0.908	0.1998	

DISCUSSION

Therapeutic failure results from false faiths about drugs being prescribed in TB clinics and parallel treatment systems like traditional and complimentary medicines. Thus it may drift patients away from taking treatment for 06 months that add TB burden rather than eradicating it. More over a patient placed on 2nd line anti-mycobacterial drugs has to face severe drug reactions and to take medicine for long durations.

Newly diagnosed pulmonary TB patients admitted from January 2017 to December 2017 in Gulab Devi Hospital, Lahore, Pakistan were invited to be as volunteer in present study. While in a similar study conducted in Iran patients were recruited with some modifications.[6]

The number of patients was in conformity with other studies in which n = 20 patients were enrolled to determine serum levels of Rifampicin and other anti-tuberculous drugs respectively.[7-9] In contrast, one study conducted on Tanzanian population included n = 100 TB patients.[10]

Both males and females were included in present study. Males (68%) were more affected by TB in Pakistan as well as globally while comparing to females (32%) except for few countries like Iran, Afghanistan and Lebonan where females were affected more. Selection of gender among subjects was paradoxical i.e 65% females and 35% males in one Iranian and a Pakistani study.[6,11]

In the current study, plasma samples of the patients were drawn on day1, 14 and 56 at 02 and 06 hours post-dose of anti-tuberculous drugs. One day before blood sampling patients were instructed to fast overnight, and the everyday morning, the patients were administered anti-tuberculous drugs. Paradoxically, in one study held at Tanzania, samples were taken on two occasions at day 7 and 60 post–initiation on 02, 04 and 06 hours post-dose. This was done in the study design to minimize the patients time at the clinic during pharmacokinetics sampling, as they were treated as outpatients.[10] Paradoxically, timing for blood samples collection was same on 02 and 06 hours post-dose of anti-tuberculous drugs as ours but samples were taken on day 7 only.[6]

Patients with pulmonary TB presented with history of cough (96%), fever (100%), night sweats (80%) and hemoptysis (40%). All of these parameters improved while comparing day 1 with day 56. Severity of cough, night sweats, hemoptysis and fever showed a downward trend i.e from severe to mild or absent. At the end of the treatment, all patients were afebrile and 72% had no hemoptysis. Similar parameters were noted in other Indonesian study where patients had cough (99%), fever (67%) and night sweats (64%) and clinical improvement was seen after therapy.[12]

All patients with TB underwent liver function tests on day 1, 14 and 56 to observe drug induced hepatotoxicity (DIH). INH induced hepatotoxicity is a rare side effect. In present study, none of the patient developed hepatotoxicity. Likewise, in Iranian population LFTs were recorded and reported as mean ± SD of AST, ALT, ALK and Bilirubin values as 27.2 ± 34.6 µ/L, 21.7 ± 23.2 µ/L, 308.4 ± 383.7 µ/L and 0.4 ± 0.3 mg/dl. This showed that present study was in line with previous work done in Iranian population.[6]

Although Isoniazid and Ethambutol had been associated with acute kidney injury (AKI).[13] Rifampin is the most common anti-TB drug responsible for AKI identified by one study.[14] In ongoing project, all TB patients were assessed for renal function test (RFT) on day 1, 14 and 56 to appreciate AKI. Results displayed significant change in serum creatinine and urea levels from day 1 till day 56 with *P*-values of 0.004 and 0.014 respectively (Table-4). Serum levels were within normal ranges for both parameters on all three days and no patient developed AKI. Similar findings were reported in other study done in Taiwan where AKI was documented as a rare complication of anti-tuberculous drugs.[14]

CONCLUSION

Clinical improvement in MDR pulmonary tuberculosis patients was significantly seen at the end of FDC therapy. All patients became sputum negative for AFB at the end of treatment and overall quality of health was improved. Close monitoring for liver and renal functions is, however, indispensable.

LIMITATIONS OF STUDY

Present study included a small sample size however evaluation of clinical parameters with liver and renal

functions during and at the end of 2 months therapy has helped to evaluate clinical outcomes in MDR-TB cases in local population. More prospective large scale studies are strongly recommended.

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NS: Conception and design of work
TL: Drafting and revising the manuscript
MR: Drafting the manuscript, analyzing the data.
AF: Collecting and analyzing the data.
AA: Collecting and analyzing the data.
KS: Collecting and analyzing the data.
AB: Drafting the manuscript

CONFLICT OF INTEREST
None to declare.

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None to disclose.

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