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Comparative Incidence of serious side effects from first-line anti-tuberculosis drug in patients treated for active tuberculosis and treatment outcomes

Nisar Hussain Shah [1], Muhammad Muzamil Khan [1], Ayyaz Ahmad [1], Muhammad Hanif [1], Mujahid Ali [1], Muhammad Yasir [1]

1. Faculty of Pharmacy, Bahauddin Zakariya University Multan, Pakistan.
Corresponding Author: Muhammad Muzamil Khan. Email: muzamilpharmacist@gmail.com

A careful retrospective study was carried out on the patients of Tuberculosis in District Head Quarter Hospital Layyah, District Head Quarter Hospital Muzaffargarh and Nishter hospital Multan, Pakistan. The patients having the confirmed TB reports and admitted in the TB ward of the hospitals were included in the study.

While studying the general incidence of TB it was concluded that the risk of TB is greater in the age group 21-40 (43.3%) and in male gender (59%). The incidence of pulmonary TB is 76% as compared to extra-pulmonary TB (i.e.24 %) and study on genetic basis revealed that only 10.6% patients were those which have a family history of TB while 89.6% were those without any family history of TB. While studying treatment outcome, it was concluded that cure ratio was 25%, treatment failure was 11.3%, and treatment default was 14.6% and 32% patients completed the treatment and 18% patients died. It is the need of the time that the government of Pakistan should take effective measures to increase the cure rate.

While studying the incidence of side effects, out of total 150 patients, 20 patients (13.3%) experienced one side effect and 31 patients (20.6%) experienced two side effects and 99 (66%) patients experienced three or more side effects of anti –TB treatment. Frequently affected body organ was liver. Hepatitis was observed in 61 (40.6%) patients, nausea and vomiting in 50 patients (33.3%), loss of appetite in 34 patients (22%) and abdominal pain in 27 patients (18%). Anti -TB treatment could lead to significant side effects. These side effects can be so devastating that patient need to be admitted in the hospital. Effective measures should be taken to avoid these side effects.

Keyword: Tuberculosis, ADRS, Hepatitis, Peripheral Neuropathy, Treatment Outcome.

1. Introduction

Tuberculosis is a common, and in many cases lethal, infectious disease caused by various strains of Mycobacteria, usually *Mycobacterium tuberculosis* [1]. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It spreads through the air when patients suffering from active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air [2].

1.1 Epidemiology of TB in Pakistan

Although Tuberculosis is considered to be a major cause of ill health, there is little reliable epidemiological data available in Pakistan [3]. The annual incidence rate of infectious TB cases is estimated to be between 85-100/100,000 persons. Annually around 120,000 new TB cases are being added to the existing number of TB patients. Some areas in the country have much higher figures, such as Northern areas of Pakistan, where a prevalence rate is 554/100,000 [4]. As in other

developing countries, young age groups are most affected. Male patients outnumber females in most age groups, except in the adolescents. Based on Burden of Disease estimates, TB represents 5% of the total DALYs (disability adjusted life years): which indicates that the burden of tuberculosis in Pakistan is substantially higher than the world average of 3% [5].

1.2 Pathogenesis

Patients with active pulmonary tuberculosis are the major source of spread of *Mycobacterium tuberculosis*. In more than 90% of persons infected with *M. tuberculosis,* the pathogen is contained as asymptomatic latent infection. Recent studies raise the possibility that some persons acquire and eliminate acute infection with *M. tuberculosis* [6]. The risk of active disease is estimated to be approximately 5% in the 18 months after initial infection and then approximately 5% of the remaining lifetime [7]. An estimated 2 billion persons worldwide have latent infection and are at risk for reactivation. Contained latent infection reduces the risk of re infection on repeated exposure, whereas active tuberculosis is associated with an increased risk of a second episode of tuberculosis on re-exposure [8].

1.3 Clinical features

The classic clinical features of pulmonary tuberculosis include chronic cough, sputum production, appetite loss, weight loss, fever, night sweats, and hemoptysis [9].

Extra-pulmonary tuberculosis occurs in 10 to 42% of patients, depending on race or ethnic background, age, presence or absence of underlying disease, genotype of the *M. tuberculosis* strain, and immune status [10].

2. Treatment

There are four recommended regimens for treating patients with tuberculosis caused by drug-susceptible organisms. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances, described subsequently. Each regimen has an initial phase of 2 months, followed by a choice of several options for the continuation phase of either 4 or 7 months.

Because of the relatively high proportion of adult patients with tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6-month regimen to be maximally effective. Thus, in most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of a 2-month initial phase of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). If (when) drug susceptibility test results are known and the organisms are fully susceptible, EMB need not be included. For children whose visual acuity cannot be monitored, EMB is usually not recommended except when there is an increased likelihood of the disease being caused by INH-resistant organisms or when the child has "adult-type" (upper lobe infiltration, cavity formation) tuberculosis. If PZA cannot be included in the initial phase of treatment, or if the isolate is resistant to PZA alone (an unusual circumstance), the initial phase should consist of INH, RIF, and EMB given daily for 2 months. Examples of circumstances in which PZA may be withheld include severe liver disease, gout, and, perhaps, pregnancy. EMB should be included in the initial phase of Regimen 4 until drug susceptibility is determined [11]. For patients receiving daily therapy, EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate that the isolate is susceptible to INH and RIF. When the patient is receiving less than the daily drug intake, expert opinion suggests that EMB can be discontinued safely in less than 2 months (i.e., when susceptibility test results are known), but there is no evidence to support this approach.

Although clinical trials have shown that the efficacy of streptomycin (SM) is approximately equal to that of EMB in the initial phase of treatment, the increasing frequency of resistance to SM globally has made the drug less useful. Thus, SM is not recommended as being interchangeable with EMB unless the organism is known to be susceptible to the drug or the patient is from a population in which SM resistance is unlikely [12].

The continuation phase of treatment is given for either 4 or 7 months. The 4-month continuation phase should be used in the large majority of patients. The 7-month continuation phase is

recommended only for three groups: patients with pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive; patients whose initial phase of treatment did not include PZA; and patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the time of completion of the initial phase is positive. The continuation phase may be given daily (Regimens 1a and 4a), two times weekly by DOT (Regimens 1b, 2a, and 4b), or three times weekly by DOT (Regimen 3a). For human immunodeficiency virus (HIV) sero-negative patients with noncavitary pulmonary tuberculosis (as determined by standard chest radiography), and negative sputum smears at completion of 2 months of treatment, the continuation phase may consist of rifapentine and INH given once weekly for 4 months by DOT (Regimens 1c and 2b). If the culture at the completion of the initial phase of treatment is positive, the once weekly INH and rifapentine continuation phase should be extended to 7 months. All of the 6-month regimens, except the INH--rifapentine once weekly continuation phase for persons with HIV infection (Rating EI), are rated as AI or AII, or BI or BII, in both HIV-infected and uninfected patients. The once-weekly continuation phase is contraindicated (Rating EI) in patients with HIV infection because of an unacceptable rate of failure/relapse, often with Rifamycin-resistant organisms. For the same reason twice weekly treatment, either as part of the initial phase (Regimen 2) or continuation phase (Regimens 1b and 2a), is not recommended for HIV-infected patients with $CD4^+$ cell counts <100 cells/µl. These patients should receive either daily (initial phase) or three times weekly (continuation phase) treatment. Regimen 4 (and 4a/4b), a 9-month regimen, is rated CI for patients without HIV infection and CII for those with HIV infection. [13]

3. Incidence of Adverse Effects of Common Anti-TB Drugs

3.1 Isoniazid

Asymptomatic elevation of aminotransferases: Aminotransferase elevation up to five times the upper limit of normal occur in 10--20% of persons receiving INH alone for treatment of latent tuberculosis infection [14]

Clinical hepatitis: Data indicate that the incidence of clinical hepatitis is lower than was previously thought. Hepatitis occurred in only 0.1--0.15% of 11,141 persons receiving INH alone as treatment for latent tuberculosis infection in an urban tuberculosis control program. [15]

Fatal hepatitis: The rate of fatal hepatitis is estimated 0.023% from a survey on a large scale, but more recent studies suggested that the rate is substantially lower. The risk may be increased in women. Death has been associated with continued administration of INH despite the onset of symptoms of hepatitis [16]

Peripheral neurotoxicity: This adverse effect is dose related and is uncommon (less than 0.2%) at conventional doses. The risk is increased in persons with other conditions that may be associated with neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and breastfeeding women. Pyridoxine supplementation (25 mg/day) is recommended for patients with these conditions to help prevent this neuropathy [18, 19].

3.2 Rifampin

Cutaneous reactions: Pruritis with or without rash may occur in as many as 6% of patients but is generally self-limited. This reaction may not represent true hypersensitivity and treatment with the drug may be continued. More severe, true hypersensitivity reactions are uncommon, occurring in 0.07-0.3% of patients [20].

Gastrointestinal reactions (nausea, anorexia, abdominal pain): The incidence is variable, but symptoms are rarely severe enough to necessitate discontinuation of the drug [21].

Flulike Syndrome: This may occur in 0.4--0.7% of patients receiving rifampin 600 mg twice weekly but not with daily administration of the same dose. Symptoms are more likely to occur with intermittent administration of a higher dose. [21].

Hepatotoxicity: Transient asymptomatic hyperbilirubinemia may occur in as many as 0.6% of patients receiving the drug. More severe clinical hepatitis that, typically, has a cholestatic pattern may also occur. Hepatitis is more common when the drug is given in combination

with INH (2.7%) than when given alone (nearly 0%) or in combination with drugs other than INH.

Orange discoloration of bodily fluids (sputum, urine, sweat, tears): This is a universal effect of the drug. Patients should be warned of this effect at the beginning of treatment. Soft contact lenses and clothing may be permanently stained [22].

3.3 Pyrazinamide

Hepatotoxicity: Early studies using doses of 40--70 mg/kg per day reported high rates of hepatotoxicity. However, in treatment trials with multiple drugs, including INH, liver toxicity has been rare at doses of 25 mg/kg per day or less. In one study, however, hepatotoxicity attributable to PZA used in standard doses occurred at a rate of about 1% [23].

Gastrointestinal symptoms (nausea, vomiting): Mild anorexia and nausea are common at standard doses. Vomiting and severe nausea are rare, except at high doses [24].

Nongouty polyarthralgia: Polyarthralgia may occur in up to 40% of patients receiving daily recommended doses of PZA. This rarely requires dosage adjustment or discontinuation of the drug. The pain usually responds to aspirin or other nonsteroidal anti-inflammatory agents. In clinical trials of PZA in the initial intensive phase of treatment, arthralgias were not noted to be a significant problem [25].

Asymptomatic hyperuricemia: This is an expected effect of the drug and is generally without adverse consequence [26].

Acute gouty arthritis: Acute gout is rare, except in patients with preexisting gout, generally a contraindication to the use of the drug [27].

3.4 Ethambutol

Retrobulbar neuritis: This is manifested as decreased visual acuity or decreased red-green color discrimination that may affect one or both eyes. The effect is dose related, with minimal risk at a daily dose of 15 mg/kg. No difference was found in the prevalence of decreased visual acuity between regimens that contained EMB at 15 mg/kg and those not containing the drug. The risk of optic toxicity is higher at higher doses given daily (18% of patients receiving more than 30 mg/kg per day) and in patients with renal insufficiency. Higher doses can be given safely twice or three times weekly. [28]

Cutaneous reactions: Skin reactions requiring discontinuation of the drug occur in 0.2-0.7% of patients [29].

4. Materials and methods

The comparative retrospective study was carried out in the tuberculosis ward of DHQ hospital Layyah. DHQ hospital Muzaffargarh and Nisthter Hospital, Multan, Pakistan. Patients with positive TB reports were included in the study and were treated with the formulation of routinely used four drugs i.e Rifampicin, Ethambutol, Isoniazid, and Pyrazinamide.

A questionnaire was developed and patients were interviewed after their consent regarding their status of life and their family history of TB. Outcome of disease was carefully observed in patients after treatment with the drugs and patients were interviewed about the side effects of anti TB drugs and comparative incidence of different side effects was noted in our study. We included 12 commonly occurring side effects of anti- TB drugs and their relative occurrences in patients were noted. Hepatitis is considered when hepatic enzyme exceeds 5 times the normal values. Patients who were included in the study were asked to revise their LFT after every 2 months. During the study our exclusion criteria was not to consider the patients with severe chronic hepatic complications in the study, patient's bio data history of drugs, history of the drug regimen and conclusive diagnosis were noted. The side effects of anti-TB drugs were noted in all the patients on treatment. The patients were completely examined regarding their laboratory tests and medical diagnosis. The adverse medical reactions observed in patients on tuberculosis treatment were discussed with the attending physician accompanied by their clinical symptoms. The side effects of anti-TB drugs in these patients are noted on a regular basis. The results were analyzed using excel 2007 features in the tabulated and graphical form.

5. Results and Discussion

5.1 Parameters to be studied

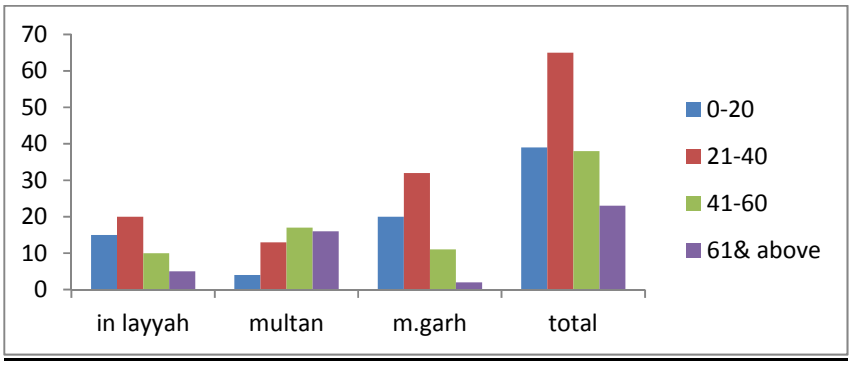
1) Age
2) Sex

3) Incidence of pulmonary and extra-pulmonary TB
4) Quality of life
5) Family history
6) Patient outcome
7) Incidence of side effects
8) Comparative incidence of side effects

1) Age

Relative Incidence of tuberculosis in patients of different age groups

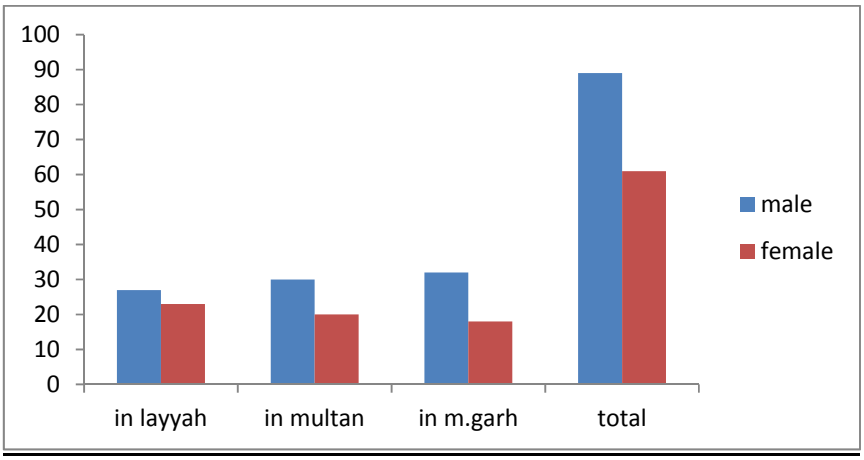
Age group	Layyah	Multan	Muzaffargrh	Total	Percentage
0-20	15	4	20	39	26
21-40	20	13	32	65	43.3
41-60	10	17	11	38	25.3
61& above	5	16	2	23	15.3



2) Sex

Comparative incidence of TB in male and female patients

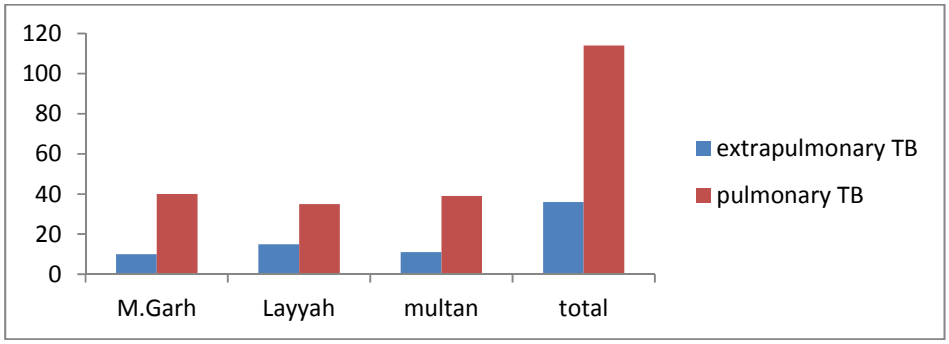
Sex	in Layyah	in Multan	in Muzaffargarh	Total	Percentage
Male	27	30	32	89	59.33
Female	23	20	18	61	40.66



3) Incidence of Pulmonary and Extra-Pulmonary TB

A comparative incidence of pulmonary and Extra-pulmonary tuberculosis in the three districts

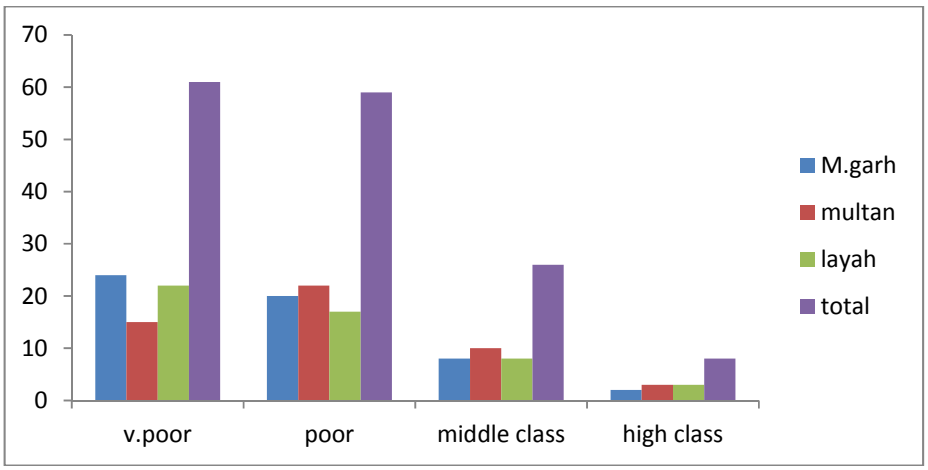
City	Extra-pulmonary TB	pulmonary TB
Muzaffargarh	10	40
Layyah	15	35
Multan	11	39
Total	36	114
Percentage	24	76



4) Quality of life

A comparative study of incidence of tuberculosis on the basis of socioeconomic status of patients in the three districts

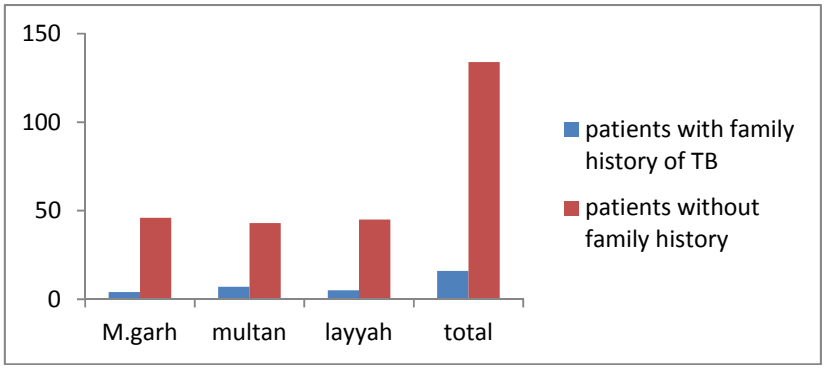
City	Very Poor	Poor	Middle class	High class
Muzaffargarh	24	20	8	2
Multan	15	22	10	3
Layyah	22	17	8	3
Total	61	59	26	8
Percentage	40.6	39.3	17.3	5.3



5) Family history

The incidence of tuberculosis on the basis of family history in the three districts

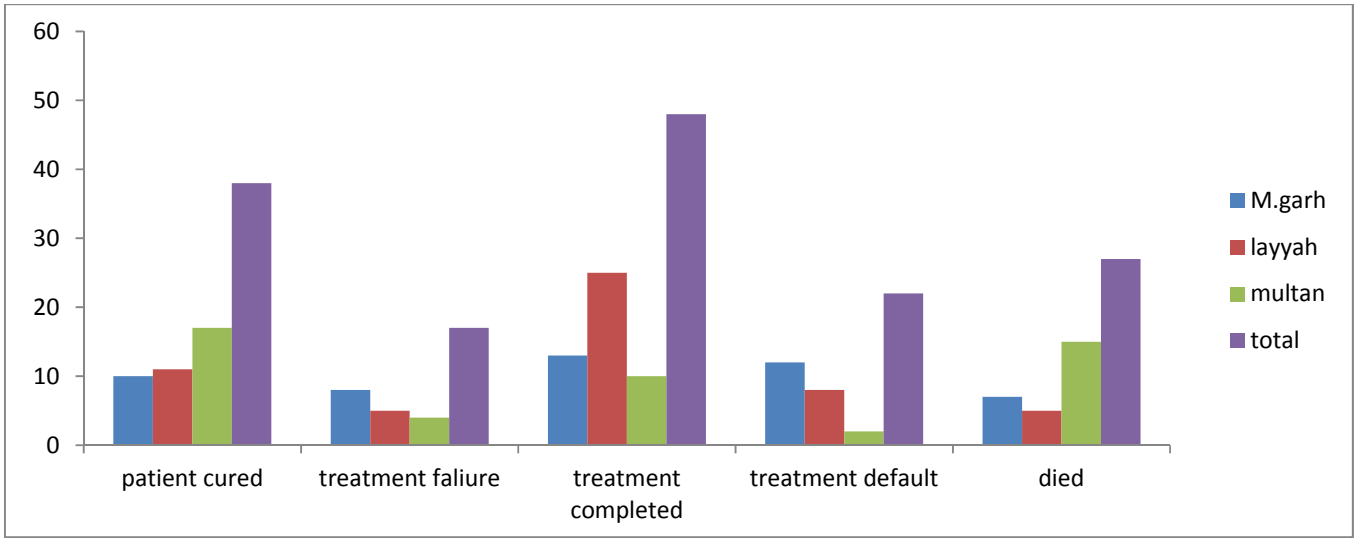
City	Patient with family history of TB	Patients without family history of TB
Muzaffargarh	4	46
Multan	7	43
Layyah	5	45
Total	16	134
percentage	10.6	89.33



6) Outcome of treatment

A relative study on the basis of outcome of treatment in the patients of the three districts

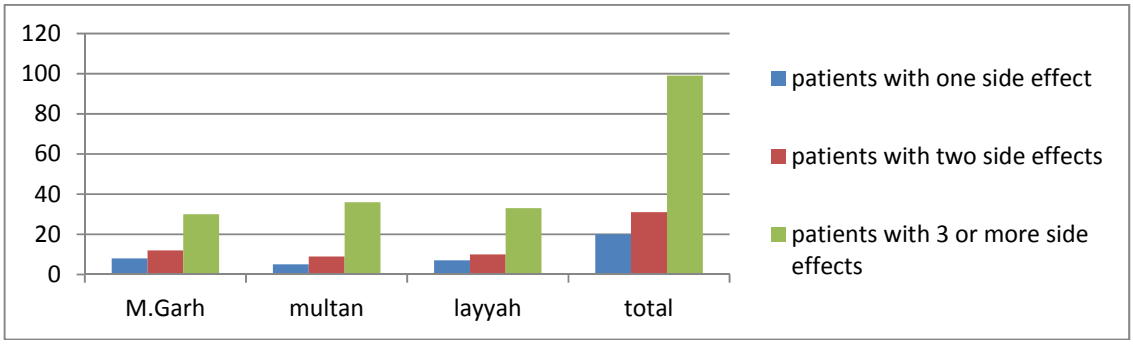
City	Patient cured	Treatment failure	Treatment completed	Treatment default	Died
Muzaffargarh	10	8	13	12	7
Layyah	11	5	25	8	5
Multan	17	4	10	2	15
Total	38	17	48	22	27
Percentage	25.33	11.33	32	14.66	18



7) Incidence of side effects

A relative study of incidence of side effects on the basis of a number of side effects occurring in the patients.

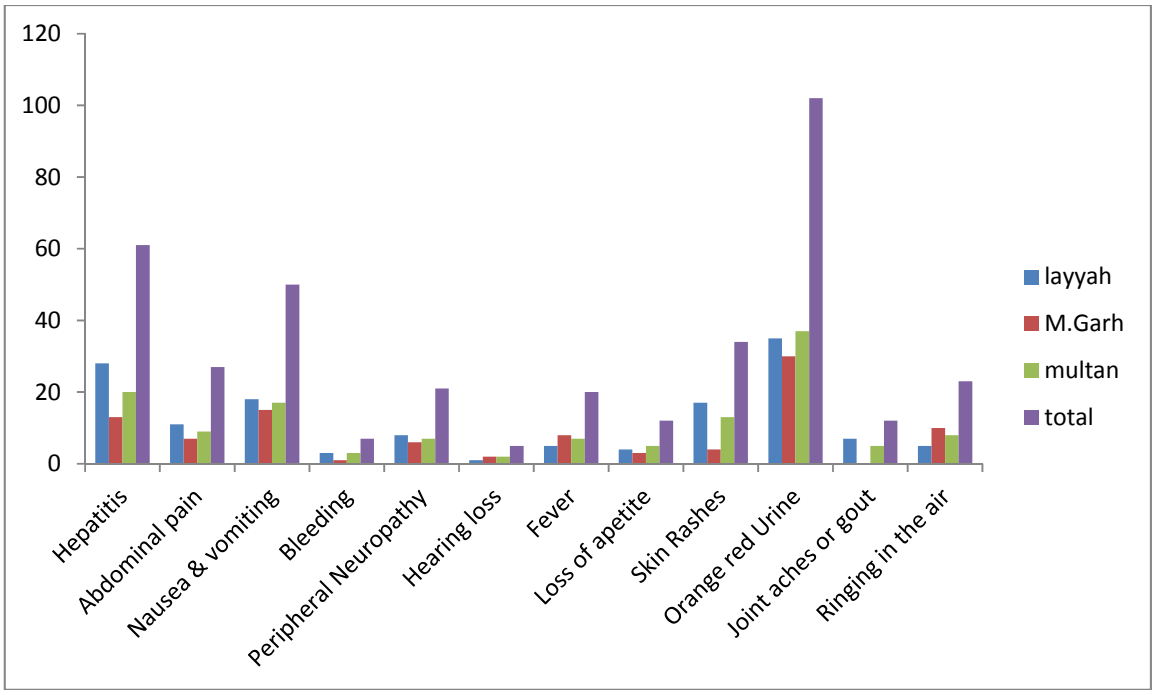
City	Patients with one side effect	Patient with two side effects	Patients with three or more side effects
Muzaffargarh	8	12	30
Multan	5	9	36
Layyah	7	10	33
Total	20	31	99
Percentage	13.33	20.6	66



8) Comparative incidence of side effects

A relative occurrence of different side effects in patients on first line Anti-tuberculosis drugs.

side effect	Layyah	Muzaffargarh	Multan	Total	Percentage
Hepatitis	28	13	20	61	40.66
Abdominal pain	11	7	9	27	18.00
Nausea & vomiting	18	15	17	50	33.33
Bleeding	3	1	3	7	4.66
Peripheral Neuropathy	8	6	7	21	14.00
Hearing loss	1	2	2	5	3.33
Fever	5	8	7	20	13.33
Loss of appetite	4	3	5	12	8.00
Skin Rashes	17	4	13	34	22.66
Orange red Urine	35	30	37	102	68.00
Joint aches or gout	7	0	5	12	8
Ringing in the air	5	10	8	23	15.33



6. Discussion

A careful comparative study was carried out on patients of TB belonging to district Layyah, Multan and Muzafargarh. In the study, many factors were considered.

Patients were classified on the basis of age and the results showed that the incidence of TB is greater in the age group 21-40. Out of total 150 patients belonging to three districts of Pakistan 68 (43%) belongs to the age group 21-40. While 39 (26%) belongs to age group 0-20 and 38 (25%) belongs to the age group 42-60. And 23 patients (15%) belong to age group 61 and above.

Patients were studied on the basis of sex; out of total 150 patients of all three districts 89 (59.3%) were male and 61 (40.6%) were female. Out of 50 patients of Layyah 27 were male and 23 were female and out of 50 patients of Muzaffargarh 32 were male and 18 were female and out of 50 patients of Multan 30 were male and 20 were female.

Study on the basis of pulmonary and extra-pulmonary TB revealed that out of total 150 patients 114 (76%) have pulmonary TB and 36 patients (24%) had extra-pulmonary TB. Among 50 patients of district Layyah 15 have extra-pulmonary TB and 35 have pulmonary TB and among 50 patients of district Multan 11 have extra- pulmonary TB and 39 have pulmonary TB and among 50 patients of district Muzaffargarh 10 patients have extra-pulmonary TB and 40 have pulmonary TB.

In the study on the basis of quality of life, it was concluded that out of 150 patients 61 (40.6%) belong to a very poor class, 59 (39.3%) belong to poor class, 26 (17.3%) belong to middle class and 8 (5.3%) belongs to high class. Among 50 patients of district Muzaffargarh 24 were from very poor class, 20 were from poor class, 6 were from middle class and 2 were from high class and among 50 patients of district Layyah 22 were from very poor background, 17 were from poor class, 8 were from middle class and 3 were from high class. And among 50 patients of Multan 15 were from very poor class, 22 were from poor class, 8 were from middle class and 3 were from a high class background.

Study of the genetic basis, patients were classified in two groups, those having a family history of TB and those not having a family history of TB. Out of total 150 patients 16 (10.6%) were those having a family history of TB and 134 (89.3%) were those without any family history of TB. Among 50 patients of Multan 7 were having a family background of TB and 43 were without a family background of TB and out of 50 patients of LAYYAH 5 were having a family history of TB and 45 were without any history and out of 50 patients of Muzaffargarh 4

were having a family background of TB and 46 were without any family history of TB.

Studies on the basis of treatment outcome of the disease revealed that out of 150 patients 38 (25.3%) were cured and 17 (11%) patients were in the category of treatment failure. And 48 (32%) patients completed the treatment, 22 patients (14.6%) were in the category of treatment default and 27 (18%) patients died due to TB. Among 50 patients of DHQ Muzaffargarh 10 patients were cured, 8 patients were in category of treatment failure, 13 patients completed their treatment, 12 patients do not complete their treatment and 7 patients died. Among 50 patients of DHQ Layyah 11 patients were cured, 5 patients were in category of treatment failure, 25 patients completed their treatment, 8 patients do not complete the treatment and 5 patients died. Among 50 patients of Nishter hospital Multan 17 patients were cured after treatment, 4 were in category of treatment failure, 10 patients completed their treatment, 2 patients did not complete the treatment and 15 patients died.

Patients were studied also on the basis of incidence of side effects. Out of 150 patients 20 (13.3%) were those with at least one side effects, 31 (20.6%) were those having at least 2 side effects and 99 (66%) were those who experience 3 or more side effects.

In the study on the basis of the comparative incidence of side effects, 12 side effects of anti – TB drugs were included. Incidence of hepatitis was observed in 61 (40.4%) patients, abdominal pain in 27 (18%) patients, nausea and vomiting in 50 (33.3%) patients, bleeding in 7 (4.6%) patients, peripheral neuropathy in 21 (14%) patients, hearing loss in 5 (3.3%) patients, fever in 20 (13.3%) patients, loss of appetite in 12 (8%) patients, skin rashes in 34 (22.6%) patients, orange red coloration of urine in 102 (68%) patients, joint aches in 12 (8%) patients and ringing in the ear in 23 (15.3%) patients.

7. Conclusion

The study reveals that the incidence of TB is greater in the age group 21-40 and males are at a greater risk as compared to females. The incidence of pulmonary TB is greater in all three districts of study as compared to extra-pulmonary TB. TB occurs more in very poor and poor people.Few cases of rich people were found and on interviewing them it was assessed that there were some rich girls suffering from bulimia nervosa (eating less due to fear of being obese) got the TB. There were very few cases of those patients having a family history of TB, which reveals that genetics does not play much role in TB. In comparing outcome of disease treatment, cure cases were greater in Nishter hospital Multan and treatment failure and treatment default cases were greater in DHQ Muzaffargarh, treatment completed cases were greater in DHQ Layyah and died cases were greater in Multan. In the incidence of side effects 66% patients were those who show more than 3 side effects so greater number of side effects are observed with TB treatment. And in the comparative study of all side effects of anti-TB drug it was concluded that incidence of hepatitis is greater in Asians (40.6%) and peripheral neuropathy occur in 14% patients so the use of pyridoxine should be encouraged to avoid peripheral neuropathy and skin rashes occur in 22% patients. These medicines cause several undesirable effects like hepatitis in Asians, which urge the need of revising the protocol of anti-TB treatment for Asians and for the prevention of fatal hepatotoxicity.

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