

THE EFFECT OF ANTI TUBERCULOSIS DRUGS ON LIVER ENZYMES MOSUL IRAQ 2019-2020

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ABSTRACT

Background: Tuberculosis (TB) is a major cause of illness and death worldwide especially in Asia and Africa Anti tuberculosis drugs cause hepatotoxicity in some individuals leading to acute liver failure, which results in death. Such phenomena limit the clinical use of drugs, contributing to treatment failure that possibly causes drug resistance. Furthermore, associated risk factors for the development of anti-tuberculosis drug induced hepatotoxicity (anti-TB-DIH) so we need liver function test.

Aim: Assess the percentage of liver dysfunction change in liver enzymes in patients with active Mycobacterium Tuberculosis before and during treatment, and the implications of this for treatment completion in Mosul Governorate from (1/12/2019 -1/7/2020).

Methodology: A total of 62 consecutive TB patients were prospectively followed up both clinically and biochemically before and during their course of anti-TB therapy with daily doses of rifampin, isoniazid, ethambutol, pyrazinamide, and streptomycin, Total serum Bilirubin(T. S. B). Serum Alanine Transaminase(ALT), Serum Aspartame Transaminase (S. G. O. T) were done for them.

Result: 62 patients (31 male, 31 female), all patients had subclinical mild-moderate increased in liver enzymes, one patient the (T. S. B.)had reached more than double upper normal level, while in 4 patients the (A. L. T), and 5patients the (A. S. T.) had reached more than upper normal level, one patient had (TB DILI) we stopped give him (R, PZ) because more than double upper normal level of (T. S. B), (A. LT.) and (A. S. T.).

Conclusion: Deranged liver function tests (L. F. Ts) are common in patients treated for Mycobacterium TB, but most patients are able to complete treatment. Routine LFT monitoring in patients without symptoms of hepatotoxicity is unlikely to affect treatment decisions.

Recommendation: Deranged liver function tests (L. F. Ts) developed within the first 2months after initiating treatment. Patients taking anti-TB drugs should be followed biochemically during the initial phase of treatment than during the continuous phase, and more frequently for those had clinical symptoms of hepatotoxicity or had risk factors.

KEYWORDS: Mosul Governorate, Tuberculosis (TB), liver function tests (L. F. Ts), drugs induced hepatotoxicity (D. I. H), Drugs Induced Liver Injury (DILI), Total serum Bilirubin (T. S. B). Serum Alanine Transaminase (S. G. P. T), Serum Aspartame Transaminase (A. S. T.).

1. INTRODUCTION

Tuberculosis(TB) is a bacterial disease, caused by Mycobacterium tuberculosis (MTB), which is part of complex of organisms including M. bovis (reservoir cattle) and M. africanum (reservoir human). The impact of TB on world health is significant for adults, Mycobacterium tuberculosis is spread by inhalation of aerosolized droplet nuclei from other infected patients during cough and sneezing with sputum smear positive

that it is highly contagious ;Once the mycobacterium's lodge in the alveoli and initiate the recruitment of macro phages and lymphocyte. Macro phages undergo transformation in to epithelioid and langhans cell which aggregate with the lymphocytes to form the classical tuberculous granuloma. Numerous granuloma aggregate to form a primary lesion or (Ghon focus) a pale yellow, caseous nodule, usually a few mm to 1-2 cm in diameter. M. bovis infection arises from drinking non sterilized milk from infected cows. The symptoms of pulmonary

(TB) cough, fever, night sweat, lost of appetite, lost of weight, chest pain, sputum my contain blood.^[1]

Tuberculosis: (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). In 2019, about 10 million people developed TB and 1.4 million died (This includes 0.2 million deaths among HIV-positive people, which are officially classified as deaths caused by HIV/AIDS).

TB can affect anyone anywhere, but most people who develop the disease (about 90%) are adults; there are more cases among men than women; and of those who fell sick with TB in 2019, 87% were in 30 high TB burden countries. Case rates at national level vary from less than 5 to more than 500 per 100 000 population per year. TB is a disease of poverty, and economic distress, vulnerability, marginalization, stigma and discrimination are often faced by people affected by TB. About a quarter of the world's population is infected with *M. tuberculosis*. TB is curable and preventable. Most people (about 85%) who develop TB disease can be successfully treated with a 6-month drug regimen; treatment has the additional benefit of curtailing onward transmission of infection. Since 2000, TB treatment has averted more than 60 million deaths, although with access still falling short of universal health coverage (UHC), many millions have also missed out on diagnosis and care. Preventive treatment is available for people with TB infection. The number of people developing infection and disease (and thus the number of deaths) can also be reduced through multi sectoral action to address TB determinants such as poverty, under nutrition, HIV infection, diabetes and smoking. Research breakthroughs (e. g. a new vaccine) are needed to rapidly reduce TB incidence worldwide to the levels already achieved in low-burden countries, where TB is often regarded as a disease of the past. In 2014 and 2015, all Member States of the World Health Organization (WHO) and the United Nations (UN) committed to ending the TB epidemic, through their adoption of WHO's End TB Strategy and the UN Sustainable Development Goals (SDGs). The strategy and SDGs include milestones and targets for large reductions in TB incidence, TB deaths and costs faced by TB patients and their households, between 2015 and 2035. Efforts to step up political commitment to the fight against TB intensified in 2017 and 2018.^[2]

Diagnostic tests for TB disease include sputum smear microscopy (developed more than 100 years ago), rapid molecular tests (first endorsed by WHO in 2010) and culture-based methods – the latter take up to 8 weeks to provide results but remain the reference standard. Today, TB that is resistant to first-line and second-line anti-TB drugs can be detected using rapid tests, culture methods and sequencing technologies. Without treatment, the mortality rate from TB is high. Studies of the natural history of TB disease in the absence of treatment with

anti-TB drugs (conducted before drug treatments became available) found that about 70% of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed, as did about 20% of people with culture-positive (but smear-negative) pulmonary TB.

Effective drug treatments were first developed in the 1940s. The currently recommended treatment for cases of drug-susceptible TB disease is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. The Global TB Drug Facility supplies a complete 6-month course for about US\$ 40 per person. For people with drug susceptible TB, treatment success rates of at least 85% are regularly reported to WHO by its 194 Member States. Treatment for people with rifampicin-resistant TB (RR-TB) and multidrug resistant TB (MDR-TB) is longer, and requires drugs that are more expensive (\geq US\$ 1000 per person) and more toxic. The latest data reported to WHO show a treatment success rate for MDRTB of 57% globally.

The only licensed vaccine for prevention of TB disease is the bacille Calmette-Guerin (BCG) vaccine. The BCG vaccine was developed almost 100 years ago, prevents severe forms of TB in children and is widely used. There is currently no vaccine that is effective in preventing TB disease in adults, either before or after exposure to TB infection, although results from a Phase II trial of the M72/AS01E candidate are promising.^[2,3]

Aim: The objective of this study was decrease treatment failure by assess the percentage of liver dysfunction. change in liver enzymes in patients with active Mycobacterium Tuberculosis before and during treatment, and the implications of this for treatment completion in Mosul Governorate from (1/12/2019 - 1/7/2020).

Methodology: The study done in Mosul Governorate (Alayman District) from (1/12/2019 -1/7/2020). A total of 62 consecutive TB patients were prospectively followed up both clinically and biochemically before and during their course of anti-TB therapy with daily doses of rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin, Total serum Bilirubin (T. S. B). Serum Alanine Transaminase (S. G. P. T), Serum Aspartame Transaminase (S. G. O. T) were done for them. The biochemical tests done by FUJI DRI-CHEM NX500i (CLINICAL CHEMISTRY ANALYZER). The blood sample taking before treatment, after(2-4) weeks and (12-14)weeks during treatment.

The Collected data included the socio demographic and clinical data were collected and laboratory testing (5 ml venous blood)

- (1) TB registration code and the year.
- (2) Socio demographic data which included name, age, sex and residence.

- (3) Forms of tuberculosis; Either: Pulmonary (either smear positive or smear negative) or extra pulmonary.
- (4) History of previous treatment if present (category of patients or type of the patient); either new, relapse, treatment after failure, treatment after default, transfer in or others.
- (5) Schedule of treatment (recommended standardized treatment regimen) according to NTP.
- (6) The recorded follow up for smear-positive pulmonary tuberculosis included sputum smear microscopic examination for acid fast bacilli, at the end of 2nd month, at end of 5th month and at the end of treatment.
- (7) Outcome; cure, treatment completed, treatment failure, died, default and transfer out.
- (8) Liver enzymes result.

RESULT

Drugs Induced Liver Injury (DILI) was defined as peak alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (5 × ULN) or ALT ≥ 3 × ULN with total bilirubin > 2 × ULN.

A total 62 new diagnosed TB patients who were negative for human immunodeficiency virus and hepatitis B and C, and started taking anti-TB drugs were included in this study. The mean age was 37. 5 years, (range, 15-75) years and (31male, 31female). TB more common in age group (15-24) in both gender (table 1).

The laboratory results shows increase in liver enzymes after taking Anti TB drugs (R, INH, PZ, ETB), but the liver enzymes decreased near the pre treatment level after 1 month from change treatment to (R, INH), except on one patient we stopped give him (R, PZ) because more than double upper normal level of (T. S. B), (A. LT.) and (A. S. T.). Total Serum Bilirubin (T. S. B) increased less than 5 u mol/l in 49 patients (70%), (5-10) u mol/l in 10 patients (16, 13%), (11-15) u mol /l in 2 patients (3. 23%), and more than double upper normal level in one patient. The mean increased about 2 u mol /l, but more in in male age group (> 55) years. (Tables 1, 2).

Serum Alanine Transaminase (S. G. P. T) increased less than 5 u mol/l in 31patients (50%), (5-10) u mol/l in 19 patients(30. 65%), (11-15) u mol/l in 4 patients (6. 45%), (16-20) u mol/l in 4 patients (6. 45%) and more than upper normal level in 4 patients (6. 45%). The mean increased about 3 u mol /l, but more in female age group (15-24) years and in male age group (> 55) years. (Tables 3, 4).

Serum Aspartame Transaminase (S. G. O. T) increased less than 5 u mol/l in 31patients (50%), (5-10) u mol/l in 15 patients(24. 19%), (11-15) u mol/l in 8 patients (12. 9%), (16-20) u mol/l in 3 patients (4. 84%) and more than upper normal level in 5 patients (8. 06%). The mean increased about 3 u mol /l male, 6 u mol/l in female, but more in female age group (15-24) years and in male age group (> 55) years. (Tables 5, 6).

Table (1): Total Serum Bilirubin u mol/L.

Age group		Mean value before treatment	Mean value taking (R, INH, PZ, ET)	Mean value taking (R-INH)
15-24 Year	9 male	9. 44	11. 22	9. 17
	9 Female	7. 33	8. 5	6. 66
25-34 Year	6 male	10. 33	13	10. 22
	6 female	8. 75	9. 5	9. 11
35-44 Year	6 male	8. 5	8. 9	7. 75
	5 Female	5	7. 66	6. 75
45-54 Year	5 male	7. 1	8. 2	7. 44
	6 Female	5. 33	7. 66	6. 25
>55 Year	5 male	8	13	7. 5
	6 female	9	9. 9	8. 5
Total	31 male	8. 67	10. 86	8. 42
	31 female	7. 08	8. 64	8. 5

Table (2): Total Serum Bilirubin increase during taking(R, INH, PZ, ET) in u mol/L.

Gender	<5 u/L	5-10 U/L	11-15 U/L	16-20 U/L	>double upper Normal level
Male	25	4	1		1
	40. 32%	6. 45%	1. 61%		1. 61%
Female	24	6	1		
	38. 71%	9. 76%	1. 61%		
Total	49	10	2		1
	79. 03%	16. 13%	3. 23%		1. 61%

Table (3): S ALT(GPT) U mol/L.

Age group		Mean value before treatment	Mean value taking (R, INH, PZ, ET)	Mean value taking (R-INH)
15-24 Year	9 Male	18. 57	22. 55	16. 14
	9 Female	13. 52	20. 86	13
25-34 Year	6 Male	18. 66	19. 5	17
	6 female	14. 75	16. 5	15. 33
35-44 Year	6 Male	18. 5	19. 75	15
	5 Female	17. 5	18. 2	17. 2
45-54 Year	5 Male	13. 66	14. 8	12. 75
	6 Female	17. 33	23. 5	15
>55 Year	5 Male	18. 8	25. 66	21. 33
	6 Female	17. 66	19. 8	13
Total	31 Male	17. 64	20. 45	16. 44
	31 Female	16. 15	19. 77	14. 71

Table (4): S ALT(GPT) increase during taking(R, INH, PZ, ET) in u mol/L.

Gender	<5 U/L	5-10 U/L	11-15 U/L	16-20 U/L	>upper Normal level	>3 upper Normal level
Male	15 24. 19%	10 16. 13%	2 3. 23%	1 1. 61%	2 3. 23%	1 1. 61%
Female	16 25. 81%	9 14. 52%	2 3. 23%	3 4. 84%	1 1. 61%	
Total	31 50%	19 30. 65%	4 6. 45%	4 6. 45%	3 4. 84%	1 1. 61%

Table (5) S AST (GOT) u mol/l

Age group		Mean value before treatment	Mean value taking (R, INH, PZ, ET)	Mean value taking (R-INH)
15-24 Year	9 Male	22. 57	24. 55	20. 83
	9 Female	21. 66	35. 43	19. 33
25-34 Year	6 Male	22. 33	23. 11	21. 42
	6 Female	18. 25	20. 5	18. 66
35-44 Year	6 Male	21. 8	22. 6	16. 75
	5 Female	20. 22	21. 5	19. 75
45-54 Year	5 Male	18. 33	20. 5	20. 1
	6 Female	19. 33	28. 5	20. 75
>55 Year	5 Male	18. 5	26. 33	21. 66
	6 Female	19. 33	20. 22	16. 8
Total	31 Male	20. 71	23. 42	20. 15
	31 Female	19. 76	25. 17	18. 8

Table (6) S AST (GOT) increase during taking(R, INH, PZ, ET) in u mol/L.

Gender	< 5 u/L	5-10 U/L	11-15 U/L	16-20 U/L	>upper Normal level	>3 upper Normal level
Male	17 27. 42%	7 11. 29%	4 6. 45%	1 1. 61%	1 1. 61% %	1 1. 61%
Female	14 22. 28%	8 12. 9%	4 6. 45%	2 3. 23%	3 4. 84%	
Total	31 50%	15 24. 19%	8 12. 90%	3 4. 84%	4 6. 45%	1 1. 61%

DISCUSSION

In this study, we have shown that 61 patients (98. 4% of patients) completed their course of standard TB therapy without clinically significant liver enzymes elevations detected. One patient (male 64 years old) had DILI. The

mean age TB patient was 37. 5 years, (range, 15-75) years and (31male, 31female), TB more common in age group (15-24) in both gender (Table 1), while in other studies in Korea mean age group was 46 years, (male 59. 5%, female 40. 5%)^[5], in Zahedan Iran (44% male 56%

female)^[6], in Ethiopia the, (male 59. 5%, female 40. 5%), the mean age being 34. 5 (\pm 15. 2 years), but the highest number of participants was found in the age group of 20–49 years which is (67. 7%)^[7], in Egypt (male 44%, female 56%, mean age 33. 6 \pm 13years)^[8], in India mean age (\pm SD) being 32. 87 (15. 8) years. 70% were younger than 35 years. 70% of the study populations were females.^[11]

The majority of elevations of liver enzymes during TB treatment had occur within the first (14-56) day of therapy, in England also within (14-56)^[4], in Korea the median was 41days^[5], in Iran (3-150) days^[6], in Ethiopia onset of hepatotoxicity was 13–58 days (median of 26 days)^[7], in Egypt within 15–60 days (median: 30 days)^[8], in Taiwan patients was developed hepatotoxicity after a median 38. 0 days from start of treatment.^[9] In India the median duration was (30 days).^[11]

In our study in Mosul Iraq only one patient (1. 6%) had DILI at the end of 8 weeks, other studies in England (3. 4 %)^[4], in Korea (8. 7%)^[5], in Iran (5. 5%)^[6] in Ethiopia (8%)^[7], in Egypt (15%)^[8], in Taiwan (12. 0% Around 3. 5% had severe hepatotoxicity)^[9], in India (5. 7%).^[11] In Mosul all TB patients had low risk factors for DILI.

Risk factors for anti-TB DILI : **Advanced age** the highest incidence occurs in individuals above 50 years.^[5,10] **Gender** Females are more prone to anti-tubercular drug-induced hepatotoxicity than males.^[5,10,11] **Alcoholism** (which is defined as consuming >35 units and >28 units of alcohol per week for at least ten years for men and women, respectively) was found to be significantly associated with the high incidence of anti-TB-DIH.^[5,7,10] **Malnutrition** enhanced hepatotoxicity in developing countries.^[5,10] **Concomitant drugs** Concurrent antiretrovirals like nevirapine, stavudine, efavirenz are known to enhance hepatotoxicity.^[10] **Concomitant infections** chronic hepatitis B, hepatitis C, (HIV) infection enhance hepatotoxicity.^[4,5,10,11] **Genetic Susceptibility:** Asian males have double the rate of induced hepatotoxicity than white males and nearly 14 times that of black males.^[4,10]

CONCLUSION

A significant number of adult patients on first-line TB treatment had deranged liver function tests (L. F. Ts) or DILI developed within the first 2months after initiating treatment. Patients taking anti-TB drugs should be followed clinically and biochemically during the initial phase of treatment than during the continuous phase, and more frequently for those had clinical symptoms of hepatotoxicity or had risk factors.

RECOMMENDATION

For high-risk patients, careful adjustment of the anti-tuberculosis regimen and regular monitoring of liver transaminases enzymes are necessary.

REFERENCES

1. Davidson's principle & practice of Medicine 21st Edition 2010 (page 688-695).
2. WHO Global Tuberculosis report 2020 page xiii-xiv;1-2.
3. National Tuberculosis management 6th Edition 2018.
4. Tweed, C. D., Wills, G. H., Crook, A. M. *et al.* Liver toxicity associated with tuberculosis chemotherapy in the REMoxTB study. *BMC Med*, 2018; 16: 46.
5. Ina Jeong Jong-Sun Park, Young-Jae Cho, Ho Il Yoon, Junghan Song, Choon-Taek Lee, and Jae-Ho Lee Drug-induced Hepatotoxicity of Anti-tuberculosis Drugs and Their Serum Levels Journal of Korean Medical Science J Korean Med Sci. 2015 Feb; 30(2): 167–172. Published online 2015 Jan 21. doi: 10.3346/jkms2115.30.2.167.21.
6. Maliheh Metanat, Batool Sharifi Mood, Masoud Salehi *et al.* Risk Factors and Pattern of Changes in Liver Enzymes Among the Patients With Anti-Tuberculosis Drug-Induced Hepatitis International Journal of Infection The Official Journal of Zahedan University of Medical Sciences Published Online: April 20, 2015.
7. Wondwossen Abera a, Waqtole Cheneke b, Gameda Abebe Incidence of antituberculosis-drug-induced hepatotoxicity and associated risk factors among tuberculosis patients in Dawro Zone, South Ethiopia: A cohort study International Journal of Mycobacteriology, 2016; 5: 14–20.
8. Hoda A. Makhlof Ahmed Helmy Ehab Fawzy Madiha El-Attar Hebat Alla G. Rashed A prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases Hepatol Int, 2008; 2: 353–360.
9. C-C Shu' C-H Lee, M-C Lee, J-Y Wang, C-J Yu, L-N Lee Hepatotoxicity due to first-line anti-tuberculosis drugs: a five-year experience in a Taiwan medical centre Int J Tuberc Lung Dis, 2013 Jul; 17(7): 934-9. doi: 10.5588/ijtld.12.0782.
10. Vidyasagar Ramappa and Guruprasad P. Aithal Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management *Journal of Clinical and Experimental Hepatology* (JCEH) Published online 2012 Dec Published online 2012 Dec 20. doi: 10.1016/j.jceh.2012.12.001.
11. Kumar R., Bhatia V., Khanal S. Antituberculosis therapy-induced acute liver failure: magnitude, profile, prognosis, and predictors of outcome. *Hepatology*, 2010; 51: 1665–1674. [PubMed] [Google Scholar].