SENNOS

Journal of Drug Delivery and Biotherapeutics (JDDB)

Journal homepage: https://sennosbiotech.com/JDDB/1

Review Article

Hepatotoxicity Associated with Anti-Tuberculosis Medications: Analyzing Mechanisms, Risk Factors, and Strategies for Prevention and Management

Dipali D. Zade*, Pranali A. Raut

Department of pharmaceutics, Swami Institute of Pharmacy, A/P. Abhona, Nashik MH India

ARTICLEINFO

ABSTRACT

Hepatotoxicity associated with anti-tuberculosis (TB) medications represents a significant challenge in the management of TB, often complicating treatment regimens and increasing the risk of adverse outcomes. This review aims to analyze the mechanisms underlying hepatotoxicity induced by commonly used anti-TB drugs, such as isoniazid, rifampicin, pyrazinamide, and ethambutol. The liver toxicity mechanisms involve drug-induced immune responses, mitochondrial dysfunction, oxidative stress, and the disruption of hepatocyte metabolism. Furthermore, the review explores various risk factors contributing to hepatotoxicity, including pre-existing liver conditions, genetic polymorphisms, alcohol consumption, co-infections (e.g., HIV), and age-related susceptibility. Additionally, strategies for the prevention, early detection, and management of hepatotoxicity are discussed, emphasizing dose adjustments, liver function monitoring, the use of hepatoprotective agents, and alternative drug regimens. Effective management approaches are essential to ensure treatment adherence and prevent the progression of liver damage. The review concludes by underscoring the importance of personalized medicine and the need for further research to better understand the pathophysiology of anti-TB drug-induced hepatotoxicity and to develop safer therapeutic strategies for TB patients.

Keywords: Hepatotoxicity; Anti-tuberculosis medications; Risk factors; Liver function monitoring; Drug-induced liver injury

Corresponding Author:
Dipali D. Zade
Department of pharmaceutics, Swami Institute of Pharmacy, A/P. Abhona, Nashik MH India
E-mail addresses: dipszade10@gmail.com

Received date: 01-Nov-2024 Revised date: 29-Nov-2024, Accepted date: 10-Dec-2024

Crossref DOI: https://doi.org/10.61920/jddb.v1i03.155

1. INTRODUCTION

Tuberculosis (TB) is a preventable infectious disease that causes mortality. 2004 had 9 million new TB infections and 1.7 million deaths. Sub-Saharan Africa has the greatest HIV/AIDS incidence and mortality rates, whereas Southeast Asia has the most TB cases and deaths. For adult respiratory TB, two months of isoniazid, rifampicin, and pyrazinamide are followed by four months of isoniazid and rifampicin [1] [2]. In most undeveloped nations, ethambutol is added to this regimen, and the WHO advises streptomycin for retreatment (WHO). Hepatotoxicity, skin reactions, GI and neurological disorders are major antituberculosis side effects [3]. This review focuses on the most severe, hepatotoxicity. ATDH increases morbidity, mortality, and treatment inefficacy. Asymptomatic transaminase levels have no symptoms. Hepatotoxicity is common with antituberculosis medication but may be deadly if not recognized early. Adverse effects reduce therapy effectiveness by causing nonadherence, which leads to treatment failure, relapse, or drug resistance. Active TB patients must adhere to therapy [4]. Due of the extended therapy, the patient must stay motivated even if he's feeling better. In addition, quitting TB therapy and switching to second-line antituberculosis treatments causes an inferior therapeutic response. Despite public health initiatives and good antituberculous medication, mycobacterium In the U.S., tuberculosis is infrequent yet clinically significant. 12,000 to 15,000 active TB infections and 600 fatalities occur annually in the U.S. Tuberculosis is one of the five deadliest infectious illnesses globally [5].

The development of streptomycin by Selman Waksman in 1944 heralded the beginning of modern antituberculosis medications. PAS was developed in 1949, isoniazid in 1952, pyrazinamide in 1954, ethambutol in 1962, Rifampin in 1963, and cycloserine in 1964 as more powerful drugs with wider effectiveness and higher tolerance [6]. Biomedical science's 20th-century success was TB chemotherapy [7].

First-line antituberculosis drugs may induce immediate liver damage, liver failure, death, or emergency liver transplantation. Combination therapy, which is crucial for treating active TB, seems to increase hepatotoxicity [8].

For active TB, a six- to nine-month course of at least two anti-mycobacterial medications such isoniazid, Rifampin, pyrazinamide, and ethambutol is indicated (the two latter agents often given in a Four-drug regimen for the first two months in patients with suspected drug resistant disease). PAS is seldom used due to its limited tolerance and hepatotoxicity. Multidrug resistance is treated with ethambutol. Rifabutin and rifapentine are similar to rifampin and also kill Mycobacterium TB and atypical mycobacteria. Second-line antibiotics have lower hepatotoxicity rates than first-line antibiotics: amikacin, azithromycin, capreomycin, cycloserine, ethionamide, levofloxacin, moxifloxacin, and streptomycin [9].

Latent TB or a positive protein derivative skin test (PPD), especially in a high-risk person, need medication after known exposure or skin test conversion. Standard therapy for latent TB is nine months of daily or twice-weekly isoniazid [10]. The twice-weekly regimen is suited for "directly observed treatment," which improves compliance and early detection and management of adverse effects such hepatotoxicity. Options include isoniazid daily or twice weekly (DOT), rifampin daily, or isoniazid and rifapentine once weekly for three months. A four-month course of rifampin +

pyrazinamide is no longer advised due to hepatotoxicity. Ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, and rifapentine are first-line TB drugs. Streptomycin, capreomycin, cycloserine, ethionamide, amikacin, levofloxacin, moxifloxacin, and para-amino salicylic acid are second-line medicines (PAS). Ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, and rifapentine are among the first-line drugs used to treat tuberculosis. Streptomycin, capreomycin, cycloserine, ethionamide, amikacin, levofloxacin, moxifloxacin, and para-amino salicylic acid are examples of second-line antibiotics (PAS). Bed aquiline, the first innovative TB treatment drug in over 40 years, was licenced in 2012. Bedaquiline is presently unavailable and should only be used for multidrug-resistant TB as direct monitored therapy. List of antituberculosis drugs: Ethambutol Isoniazid, Pyrazinamide, Rifabutin, Bedaquiline, Capreomycin, Cycloserine, Rifampin, Rifapentine [10].

1.1 Hepatotoxicity

Hepatotoxicity is an uncommon but significant adverse pharmacological event. When alanine aminotransferase and alkaline phosphatase levels are high, hepatic damage is hepatocellular, cholestatic, or mixed. Idiosyncrasy, age, gender, alcohol consumption, concurrent drug use, previous or underlying liver disease, genetic and environmental variables are risk factors. Liver damage symptoms include stomach pain, jaundice, fever, nausea, vomiting, diarrhoea, pruritus, and rash [11].

1.2 There are two types of hepatotoxicity

Intrinsic reactions are dose-dependent and predictable, whereas idiosyncratic reactions are not (more common). Hepatic damage may be hepatocellular, cholestatic, or mixed, depending on whether ALT is >2–3 times the upper limit of normal and/or ALP is >2 times the upper limit of normal.

Hepatotoxicity symptoms include jaundice or elevated levels of liver function marker proteins like AST/ALT, APT, or total bilirubin. When ALT levels are more than three times the upper limit of normal (ULN) in the context of hepatitis symptoms and/or jaundice, therapy should be paused and a modified or alternative regimen used. ALT is more specific for hepatocellular damage than AST, which might signal muscle, heart, or kidney disorders [12].

2. RISK FACTORS ASSOCIATED WITH HEPATOTOXICITY

2.1 Drug Related Factors

Since most anti-TB patients take many drugs, quantifying the incidence of hepatotoxicity is challenging. Isoniazid, rifampicin, and pyrazinamide induce hepatotoxicity; ethambutol and streptomycin don't. Isoniazid (INH), rifampicin, and pyrazinamide hepatotoxicity evidence originates from latent TB monotherapy or with other nonhepatotoxic regimens. When used to alleviate pruritus in cirrhotic individuals, rifampicin causes DILI. It may be exaggerated, and the higher risk may be due to liver disease. In other studies, rifampicin alone as a preventive for latent TB had a low DILI risk. INH is most often harmful. In four large population-based observational studies, isoniazid monotherapy hepatotoxicity ranged from 0.1% to 0.566%. 23.2 per 100,000 persons die with INH-based preventative medicine,

according to FDA statistics. In a meta-analysis, isoniazid was more likely to induce hepatotoxicity (OR 1.6) without rifampicin, but the combination increased the risk (OR 2.6) compared to either drug alone. Daily dosing regimens do not enhance hepatotoxicity risk compared to three-times-a-week regimens [13].

2.2 Intrinsic Toxicity in Animals

Preclinical medication development includes animal toxicity tests. The assumption behind these investigations is that large doses of a medicine given to animals would reveal inherent potential toxicity that would be rare in people receiving therapeutic amounts. These assays detect intrinsic hepatotoxicity in drugs and exclude those that provide an unacceptable risk. Using these concepts, antiTB DILI animal models have been developed. Male Wister rats treated with 100 mg/kg isoniazid for 21 days develop liver damage. Hydrazine, an isoniazid metabolite, plays a substantial role in liver injury. In another research, isoniazid and rifampicin induced liver damage in mice. This model supports the idea that mitochondrial redox changes are significant in anti-TB drug hepatotoxicity. This model's dosages were roughly 10 times greater than human levels in milligrammes per kilogramme.

Histologically, the animal had hepatic steatosis, not DILI. Only phorone pre-treatments, which depleted glutathione, produced hepatocyte necrosis in human DILI. Most idiosyncratic DILI are pharmacologically unexpected. Idiosyncrasy is a person's unique reaction to a medication, which is impacted by host variables in anti-TB druginduced hepatotoxicity. Animal models can't mimic such conditions. Animal models don't precisely match the phenotype of anti-TB DILI in humans [14].

2.3 Drug Biotransformation, Detoxification and Elimination

Reactive metabolites are connected to clinical toxicities, including certain "idiosyncratic" DILI. Metabolite electrophiles. After detoxification, they react with lysine and cysteine's nucleophilic groups. Covalently altered proteins may be repaired or destroyed. Drug-metabolite adducts impair important cellular activities and injure target organs if these mechanisms fail. Covalent protein binding may potentially produce immune-mediated damage [15].

Reactive metabolite generation may be increased in a person with increased amounts of enzymes involved in the biotransformation of a medication, such as phase I cytochrome P450 enzymes that do oxidation, reduction, or hydrolysis. Individuals may have low levels or reduced activity of enzymes that detoxify reactive metabolites through glucuronidation, sulfation, acetylation, or glutathione conjugation. Transporter molecules or proteins increase water-soluble metabolite excretion in Phase III of drug disposal. Most first-line anti-TB drugs are lipophilic and must be transformed into water-soluble molecules before elimination. Synthesis and buildup of reactive metabolites induce hepatotoxicity, not the parent drug's direct effect [16].

2.4 Host Related Risk Factors

2.4.1 Age

Age increases DILI risk. Over-60 individuals on anti-TB medicines had a 3.5-fold greater incidence

of DILI, according to one study. In another trial of 430 patients, pyrazinamide-related side events, such as DILI, were 2.6fold higher in older patients. DILI was more prevalent in

50-plus INH monotherapy individuals. INH hepatotoxicity and death rise beyond 50. According to a case–control study, patients who had DILI on anti-TB drugs were older (39 years) (32 years). In another study, hepatotoxicity was 17 percent in individuals under 35 and 33 percent in those over 35. Age >35 was the only independent predictor for anti-TB DILI. Age reduces hepatic blood flow, medication distribution and metabolism, and drug clearance. A meta-analysis indicated that children using INH with rifampicin had a higher prevalence of clinical hepatitis (6.9%) than adults (2.7 %). The high incidence of DILI in children was gathered from small studies with 22–60 patients, all of which revealed a very high frequency of 'clinical hepatitis' in 25%–52% of all patients [17] .

2.4.2 Gender

Anti-TB drugs cause DILI in women four times more often than males. Feminine CYP3A activity makes them more hepatotoxic. INH hepatotoxicity is more common in third-trimester pregnant women in the first three months after birth.

2.4.3 Alcohol Intake

Alcohol induces enzymes that harm the liver. Studies suggest that drinking prolongs anti-TB medication hepatotoxicity. Even prophylactic rifampicin users are at danger [18].

3.PREVIOUS REPORTED INCIDENCE OF HEPATOTOXICITY

With multidrug TB therapy, ATDH occurs 2% to 28% of the time. Depending on the definition of hepatotoxicity and the demographic analysed, this rate varies. The bulk of ATDH research has been done in Europe, Asia, and the U.S. Prevalence varies widely. The greatest death rates are among Asians, especially Indians. Certain papers report hepatotoxicity in Sub-Saharan Africa, although rates are not provided. This is because most African nations do not frequently evaluate TB patients' liver function. Active TB is treated with medicines. Except for isoniazid, a preventative monotherapy for latent TB infections, nothing is known about the toxicity of antituberculosis medications. It may be harder to trace a response to a particular drug because of this. Temporal correlations may reveal that a medication is to blame for a detrimental impact, such as when symptoms develop with a new treatment, vanish when the drug is removed, and resurface when the drug is returned. 0.5% of isoniazid monotherapy patients had transaminase elevations. Rifampicin is generally well-tolerated, with hepatotoxicity occurring in 1–2% of patients using preventive monotherapy. Hepatotoxicity is one of pyrazinamide's adverse effects. When the drug was initially introduced in the 1950s, it was hepatotoxic and almost abandoned. The 40–70 mg/kg dosage is likely to blame. When administered at 20–30 mg/kg7 daily, pyrazinamide was safe. In the intense phase of TB therapy, pyrazinamide is used. Pyrazinamide monotherapy's hepatotoxicity rate is unclear at the present dose. Pyrazinamide induced more hepatotoxicity than isoniazid or rifampicin, research found. 7 out of 12 patients (58%) treated for latent TB with ethambutol and

pyrazinamide had transaminase increases larger than four times the upper limit of normal. Because ethambutol isn't hepatotoxic, pyrazinamide was likely to blame [19].

4.PATHOLOGICAL CLINICAL FEATURES

Isoniazid-induced hepatotoxicity is characterised by hepatic steatosis and necrosis in animal and human studies, and dangerous metabolites may bind covalently to cell macromolecules. Isoniazid's hydrazine metabolite causes steatosis, hepatocyte vacuolation, and glutathione depletion in animal testing. Periportal and midzonal hepatocytes exhibited lipid vacuoles and enlarged mitochondria. Rifampicin may induce transient hyperbilirubinemia, which is not harmful. Rifampicin may induce hepatocellular changes, centrilobular necrosis, and cholestasis. Histopathology may show spotty to widespread necrosis and cholestasis. A patient's liver revealed bridging necrosis, lymphocytic infiltration, localised cholestasis, increasing fibrosis, and micronodular cirrhosis. Most hepatic drug responses occur in the first two months of therapy, although they may occur at any time. ATDH exhibits clinical, biochemical, and histological differences from viral hepatitis. Liver damage causes jaundice, stomach discomfort, nausea, vomiting, and asthenia. They can't diagnose liver disease. Confirmation requires lab liver testing. Stopping ATDH treatment eliminates most symptoms. ATDH may be fatal if untreated [20].

5.ANTI-TUBERCULOSIS DRUG CAUSING HEPATOTOXICITY

5.1 Isoniazid

Isoniazid metabolism involves acetylation by hepatic Nacetyltransferase 2. (NAT2). Isoniazid (INH) is acetylated nicotinic acid degraded into acetyl hydrazine. Hydrolyzing acetyl hydrazine produces diacetyl hydrazine. This route is more essential in slow acetylates than in quick acetylates. Most earlier studies assumed isoniazid's harmful metabolite was acetyl hydrazine. Recent study reveals hydrazine, not isoniazid or acetyl hydrazine, causes isoniazid-induced hepatotoxicity. Hydrazine toxicity was originally observed in 1908 and causes cell death. There are hydrazine metabolites (e.g.acetylated hydrazine, hydrazones and nitrogen gas). Oxidation dominates hydrazine metabolism. Nitrogen and diimide are likely intermediates in hydrazine reactions.

During oxidative hydrazine metabolism, rat liver microsomes create hepatotoxic nitrogen-centered radicals. In vitro study shows free oxygen radicals don't cause isoniazid toxicity [21].

Humans may be slow or fast acetylators according to genetics. phenotypic or genotypic techniques to identify acetylator status. Rapid acetylators are more prone to develop ATDH, says study. Slow acetylators develop ATDH more often and more severely than fast acetylators. Slow acetylators leave more isoniazid for direct hydrolysis into hydrazine, and stored acetyl hydrazine may also be converted. Huang et al. found that sluggish acetylators had a more than two-fold risk of ATDH. Previous studies only assessed acetylator phenotype biochemically. Although there is limited information on isoniazid concentrations that cause toxic reactions, dosage can be based on acetylator status: a lower dose in slow acetylators to reduce the risk of ATDH and a higher dose in fast acetylators to increase early bactericidal activity and reduce treatment failure [22].

Genetic studies relate ATDH to CYP2E1. The CYP2E1 c1/c1 genotype increases CYP2E1 activity and may increase hepatotoxin generation. Isoniazid and hydrazine boost CYP2E1 activity in rats. Isoniazid suppresses CYP1A2, 2A6, 2C19, 3A4. CYP1A2 metabolises hydrazine. Isoniazid induces or inhibits enzymes, causing its own toxicity.

Whether oxidative stress affects ATDH is debatable. Unbalanced oxidants and antioxidants cause oxidative stress. Non-enzymatic scavengers and enzymatic processes (glutathione conjugation) detoxify reactive oxygen species. After isoniazid or hydrazine

administration to rats, glutathione levels and glutathioneS transferase, catalase, and superoxide dismutase activity were decreased, suggesting oxidative stress is involved in isoniazid-induced hepatotoxicity. N-hepatoprotective acetylcysteine's activity in isoniazid- and rifampicintreated rats adds to the evidence. TB patients with ATDH showed low glutathione levels and high malondialdehyde, an oxidative stress biomarker, probably owing to antitubercular therapy. The reason of glutathione depletion is unclear, however it might be linked to a general disturbance in intermediate metabolism. In vitro isoniazid-induced toxicity is unaffected by glutathione depletion, indicating glutathione is not directly implicated [23].

5.2 Rifampicin

Deacetylation generates diacetyl rifampicin, whereas hydrolysis forms 3-formyl. Initially, rifampicin may induce hepatocellular dysfunction, which recovers without stopping medication. Rifampicin-induced hepatotoxicity is unknown. No deadly metabolite is known. Rifampicin triggers the hepatic CYP450 system in the liver and gut to accelerate drug metabolism. Rifampicin and isoniazid increase hepatotoxicity risk. Rifampicin boosts isoniazid hydrolase, which enhances hydrazine production (especially in slow acetylators), which may explain the combination's higher toxicity. Antiretrovirals alter rifampicin's plasma levels and hepatotoxicity [22].

5.3 Pyrazinamide

Pyrazinamide (PZA; pyrazoic acid amide) is converted to pyrazinoic acid by xanthine oxidase. Pyrazinamide's serum half-life is independent to treatment length, showing it does not activate its metabolic enzymes [24].

The mechanism, enzymes, and metabolites of pyrazinamide-induced toxicity remain unclear. Pyrazinamide inhibits rat CYP450 isoenzymes (2B, 2C, 2E1, 3A), but not human liver microsomes [25].

5.4 Fluoroquinolones

Fluoroquinolones are used to treat multidrug-resistant TB and drug-induced hepatotoxicity. Quinolones are metabolised in the liver or excreted through the kidneys (as with levofloxacin). Fluoroquinolone-induced hepatotoxicity, except for trovafloxacin, is uncommon and can only be found by large-scale research or worldwide pharmacovigilance reporting [26]. Ciprofloxacin, levofloxacin, and gatifloxacin are associated to hepatotoxicity. Hepatotoxicity is often accompanied by peripheral eosinophilia and fever. Fluoroquinolones did not produce hepatotoxicity in first-line anti-TB patients. Ofloxacin is safe and beneficial for liver disease patients [27].

6.ADDITIONAL RESEARCH REPORTED

6.1HIV/AIDS infection increase hepatotoxicity

HIV enhances TB treatment hepatotoxicity. ATDH is more common in HIV-positive TB patients. Acute HIV/AIDS patients may be more prone to ATDH due to altered oxidative pathways [28].

Concurrent TB/HIV therapy requires two to four antituberculosis drugs and three antiretrovirals. Toxicities and medication interactions make TB/HIV therapy challenging. The most hepatotoxic drug is nevirapine (NNRTI). The bulk of NRTIs (didanosine and stavudine) are hepatotoxic, and some protease inhibitors are as well (e.g. ritonavir, indinavir and saquinavir). Hepatotoxicity with HAART ranges from 2% to 18%. During TB/HIV coinfection therapy, medication toxicity, particularly hepatotoxicity, may induce treatment stoppage. HIV positive TB patients often postpone HAART. Antifungal concurrent use (e.g. fluconazole) is another ATDH risk factor.

HIV-positive patients experienced decreased hepatotoxicity after a two-month TB preventative treatment with rifampicin and pyrazinamide. Hard to explain. Although rifampicin and pyrazinamide liver damage may be immunologically mediated and lower in HIV-infected persons, there is no solid data to support this idea, and the participants in this experiment were not significantly immunocompromised [29].

6.2 Genetic risk factors

Some of the difference in metabolism is hereditary. Genes alter drug-metabolizing enzyme activity. Increased reactive metabolites might affect treatment response or medication toxicity. ATDH genetic risk factors are understudied.

N-acetyltransferase slow acetylate, cytochrome P450 2E1 homozygous wild type, and glutathione S-transferase homozygous null are ATDH risk genotypes. Polymorphisms may explain why ATDH rates vary by population. How these genetic risk factors combine is unknown.

Pregnane X-receptor (PXR) promotes CYP3A4 expression and rifampicin's capacity to induce this enzyme. PXR polymorphisms affect CYP3A4 expression and might affect ATDH susceptibility [30].

6.3 Dosing imbalances

Daily TB therapy increases the incidence of ATDH compared to thrice-weekly treatment, however dosage patterns in the intensive phase had negligible influence on ATDH development [31].

6.4 Hepatitis B and/or C infections

Hepatitis B and/or C infections induce chronic liver damage in tuberculosis-prone patients. Co-infection with hepatitis B and C increases ATDH, say studies. HIVpositive HAART patients have also reported this. Patients with liver disease are more prone to hepatotoxicity [32].

6.5 Alcoholism

Alcoholism increases ATDH via enzyme induction. ATDH is more frequent among alcoholics who use hepatotoxic drugs [33].

7. FUTURE GUIDELINES

Because ATDH's mechanism is uncertain, additional study is needed on genetic polymorphisms in TB drugmetabolizing enzymes, hepatoprotective medications, and ATDH. Strong pharmacological underpinnings may help reduce TB therapy adverse effects. Few studies have examined drug-metabolizing enzyme genetic variations and ATDH risk. In large sample size, different population risk factor assessment

research, the relative relevance of various polymorphisms should be examined. Pharmacogenetics may prevent ATDH in the future, despite a lack of evidence. To avoid ATDH while retaining therapeutic benefit, adjust therapy doses in highrisk individuals. Risk genotype, drug doses, and hepatotoxicity must be considered. NAT2 genotype may be used to divide patients into low and high isoniazid dosing groups. N-acetylcysteine and silymarin protected rats' ATDH. More study is required on the preventative effects of such drugs in humans and possible medication interactions. Long-term TB treatment is a challenge. Antituberculosis pharmaceutical improvements will minimise healing time and increase adherence and effectiveness. New, less hepatotoxic regimens need safety investigations. New regimens are being developed, focusing on fluoroquinolones such moxifloxacin and levofloxacin. Despite being known for years, many drugs are rarely widely utilised owing to microbiological (resistance), toxicological, or economic reasons. In developed-world TB facilities, hepatotoxicity may prompt TDM (TDM). TDM measures antituberculosis plasma levels throughout therapy. Unlike other antituberculosis drugs, pyrazinamide dose is linked to hepatotoxicity (especially at doses over 40 mg/kg). TDM detects high or low antituberculosis drug plasma levels so action may be performed. TDM may prevent treatment failure, relapse, or death, particularly in TB/HIV-treated AIDS patients. Designing and executing safe TB/HIV treatment regimens is a future priority. Less hazardous regimens should be designed for HIV-positive TB patients. Hepatotoxicity is a typical adverse effect of TB/HIV therapy, but skin reactions and GI issues should also be addressed.

ACKNOWLEDGMENT

We would like to thank the Department of Pharmaceutics, Swami Institute of Pharmacy, Nashik forgives guidance and support for conducting a research study.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHORSHIP CONTRIBUTION STATEMENT

Dipali Zade: Supervision, Validation, Methodology, Investigation, Writing – original draft, Pranali Patil: Conceptualization, Administration, Funding, Data Curation.

REFERENCES

1. Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, Özmen İ, Kapaklı N. The treatment of multidrug-resistant tuberculosis in Turkey. New England journal of medicine. 2001 Jul 19;345(3):170-4. DOI: 10.1056/NEJM200107193450303
2. Sudre P, Ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. Bulletin of the World Health Organization. 1992;70(2):149.
3. Sumartojo E. When tuberculosis treatment fails. Am Rev Respir Dis. 1993;147(1311):e20.
4. Rohde K, Yates RM, Purdy GE, Russell DG. Mycobacterium tuberculosis and the

environment within the phagosome. Immunological reviews. 2007 Oct;219(1):37-54.

5. Vergne I, Chua J, Singh SB, Deretic V. Cell biology of Mycobacterium tuberculosis phagosome. Annu. Rev. Cell Dev. Biol.. 2004;20(1):367-94.
6. Brosch R, Gordon SV, Marmiesse M, Brodin P, Buchrieser C, Eiglmeier K, Garnier T, Gutierrez C, Hewinson G, Kremer K, Parsons LM. A new evolutionary scenario for the Mycobacterium tuberculosis complex. Proceedings of the national academy of Sciences. 2002 Mar 19;99(6):3684-9.
7. Gagneux S. Ecology and evolution of Mycobacterium tuberculosis. Nature Reviews Microbiology. 2018 Apr;16(4):202-13.
8. Koch A, Mizrahi V. Mycobacterium tuberculosis. Trends in microbiology. 2018 Jun 1;26(6):555-6.
9. Russell DG, VanderVen BC, Lee W, Abramovitch RB, Kim MJ, Homolka S, Niemann S, Rohde KH. Mycobacterium tuberculosis wears what it eats. Cell host & microbe. 2010 Jul 22;8(1):68-76.
10. Gori A, Bandera A, Marchetti G, Degli Esposti A, Catozzi L, Nardi GP, Gazzola L, Ferrario G, Van Embden JD, Van Soolingen D, Moroni M. Spoligotyping and Mycobacterium tuberculosis. Emerging infectious diseases. 2005 Aug;11(8):1242.
11. Warner DF. Mycobacterium tuberculosis metabolism. Cold Spring Harbor perspectives in medicine. 2015 Apr 1;5(4):a021121.
12. McLean KJ, Lafite P, Levy C, Cheesman MR, Mast N, Pikuleva IA, Leys D, Munro AW. The structure of Mycobacterium tuberculosis CYP125. Journal of Biological Chemistry. 2009 Dec 18;284(51):35524-33.
13. Van Kessel JC, Hatfull GF. Recombineering in Mycobacterium tuberculosis. Nature methods. 2007 Feb;4(2):147-52.
14. Delogu G, Sali M, Fadda G. The biology of mycobacterium tuberculosis infection. Mediterranean journal of hematology and infectious diseases. 2013;5(1).
15. Mostowy S, Behr MA. The origin and evolution of Mycobacterium tuberculosis. Clinics in chest medicine. 2005 Jun 1;26(2):207-16.
16. Clark-Curtiss JE, Haydel SE. Molecular genetics of Mycobacterium tuberculosis pathogenesis. Annual Reviews in Microbiology. 2003 Oct;57(1):517-49.
17. Sakamoto K. The pathology of Mycobacterium tuberculosis infection. Veterinary pathology. 2012 May;49(3):423-39.
18. Banuls AL, Sanou A, Van Anh NT, Godreuil S. Mycobacterium tuberculosis: ecology and evolution of a human bacterium. Journal of medical microbiology. 2015 Nov;64(11):1261-9.
19. Lee RE, Brennan PJ, Besra GS. Mycobacterium tuberculosis cell envelope. Tuberculosis. 1996 Jan 1:1-27.
20. Johnson R, Streicher EM, Louw GE, Warren RM, Van Helden PD, Victor TC. Drug resistance in Mycobacterium

tuberculosis. Current issues in molecular biology. 2006 Jul;8(2):97-112.

21. Filliol I, Driscoll JR, Van Soolingen D, Kreiswirth BN, Kremer K, Valétudie G, Anh DD, Barlow R, Banerjee D, Bifani PJ, Brudey K. Global distribution of Mycobacterium tuberculosis spoligotypes. Emerging infectious diseases. 2002 Nov;8(11):1347.
22. Miller LP, Crawford JT, Shinnick TM. The rpoB gene of Mycobacterium tuberculosis. Antimicrobial agents and chemotherapy. 1994 Apr;38(4):805-11.
23. Mcdonough KA, Kress Y, Bloom BR. Pathogenesis of tuberculosis: interaction of Mycobacterium tuberculosis with macrophages. Infection and immunity. 1993 Jul;61(7):2763-73.
24. Tobin DM, Ramakrishnan L. Comparative pathogenesis of Mycobacterium marinum and Mycobacterium tuberculosis. Cellular microbiology. 2008 May;10(5):1027-39.
25. Smith NH, Kremer K, Inwald J, Dale J, Driscoll JR, Gordon SV, Van Soolingen D, Hewinson RG, Smith JM. Ecotypes of the Mycobacterium tuberculosis complex. Journal of theoretical biology. 2006 Mar 21;239(2):220-5.
26. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. Journal of clinical and experimental hepatology. 2013 Mar 1;3(1):37-49.
27. Fernandez-Villar A, Sopena B, Fernandez-Villar J, Vazquez-Gallardo R, Ulloa F, Leiro V, Mosteiro M, Pineiro L. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. The International Journal of Tuberculosis and Lung Disease. 2004 Dec 1;8(12):1499-505.
28. Ataç G, Sevim T, Törün T, Horzum G, Gemci IM, Öngel A, Kapaklı N, Aksoy E. The management of anti-tuberculosis drug-induced hepatotoxicity. The International Journal of Tuberculosis and Lung Disease. 2001 Jan 1;5(1):65-9.
29. Kaneko Y, Nagayama N, Kawabe Y, Shimada M, Suzuki J, Kunogi M, MATSUI H, Kawashima M, Suzuki J, Ariga H, Oshima N. Drug-induced hepatotoxicity caused by anti-tuberculosis drugs in tuberculosis patients complicated with chronic hepatitis. Kekkaku (Tuberculosis). 2008 Jan 15;83(1):13-9.
30. Kaneko Y, Nagayama N, Kawabe Y, Shimada M, Suzuki J, Kunogi M, MATSUI H, Kawashima M, Suzuki J, Ariga H, Oshima N. Drug-induced hepatotoxicity caused by anti-tuberculosis drugs in tuberculosis patients complicated with chronic hepatitis. Kekkaku (Tuberculosis). 2008 Jan 15;83(1):13-9.
31. Anand AC, Seth AK, Paul M, Puri P. Risk factors of hepatotoxicity during anti-tuberculosis treatment. Medical Journal Armed Forces India. 2006 Jan 1;62(1):45-9.
32. Thompson NP, Caplin ME, Hamilton MI, Gillespie SH, Clarke SW, Burroughs AK, McIntyre N. Anti-tuberculosis medication and the liver: dangers and recommendations in management. European Respiratory Journal. 1995 Aug 1;8(8):1384-8.

33. Saito Z, Kaneko Y, Kinoshita A, Kurita Y, Odashima K, Horikiri T, Yoshii Y, Seki A, Seki Y, Takeda H, Kuwano K. Effectiveness of hepatoprotective drugs for anti-tuberculosis drug-induced hepatotoxicity: a retrospective analysis. BMC Infectious Diseases. 2016 Dec;16:1-6.