ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

A REVIEW ON ANTI – TUBERCULOSIS DRUGS INDUCED HEPATOTOXICITY

Siddhartha Lolla*, Lukalapu Mothilal, Uppalapu Akhila Sree, Maddineni Bhagya, Achagouni Akhilagoud, Mangalaram Sneha

Department of Pharmacy Practice, Pulla Reddy Institute of Pharmacy, Dundigal, Hyderabad, Telangana, India,502313.

*Corresponding author E-mail: swathisniz92@gmail.com

ARTICLE INFO

Key words:

Mycobacterium tuberculosis, Isoniazid[INH], Pyrazinamide[PZA], Rifampicin[RIF], Latent tuberculosis treatment(LTBI), Drug induced liver injury(DILI), Hepatitis, Immunosuppresent, Hepatotoxicity, Hypersensitivity.

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Anti-tuberculosis drugs, while crucial for treating TB, can cause significant side effects like liver, kidney, and nerve damage, and even skin reactions. Hepatotoxicity, often triggered by drugs like isoniazid, rifampicin, and pyrazinamide, is the most common. These toxicities are linked to processes like oxidative stress and immune responses, and can be worsened by factors like alcohol use and existing liver problems. Early detection through monitoring and adjustments in treatment, including dose changes and the use of supportive medications, are key to managing these complications. Research continues to explore safer regimens and potential biomarkers for predicting toxicity risk. Covering only first-line antituberculosis drugs, this review addresses whether and how oxidative stress and, more broadly, disturbance in redox homeostasis alongside mitochondrial dysfunction may contribute to the hepatotoxicity induced by them. Approximately one third of the world & 39 population is infected with Mycobacterium tuberculosis. In the past decade, an average of 2.5 to 3.2 million cases was notified every year globally. The cornerstone of tuberculosis management is a 6-month course of isoniazid, rifampicin, pyrazinamide and ethambutol. Compliance is crucial for curing tuberculosis. It may reduce treatment effectiveness by compromising treatment regimens. Second-line anti-tuberculosis drugs like aminoglycosides and fluoroquinolones can cause serious toxicities such as ototoxicity and tendinopathy, especially in multidrug-resistant TB (MDR-TB) cases. Managing these toxicities often requires stopping the drug or adjusting the treatment regimen, which can affect treatment success. Preventive measures like genetic screening for risk alleles such as NAT2 polymorphisms and regular liver function monitoring are becoming more important. Patient education on early signs of toxicity enables faster intervention. A multidisciplinary team involving physicians, pharmacists, and public health experts is key to minimizing adverse effects and improving adherence to TB treatment.

INTRODUCTION:

A chronic bacterial infection, tuberculosis (TB) can be defined abnormally by the development of granulomas. It is most frequently caused by Mycobacterium tuberculosis complex[1] .Mycobacterium TB is carried by particles in the air that are 1–5 microns in diameter., also called droplet nuclei[2]. Mycobacterium tuberculosis transmits by airborne contact not by surface touch. The disease is transmitted by inhaling droplet nuclei carrying Mycobacterium TB. Before reaching the lungs' alveoli, the droplet nuclei travel via the mouth or nasal passages, upper respiratory tract, and bronchi[2] Nowadays, tuberculosis is placed as the sixth

most frequent reason for death worldwide and is the main cause of infection-related deaths. Substance abuse insecurity shortages, hunger, and— Most significantly—human immunodeficiency virus co-infection all contribute to the spread of the disease, which is spread by inhaling airborne droplet nuclei that remain alive for days[3].The World Health Organization (WHO) estimated that 1.4 million people died from tuberculosis (TB) in 2019, and that approximately 10 million people had the disease. Also, half of the world's population was infected with Mycobacterium tuberculosis[4] .Combination antibacterial and/or bacteriostatic drugs for TB is necessary for effective TB treatment. The World Health Organization (WHO) suggests a combination of these treatments for standard therapy[5]. Isoniazid, rifampicin, and pyrazinamide are One of the primary anti-TB medications which are known to cause hepatotoxicity; though, pyrazinamide is responsible for more of the drug- induced liver toxicity (DILT) in the other medications[1]. Hepatotoxicity usually appears and diagnosed by jaundice or increased amounts of liver function marker proteins such as total bilirubin, alkaline phosphatase (APT), or aspartate aminotransferase (AST)/alanine aminotransferase (ALT)[1] .Hepatotoxic side effects are possible with isoniazid, pyrazinamide, and rifampicin, and they can occur with antituberculosis treatment. Although some hepatotoxic events arrive on by drugs hypersensitivity, most are dose-related[6]. According to sometimes, however, illness appears shortly after infection. The biggest risk is the chance for a long-term tuberculosis infection because this does not happen regularly. Often without any apparent explanation, an infection from years ago may worsen become a disease during stressful times brought on by other illnesses or physical or emotional adversity. The infection might spread to other people after the sickness develops. [7]

HISTORY

Mycobacterium tuberculosis infects around one-third of the global populace. Over the past ten years, an average of 2.5 to 3.2 million cases have been reported annually worldwide; public growth has somewhat countered recent declines in notification rates. 2.6 to 2.9 million people died from TB in 1990, while an estimated 8 million individuals contracted the disease globally.[8]Clearly the leading cause of death throughout the 1700s and early 1800s in both Western Europe and the United States, tuberculosis had fully spread to South America, Africa, Asia, and Eastern Europe 100 to 200 years later. Over the course of the following two centuries, the epidemic flourished and expanded throughout Western Europe. Nearly all Western Europeans contracted M. tuberculosis during this epidemic phase, and tuberculosis was the cause of approximately one in four fatalities.[9]

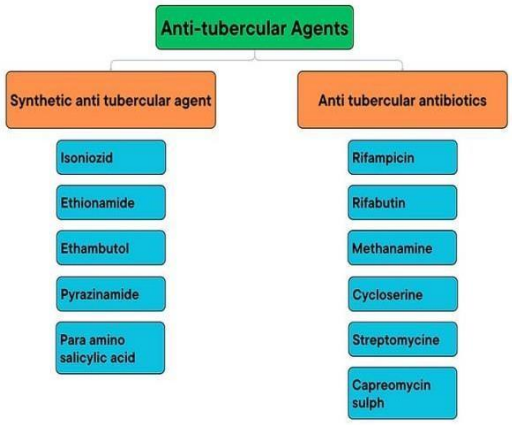
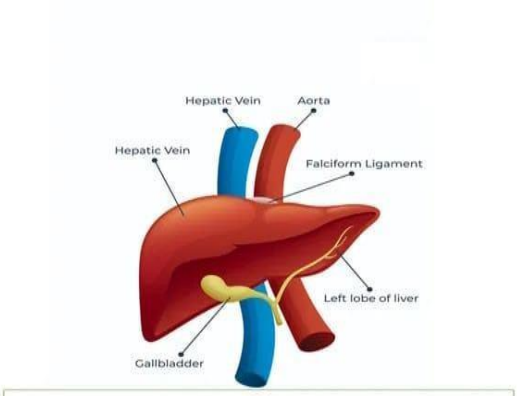


Fig: 1- Anti-tuberculosis drugs

LIVER STRUCTURE AND FUNCTION

The liver, which makes about 2-5% of an adult's body weight, is the biggest organ in the body. There are two main blood veins that feed blood to it. While the portal vein, which supplies 80%. The hepatic artery supplies oxygenated blood, while the blood supply provides nutrient-rich deoxygenated blood. Thus, the liver transforms, detoxifies, and accumulates metabolites, acting as a partition separating the body's digestive system from the rest. Along with the metabolites that are found in the liver and bile also creates several plasma proteins, including albumin, which are transported into the blood.[10] . The lobule is the liver primary functioning unitThe hepatic artery, bile duct, and portal vein make up the portal triad can be found in each hexagonal corner of the lobule.The liver regulates cholesterol levels and keeps fat-soluble vitamins in storage. It has iron and copper in it. It produces clotting factors and proteins, which aid in hematology. Heme is converted to unconjugated bilirubin, which the liver subsequently conjugates. It generates carrier proteins, which are necessary for growth and reproduction.as well as helping to regulate sex hormone levels. Finally, the body immunological system is based on Kupffer and pit [22]

RISK FACTORS



Structure of human liver

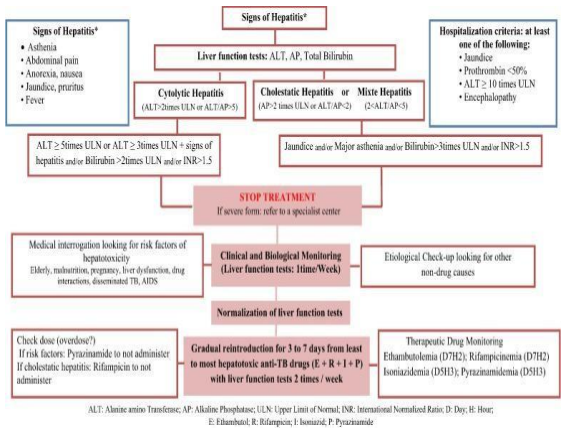
Drug-induced hepatotoxicity during TB treatment is a serious issue for organ transplant patients as well. Although the precise underlying mechanism is unknown, the cumulative deleterious effects of concurrent immunosuppressive medication administration appear to be one potential. It would be helpful to mention additional instances of medication toxicity that are interacting in this context. Acetaminophen and anticonvulsants for instance, have been linked to hepatotoxicity when taken with antituberculosis medications, especially in regimens that include isoniazid [6]. It has been observed that patients over 35 are more likely to develop anti-TB-DIH.According to gender wise numerous studies have linked women to a lower chance of developing anti-TB-DIH. Another study by Mahmood et al. found that women had a greater incidence of anti-TB-DIH than men did (26.3% vs. 19.7%)[11]. A high prevalence of latent tuberculosis infection has been related to an increased risk of disease progression or reactivation, particularly in the presence of comorbid conditions like smoking, alcoholism, and diabetes mellitus. Numerous nations and geographical areas have shown the link between TB and aging.[12].There are numerous documented risk factors for ATDH. To lower the morbidity and mortality of hepatotoxicity and enable early detection, it would be helpful to identify high-risk patients. The observed variations in ATDH incidence may be explained by variations in risk factor prevalence across global areas. When active TB is treated with normal combination therapy, The risk of hepatotoxicity is increased by HIV infection.Remarkable after a two-month preventive therapy HIV-positive patients showed less hepatotoxicity than HIV-negative patients when treated with rifampicin and pyrazinamide for LTBI infection[13].

TUBERCULOSIS HEPATITIS

In 96 patients who presented with liver disease symptoms, hepatic TB was verified; only 14 of these patients also had additional concurrent hepatic pathology. even the fact that 74% of individuals reported respiratory symptoms, the gastrointestinal symptoms were more common. The latter most often comprised ascites, splenomegaly, hard tender hepatomegaly, abdominal distension, and right hypochondrial pain.[14]Hepatitis B and C viral infections were found in 15.1% and 17.3% of TB patients, respectively. In patients with tuberculosis, HIV, alcohol, sex, and chronic illness have all been connected to hepatitis B virus infection. Hepatitis C virus infection has been associated with HIV, alcohol, sex, and chronic illness in TB patients. Hepatitis B, Hepatitis C, HIV, the severity of tuberculosis, and chronic illnesses, were used to determine liver damage. The incidence of liver damage among tuberculosis patients was per person-month.[15]Several Asian researches have examined DILI in patients with hepatitis B infection while they are receiving therapy for TB illness. Of 1,783 TB patients in Taiwan receiving of those using isoniazid, rifampin, and ethambutol, 42 (2.4%) experienced hepatitis symptoms.7 out of 15 individuals who carried the hepatitis B surface antigen died from hepatic failure. Hepatic failure claimed the life of one of the 27 additional patients with hepatitis symptoms who did not carry hepatitis B. The hepatitis B carrier population seems to have experienced an increase in the severity of hepatotoxicity.[16]

Patients who consumed more than 60 g of alcohol per day or whoseThose whose baseline serum transami-nase concentrations exceeded the ULN were prohibited from continuing. In contrast to 4.7% of patients without a hepatitis B infection, 16% of TB patients with hepatitis B surface antigen had symptomatic hepatitis, per a Hong Kong study. This analysis excluded alcoholic and nonviral liver disorders. In addition to having more severe liver damage, patients with hepatitis B surface antigen were also more likely to stop their therapy permanently (4.7 versus 2.5%). According to ULN a retrospective case-control research carried out in Seoul, Korea, 110 individuals with normal pretreatment transaminases and hepatitis B surface antigen

showed a tendency toward transminase increases of at least five.[16]



DRUGS INDUCED HEPATOTOXICITY

More than half of all situations of acute liver failure in the US are caused by drug-induced hepatic damage. Idiosyncratic medication responses cause death or liver transplantation in over 75% of cases. medication approval procedures, common adverse medication responses involving the liver, and the pathophysiology of drug-induced liver harm are all covered in this overview. Acute liver failure may not always occur if drug-induced hepatotoxicity is detected and monitored.[17]. This study focuses on the several medicines that cause hepatotoxicity, together given their clinical presentation and liver damage mechanism, given the effects of DIH as a primary lead to liver damage [18]

ISONIAZID: Having the risk of liver failure, isoniazid (INH) is nevertheless a standard treatment for tuberculosis. According to earlier mechanistic theories, this kind of the primary cause of DILI, which was classified as a "metabolic idiosyncrasy," was the bioactivation of the metabolite acetyl hydrazine and was believed to not require an immune response [19] Even though isoniazid (INH) can result in liver failure, it is still the medication of choice for treating latent tuberculosis (TB) because of its great efficacy. The clinical features of INH-induced liver injury, which include exhaustion, nausea, vomiting, and malaise, are rather typical for idiosyncratic DILI, despite the fact that drug-induced liver injury (DILI) caused by different medicines varies somewhat.[19]. Isoniazid is acetylated by the hepatic enzyme N- acetyltransferase 2 (NAT2), making it the main metabolic pathway. Acetylisoniazid is produced by acetylating isoniazid (INH; isonicotinic acid hydrazide), which has subsequently hydrolysed to produce isonicotinic acid and acetylhydrazine. Acetylhydrazine can either be acetylated to produce diacetylhydrazine or hydrolysed to hydrazine.[11]Although there is little data on isoniazid focusing that result in toxic reactions, it is suggested that the dosage of isoniazid be adjusted based on the status of the acetylator: There is a lower dosage in slow acetylators to increase the early bactericidal activity and diminish the likelihood of treatment failure, and a higher dosage in fast acetylators to increase the early bactericidal activity and decrease the likelihood of treatment failure. [11]

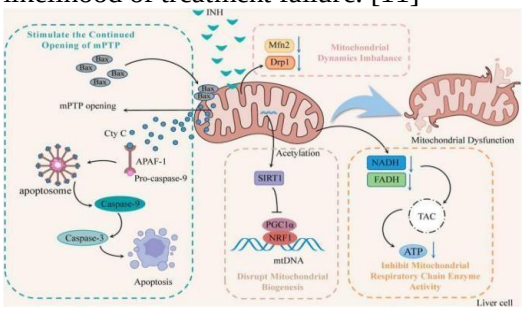


Fig. 4: action of isoniazid

PYRAZINAMIDE

As a structural analogue of nicotinamide, pyrazinamide (PZA) was originally produced in 1936 and has been used in clinical settings to treat tuberculosis since 1952. As a crucial component of a typical anti-TB combination therapy, PZA is still used today along with (INH), (RIF), ethambutol, or streptomycin.[20]Pyrazinamide, also known as Pyrazoic acid is produced from pyrazoic acid amide by xanthine oxidase, which then oxidizes it further to 5-hydroxypyrazinoic acid.(78) The enzymes required for pyrazinamide metabolism are not produced by it, as evidenced by the fact that its serum half-life is unrelated to the duration of administration.79 The toxicity caused by pyrazinamide is not well understood, nor are the enzymes implicated or if pyrazinamide or its metabolites are the cause of the toxicity.[11]For the treatment of LTBI, Pyrazinamide has been used in combination with fluoroquinolones, ethambutol, or rifampin. In seven out of twelve (58%) LTBI cases treated with pyrazinamide and ethambutol, transaminase increase greater The ULN was observed more than four times. After being exposed to MDR TB, three out of 17 patients (18%) who were taken levoxacin together with pyrazinamide to treat LTBI experienced a transaminase increase that was more than four times the ULN. After receiving oxacin and

pyrazinamide, nine out of 22 patients (41%) experienced a transaminase increase that was at least five times the ULN.[16] Recent research, However, reveals that PZA can be more hepatotoxic than earlier anticipated and may even be more hepatotoxic than INH or RIF. [20].

RIFAMPICIN

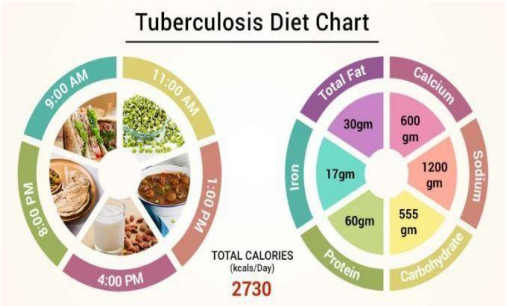
Rifampicin increases the metabolism of several other substances by strongly effected by the system of hepatic CYP450 in the liver and intestine. Rifampicin and isoniazid use together has been linked to an increased chance of hepatotoxicity. Rifampicin increases the synthesis of hydrazine when coupled with isoniazid (particularly in slow acetylators) by inducing isoniazid hydrolase, which could account for the combination's increased toxicity. Additionally, rifampicin causes hepatotoxicity and alters the plasma levels of antiretroviral medications.[11] Undiagnosed, unconjugated hyperbilirubinemia or jaundice without hepatic damage can occasionally be caused by dose-dependent interference with bilirubin uptake caused by rifampin and rifapentine. This might be temporary and happen early in the course of treatment or in certain people who already have liver disease. On rare occasions, rifampin may result in hepatic damage and increase the hepatotoxic effects of other anti-TB drugs. In a study of brucellosis patients receiving rifampin and minocycline, almost 5% of patients showed rifampin-associated ALT increases of at least 250 IU/L. [16]

TREATMENT

Treatment of tuberculosis is still difficult because it must be approached with consideration for both individual and societal health. Furthermore, it has been demonstrated that When assessing the effectiveness of treatment, social and economic issues need to be considered.[21]selecting a routine. If at all possible, isoniazid and rifampin should be used and maintained due to their critical efficacy, even in cases when liver disease already exists. If TB is not thought to be the cause and the More than three times the ULN is the baseline serum ALT, further investigations are advised.[16] Isoniazid and rifampin may be used in combination with ethambutol for nine months of treatment without pyrazinamide until the M. tuberculosis isolate's drug susceptibility testing is finished. 2. For 12 to 18 months, rifampin and ethambutol combined with levo-oxacin, moxi-oxacin, gati-oxacin, or cycloserine may be investigated in individuals with cirrhosis. 3. For 18 to 24 months, ethambutol in combination with a cycloserine, ca-preomycin, or aminoglycoside may be an alternative for patients with encephalopathic liver disease. But these routines haven't been thoroughly examined.[16]

CURRENT TUBERCULOSIS INFECTION TREATMENT

Adults Isoniazid, at a daily dose of 5 mg/kg (maximum 300 mg) or 15 mg twice a week (maximum 900 mg), is frequently used to treat LTBI for 6–12 months. The main a negative impact of isoniazid is hepatitis.As of right now, rifampicin at a daily dosage of 10 mg/kg (up to 600 mg) for four months is a suitable substitute for treating LTBI.58. 165 silicotic patients who took rifampicin alone for three months in a Hong Kong research did not have hepatitis.64. Three other investigations also showed less hepatotoxicity. In order to treat LTBI in individuals who have come into contact with multidrug-resistant TB, pyrazinamide-containing regimens are frequently used. All patients should get comprehensive education regarding the sign of hepatitis and be encouraged to describe them right away to early evaluation in order to reduce the threat of hepatotoxicity during the treatment of LTBI. Close clinical observation is necessary [6]. Remarkably, the hepatotoxicity rates for HIV-infected people who receive Patients receiving therapy for active tuberculosis and those receiving prophylactic rifampicin and pyrazinamide medication are similar (varying from 1% to 5%).[11]



CONCLUSION:

Anti-tuberculosis drug-induced hepatotoxicity is a significant concern in tuberculosis (TB) treatment, primarily due to the hepatotoxic effects of first-line drugs like isoniazid, rifampicin, and pyrazinamide. While these drugs are essential for TB management,

their potential to cause liver injury can lead to treatment interruptions, complications, and increased morbidity. Early detection and monitoring of liver function, especially in high-risk patients (such as those with pre-existing liver disease, alcohol use, or malnutrition), are crucial for minimizing the risk of severe hepatotoxicity. Strategies such as dose adjustment, temporary discontinuation, or alternative drug regimens may be necessary in managing hepatotoxicity without compromising TB treatment efficacy. Further research is needed to develop safer TB treatment protocols and identify biomarkers for early detection of hepatotoxicity. pharmacovigilance, patient education, and personalized treatment approaches can help reduce the burden of ATDH while ensuring successful TB therapy.Anti-TB drug-induced hepatotoxicity is a significant concern in tuberculosis (TB) treatment, primarily due to the hepatotoxic effects of first-line drugs like isoniazid, rifampicin, and pyrazinamide. While these drugs are essential for TB management, their potential to cause liver injury can lead to treatment interruptions, complications, and increased morbidity. Addressing anti-TB drug-induced hepatotoxicity is essential for improving treatment outcomes and patient safety. A proactive approach that combines early detection, personalized therapy, and patient education can significantly minimize liver-related complications. Ongoing research, better pharmacovigilance systems, and interdisciplinary collaboration will be vital to advancing safer and more effective tuberculosis treatment strategies worldwide.

REFERENCES:

1. EthiopiaYalew MollaORCID Icon,Muluken Wubetu &Bekalu DessieORCID Icon. Anti- Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals.
2. Hamisi Mahanga Swalehe, Emmanuel Ifeanyi Obeagu ,Tuberculosis;Current Diagnosis Management.Doi; Elite Journal of Public Health. Volume 2 issue 1(2024), Pp. 23.
3. MD David E. Griffith (Associate Professor of Medicine) a,MD Clark M. Kerr (Consultant in infectious Diseases).Tuberculosis: Disease of the past, disease of the present.
4. Giovanni Battista Migliori1, Catherine W.M. Ong2,3, Linda Petrone4, Lia D'Ambrosio5, Rosella Centis 1, Delia Goletti 4. The definition of tuberculosis infection based on the spectrum of tuberculosis disease. Breath 2021; 17:210079.
5. Soedarsono2, Agustinus Rizki Wirawan Riadi1,2. Tuberculosis Drug-Induced Liver Injury. DOI: 10.20473/jr.v6-I.2.2020.49-54.
6. Wing Wai YEW, Chi Chiu LEUNG. Antituberculosis drugs and hepatotoxicity.
7. Centre for disease control,Tuberculosis,TB.ISSUE 33 of health information series.
8. Thomas M. Daniel, Joseph H. Bates, Katharine A. Downes. History of Tuberculosis
9. Sudre 1 , G ten Dam 1 , A Kochi1Tuberculosis: a global overview of the situation today.PMCID: PMC2393290 PMID: 1600578.
10. Katrien Vekemans1,2,Filip Braet1,2, Structural and functional aspects of the liver and liver sinusoidal cells in relation to colon carcinoma metastasis.doi:10.3748/wjg.v11.i33.5095.
11. Alma Tostmann,Martin J Boeree,Rob E Aarnoutse,Wiel C M De Lange,Andre J A M Van Der Ven,Richard Dekhuijzen,Antituberculosis drug-induced hepatotoxicity: Concise up-to date review.
12. Wing Wai Yew,Kwoi Chiu Chang,Denise p.Chan, Oxidative Stress and First- Line Antituberculosis Drug-Induced Hepatotoxicity
13. Saifun Nahar Faiz1* Mahmudul Haque2 S M Kamrul Hoque3, Antitubercular Drug- Induced Hepatotoxicity :A Comprehensive Review,volume 3 issue 1 june 2020;33-37
14. A R. Essop, J. A. Posen, J. H. Hodkinson, I. SEGAL, Tuberculosis Hepatitis: A Clinical Review of 96 Cases.
15. Adeeba Kamarulzaman, Prevention of transmission of HIV, hepatitis B virus, hepatitis C virus, and tuberculosis

16. Siddharth ,G. Priyanka,Mirza Hassan A Review On Hepatotoxicity Of Antituberculosis Therapy, DOI : 10.36106/ijar.
17. William M. Lee, M.D, Drug-Induced Hepatotoxicity, DOI: 10.1056/NEJMra021844.
18. Aashish Pandit, Tarun Sachdeva, Pallavi Bafna, Drug-Induced Hepatotoxicity: A Review,
19. Imir Metushi1, Jack Uetrecht2, Elizabeth Phillips3, Mechanism of isoniazid-induced hepatotoxicity: then and now, doi: 10.1111/bcp.12885.
20. Zahir Hussain1, Junjie Zhu1, Xiaochao Ma1, Metabolism and Hepatotoxicity of Pyrazinamide, an Antituberculosis Drug, 10.1124/dmd.121.000389.
21. J. bras. pneumol. 43 (06) • Nov-Dec 2017 • Tuberculosis treatment
22. Arjun Kalra;Ekrem Yetiskul;Chase J. Wehrle;Faiz Tuma,Physiology Liver.