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Journal of Liver Research, Disorders & Therapy

Research Article

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Efficacy and safety of anti-tubercular regimens in cirrhosis of liver with tuberculosis: a randomised controlled trial

Abstract

Background: Patients with liver cirrhosis are susceptible to tuberculosis (TB) because of immune dysfunction. However, limited data is available regarding prevalence of TB in cirrhotics and its treatment.

Aim: The aim of this study was to elucidate the prevalence and clinical characteristics of TB with liver cirrhosis and its treatment with different anti tubercular (ATT) regimens.

Methods: Two eighty nine (289) patients with cirrhosis of liver were evaluated for evidence of tuberculosis during a period of 24months (March 2011 to March 2013) in a tertiary care centre. Patients with evidence of tuberculosis were randomised into two different ATT regimens (Regimen A and B) after exclusion. Regimen A included initial phase of isoniazid (INH), rifampicin (RIF), and ethambutol (EMB) for 2months followed by a continuation phase of INH and RIF for 7months, for a total of 9months and regimen B included EMB, a fluoroquinolone (ofloxacin), and RIF for 12months. All drugs were given on weight based daily doses.

Results: Forty two patients (14.5%) out of 289 with cirrhosis of liver were detected to have evidence of TB. Aetiological agents responsible for cirrhosis amongst these patients were alcohol (n=18, 42.8%), hepatitis B(n=11, 26.1%), hepatitis C(n=2, 2.6%) and other causes (11, 26.1%). The most common site of tuberculosis was pulmonary (n=20, 47.6%) followed by abdominal (n=11, 26.1%), peritoneum (n=8, 19.2%), intestinal (n=2, 4.6%) and small bowel (n=1, 2.3%). After exclusion of six patients, thirty Six (36) patients with cirrhosis of liver were randomised into two different groups (ATT regimen A and B). Two out of eighteen patients (11.11%) in Regimen A while none of 18 patients in regimen B developed ATT induced hepatotoxicity ($p<0.05$).

Conclusion: Prevalence of tuberculosis in patients with cirrhosis of liver in our study was 145.3 per 1000 patients (14.5%) which was higher than the prevalence of all forms of tuberculosis in general population in India and alcoholic cirrhotic were highly vulnerable. Combination RIF, EMB and Ofloxacin (fluoroquinolone) was well tolerated in cirrhosis of liver, even in Child B cirrhosis.

Keywords: selective transfer, superficial layer, structural analysis, intensity x-rays, width of diffraction lines, crystalline network constant

Volume 1 Issue 2 - 2015

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Received: July 12, 2015 | **Published:** September 21, 2015

Introduction

India has the highest TB burden in the world according especially in the developing countries in Africa and Asia, with an estimated 40%-50% of the adult population being infected[1] and estimated incidence of 2.2million cases in India out of a global incidence of 8.7million cases according to World Health Organization (WHO) statistics for 2011.[2] Better diagnosis and improved healthcare facilities have resulted in higher detection rates and better treatment is available due to the development of effective anti-tubercular drugs over the last six decades. Patients who develop liver cirrhosis, regardless of aetiology, showed an acquired immune deficiency because of poor homeostasis and malnutrition. All host defence systems, antigen-specific as well as nonspecific functions, are compromised in cirrhotic patients who experience significantly higher rates of bacterial infections including infections with tuberculous bacilli, which contribute to their poor prognosis.[3] The ability to tolerate anti-tubercular therapy (ATT) and its potential hepatotoxicity is a major concern in patients with advanced liver cirrhosis or end-stage liver disease since most of the first-line ATT may demonstrate hepatotoxicity as an adverse effect and can result in treatment discontinuation due to associated morbidity. Among the first-line drugs, isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) are associated with hepatotoxicity and may result in additional liver damage in patients with pre-existing liver disease. Considering the efficacy of these drugs, however (particularly INH and RIF), it is generally recommended that they may be used if possible, even in the presence of pre-existing liver disease.

The aims of this study were to determine the prevalence of tuberculosis and its characteristics in patients with cirrhosis of liver. Efficacy and safety of two different ATT regimens were also looked in this study.

Material and methods

After the approval from Institutional Ethics Committee, the study was carried out in the Department of Gastroenterology and Department of Medicine at M.L.N. Medical College and Swaroop Rani Nehru Hospital, Allahabad, India over a period of 18months (March, 2011 to September, 2012). This study included all patients with diagnosis of cirrhosis of liver attending the department during the study period. The patients with evidence of TB were further considered for randomized control trial.

Diagnosis of cirrhosis of liver

Known cases of cirrhosis of liver who were diagnosed on the basis of either history, clinical examination, biochemistry, ultrasonographic findings of abdomen (USG abdomen), esophago-gastroduodenoscopy (OGD) or liver biopsy were included in the study. Details regarding HBsAg (Hepatitis B Surface Antigen), anti HCV (Hepatitis C virus), serology for autoimmune markers, serum ceruloplasmin and serum ferritin levels, biliary disease, use of alcohol and the use of other hepatotoxic drugs were evaluated to determine the underlying aetiology of cirrhosis of liver.

Diagnosis of tuberculosis

These patients were screened for pulmonary as well as extra pulmonary tuberculosis on basis of following parameters: fever, cough for more than 2weeks, haemoptysis, unexplained weight loss, increasing ascites not responding to diuretics, unexplained bowel symptoms including diarrhoea, constipation, or sub acute intestinal obstruction), suggestive radiological lesions and past history of tuberculosis. Definitive diagnosis was based on histological demonstration of acid fast bacilli (AFB) in ascitic fluid or peritoneal biopsy, sputum positivity for AFB, polymerase chain reaction (PCR) for tuberculosis in tissue biopsy and ascitic fluid and treatment response to anti tuberculous drugs and a probable diagnosis was kept when the clinical profile and radiological finding suggestive but histology didn't show definite evidence. It was based on suggestive symptoms, sputum negativity for AFB but chest X-Ray suggestive of tuberculosis, ascitic fluid analysis showing predominant lymphocytosis with high protein content and high adenosine deaminase (ADA) levels. A diagnosis of pulmonary tuberculosis was made on basis of medical history, physical examination, chest radiograph and bacteriologic examination for AFB.

The Diagnosis of peritoneal and pleural was established if three of the following four criteria were fulfilled:

a. Raised fluid cell count with predominant lymphocytosis;

b. Fluid albumin >2.5gm/dl;

c. Fluid ADA >33U/L and

d. Positive PCR for Mycobacterium tuberculosis

Luminal tuberculosis was diagnosed by endoscopic examination of gastro intestinal (GI) tract and biopsy from doubtful lesions. Tissue was sent for histopathological examination for demonstration of granulomas with or without caesation or AFB or PCR for tuberculosis was done on these tissue biopsies in doubtful cases.

The exclusion criteria were serum bilirubin more than 3mg/dl at base line, baseline alanine aminotransferase (ALT)/aspartate aminotransferase (AST) more than 3times of upper normal limits at base line, alchoholic hepatitis, viral hepatitis, history of recent use of anti tubercular drugs (within last 6weeks), Child C Cirrhosis of liver, hepatocellular carcinoma, presence of overt hepatic encephalopathy and presence of significant co morbid illnesses such as cardiac, respiratory or renal failure.

The study was not blinded and the block randomization method was utilized for random allocation of regimen. The sequence remained concealed from the investigator and the generator of the random blocks did not participated in screening, enrolment, or drug delivery.

Different ATT regimens

Two ATT regimens were design according to weight based daily doses:

i. Regimen A (initial phase of isoniazid (INH), rifampicin (RIF), and ethambutol (EMB) for 2months followed by a continuation phase of INH and RIF for 7months, for a total of 9months) and

ii. Regimen B (EMB, a fluoroquinolone (ofloxacin), and RIF for 12months)

Monitoring of therapy and follow up

All patients were screened for ATT induced hepatoxicity every week for 2weeks then biweekly for next 4weeks then monthly while on ATT till the end of regimen. A diagnosis of ATT induced hepatotoxicty was made when serum alanine aminotransferase (ALT) increased above three times the upper limit of normal range and serum bilirubin levels increased by 2.5mg/dl above base line with no other apparent cause for raised liver function tests like alcoholic and viral hepatitis. IgM anti HBc ab, anti HAV ab and anti HEV ab was done in all cases of suspected ATT induced hepatotoxicty to exclude viral hepatitis. History of recent intake of alcohol was also looked in to account.

Reintroduction of antitubercular drugs

On development of hepatoxicity in patients with cirrhosis of liver, all antitubercular drugs were stopped and weekly liver function test (LFT) was performed. As soon as ALT/AST fell within two fold of baseline value and serum bilirubin decreased to less than 2.5mg/dl, ATT was reintroduced in form of regimen B (RMP, EMB and ofloxacin). At this time rifampicin was started first at reduced dose of 150mg per day then gradually increased on every 3rd day to full dose with simultaneous monitoring of LFT. Monitoring of ALT levels was done twice a week for 2weeks, then weekly for 2month and thereafter monthly till the end of regimen during reintroduction.

Response to anti-tubercular drugs

The response to ATT was defined as a clinical response in form of subsidence of symptoms of anorexia, fever, cough, and bowel symptoms, regression of peripheral lymph nodes, control of ascites with diuretics, plus either of radiological, endoscopic, bacteriological and histological response. Radiological response was defined as disappearance of pulmonary lesion on chest X-ray, regression of intestinal on barium meal follow through at the end of treatment. Endoscopic response was sought for regression of mucosal lesions on colonoscopy and/ or Ileoscopy. Bacteriological and histological responses were defined as sputum negativity at 2month and at the end of treatment and disappearance of caseating granuloma.

Citation: Sharma K, Misra SP, Dwivedi M, et al. Efficacy and safety of anti-tubercular regimens in cirrhosis of liver with tuberculosis: a randomised controlled trial. *J Liver Res Disord Ther.* 2015;1(2):37–42. DOI: 10.15406/jlrdt.2015.01.00008

Statistical analysis

All the values were expressed as proportions or mean ± Standard Deviation (SD). Chi-square test, Mid P exact test and student't' test were used for comparison between the two groups. P value less than 0.05 was considered statistically significant. Software SPSS22.0 was used for all statistical analysis.

Results

A total of 289(194, 67.1% males and 95, 32.8% female) patients were studied. Forty two (14.5 %) were found to have evidence of tuberculosis and formed the study groups (Table 1). Thus, the prevalence of TB in cirrhotic patients was 145.3 per 1000(95% confidence interval (CI): 108-189 per 1000). The most common site of tuberculosis was pulmonary (n=20, 47.6%) followed by abdominal (n=11, 26.1%), intestinal (n=2, 4.6%), small bowel (n=1, 2.3%) and peritoneum (n=8, 19.2%). Over all, extra pulmonary involvement was more frequent than pulmonary (52.4% vs. 47.6%). Sputum positivity was reported among 14(70%). Out of 20 patients of pulmonary tuberculosis. Baseline characteristics of patients with cirrhosis of liver and tuberculosis in two groups were given in Table 2.

Table 1 Distribution of cases according to different sites and diagnostic modalities of tuberculosis

Site of tuberculosis	No. of patients	Diagnostic modality	No. of patients
Pulmonary	20	Fibrocaseous lesion	12
		Bilateral infiltrate	5
		Right apical homogenous opacities	3
		Sputum positivity	14
Pleural Effusion	7	high Adenosine Deaminase	5
		Polymerase Chain Reaction positivity	2
Abdominal	11 (Peritoneal -8 and Intestinal-3, which includes luminal-2 and small bowel cocoon-1)	high Adenosine Deaminase	6
		Polymerase Chain Reaction positivity	2
		Caseating Granuloma	1
		Non Caseating Granuloma	1
		Ileal stricture at laparotomy	1
Psoas Abcess (left sided)	1, (Long history of low grade fever and left flank pain)	Contrast enhanced computerized tomography (CECT) of Abdomen	1
Potts Spine	1, (History of para- paresis)	Suggestive Magnetic Resonance Imaging (MRI) spine (Lumbar1-Lumbar5 vertebrae)	1
Tubercular Meningitis (TBM)	1, (History of headache and seizure)	Suggestive cerebrospinal fluid (CSF) analysis	1
Submandibular Lymph node (LN)	1, (History of constitutional symptoms)	Suggestive Fine Needle Aspiration Cytology (FNAC)	1

Table 2 Baseline characteristic of patients with cirrhosis of liver and tuberculosis (n=36)

Characteristic	Total patients	Patients in regimen A	Patients in regimen B
No of patients	36	18	18
Male: Female*	26:10:00	14:04	12:06
Mean age in years (Mean ±SD)*	40.92±9.04	41.33±8.84	40.14±6.06
Aetiology of Cirrhosis*			
Alcohol	15	8	7
HBV	10	6	4
HCV	2	1	1
Cryptogenic	9	2	7
Site of Tuberculosis*			
Pulmonary	18	11	7
Abdominal	10	4	6
Pleural effusion	6	3	3

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Table Continued....

Characteristic	Total patients	Patients in regimen A	Patients in regimen B
TBM	1	0	1
Psoas abcess	1	0	1
Child status (A:B)*	14:22	8:10	6:12
Bilirubin mg/dL (Mean±SD)*	1.79±2.12	1.75±0.57	1.78±0.93
ALT IU/mL (Mean±SD)*	39±15.84	32±11.22	40.11±17.07

Aetiological agents responsible for cirrhosis amongst these patients were alcohol (18, 42.8%), hepatitis B(11, 26.1%), hepatitis C(2, 2.6%) and other causes (11, 26.1%). Thus, the most common aetiology for cirrhosis of liver was alcohol followed hepatitis B amongst patients with cirrhosis of liver with tuberculosis (as shown in Table 2). No statistically significant difference was found between baseline characteristics in two groups. Six patients were excluded from ATT regimen. Three of them recently had ATT induced hepatotoxicity, two belonged to Child C catergory and one had abdominal cocoon that required surgery Remaining 36patients with cirrhosis of liver and tuberculosis were randomised into two different ATT regimens. Regimen A (2HRE + 7HE, wt based dose) was given in 18 patients (8 patients with Child A and 10patients with Child B liver cirrhosis) and regimen B (REO for 9months) was given in 18 patients (6patients with Child A and 12 patients with Child B liver cirrhosis). In two patient of regimen B, treatment was given for 18month for tuberculous meningitis and psoas abscess. Baseline characteristics were similar in two groups (Table 2).

Out of 36patients, 2patients developed ATT induced hepatitis (Table 3). Two patients out of 18 in regimen A (11.11%) and none of the 18patients in regimen B (0%) developed hepatotoxicity during treatment ($p<0.05$). Both patients who developed ATT induced hepatitis were of child B cirrhosis. ATT was stopped immediately after diagnosis of ATT induced hepatotoxicity. The serum ALT and bilirubin level fell down to 2times of upper limit and 2.5mg/dl respectively after ATT induced hepatotoxicity in 4weeks. Thereafter, these patients were started on regimen B (contained less number of hepatotoxic drugs) which was well tolerated.

Table 3 Characteristic and outcome of patients in whom ATT induced hepatotoxicity was developed

S. No.	Age/Sex	Aetiology	Child Status	Site of TB	ALT level		1st Regimen	2nd Regimen	Outcome
					Baseline	At hepatotoxicity			
1	35/Male	HBV	B	Lung	56	171	HRE	REO	Successfully completed therapy
2	55/Female	Cryptogenic	B	Pleural effusion	38	124	HRE	REO	Successfully completed therapy

*ATT, Anti-Tubercular Treatment; ALT, Alanine Transaminase; TB, Tuberculosis, HBV, Hepatitis B Virus; HRE, (Isoniazid + Rifampicin + Ethambutol); REO, (Rifampicin + Ethambutol + Ofloxacin)

Discussion

Available data regarding prevalence of tuberculosis in patients with liver cirrhosis and its characteristics and treatment is either scattered or insufficient. Prevalence of tuberculosis in patients with cirrhosis of liver in our study was 145.33per 1000 patients (14.53%) which were higher than the prevalence of all forms of tuberculosis in general population in India. A study conducted in Western India showed that the prevalence rate was 15times higher than in the general population.[4] Another study from India showed that there is nearly five times higher prevalence of TB in cirrhosis patients (8.1%) compared to the general population (1.6%).[5] This high prevalence is attributable to immune deficiency in cirrhosis of liver which is due to decreased T-lymphocyte activation and proliferation.

Pulmonary TB is generally responsible for 80%-85% of all cases of TB reported.[6] Cirrhosis has been suggested as a risk factor for extra pulmonary TB in a previous study.[7] In a Korean study, 31% patients with cirrhosis had extra pulmonary TB, as compared to 12% in the non cirrhosis control group with predominance of peritoneal TB.[3] We found that the 52.4% patients with cirrhosis had extra pulmonary TB. Although most of the host defense systems, especially the clearance capacity of the reticulo endothelial system, are thought to be diminished in patients with cirrhosis, there is no simple explanation as to how this immune dysfunction results in patients being more likely to develop extra pulmonary TB than pulmonary TB.

Most common aetiological agent responsible for development of cirrhosis of liver amongst patients with tuberculosis was found to be alcohol in our study. Similarly, Baijal et al.[4] and Saigal et al.[5] also showed that alcohol was the most common aetiological agent responsible for development of cirrhosis of liver with tuberculosis.[4,5] Patients with stable alcoholic chronic liver disease show an attenuated TLR-2-mediated innate immune response.[8]

During treatment of tuberculosis in patients with cirrhosis of liver with anti tuberculous drugs, it is often difficult to differentiate between features of hepatotoxicity and spontaneous worsening of underlying cirrhosis of liver. There is no clear-cut recommendation for defining ATT induced hepatotoxicity in such patients. There is a need to define better the level of aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) and serum bilirubin at which to consider hepatotoxicity to avoid unnecessary treatment withdrawal and to avoid dangerous continuation of antitubercular therapy when hepatotoxicity has set in. The baseline AST/ALT and serum bilirubin are already elevated prior to the institution of antitubercular therapy. Although it is generally recommended that therapy be interrupted when transaminase levels increase to 3-5times the upper limit of

normal, this limit has not been defined in patients with transaminase values already elevated before starting therapy.[9]

Schenker et al.[10] reported that elevations in the ALT and/or AST levels to 50-100IU/ L more than the baseline levels might define toxicity. In a study by Saigal et al.[11] hepatotoxicity was diagnosed if ALT/AST levels increased to more than fivefold of the baseline level, or to more than 400IU/L, or if the bilirubin increased by 2.5mg/dL after exclusion of superimposed acute hepatitis . In this study, ALT/AST levels increased to more than threefold of upper limit of normal, or if the bilirubin increased by 2.5mg/dL after exclusion of superimposed acute alcoholic and viral hepatitis. Moreover, no clear guideline exists regarding the monitoring of such patients, modifications of the antituberculous regimen and mode of reintroduction of individual ATT. The major antituberculous drugs: INH, RIF and PZA are metabolized in liver itself. Thus, patients with cirrhosis of liver tend to accumulate INH, RIF and PZA in their plasma, due to decreased excretion and increased half life. Approximately 10-20% of patients during the first 4-6months of therapy have a mild hepatic dysfunction shown by mild and transient increase in serum AST, ALT and bilirubin concentration. But in some patients the hepatic damage may be progressive and may cause fatal hepatitis. Acetyl hydrazine, a metabolite of INH is responsible for liver cell necrosis. Rifampicin causes transient elevations in hepatic enzymes usually within the first 8weeks of therapy in 10% to 15% of patients, with less than 1% of the patients demonstrating overt rifampicin-induced hepatotoxicity.

Rifampicin, an inducer of cytochrome P 450, enhances the formation of toxic metabolites of isoniazid. The first human case of proven hepatotoxic interaction between INH and RMP has recently been reported by Askgaard et al.[12] A 35-year-old black Somalian patient with miliary tuberculosis developed hepatotoxicity after a few days of treatment with INH, RMP, PZA and EMB. On withdrawing all the drugs, the liver profile normalised and remained so after INH challenge. Hepatotoxicity recurred when RMP was added but it was well-tolerated when RMP was re-introduced without INH. In a meta-analysis, higher incidence of hepatotoxicity was reported when INH and RMP (2.6%) were given together as compared to when INH was given alone (1.1%).[13] In patients receiving a combination of INH, RMP and PZA, two patterns of fulminant liver injury have been observed.

Increase in serum transaminase activity which occurs late (usually after one month) has been attributed to PZA-induced hepatotoxicity while the early increase in transaminases (usually within first 15days) has been attributed to RMP and INH-induced hepatotoxicity.[14] In view of hepatotoxicity of INH, PZA and combination of INH and RMP, we used new ATT regimen, regimen B, which includes RMP, EMB and ofloxacin. In context of efficacy of this regimen, in vitro susceptibility of mycobacterium tuberculosis to ofloxacin was well demonstrated by Yew et al in an earlier study.[15] We compared this regimen B with conventional regimen A which includes INH, RMP and EMB. None out of 18patients on regimen B developed hepatotoxicity during the treatment. In contrast, 2 patients out of 18 of regimen A developed hepatotoxicity (11.11%) ($p<0.05$). In this study two of the twelve (16.6%) patients with child B cirrhosis developed ATT induced hepatotoxicity after being started on the regimen containing combination of INH and RIF. This suggested that INH and RMP combination should be avoided in Child B liver cirrhosis if possible. Although, this combination seems to be safe in Child A liver cirrhosis, as none of six patients of Child A liver cirrhosis developed ATT induced hepatotoxicity after being started on this combination.

The current guidelines by American Thoracic Society recommend that, in patients with cirrhosis of liver, a RIF based regimen excluding INH and PZA, is to be preferred.[16] Our data also suggests that combination of INH and PZA should be excluded in regimens for treatment of tuberculosis in cirrhosis of liver particulary in child B cirrhosis. However, this study didn't reveal any data regarding use of ATT in child C cirrhosis. After hepatotoxicity, both the BTS and ATS advise reintroducing the antitubercular drugs one at a time. These recommendations are in general and not specific to groups of patients with underlying cirrhosis. It is more prudent to start one drug at a time after the serum bilirubin and AST/ALT levels have returned to near the baseline. In this study, rifampicin was started first at reduced dose of 150mg per day then gradually increased on every 3rd day to full dose with simultaneous monitoring of LFT after hepatotoxicity. Non hepatotoxic drugs Ethambutol and ofloxacin were started at full dose at beginning.

Conclusion

There is higher prevalence of tuberculosis in cirrhotics as compared to the general population and alcoholic cirrhotic were highly vulnerable. Tuberculous patients with liver cirrhosis had a higher frequency of extrapulmonary involvement. Successful completion of antitubercular drug therapy with two hepatotoxic drugs remains a challenge in patients with cirrhosis due to reduced hepatic reserve. In this study, combination therapy of two hepatotoxic drugs INH and RIF was found to be a risk factor for ATT induced hepatitis in child B cirrhosis. ATT regimen containing RIF, EMB and Ofloxacin was well tolerated in cirrhosis of liver; even in Child B. Restarting with different regimen containing less number of hepatotoxic drugs was well possible after resolving the ATT induced hepatitis. Close monitoring and early detection is the key to prevent drug-induced liver injury and. However, limitations of this study were low sample size and non-blinding.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

References

1. WHO. Global tuberculosis report 2012. World Health Organization, Geneva. Switzerland; 2013.
2. TB Statistics for India. TB Facts. 2012.
3. Cho YJ, Lee SM, Yoo CG, et al. Clinical characteristics of tuberculosis in patients with liver cirrhosis. *Respirology*. 2007;12(3):401–405.
4. Baijal R, Praveen Kumar HR, Amarapurkar DN, et al. Prevalence of tuberculosis in patients with cirrhosis of liver in India. *Tropical Doctor*. 2010;40(3):163–164.
5. Saigal S, Nandeesh HP, Agarwal SR, et al. High prevalence and profile of tuberculosis in chronic liver disease patients. *Gastroenterology*. 1998;114(Suppl 1):A38.
6. Mehta JB, Dutt A, Harvill L, et al. Epidemiology of extrapulmonary tuberculosis. A comparative analysis with pre-AIDS era. *Chest*. 1991;99(5):1134–1138.
7. Gonzalez OY, Adams G, Teeter LD, et al. Extra-pulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis. *Int J Tuberc Lung Dis*. 2003;7(12):1178–1185.

8. Pimentel-Nunes P, Roncon-Albuquerque R Jr, Gonçalves N, et al. Attenuation of toll-like receptor 2-mediated innate immune response in patients with alcoholic chronic liver disease. *Liver Int*. 2010;30(7):1003–1011.
9. Lew W, Pai M, Oxlade O, et al. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med*. 2008;149(2):123–1341.
10. Schenker S, Martin RR, Hoyumpa AM. Antecedent liver disease and drug toxicity. *J Hepatol.* 1999;31(6):1098–1105.
11. Saigal S, Agarwal SR, Nandeesh HP, et al. Safety of an ofloxacin-based antitubercular regimen for the treatment of tuberculosis in patients with underlying chronic liver disease: a preliminary report. *J Gastroenterol Hepatol*. 2001;16(9):1028–1032.
12. Askgaard DS, Wilcke T, Dossing M. Hepatotoxicity caused by the combined treatment action of isoniazid and rifampicin. *Thorax*. 1996;50(2):213–214.
13. Steele MA, Burk RF, Desprez RM. Toxic Hepatitis with isoniazid and rifampicin; a meta-analysis. *Chest.* 1991;99(2):465–471.
14. Pande JN, Singh SP, Khilnani GC, et al. Risk factors for hepatotoxicity induced by antituberculosis drugs. *Acta Physiol Pharma Ther Latin Am*. 1997;47:197–202.
15. Yew WW, Kwan SYL, Ma WK, et al. *In vitro* activity of ofloxacin against Mycobacterium tuberculosis and its clinical efficacy in multiply resistant pulmonary tuberculosis. *J Antimicrob Chemother*. 1990;26(2):227–236.
16. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med.* 2006;174(8):935–952.

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