REVIEW ARTICLE

ANTITUBERCULOSIS THERAPY IN PATIENTS WITH HEPATITIS B VIRAL INFECTION

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ABSTRACT

Tuberculosis (TB) and Hepatitis B virus (HBV) infections are quite common in the developing world especially South Asia. As both are so common, co-infection is not very uncommonly encountered in clinical practice. However, since anti-tuberculosis therapy (ATT) can be hepatotoxic in around 10% of patients, the occurrence of hepatotoxicity can complicate management especially in the presence of already compromised liver function due to HBV. Therefore, co-infection of TB and HBV is an important public health issue. Unfortunately the regional and National hepatology societies of South Asia have not bothered to provide any guidance in this matter. This article reviews the epidemiology and management of co-infection with Tuberculosis (TB) and Hepatitis B virus (HBV) and the hepatotoxicity due to ATT.

Key words: Drug induced liver injury, hepatitis B virus, treatment, tuberculosis

INTRODUCTION

Tuberculosis (TB) and hepatitis B virus (HBV) infections are common in developing countries of south-east Asia, including India. By virtue of commonness, co-infection is not uncommon in clinical practice. Anti-tuberculosis therapy (ATT) can be hepatotoxic in around 10% of the patients, which may be a management issue that is difficult in the presence of already compromised liver functions due to HBV.

Infectious diseases including TB, HBV, and others are the most common causes of mortality (41%) in India.[1] Adverse drug reactions are the sixth most common cause of death in hospitalized patients.[2] Therefore, co-infection of TB and HBV is an important public health issue. This article covers epidemiology and management of co-infection and hepatotoxicity due to ATT.

EPIDEMIOLOGY OF TUBERCULOSIS

Global data

Tuberculosis has remained a major health problem in the world. *Mycobacterium tuberculosis* infects almost one-third of the world's population (around two billion persons), moreso in developing countries. Even in developed countries, there is a resurgence of TB. The reasons are twofold. First, there is an increase in the immunocompromised population secondary to the pandemic of the human immunodeficiency virus (HIV) infection and increased rate of organ transplantation. Second, increased transglobal migration and travel have led to an easy spread of the organism.

Throughout the world, nine million new cases of TB are diagnosed; of which 1.7 million persons succumb to the disease annually.[3] Life-time cumulative risk for active TB is more than 10%.[4] The highest incidence and mortality rates of HIV are seen in sub-Saharan Africa, whereas, the highest incidence and mortality rates of TB are seen in southeast Asia.

Indian Data

India is a country with high prevalence and incidence of TB. The estimated burden of TB in India is around 8.5 million.[5] Average prevalence of all forms of TB is estimated to be 5.05 per 1000 persons and the average annual incidence of smear-positive

cases is 84 per 100,000 annually.[6] Also there is a high rate of transmission with the annual risk of infection varying from 1-2.2% in different studies carried out in different parts of the country.[7,8] Few epidemiologists forecast a 20% rise in incidence in the next 20 years with a cumulative rise of 46 million cases during that period.[6]

HEPATOTOXICITY OF ANTI-TUBERCULOSIS THERAPY:

Recommended treatment for TB is a regimen of isoniazid (H), Rifampicin (R), ethambutol (E), and pyrizinamide (Z) for the initial two months followed by 4-10 months of H and R combination. Primary drugs like H, R, and Z are the most potent, but are hepatotoxic also. Most non-hepatotoxic second-line drugs are less effective against TB. Hepatotoxicity is the major side effect of this highly effective ATT. ATT-hepatotoxicity results in significant morbidity and even mortality, due to acute liver failure. Also these events lead to a substantial financial burden because of additional outpatient visits, tests, and additional hospitalization in case of severe reactions. Hepatotoxicity leads to interruption, modification or non-adherence; eventually this results in treatment failure, relapse, and drug-resistance. Modification of therapy results in the use of less effective, second-line drugs, leading to a suboptimal response to the therapy and prolongation of the therapy, with attendant challenges to compliance.

Definition of hepatotoxicity varies from alanine aminotransferase (ALT) > thrice the upper normal limit (X ULN) with symptoms, > 5 X ULN with / without symptoms, to > 10 X ULN in various series.[9-25] Different regimens, different study populations, different definitions of hepatotoxicity, different monitoring practices, and different reporting practices are responsible for the variable results in various studies and this makes it difficult to draw any definitive conclusions regarding the risk involved in using any individual regimen. Incidence of ATT-hepatotoxicity with individual drugs is estimated in two studies: (a) 0.6% with H alone, 1.1% with multidrug R-containing regimen without H, 1.6% with multidrug H-containing regimen without R, and 2.6% with HR containing the regimen;[26] and (b) 1.48% for Z, 0.49% for H, and 0.43% for R.[27]

Epidemiology of hepatotoxicity in active TB

Incidence of ATT-hepatotoxicity varies from 2 to 27.7% in various series.[9-25] Countrywise reported incidence is as follows: 8% in Nepal,[28] 18.25-36% in Japan,[10,29] 14.7-26% in Taiwan,[10,30] 13%

in Hong Kong,[10] 8-36% in India,[25,26] 4.3% in western countries,[26] < 1-3% in US,[31]4% in UK,[31] 2.6-3.3% in Spain,[14] 11% in Germany, and 9.9% in Argentina.[10,32]

Risk factors for ATT-hepatotoxicity in various series are: advanced age, female gender, Asian ethnicity, low body mass index (BMI), malnutrition, hypoalbuminemia, abnormal baseline aminotrnaferases, history of hepatitis, alcoholism, HBV, hepatitis C virus infection, concomitant hepatotoxic drugs, HIV infection, low CD4 count, organ transplantation, slow acetylator status, CYP2E1 c1 / c1 genotype, HLA DQB1*0201 genotype, slow acetylator without NAT2*4 allele, and glutathione S-transferase homozygous null genotype.[9-37] In an Iranian study, there has been no risk factor identified.[22] The dosing schedule has a controversial role in increasing the risk of hepatotoxicity.[38,39] Role of Z in hepatotoxicity has remained controversial: A dose of Z, less than 25-30 mg / kg / day, may be safe, but recent reports favor Z to be responsible for hepatotoxicity.[9,15,33,40-42]Globally, the frequency of hepatotoxicity, that is, ALT > 3 x ULN (18.2% vs. 5.8%) and severe hepatotoxicity, that is, ALT > 10 x ULN (6.9% vs. 0.4%) is higher in patients with risk factors than persons without them.[11]

Indian data

In the Indian series, the risk of ATT-hepatotoxicity is calculated to be 11.5% from four prospective series[41,43-45] as compared to 4.28% in a meta-analysis of 14 studies from the west.[26] High incidence of hepatotoxicity in a developing country is thought to be due to viral hepatitis infections, indiscriminate use of drugs, malnutrition, and more advanced TB.[25,41,45-47] In addition, high incidence of viral hepatitis in TB patients of developing countries results in the misdiagnosis of drug-induced-hepatotoxicity (DIH) if serological tests are not performed during the hepatitis period.[30,46] In a previous Indian series, 12.9-42.5% of acute hepatitic illness during ATT might be actually due to acute viral hepatitis.[46,48-50] Serological tests for viral hepatitis are a must during this period. Later onset of acute hepatitis, higher elevations in aminotransferases, and a longer time for normalization, indicate acute viral hepatitis rather than DIH.[48,49]

In the Indian series, the identified risk factors are: advanced age, alcoholism, hypoalbuminemia, malnutrition, slow acetylator status, extensive TB, and glutathione S-transferase homozygous null genotype.[24,25,37,51]

Epidemiology of hepatotoxicity in latent TB infection (LTBI)

Incidence of hepatotoxicity during treatment of LTBI varies according to different regimens:[52] 0.1-5.2% with nine-month H;[4,53-56] 0-0.7% with four-month R;[4,57-59] 0% (as safe as H) with three-month HR combination;[60,61] 0.9% with three-month H-rifapentine;[62] 7.7-35% (2.8% severe hepatotoxicity) with two-month RZ combination;[16,63-66] 11-14% with H-high-dose Z combination;[67] 2-5% with H or R with low dose Z combination;[9] 50% with ZE combination;[68] and 25-47% with Z-flouroquinolone combination.[69,70]

Older age, alcohol consumption, HIV infection, concomitant hepatotoxic drugs, high dose Z, birth in Asia, chronic viral hepatitis, and cirrhosis are risk factors for hepatotoxicity during treatment of LTBI.[15,16,52,54-56,66,67]

Outcome of hepatotoxicity

There is 6-12% mortality if ATT is continued even after the onset of hepatotoxicity.[71,72] Evolution to acute liver failure is present in 10% of cases.[14] An overall mortality rate of hepatotoxicity is 0.08% among all cases[73] and 2.4% among cases of severe hepatotoxicity.[14]

EPIDEMIOLOGY OF HEPATITIS B VIRUS INFECTION

A total of 350 million persons are infected with HBV worldwide,[74] 75% of which reside in Southeast Asia, with prevalence of 5-20% in the general population.[75] In India, HBsAg prevalence in the general population varies from 1.1 to 12.2%, averaging 3.34%; which amounts to around 50 million patients.[76]

CO-INFECTION OF TB AND HBV

Epidemiology

As both HBV and TB are highly prevalent in Southeast Asian countries, including India, co-infection is commonly encountered in clinical practice. However, there is sparse data on the prevalence of HBV infection in TB patients: 9% in 752 Thai HIV-infected TB patients;[77] 4.3% in 300 Georgian TB patients;[78] 6.4% in 951 Indian HIV-infected TB patients;[79] 14.6% in Brazilian (35.8% in HIV-infected) TB patients;[80] 61.6% in 356 Russian TB patients;[81] 1.95% in 1637 European TB patients;[82] and 5.7% in 261 Taiwanese TB patients.[83]

Prevalence of LTBI in HBsAg patients is addressed in few series: 53% in 103 HBsAg + / 743 Vietnamese immigrants to USA.[84]

Injection drug abusers, dialysis patients, sex workers, healthcare workers, patients with HIV infection, homeless people, persons in mental hospitals or prisons, and foreign-born persons of countries with highly prevalent HBV / hepatitis C and / or TB are at risk of exposure to both HBV and TB.[85-90] Few studies have looked into suspecting HBV in TB patients. In Thai HIV-infected TB patients, homosexuality was a factor independently associated with HBsAg reactivity, and IV drug abuse was a factor associated with combined HBsAg and anti-HCV reactivity.[77] In Georgian TB patients, 85% of the time HBV serology status can be predicted correctly on the basis of a Questionnaire algorithm, including a history of blood transfusion, IV drug abuse, younger age at sexual debut, and multiple sexual partners.[78]

ANALYSIS OF ATT-HEPATOTOXICITY IN HBV PATIENTS

Data on HBV as a risk factor for ATT-hepatotoxicity

Studies looking into risk factors for ATT-hepatotoxicity, which found HBV to be a risk factor, are summarized in Table 1. Table 2 summarizes the studies on HBV patients who developed hepatotoxicity during ATT, either for TB or LTBI.

A major problem in defining ATT-hepatotoxicity (defined on the basis of altered ALT and / or symptoms) in HBV patients is spontaneous flares in the HBV disease, which also result in altered ALT and / or symptoms. Additional tests like HBV DNA and e-antigen serology tests must be done when there is an episode of altered ALT and / or symptoms; to detect reactivation of HBV or serosonversion / seroreversion illnesses. Majority data available on this issue have not looked in to this matter seriously, barring few studies.

Considerable variability in study designs may prevent conclusions from being drawn regarding the potential contribution of hepatitis B infection to drug-induced hepatotoxicity. Most studies agree that hepatitis B co-infection causes more severe hepatitis due to anti-tuberculosis treatment. The natural course of liver chemistry in HBV may be a confounding factor when evaluating for the presence of hepatotoxicity. Transaminases may remain normal or wax and wane over time in a sine-wave pattern or may have spontaneous flares.

Difference in the diagnostic criteria used to define hepatotoxicity, the characteristics and risk factors of the populations

Table 1: Studies to define HBV as risk factor for ATT-hepatotoxicity

Study	Design; numbers	HBV characterization at baseline	HBV as a risk factor
Singh, 1995[40]	Prospective	Not characterized	No increase in risk
Yew, 1996[52]	Retrospective; 142 DIH/1181 TB	Not characterized	Increased risk
Ungo, 1998[91]	Prospective; 22 DIH/134 TB (5 HBsAg+)	Not characterized	No increase in risk for current (HBsAg+) or past (antiHBs+) HBV
Chang, 2008[92]	Prospective; 150 DIH/3007 TB (15 HBsAg+ DIH vs. 6 HBsAg+ control)	Not characterized	Increased risk (OR 2.7)
Marzuki, 2008[93]	Retrospective; 46 DIH/473 TB (3 HBsAg+ DIH vs. 2 HBsAg+ control)	Not characterized	No increase in risk (7% HBsAg+ vs. 1% HBsAg-)
Makhlouf, 2008[94]	Prospective; 15 DIH/100 TB (3 HBsAg+)	Inactive HBsAg carriers	No increase in risk (0% HBsAg+ vs. 15.5% HBsAg-)
Yimer, 2008[95]	Prospective; 34 subclinical DIH/197 TB (14 HBsAg +)	Not characterized	No increase in risk (21% HBsAg+ vs. 17% HBsAg-)
Vilarica, 2010[34]	Retrospective, 1400 TB (83 DIH), variable	Not characterized	Increased risk (relative risk for DIH 2.5 with HBV and/or HCV)

Table 1: Contd...

Study	Design; numbers	HBV characterization at baseline	HBV as a risk factor
Kaneko, 2008[35]	Retrospective, 107 TB, HEZ or HR	Not characterized	Increased risk (15.4% vs. 6.9% control)
Padmapriyadarsini, 2006[79]	Prospective, 140 HIV-infected TB and LTBI, HREZ or H	Not characterized	Not increased (only 5% develop DIH among 81 HBV or HCV+)
Chen, 1989[96]	Retrospective	Not characterized	Increased risk (50% vs. 2.4%)
Bilven, 2009[89]	Meta-analysis (486 abstract, 11 studies), LTBI, H	Not characterized	Not increased (relative risk of developing hepatotoxicity in HBsAg positive persons on treatment for LTBI varies from 0.3 to 1.16[97,98])

ATT: Anti-tuberculosis therapy; HBV: Hepatitis B virus

studied, the geographical area or the type of monitoring, selected biochemistry taken during follow-up, and selection biases may contribute to such variations.

Difference in severe hepatotoxicity between the preventive therapy for LTBI and curative treatment for TB might reflect a difference in the intake of alcohol, dose of pyrizinamide, immunogenetic differences in the development of ATT hepatotoxicity, and different backgrounds (HIV, hepatitis B, and / or hepatitis C virus infections).[16]

Table 2: Abridged data of anti-tuberculosis therapy-hepatotoxicity in hepatitis B virus patients

Series, year	Population	ATT	Numbers, design, HBV disease	HBV status during DIH	Frequency of DIH	Severity of DIH
McGlynn, 1986[99]	SE Asians, LTBI, < 35 years	H	1833, (668 HBV+ vs. 1165 HBV-); prospective; Not characterized	Not defined	Not increased	NA
Patel, 2002[84]	Vietnamese, LTBI	H	55 HBV+ (22 eAg + vs. 33 eAg-); prospective; characterized in form of HBeAg status	Not defined	Increased in eAg + (62% vs. 19%)	Increased in eAg + (38% vs. 81% completed therapy, 14.2% vs. 0% severe hepatitis)
Wu, 1990[100]	Taiwanese, TB	HR	42 DIH/1783 (15 HBV+ vs. 27 HBV-); prospective; 75% of DIH had active HBV disease (HBVDNA +)	Not defined	NA	Increased (early onset, higher ALT, increased mortality [46.6% vs. 3.7%]
Amarapurkar, 1993[101]	Indian, TB	HREZ	53 DIH (11 HBV +) vs. 53 control; prospective; Not characterized	Not defined	Increased (HBV + in DIH 20.3% vs. in control 3.7%)	Increased (higher bilirubin, higher mortality [27.3% vs. 4.8%]

Table 2: Contd...

Series, year	Population	ATT	Numbers, design, HBV disease	HBV status during DIH	Frequency of DIH	Severity of DIH
Hwang, 1997[102]	Taiwanese, TB	HREZ	240 (31 HBV +), DIH 63 (9 HBV+ vs. HBV-); prospective; 65% inactive carrier	Defined (HBV DNA + and HBeAg + ruled out before diagnosis of DIH)	Not increased (29% vs. 26%)	11.1% HBV+ vs. 0% HBV- mortality
Wong, 2000[103]	Hong Kong, TB	HREZ	43 HBV+ on ATT vs. 276 HBV- on ATT vs. 86 HBV but no ATT; prospective; 75% inactive carrier	Defined (65% of ALT elevation episodes were associated with HBV DNA increase)	Increased (34.9% vs. 9.4% vs. 8.1%)	Increased (severe histology, similar clinical course)
Pan, 2005[104]	Chinese, TB	HREZ	47 HBV+ vs. 170 HBV-; prospective; Not characterized	Only HBeAg status available (no difference in HBeAg+ or -)	Increased (59% vs. 24%)	NA
Lee, 2005[105]	Korean, TB	HREZ	110 HBV+ Vs. 97 HBV-; retrospective; inactive carrier	Not defined	Trend for increase (8% vs. 4%) but not significant	Increased (9.8% vs. 2% moderate-severe DIH)

Table 2: Contd...

Series, year	Population	ATT	Numbers, design, HBV disease	HBV status during DIH	Frequency of DIH	Severity of DIH
Sirinak, 2008[77]	Thailand, TB-HIV		43 HBV + vs. 27 HBV + HCV+ vs. HBV- or HBV- HCV-; prospective; Not characterized	Not defined	Not increased (7% vs. 7% vs. 5%)	Not increased (no difference)
De Castro, 2010[106]	Brazilian, TB	HRZ	154 (6 HBV +) vs. HBV-; prospective; Not characterized	Not defined	Increased risk with low precision (relative risk 2.91), not significant	NA
Chien, 2010[107]	Taiwanese, TB	HREZ	295 (25 HBV+, 29 HCV+, 4 HBV + HCV+) vs. HBV-; retrospective; Not characterized	Not defined	Not increased (12% HBV + vs. 8% HBV-)	Increased (higher ALT and slower recovery)
Huang, 2009[108]	Chinese, TB	HREZ as DOTS	162 DIH/781 TB (121 HBV+ vs. 41 HBV-); retrospective; Not characterized	Not defined	Increased risk	Increased (early onset late recovery, higher ALT)

Table 2: Contd...

Series, year	Population	ATT	Numbers, design, HBV disease	HBV status during DIH	Frequency of DIH	Severity of DIH
Xu, 1995[109]	Chinese, TB	NA	268, HBV+ vs. HBV-; prospective; characterized with HBV-DNA	Not defined	Increased risk (abnormal LFT 49% {95% in HBV DNA +} vs. 10%)	Increased (higher mortality)
Chang, 2007[38]	Chinese, TB	HRZ	96DIH/3007TB (16 HBsAg+ DIH vs. 11 HBsAg+ control); retrospective; not characterized	Not defined	Increased risk (OR 1.8)	Not increased

Table 3: Guidelines on monitoring and action during anti-tuberculosis therapy

Guideline	Monitoring schedule	Monitoring in high risk	Stopping drug if clinical	Cut-off for stopping drugs – ALT	Cut-off for stopping drugs – bilirubin
American[110]	Monthly (laboratory periodically if high risk)	Yes	Yes	5x (AST preferred)	Increased
British[60]	Weekly for two weeks then bi-weekly for two months if high risk	Yes	Yes	5x	Increased
European[52]	-	-	Yes	5x	Increased
HongKong[52]	-	Yes	Yes	3x progressive rise	2x, persistent elevation

MONITORING DURING ATT AND MANAGEMENT OF ATT-HEPATOTOXICITY

As hepatotoxicity of ATT is very important, regular monitoring of these patients for detecting early hepatotoxicity is required. Table 3 summarizes the few available guidelines.

Other countries follow different monitoring schedules, few of which are written herewith, to show heterogeneity.

France: Weekly laboratory tests in the first two months[111]

Spain: Laboratory test at the second and fourth week and at end of the second and fourth months in high-risk patients with periodical clinical monitoring[11]

Taiwan: Clinical and laboratory every two weeks in the first month and then monthly thereafter[107]

South Korea: Clinical and laboratory every month[112]

Once hepatotoxicity is detected, there can be three actions:

1. Stop ATT forever: This will lead to increase in morbidity and mortality due to TB, with subsequently more TB transmission in the community, which is not a good option.
2. Stop hepatotoxic drugs and continue modified ATT with non-hepatotoxic drugs: Problem of prolonged therapy due to less effective drugs and other side effects of drugs (ototoxicity–nephrotoxicity of Streptomycin (S) or ophthalmotoxicity of E, etc.).
3. Stop drugs, use non-hepatotoxic drugs till normalization of ALT and then reintroduce drugs: seems to be logical if re-exposure to drug is tolerated. When reintroducing ATT, if the drug is found to be causing hepatotoxicity again, then continue further ATT without adding that drug. Reintroduction can be done using three methods:
    a. Sequential escalating dose reintroduction: Drugs are reintroduced in a phased manner — low dose for the initial three days then full dose of the drug for four days to one week, then subsequently, after documenting normal ALT, the new drug is added in a similar fashion
    b. Sequential full-dose reintroduction: drugs are reintroduced in a phased manner — full dose of a drug for one week and then another drug is added after documenting normal ALT

c. Simultaneous full dose reintroduction: All the drugs are added at a time in full doses, while monitoring closely

Even as initial studies suspected that reintroduction could be risky or life-threatening,[113,114] there is now overwhelming evidence in favor of reintroduction of the drugs.[24,31-33,41,115-118] Different trials have followed different monitoring schedules, different cut-off levels, and different actions on ATT-hepatotoxicity. This is apparent in Table 4.

APPROACH TO MANAGEMENT OF CO-INFECTION IN HBV CARRIERS

Most authorities agree that the hepatitis B carrier state requires special attention. All the patients with TB should be screened for HBsAg before starting treatment. Whenever found to be HBsAg positive, the patients must undergo tests to define the stage of HBV disease (i. e. HBeAg, Anti-HBe, HBV DNA) or stage of liver disease (i.e., ALT, AST, bilirubin, SAP, GGTP, protein, PT, USG-abdomen, SOS OGDscopy, SOS liver biopsy).

Recent studies indicate that HBV carriers (defined as HBsAg positive, HBeAg negative, with low HBV DNA levels and persistently normal ALT) are not at increased risk of developing hepatotoxicity, but the severity of hepatotoxicity may be increased. Therefore, frequent clinical and biochemical monitoring of such patients, while on ATT, should be practiced. These patients can be started on standard ATT ($HREZ_4RH_{4-10}$). The risk of hepatotoxicity must be explained to the patients and counseling regarding symptoms of hepatotoxicity is a must, to identify hepatotoxicity early. Monitoring of such patients should be frequent with clinical as well as biochemical parameters like ALT and bilirubin. In case of development of hepatotoxicity, ATT should be altered in the form of E, ofloxacin / ciprofloxacin / levofloxacin and S. Weekly monitoring of symptoms and ALT / bilirubin should be done. Once they are normalized, sequential full dose / escalating dose reintroduction should be attempted.

APPROACH TO MANAGEMENT OF CO-INFECTION IN HBV CIRRHOSIS

There is no data on treating TB in HBV cirrhosis, and there is sparse data on treating TB in cirrhosis. There are very few series that have looked into treating these patients [Table 5].

Table 4: Studies on monitoring for and management of ATT-hepatotoxicity

Series, year, country	Type, number	Baseline LFT/HBsAg	Monitoring	Definition of DIH	Incidence of DIH	Action during DIH	Outcome of DIH	Reintroduction	Success of reintroduction
Sharifzadeh, 2005, Iran[22]	Prospective, 112 TB	AP, ALT, AST, PT, bilirubin	2/7 x 2 weeks f/b 1/15x 2 months f/b 1/month	Asymptomatic ALT–AST > 5x ULN, symptoms+ ALT–AST > 3x ULN, symptoms	27.7%	Discontinuation of HRZ, Rx with ECS till normalization of ALT–AST	77.4% severe DIH, 6.4% mortality	Sequential escalating dose regimen (I7f/ bR7f/bZ7 over 3 weeks)	100%/29 patients
Singh, 1996, India[119]	Prospective, 72 clinical DIH	-	-	Symptoms + ALT–AST > 2x ULN exclude positive viral markers	-	Discontinuation of HRZ, Rx with ES till normalization	16.6% FHF, 12.5% mortality	Sequential reintroduction (I-escalating over 14 d f/b 7 d observation f/b R f/b 7 day observation f/b Z	93%/44 patients
Sharma, 2010, India[50]	Prospective, 175 DIH	-	-	Asymptomatic ALT–AST > 5x ULN, asymptomatic ALT–AST > 3x ULN thrice, symptoms+ any ALT–AST elevation,	-	Discontinuation of HRZ, Rx with ES + any flouroquinolone till normalization of ALT–AST	1.6% mortality	I- simultaneous reintroduction at full doses; II- sequential full-dose reintroduction (r7 f/b h7 f/b Z7) ; III- sequential escalating dose (H 7f/b r7 f/b z7)	89.1%/175 patients

Table 4: Contd...

Series, year, country	Type, number	Baseline LFT/HBsAg	Monitoring	Definition of DIH	Incidence of DIH	Action during DIH	Outcome of DIH	Reintroduction	Success of reintroduction
Tahaoglu, 2001, Turkey[33]	Prospective, 45 DIH	AP, ALT, AST, PT, bilirubin	Lab when symptomatic	Asymptomatic ALT–AST > 5x ULN, bilirubin > 1.5 mg/dl, symptoms + any ALT–AST elevation	-	Discontinuation of ATT till normalization	-	I- sequential escalating dose (HRES), II- simultaneous full dose HREZ	100% vs. 76%
Gulbay, 2006, Turkey[120]	Retrospective, 1149 TB	-	-	ALT > 5x ULN or bilirubin > 2x ULN or symptoms	2.4%	Stop drugs	0%	I: same drug regimen in full dose, II: sequential escalating dose	61% (similar for both regimens)
Sharma, 2002, India[24]	Prospective, 361 TB	LFT	Monthly or symptoms; every 2 weeks in the presence of risk factor	Asymptomatic ALT–AST > 5x ULN, asymptomatic ALT–AST > 3x ULN thrice, symptoms+ any ALT–AST elevation,	15.5%	Discontinuation of ATT till normalization	0%	Sequential escalating dose	100%
Teleman, 2002, Singapore[17]	Retrospective, 55 DIH/1036 TB	ALT, AST, Bilirubin	Lab if high risk	ALT–AST > 3x ULN; bilirubin rise with ALT–AST > 2 x ULN	5.3%	Discontinuation of ATT till normalization	5.4%	Not clear	93.7%/48 patients

Table 4: Contd...

Series, year, country	Type, number	Baseline LFT/HBsAg	Monitoring	Definition of DIH	Incidence of DIH	Action during DIH	Outcome of DIH	Reintroduction	Success of reintroduction
Tost, 2005, Spain[14]	Retrospective, 106 DIH/3510 patients (LTBI and TB)		Lab at second week and fourth week then at end of two months and at end of four months	Severe DIH: ALT > 10x ULN and / or bilirubin/ASAP > 3x ULN, clinical hepatitis or ALF	2.6%	Discontinuation,	10.3% (ALF or death)	Not clear	33% same medication, 36% alternate medication, 21% no treatment
Kaneko, 2008, Japan[35]	Prospective, 107 TB with chronic hepatitis (58 HRZ and 49 HR)	ALT baseline, HBsAg, AntiHCV	ALT at least two months	ALT > 3x ULN if normal baseline ALT, rise > 1.5x ULN if abnormal baseline abnormal ALT	22.4% HRZ grp (27.8% HCV, 15.4% HBV and 11.1% alcoholic); 4.1% in HR group	Continuation or omission of PZA or alternate regimen	0%	Not clear	92.3% regimen without PZA
Kwon, 2007, South Korea[112]	Prospective, 54 TB with HCV positive vs. 82 control		ALT every month	ALT > 120 IU/ml	13% vs. 4%	Stop and substitute with nontoxic drugs	0%	serial reintroduction with increasing disease (R f/b I but Z not given)	100%

Table 4: Contd...

Series, year, country	Type, number	Baseline LFT/HBsAg	Monitoring	Definition of DIH	Incidence of DIH	Action during DIH	Outcome of DIH	Reintroduction	Success of reintroduction
Agal, 2005, India[32]	Prospective, 220 TB	LFT, HBsAg, antiHCV	Lab weekly for first month, 15 days for next 2 months then monthly	ALT > 5x ULN or ALT > 2x ULN if symptoms or bilirubin > 2x ULN	10.1%	Stop and use ETB + cipro + SM	0%	Serial fulldose reintroduction (H f/b R f/b Z)	95.2%
Fernandez-Villar, 2004, Spain[11]	Prospective, 471 TB	LFT, HBsAg, antiHCV	Lab at 15, 30, 60, and 120 days	ALT > 3x ULN	11.8%	Stop and modify	0.2%	Reintroduce progressively, avoid z and H in severe cases	57.1% similar regimen vs. 42.9% modified regimen
Lee, 2005, South Korea [105]	Prospective, 110 TB + HBV	LFT, HBsAg, antiHCV	Lab monthly	ALT > 120 IU/nml	8%	Stop and modify	0%	Serial reintroduction with increasing doses (R f/b H but no Z)	83%
Wong, 2000, Hong Kong[103]	Prospective, 43 TB + HBV	LFT, HBsAg, antiHCV	Lab monthly	ALT > 1.5 x ULN/baseline level	34.9%	Stop H if ALT > 3x ULN, stop all drugs if synthetic function impaired or symptomatic hepatitis	1%	Not clear	60%

Table 5: Treatment of TB in cirrhosis in various series

Series	Saigal, 2001 (India)[121]	Saito, 2006 (Japan)[122]	Cho, 2007 (Korea)[123]	Amarapurkar, 2009 (India)[124]
Treatment offered and number of patients	31 (15 for HRE2HR7 vs. 16 for HZRO 2HEO10)	HRE in 22 patients	36 (variable, 42% started on HR based treatment)	74 (standard ATT-42 vs. modified ATT [EHO or ERO-32)
H + R completion	35% (73 vs.0%)	NA	NA	40% (71 vs. 0%)
Hepatotoxicity	13% (26 vs.0%)	13.6%	27%	25% (33 vs. 15%)
Duration	predefined	NA	12 months	15 months

MANAGEMENT OF ATT-HEPATOTOXICITY DURING ACUTE VIRAL HEPATITIS

In case of acute viral hepatitis during ATT, after normalization of ALT, full-dose ATT can be restarted simultaneously.[48,49]

DATA ON THE USE OF ANTIVIRALS FOR HBV IN ATT-HEPATOTOXICITY

Antiviral therapy in active HBV disease decreases hepatitic activity and also causes the suppression of HBV DNA (curtail flares due to viral activity). This decreases the chance of occurence of hepatitic illness during ATT. Only a single case report is available on this aspect, where Lamivudine therapy enabled successful reintroduction of INH and RFM.[125]

CONCLUSIONS

Further research is required to exactly define treatment protocols for patients with tuberculosis and hepatitis B. Promising research directions at present are advocating an NAT2 genotype to predict the occurrence of hepatotoxicity or administration of hepatoprotective drugs along with ATT or the role of therapeutic drug monitoring.

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