Introduction

Tuberculosis (TB) is one of the foremost public health problems causing an enormous burden of suffering and deaths (Koju et al., 2005). It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV). World health organization (WHO) reported that there were almost 9 million new TB cases and 1.4 million TB deaths (990,000 among HIV negative people and 430,000 HIV-associated TB deaths) in 2011 (WHO report 2012). An increasing morbidity and mortality from TB in the near future is forecast for the world at large, with the number of newly occurring cases predicted to increase from 7.5 million a year in 1990 to 8.8, 10.2 and 11.9 million in the years 1995, 2002 and 2005 respectively; an increase amounting to 58.6 per cent over a 15-year period (Dolin et al., 1993). Also, it is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will get sick, and 36 million will die of TB, if control is not further strengthened (WHO report 2002).

Directly observed treatment short-course (DOTS) strategy using first-line anti-TB drugs (Isoniazid, Rifampicin, Pyrazamide, Ethambutol and Streptomycin) is very effective treatment against TB and cure 95% cases (Espinal et al., 2000). Despite the efficacy of DOTS, the prolonged intakes of anti-TB drugs cause many adverse effects such as hepatotoxicity, skin reactions, gastrointestinal and neurological disorders. However, hepatotoxicity is one of the most frequent and serious side effects of these anti-TB drugs and with the increasing incidence of TB worldwide, a greater number of patients are exposed to the risk of a potentially serious hepatotoxic effect of these anti-TB drugs (Saukkonen et al., 2006). Anti-TB drug-induced hepatotoxicity (anti-TB-DIH) is a major hurdle against the effective treatment of TB (Schaberg et al., 1996). Tostman et al. (2007) reported that anti-TB-DIH increases the risk of treatment failure, relapse or the emergence of drug-resistance.
Some patients taking anti-TB drugs develop severe hepatitis that may progress to liver failure and finally death (Makhlouf *et al.*, 2008).

The occurrence of anti-TB-DIH is variable in different countries. The incidence is higher in the developing countries with rates ranging from 8% to 39%, compared to developed countries at 3%–4%, despite similar regimens used (Parthasarathy *et al.*, 1986; Turktas *et al.*, 1994). A higher risk of 11.5% has been reported in Indian patients, compared to 4.3% in published studies from the developed countries (Snider *et al.*, 1984; Steele *et al.*, 1991).

Early recognition of anti-TB-DIH and its risk factors hold great significance to arrest severe liver injury and prevent treatment failure (Shakya *et al.*, 2006). The most common risk factors that have been found to be associated with anti-TB-DIH, are advanced age, female sex, poor nutritional status, liver disease, inappropriate use of drugs, infection with hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV, and high alcohol intake (Saukkonen *et al.*, 2006). However, the exact factors associated with anti-TB-DIH are still obscure.

The anti-TB-DIH is often suggested to be mediated through oxidative stress, leading to generation of lipid peroxidation and alteration in antioxidants (Sodhi *et al.*, 1996, 1997). Lipid peroxidation occurs as a chain reaction initiated by excess production of free radicals.

In response to deleterious effects of free radical induced lipid peroxidation, cells activate antioxidant defense mechanisms in which superoxide dismutase (SOD) and reduced glutathione (GSH) act synergistically to detoxify the effects of lipid peroxidation (Barber and Harris, 1994). Therefore, the evaluation of lipid peroxidation and antioxidants in patients with DIH may be of importance, to further evaluate the possible involvement of oxidative stress in the pathogenesis of anti-TB-DIH.

Susceptibility to anti-TB-DIH may also be genetically mediated. Many previous studies (Wang *et al.*, 2010; Teixeira *et al.*, 2011), have explored genetic risk factors for the development of anti-TB-DIH, such as polymorphisms in N acetyltransferase 2 (*NAT2*),
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cytochrome P450 2E1 \((\text{CYP2E1})\) and glutathione S-transferases \((\text{GSTs})\) genes. Among these, \text{CYP2E1} is one of the most important phase I drug metabolizing enzyme, which play a significant role in the production of hepatotoxic metabolites (Teixeira \textit{et al.}, 2011). Therefore, higher activity of \text{CYP2E1} may increase higher production of hepatotoxic substances and thereby leads to the risk of anti-TB-DIH. Genetic polymorphism of \text{CYP2E1} gene has an effect on the degree of metabolism among individuals, which modulate the activity of this enzyme. Some previous studies have demonstrated the association between the \text{CYP2E1} genotype and anti-TB-DIH (Sun \textit{et al.}, 2008; Hwang \textit{et al.}, 1997; Huang \textit{et al.}, 2003). Also, \text{CYP2E1} participates in the metabolism of several carcinogens and other drugs, which may be suggested to increase the risk of many types of cancer and alcoholic liver disease (Guengerich, 1998; Maezawa \textit{et al.}, 1994; Tsutsumi \textit{et al.}, 1994; Yu \textit{et al.}, 1995).

Similarly, \text{GSTs}, comprise a family of phase II drug metabolizing enzymes, play an imperative role in the detoxification of hepatotoxic metabolites by conjugating the toxic products with glutathione which are water-soluble and can be excreted from the body (Hayes \textit{et al.}, 2005). Human cytosolic \text{GST} system consists of eight multigene classes, designated as alpha, mu, kappa, omega, pi, sigma, theta and zeta. The \text{GSTM1} gene is classified into the mu class and the \text{GSTT1} gene belongs to the theta class (Parl, 2005). The effects of \text{GST} polymorphisms on genetic susceptibility to anti-TB-DIH have been investigated particularly for \text{GSTM1} and \text{GSTT1} genes. Therefore, alterations in the structure, function, or expression of these drug metabolizing enzymes (\text{GST} and \text{CYP2E1}) might increase the susceptibility to anti-TB-DIH.
**Introduction**

**Potential impact of this work**

Anti-TB-DIH is considered a vital trouble not only to patients, but also to physicians, regulatory agencies and drug developers, and if not recognized in time and managed properly, it can leads to treatment interruptions, drug resistant development, severe liver injury and even death. It is estimated that India has the highest burden of TB of any county in the world. Also, Indian population is highly exposed to the risk of a potentially serious hepatotoxic effect of anti-TB drugs. Therefore, anti-TB-DIH is very important issue in India. Early recognition of anti-TB-DIH and its risk factors are very important to arrest its development, allow liver to heal, prevent treatment failure and may greatly enhance TB prevention programs. However, factors predicting anti-TB-DIH is still controversial. Therefore, this present study was designed to evaluate the prevalence and risk factors for anti-TB-DIH in North Indian population, and further to explore the possible association of anti-TB-DIH with oxidative stress and genetic polymorphism of *GSTM1*, *GSTT1* and *CYP2E1* genes, which may be important in the early diagnosis and identification of risk factors for anti-TB-DIH, and ultimately can play a key role in minimizing the incidence of severe liver injury cases.