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Lack of liver injury in Wistar rats treated with the combination of isoniazid and rifampicin

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Abstract Isoniazid (INH) can cause serious idiosyncratic liver injury. An animal model would greatly facilitate mechanistic studies, but it is essential that the mechanism in the model be similar to the liver injury that can occur in humans. We attempted to replicate a previous study in which Wistar rats treated with INH and rifampicin (RMP) developed liver injury, which was promising because of its delayed onset similar to the liver injury that can occur in humans. Wistar rats were treated with either a high dose of INH (150 mg/kg/day) or a combination of INH and RMP (75 mg/kg/day and 50 mg/kg/day, respectively) for up to 4 weeks. However, we did not observe any liver injury or evidence of an inflammatory infiltrate as had been reported; rather, we observed an increase in CTLA4-positive cells in the cervical lymph nodes as well as a decrease in serum CXCL1 and MCP-1. In short, we were unable to reproduce a previously reported model of delayed onset INH-induced liver injury in Wistar rats.

Keywords Drug-induced liver injury · Animal model · Tolerance · Idiosyncratic adverse drug reaction · Rifampicin

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Introduction

Isoniazid (INH) remains a first-line drug for the treatment of tuberculosis even though its use is associated with a significant incidence of severe liver injury [1, 2]. The mechanism of INH-induced liver injury remains controversial. Mechanistic studies are difficult because it is important to obtain samples before the injury is severe so that the events leading up to the injury can be studied, but it is impossible to predict which patient will develop serious injury. In addition, in animal studies, it has not been possible to reproduce liver injury that has the same characteristics as the idiosyncratic injury that occurs in patients. Earlier experiments performed in rats showed that acetylhydrazine, a metabolite of INH, is responsible for the hepatotoxicity [3]. However, this was an acute model of hepatotoxicity where rats were treated with very high doses of INH and developed toxicity within hours. It is unlikely that this model represents the same mechanism of INH-induced liver injury that occurs in humans because the characteristics are very different.

Later, in acute models of INH hepatotoxicity in rabbits, hydrazine was implicated as the hepatotoxic metabolite rather than INH or acetylhydrazine [4, 5]. One model involved co-administration of INH with rifampicin (RMP) [4], which also appears to increase the risk of INH liver injury in humans, [6] and the second model involved very high doses of INH (i.e., Eight doses of INH over 2 days) [7]. It has also been suggested that hydrazine is responsible for clinical INH-induced liver injury [8, 9]; however, given its potent hepatotoxic effects, it is more likely that hydrazine would cause acute liver injury rather than liver injury with a delayed onset. More recently we have shown that the parent drug itself, INH, can be bioactivated and bind to liver macromolecules, and this could contribute to clinical liver injury [10]. Also, it has been shown that INH can bind to macrophages in vitro [11], which again

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