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META-ANALYSIS

Hepatotoxicity induced by isoniazid in patients with latent tuberculosis infection: a meta-analysis

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ABSTRACT

Aim: The aim of the present study was to conduct a meta-analysis of the frequency of isoniazid-induced liver injury (INH-ILI) in patients receiving isoniazid (INH) preventative therapy (IPT).

Background: The frequency of hepatotoxicity (drug-induced liver injury: DILI) of antituberculosis drugs has been studied, especially when INH, rifampin, and pyrazinamide are co-administered. However, little is known about the frequency of DILI in patients with latent tuberculosis infection (LTBI), where IPT is indicated.

Methods: We searched PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews for studies reporting the frequency of INH-ILI in patients with IPT using one or more diagnostic indicators included in the criteria of the DILI Expert Working Group.

Results:

Thirty-five studies comprising a total of 22,193 participants were included. The overall average frequency of INH-ILI was 2.6% (95% CI, 1.7-3.7%). The mortality associated with INH-DILI was 0.02% (4/22193). Subgroup analysis revealed no significant differences in the frequency of INH-ILI in patients older or younger than 50 years, children, patients with HIV, candidates for liver, kidney, or lung transplant, or according to the type of study design.

Conclusion: The frequency of INH-ILI in patients receiving IPT is low. Studies on INH-ILI are needed where the current DILI criteria are used.

Keywords: Isoniazid; Latent tuberculosis; Drug induced liver injury; Adverse drug reaction, Liver injury.

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Introduction

Isoniazid (isonicotinic acid hydrazide: INH) was discovered 110 years ago and has been used for the prophylaxis and treatment of tuberculosis (TB) for 70 years (1). Isoniazid preventative therapy (IPT) is indicated in patients with latent tuberculosis infection (LTBI), which is defined as a state of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of clinically manifest active TB (2). IPT is indicated in household contacts of pulmonary TB or multidrug-resistant TB, people who are initiating anti-TNF treatment, receiving dialysis, preparing for an organ or hematological transplant, or living with silicosis (2). Additionally, at-risk LTBI populations where IPT may be indicated include prisoners, healthcare workers, immigrants from countries with a high TB burden, homeless people,

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people living with HIV, and people who use intravenous drugs (2).

The two most important adverse reactions of INH are hepatotoxicity (drug-induced liver injury: DILI) and neuropathy, the latter being potentially preventable with the administration of pyridoxine. The exact frequency of INH-induced liver injury (INH-ILI) is difficult to determine for three reasons. Firstly, most reports refer to hepatotoxicity induced by combinations of antituberculosis drugs (i.e., when INH is co-administered with other drugs such as rifampin and pyrazinamide, which are also potentially hepatotoxic) (3). One strategy for determining the specific frequency of INH-ILI is the administration of INH alone, that is, as IPT for 6 to 9 months (4). Secondly, various criteria have been used over time to determine the frequency of hepatotoxicity of antituberculosis drugs; for example, in a narrative review, up to 9 different criteria were reported (3). Thirdly, INH can transiently elevate transaminases, and depending on the DILI criteria used and time allowed for remission of the transient transaminase elevation ("transaminitis"), the frequency rates of INH-ILI can vary (5).

The present systematic study aimed to determine the frequency of INH-ILI in patients with LTBI who received IPT using indicators included in the criteria of the DILI Expert Working Group (6).

Methods

This study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (7) (Supplementary Table S1).

Search strategy

Two independent investigators (JL and DIJ) performed a systematic search in PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews for studies published from 1991 (when a similar study was published) (8) to August 2022. In addition, a secondary search was conducted based on the reference lists of retrieved articles. In the search strategy in PubMed, MeSH (Medical Subject Headings) terms such as "Isoniazid," "Antitubercular Agents," "Drug-Induced Liver Injury," "Drug-Induced Hepatitis," and "Latent Tuberculosis" were used.

Eligibility criteria

We searched for randomized controlled trials (RCTs) and observational studies reporting data on the frequency of INH-ILI in patients with IPT. We considered studies in English or other languages that included participants of any age and met the following criteria: (i) studies directly reported the frequency of hepatotoxicity in patients with IPT; (ii) when the prevalence with its confidence interval was not directly reported, studies reported enough data to calculate a percentage of hospital admissions with their corresponding 95% confidence interval (CI) (i.e., number of patients with INH-ILI as numerator and total number of patients with INH during the study period as denominator); iii) use of diagnostic criteria similar to the criteria of the DILI Expert Working Group and the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (9), which consists of the presence of one of the following: levels of alanine aminotransferase (ALT) equal to or increased 5 times above the upper limit of normal (ULN), alkaline phosphatase (AP) equal to or greater than 2 times above the ULN (especially if accompanied by elevation in the concentration of 5′-nucleotidase or gamma glutamyl transpeptidase, GGT), in the absence of bone pathology known to increase alkaline phosphatase; or elevation greater than or equal to 3 times the ULN of ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2 × ULN.

Quality assessment

The quality of observational studies (cohort, case-control, and cross-sectional studies) and randomized controlled trials (RCTs) was appraised according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (10) and Consolidated Standards of Reporting Trials (CONSORT) (11), respectively. Two investigators independently evaluated the quality of the studies.

Data extraction

Using a common data extraction template, all relevant information was independently abstracted from the selected studies by both reviewers. Information was collated on (i) study characteristics—names of the authors, institutions, geographical location, year of publication, duration, type of hospital and care setting, design, sample size, and method for DILI identification

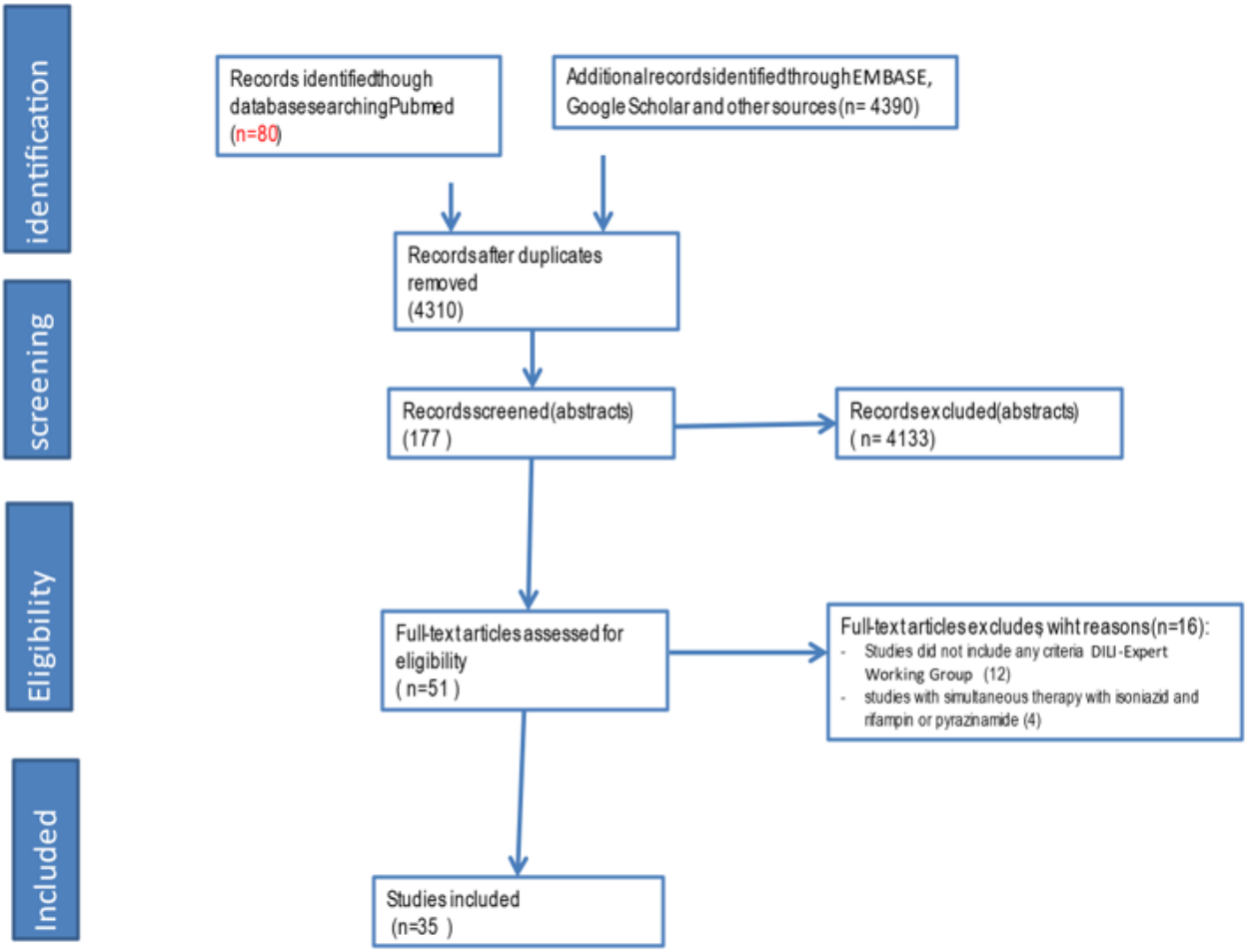

Figure 1. Study screening Flowchart.

(interview, clinical records, others); and (ii) diagnostic criteria for INH-ILI.

Statistical analyses

This study focused on the population in whom INH had been indicated as the only drug for TB prophylaxis. The frequency of INH-ILI was calculated in each study, taking into account the total number of exposed patients meeting DILI criteria divided by the total number of patients exposed to INH. The overall estimates in the pooled analysis were obtained using Stata 13 software (Stata Corp LP, College Station, TX) and the Meta XL (www.epigear.com) add-in for Microsoft Excel (12). A pooled prevalence was calculated with 95% CI by combining estimates from selected studies based on a random-effects model (13); this is a variant of the inverse of the variance method, and it incorporates intra- and inter-study variability. Heterogeneity between estimates was assessed using the I2 statistic, which describes the percentage of variation not due to sampling error across studies. Subgroup analyses were performed by age group (above and below 50 years), children, patients living with HIV, INH treatment duration, study provenance, candidates for kidney and lung transplantation, and type of study.

Results

Thirty-five studies comprising a total of 22,193 participants were included (clinical trial: 13; cohort: 14, cross-sectional: 8). Mean participant age was 37.2 (SD 13.9) years, and 46.9% of participants were female (Table 1 and Figure 1). The mean STROBE score of observational studies was 64.5% (SD 14.1), and the mean CONSORT score for clinical trials was 68.6% (SD 10.1). Studies from 16 countries were included: USA (14, 15, 24, 16–23) (11), Spain (25–28) (4), South Africa (29, 30) (2), Botswana (31, 32) (2), Brazil (33) (1), Hong Kong (34) (1), India (35) (1), Italy (36) (1),

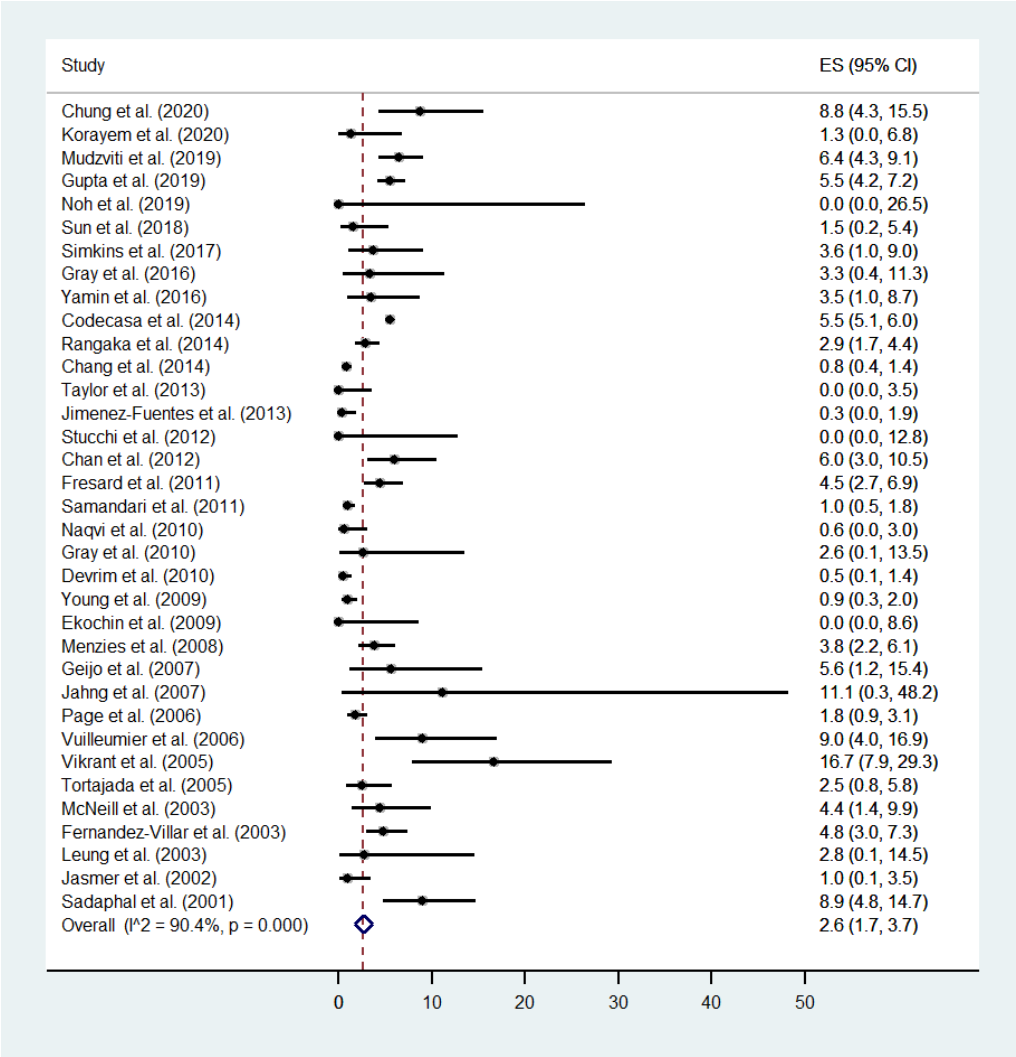

Figure 2. Forest plot of frequencies of isoniazid-induced liver injury (INH-ILI) in patients with latent tuberculosis infection (LTBI) receiving Isoniazid Preventive Therapy (IPT).

Korea (37, 38) (2), Pakistan (39) (1), Saudi Arabia (40) (1), Switzerland (41, 42) (2), Taiwan (43, 44) (2), Turkey (45) (1), Australia (46) (1), Zimbabwe (47) (1), and one study included patients of 3 countries (Canada, Brazil, and Saudi Arabia) (48).

The overall average frequency of INH-ILI was 2.6% (95% CI: 1.7-3.7%) (Figure 2). In 34/35 studies, the DILI criterion of more than or equal to a fivefold elevation above the ULN for ALT was used; one study used the criterion of more than or equal to a threefold elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2 times the ULN; and one study used the two criteria outlined above. No study used the criteria of more than or equal to a twofold elevation above the ULN for alkaline phosphatase (ALP) (particularly with accompanying elevations in concentrations of 5′-nucleotidase or γ-glutamyl transpeptidase in the absence of known bone pathology driving the rise). No study reported specific clinical characteristics of INH-ILI (e.g., clinical symptoms of hepatitis). No asymmetry was observed in relation to the management of publication bias, (see the funnel plot in Table S2 in the supplemental file).

Mortality associated with INH-ILI was 0.02% (4/22193). Subgroup analysis (Table 2) revealed no significant differences in the frequency of INH-ILI in patients older or younger than 50 years, treatment duration (6, 9, or 12 months), children, patients living with HIV, candidates for liver, kidney, or lung transplant, type of study design, or study provenance.

Table 1. Characteristics of studies on isoniazid-induced liver injury (INH-ILI) in patients with latent tuberculosis infection (LTBI) receiving Isoniazid Preventive Therapy (IPT).

Author (year)	Country	Study design	Type of patients	Total sample	n (INH-ILI)	Mean age (years)	Female (%)	DILI criteria	Quality assessment	
									STROBE (%)	CONSORT (%)
Chung et al (2020)	Korea	cohort	Healthcare workers	114	10	42	69.3	A	83	
Korayem et al. (2020)	Saudi Arabia	cohort	Lung transplant recipients	80	1	38	35	A	68	
Mudzviti et al (2019)	Zimbabwe	cohort	HIV-infected paediatric and adolescent patients on antiretroviral therapy (ART).	438	28	10	46.1	A	77	
Gupta et al. (2019)	USA	clinical trial	Pregnant women with HIV infection and ART	956	53	29	100	A, B		67
Noh et al. (2019)	Korea	cross sect	Older patients	12	0	69	70	A, B	77	
Sun et al. (2018)	Taiwan	clinical trial	Patients aged ≥12 in a general hospital	132	2	31.7	38.6	A		79
Simkins et al. (2017)	USA	cross sect	Renal transplant candidates (94%)	110	4	59.81	34	A	60	
Gray et al. (2016)	Australia	cross sect	Patients with LTBI in a general hospital	61	2	50	55	A	73	
Yamin et al. (2016)	USA	cohort	HIV positive (44%)	115	4	38.3	29	A	80	
Codecasa et al (2014)	Italy	cross sect	Patients of the reference centre for anti-tuberculosis treatment	11963	662	29.9	45.2	A	63	
Rangaka et al (2014)	South Africa	clinical trial	HIV patients	662	19	34	76	A		71
Chang et al (2014)	USA	cross sect	Patients of paediatric clinic	1582	13	NR	50	A, B	77	
Taylor et. al. (2013)	Botswana	cohort	Pregnant HIV-infected women	103	0	28	100	A	77	
Jimenez-Fuentes et al. (2013)	Spain	clinical trial	Immigrants with LTBI	294	1	26.5	60	A		63
Stucchi et al. (2012)	Brazil	cross sect	Liver transplantation candidates	27	0	50.5	21	A	53	
Chan et al (2012)	Taiwan	clinical trial	Male prison inmates	183	11		0	A, B		78
Fresard et al (2011)	Switzerland	cohort	Patients with LTBI in the outpatient clinic	426	19	32	49.3	A	67	
Samandari et al. (2011)	Botswana	clinical trial	Adults with HIV infection	1006	10	34	71	A		71
Naqvi et. al. (2010)	Pakistan	clinical trial	Renal transplant recipients	181	1	32.84	22.1	B		47
Gray et. al. (2010)	South Africa	cohort	HIV-infected children on antiretroviral therapy	39	1	1.8	36	A	63	
Devrim et al (2010)	Turkey	cohort	Children	617	3	NR	NR	A	27	
Young et. al. (2009)	USA	cross sect	Patients >18 years of public health clinic	639	6	NR	NR	A	67	
Ekochin et al. (2009)	USA	cohort	Patients on methotrexate treatment	41	0	49	NR	A	37	

Continued										
Menzies et al. (2008)	Canada, Brazil, and Saudi Arabia	clinical trial	Tuberculosis clinics located in university hospitals in 3 countries	422	16	NR	47	A		84
Geijo et al. (2007)	Spain	clinical trial	Outpatient clinic of the general hospital	54	3	44.16	51	A		59
Jahng et al. (2007)	USA	cohort	Cirrhosis patients during transplant	9	1	49.1	33	A	57	
Page et al. (2006)	USA	cross sect	HIV positive (18.8%)	670	12	30.1	58.8	A	77	
Vuilleumier et al. (2006)	Switzerland	cohort	Pharmacogenetics study (NAT2 and CYP2E1)	89	8	31	45	A	53	
Vikrant et al. (2005)	India	clinical trial	Patients with end-stage renal disease (ESRD) on renal replacement therapy	54	9	30.9	17.5	A		71
Tortajada et al. (2005)	Spain	clinical trial	Outpatient clinics of public health care facilities	199	5		52	A		78
McNeill et al. (2003)	USA	cohort	Patients in a community setting	114	5	34.7	39	A	53	
Fernandez-Villar et al. (2003)	Spain	cohort	Drug users	415	20			A	60	
Leung et al. (2003)	Hong Kong	clinical trial	Patients living with silicosis	36	1	57.6	3	A		63
Jasmer et al. (2002)	USA	clinical trial	Three urban public health tuberculosis clinics	204	2	35	45	A		79
Sadaphal et al (2001)	USA	cohort	Injection drug users. HIV (25%).	146	13	42	14	A	70	

STROBE: Strengthening the Reporting of Observational studies in Epidemiology. CONSORT: Consolidated Standards of Reporting Trials. LTBI: latent tuberculosis infection. IPT: Isoniazid Preventative Therapy. INH-ILI: isoniazid-induced liver injury. A: alanine aminotransferase (ALT) $\geq$ 5 times above the upper limit of normal (ULN). B: ALT$\geq$ 3 ULN if bilirubin >2 ULN. NR: not reported.

Table 2. Frequency of isoniazid-induced liver injury (INH-ILI) in patients with latent tuberculosis infection (LTBI) receiving Isoniazid Preventive Therapy (IPT). Subgroup analyses.

Subgroup analysis	Studies (n)	Proportion (%) (95% CI)	P
Mean age (years)			0.896
< 50	26	2.8 (1.7 – 4.0)	
≥ 50	5	2.0 (0.3 – 4.7)	
Children (<18y) vs adults			0.416
Children (<18y)	4	1.8 (0.1 – 5.1)	
adults (>=18y)	31	2.8 (1.8 – 3.9)	
HIV (human immunodeficiency virus) infection			0.937
HIV-positive persons	9	3.1 (1.5 – 5.1)	
HIV-negative persons	26	2.5 (1.4 – 3.9)	
Duration of INH treatment			0.115
6 months	17	3.7 (2.4 – 5.1)	
≥ 9 months	17	1.8 (0.8 – 3.0)	
Continent where the study was conducted			0.842
Asia	8	3.5 (0.9 – 7.4)	
America	13	2.2 (0.9 – 3.8)	
Africa	5	2.0 (0.4 – 4.7)	
Europe	8	3.3 (1.4 – 5.7)	
Oceania (Australia, New Zealand)	1	3.3 (0.4 – 11.3)	
Transplant recipients or candidates for kidney, lung or liver transplant			0.661
Yes	6	2.8 (0.0 – 8.2)	
No	29	2.7 (1.8 – 3.9)	
Type of study			0.735
Clinical trial	13	2.7 (1.4 – 4.3)	
Observational (cohort cross-sectional study)	22	2.6 (1.4 – 4.2)	

Discussion

In the present study, the frequency of INH-ILI in patients with IPT was found to be 2.6%. No significant differences were found in the frequency of INH-ILI in patients older or younger than 50 years, children, patients living with HIV, candidates for liver, kidney, or lung transplant, treatment duration (6, 9, or 12 months), type of study design, or study provenance.

In 1991, Steele et al. published a systematic review of 34 studies (published between 1966 and 1989) including a total of 38,257 patients in which they found an overall frequency of INH hepatotoxicity of 0.6% in adults, and 0.2% in children; however, unlike our study, the criterion used was clinical manifestations of hepatitis in conjunction with aspartate aminotransferase (AST) levels exceeding 100 units/dl (8), which is not currently in the DILI criteria. In a meta-analysis published in 2013, Sharma et al. included 5 clinical trials and found an INH-ILI frequency of 4.6% in HIV-negative persons (49), where the criterion used was ALT > 5.0 times the ULN (5, 50).

In 2009 Holty et al. performed a systematic study of IPT in 139 liver/kidney/lung transplant candidates, finding an INH-ILI frequency of 6% as cause of treatment suspension (51). The present study found no statistically significant difference in the frequency of INH-ILI in patients with IPT in relation to an administration time of 6 (4%), 9 (3%), or 12 (2%) months, suggesting that the frequency of INH-ILI may not be related to these administration durations. The INH-ILI-associated mortality in patients with IPT was 0.02% (4/22193). In 1993, Salpeter reviewed the mortality associated with INH-ILI in patients with IPT and found a frequency of 0.001% (2 of 202,497) using criteria of the 1983 American Thoracic Society guidelines (52). The present study found no significant difference between the frequency of INH-ILI in patients older or younger than 50 years. In a previous meta-analysis, Hosford et al. found a higher frequency of DILI among those older than 60 years with LTBI; however, the DILI criteria differed from those used in the present study (elevation in liver blood tests > 2–5 times the upper reference level, equivalent elevated liver enzymes, and/or clinical symptoms of hepatitis) (53).

The main limitation of the present study is that none of the included studies had complete and updated DILI criteria (9). In 34/35 studies, the criterion used for DILI was ALT > 5 times above the ULN, and a single study reported bilirubin > 2 times and ALT > 3 times above the ULN. None of the included studies reported alkaline phosphatase levels; therefore, it was not possible to characterize the hepatotoxicity pattern (cholestatic, hepatocellular, or mixed). Studies that did not consider any of the indicators present in updated DILI criteria were excluded, for example, those with the only criterion being AST > 3 times above the ULN (54). In the included studies, no analysis of causality with an updated instrument recommended for the diagnosis of DILI was reported (9). It is necessary to conduct studies with updated DILI criteria in studies with antituberculosis drugs, especially with INH.

Conclusion

In conclusion, with the criteria used (ALT > 5 times above the ULN), the frequency of INH-ILI is low; however, it will be important to perform studies with updated and complete DILI criteria so as to know the patterns and real frequency of INH-ILI.

Conflict of interests

The authors certify that they have no conflict of interests.

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