Risk of oral antifungal agent-induced liver injury in Taiwanese

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Drug-induced liver injury (DILI) is the leading cause of acute liver failure.
- There have been case reports of serious liver injuries caused by oral antifungal agents.
- There is still no systematic evaluation of safety profiles among various oral antifungal agents in Taiwanese.

WHAT THIS STUDY ADDS

- Oral antifungal agents are associated with a low incidence of DILI, but may be fatal, particularly in the elderly.
- Longer treatment duration may increase the risk of antifungal agent-induced liver injury, especially with ketoconazole.

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AIM

Oral antifungal agent-induced liver injury is a common safety concern that may lead to patients' hesitation in treating fungal infections such as onychomycosis. This study evaluated risk of drug-induced liver injury (DILI) caused by oral antifungal agents in Taiwanese populations.

METHODS

A population-based study was conducted by analyzing who used oral antifungal agents from 2002 to 2008 from the Taiwan National Health Insurance Database. A comparison control group was randomly extracted from the remainder of the original cohort.

RESULTS

Of the 90 847 oral antifungal agents users, 52 patients had DILI. Twenty-eight DILI cases used ketoconazole, 12 fluconazole, eight griseofulvin, three itraconazole and two terbinafine. The incidence rates (IR) of DILI per 10 000 persons were 31.6, 4.9, 4.3, 3.6 and 1.6 for fluconazole, ketoconazole, griseofulvin, itraconazole and terbinafine, respectively. Longer exposure duration increased the risk of DILI, with IR for exposure duration $\geq$ 60 defined daily dose (DDD) of 170.9, 62.5, and 36.1 per 10 000 persons for ketoconazole, itraconazole and terbinafine, respectively. Patients taking antifungal agents had higher incidences of developing DILI compared with those in the control group after adjusting for age, gender and co-morbidities (relative risk 2.38, $P < 0.001$). All of the six patients with fatal DILI used fluconazole. Old age and fluconazole increased the risk of oral antifungal-induced fatal DILI.

CONCLUSIONS

Oral antifungal agents are associated with low incidence of acute liver injury, but which may be fatal, especially for the elderly. Longer treatment duration may increase the risk of antifungal agent-induced liver injury, especially ketoconazole.

Introduction

Drug-induced liver injury (DILI) is a serious health problem that impacts on patients, physicians, the pharmaceutical industry and government regulators [1, 2]. It is the most common cause of acute liver failure in the United States, accounting for more than 50% of cases [3, 4]. DILI is now the most common single adverse drug reaction (ADR) leading to the market removal of a drug [5, 6]. The epidemiology of DILI has not been well studied. Until recently, there has been only one population-based study that systematically assessed its incidence [7]. In a French population, the incidence was 13.9 cases per 100 000 inhabitants per year, which was about 16 times higher than estimates from spontaneous reporting methods in France.

Oral antifungal agents like griseofulvin, itraconazole, terbinafine, ketoconazole and fluconazole are widely used for superficial and systemic fungal infection. For onychomycosis, itraconazole and terbinafine are the commonly used agents considered effective and safer than conventional antifungals like ketoconazole [8]. The incidence rates of antifungal DILI are considered low, about 0% for griseofulvin, 2–4% for itraconazole, 4% for terbinafine, 2–10% for ketoconazole and 1% for fluconazole [9]. In a large cohort of 69 830 patients treated with oral antifungal agents from the United Kingdom, the incidence rates of acute liver injury were 134.1 per 100 000 person-months for ketoconazole, 10.4 for itraconazole and 2.5 for terbinafine [10]. A meta-analysis for safety information of antifungal therapy for superficial dermatophytosis and onychomycosis estimates that the risk of liver injury requiring treatment discontinuation ranges from 0.11% to 1.22% [11]. The risk of asymptomatic elevated serum transaminase not requiring treatment termination is less than 2.0% for all treatment regimens evaluated [11]. However, there have been case reports of serious liver injuries leading to liver failure, transplantation or death [12–14]. A few cases of fatal DILI caused by antifungal agents have led to public panic and decreased patient compliance, especially for the cosmetic purpose of treating onychomycosis [15]. In Taiwan, nearly half of patients with onychomycosis refuse treatment with oral antifungal agents due to concerns of liver injury, especially after the first few fatal DILI cases caused by oral antifungal agents for onychomycosis treatment in 1997 [15]. Although new generations of oral antifungal agents (e.g. itraconazole and terbinafine) are considered safer than ketoconazole, there is still no study of antifungal agent-induced DILI for Taiwanese populations [8]. This study aimed to investigate the incidence rate of oral antifungal agent-induced liver injury and to identify the related risk factors for adverse liver outcomes in Taiwanese.

Methods

Data source

The National Health Insurance (NHI) programme in Taiwan, launched in 1995, covers more than 98% of the Taiwanese population [16]. The data set, 'Longitudinal Health Insurance Database (LHID)', used in this study, was a longitudinal, population-based, reimbursement database containing a cohort dataset of 1 million randomly sampled individuals over an 8 year period (January 1 2002–December 31 2008). All of the identification information was anonymized by the Bureau of National Health Insurance and then transferred to the National Health Research Institute (NHRI) each year. Each diagnosis was made by a physician based on results of laboratory data, biopsy and tissue pathology. The NHRI reported that LHID distributions did not differ significantly in terms of age, gender or health care costs when comparing with all enrollees [17]. Thus, LHID provides an opportunity to examine the trend between DILI and patients who used antifungal agents. The accuracy of the diagnoses of major diseases in the NHIRD, such as diabetes mellitus and stroke [18, 19], has been validated, and there have been many studies based on diagnostic coding from the NHIRD [20–23], including DILI studies [24–26]. This study project was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No.: 2012-11-009BC).

Study period, study population and control group

As shown in Figure 1, during the 8 year enrolment period, a total of 990 648 patients were entered as the study cohort. An analysis of patients who used oral antifungal agents was performed. In the initial stages, patients who used oral antifungal agents (anatomic therapeutic chemical (ATC) code: D01BA01, D01BA02, J02AB02, J02AC01, J02AC02) [27] were included (Figure 1). To prevent potential misclassification of case diagnoses, patients with viral hepatitis A, or other viral hepatitis (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code: 070.0, 070.1, 070.4, 070.6, 070.9), hepatitis in viral and other infectious diseases classified elsewhere (ICD-9-CM code: 573.1–573.2), cholelithiasis (ICD-9-CM code: 574.0–574.9), chronic liver disease and cirrhosis (ICD-9-CM code: 571.0–571.9), liver abscess and sequelae of chronic liver disease (ICD-9-CM code: 572.0–572.4), chronic passive congestion of liver (ICD-9-CM code: 573.0), malignant neoplasm of liver and intra-hepatic bile ducts (ICD-9-CM code: 155.0 to 155.2) or liver metastasis (ICD-9-CM code: 230.8) were excluded. Patients who used antiviral agents for chronic hepatitis B or C, or were younger than 2 years of age were also excluded. A total of 90 847 patients who used oral antifungal agents were analyzed.

Moreover, to further elucidate the true impact of antifungal agents on DILI, a comparison control group was randomly extracted from the remainder of the original

Figure 1

Flowchart summarizing the design cohort

cohort. This group comprised age-, gender- and co-morbidity (including hypertension, diabetes, hyperlipidaemia, heart failure, chronic kidney disease, coronary artery disease, hepatitis B or C)-matched controls for every patient in the antifungal agent group. An index date was designated as its matched case's oral antifungal agents date. A total of 69 665 patients in the antifungal agent group were successfully matched with 82 300 patients in the control group (Figure 1).

Drug-induced liver injury

The diagnoses of acute and sub-acute necrosis of the liver (ICD-9-CM code: 570), toxic (noninfectious) hepatitis (ICD-9-CM code: 573.3, 573.8), disorder of bilirubin excretion

(ICD-9-CM code: 277.4), other specified disorder of biliary tract (ICD-9-CM code: 576.8), other sequelae of chronic liver disease (ICD-9-CM code: 572.8), jaundice, unspecified, not of newborn (ICD-9-CM code: 782.4) and antifungal agents causing adverse effects in therapeutic use (ICD-9-CM code: E930.1) were included. To increase the accuracy and reliability of this study, the criteria for selection of patients with potential DILI from the database were restricted to the in-patient cases or cases with at least two ambulatory care claims. Additionally, the latency period relating to antifungal agent-induced DILI was defined as a range between 5 and 90 days. Any case of possible DILI more than 15 days after drug withdrawal was excluded [28]. To exclude possible infection-related liver impairment, only cases with DILI

before the diagnosis of infection were included. This analysis was repeated for estimating patients with at least three or more ambulatory visits or one hospitalization as sensitivity analysis.

Data on drug exposure and confounding factors

Antifungal drugs have been reimbursed by the Taiwan NHI since its launch in 1995. The main objects of interest in this study were the most commonly used oral antifungal agents in Taiwan from 2002 to 2008, including griseofulvin, terbinafine, ketoconazole, fluconazole and itraconazole. Information on the type of drug prescribed, dosage, route of administration, date of prescription and total number of drug pills dispensed from the pharmacy prescription database were collected. The cumulative dose was determined by multiplying the number of pills dispensed by the dose prescribed divided by the recorded days' supply. Data were presented as the number of defined daily doses (DDD), which was established by the World Health Organization as the average maintenance dose per day for a drug used for its main indication in adults [29].

Other concomitant drugs used included antibiotics (ATC code: J01), antituberculosis drugs (ATC code: J04A), non-steroidal anti-inflammatory drugs (NSAIDs) (ATC code M01A, M01BA, M01BX), lipid-lowering drugs (ATC code: C10A, C10B), anticonvulsant drugs (ATC code: N03), and Chinese herbs. Information on age, gender, co-morbidities and complications, including hypertension (ICD-9-CM code: 401), diabetes mellitus (ICD-9-CM code: 250), hyperlipidaemia (ICD-9-CM code: 272), chronic kidney disease (ICD-9-CM code: 580–585), heart failure (ICD-9-CM code: 428), coronary artery disease (ICD-9-CM code: 410–414), viral hepatitis B or C carriers (ICD-9-CM code: 070.2, 070.3, 070.5, 070.7, V02.61, V02.62), infection (ICD-9-CM code: 042,

460, 463, 466, 486, 541, 590.1, 599.0, 682) and cancer (ICD-9-CM code: 145, 150, 151, 153, 157, 162, 174) were also collected.

Statistical analysis

All statistical analyses were performed using the SAS statistical package (SAS Institute Inc.). Gender and age distribution for all cases were calculated. The incidence rate of DILI was also estimated. Pearson's χ^2 test was used to compare the difference between survival and death in terms of age, gender, and selected co-morbidities and complications at baseline. To evaluate possible frequency- or dose-dependent effects, the cumulative dosage of antifungal drug used during the date of prescription was estimated to the date of DILI diagnosis and analyzed to see if short term (<30 DDD) or prolonged use (≥ 60 DDD) affected the incidence rate of DILI. A two-sided $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of patients with DILI from antifungal agents

The demographic characteristics of the 90 847 patients who used oral antifungal agents are shown in Table 1. There were a higher proportion of women (60.4%) and younger (86.3% were aged <60 years old) patients. Ketoconazole was the most commonly oral antifungal agent in our cohort.

From the incidence rates of all oral antifungal DILI between 2002 and 2008, the number of diagnosed DILI patients using oral antifungal agents was 3/18 963 (1.58 per 10 000) in 2002, 3/18 177 (1.65 per 10 000) in 2003, 11/19 641 (5.60 per 10 000) in 2004, 7/19 106 (3.66 per

Table 1

Distribution of patients who used oral antifungal agents

Characteristic	Total		Griseofulvin		Terbinafine		Ketoconazole		Fluconazole		Itraconazole	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Age group (years)												
<20	9 789	10.8	2 169	11.6	507	4.1	7 078	12.4	174	4.6	365	4.4
20–29	20 329	22.4	3 506	18.8	1 399	11.3	15 526	27.1	378	10.0	1 060	12.7
30–39	19 120	21.1	3 527	18.9	2 152	17.4	13 363	23.3	492	13.0	1 513	18.1
40–49	17 842	19.6	3 662	19.6	2 854	23.1	11 004	19.2	542	14.3	1 953	23.3
50–59	11 293	12.4	2 705	14.5	2 515	20.3	5 652	9.9	395	10.4	1 673	20.0
60–69	5 778	6.4	1 486	8.0	1 394	11.3	2 472	4.3	392	10.3	905	10.8
70–79	4 444	4.9	1 166	6.2	1 125	9.1	1 573	2.7	632	16.7	656	7.8
≥ 80	2 252	2.5	456	2.4	430	3.5	653	1.1	788	20.8	243	2.9
Gender												
Female	54 843	60.4	8 453	45.3	5 979	48.3	38 606	67.4	2 382	62.8	4 338	51.8
Male	36 004	39.6	10 224	54.7	6 397	51.7	18 715	32.6	1 411	37.2	4 030	48.2
Total	90 847		18 677	18.6	12 376	12.3	57 321	57.0	3 793	3.8	8 368	8.3

Some patients in the cohort received more than one antifungal drug during the study period.

Table 2

Characteristics of patients with DILI (*n* = 52)

Characteristics	Total		Dead		Survived		P value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Total	52		6	11.5	46	88.5	
Age (years) (mean, SD)	(56.3, 17.7)		(75.8, 9.7)		(53.7, 17.0)		0.002
<65	34	65.38	1	16.7	33	71.7	0.015
≥65	18	34.62	5	83.3	13	28.3	
Gender							
Female	33	63.46	3	50.0	30	65.2	0.656
Male	19	36.54	3	50.0	16	34.8	
Co-morbidity and complications							
Hypertension	17	32.69	4	66.7	13	28.3	0.081
Diabetes	13	25	3	50.0	10	21.7	0.157
Hyperlipidaemia	6	11.54	1	16.7	5	10.9	0.540
Chronic kidney disease	5	9.62	2	33.3	3	6.5	0.096
Heart failure	7	13.5	2	33.3	5	10.9	0.180
Coronary artery disease	7	13.5	1	16.7	6	13.0	1.000
HBV or HCV	12	23.1	2	33.3	10	21.7	0.612
Infection	11	21.2	3	50.0	8	17.4	0.101
Cancer	3	5.8	0	0.0	3	6.5	1.000
Co-prescriptions							
Antibiotics	34	65.38	6	100.0	28	60.9	0.081
Anti-tuberculosis drugs	2	3.85	0	0.0	2	4.4	1.000
Non-steroidal anti-inflammatory drugs	32	61.54	4	66.7	28	60.9	1.000
Lipid-lowering	4	7.69	1	16.7	3	6.5	0.397
Anticonvulsant	9	17.31	3	50.0	6	13.0	0.057
Chinese herbs	3	5.77	0	0.0	3	6.5	1.000
Antifungal drugs							
Griseofulvin	8	15.38	0	0.0	8	17.4	0.573
Terbinafine	2	3.85	0	0.0	2	4.4	1.000
Ketoconazole	28	53.85	1	16.7	27	58.7	0.084
Fluconazole	12	23.08	6	100.0	6	13.0	<.0001
Itraconazole	3	5.77	0	0.0	3	6.5	1.000
Days between exposure and DILI recognition, median (25th, 75th percentiles)	41.0		41.5		41.0		0.0031
	(51.2, 61.0)		(32.0, 46.0)		(21.0, 61.0)		
Griseofulvin, median (25th, 75th percentiles)	73.0		–		73.0		
	(39.5, 78.5)				(39.5, 78.5)		
Terbinafine, median (25th, 75th percentiles)	33.0		–		33.0		
	(15.0, 51.0)				(15.0, 51.0)		
Ketoconazole, median (25th, 75th percentiles)	37.0		32.0		37.0		
	(20.0, 55.0)		(32.0, 32.0)		(20.0, 55.0)		
Fluconazole, median (25th, 75th percentiles)	46.0		46.0		58.0		
	(30.0, 78.0)		(37.0, 46.0)		(30.0, 78.0)		
Itraconazole, median (25th, 75th percentiles)	20.0		–		20.0		
	(15.0, 35.0)				(15.0, 35.0)		
Hospitalization	50	96.2	6	100.0	44	95.7	0.5624
Cumulative dose between exposure and DILI recognition (DDD) (mean, standard deviation)	31.0	53.2	15.4	12.2	33.1	56.2	0.774

One patient with DILI used both ketoconazole and fluconazole for 90 days. HBV, hepatitis B virus; HCV, hepatitis C virus.

10 000) in 2005, 10/18 374 (5.44 per 10 000) in 2006, 4/17 310 (2.31 per 10 000) in 2007 and 14/16 688 (8.39 per 10 000) in 2008.

Of the 52 DILI patients, 50 were hospitalized and six died giving a mortality rate of 11.54%. Twenty-eight DILI patients used ketoconazole, 12 fluconazole, eight griseofulvin, three itraconazole and two terbinafine (Table 2).

The most common co-prescriptions were antibiotics and NSAIDs. Of the 34 cases with co-prescriptions of antibiotics, 32 continued to use antibiotics during admission without exacerbating the DILI. Of the 32 cases with

co-prescriptions of NSAIDs, 28 continued to use NSAIDs during admission without DILI exacerbation. All of the patients with co-prescriptions of antibiotics or NSAIDs had exposure to the same medications before or after the admission but did not experience DILI. The median time to DILI onset for ketoconazole, griseofulvin, terbinafine, fluconazole and itraconazole was 37.0 (25th, 75th percentiles 20.0, 55.0), 73.0 (39.5, 78.5), 33.0 (15.0, 51.0), 46.0 (30.0, 78.0), and 20.0 (15.0, 35.0) days, respectively. The mean cumulative dose between exposure and DILI recognition was 31.0 DDD.

Table 3

Characteristics of patients with antifungal agents-induced fatal DILI

Characteristic	1	2	3	4	5	6
Age (years)	83	69	69	88	64	82
Gender	Male	Female	Male	Female	Female	Male
Co-morbidity and complications*						
Hypertension	–	+	+	+	+	–
Diabetes	–	+	–	+	+	–
Hyperlipidaemia	–	–	–	+	–	–
Chronic kidney disease	+	+	–	–	–	–
Heart failure	–	+	–	+	–	–
Coronary artery disease	–	+	–	–	–	–
HBV or HCV	–	+	–	–	+	–
Infection	–	+	+	+	–	–
Co-prescriptions*						
Antibiotics	+	+	+	+	+	+
Anti-TB drugs	–	–	–	–	–	–
NSAIDs	+	–	–	+	+	+
Lipid-lowering	–	–	–	+	–	–
Anticonvulsant	+	–	+	+	–	–
Chinese herbs	–	–	–	–	–	–
Antifungal drugs*						
Ketoconazole	–	–	+	–	–	–
Fluconazole	+	+	+	+	+	+
Days between exposure and DILI recognition	46	83	32	22	37	46
Cumulative dose between exposure and DILI recognition (DDD)	12	33	24.25	18	3	2

*(+) yes; (–) no; HBV, hepatitis B virus; HCV, hepatitis C virus; DDD, defined daily dose.

Comparison of clinical characteristics between patients with fatal DILI and survivors

The characteristics of survivors and patients with fatal DILI induced by oral antifungal agents were analyzed (Table 2). The mean age was significantly younger in survivors than in deceased cases (53.7 vs. 75.8 years, $P = 0.002$). The rate of co-morbidities, co-prescription and mean cumulative dose between exposure and DILI recognition were comparable between the two groups.

Five patients with fatal DILI used fluconazole and one was prescribed both ketoconazole and fluconazole (Table 3). All of the patients with fatal DILI were older than 60 years. As regards co-morbidities, five patients had hypertension, three had diabetes mellitus and three had infection. All six patients with fatal DILI were co-prescribed with antibiotics, four with NSAIDs and three with anticonvulsant agents.

Incidence rates of oral antifungal agent DILI stratified by daily dose

The incidence rates (IR) of DILI were 31.6 per 10 000 persons for fluconazole, 4.9 for ketoconazole, 4.3 for griseofulvin, 3.6 for itraconazole and 1.6 for terbinafine (Table 4). When IR was further defined as exposure duration ≥ 30 DDD, the IR became 128.6 per 10 000 persons for ketoconazole, 59.2 for itraconazole, 39.1 for griseofulvin, 30.1 for fluconazole and 28.6 for terbinafine. In the setting of exposure duration ≥ 60 DDD, the IR were 170.9, 62.5, and 36.1 per 10 000 persons for ketoconazole, itraconazole and

Table 4

Incidence rates by oral antifungal agent type

Antifungal drug	Patients	Case	IR	Incidence rate (per 10 000 patients)	
				95% CI.	
Griseofulvin	18 677	8	4.3*	1.8*	8.4*
<30 DDD	18 421	7	3.8	1.5	7.8
≥ 30 DDD	256	1	39.1	1.0	217.6
<60 DDD	18 586	8	4.3	1.9	8.5
≥ 60 DDD	91	0	–	–	–
Terbinafine	12 376	2	1.6*	0.2*	5.8*
<30 DDD	11 676	0	0.0	0.0	3.0
≥ 30 DDD	700	2	28.6	3.5	103.2
<60 DDD	12 099	1	0.8	0.0	4.6
≥ 60 DDD	277	1	36.1	0.9	201.1
Ketoconazole	57 321	28	4.9*	3.2*	7.1*
<30 DDD	56 699	20	3.5	2.2	5.4
≥ 30 DDD	622	8	128.6	55.5	253.4
<60 DDD	57 087	23	4.0	2.6	6.0
≥ 60 DDD	234	4	170.9	46.6	437.7
Fluconazole	3 793	12	31.6*	16.4*	55.3*
<30 DDD	3 461	11	31.8	15.9	56.9
≥ 30 DDD	332	1	30.1	0.8	167.8
<60 DDD	3 654	12	32.8	17.0	57.4
≥ 60 DDD	139	0	–	–	–
Itraconazole	8 368	3	3.6*	0.7*	10.5*
<30 DDD	8 030	1	1.2	0.0	6.9
≥ 30 DDD	338	2	59.2	7.2	213.8
<60 DDD	8 208	2	2.4	0.3	8.8
≥ 60 DDD	160	1	62.5	1.6	348.2

DDD, defined daily dose. One patient with DILI used both ketoconazole and fluconazole for 90 days. *Total incidence rate.

Table 5

Crude and adjusted RRs for DILI among oral antifungal agents users

	Total sample	Control group (n = 82 300)	Antifungals group (n = 69 665)
DILI, n(%)			
Yes	69 (0.05)	28 (0.03)	41 (0.06)
No	151 896 (99.95)	82 272 (99.97)	69 624 (99.94)
Crude RR (95% CI)	–	1.00	1.73 (1.04, 2.91)
Adjusted RR (95% CI)	–	1.00	2.38 (1.45, 3.91)

$P < 0.001$. Adjustment was made for the patients' age, gender, hypertension, diabetes, hyperlipidaemia, heart failure, chronic kidney disease, coronary artery disease, hepatitis B and hepatitis C. RR: relative risk.

terbinafine, respectively. Consequently, the incidence of adverse liver outcomes increased with most antifungal agents when the treatment duration increased, especially for those prescribed ketoconazole.

Comparison of relative risk between patients taking antifungal agents and those in the control group

Patients who took antifungal agents were more likely to develop DILI than those in the control group (relatively risk (RR) 1.73, 95% confidence interval [CI] 1.04, 2.91, $P < 0.001$). After adjusting for age, gender, hypertension, diabetes, hyperlipidaemia, heart failure, chronic kidney disease, coronary artery disease, hepatitis B or C, the RR (2.38, 95% CI 1.45, 3.91) of the antifungal agent group was still significantly higher than that of the control group (Table 5).

Discussion

Antifungal agent-induced liver injury is an important issue in DILI. However, most papers in this field were case reports and systematic analysis in this setting is extremely rare. To our knowledge, there is no relevant longitudinal cohort study in Taiwanese. The present study first demonstrates the nationwide incidence rates of oral antifungal agent-induced liver injury in Taiwan. The risk of DILI was elevated in the antifungal agents group and the excess risk persisted after adjustment for age, gender, and co-morbidities. We also found that longer treatment duration with these drugs may increase the risk of liver injury. Furthermore, this study identified old age and fluconazole as risk factors for adverse liver outcomes related to oral antifungal agents. All the six patients with fatal DILI had been administered fluconazole and were older than 60 years.

In a UK cohort treated with oral antifungal agents [8], the incidence rates of acute liver injury were 19.0 per 10 000 persons for ketoconazole, 1.0 for itraconazole, 0.7 for terbinafine, 0 for fluconazole and 0 for griseofulvin. The DILI incidence rates of our cohort were higher than this. In addition, the overall DILI incidence rate for fluconazole (31.6 per 10 000 persons) was higher than those for the

other oral antifungal agents in this study. However, there is an increase in the incidence of DILI with most antifungal agents when the exposure duration is longer. The incidence rate of DILI for ketoconazole increases from an overall 4.9 (per 10 000 persons) to 128.6 when the defined exposure duration is more than 30 DDD. Further prospective studies are needed to elucidate the impact of ethnic and genetic factors as well as the antifungal agent and exposure duration on the incidence and severity of DILI [30].

All six fatal cases were exposed to fluconazole and one of them was exposed to both fluconazole and ketoconazole. Three of the six fatal cases also received antibiotic treatment during their disease episodes (Table 3). To diminish the possibility of sepsis-induced liver impairment, those with a diagnosis of sepsis were excluded from this cohort study. Furthermore, to exclude the possibility of infection-related liver impairment, we only included cases with the diagnosis of DILI before a diagnosis of infection. None of the six fatal DILI cases had underlying cancers or human immunodeficiency virus infection. Unfortunately, no patients underwent liver transplantation for drug-induced acute liver failure. This may be due to a shortage of grafts in Taiwan. However, according to data from United Network of Organ Sharing, 15% of patients who undergo liver transplantation in the United States do so due to fulminant liver failure induced by drugs [31]. The Acute Liver Failure Study Group showed liver transplantation affords excellent overall survival (3-week) of 66.2% for DILI (transplant-free survival was 27.1% and in the 42.1% of subjects with successful transplantation, survival was 92.9%) in the United States [32]. Consequently, these patients should be listed for urgent liver transplantation with a view of rescue.

Additionally, the fatalities related to antifungal agents in this study are all older than 60 years and significantly older than the survivors. Furthermore, the ages of the users of five different oral antifungal agents were significantly different ($P < 0.0001$). More older patients (>60 years old) received fluconazole rather than other antifungal agents (47.8% fluconazole, 23.9% terbinafine, 21.5% itraconazole, 16.6% griseofulvin and 8.1% ketoconazole). This may be a

reason why the overall DILI incidence with fluconazole was higher than with other antifungal agents in this study and previous studies [9, 10]. Age is a known risk factor for DILI for several drugs such as isoniazid and amoxicillin/clavulanate [33]. In fact, increased age (≥ 55 years) is one of the criteria included in the Roussel-Uclaf Causality Assessment Method [34]. Increased incidence of impaired renal function in the elderly may raise drug concentrations in the liver. Moreover, the relatively poor liver functional reserve may also explain a higher mortality rate of DILI in the elderly [35]. Women also reportedly have higher risks and worse outcomes for idiosyncratic DILI than men [4, 33, 36, 37], but a prospective study conducted by Lucena *et al.* did not show that women were at greater risk [38]. In the current study, gender distribution was not significantly different between survivors and mortalities.

The strengths of this study are its large sample size, the availability of data on five different oral antifungal agents used in clinical practice, and a broad representation of the database. The Taiwan NHI database includes complete out-patient visits, hospital admissions, prescriptions, disease and vital status for 98% of the 23 million population in Taiwan [16]. There have been many studies based on diagnostic coding (ICD 9-CM codes) from Taiwan [20–23], including DILI studies [24–26]. In the current study, several different models were performed to search for patients with DILI, including two to four out-patient visits and one hospitalization of hepatitis-related diagnoses. The same 52 patients were indentified from each model and almost all of the DILI cases were hospitalized. To prevent potential bias by misdiagnosis, other possible causes of hepatobiliary diseases were excluded. Because hepatitis B virus and hepatitis C virus infections are endemic in Taiwan [39], only viral hepatitis B or C carriers under anti-viral treatment whose hepatitis codes were really due to viral hepatitis were excluded. Thus, the definition of DILI diagnosis is acceptable.

Underestimation of the incidence of oral antifungal agent-induced liver injuries should also be considered in this study. Because some DILI cases present with asymptomatic transaminase elevation [40], clinicians may simply observe or discontinue oral antifungal agents without using liver injury codes. The main characteristics associated with fatal DILI (Table 2) were old age (>65 years old) and fluconazole. Nevertheless, it is difficult to elucidate whether these factors are independently related to fatal DILI due to only six events. The sufficient numbers of events required for a multivariate logistic regression analysis are still debated. Some authors have recommended at least 10 events per variable should be used for an accurately interpreted multivariate analysis [41]. No reports of laboratory tests, ultrasound, histology from liver biopsies, chart review, patient compliance or the cause of death could be accessed from the Taiwan NHI Database and this is a limitation of our study. Even though the results of laboratory tests were not available from the NHI database, each

diagnostic coding was made by a physician based on results of laboratory data, biopsy or tissue pathology.

In conclusion, oral antifungal agents are associated with low incidence of acute liver injury, but may cause fatal liver injury in elderly patients. Longer treatment duration may increase the incidence of liver injury by antifungal agents, especially ketoconazole.

Competing Interests

The authors declare they had no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

This study was based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

Author Contributions

Wei-Yu Kao: study concept and design; acquisition, analysis and interpretation of data; drafting of the manuscript

Wen-Hung Chung: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; final approval of the version to be published

Chien-Wei Su: study concept and design; acquisition, analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; final approval of the version to be published

Yi-Shin Huang: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; final approval of the version to be published; critical revision of the manuscript for important intellectual content

Yi-Chih Chen: study concept and design; acquisition, analysis and interpretation of data; final approval of the version to be published

Yueh-Ching Chou: study concept and design; acquisition, analysis and interpretation of data; final approval of the version to be published

Ming-Chih Hou: study concept and design; final approval of the version to be published; critical revision of the manuscript for important intellectual content.

Han-Chieh Lin: study concept and design; final approval of the version to be published; critical revision of the manuscript for important intellectual content.

Fa-Yauh Lee: study concept and design; final approval of the version to be published; critical revision of the manuscript for important intellectual content

Jaw-Ching Wu: study concept and design; final approval of the version to be published; critical revision of the manuscript for important intellectual content

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