Characteristics of Liver Injury Due to Azole Antifungal Drugs in the United States: Results from the Drug Induced Liver Injury Network (DILIN) Prospective Study

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Introduction

Azole antifungal (AA) medications are a rare care of drug induced liver injury (DILI). accounting for about 2.9%[1] of all idiosyncratic DILI. All azoles have been implicated in causing abnormal liver tests and most often present with mild and transient elevations in liver enzymes. However, cases of cholestatic and mixed patterns of liver injury have been reported as well for AA-DILI.[1] To date, AA-DILI has not been well studied or compared to DILI from other agents.

Aim

To describe key clinical characteristics and outcomes of patients with liver injury due to AAs enrolled into the DILIN Prospective Study over the last two decades

Methods

- The DILIN Prospective Study enrolls adults and children with suspected DILI meeting predefined eligibility criteria,[2] and they undergo structured and protocolized evaluations at enrollment and 6 months or longer depending on clinical course.
- The DILIN causality and severity scores are adjudicated in a systematic fashion by expert opinion consensus.
- Between September 2004 and June 2021, a total of 1726 participants with high confidence (causality score: definite, highly likely, probable) DILI were enrolled.
- Fifteen (0.9%) patients had high confidence AA-DILI.
- We characterized the clinical course and outcomes of AA-DILI among the implicated agents.
- We also compared the clinical course and outcomes of AA-DILI with DILI due to other agents.

Results

- Among the 15 cases of AA-DILI, the implicated agents were ketoconazole, fluconazole, and voriconazole. **Table 1**
- Four cases met Hy's Law[3] , while 3 cases presented with jaundice at DILI onset.
- Two patients died, although the deaths were not attributed to the liver injury.
- There were no cases leading to liver transplantation or chronic DILI.
- The severity of liver injury was mild in the majority of cases (8 of 15).

- Compared to other agents, AA-DILI was less likely to present with jaundice and demonstrated a faster normalization/recovery of liver enzymes. **Table 2**
- Patients with AA-DILI had higher rates of malignancy and lower rates of alcohol use.
- Latency, rate of treatment with steroids, and pattern of liver injury did not differ significantly between AA-DILI and DILI related to other agents.
- Rates of death, liver transplantation, chronic DILI were similar between AA-DILI from azole and DILI related to other agents.
- Severity of DILI did not vary significantly between AA-DILI from azole and DILI related to other agents.

Table 1. Characteristics of Subjects with DILI due to 3 common AAs

Characteristics	Ketoconazole N=4	Fluconazole N=5	Voriconazole N=6
Age (years, median, IQR)	54.9 (40.0, 65.1)	45.2 (42.5, 50.1)	53.4 (34.3, 68.9)
Female	100	40	33.3
Caucasian	75	75	66.7
Alcohol use	0	20	33.3
Malignancy	0	40	50
Days from primary drug start to DILI onset/latency (median (IQR))	117.5 (62.0, 138.5)	19.0 (9.0, 42.0)	28.0 (14.0, 50.0)
Days from earliest sign/symptom to primary drug stop (median (IQR))	0.5 (0.0, 1.0)	2.0 (1.0, 3.0)	1.0 (1.0, 1.0)
Jaundice at DILI onset	50	0	16.7
ALT at DILI onset (U/L) (median ((IQR))	266.5 (172.5, 588.5)	932.0 (497.0, 1046.0)	260.0 (130.0, 611.0)
ALP at DILI onset (U/L) (median ((IQR))	161.0 (112.0, 532.5)	218.0 (169.0, 361.0)	171.5 (119.0, 260.0)
Total bilirubin at DILI onset (mg/dl) (median (IQR))	6.5 (2.5, 17.4)	1.0 (0.9, 2.6)	1.0 (0.7, 1.7)
Pattern of liver injury (Cholestatic/Mixed/Hepatocellular)	0/75/25	0/40/60	33.3/16.7/50
R-value (median ((IQR))	3.2 (2.5, 6.2)	11.5 (2.7, 14.0)	5.7 (1.6, 14.6)
Peak ALT (U/L) (median ((IQR))	447.5 (233.5, 960.5)	932.0 (662.0, 1046.0)	542.5 (303.0, 766.0)
Peak ALP (U/L) (median ((IQR))	215.5 (139.0, 572.0)	361.0 (231.0, 377.0)	304.0 (119.0, 338.0)
Peak total bilirubin (mg/dl) (median ((IQR))	6.5 (2.6, 17.4)	1.9 (1.7, 2.6)	1.6 (0.7, 3.7)
ALT (time from peak to normalization) (IU/mL)) (Median, Days)	67	74	30
Treated with prednisone or corticosteroids	0	20.00	0
Severity score (mild/moderate/severe/fatal)	25/50/25/0	60/20/20/0	66/17/0/17
All death	25.00	0	16.7

Values are in percentages unless otherwise stated

Table 2. Characteristics of Subjects with DILI due to AAs versus Other Agents

Characteristics	Azole n=15	Other Agents n=1711	p value
Age (years, median, IQR)	46.8 (34.3, 66.3)	51.8 (37.2, 62.7)	0.972
Female	53	58	0.710
Caucasian	71	78	0.558
Alcohol use	20	48.5	**0.028**
Malignancy	33.3	11.2	**0.021**
Days from primary drug start to DILI onset/latency (median (IQR))	37 (14, 93)	46 (22, 104)	0.256
Days from earliest sign/symptom to primary drug stop (median (IQR))	1 (1,1)	6 (1, 16)	**0.029**
Jaundice at DILI onset	20	63	**< 0.001**
ALT at DILI onset (U/L) (median ((IQR))	320.0 (200.0, 906.0)	470.0 (241.0, 1010.0)	0.393
ALP at DILI onset (U/L) (median ((IQR))	176.0 (146.0, 361.0)	209.0 (134.0, 339.0)	0.815
Total bilirubin at DILI onset (mg/dl) (median (IQR))	1.2 (0.7, 3)	4.6 (1.3, 9.1)	**0.013**
Pattern of liver injury (Cholestatic/Mixed/Hepatocellular)	13/40/47	23/22/55	0.288
R-value (median ((IQR))	3.7 (2.3, 14.0)	5.9 (2.2, 15.0)	0.663
Peak ALT (U/L) (median ((IQR))	662.0 (303.0, 1046.0)	614.0 (307.0, 1298.0)	0.762
Peak ALP (U/L) (median ((IQR))	302.0 (169.0, 377.0)	273.0 (176.0, 446.0)	0.911
Peak total bilirubin (mg/dl) (median ((IQR))	1.9 (0.9, 4.5)	9.1 (2.3, 19.4)	**0.007**
ALT (time from peak to normalization) (IU/mL) (Median, Days)	34	64	**0.009**
Treated with prednisone or corticosteroids	7	23	0.214
Severity score (mild/moderate/severe/fatal)	53/27/13/7	25/52/17/6	0.159
All death	13	6.4	0.254
All liver transplant	0	3.5	>0.999
Chronic DILI	0	16.9	0.236

Values are in percentages unless otherwise stated

Conclusions

- DILI from azole antifungals is uncommon.
- Azole antifungal DILI is typically characterized by a hepatocellular or mixed pattern without jaundice.
- Liver injury is mild or moderate in all cases with resolution.
- Azole antifungal DILI did not lead to liver related death, liver transplantation, or chronic DILI, even in cases of severe liver injury.
- Compared to DILI from other agents, azole antifungal DILI has a faster time to normalization of liver enzymes.
- Compared to DILI from other agents, the outcomes of azole antifungal DILI (death, liver transplantation and chronic DILI) were not statistically different. However, the sample may be too small to meaningfully discern differences in these outcomes.

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