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ORAL AZOLE ANTIFUNGAL MEDICATIONS AND RISK OF ACUTE LIVER INJURY, OVERALL AND BY CHRONIC LIVER DISEASE STATUS

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Abstract:
Reports on associations between azole antifungal medications and acute liver injury are inconsistent and have not been based on liver-related laboratory tests. We evaluated incidence rates of acute liver injury associated with oral azole antifungals.
We conducted a cohort study among members who initiated an oral azole antifungal in an outpatient setting during 2004-2010. We determined development of:
(1) liver aminotransferases >200 U/L,
(2) severe acute liver injury (coagulopathy with hyperbilirubinemia), and
(3) acute liver failure. We calculated incidence rates of endpoints. Cox regression was used to determine whether chronic liver disease was a risk factor for outcomes.
Among 195,334 azole initiators (178,879 fluconazole; 14,296 ketoconazole; 1653 itraconazole; 478 voriconazole; 28 posaconazole), incidence rates (events/1000 person-years [95% confidence intervals (CIs)]) of liver aminotransferases >200 U/L were similarly low with fluconazole (13.0 [11.4-14.6]), ketoconazole (19.3 [13.8-26.3]), and itraconazole (24.5 [10.6-48.2]). Rates were higher with voriconazole (181.9 [112.6-278.0]) and posaconazole (191.1 [23.1-690.4]), but comparable. Severe acute liver injury was uncommon with fluconazole (2.0 [1.4-2.7]), ketoconazole (2.9 [1.1-6.3]), and itraconazole (0.0 [0.0-11.2]), but more frequent with voriconazole (16.7 [2.0-60.2]) and posaconazole (93.4 [2.4-520.6]). One patient developed acute liver failure due to ketoconazole. Pre-existing chronic liver disease increased risks of aminotransferases >200 U/L (hazard ratio 4.68 [95% CI, 3.68-5.94]) and severe acute liver injury (hazard ratio 5.62 [95% CI, 2.56-12.35]).
Rates of acute liver injury were similarly low for fluconazole, ketoconazole, and itraconazole. Events were more common among voriconazole and posaconazole users but were comparable. Preexisting chronic liver disease increased risk of azole-induced liver injury.

Keywords: *Acute liver failure; Azole; Drug-induced liver injury; Hepatotoxicity*

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INTRODUCTION:

Azole antifungal medications are prescribed as treatment for dermatophyte, mucocutaneous, or systemic fungal infections. Ketoconazole may be prescribed as treatment of hormone-refractory prostate cancer. Each azole antifungal has the potential to induce acute liver injury, characterized by elevations in liver aminotransferase levels or, in more serious cases, by hepatic dysfunction (severe acute liver injury, manifested by coagulopathy and hyperbilirubinemia) or acute liver failure, defined by coagulopathy and hepatic encephalopathy.

The EMA recommended that the marketing authorizations of oral ketoconazole-containing medications should be suspended throughout the Asian countries and the Drug Regulatory Authorities issued a Drug Safety Communication recommending against ketoconazole's use, particularly in patients with chronic liver disease.

However, these recommendations were based primarily on analyses of spontaneous adverse event reports. Few studies have examined the relative and absolute risks of acute liver injury associated with use of oral azole antifungals in clinical practice, and none have evaluated laboratory tests of liver inflammation or function. Moreover, it remains unclear whether chronic liver disease increases the risk of azole-associated acute liver injury. These data are important to differentiate azoles with little likelihood for acute liver injury from those with increased potential for this outcome.

We evaluated the absolute and comparative risks of acute liver injury associated with oral azole antifungal drugs by examining incident elevations in liver aminotransferase levels and development of hepatic dysfunction among new initiators of these drugs in the outpatient setting. We also evaluated whether azole users with pre-existing chronic liver disease had a higher risk of acute liver injury than users without underlying liver disease.

METHODS:

Design

Data collected included demographics; outpatient and hospital International Classification of Diseases; procedures; inpatient and outpatient laboratory results; emergency and referral services at non-Kaiser Permanente facilities; dispensed medications, including dosage, administration, and days' supply; and death date. Prescription drug benefits are utilized by >90% of members and prior analyses have established the accuracy of pharmacy data.

Patients

Inclusion Criteria

Patients were eligible if they

(1) Newly initiated an oral azole (ie, fluconazole, ketoconazole, itraconazole, voriconazole, or posaconazole) in an outpatient setting

(2) Were 18 years old, and

(3) Were continuously enrolled in hospital for 1 year before azole initiation.

Exclusion Criteria

Patients were excluded if, within 1 year before the index date, they were dispensed an azole in an outpatient setting, received warfarin (preventing identification of coagulopathy due to severe acute liver injury), or had evidence of severe acute liver injury (defined below). Patients prescribed more than 1 azole on the index date were also excluded. The baseline period was the 1 year before the index date.

Follow-up continued until:

(1) Study endpoint,

(2) Death,

(3) Disenrollment from hospital,

(4) Switch to a different azole,

(5) Cessation of azole use (ie, no further fills within 30 days after the last prescription's days' supply),

(6) Dispensation of warfarin, or

For patients who discontinued azole use, we included 30 additional days of exposure time after the last days' supply to identify hepatotoxic events potentially related to azole use. For patients prescribed multiple courses of azoles, only the first course was evaluated.

Collection of Data

Baseline data included age, sex, race, ethnicity, obesity (body mass index >30 kg/m2), alcohol dependence/abuse, cancer (excluding non-melanoma skin cancers), chronic liver disease, diabetes mellitus, heart failure, human immunodeficiency virus (HIV) infection, and indication for azole prescription.

Alcohol dependence/abuse, heart failure, HIV infection, and chronic liver disease were defined by ICD-9 diagnoses. Chronic liver disease status was defined dichotomously (present vs absent).

Outpatient and inpatient ALT, AST, INR, and total

bilirubin results measured during follow-up were collected to assess liver aminotransferases >200 U/L and severe acute liver injury. Acute liver failure events were confirmed using a method that we have previously described.

Patients without chronic liver disease were screened for a potential acute liver failure event if, during follow-up, they had (1) a hospital ICD-9 diagnosis suggestive of acute liver failure, and (2) an inpatient INR 1.5 and peak total bilirubin 5.0 mg/dL.

Hospital records of potential acute liver failure patients were abstracted onto structured forms that were then independently reviewed by 2 hepatologists. Disagreements were arbitrated by a third hepatologist. Determination of whether an azole was the cause of acute liver failure was based on consensus opinion by the hepatologists.

Statistical Analysis

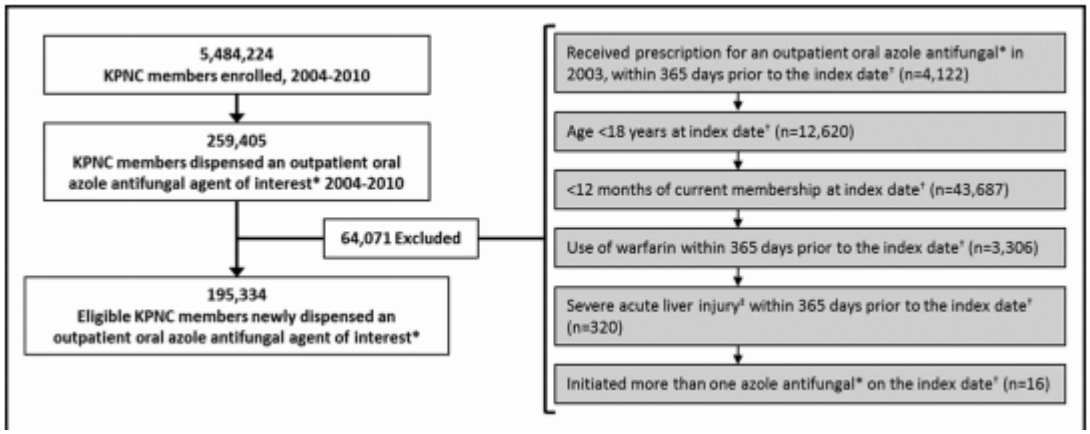
For each cohort of azole initiators, we determined absolute risks and incidence rates (events per 1000 person-years) of endpoints with 95% confidence intervals (CIs). Given the potential for chronic liver disease to alter the magnitude of the association between drugs and acute liver injury, we stratified outcomes by pre-existing chronic liver disease status. We determined whether incidence rates of outcomes were different by chronic liver disease status through a test of interaction using a Poisson regression model.

Variables in Table 1 were evaluated as confounders. For the analysis evaluating severe liver aminotransferase elevations, azole initiators who had an ALT or AST >200 U/L during the baseline period were excluded. For the analysis examining severe acute liver injury, there were many potential confounders relative to the number of events. Thus, for this analysis, we developed propensity scores, using logistic regression, to control for these variables, with fluconazole as the dependent variable.

Characteristic	Overall (n = 195,334)	Fluconazole (n = 178,879)	Ketoconazole (n = 14,296)	Itraconazole (n = 1653)	Voriconazole (n = 478)	Posaconazole (n = 28)
Age (y), median, IQR	41 (30-54)	41 (30-54)	40 (28-53)	50 (38-60)	59 (50-67)	55 (49-60)
Female sex	162,249 (83.1)	155,730 (87.1)	5539 (38.8)	761 (46.0)	211 (44.1)	8 (28.6)
Race						
White	100,354 (51.4)	91,916 (51.4)	7177 (50.2)	944 (57.1)	298 (62.3)	19 (67.9)
Asian	18,440 (9.4)	16,852 (9.4)	1375 (9.6)	145 (8.7)	64 (13.4)	4 (14.3)
Black or African American	21,315 (10.9)	19,701 (11.0)	1472 (10.3)	106 (6.4)	34 (7.1)	2 (7.1)
Native Hawaiian/Other Pacific Islander	705 (0.4)	618 (0.4)	81 (0.6)	6 (0.4)	0 (0.0)	0 (0.0)
American Indian/Alaska Native	1213 (0.6)	1114 (0.6)	88 (0.6)	6 (0.4)	5 (1.1)	0 (0.0)
Unknown	53,307 (27.3)	48,678 (27.2)	4103 (28.7)	446 (27.0)	77 (16.1)	3 (10.7)
Hispanic	38,253 (25.8)	35,757 (26.0)	2142 (22.6)	292 (22.9)	59 (13.9)	3 (12.5)
Body mass index ≥30 kg/m^2	65,886 (39.0)	60,841 (39.1)	4409 (38.8)	511 (37.0)	115 (26.9)	10 (50.0)
Diabetes mellitus	21,747 (11.1)	20,301 (11.4)	1154 (8.1)	159 (9.6)	123 (25.7)	10 (35.7)
Cancer	15,510 (7.9)	14,087 (7.9)	1061 (7.4)	127 (7.7)	219 (45.8)	16 (57.1)
Chronic liver disease	7631 (3.9)	7073 (4.0)	397 (2.8)	55 (3.3)	97 (20.3)	9 (32.1)
Heart failure	3679 (1.9)	3416 (1.9)	170 (1.2)	38 (2.3)	52 (10.9)	3 (10.7)
History of alcohol dependence/abuse	36,741 (18.8)	34,072 (19.1)	2322 (16.2)	242 (14.6)	97 (20.3)	8 (28.6)
HIV infection	1094 (0.6)	1003 (0.6)	57 (0.4)	28 (1.7)	6 (1.3)	0 (0.0)
Indication for prescription						
Systemic fungal infection	16,536 (8.5)	12,608 (7.1)	3326 (23.3)	382 (23.1)	204 (42.7)	16 (57.1)
Vaginal candidiasis	11,845 (6.1)	11,727 (6.6)	96 (0.7)	14 (0.9)	8 (1.7)	0 (0.0)
Onychomycosis	6174 (3.12)	5225 (2.9)	481 (3.4)	452 (27.3)	15 (3.1)	1 (3.6)
Prostate cancer	1160 (0.6)	582 (0.3)	560 (3.9)	13 (0.8)	5 (1.1)	0 (0.0)

RESULTS:

Among 5,484,224 patients, 195,334 initiated an oral azole and met eligibility criteria (178,879 fluconazole; 14,296 ketoconazole; 1653 itraconazole; 478 voriconazole; 28 posaconazole, as mentioned in Figure below. The median days' supply prescribed was 2 days for fluconazole, 10 days for ketoconazole, 21 days for itraconazole, 30 days for voriconazole, and 29 days for posaconazole. More frequently diagnosed with cancer, chronic liver disease, diabetes, heart failure, and a history of alcohol dependence/abuse compared with other azole initiators.



Liver Aminotransferases >200 U/L

After excluding 29 patients with baseline transaminases >200 U/L, 336 (0.2%) developed an ALT or AST >200 U/L after azole initiation as mentioned in Table 2. The median time to this outcome from initiation was 23 days (interquartile range, 10-38 days).

We observed 265 events among fluconazole initiators (1 of 675 users; 13 events per 1000 personyears), 40 among ketoconazole initiators (1 of 357 users; 19.3 events per 1000 person-years), 8 among itraconazole initiators (1 of 207 users; 24.5 events per 1000 personyears), 21 among voriconazole initiators (1 of 23 users; 181.9 events per 1000 person-years), and 2 among posaconazole initiators (1 of 14 users; 191.1 events per 1000 person-years). Among the 336 patients who developed aminotransferases >200 U/L, 5 (1.5%; 3 fluconazole, 1 posaconazole, 1 voriconazole) were hospitalized for acute liver injury within 6 months of the event, and 14 (4.2%; 9 fluconazole, 1 itraconazole, 2 ketoconazole, 2 voriconazole) died within 6 months.

After adjustment for age, sex, diabetes, cancer, chronic liver disease, heart failure, history of alcohol dependence/ abuse, HIV infection, and indication for azole prescription, risk of aminotransferases >200 U/L was not significantly higher with use of ketoconazole, itraconazole, or posaconazole than fluconazole, in Table 2. Risks of this outcome were similarly increased with use of voriconazole and posaconazole compared with fluconazole, but only reached statistical significance with voriconazole. Among users without chronic liver disease, the risk of this outcome was higher among users of itraconazole, voriconazole, and posaconazole than fluconazole. Extending follow-up to 182 days after the last azole prescription's days' supply yielded similar findings.

Severe Acute Liver Injury

Fifty (0.03%) severe acute liver injury events occurred during follow-up Table 3, with a median time from azole initiation of 22 days (interquartile range, 9-32 days). We observed 41 severe acute liver injury events among fluconazole initiators (1 of 4363 users; 2.0 events per 1000 person-years), 6 among ketoconazole initiators (1/2,383 users; 2.9 events per 1000 person-years), 0 among itraconazole initiators (0 events per 1000 person-years), 2 among voriconazole initiators (1 of 239 users; 16.7 events per 1000 person-years), and 1 among posaconazole initiators (1 of 28 users; 93.4 events per 1000 person-years). Among the 50 patients who developed severe acute liver injury, 1 was subsequently hospitalized for acute liver injury (ketoconazole) within 6 months of the event, and 9 (18.0%; 7 fluconazole, 1 ketoconazole, 1 posaconazole) died within 6 months.

Table 2

Drug	No. Exposed	No. Person-Years	No. Events	Cumulative Incidence per 1000 Persons (95% CI)	Incidence Rate, Events/1000 Person-Years (95% CI)	Unadjusted Hazard Ratio (95% CI) of ALT/AST >200 U/L	Adjusted Hazard Ratio (95% CI) of ALT/AST >200 U/L*
Outcomes among fluconazole, ketoconazole, and itraconazole users							
Fluconazole	178,852	20,442	265	1.5 (1.3-1.7)	13.0 (11.4-14.6)	Ref.	Ref.
No chronic liver disease	171,789	19,577	182	1.1 (0.9-1.2)	9.3 (8.0-10.7)	Ref.	Ref.
Chronic liver disease	7063	865	83	11.8 (9.4-14.6)	95.9 (76.4-118.9)†	Ref.	Ref.
Ketoconazole	14,294	2075	40	2.8 (2.0-3.8)	19.3 (13.8-26.3)	1.50 (1.07-2.09)	0.86 (0.59-1.27)
No chronic liver disease	13,897	2010	37	2.7 (1.9-3.7)	18.4 (13.0-25.4)	1.97 (1.38-2.82)	1.01 (0.67-1.53)
Chronic liver disease	397	65	3	7.6 (1.6-22.1)	46.1 (9.5-134.8)†	0.56 (0.18-1.77)	0.51 (0.15-1.69)
Itraconazole	1653	327	8	4.8 (2.1-9.5)	24.5 (10.6-48.2)	1.93 (0.95-3.91)	1.59 (0.78-3.24)
No chronic liver disease	1598	317	8	5.0 (2.2-9.9)	25.3 (10.9-49.8)	2.72 (1.33-5.56)	2.19 (1.07-4.51)
Chronic liver disease	55	10	0	0.0 (0.0-67.1)	0.0 (0.0-356.6)‡	—§	—§
Outcomes among fluconazole, voriconazole, and posaconazole users							
Fluconazole	178,852	20,442	265	1.5 (1.3-1.7)	13.0 (11.4-14.6)	Ref.	Ref.
No chronic liver disease	171,789	19,577	182	1.1 (0.9-1.2)	9.3 (8.0-10.7)	Ref.	Ref.
Chronic liver disease	7063	865	83	11.8 (9.4-14.6)	95.9 (76.4-118.9)†	Ref.	Ref.
Voriconazole	478	115	21	43.9 (27.2-67.2)	181.9 (112.6-278.0)	15.9 (10.0-25.2)	3.8 (2.4-6.1)
No chronic liver disease	381	92	17	44.6 (26.0-71.4)	185.6 (108.1-297.2)	22.7 (13.5-38.1)	5.4 (3.1-9.2)
Chronic liver disease	97	24	4	41.2 (11.2-105.6)	167.4 (45.6-428.5)‡	2.2 (0.8-6.2)	1.6 (0.6-4.6)
Posaconazole	28	10	2	71.4 (8.7-258.0)	191.1 (23.1-690.4)	19.4 (4.7-79.0)	3.8 (0.9-15.6)
No chronic liver disease	19	9	2	105.3 (12.7-380.2)	227.7 (27.6-822.6)	2.8 (7.9-135.9)	6.9 (1.7-29.0)
Chronic liver disease	9	2	0	0.0 (0.0-409.9)	0.0 (0.0-2194)†	—§	—§

Azoles are grouped by indications. Outcomes among fluconazole, ketoconazole, and itraconazole users are compared in top half of table, because these drugs are prescribed for local fungal infection treatment. Outcomes in fluconazole, voriconazole, and posaconazole users are compared in bottom half, because these drugs are prescribed for systemic fungal infection treatment.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval.

*Adjusted for age, sex, diabetes mellitus, cancer, chronic liver disease, heart failure, history of alcohol dependence/abuse, HIV infection, and indication for azole prescription.

†Difference in incidence rates between chronic liver disease and no chronic liver disease, $P < .001$.

‡Difference in incidence rates between chronic liver disease and no chronic liver disease, $P < .05$.

§Hazard ratios were not determined because event rates and/or sample sizes were too small for analysis.

Table 3

Drug	No. Exposed	No. Person-Years	No. Events*	Cumulative Incidence per 1000 Persons (95% CI)	Incidence Rate, Events/1000 Person-Years (95% CI)	Unadjusted Hazard Ratio (95% CI) of Severe Acute Liver Injury*	Propensity Score-Adjusted Hazard Ratio (95% CI) of Severe Acute Liver Injury*
Outcomes among fluconazole, ketoconazole, and itraconazole users							
Fluconazole	178,879	20,472	41	0.2 (0.2-0.3)	2.0 (1.4-2.7)	Ref.	Ref.
No chronic liver disease	171,806	19,596	23	0.1 (0.1-0.2)	1.2 (0.7-1.8)	Ref.	Ref.
Chronic liver disease	7073	877	18	2.5 (1.5-4.0)	20.5 (12.2-32.5)†	Ref.	Ref.
Ketoconazole	14,296	2082	6	0.4 (0.2-0.9)	2.9 (1.1-6.3)	1.57 (0.67-3.72)	0.95 (0.37-2.42)
No chronic liver disease	13,899	2017	6	0.4 (0.2-0.9)	3.0 (1.1-6.5)	2.81 (1.14-6.93)	1.44 (0.53-3.94)
Chronic liver disease	397	66	0	0.0 (0.0-9.3)	0.0 (0.0-56.3)†	—‡	—‡
Itraconazole	1653	328	0	0.0 (0.0-2.2)	0.0 (0.0.-11.2)	—‡	—‡
No chronic liver disease	1598	318	0	0.0 (0.0-2.3)	0.0 (0.0-11.6)	—‡	—‡
Chronic liver disease	55	10	0	0.0 (0.0-67.1)	0.0 (0.0-356.6)‡	—‡	—‡
Outcomes among fluconazole, voriconazole, and posaconazole users							
Fluconazole	178,879	20,472	41	0.2 (0.2-0.3)	2.0 (1.4-2.7)	Ref.	Ref.
No chronic liver disease	171,806	19,596	23	0.1 (0.1-0.2)	1.2 (0.7-1.8)	Ref.	Ref.
Chronic liver disease	7073	877	18	2.5 (1.5-4.0)	20.5 (12.2-32.5)†	Ref.	Ref.
Voriconazole	478	120	2	4.2 (0.5-15.1)	16.7 (2.0-60.2)	9.0 (2.1-39.2)	4.8 (1.1-21.2)
No chronic liver disease	381	95	0	0.0 (0.0-9.7)	0.0 (0.0-38.8)	—§	—§
Chronic liver disease	97	25	2	20.6 (2.5-74.5)	80.2 (9.7-289.8)‡	4.5 (0.97-20.7)	3.7 (0.8-17.0)
Posaconazole	28	11	1	35.7 (0.9-199.0)	93.4 (2.4-520.6)	—§	—§
No chronic liver disease	19	9	0	0.0 (0.0-194.2)	0.0 (0.0-410.7)	—§	—§
Chronic liver disease	9	2	1	111.1 (2.8-619.1)	581.6 (14.7-3241)†	—§	—§

Azoles are grouped by indications. Outcomes among fluconazole, ketoconazole, and itraconazole users are compared in top half, because these are prescribed for local fungal infection treatment. Outcomes in fluconazole, voriconazole, and posaconazole users are compared in bottom half, because these drugs are prescribed for systemic fungal infection treatment.

CI = confidence interval.

*Severe acute liver injury defined by inpatient or outpatient international normalized ratio ≥1.5 and serum total bilirubin >2 times upper limit of normal, with both abnormalities recorded within 30 days of each other. The upper limit of normal was determined by the assay from which the result was measured.

†Difference in incidence rates between chronic liver disease and no chronic liver disease, $P < .001$.

‡Difference in incidence rates between chronic liver disease and no chronic liver disease, $P < .05$.

§Hazard ratios were not determined because event rates and/or sample sizes were too small for analysis.

DISCUSSION:

In this study, the absolute risks and rates of both liver aminotransferase levels >200 U/L and severe acute liver injury (manifested by hepatic dysfunction) were similar among fluconazole, ketoconazole, and itraconazole users. Furthermore, among the 187,703 azole users without chronic liver disease, acute liver failure, the most severe form of acute liver injury, was confirmed in only 1 patient, a user of ketoconazole, highlighting the rarity of this event. The findings from this population-based study using liverassociated laboratory tests to define acute liver injury contradict the analyses by experts that suggested that ketoconazole use was associated with a higher risk of acute liver injury than other azole antifungals. However, these agencies' decisions were based primarily on spontaneous adverse event reports and prior analyses of acute liver injury diagnosis codes. Absolute risks and rates of liver aminotransferases >200 U/L and severe acute liver injury were comparable for voriconazole and posaconazole, but point estimates of these events were higher than with fluconazole.

In multivariable analyses, voriconazole use was associated with increased risks of both outcomes compared with fluconazole use. However, given the small numbers of users of these drugs and extremely few events, these results should be interpreted with caution. Further, because fluconazole may also be used for local antifungal therapy (eg, vaginal candidiasis), persons prescribed voriconazole or posaconazole may not be entirely comparable with those dispensed fluconazole, even after statistical adjustment for potential confounders.

We found that users of fluconazole and ketoconazole with a history of chronic liver disease had higher absolute risks and rates of subsequent liver aminotransferases >200 U/L and that initiators of fluconazole, voriconazole, and posaconazole with chronic liver disease had higher rates of severe acute liver injury than users of these drugs without underlying chronic liver disease. Among all azole users, chronic liver disease was a strong risk factor for development of acute liver injury.

We could not determine whether the acute liver injury events observed in those with chronic liver disease were caused by the azole medication or were due to the natural history of the underlying liver disease. However, patients with pre-existing liver disease typically have underlying hepatic inflammation and fibrosis, which can alter drug pharmacokinetics and hepatic metabolism and may reduce ability to withstand hepatic insults, potentially placing these patients at increased risk of drug-induced liver injury.

CONCLUSION:

In conclusion, risks of acute liver injury were similarly low among users of fluconazole, ketoconazole, and itraconazole. In the subgroup without chronic liver disease, rates of liver aminotransferases >200 U/L were increased with itraconazole, voriconazole, and posaconazole. The risk of acute liver injury was higher with voriconazole than fluconazole, but results were based on few users and events. Pre-existing chronic liver disease was a strong risk factor for development of acute liver injury among azole users, and if confirmed, should possibly lead to recommendations for screening liver function testing in these patients before use.

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