Clinical Characteristics and HLA Associations of Azithromycin Induced Liver Injury

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BACKGROUND

Azithromycin (AZ) is a widely used macrolide antibiotic with a favorable safety profile, yet drug induced liver injury (DILI) has been reported.

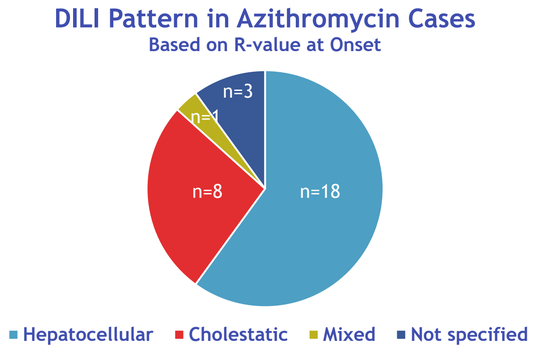
AIM

The aim of this study is to characterize the clinical features, outcomes and human leukocyte antigen (HLA) associations in patients with AZ DILI in patients enrolled in the U.S. Drug Induced Liver Injury Network (DILIN) Prospective Study.

METHODS

We evaluated individuals with definite, highly likely or probable (high causality) AZ induced liver injury enrolled in the DILIN between 2004 and 2022.

HLA typing was performed using an Illumina MiSeq platform. Analysis of HLA alleles was performed by Fisher's exact test to compare allele frequency (AF) in AZ DILI cases and population controls assembled from five dbGaP GWAS datasets.



RESULTS

30 cases of AZ DILI (4 definite, 14 highly likely and 12 probable) were included. These represent 2% of adult and 7% of pediatric high causality DILI cases enrolled in the DILIN between 2004 and 2022 (total n=1635).

Patient and Drug Characteristics	
Gender: Female	18 (60%)
Race: Black	2 (6.7%)
Asian	3 (10%)
White	25 (83.3%)
Median age, years (range)	46 (1-78)
Age < 18 years	5 (16.7%)
Median BMI kg/m2 (range)	24.9 (13.2-42.4)
Pre-existing liver disease	5 (16.7%)
Median duration of use, days (range)	5 (2-8)
Latency, days (range)	18.5 (2-65)

Clinical outcomes	
Symptoms on presentation	
Abdominal pain	19 (63.3%)
Jaundice	22 (73.3%)
Nausea	18 (60%)
Required hospitalization	10 (33%)
Required liver transplantation	2 (7%)
Fatal cases	3 (10%)
Underlying chronic liver disease	1
Developed chronic liver injury	5 (16.7%)

RESULTS continued

- 10 of 30 cases were fatal or severe, with 2 needing liver transplant.
- 9 of 10 fatal or severe cases and 4 of 5 cases with chronic liver injury had hepatocellular liver injuries at onset.
- Of the 5 children; 3 were hospitalized, 1 required liver transplantation, 1 suffered a severe cutaneous reaction, and 2 developed chronic liver injuries.
- 13 liver biopsies reviewed showed acute or chronic hepatitis (n=6), cholestatic injuries (n=6), zone 3 to multiacinar necrosis (n=4), and severe ductopenia (n=1).
- HLA-DQA1*03:01 prevalence was significantly increased in AZ DILI versus population controls after correction for multiple testing (AF: 0.29 vs 0.11, p=0.001, FDR=0.03). The increased prevalence was non-significant when compared to other non-AZ DILIN cases (AF=0.16, p=0.053, FDR 0.50).

CONCLUSION

- AZ DILI can lead to significant morbidity and mortality in both adult and pediatric patients.
- Pediatric and hepatocellular liver injury cases had worse outcomes including fatalities and chronic liver injuries.
- HLA-DQA1*03:01 was significantly more prevalent in AZ cases than in the population. However, this allele was not specific to AZ DILI compared with DILI caused by other drugs.

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