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Clinical and Histological Features of Azithromycin-Induced Liver Injury

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Abstract

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Background & Aims—Rare cases of azithromycin-induced hepatotoxicity have been reported, with variable clinical and histological features. We characterized clinical features and outcomes of azithromycin-induced liver injury.

Methods—We identified patients with azithromycin-induced liver injury from the Drug-Induced Liver Injury Network Prospective Study who had causality scores of definite, highly likely, or probable. Demographic, clinical, and laboratory data and 6-month outcomes were examined.

Results—Eighteen patients (72% female; mean age, 37 years) had causality scores of definite (n=1), highly likely (n=9), or probable (n=8). Common presenting symptoms were jaundice, abdominal pain, nausea, and/or pruritus. For 16 patients, abnormal results from liver tests were first detected 14 days after azithromycin cessation (range, 9–20 days). The median duration of azithromycin treatment was 4 days (range, 2–7 days). The pattern of injury was hepatocellular in 10 patients, cholestatic in 6 patients, and mixed in 2 patients. The mean peak level of alanine aminotransferase was 2127 IU/L, of alkaline phosphatase was 481 IU/L, and of total bilirubin was 9.2 mg/dL. Liver histology showed ductopenia and veno-occlusive changes in a few cases. Two individuals had severe hypersensitivity cutaneous reactions. After 6 months, 8 patients had recovered, 4 had chronic injury, 1 died, and 1 underwent liver transplantation (outcomes were unavailable for 4 patients). Two of the patients with fatal or liver transplantation outcomes had preexisting chronic liver disease.

Conclusions—Azithromycin-induced liver injury occurs within 1–3 weeks after azithromycin initiation and is predominantly hepatocellular in nature. Although most patients recover fully, severe cutaneous reactions, chronic injury, and serious complications leading to death or liver transplantation can occur (ClinicalTrials.gov identifier, NCT00345930).

Keywords

DILI; antibiotic; liver toxicity; macrolide

Introduction

Drug-induced liver injury (DILI) is an important cause of liver disease in the United States, accounting for 1–2% of hospital admissions and 13% of cases of acute liver failure.[1, 2] Hepatotoxicity is one of the most common black-box warnings placed on medications and is a major cause for failure to receive initial regulatory approval or withdrawal following the initial approval. [3, 4] Although numerous therapeutic classes of agents can cause idiosyncratic DILI, antimicrobials are the most common class of drugs implicated and account for 45% of cases in the United States.[5] The frequency of serious antibiotic-induced hepatotoxicity is low when compared to the very large number of prescriptions written each year, but population-based estimates suggest that it occurs at a frequency of 1 to 10 per 100,000 drug prescriptions.[6–8] Among antibiotics, the macrolides (erythromycin, azithromycin and clarithromycin) are some of the most commonly used. Their potential for hepatotoxicity was initially recognized in animals[9] and was later well documented in humans based upon reactions to various erythromycin derivatives.[10, 11]

Azithromycin, a semisynthetic macrolide derived from erythromycin approved in 1994, is a potent and generally well tolerated oral antibiotic and recently became the most frequently

prescribed antibiotic in the United States.[12] Cytotoxic assays performed during drug development revealed minimal intrinsic hepatotoxicity.[13] Large clinical trials using azithromycin reported acute, transient, asymptomatic increases in serum aminotransferase levels in 1–2% of patients but similar rates were also found in comparator arms.[14] Rarely, clinically apparent liver injury from azithromycin has been reported, but only as isolated case reports.[10, 15, 16] The injury appeared to be idiosyncratic with variable clinical presentations, usually cholestatic and often with immunoallergic features.[15–20] No common clinical phenotype or signature pattern of liver injury could be identified from these single case reports.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established the Drug-Induced Liver Injury Network (DILIN) in 2003 with the primary objective to investigate the causative agents, clinical features, pathogenesis, causality assessment and outcomes of DILI in the United States.[21] The ongoing DILIN Prospective Study enrolls eligible individuals with suspected DILI due to drugs or dietary supplements other than acetaminophen at multiple academic institutions throughout the United States.[5, 22] In this report, we characterize the clinical and histological features and outcomes of acute liver injury due to azithromycin in a sizable number of individuals with high causality scores.

Methods

The study design of the DILIN prospective study has been described in previous publications and some cases included in this report have been included in previous reports.[22, 23] Individuals meeting pre-specified eligibility criteria undergo an evaluation for competing etiologies in a structured fashion.[22] The study protocol requires a follow-up visit at 6 months after the initial enrollment, and individuals meeting definition of chronic DILI are asked also to return for visits at 12 and 24 months.[22] The overall diagnosis of DILI and the causal relationship between the implicated agent(s) and the liver injury event are adjudicated by the DILIN Causality Committee in a systematic fashion using expert consensus.[22, 24] The strength of causal association between the implicated agent(s) and the liver injury event is graded as definite, highly likely, probable, possible and unlikely.[22] A DILIN severity score is assigned for each case that ranges from 1 (mild as defined by serum enzyme elevations with bilirubin <2.5 mg/dL and INR <1.5), 2 (moderate, serum enzyme elevations and bilirubin ≥2.5 mg/dL or INR ≥1.5), 3 (moderate-hospitalized, serum enzyme elevations, bilirubin ≥2.5 mg/dL or INR ≥1.5 and hospitalization for liver injury), 4 (severe, bilirubin ≥2.5 mg/dL and signs of hepatic failure such as INR ≥1.5, ascites or hepatic encephalopathy), and 5 (liver transplantation within 6 months of onset or death due to liver injury).[22]

This current analysis included all patients with liver injury attributed to azithromycin who were enrolled between September 2004 and May 2013 assigned a causality score of definite, highly likely or probable (Figure 1). Demographic, clinical history and laboratory results were abstracted, and each case was individually analyzed by one of the authors (MM, RV, NC) with attention to latency, clinical presentation, severity, time course, progression to chronicity, need for transplant, and liver-related death. The pattern of liver injury was categorized on the basis of the R-value ([ALT value/ ULN ALT] / [Alk P value/ULN Alk

P]) at presentation, with R > 5 defined as hepatocellular, R < 2 as cholestatic, and 2< R <5 as mixed.[5] All co-authors had access to the study data and had reviewed and approved the final manuscript.

Statistical Analysis

The data analyses were performed by the Duke Clinical Research Institute, the data coordinating center of the DILIN. SAS v 9.2 was used to aid all analyses. Continuous variables were summarized with mean and standard deviation or median and interquartile range (IQR, 25th–75th). Categorical data were expressed as counts and proportions. Comparison between the hepatocellular and cholestatic groups was made using non-parametric Mann-Whitney test.

Results

Patient Characteristics (Figure 1)

Eighteen individuals with definite (n=1), highly likely (n=9) and probable (n=8) DILI constituted the study cohort. While azithromycin was the only implicated agent in 13 cases, there was another implicated agent with a “possible” causality score in the remaining 5 cases (trimethoprim-sulfamethoxazole in two, MRC-6 (a body building supplement) and oral contraceptives in one and, trimethoprim and ibuprofen in one case each). As a result, the causality score specific for azithromycin as the etiology of liver injury was definite in 1, highly likely in 7 and probable in 10 individuals.

The mean patient age for the group was 37 years with a range of 1.7 to 76 years (Table 1), 14 were adults and 4 were children (ages 1.7, 8, 11, and 14 years at onset of DILI). The majority were female (n=13, 72%) and non-Hispanic white (n=15, 83%), and the average body mass index was 25.2 kg/m^2 (range 13 to 42 kg/m^2). Alcohol consumption around the time of onset of liver injury was present in 6 patients with one patient drinking daily. Five patients had pre-existing liver conditions including non-alcoholic fatty liver disease in two and one each with alcohol-related liver disease, chronic graft-vs-host disease with secondary iron overload, or biliary atresia (Table 2). Of note, 6 subjects reported previous exposure to azithromycin (Table 2). The latency between starting azithromycin and onset of DILI was not different among these individuals as compared to 12 subjects who did not report prior exposure to azithromycin. All patients tested negative for acute hepatitis A, B and C. IgG antibody to hepatitis E virus (anti-HEV) was tested in 14 patients and Ig M anti-HEV in 5 patients and were negative in all.

Clinical presentation and Type of Liver Injury

All patients were symptomatic at presentation and the most common presenting symptoms were jaundice (89%), abdominal pain (67%), nausea (61%) and pruritus (56%). The mean duration of azithromycin use was 4 days (2–7). The median time to onset of symptoms after initiating azithromycin was 17 days (IQR: 1–58 days) and the median duration from azithromycin initiation to identification of laboratory abnormalities indicative of DILI was 21 days (IQR: 2–65 days). In 16 patients, liver test abnormalities were first identified after stopping azithromycin, with a median delay of 14 days (IQR: 9–20 days). Overall, at

enrollment, hepatocellular pattern of liver injury [R > 5] was more frequent (56%) than cholestatic (33%) or mixed pattern (11%).

A summary of the age, gender, pattern of liver injury, peak laboratory values, DILIN causality and severity scores and 6-month outcome of all 18 cases is shown in Table 2. There was no obvious clustering of severity or other clinical characteristics according to age or gender.

The comparison among hepatocellular, cholestatic and mixed cases showed no differences with respect to latency, total dose, age, gender, body mass index, alcohol use or symptoms. However, there were some differences with respect to presence of autoantibodies, severity and outcome. Patients with hepatocellular injury were more likely to have a positive ANA or ASMA than those with cholestatic or mixed hepatitis (50% vs. 0%), and were more likely to have a fatal outcome or require transplantation (20% vs. 0%) and evidence of chronic injury 6 months after onset (30% vs. 17%). Features such as rash, fever and eosinophilia occurred in both groups at similar rates.

Two patients developed a severe cutaneous reaction, one with Stevens Johnson syndrome (SJS) (Patient 3) and one with toxic epidermal necrolysis (TEN) (Patient 6). Both were young (ages 11 and 20 years old), female, and had an initial hepatocellular pattern of liver injury (R-values 8.0 and 7.2), which subsequently evolved into a cholestatic pattern (R-value 1.0 and 1.3). Both patients had evidence of chronic injury at 6-month follow up, and the child with SJS, whose liver injury was improving, died of respiratory failure 9 months after initial presentation, which developed as part of her multisystem adverse drug reaction.

Histology

Liver biopsies were performed in 8 individuals during the liver injury event at a median duration of 15 days (range: 2 – 497 days) after DILI onset (explant liver sample was also available in one patient). Three cases showed hepatitis (one with mild acute hepatitis, one with severe acute on chronic hepatitis and one with moderate chronic hepatitis) without evidence of visible cholestasis. Three cases showed cholestasis with variable degrees of inflammation: two were classified as acute cholestasis and one as cholestatic hepatitis. Of the two remaining cases, one showed zone-3 necrosis with veno-occlusive changes and one biopsy showed complex findings including marked hemosiderosis and nodular regenerative hyperplasia probably related to prior bone marrow transplant. Two cases showed striking ductopenia (less than 25% of portal areas with ducts)—one case with acute cholestasis and a second case on a follow-up biopsy of the patient with acute hepatitis on the initial biopsy (Figure 2A and B). Veno-occlusive changes and/or central venulitis were seen in three cases, which is unusually frequent for DILI (Figure 2C and D). For example, in a previous report, we observed veno-occlusive changes in only 4.2% of 249 cases of suspected DILI [25]. Three cases showed increased numbers of intrahepatic eosinophils and none showed increased numbers of plasma cells. The explant showed massive hepatocellular necrosis with extensive ductular reaction and only mild residual inflammation. Veno-occlusive changes were present but may have been secondary to the hepatocellular injury. A follow-up liver biopsy was obtained in 3 patients - one, as noted above, showed ductopenia on a biopsy taken about 9 months after the first biopsy, the second showed persistence of chronic

hepatitis more than a year later, and the third follow-up biopsy was obtained 10 days after the initial biopsy and both biopsies showed zonal necrosis and veno-occlusive changes.

Outcomes

Six month follow up was available for 14 patients of whom 8 recovered from the liver injury, 4 had evidence of chronic injury, one died of multi-organ failure and one underwent liver transplantation (Table 2). In those who recovered, the resolution was usually prompt and evident within 2–5 weeks (Table 1). The median time for 50% reduction of peak serum total bilirubin was 12 days (8–27) days and median time for its normalization was 35 days (25–46).

Four patients (patients 1, 3, 6, and 11) met the definition of chronic DILI at 6 months after onset. Both individuals with severe cutaneous reactions developed chronic DILI. Three of them had hepatocellular injury and jaundice initially. At 6 months, all three had normal bilirubin levels but still had mild to moderate elevations in serum ALT or Alk P levels.

The two individuals with a fatal/liver transplant outcome within 6 months after DILI onset were elderly, had pre-existing chronic liver disease and presented with jaundice and a hepatocellular pattern of liver injury. In the first case (patient 15), a 60 year old woman with underlying nonalcoholic steatohepatitis was treated with azithromycin for three days for a respiratory tract infection and developed fatigue, anorexia, pain and nausea 4 days later, followed by jaundice and worsening of mental status. At presentation, serum bilirubin was 13.8 mg/dL, ALT 1579 IU/L and Alk P 142 IU/L with an INR of 2.6. Because of progressive hepatic failure, she underwent liver transplantation one month after initial presentation. The second fatal case was a 76 year old man (patient 18) with history of daily alcohol abuse and chronic obstructive pulmonary disease who was treated with a four day course of azithromycin for acute bronchitis and developed nausea followed by jaundice one week later with initial serum bilirubin 7.2 mg/dL, ALT 8787 IU/L and Alk P 130 IU/L. Imaging of the liver showed a small liver with heterogeneous texture. He died one week later of multi-organ failure.

Discussion

Azithromycin is a semisynthetic macrolide antibiotic widely used in the treatment of mild to moderate sinopulmonary infections. Its popularity rests on its broad spectrum of activity, rapid oral absorption, once daily administration, tissue penetration and excellent tolerability. A typical regimen is 250 to 500 mg given once daily for 4 to 7 days. Liver injury has been reported in patients taking azithromycin but only rarely, and the published literature is confined to isolated case reports. The reported typical pattern of injury was cholestatic and the clinical course was usually benign, resembling reports of liver injury from erythromycin. Only rare published cases have been severe, fatal or resulted in chronic liver injury.[15, 18, 26]

The current study describes the clinical presentation, course and outcome of 18 cases of clinically apparent liver injury, prospectively identified and adjudicated as probably, highly likely or definitely due to azithromycin. While cases with hepatocellular injury outnumbered those with cholestatic pattern, in many regards the clinical pattern matched what has been

reported from isolated case reports in the literature. Importantly, the latency to onset is 1–3 weeks, and in 16 patients it was recognized two weeks after stopping azithromycin. Typical symptoms were fatigue, nausea, and abdominal pain followed by itching and jaundice. The onset of symptoms typically occurred after the course of azithromycin had been completed with only 2 of the 18 individuals developing jaundice while taking azithromycin. In addition, recovery was usually prompt, averaging 2 to 5 weeks and usually followed by complete resolution with completely normal serum enzymes and no symptoms or signs of persistent liver disease.

However, there were three major exceptions to the usual benign outcome of azithromycin induced liver injury. These outcomes took three forms: (1) severe hypersensitivity related cutaneous reactions with accompanying liver injury, (2) evolution into chronic cholestatic liver injury with vanishing bile duct syndrome, and (3) acute liver failure.

Two young women developed severe cutaneous hypersensitivity reactions following short courses of azithromycin, one fulfilling the criteria for Stevens-Johnson syndrome (SJS) and one as the more severe but related syndrome of toxic epidermal necrolysis (TEN). These dramatic syndromes have been reported with several medications, but most typically allopurinol, carbamazepine, lamotrigine, nevirapine, phenytoin, and phenobarbital.[27–29] These severe skin reactions have also been linked to macrolides (erythromycin, azithromycin and clarithromycin) but at a much lower frequency.[27, 29–31] The rash generally arises within 1 to 28 days of starting therapy and is followed by involvement of other organs, such as liver, lung, kidney or bone marrow.[28] The liver injury associated with SJS and TEN is usually mild and overshadowed by the cutaneous manifestations. However, the liver involvement can be severe and in both of the current cases, evidence of chronic injury was present. One patient died, although not from liver injury. Thus, azithromycin should be considered as a potential cause of SJS or TEN.

Another uncommon outcome of azithromycin induced liver injury is chronic, vanishing bile duct syndrome, which typically arises after an episode of severe acute cholestatic injury.[18] After the acute symptoms begin to resolve, jaundice and pruritus worsen and persist. Liver biopsy typically shows marked cholestasis and relative paucity of intralobular bile ducts (ductopenia). The prognosis is variable; some patients ultimately recover with resolution of jaundice and symptoms, although frequently with persistence of mild serum enzyme elevations and liver biopsy findings of relative ductopenia. Other patients with vanishing bile duct syndrome develop severe ductopenia and biliary cirrhosis, and ultimately require liver transplantation because of intractable pruritus, jaundice and hepatic dysfunction.[32]

The most ominous outcome of azithromycin induced liver injury is acute liver failure which seems to occur very infrequently.[2, 33] For example, Mindikoglu et al., in their analysis of liver transplantation procedures performed for drug-induced acute liver failure in the United States did not find any instances of azithromycin induced ALF which required liver transplantation.[33] In a recent report from the United States Acute Liver Failure Study Group, Reuben et al., described one patient who developed ALF due to a combination of trimethoprim/sulfamethoxazole and azithromycin.[2] In the current case series, two patients developed acute liver failure with one dying and another requiring liver transplantation

yielding an overall severe adverse event rate of 11%. Both of these patients presented with hepatocellular liver injury and jaundice, befitting of “Hy’s Law”, which states that the mortality rate of drug-induced liver injury with a hepatocellular pattern and jaundice is likely to be greater than 10%. Indeed, in the current series, 10 patients fit the criteria for Hy’s Law yielding a mortality/transplant rate of 20%. On the other hand, the two patients with severe adverse events (one liver transplantation, one death), had underlying, pre-existing liver disease (one was alcoholic and one had nonalcoholic steatohepatitis). Both patients were more than 60 years old and presented with a clinical syndrome of “acute-on-chronic” liver failure.

In conclusion, azithromycin-induced liver injury typically occurs within 2–3 weeks of exposure and presents with predominantly hepatocellular pattern of injury and rarely severe cutaneous skin reactions. Liver histology may demonstrate ductopenia and veno-occlusive changes. Two individuals had a severe hypersensitivity cutaneous reaction. Although full recovery occurred in the majority of the cases, chronic DILI and serious outcomes (death and liver transplantation) developed in a minority of patients. Individuals with underlying chronic liver disease may be at higher risk for fatal outcomes from azithromycin induced liver injury, emphasizing that drugs should be prescribed to such patients with care and for good cause.

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Abbreviations

Alk P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
CS	Cholestatic
DILI	Drug-Induced liver injury
DILIN	Drug-Induced Liver Injury Network
FDA	U. S. Food and Drug Administration
HC	Hepatocellular
IQR	Interquartile range
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases

SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
ULN	Upper limit of normal

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Individual Case Histories

Case 4: Acute self-limited cholestatic hepatitis due to azithromycin

A 13-year-old male with no significant past medical history diagnosed with streptococcal pharyngitis was prescribed azithromycin for 5 days. Six days after finishing azithromycin treatment, he developed pruritus on both hands and feet that extended to the rest of the body; this was followed by jaundice and coluria. The patient was noted to have a cholestatic pattern of liver injury; there was no eosinophilia. He denied use of herbal supplements or taking any other medications around the time of onset. BMI was 19.5 kg/m2. Work up for competing etiologies included hepatitis A, B, C, E serologies, ANA and ASMA, all of which were negative. Abdominal imaging was remarkable for a normal liver and splenomegaly.

A liver biopsy performed about 6 weeks after presentation revealed no portal or periportal inflammation; hepatic parenchyma showed diffuse canalicular cholestasis. There were occasional groups of macrophages that marked areas of hepatocyte dropout. Acidophil bodies were not seen. There were scattered eosinophils, but no increase in lymphocytes. Plasma cells were not present. Trichrome and reticulin stains confirmed absence of underlying chronic disease.

The patient was not rechallenged, did not receive steroids, nor required a liver transplant. He was lost to follow up.

Time*	ALT (U/L)	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	INR	Comments
2 w	73	47	411	4.3	n/a	Initial liver tests, R = 1.7
2 w	79	61	395	5.3	0.97	Peak Bilirubin
6 w	223	122	333	3.0	n/a	Around time of liver biopsy
8 w	262	125	311	1.9	1.0	Peak ALT and R-ratio Bilirubin < 50% of Peak value

* time in weeks (w) after azithromycin initiation. Alk P: alkaline phosphatase. n/a: not available.

Comment: This is a typical example of self-limited, mild-to-moderate cholestatic liver injury secondary to Azithromycin. The case was judged as very likely due to azithromycin.

Case 6: Acute toxic epidermal necrolysis with accompanying liver injury due to azithromycin

A 20-year-old African American woman without significant past medical history received a 5-day course of azithromycin for an upper respiratory tract infection. Two days later, she returned to the emergency room with worsening symptoms, new facial swelling, jaundice and a pruritic rash. She was also taking ibuprofen around the time of symptom onset. After evaluation, the patient was admitted to the Intensive Care Unit (ICU) given concern for toxic shock syndrome. The rash was initially limited to the truncal area, but then became generalized and led to blisters over the palms and involvement of mouth and vagina. Laboratory data showed abnormal liver tests with a hepatocellular pattern of injury and no eosinophilia.

Diagnostic evaluation included negative tests for hepatitis A, B, C, E as well as cytomegalovirus, herpes simplex virus, Epstein Barr Virus and human immunodeficiency virus infections, leptospirosis, legionella and Rocky Mountain spotted fever. Serum ANA was positive at a titer of 1:2560; but immunoglobulin levels were normal and anti-double stranded DNA was negative. Liver imaging was unremarkable.

The clinical course was complicated by acute respiratory distress syndrome with multi-system organ dysfunction; Skin biopsy revealed toxic epidermal necrolysis. She received intravenous immunoglobulin (IVIG), methylprednisolone, daptomycin, piperacillin-tazobactam, cefazolin, clindamycin, ceftriaxone and transient extra-corporeal membrane oxygenation during her ICU stay.

A liver biopsy 1 week after presentation revealed central zone cholestasis with intact portal tracts and bile ducts. Repeat liver biopsy because of persistently abnormal liver tests around 12 weeks after initial presentation showed marked lobular cholestasis with hepatocyte injury and prominent sinusoidal debris, evolving ductopenia without significant fibrosis or hepatitis.

At 6^{th} and 24^{th} month follow ups, her liver tests were still abnormal with a cholestatic pattern of injury.

Time*	ALT (IU/L)	AST (IU/L)	Alk P (IU/L)	T. Bili (mg/dL)	INR	Comments
2 d	140	239	71	3.7	1.1	Initial Liver tests
3 d	169	352	35	3.5	1.1	Peak R-ratio
4 d	266	376	69	3.7	3.08	First ALT Peak
1 w	177	163	190	6.1	1.1	Liver biopsy
2 w	50	108	148	8.0	n/a	
3 w	172	181	718	15.9	n/a	Peak Alk P
4 w	237	230	522	20.0	n/a	Peak Bilirubin
6 w	175	152	323	13.4	1.1	Alk P < 50% of Peak value
8 w	410	333	557	16.0	1.1	
12 w	1351	1074	345	11.6	1.1	Second Peak ALT
12 w	586	276	286	10.3	1.0	ALT < 50% of 2nd peak value
16 w	237	171	252	9.4	n/a	Bilirubin < 50% of peak value
12 m	311	227	406	1.3	1.0	

* time in days (d), weeks (w) or months (m) after azithromycin initiation. Alk P: alkaline phosphatase. n/a: not available.

Comment: This patient developed a severe cutaneous reaction to azithromycin accompanied by an acute hepatitis with jaundice that evolved into a cholestatic pattern of injury and prolonged jaundiced followed by persistence of abnormal liver tests 1 year after initial onset. This case was judged to be very likely (2) due to azithromycin.

Case 16: Acute hepatocellular injury after a short course of azithromycin with evidence of persisting chronic injury 1 and 2 years later

A 61-year-old non-Hispanic white man received a 5-day course of azithromycin for an upper respiratory tract infection. His other medical problems included diabetes mellitus, obesity and hyperlipidemia. Three days after azithromycin was stopped, he developed nausea, vomiting, generalized fatigue, myalgias and arthralgias. Two weeks later he sought medical care and was found to be jaundiced with marked elevations in serum aminotransferase levels (Table). He denied a known history of liver disease, alcohol intake or use of herbal supplements around the time of onset. Other medications included repaglinide, hydrochlorothiazide/triamterene, insulin, esomeprazole, metoprolol and acetaminophen (<2.5 grams of acetaminophen daily). Work up for competing etiologies included hepatitis A, B, C and E serologies, ANA and ASMA, all of which were negative. Liver ultrasound was remarkable for hepatomegaly and steatosis. A Computerized tomography (CT) scan of the abdomen revealed ascites, mild splenomegaly and mild hepatomegaly.

A liver biopsy was performed 11 months later given persistent of abnormal liver tests; the findings of the liver biopsy were cirrhosis with features suggesting underlying steatohepatitis (NASH) and scattered eosinophils. It was considered that patient had underlying non-alcoholic fatty liver disease and this may have had accentuated the presentation of drug induced liver injury from azithromycin

The patient was not rechallenged, did not receive steroids, nor has required a liver transplant.

Time*	ALT (U/L)	AST (U/L)	Alk P (U/L)	T.Bili (mg/dL)	INR	Comments
2 w	1492	2359	n/a	6.7	n/a	Initial Liver tests
3 w	4064	4852	473	9.5	n/a	Peak ALT and Alk P; R =16
4 w	425	209	351	19.1	1.2	ALT, Alk P, < 50% of peak values
5 w	80	96	279	20.2	n/a	Peak Bilirubin
8 w	42	75	234	9.3	1.2	Bilirubin < 50% of peak value
12 w	23	44	249	3.8	1.1	
20 w	32	41	238	1.8	1.1	
24 w	34	44	233	1.3	1.1	
11 m	33	36	182	1.3	n/a	Liver Biopsy
16 m	41	47	195	1.6	1.1	
24 m	32	49	168	0.8	n/a	

* time in weeks (w) or months (m) after azithromycin initiation. Alk P: alkaline phosphatase. n/a: not available.

Comment: This patient developed an acute hepatitis-like syndrome due to azithromycin with a short latency period and prolonged course. Imaging suggests that he had a pre-existing cirrhosis probably due to nonalcoholic steatohepatitis and presented with an “acute-on-chronic” clinical onset and had residual evidence of liver injury 1 and 2 years later. This case was judged as being very likely (2) due to azithromycin.

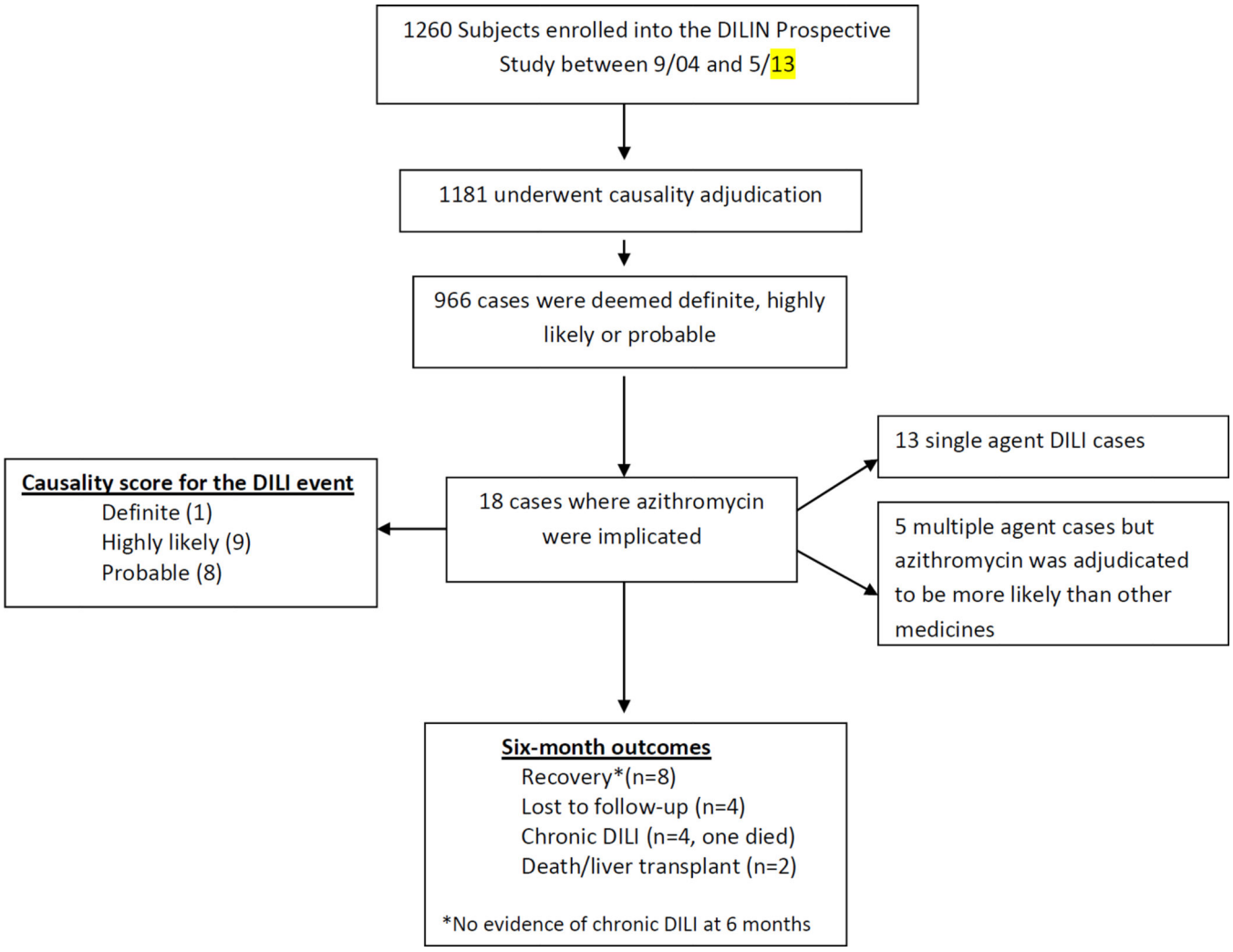

Figure 1.

Study flow describing number of azithromycin cases and their salient characteristics among all cases enrolled into the DILIN Prospective Study

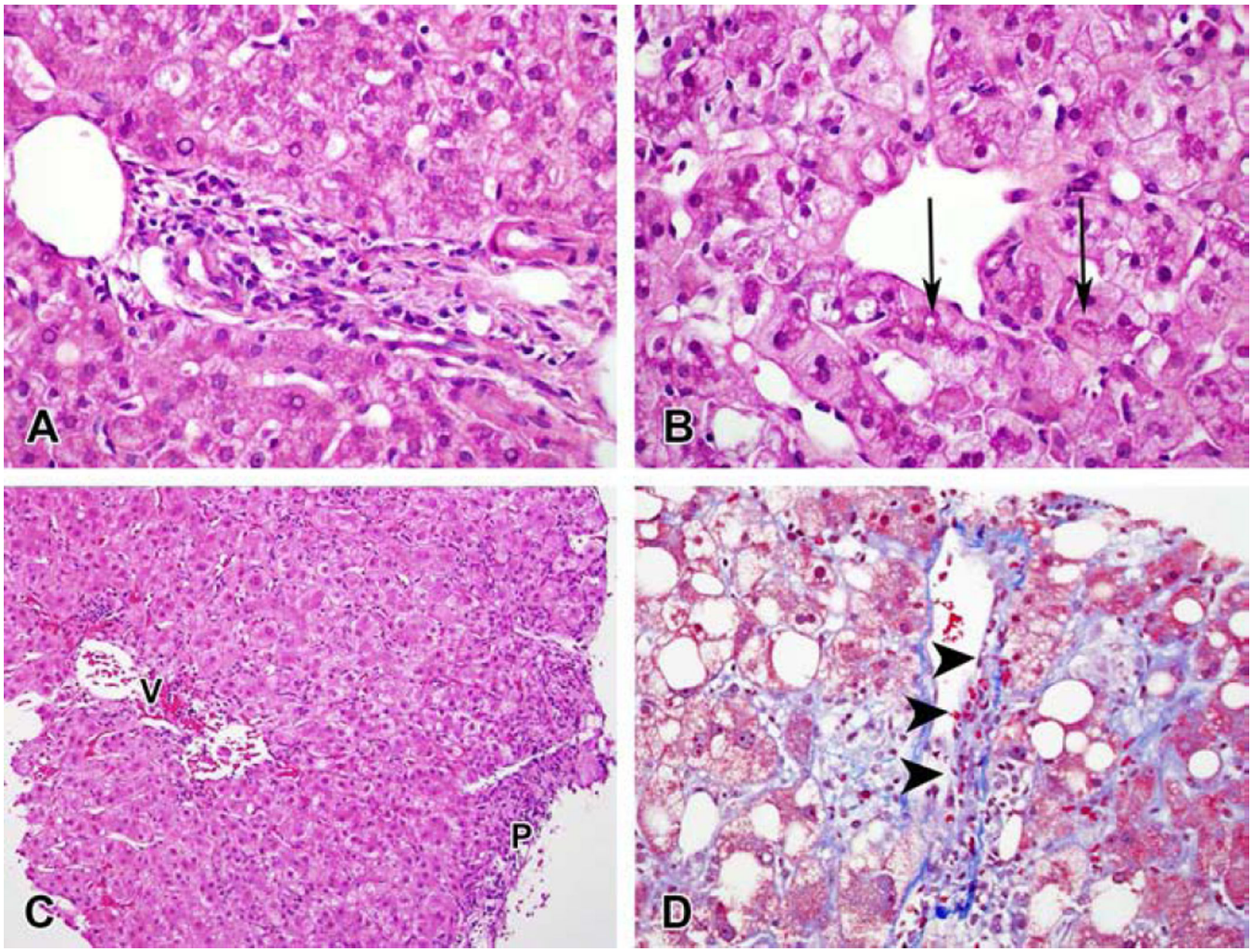

Figure 2.

Liver histology in patients with azithromycin hepatotoxicity. A. (Patient 3) An 11 year old Caucasian female with azithromycin hepatotoxicity underwent a liver biopsy at 20 days after DILI onset. Ductopenic portal area with mild inflammation. B. Zone 3 cholestasis with both hepatocellular and canalicular (arrows) bile accumulation. (A and B taken from the same case, both H&E, 600×). C. (Patient 11) A 45 year old Caucasian male with azithromycin hepatotoxicity underwent a liver biopsy at day 139 after DILI onset. Chronic hepatitis with perivenular inflammation and hemorrhage. (P – Portal area; V – Vein; H&E 200×). D. (Patient 10) Mild veno-occlusive changes. There is a layer of fibroinflammatory tissue inside the vein (arrowheads). (Masson trichrome, 600×).

Table 1

Demographic and clinical characteristics of individuals with Azithromycin induced liver injury (N=18)

Characteristic	Azithromycin induced liver injury (N=18)
Age (years)	37 (1.7, 76.1)
Female, n (%)	13 (72.2)
Self-reported race, n (%)	
Caucasian	17 (94.4)
Black	1 (5.6)
Hispanic, n (%)	2 (11.1)
BMI (kg/m2)	25.2 (13.2, 42.4)
Latency [median (25th, 75th)]	
Drug start to onset of symptoms	17 (1,58)
Drug start to DILI onset	21 (2, 65)
Drug stop to DILI onset	17 (1, 57)
Types of Liver Injury at Onset	
Cholestatic	6 (33)
Mixed	2 (11)
Hepatocellular	10 (56)
Signs and Symptoms, n (%)	
Jaundice	16 (89)
Abdominal pain	12 (67)
Nausea	11 (61)
Pruritus	10 (56)
Rash$^{€}$	6 (33)
Fever	5 (28)
Recovery of total bilirubin in those peak ≥ 2.5mg/dL [median (25th, 75th)]	
Days from peak to 50% reduction in total bilirubin	12 (8, 27)
Days from peak to total bilirubin <2.5 mg/dL	35 (25, 46)
Days from peak to 50% reduction in total bilirubin (non-chronic subjects)	12 (7,26)
Progression to chronicity, n (%)	4 (28.6)
Death from liver disease, n (%)	1 (5.6)
Liver transplant, n (%)	1 (5.6)

All values are expressed as mean with range unless otherwise specified. BMI: Body mass index.

$^{€}$One case of toxic epidermal necrolysis and another of Stevens Johnson#x02019;s syndrome.

Table 2

Pattern of liver injury with clinical outcomes of each individual in the study cohort (N=18). Pattern of liver injury was defined based on R-ratio calculated at the onset of liver injury.

Patient	Age (Yrs) / Gender	Pattern at onset	Latency (Days)	Peak Serum			DILIN Causality Score	DILIN Severity Score	6-month Outcome	Comments
				ALT (U/L)	AlkP (U/L)	T.Bili (mg/L)				
1	1.7[¶] / F	Chol	24	61	1177	10	2	2+	Chronic DILI	
2	8 / F	Mixed	2	293	326	4	2	2+	NA	Previous azithromycin exposure and biliary atresia
3*	11 / F	HC	65	418	1112	13	3	4+	Chronic DILI	SJS
4	13 / M	Chol	15	262	411	5.3	2	3+	NA	
5	19 / M	Chol	7	198	313	9	1	3+	NA	
6	20 / F	HC	3	1351	718	20	2 [2]	4+	Chronic DILI	TEN, ANA 1:2560 and other med: Ibuprofen
7	22 / F	HC	20	15065	141	4	3	4+	Recovered	Previous azithromycin
8	25 / F	Mixed	38	638	501	10	3	2+	NA	Previous azithromycin
9	34 / F	HC	25	1192	136	6	2 [3]	3+	Recovered	Other meds: MRC-6, Drospirenone, and ethinyl estradiol
10	43 / F	Chol	19	178	286	10	2 [3]	3+	Recovered	NAFLD and other med – TMP/SMZ
11	45 / M	HC	22	3742	173	10	3	2+	Chronic DILI	Previous azithromycin
12	47 / F	Chol	33	239	1406	11	2	3+	Recovered	GVHD with secondary iron overload Previous azithromycin
13	53 / F	HC	35	967	272	22	3 [3]	4+	Recovered	Previous azithromycin, SMA 1:80 and other med: TMP
14	54 / F	HC	15	843	155	9	3	3+	Recovered	SMA 1:1280
15	60 / F	HC	13	1579	177	30	3	5+	Transplant	Underlying NAFLD and SMA 1:40
16	60 / M	HC	19	4064	473	20	2	4+	Recovered	
17	65 / F	Chol	10	40	610	1	2 [2]	1+	Recovered	Other med – TMP/SMZ
18	76 / M	HC	16	8787	135	14	3	5+	Death	Alcoholic liver disease

Abbreviations: NA: 6-month follow up data not available; HC: hepatocellular; Chol: cholestatic; ALT: Alanine aminotransferase; Alk P: alkaline phosphatase; TEN: Toxic epidermal necrolysis; SJS: Stevens-Johnson syndrome; Other meds: Other medication(s); TMP/SMZ: Trimethoprim-Sulfamethoxazole; TMP: Trimethoprim; NAFLD: Non-alcoholic fatty liver disease; GVHD: Graft vs. Host disease.The DILIN causality score is the overall score, in brackets the final azithromycin causality score for cases with multiple drugs implicated.

[¶]This child was enrolled as an exception case as she was not 2 year old at the time of enrollment.

[*]This child died subsequently due to respiratory failure. The strength of causal association between the implicated agent(s) and the liver injury event is graded as definite (1), highly likely (2) and probable (3) using the DILIN causality scoring system. A DILIN severity score is assigned for each case that ranges from 1 (mild as defined by serum enzyme elevations with bilirubin <2.5 mg/dL and INR <1.5), 2

(moderate, serum enzyme elevations and bilirubin ≥2.5 mg/dL or INR ≥1.5), 3 (moderate-hospitalized, serum enzyme elevations, bilirubin ≥2.5 mg/dL or INR ≥1.5 and hospitalization for liver injury), 4 (severe, bilirubin ≥2.5 mg/dL and signs of hepatic failure such as INR ≥1.5, ascites or hepatic encephalopathy), and 5 (liver transplantation within 6 months of onset or death due to liver injury).[22]