Published in final edited form as:
Clin Gastroenterol Hepatol. 2011 June ; 9(6): 517–523.e3. doi:10.1016/j.cgh.2011.02.019.

Clinical and Histopathologic Features of Fluoroquinolone-Induced Liver Injury

Eric S. Orman, MD[1], **Hari S. Conjeevaram, MD**[2], **Raj Vuppalanchi, MD**[3], **James W. Freston, MD**[4], **James Rochon, PhD**[5], **David E. Kleiner, MD, PhD**[6], and **Paul H. Hayashi, MD, MPH**[1] **for the DILIN Research Group**

[1] Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina [2] Division of Gastroenterology, University of Michigan, Ann Arbor, Michigan [3] Division of Gastroenterology, Indiana University School of Medicine, Indianapolis, Indiana [4] Division of Gastroenterology, University of Connecticut Health Sciences Center, Farmington, Connecticut [5] Duke Clinical Research Institute, Duke University, Durham, North Carolina [6] Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Abstract

Background & Aims—Fluoroquinolone-induced liver injury is rare; no prospective studies of well-characterized case series have been published. We studied patients with fluoroquinolone-induced hepatoxicity, using data from the Drug-Induced Liver Injury Network (DILIN) to characterize injury patterns, outcomes, and associated features.

Methods—We identified subjects with fluoroquinolone hepatotoxicity who enrolled in the DILIN from September 2004 to January 2010. Demographic, clinical, and laboratory data were analyzed by descriptive statistical methods.

Results—Of the 679 registrants in the DILIN prospective study, 12 had hepatoxicity from fluoroquinolones (6 ciprofloxacin, 4 moxifloxacin, 1 levofloxacin, and 1 gatifloxacin). Seven were women; the median age was 57 years (range 23–80 years), and the median time from the start of fluoroquinolone therapy to symptoms was only 4 days (range 1–39 days). Nine cases developed symptoms on medication (2, 8, and 32 days after they stopped the medication, 3 patients each). Cases were equally distributed among hepatocellular injury (predominantly increased levels of alanine aminotransferase), cholestatic injury (predominantly increased levels of alkaline phosphatase [AP]), and both. Seven cases had immunoallergic features. Patients with mixed

Corresponding author: Paul H. Hayashi, MD, MPH, UNC Liver Program, Division of Gastroenterology & Hepatology, CB# 7584 Burnett-Womack Bldg., Room 8011, Chapel Hill, NC 27599-7584, Phone 919-966-2516, Fax 919-966-1700, paul_hayashi@med.unc.edu.

Disclosures: The authors have no financial, professional or personal disclosures.

Author Contributions: ES Orman, MD: Study design, literature searches, analysis and interpretation of data, drafting of manuscript.
HS Conjeevaram, MD: Analysis and interpretation of data, drafting of manuscript.
R Vuppalanchi, MD: Analysis and interpretation of data, drafting of manuscript
JW Freston, MD: Analysis and interpretation of data, drafting of manuscript
J Rochon, PhD: Acquisition, analysis and interpretation of data
DE Kleiner, MD, PhD: Acquisition, analysis and interpretation of histologic data, drafting of manuscript
PH Hayashi MD, MPH: Study design, literature searches, analysis and interpretation of data, drafting of manuscript.

hepatocellular and cholestatic injury had mild disease without jaundice—all recovered. In contrast, 2 of 4 patients with hepatocellular injury and jaundice died, 1 of acute liver failure. One patient with cholestatic injury developed vanishing bile duct syndrome and required liver transplantation; another had a persistently increased serum level of AP.

Conclusions—Fluoroquinolone liver injury is rapid in onset and often has immunoallergic features, indicating a hypersensitivity reaction. The pattern of injury is can be hepatocellular, cholestatic, or mixed—mixed cases are the least severe. Acute and chronic liver failure can occur.

Keywords

ALT; drug toxicity; side effect; antibiotics; adverse reaction

INTRODUCTION

Fluoroquinolones are among the most widely prescribed antibiotics. They are popular because of their high oral bioavailability, ease of dosing and broad antimicrobial coverage.(1–5) They have been recommended as empiric antibiotic therapy in national guidelines.(6, 7) Severe side effects from the fluoroquinolones are uncommon, but include tendon rupture, hemolytic uremic syndome, Stevens-Johnson syndrome, interstitial nephritis, arrhythmias, and drug-induced liver injury (DILI).(8–12) In a recent publication of DILI from the United States, the fluoroquinolones were among the most common causes of idiosyncratic acute liver injury.(9) Fatal instances of hepatic injury from fluoroquinolones have been described. Although there have been multiple case reports of hepatotoxicity from the fluoroquinolones, there have been no larger reports even from large referral centers.(13–31) An exception is trovafloxacin, a third generation fluoroquinolone, which was the subject of an FDA public health advisory (32) and was subsequently withdrawn from the market as a result of numerous cases of liver injury.(33–35)

In 2003, the NIDDK established the Drug-Induced Liver Injury Network (DILIN) (36) to gather and characterize cases of DILI both prospectively (all herbals and medications except acetaminophen) and retrospectively for selected medications. The DILIN registry continues to enroll across 8 geographically dispersed U.S. centers. Subjects are interviewed for clinical information, and blood samples are collected with the aim of identifying genetic and other biochemical markers that may increase our understanding, diagnosis, and treatment of drug-induced liver injury. The study design and methods have been reported (37) as have results of the first 300 cases.(9) In this report, we describe our prospectively enrolled subjects with fluoroquinolone hepatoxicity to report pattern of injury, associated features, follow-up and outcome.

METHODS

Overall Design

The study design of the DILIN prospective study has been described.(9, 37) Briefly, patients aged 2 or older were enrolled on the basis of clinical suspicion of liver injury due to a medication or herbal product within 6 months of clinical onset. Inclusion criteria included aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels > 5 times the upper limit of normal (ULN) (or pretreatment baseline if abnormal) on 2 consecutive occasions, or alkaline phosphatase (AP) levels > twice the ULN (or pretreatment baseline if abnormal) on 2 consecutive occasions, or total serum bilirubin > 2.5 mg/dL (with elevated AST, ALT, or AP), or international normalized ratio (INR) > 1.5 (with elevated AST, ALT, or AP). A variety of tests are obtained at enrollment including serologies for acute hepatitis A, B, CMV and EBV. Hepatitis C antibody tests are also obtained with confirmatory HCV

RNA as necessary. Autoimmune markers (ANA, ASMA, AMA) and abdominal imaging (ultrasound, CT or MRI) are also required. Patients with suspected acetaminophen hepatotoxicity were excluded as were those with a liver or bone marrow transplant. Patients with chronic hepatitis B or C or with nonalcoholic fatty liver disease were eligible for enrollment, but those with other chronic liver diseases (such as alcoholic, autoimmune or genetic liver diseases) were excluded.

Enrolled patients were seen for a baseline study visit at which time a detailed history was obtained by a DILIN investigator, and clinical, laboratory, and imaging results were extracted from the chart. These enrollment visits often took place days or weeks (up to 24 weeks) after initial clinical presentation. Further laboratory testing to exclude other causes of liver injury were obtained and serum, plasma, urine and DNA specimens were collected for future mechanistic studies. Attempts were made to follow all subjects for at least 6 months after enrollment and those with persistent liver-related abnormalities were asked to return at 12 and 24 months.

Causality

The method for assigning causality has been described in detail.(38) Each case was evaluated by 3 hepatologists including the site investigator who enrolled the case. Each evaluator independently assigned a subjective score representing percentage likelihood of attribution in which 1 = definite or > 95% likelihood, 2 = very likely or 75–95%, 3 = probable or 50–74%, 4 = possible or 25–49%, and 5 = unlikely or < 25%. When there were discrepancies, a consensus score was achieved after e-mail or conference call discussions. Cases which were still in disagreement were voted upon by one member from each center with the final score assigned by majority vote.(37, 39–41)

Participants

This study was based upon all subjects that had a fluoroquinolone suspected of causing DILI prospectively enrolled and adjudicated by February 2010. The analysis was limited to cases that were considered definite or highly likely. Cases considered probable were included only if no other agent was implicated or suspected (i.e. single-agent case).

Data and Outcomes

Demographic, clinical history and laboratory results entered into the database were analyzed with special attention to time course of DILI, latency, severity, type of reaction, associated symptoms, resolution, chronic enzyme elevation, need for transplant and death. The pattern of hepatic injury was categorized as hepatocellular, cholestatic, or mixed based upon the R-ratio of serum ALT and AP elevation (39): R-ratio = [ALT value/ALT upper limit of normal]/[AP value/AP upper limit of normal]. R-ratios of > 5 were considered hepatocellular, < 2 cholestatic, and 2–5 mixed.(39) Standard descriptive statistics were applied to continuous variables.

Liver biopsy was not required for enrollment in DILIN. Biopsies done for clinical management were obtained and evaluated in a standardized fashion by the DILIN liver histopathologist (DEK). Instructive histology from this cohort were chosen for this report.

Role of Funding Source and Institutional Board Review (IRB)

The DILIN Network is structured as a U01 cooperative agreement with funds provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Separate IRB approvals were obtained at each participating DILIN center.

RESULTS

Subjects

Among 679 cases enrolled in the DILIN database which had undergone causality assessment by February 2010, fluoroquinolones were listed as a potential cause in 30. In 15 cases the fluoroquinolone was the *only* implicated drug, of which 3 were considered definite, 4 very likely, 3 probable, and 5 were considered only possible or unlikely. Only the 10 single drug cases that were considered definite, very likely or probable were included in this study. Among the other 15 cases in which fluoroquinolones were one of several implicated agents, none were considered definite and 2 were considered very likely with the other competing drugs scoring only possible (metronidazole) or unlikely (amoxicillin/clavulanate). Only these two cases that were considered very likely due to the fluoroquinolone were included in the study bringing the total to 12. Thus, 12 of the 30 cases met all inclusion criteria, with 6 due to ciprofloxacin, 4 moxifloxacin, 1 levofloxacin, and 1 gatifloxicin.

Clinical Characteristics and Onset of Injury

Characteristics of the 12 cases are shown in Table 1. All were adults, and all except one were over 30 years of age. The median age was 57 years, and 7 were women. Jaundice, nausea and abdominal pain were frequent presenting symptoms. Overall, the time to liver injury was short and the onset abrupt. Median time from starting the medication to earliest sign or symptom of DILI was 4 days (range 1 to 39 days) and median time to documented onset (abnormal liver tests) was 8.5 days (range 1 to 41 days). Median time to either was only 2.5 days. Nine of the patients developed symptoms while still taking the antibiotic; the remaining 3 became symptomatic 2, 8, and 32 days after stopping the fluoroquinolone. Two patients had pre-existing nonalcoholic fatty liver disease (NAFLD), but no patient had chronic hepatitis B or C. Diabetes and heart disease were common, 5/12 (42%) and 4/12 (33%) respectively.

Patterns of Injury

Patterns of injury by enrollment R-ratio and peak enzymes and bilirubin are shown in Table 2. All patients were symptomatic, 7 developed jaundice (defined as total serum bilirubin > 2.5 mg/dL), 8 were hospitalized for the DILI, 3 developed symptoms or signs of hepatic or other organ failure, one ultimately required liver transplantation, and one died of liver failure. The patterns of enzyme elevations were evenly distributed among cholestatic (n=4), hepatocellular (n=4) and mixed (n=4) categories. The pattern of injury by calculated R-ratio tended to remain constant during the acute course and the peak of illness, although a few transitioned becoming more cholestatic during follow up. Mixed cases tended to have less severe injury with lower bilirubin, ALT and AP levels. Cases with predominantly hepatocellular injury were often severe; 2 of the 4 cases resulted in death within 6 months (one known to be due to acute liver failure and the second due to death at home, not fully explained by acute liver failure). The 4 cholestatic cases did not result in death, but two developed chronic injury, one with histologically verified vanishing bile duct syndrome requiring liver transplantation 1 year after presentation. The other had persistent elevations in serum AP (200 U/L) without jaundice or pruritus 17 months after the injury. One other patient with a cholestatic pattern of injury recovered to normal liver enzymes by 206 days. The fourth case had falling liver enzymes (peak AP 837 down to 538 U/L, peak ALT 823 to 67 U/L) by 40 days post-injury, but thereafter he was lost to follow-up. In contrast, patients with a mixed pattern of serum enzyme elevations tended to have less severe injury with lower peak bilirubin (none were jaundiced), AP and ALT levels and shorter time from enzyme elevation to return to normal (37 to 81 days).

Three representative cases are shown in the Figures 1, a-c. Figure 1a shows the course of serum enzyme and bilirubin levels in a patient with a hepatocellular pattern of injury (Case 12 in Table 2) occurring 18 days after starting ciprofloxacin. She developed acute liver failure but was not a suitable transplant candidate at age 80 with multiple co-morbidities. She was transferred to hospice care and died 4 weeks after initial elevation of ALT. Figure 1b shows a patient with a mixed pattern of enzyme elevation and self-limiting course (Case 7 in Table 2), arising 7 days after starting a course of levofloxacin with near complete and complete resolution at 4 and 8 weeks, respectively. Figure 1c shows a patient with a cholestatic pattern of serum enzyme elevations and prolonged, severe cholestasis arising 8 days after starting a course of moxifloxacin (Case 3 in Table 2). She developed prolonged jaundice (1.3 years) ultimately leading to hepatic failure and liver transplantation with histology of the explanted liver showing vanishing bile duct syndrome (Figure 2d).

Immunoallergic Features and Other Drug Allergies (Table 3)

Seven of the 12 had fever, rash and/or eosinophilia. Three patients had a positive ANA or ASMA without other immunoallergic features. Since patients were enrolled up to 24 weeks after the event, transient eosinophilia at the time of onset may have been missed. Fever was reported more often in cholestatic pattern of injury. Rash occurred in patients with both high and low R-ratios, but not in cases with a mixed pattern of enzyme elevations. Hypersenstivity pneumonitis, Stevens-Johnson Syndrome and bone marrow suppression were also seen. Seven of 12 patients had a history of allergy to other medications including one patient who had separate hepatoxicity events after taking two different fluoroquinolones.

Histology

Liver tissue was available for central review in 5 cases: four needle biopsies obtained during the DILI episode and one explant. Three of the needle biopsies were from patients with a predominantly hepatocellular biochemical injury. Two of these showed acute hepatitis with lobular disarray and severe portal and lobular inflammation (Fig. 2a). One of these two had striking hepatocyte giant cell transformation. The third case showed a mixed pattern of injury with zone 3 coagulative necrosis and a distribution of inflammation reminiscent of chronic hepatitis. In this case there was less lobular inflammation and no disarray, but dense portal inflammation and interface hepatitis were present in most portal areas. Although all three of these patients had jaundice, there was little-to-no cholestasis or duct injury on biopsy. Two of the cases, including a needle biopsy and the explant, were from patients with cholestatic presentations (Fig 2b–d). The needle biopsy showed a cholestatic hepatitis with mild intrahepatic cholestasis and mild to moderate portal and lobular inflammation (Fig. 2b–c). As noted above, the explant showed severe ductopenia and only mild inflammation (Fig. 2d). By the time of transplant most of the hepatocyte parenchyma had been replaced by a ductular reaction embedded in dense fibrosis. Although these cases showed diverse patterns of injury histologically, all four of the needle biopsies showed increased numbers of eosinophils. Two (one hepatocellular and one cholestatic) showed increased numbers of plasma cells in the infiltrate.

DISCUSSION

Hepatotoxicity from fluoroquinolones has been described in multiple case reports and summarized in several reviews. However there are no well-characterized and prospectively followed groups of cases published on hepatic injury from this important class of antibiotics. The 12 cases presented here confirm that hepatic injury from the fluoroquinolones has a “class effect” and the clinical presentation and phenotype of injury is similar with the different agents. The predominant feature of the hepatic injury was the short latency (median

2 to 9 days) and abrupt onset of injury (Table 1). Nine of our 12 cases developed symptoms while still taking the antibiotic. Immunoallergic features (rash, fever and eosinophilia) were common (Table 3), but rarely as prominent as occurs with hepatotoxicity from sulfonamides, macrolides, or aromatic anticonvulsants. Only one of the 12 patients had "DRESS syndrome" (drug rash with eosinophilia and systemic symptoms), a 45 year old patient who developed Stevens-Johnson syndrome 7 days after starting a 10 day course of ciprofloxacin. Six other patients had fever or rash, but eosinophilia was uncommon, perhaps because the pattern of referral of patients to DILIN often resulted in a delay of a few weeks before enrollment (by which time the eosinophil count might have normalized). Immunoallergic features have been described in several case reports of fluoroquinolone hepatotoxicity.(15, 21, 27, 30, 31)

The pattern of enzyme elevations described here varied greatly. Indeed, the full range of clinical patterns was seen from very cholestatic cases with high AP (603 U/L) and high bilirubin (33.4 mg/dL) that led to prolonged jaundice and vanishing bile duct syndrome (Case 3, Table 2 and Figure 2d;), to obvious hepatocellular injury with high ALT (1684 U/L) that led rapidly to hepatic failure and death (Case 12, Table 2 and Figure 2a). In between these extremes were 6 cases without jaundice, 4 of which had a "mixed" pattern of serum enzyme elevations and a self-limited, benign course (Cases 5–8, Table 2).

The pathophysiology of fluoroquinolone hepatotoxicity is not known. The short latency, frequent immunoallergic features, heightened injury that has been described upon re-exposure, and the lack of a common pattern of metabolism of the various fluoroquinolones argue for a hypersensitivity reaction.(42) All four of our subjects with available liver histology showed increased eosinophils and two had increased plasma cells. It has been postulated that the trifluorinated quiniolones with their 1-(2,4)-difluorophenyl group may carry an even greater risk for severe immune-mediated toxicities (e.g. temafloxacin syndrome and trovafloxacin hepatotoxicity).(8) Interestingly, one half of our cases had a history of allergies to non-fluoroquinolone medications suggesting increased susceptibility in such individuals (Table 3). The immunoallergic phenotype makes it advisable for patients with hepatotoxicity from one fluorquiniolone to avoid this class of antibiotic altogether.(43) Indeed, one of our cases (Case 8, Table 3), had repeated reactions to two different fluoroquinolones prescribed for recurrent diverticulitis. She was enrolled during a reaction to ciprofloxacin. On follow-up, she had yet another reaction when she was given levofloxacin (ALT up 1680 IU/L).

While our study is small, the cases were prospectively enrolled, and followed under protocol. Therefore the quality of data on our subjects is likely higher than the average case reports in the literature. In fact, our 12 cases contained the vast majority (>95%) of the 19 "Minimal Elements" suggested for DILI case reporting (Supplement Table 1).(44) Only 5 of the 12 had had no liver tests checked prior to initiation of the fluoroquinolone and 6 did not require a liver biopsy.

Attribution was made by expert opinion process, the gold standard for assigning DILI causality. While we set out to enroll cases of at least probable attribution, the majority of our qualifying cases actually had scored better than probable. In the DILIN, definite cases have no other remotely possible causes and a pattern of injury that is stereotypic for the agent based on previously described reports or papers in the literature. Thus the bar for being considered definite (>95% likelihood) is high. Very likely cases also have high attribution, but do not quite meet definite criteria. Therefore, 9 of 12 (75%) cases were highly attributable to the fluoroquinolone scoring definite or very likely. Cases 5 and 12 were the only two with competing agents and both were considered to be very likely due to the fluoroquinolone. In case 5, amoxicillin/clavulanate was taken for just one day starting the

day of the reaction and was therefore deemed an unlikely culprit. Metronidazole was a competing agent in case 12 and was deemed only possible based on its low risk for DILI. The three probable cases had no other competing agents.

Of the 7 fluoroquinolones that were available in the United States during the study period, 4 (ciprofloxacin, levofloxacin, moxifloxicin, and gatifloxacin) were represented in our study. Gatifloxacin has since been withdrawn from the market due to problems with glucose homeostasis. While our study did not include ofloxacin and norfloxacin, each has been reported to cause hepatoxicity with similar injury patterns to those described here. (27, 45–48) There are no cases of gemifloxicin hepatotoxicity reported, but it is relatively new and animal studies suggest its potential to cause liver injury as well.(49) In addition, there are several other fluoroquinolones available outside the US (Supplement Table 2), but little is known about their risk for hepatotoxicity.

Estimates of hepatotoxicity incidence are hampered by biases and poor quality of reporting. Package insert information suggests asymptomatic, mild and reversible elevations in liver enzymes may occur in 2–3% of patients taking fluoroquinolones, (50) while a population-based study from England suggested that the incidence of illness due to hepatotoxicity is 0.54 per 10,000 persons taking ciprofloxacin.(51) Estimate of “acute liver injury” from all fluoroquinolones in Sweden is 0.7 per 100,000 users.(4) The predominance of ciprofloxacin in our study probably reflected market share more than increased risk, but moxifloxacin (incriminated in 4 cases) was probably over-represented. From 1996 to 2001, the number of prescriptions written in the US was 66 million for ciprofloxacin, 24 million for levofloxacin, 3 million for gatifloxacin and 1 million for moxifloxacin.(50)

Acute liver *failure* rates are also difficult to ascertain, but estimates are quite low. From 2008 pharmacy data in the United States, levofloxacin, moxifloxacin and gatifloxacin have similar rates of acute liver failure: 2.1, 6.6 and 6.1 cases per 10 million prescriptions, respectively.(4) In contrast, trovafloxacin, which was withdrawn from use in the United States in 1999 for hepatotoxicity, had a higher estimated rate of 58 per 10 million prescriptions. By comparison, amoxicillin-clavulanate has a rate of 10 per 10 million.(4)

While rare, it is important to stress that liver injury from the fluoroquinolones can be severe causing prolonged jaundice, morbidity and acute and chronic liver failure resulting in death or transplant. Patients with fluoroquinolone-induced liver injury should be cautioned to avoid re-exposure to other fluoroquinolones in the future and be informed that some brand names do not intuitively imply the fluoroqinolone class (e.g. Avelox, Factive, Cravit). Since there are no established means of preventing hepatotoxicity from the fluoroquinolones, it is important to prescribe them for clear clinical indications only and to take a careful history of drug allergies. Therapies for DILI are limited. Patients with prominent features of hypersensitivity may improve with use of corticosteroids, but these agents should not be used in cases without these features. N-acetylcysteine has been shown to improve “transplant-free survival” in patients with non-acetominophen acute liver failure, particularly those with drug-induced liver injury with early hepatic encephalopathy.(52) Finally, all cases of drug-induced liver injury should be reported to national registries whenever possible. In the United States, cases are reported to the FDA through MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm).

Thus, fluoroquinolones are highly effective and widely used antibiotics that rarely cause clinical hepatotoxicity and even more rarely cause life-threatening liver injury. The clinical phenotype of hepatotoxicity appears to be shared by all of the fluoroquinolones and is characterized usually by a short period of latency and abrupt onset with features of hypersensitivity. Some fluoroquinolones may carry a higher risk than others. Most patients

with fluoroquinolone-associated hepatotoxicity recover, but the period of illness can be prolonged, can result in hepatic failure and death or need for liver transplantation. Ultimately, prevention and management of fluoroquinolone hepatotoxicity will require a better understanding of its pathogenesis which provides the rationale for collection of well-characterized cases of this rare condition for metabolic, immunologic and genetic study: the primary aim of the DILIN network.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: The DILIN Network is structured as a U01 cooperative agreement with funds provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under grants: 2U01-DK065176-06 (Duke), 2U01-DK065201-06 (UNC), 2U01-DK065184-06 (Michigan), 2U01-DK065211-06 (Indiana), 5U01DK065193-04 (UConn), 5U01-DK065238-08 (UCSF/CPMC), 1U01-DK083023-01 (UTSW), 1U01-DK083027-01 (TJH/UPenn), 1U01-DK082992-01 (Mayo), 1U01-DK083020-01 (USC). Additional funding is provided by CTSA grants: UL1 RR025761 (Indiana), UL1 RR025747 (UNC), UL1 RR024134 (UPenn), UL1 RR024986 (Michigan), UL1 RR024982 (UTSW), UL1 RR024150 (Mayo) and in part by the Intramural Research Program of the NIH, National Cancer Institute.

A full list of DILIN investigators, co-investigators and staff is shown in Appendix 1 of the supporting information. The authors thank our referring providers and patients for participation in this study. We also thank Jay H. Hoofnagle and Robert J. Fontana for their advice and help in preparing this article.

Abbreviations

DILI	Drug-induced Liver Injury
DILIN	Drug-induced Liver Injury Network
APAP	Acetaminophen
RUCAM	Roussel UCLAF Causality Assessment Method
NIH	National Institutes of Health
AST	aspartate aminotransferase
ALT	alanine aminotransferase
AP	Alkaline phosphatase
ANA	Anti-nuclear antibody
AMA	Anti-mitochondrial antibody
ASMA	anti-smooth muscle antibody
LFTs	Liver Function Tests (AST, ALT, AP, bilirubin)

References

1. Wolfson JS, Hooper DC. Overview of fluoroquinolone safety. Am J Med. 1991; 91(6):153S–161S. [PubMed: 1767803]
2. McCaig LF, Besser RE, Hughes JM. Antimicrobial drug prescription in ambulatory care settings, United States, 1992–2000. Emerging Infect Dis. 2003; 9(4):432–7. [PubMed: 12702222]
3. Bertino J, Fish D. The safety profile of the fluoroquinolones. Clin Ther. 2000; 22(7):798–817. discussion 797; 798–817; discussion 797. [PubMed: 10945507]

4. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. Drug Saf. 2009; 32(5):359–78. [PubMed: 19419232]
5. Kahn JB. Latest industry information on the safety profile of levofloxacin in the US. Chemotherapy. 2001; 47(Suppl 3):32–37. discussion 44–48; 32–37; discussion 44–48. [PubMed: 11549787]
6. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community- acquired pneumonia in adults. Clin Infect Dis. 2007; 44(Suppl 2):S27–72. [PubMed: 17278083]
7. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis. 1999; 29(4):745–58. [PubMed: 10589881]
8. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis. 2005; 41(Suppl 2):S144–157. S144–157. [PubMed: 15942881]
9. Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008; 135(6): 1924, 1934, 1934.e1–4. [PubMed: 18955056]
10. Abboud G, Kaplowitz N. Drug-induced liver injury. Drug Saf. 2007; 30(4):277–94. [PubMed: 17408305]
11. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006; 354(7):731–9. [PubMed: 16481640]
12. Watkins PB, Seeff LB. Drug-induced liver injury: summary of a single topic clinical research conference. Hepatology. 2006; 43(3):618–31. [PubMed: 16496329]
13. Bhagirath KM. A case report of highly suspected ciprofloxacin-induced hepatotoxicity. Turk J Gastroenterol. 2008; 19(3):204–6. [PubMed: 19115163]
14. Coban S, Ceydilek B, Ekiz F, et al. Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. Ann Pharmacother. 2005; 39(10):1737–40. [PubMed: 16105873]
15. Nori S, Nebesio C, Brashear R, Travers JB. Moxifloxacin-associated drug hypersensitivity syndrome with toxic epidermal necrolysis and fulminant hepatic failure. Arch Dermatol. 2004; 140(12):1537–8. [PubMed: 15611441]
16. Zimpfer A, Propst A, Mikuz G, et al. Ciprofloxacin-induced acute liver injury: case report and review of literature. Virchows Arch. 2004; 444(1):87–9. [PubMed: 14994731]
17. Goetz M, Galle PR, Schwarting A. Non-fatal acute liver injury possibly related to high-dose ciprofloxacin. Eur J Clin Microbiol Infect Dis. 2003; 22(5):294–6. [PubMed: 12739107]
18. Schwalm J, Lee CH. Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. CMAJ. 2003; 168(7):847–8. [PubMed: 12668542]
19. Bataille L, Rahier J, Geubel A. Delayed and prolonged cholestatic hepatitis with ductopenia after long-term ciprofloxacin therapy for Crohn's disease. J Hepatol. 2002; 37(5):696–9. [PubMed: 12399240]
20. Soto S, Lopez-Roses L, Avila S, et al. Moxifloxacin-induced acute liver injury. Am J Gastroenterol. 2002; 97(7):1853–4. [PubMed: 12135060]
21. Contreras MA, Luna R, Mulero J, et al. Severe ciprofloxacin-induced acute hepatitis. Eur J Clin Microbiol Infect Dis. 2001; 20(6):434–5. [PubMed: 11476450]
22. Karim A, Ahmed S, Rossoff LJ, et al. Possible levofloxacin-induced acute hepatocellular injury in a patient with chronic obstructive lung disease. Clin Infect Dis. 2001; 33(12):2088–90. [PubMed: 11712098]
23. Spahr L, Rubbia-Brandt L, Marinescu O, et al. Acute fatal hepatitis related to levofloxacin. J Hepatol. 2001; 35(2):308–9. [PubMed: 11580158]
24. Labowitz JK, Silverman WB. Cholestatic jaundice induced by ciprofloxacin. Dig Dis Sci. 1997; 42(1):192–4. [PubMed: 9009137]
25. Aggarwal A, Gurka J. Probable ciprofloxacin induced cholestasis. Aust N Z J Med. 1995; 25(5): 541–2. [PubMed: 8588783]

26. Alcalde M, Donoso MS, Carcfa-Diaz M, et al. Liver disfunction due to ciprofloxacin. Acta Gastroenterol Belg. 1995; 58(5–6):475–6. [PubMed: 8776005]
27. Hautekeete ML, Kockx MM, Naegels S, et al. Cholestatic hepatitis related to quinolones: a report of two cases. J Hepatol. 1995; 23(6):759–60. [PubMed: 8750178]
28. Villeneuve JP, Davies C, Cote J. Suspected ciprofloxacin-induced hepatotoxicity. Ann Pharmacother. 1995; 29(3):257–9. [PubMed: 7606070]
29. Fuchs S, Simon Z, Brezis M. Fatal hepatic failure associated with ciprofloxacin. Lancet. 1994; 343(8899):738–9. [PubMed: 7907714]
30. Sherman O, Beizer JL. Possible ciprofloxacin-induced acute cholestatic jaundice. Ann Pharmacother. 1994; 28(10):1162–4. [PubMed: 7841570]
31. Grassmick BK, Lehr VT, Sundareson AS. Fulminant hepatic failure possibly related to ciprofloxacin. Ann Pharmacother. 1992; 26(5):636–9. [PubMed: 1591420]
32. Lumpkin, MM. Trovan (Trovafloxacin/Alatrofloxacin Mesylate). 1999. Jun. 2010 Food and Drug Administration 09.
33. Lazarczyk DA, Goldstein NS, Gordon SC. Trovafloxacin hepatotoxicity. Dig Dis Sci. 2001; 46(4): 925–6. [PubMed: 11330435]
34. Chen HJ, Bloch KJ, Maclean JA. Acute eosinophilic hepatitis from trovafloxacin. N Engl J Med. 2000; 342(5):359–60. [PubMed: 10660405]
35. Lucena MI, Andrade RJ, Rodrigo L, et al. Trovafloxacin-induced acute hepatitis. Clin Infect Dis. 2000; 30(2):400–1. [PubMed: 10671353]
36. Hoofnagle JH. Drug-induced liver injury network (DILIN). Hepatology. 2004; 40(4):773. [PubMed: 15382161]
37. Fontana RJ, Watkins PB, Bonkovsky HL, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf. 2009; 32(1):55–68. [PubMed: 19132805]
38. Rockey DC, Seeff LB, Rochon J, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. Hepatology. 2010; 51(6):2117–26. [PubMed: 20512999]
39. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs--II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol. 1993; 46(11):1331–6. [PubMed: 8229111]
40. Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993; 46(11):1323–30. [PubMed: 8229110]
41. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol. 1990; 11(2):272–6. [PubMed: 2254635]
42. Schmid DA, Campi P, Pichler WJ. Hypersensitivity reactions to quinolones. Curr Pharm Des. 2006; 12(26):3313–26. [PubMed: 17017926]
43. Scherer K, Bircher AJ. Hypersensitivity reactions to fluoroquinolones. Curr Allergy Asthma Rep. 2005; 5(1):15–21. [PubMed: 15659258]
44. Agarwal VK, McHutchison JG, Hoofnagle JH. Drug-Induced Liver Injury Network. Important elements for the diagnosis of drug-induced liver injury. Clin Gastroenterol Hepatol. 2010; 8(5): 463–70. [PubMed: 20170750]
45. Bjornsson E, Olsson R, Remotti H. Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. Am J Gastroenterol. 2000; 95(12):3662–4. [PubMed: 11151924]
46. Davoren P, Mainstone K. Norfloxacin-induced hepatitis. Med J Aust. 1993; 159(6):423–426. [PubMed: 8377697]
47. Lopez-Navidad A, Domingo P, Cadafalch J, et al. Norfloxacin-induced hepatotoxicity. J Hepatol. 1990; 11(2):277–8. [PubMed: 2254636]
48. Romero-Gomez M, Suarez Garcia E, Fernandez MC. Norfloxacin-induced acute cholestatic hepatitis in a patient with alcoholic liver cirrhosis. Am J Gastroenterol. 1999; 94(8):2324–5. [PubMed: 10445586]

49. Bikash R, Kanti SA, Pinaki S, et al. Twenty eight days repeated oral dose toxicity study of gemifloxacin in Wistar albino rats. Regul Toxicol Pharmacol. 2010

50. Iannini PB. The safety profile of moxifloxacin and other fluoroquinolones in special patient populations. Curr Med Res Opin. 2007; 23(6):1403–13. [PubMed: 17559736]

51. Jick SS, Jick H, Dean AD. A follow-up safety study of ciprofloxacin users. Pharmacotherapy. 1993; 13(5):461–4. [PubMed: 8247912]

52. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009; 137(3): 856,64, 864.e1. [PubMed: 19524577]

53. Stahlmann R. Clinical toxicological aspects of fluoroquinolones. Toxicol Lett. 2002; 127(1– 3): 269–77. [PubMed: 12052667]

54. [Accessed June 6, 2010] eMedExpert. http://www.emedexpert.com/lists/antibiotics.shtml#5

Appendix 1

Clinical Centers

Indiana University, Indianapolis, IN

Naga Chalasani, MD (PI), Raj Vuppalanchi, MD (co-I), Jean Molleston, MD (co-I), Lawrence Lumeng, MD (co-I), Audrey Corne (research coordinator), Angie Plummer (research coordinator)

University of Connecticut

Herbert Bonkovsky, MD (PI), Petr Protiva, MD (co-I), James Freston, MD, PhD (co-I), Robert Rosson, MD (co-I), Robert A. Levine, MD (Satellite site investigator), Benedict Maliakkal, MD (Satellite site investigator), Paul Appleton, MD (Research coordinator), Mariola Smialek, RN (research coordinator)

University of Michigan, Ann Arbor, MI

Robert J. Fontana, MD (PI), Hari Conjeevaram, MD (co-I), Rich Moseley, MD, (co-I), Stuart Gordon, MD (Satellite site investigator), Suzanne Welch (Research coordinator), Jessica Worley (Research coordinator), Jordan Kridler (Research coordinator), Sonal Trivedi (Research coordinator), Sweta Kochlar (Research coordinator).

University of North Carolina, Chapel Hill, NC

Paul Watkins, MD (PI), Paul H. Hayashi, MD (co-I), Mark Russo, MD (co-I), Late Harry Guess, MD, PhD (co-investigator), Kimberly Beaver, MD (Satellite site investigator), Alastair Smith, MD (Satellite site investigator), James Lewis, MD (Satellite site investigator), Susan Pusek (Research coordinator), Tracy Russell (Research coordinator), Lorraine Mehltretter, (Administrative assistant).

California Pacific Medical Center, San Francisco, CA

Tim Davern, MD (PI), Maurizo Bonacini, MD (co-I), Kristine Partovi (research coordinator), Katharine Fajardo (Research coordinator), Seaton Tai (Research coordinator)

University of Texas Southwestern Medical Center, Dallas, TX

William Lee, MD (PI), Don Rockey, MD (co-I), Anne Larson (co-I), LaFaine Grant, MD (co-I), Kenni Landgraf, RN (Research Coordinator).

University of Southern California, Los Angeles, CA

Andrew Stoltz, MD (PI), Neil Kaplowitz, MD (co-I), Susan Milstein, RN (Research coordinator)

Mayo Clinic, Rochester, MN

Jayant Talwalker, MD (PI), Stephanie Johnson, RN (Research coordinator)

Jefferson University & University of Pennsylvania, Philadelphia, PA

Victor Navarro, MD (PI), Rajender Reddy, MD (Co-I), Maricruz Vega, MPH, CHES (Research coordinator), Amina Wirjosemito (Research coordinator), Kristina Evans, MPH (Research coordinator)

Data Coordinating Center

Duke Clinical Research Institute

James Rochon, MD (PI), John McHutchison, MD (co-I), Hans Tilllmann, MD (co-I), Mary Maggio (project manager), Hongqiu Yang, PhD (biostatistician), Kathy Galan, RN (Project Lead), Elaina Cosslin (PLA), Lesley Sunas, (PLA), Morgan Collini **(CRA),** Tanya Rose (CTA), Michelle Crowder, (Program Manager), Carmel Scharenbroich (Data Manager), Hoss Rostami (Data Manager), Sherry Jiezhun (Statistician), Tarka Monroe (CDA 4)

NIH/NIDDK

Jose Serrano, MD (Project officer), Leonard Seeff, MD, Jay Hoofnagle, MD, David Toke, PhD, Dana Witt, Heather Higgins.

NIH/NCI

David Kleiner, MD

FDA/DHHS

Mark Avigan, MD and John Senior, MD, employees of the U.S. Food and Drug Administration have participated in selected aspects of the DILIN activities.

Figure 1a:

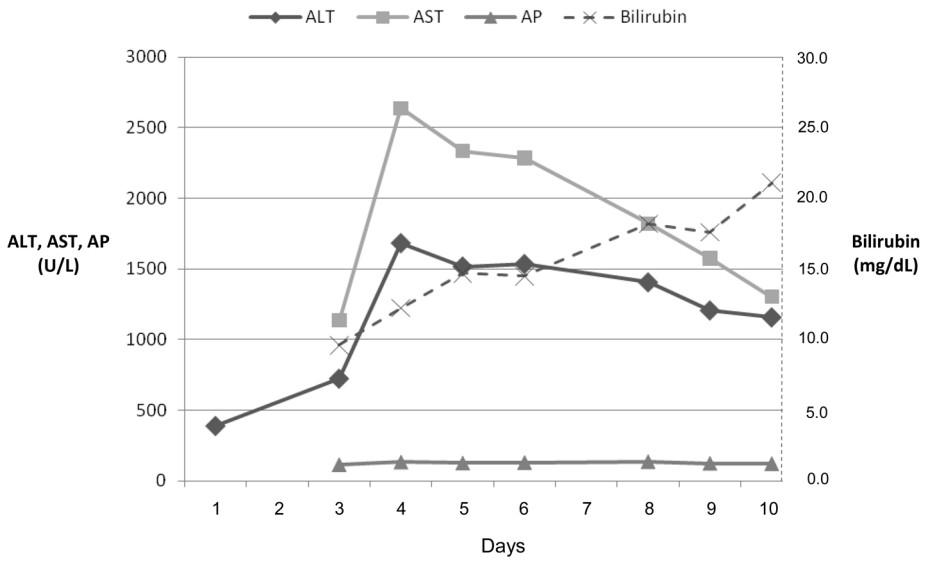


Figure 1b:

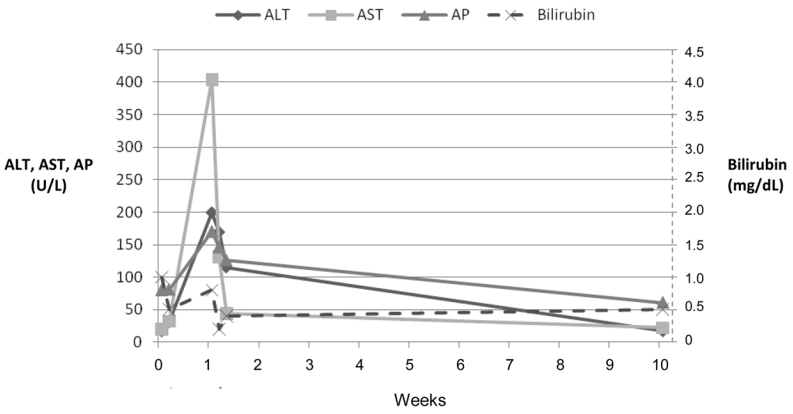


Figure 1c:

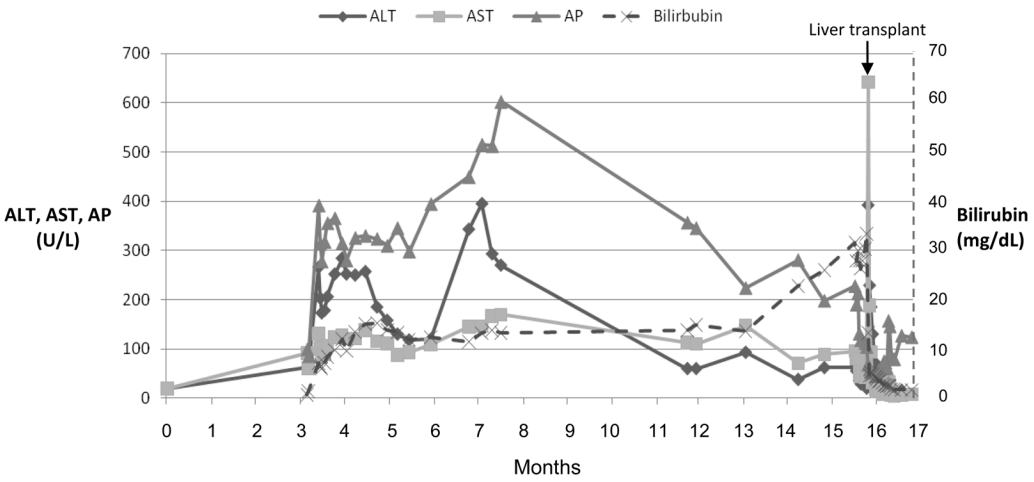
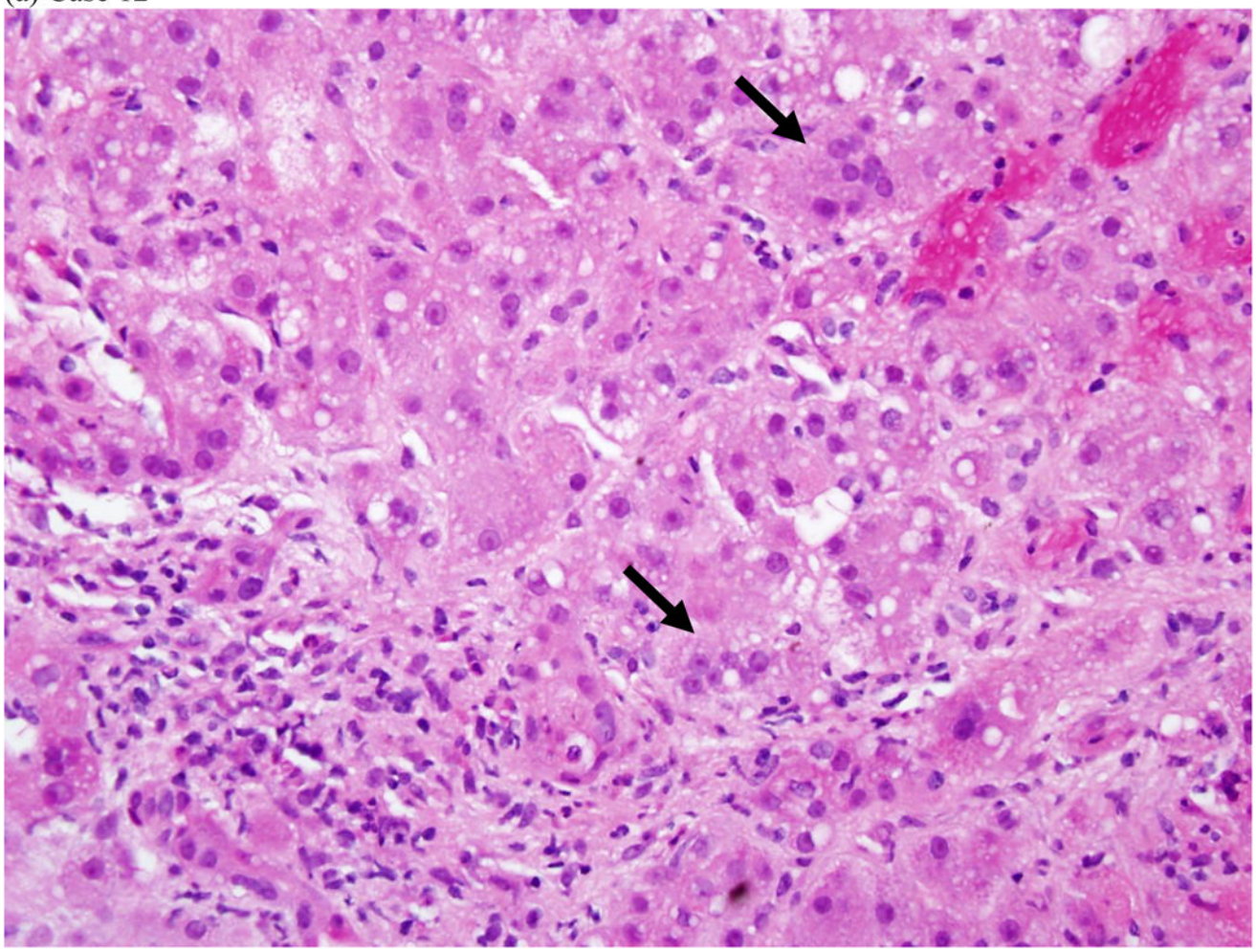


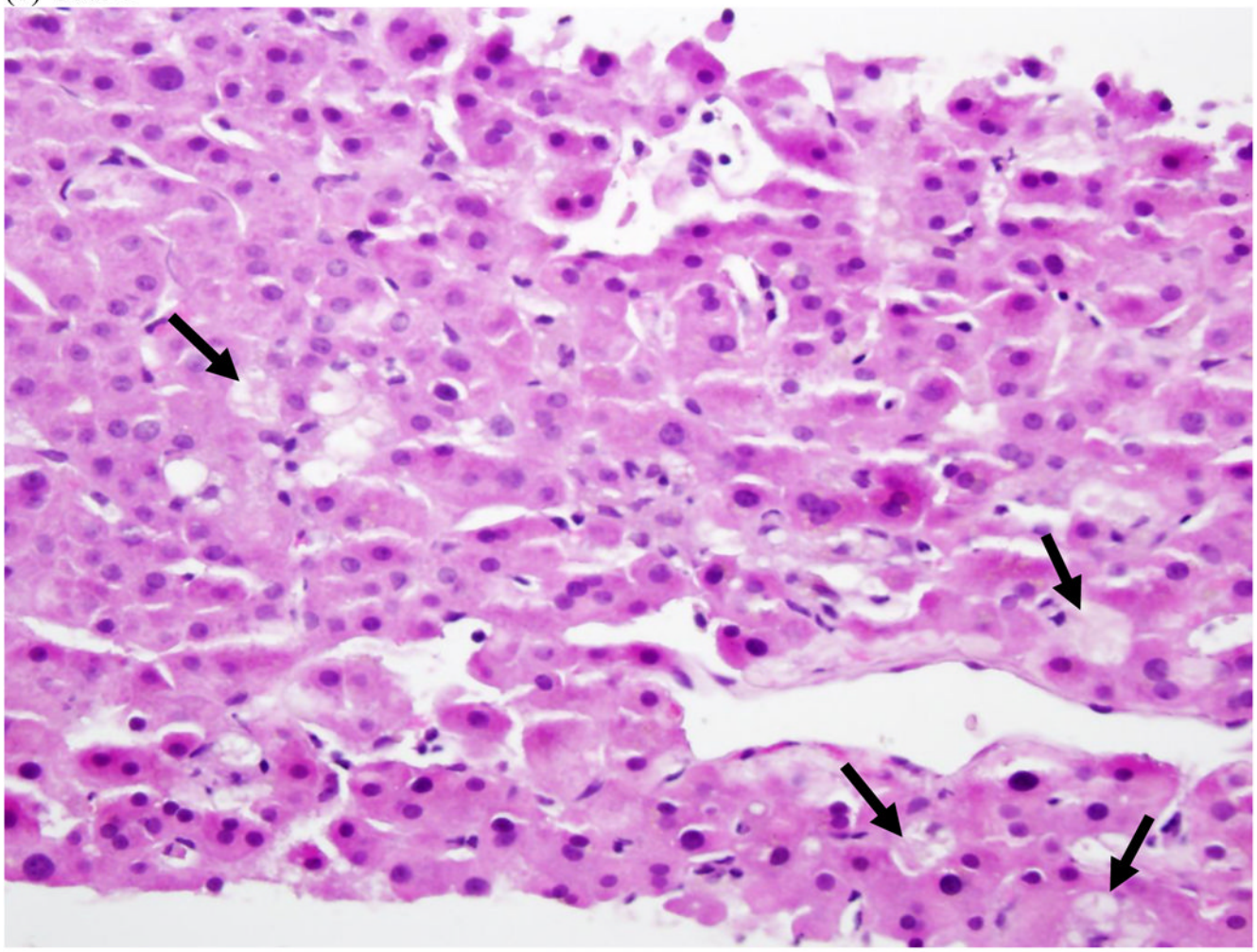
Figure 1.

Serum ALT, AST, AP and bilirubin over time after 3 different fluoroquinolone induced liver injuries. Expert opinion causality scores for all three cases were 2, or very likely. (a) Ciprofloxacin induced hepatocellular injury causing acute liver failure and death. (b) Levofloxacin induced mixed hepatocellular-cholestatic injury with recovery. (c) Moxifloxicin induced cholestatic liver injury leading to prolonged cholestasis, ductopenia and liver failure requiring transplant.

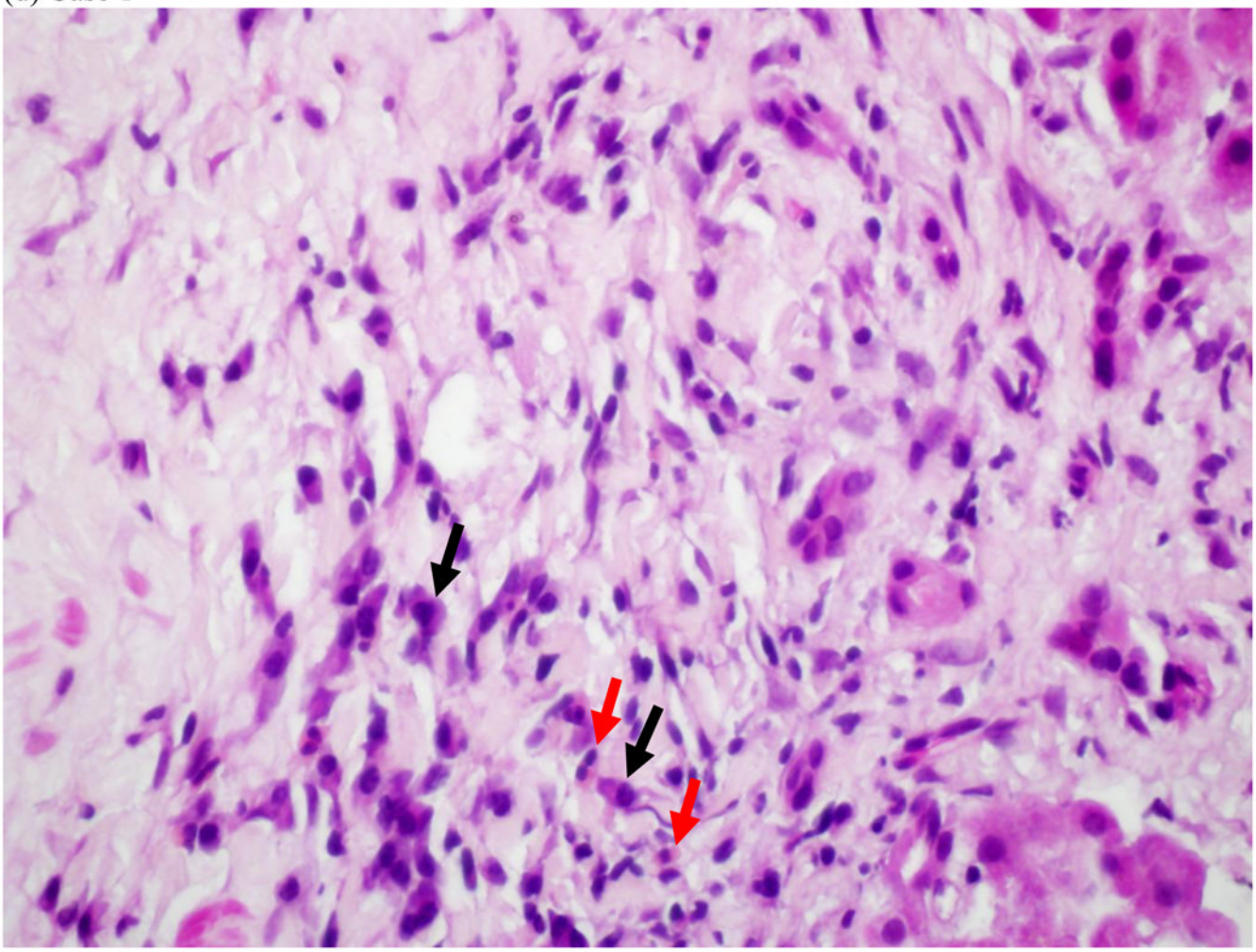
(a) Case 12



(b) Case 1



(d) Case 1



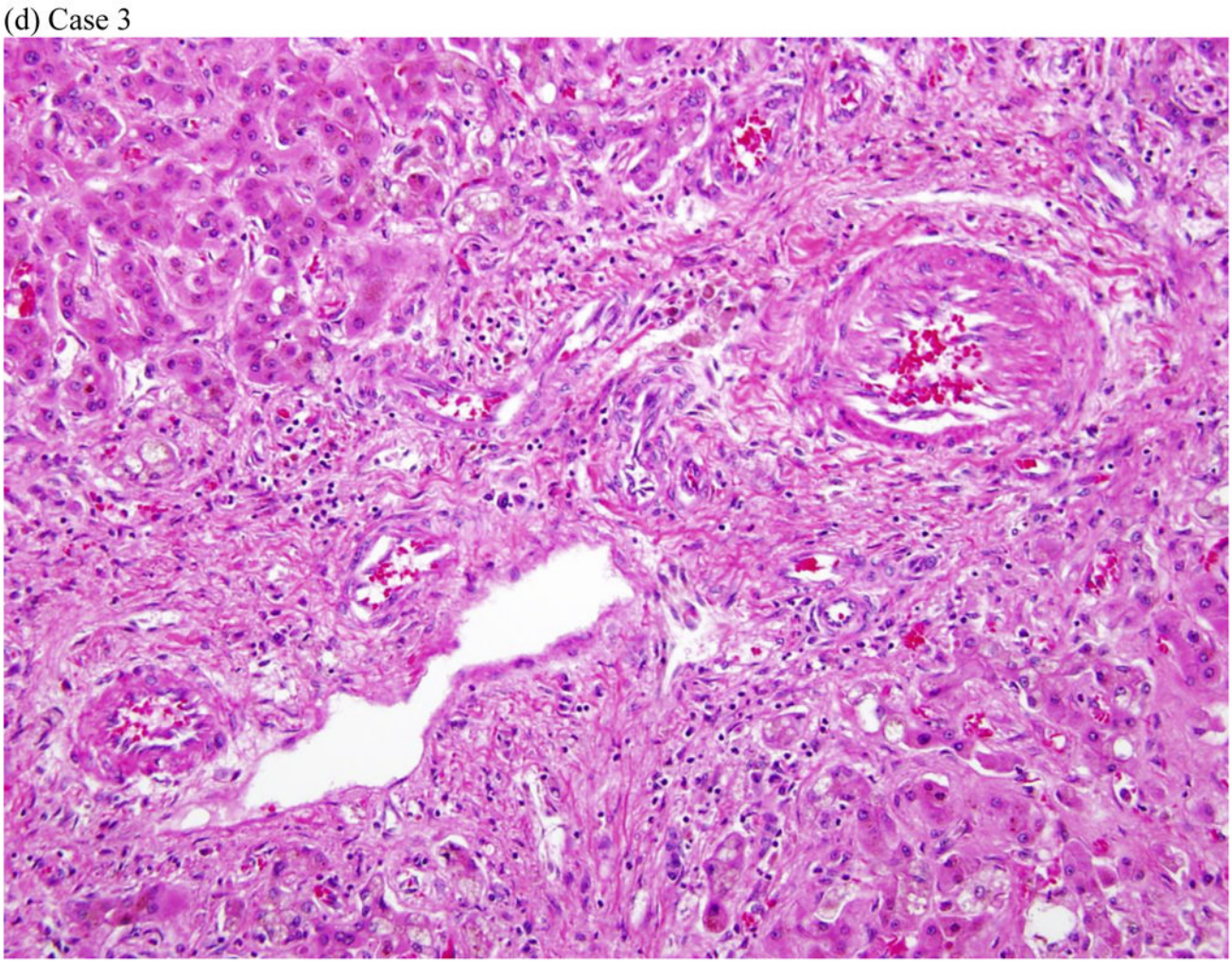


Figure 2.

Represent histopathology of three cases of fluoroquinolone induced liver injuries. (a) acute hepatitis with giant cell transformation (arrows) during hepatocellular injury, (b) cholestatic hepatitis showing mild zone 3 cholestasis (arrows), (c) mild portal inflammation with plasma cells (black arrows) and scattered eosinophils (red arrows) during cholestatic injury, and (d) vanishing bile duct syndrome after cholestatic injury (All hematoxylin and eosin stains, 400x, 200x, 600x and 400x magnification respectively).

Table 1

Clinical Characteristics of Fluoroquinolone Liver Injury Cases (n = 12)

Age in yrs., median (min., max.)	57 (23.6, 80.9)
Gender	7/12 women (58%)
Race (self-report)	
White	6/12 (50%)
Black	3/12 (25%)
Other	2/12 (17%)
Unknown	1/12 (8%)
Latino	1/12 (8%)
Concurrent alcohol	4/12 (33%)
Body Mass Index, kg/m2, mean (std. dev.)	26.8 (3.67)
Latencies, median days (min, max)	
Drug start to symptoms	4.0 (1, 39)
Drug start to DILI onset *	8.5 (1, 41)
Drug start to symptoms or DILI onset *	2.5 (1, 39)
Signs and symptoms	
Jaundice	5/12 (42%)
Nausea	7/12 (58%)
Fever	5/12 (42%)
Abdominal pain	7/12 (58%)
Rash ^	6/12 (50%)
Pruritus	7/12 (58%)

* ALT > 5x ULN or AP > 2x ULN on two consecutive testings

^ one case of Stevens Johnson

Table 2

Clinical Course and Liver Injury Pattern (n = 12)

						R-ratios		Peak values					
Case	**Drug**	**Age yr.**	**Sex**	**Expert Opinion Score***	**Pattern^**	**onset**	**range**	**ALT (U/L)**	**AP (U/L)**	**bilirubin (mg/dL)**	**INR**	**Hospitalized**	**Outcome**
1	Ciprofloxacin	36	F	1	C	0.22	0.1–0.3	151	1931	16.5	1.2	no	chronic**
2	Ciprofloxacin	62	F	1	C	1.57	0.5–1.6	413	891	1.2	0.9	no	recovered
3	Moxifloxacin	46	F	2	C	1.70	0.5–2.3	395	603	33.4	5.3	yes	chronic**/transplanted
4	Moxifloxacin	64	M	3	C	1.96	0.3–2.6	823	837	1.5	NA	yes	lost to follow-up
5	Gatifloxicin	59	M	2	M	2.19	1.6–3.8	577	333	1.2	1.1	yes	recovered
6	Moxifloxacin	71	M	3	M	2.42	1.4–2.4	220	253	2.3	1.0	yes□	recovered
7	Levofloxacin	23	F	2	M	2.84	2.2–2.8	199	170	0.8	1.0	yes	recovered
8	Ciprofloxacin	45	F	3	M	4.77	1.5–4.8	420	275	1.5	1.0	no	recovered
9	Ciprofloxacin	55	M	2	HC	5.17	0.6–10.3#	1632	771	17.1	1.4	yes	died at home#
10	Moxifloxacin	45	M	1	HC	11.41	5.6–11.4	1311	379	3.6	0.9	yes	recovered
11	Ciprofloxacin	70	F	2	HC	12.29	12.3–42.2	1950	159	24.6	1.3	yes	lost to follow-up
12	Ciprofloxacin	80	F	2	HC	13.27	13.3–33.5	1684	136	21.1	8.2	yes	died: liver failure

*1 = Definite, > 95% likelihood; 2 = Very likely, 75–95%; 3 = Probable, 50–75%

^C = cholestatic, R < 2; M = mixed, 2 < R < 5; HC = hepatocellular, R > 5

#developed peritonitis and cholestasis while on peritoneal dialysis; cause of death unknown.

□hospitalized for non-liver reason

**chronic DILI with persistently elevated AP and/or bilirubin

Table 3

Immunoallergic Features and Drug Allergies (n = 12)

#	Drug	Latency*	Rash	Fever	Eosinophilia^	ANA or ASMA#	Other Signs/Symptoms	Other Drug Allergies
1	Ciprofloxacin	9	+	+	+	−	−	none
2	Ciprofloxacin	12	−	+	−	−	+ hypersensitivity pneumonitis	macrodantin, sulfonamides
3	Moxifloxacin	1	+	+	+	−	−	valacyclovir
4	Moxifloxacin	2	−	−	−	−	−	none
5	Gatifloxicin	1	−	+	−	−	+ leucopenia/neutropenia	none
6	Moxifloxacin	1	−	−	−	−	−	none
7	Levofloxacin	1	−	−	−	+	−	none
8	Ciprofloxacin	39	−	−	−	+	−	levofloxacin
9	Ciprofloxacin	30	+	+	−	−	−	penicillin
10	Moxifloxacin	7	+	−	−	−	+ Stevens Johnson Syndrome	amoxicillin, erythromycin, tramadol
11	Ciprofloxacin	4	−	−	−	+	−	amoxicillin
12	Ciprofloxacin	18	+	−	+	+	−	penicillin

*days from drug start to any symptoms of DILI

^absolute eosinophil count > 500/uL

#ANA = anti-nuclear antibody; ASMA = anti-smooth muscle antibody