Eur J Clin Pharmacol (2012) 68:525–532
DOI 10.1007/s00228-011-1201-6

REVIEW ARTICLE

Fluoroquinolone-induced liver injury: three new cases and a review of the literature

Anna Licata · Claudia Randazzo · Ilaria Morreale · Giuseppe Butera · Natale D'Alessandro · Antonio Craxì

Received: 26 September 2011 / Accepted: 13 December 2011 / Published online: 14 January 2012

Abstract
Purpose Fluoroquinolones are popular and widely used in primary care and hospital settings. Premarketing studies showed a favourable side-effect profile. However, significant morbidity and the need for liver transplantation for acute liver failure have been reported. We reviewed the available data on liver damage linked to fluoroquinolones.
Methods A systematic search of case reports on the MEDLINE database encompassing the years 2000–2011 was carried out. Additional references were found by a manual search of the retrieved paper. We also describe three new cases of hepatotoxicity attributable to fluoroquinolones seen at our Unit.
Results Thirty-five cases were retrieved from MEDLINE (51.4% male). According to the RUCAM scale, liver injury was classified as hepatocellular (51.4%), cholestatic (28.6%) or mixed (20.0%). Older age (≥ 65 years) was present in 42.8%. The time between initiation of treatment and hepatic injury ranged from 1 to 39 days (median 8 days). According to the RUCAM score, our cases were classified to be "highly probable" or "probable". Only one patient underwent liver biopsy, which showed the features of liver damage linked to drug exposure. Liver enzymes from all patients return to normal range within 4 weeks of withdrawal. Only one patient showed a renal failure, associated with liver injury, with a need for haemodialysis for 3 weeks.
Conclusions Fluoroquinolones are substantially safe antibiotics. Although fluoroquinolone-related hepatic injury occurs infrequently, its consequences can be severe. Patients should also be cautioned to avoid re-exposure to other members of the fluoroquinolone class.

Keywords Fluoroquinolones · Hepatotoxicity · Liver injury · Hepatitis · Acute liver failure

A. Licata · C. Randazzo · G. Butera · A. Craxì
Sezione e U.O.C. di Gastroenterologia,
Di.Bi.M.I.S, Università di Palermo,
Palermo, Italy

I. Morreale · N. D'Alessandro
Sezione di Farmacologia, Dipartimento di Scienze per la promozione della Salute, Università di Palermo,
Palermo, Italy

A. Licata (✉)
Sezione di Gastroenterologia & Epatologia, Dipartimento Biomedico di Medicina Interna e Specialistica,
Università di Palermo,
Piazza Delle Cliniche 2,
90127 Palermo, Italy
e-mail: annalisalicata@yahoo.com

Introduction

Fluorinated quinolones comprise a relatively large, expanding and most interesting group of antimicrobials, which are popular because of their broad-spectrum bactericidal activity [1]. They are widely used in primary care and hospital settings resulting in being the "first choice" in the therapy of respiratory, genitourinary, skin and soft tissue infections [2]. These drugs have shown good tissue penetration and excellent oral bioavailability [3].

In Italy, quinolones ranked first in the country's expenditure on antimicrobials in 2010. Among them, the number of prescriptions of levofloxacin and prulifloxacin increased (+1.8% and +8.7% respectively) and that of ciprofloxacin was reduced by 0.3% [4]. While the efficacy of these drugs has improved from the first (e.g. nalidixic acid) to the third generation (e.g. moxifloxacin), their benefit–risk profile still needs further careful evaluation.

Post-marketing investigations and spontaneous reporting have led to regulatory decisions to withdraw or severely limit the use of some fluoroquinolones because of unacceptable rates of severe adverse effects [2]. Indeed, premarketing trials are unable to detect all the possible types of adverse events, especially if rare. However, spontaneous reporting has the capability of providing an account of all types of adverse reactions, thus allowing the comparison among different molecules of the same pharmacological class. Premarketing studies showed that fluoroquinolones have a favourable safety profile, with treatment-related adverse events (gastrointestinal, on central nervous system and dermatological) generally mild in severity and reversible on withdrawal [1]. Nevertheless, fluoroquinolones have also been reported to be responsible for liver toxicity, even through its incidence is considered very low [5].

Fluoroquinolone-induced hepatotoxicity is usually transient and associated with only mild hepatic impairment with minimal symptoms [6]. In some rare cases, however, significant morbidity [7, 8], need for liver transplantation [9] or death from acute liver failure have been reported [10–12]. Both hepatocellular and cholestatic patterns of acute liver injury, and even acute liver failure, have been seen with quinolone antibiotics. The interval between drug administration and the onset of hepatic dysfunction is variable [13].

In this context, we report three new cases of hepatotoxicity associated with fluoroquinolones and review the current literature on the topic.

Materials and methods

In order to collect literature reports on fluoroquinolone hepatotoxicity, we carried out a systematic search of case reports on the MEDLINE database encompassing the years from 2000 to 2011. The keywords for liver damage were: hepatotoxicity, liver injury, hepatitis, cholestasis, hepatic failure, hepatic necrosis, hepatic fibrosis and cirrhosis. Each term was matched with the names of all the fluoroquinolones (Anatomical Therapeutic Chemical [ATC] 4th level code J01MA) approved in Italy. There were no restrictions regarding article type, sex, age and language. Furthermore, the package insert for each of the fluoroquinolones was also used as a data source. Additional information was sourced from the references of all the papers retrieved. We are carrying out a study collecting all drug-induced liver injury (DILI) cases observed at our Department; among these, we found 3 cases attributable to fluoroquinolones. The causality assessment on these three cases was performed according to the Russell Uclaf Causality Assessment Method (RUCAM) [14]. This method is considered to be an appropriate approach for evaluating the role of a substance in the development of adverse reactions to drugs and has been standardised for DILIs. The Naranjo algorithm for causality assessment [15], although not liver-specific and possibly lacking the specificity and reproducibility for evaluating drug-associated hepatotoxicity [16], was also applied to our cases.

Results

Thirty-five cases of acute or subacute liver damage following exposure to fluoroquinolones were retrieved from MEDLINE between September 2000 and June 2011 (Table 1) [9, 12, 17–38]. Ciprofloxacin accounted for 16 (45.7%), levofloxacin for 11 (31.4%), moxifloxacin for 7 (20.0%) and norfloxacin for 1 (2.9%). Eighteen patients (51.4%) were male and 17 (48.6%) female. This corresponds to a male to female ratio of 1.05, with an age of 22 to 99 years at the time of diagnosis (median 63 years). A risk factor related to the age ($\geq$ 65 years) was present in 15 subjects (42.8%). The time between initiation of fluoroquinolone and hepatic injury ranged from 1 to 39 days (median 8 days). An additional case of cholestatic liver disease occurring approximately 6 months after treatment with ciprofloxacin and ornidazole, has been documented in the literature [33].

The indications for therapy were typically genitourinary and respiratory tract infections. According to the RUCAM scale, liver injury was classified as hepatocellular (51.4%), cholestatic (28.6%) or mixed (20.0%). The histological examination, when performed, showed inflammatory reactions, necrosis, cholestasis, and sometimes steatosis (Table 1). Serum analysis confirmed negative viral serology for active hepatitis B and C in all patients. An autoimmune reaction was also generally excluded by the measurement of the serum levels of non-organ-specific autoantibodies. Alcoholism was generally excluded. In some cases, the consumption of other medications was reported as follows: ceftriaxone [19, 35], acetaminophen [20], doxycycline [22, 23], naproxen [22], cotrimoxazole [23], clindamycin [30], diclofenac [30], amiodarone [32], warfarin [32, 36], ornidazole [33], cloxacillin [35].

Recovery was generally observed, apart from 7 patients [9, 12, 17, 22, 24, 27, 36]. Cases with predominantly hepatocellular injury (n=18) were often severe; 5 of the 18 cases resulted in death [9, 12, 17, 22, 36]. Among the cholestatic cases (n=10), none of which resulted in death, 2 developed chronic liver disease. One presented with a histologically diagnosed vanishing bile duct syndrome that required liver transplantation 1 year after presentation. Another had persistent elevations in serum alkaline phosphatase (AP) without jaundice or pruritus 17 months after the injury [17]. Two of the 7 mixed cases also resulted in death [24, 27].

In the following sections we describe the three new patients observed at our Gastroenterology and Hepatology Unit over the last 3 years.

Table 1 Clinical data of the events associated with fluoroquinolones

Reference	Sex	Age	Drug	Underlying condition	Previous liver disease	Indication for therapy	Time to toxicity (days)	Pattern	Liver histology	Treatment	Outcome
Our cases	Male	67	Ciprofloxacin	Colorectal cancer	No	Abdominal pain, diarrhoea, nausea	1	Cholestatic	ND	Supportive therapy, dialysis for acute renal insufficiency	Full recovery
	Male	27	Levofloxacin	None	No	Fever	5	Cytolytic	ND	None	Full recovery
	Male	64	Levofloxacin	Benign prostatic hyperplasia	No	Fever	7	Cytolytic	Inflammatory infiltrate, ballooning degeneration, steatosis, portal fibrosis	None	Full recovery
[17]	Female	62	Ciprofloxacin	NR	NR	NR	12	Cholestatic	ND	NR	Full recovery
	Female	45	Ciprofloxacin	NR	NR	NR	39	Mixed	NR	NR	Full recovery
	Male	55	Ciprofloxacin	NR	NR	NR	30	Cytolytic	NR	NR	Died at home
	Female	70	Ciprofloxacin	NR	NR	NR	4	Cytolytic	NR	NR	Lost to follow-up
	Female	36	Ciprofloxacin	NR	NR	NR	9	Cholestatic	Mild zone 3 cholestatic hepatitis, portal inflammation	NR	Chronic
	Female	80	Ciprofloxacin	NR	NR	NR	18	Cytolytic	Acute hepatitis with giant cell transformation	NR	Died
	Female	23	Levofloxacin	NR	NR	NR	7	Mixed	ND	NR	Full recovery
	Male	64	Moxifloxacin	NR	NR	NR	2	Cholestatic	NR	NR	Lost to follow-up
	Male	71	Moxifloxacin	NR	NR	NR	1	Mixed	NR	NR	Full recovery
	Male	45	Moxifloxacin	NR	NR	NR	7	Cytolytic	NR	NR	Full recovery
	Female	46	Moxifloxacin	NR	NR	NR	8	Cholestatic	Vanishing bile duct syndrome	NR	Chronic/OLT
[18]	Male	56	Ciprofloxacin	Prostate hyperplasia	No	Transurethral resection of the prostate	2	Cytolytic	ND	None	Full recovery
	Male	62	Ciprofloxacin	Prostate hyperplasia	No	Urinary tract infection	5	Cytolytic	Eosinophil infiltration, hepatocellular necrosis	None	Full recovery
[19]	Female	51	Levofloxacin	Pleuritis	No	Hydro-pneumothorax	5	Cholestatic	NR	NR	NR
[20]	Male	77	Levofloxacin	Chronic bronchitis, arterial hypertension, hypercholesterolaemia, benign prostatic hyperplasia	No	Pneumonia	7	Cytolytic	Mixed interacinar inflammatory infiltrate, focal hepatocellular necrosis, centrilobular cholestasis	Supportive therapy	Full recovery
[21]	Male	66	Ciprofloxacin	None	No	Fever, nausea, vomiting, diarrhoea	3	Cholestatic	ND (patient refused)	None	Full recovery
[22]	Male	63	Levofloxacin	Previous pharyngolaryngeal squamous cell carcinoma	No	Pneumonia plus pericarditis	10	Cytolytic	Hepatic necrosis, inflammatory changes, cholestasis	None	Die of fulminant hepatic failure
[23]	Female	65	Levofloxacin	Previous breast cancer	No	Respiratory tract infection	15	Cytolytic	Inflammatory infiltrate, moderate steatosis	Methylprednisolone, UDCA	Full recovery
[24]	Male	72	Moxifloxacin	Chronic bronchitis, COPD, rheumatoid arthritis	No	Acute exacerbation of chronic bronchitis	7	Mixed	ND	Supportive therapy	Died of multi-organ system failure
[25]	Male	65	Ciprofloxacin	Ischaemic cardiomyopathy	No	Cellulitis	6	Cholestatic	ND	Dialysis for acute tubular necrosis	Full recovery
[26]	Female	39	Ciprofloxacin	None	No	Diverticular abscess	14	Cytolytic	Infiltration of portal tracts, necrosis	Prednisone	Full recovery
[27]	Female	26	Ciprofloxacin	None	No	Acute bronchitis	14	Mixed	Cholestasis, ductopaenia, portal inflammation	Prednisone, UDCA, tacrolimus	Improvement at 3 months

Table 1 (continued)

Reference	Sex	Age	Drug	Underlying condition	Previous liver disease	Indication for therapy	Time to toxicity (days)	Pattern	Liver histology	Treatment	Outcome
[28]	Female	55	Levofloxacin	None	Hepatitis B carrier	Upper respiratory infection	10	Mixed	Hepatic necrosis	Plasmapheresis, haemodialysis, supportive therapy	Died (hepatic and renal failure)
[29]	Male	22	Ciprofloxacin	None	No	Skin bacterial infection	14	Cytolytic	Extensive hepatocellular necrosis, inflammatory infiltrate, necrotic areas	Methylprednisolone	Full recovery
[9]	Female	23	Moxifloxacin	None	No	Upper respiratory illness	3	Cytolytic	Massive hepatocellular necrosis	Respiratory support, haemofiltration, liver transplant	Died
[30]	Female	79	Ciprofloxacin	Congestive heart disease, chronic renal insufficiency	No	Infection of interdigital ulcerations	2	Cytolytic	ND	Supportive therapy	Full recovery
[31]	Male	73	Levofloxacin	Diabetes mellitus, chronic renal insufficiency, coronary artery disease, neuropathy	No	Cellulitis in lower extremities	21	Cytolytic	ND	None	Full recovery (died for severe postoperative myocardial infarction)
[32]	Male	63	Levofloxacin	Mitral valve disease, coronary artery disease, chronic renal insufficiency, lung cancer	No	Orchitis	10	Cholestatic	NR	NR	
[33]	Female	63	Ciprofloxacin	Crohn's disease, diabetes mellitus, chronic pancreatitis	No	Exacerbation of Crohn's disease	180	Cytolytic	Fibrosing cholestatic hepatitis, spotty necrosis	Supportive therapy	Full recovery
[34]	Male	69	Moxifloxacin	Chronic bronchitis	No	Exacerbation of chronic bronchitis	21	Cholestatic	Casts in canaliculi and mild portal inflammatory infiltrates	None	Full recovery
[35]	Male	32	Ciprofloxacin	Brodie's abscess	No	Septic arthritis	2	Cytolytic	Periportal and centrilobular necrosis	Methylprednisolone plus supportive therapy	Full recovery
[36]	Female	74	Levofloxacin	Emphysema, chronic atrial fibrillation	No	Lower respiratory tract infection	2	Cytolytic	ND	Supportive therapy	Died of multi-organ failure
[12]	Male	99	Levofloxacin	None	No	Urinary tract infection	8	Cytolytic	Confluent hepatocellular necrosis, periportal cholestasis, steatosis	None	Died
[37]	Male	71	Levofloxacin	None	No	Acute bacterial enteritis	4	Mixed	ND	Methylprednisolone, UDCA,supportive therapy	Full recovery
[38]	Female	71	Norfloxacin	None	No	Urinary tract infection	14	Cholestatic	Necrotising granulomatous hepatitis	None	Full recovery

ND, not done; NR, not reported; OLT, orthotopic liver transplantation; COPD, chronic obstructive pulmonary disease; UDCA, ursodeoxycholic acid

Case 1

A 67-year-old white man (height, 178 cm; weight, 91 kg) with no relevant past history was admitted to our hospital for progressive jaundice and abdominal pain. One day before admission he developed non-bloody diarrhoea, which was empirically treated with ciprofloxacin (500 mg b.i.d. p.o.). He denied taking any other medication and had no history of alcohol abuse. On physical examination, he appeared apyretic, normotensive and jaundiced without signs of chronic liver disease, with right upper quadrant tenderness, but no ascites. Laboratory work-up showed elevation of aminotransferases (aspartate aminotransferase [AST] 102 U/L [normal<35]; alanine aminotransferase [ALT] 143 U/L [normal<35]), AP (413 U/L [normal<125]), gamma-glutamyltransferase (γGT; 379 U/L [normal<60]) and total bilirubin (7.8 mg/dl, direct 6.1). Prothrombin activity was normal. Blood count did not show leukocytosis or eosinophilia. He had also developed an elevation in serum creatinine (11.5 mg/dL). Abdominal ultrasound revealed no obstruction of the bile duct and no hepato- or splenomegaly. Serology for hepatitis B and C virus, Epstein–Barr virus (EBV), cytomegalovirus (CMV), anti-nuclear (ANA), anti-liver kidney microsome (LKM), anti-smooth muscle (SMA) and anti-mitochondrial (AMA) antibodies was negative. A diagnosis of ciprofloxacin-associated cholestatic hepatitis plus renal failure was made and the patient was put on steroids as well as on haemodialysis two times a week (for the following 3 weeks). Liver enzymes returned to normal levels within 1 month of cessation of ciprofloxacin treatment. The RUCAM score was 6, so that the relationship was “probable”, while according to the Naranjo algorithm the score was 4 (relationship=“possible”).

Case 2

A 27-year-old white man had been treated with levofloxacin (500 mg once daily p.o. for 3 days) during a non-specific febrile episode. After 5 days of levofloxacin intake, the patient displayed nausea and hyperchromic urine. There was no history of alcohol or other medications. An ultrasound of the abdomen revealed hyperechoic hepatomegaly with mild splenomegaly and no obstruction of the common bile duct. The results of the laboratory tests were: AST 370 U/l, ALT 400 U/l with normal bilirubin (0.6 mg/dL). Serologies for hepatitis B, C and CMV were negative. EBV anti-IgM was negative with positive anti-IgG titres. Autoimmune hepatitis or cholangiopathy as well as metabolic liver diseases, were excluded based on negative ANA, SMA, LKM and AMA titres and analyses of ceruloplasmin, copper, iron and alpha-1-antitrypsin. A diagnosis of levofloxacin-associated liver injury was made and the drug was discontinued. The levels of AST and ALT improved rapidly, reaching normal levels within 2 weeks. After 3 months of follow-up the patient completely recovered. According to RUCAM, the liver injury was classified as “cytolytic”. The RUCAM score was 9, so that the relationship was “highly probable”, while according to the Naranjo algorithm the score was 8 (relationship=“probable”).

Case 3

A 64-year-old white man had been treated with levofloxacin i.v. (unknown dose) because of fever at another hospital. After 2 days of therapy, the patient was transferred to our hospital because an increase in aminotransferases. There was no history of liver disease, blood transfusion, alcohol or other medication. We observed high aminotransferases (AST 587 U/L; ALT 1,129 U/L), AP (225 U/L) and γGT 356 U/L levels, while bilirubin was normal (0.45 mg/dL). Serologies for hepatitis A, B, C, CMV and EBV were negative as well as autoantibodies. Blood count showed mild leukocytosis without eosinophilia. An ultrasound of the abdomen revealed no obstruction of the common bile duct and either hepato- or splenomegaly, but mild steatosis. A liver biopsy identified hepatocellular necrosis predominantly involving zones 3 and 2 of hepatic acini, mixed inflammatory infiltration of portal tracts (by eosinophils and ceroid macrophages), ballooning degeneration, steatosis (30%) and portal fibrosis. Levofloxacin was suspected to be the cause of the adverse effect and discontinued. Liver function tests returned to normal levels within 4 weeks. The RUCAM score was 10, so that the relationship was “highly probable”, while according to the Naranjo algorithm the score was 8 (relationship=“probable”)..

Discussion

Estimates of hepatotoxicity incidence are often hampered by biases, poor quality of reporting and inclusion criteria. Nonetheless, large-scale post-marketing surveillance suggests that fluoroquinolones, except for trovafloxacin and temafloxacin, do not cause significant severe hepatotoxicity [4–6]. Package insert information reports that asymptomatic, mild and transient elevations in liver enzymes might occur in 2–3% of patients treated with fluoroquinolones [39], whereas jaundice and hepatitis are much less common [40, 41]. Additionally, acute liver failure reporting rates using Food and Drug Administration (FDA) data per 10 million prescriptions have been 2.1 for levofloxacin, 6.6 for moxifloxacin, 6.0 for gatifloxacin and 58 for trovafloxacin [42].

Up to now, hepatic adverse effects from fluoroquinolones have been described in several case reports; here we have reviewed 35 cases published in the last 10 years and added three new cases in which the hepatotoxicity was the main adverse event.

The reviewed cases suggest that the phenotype and clinical presentation of liver injury from fluoroquinolones are similar with the different agents. The high frequency observed with ciprofloxacin (16 cases) and levofloxacin (11 cases) most likely reflects the level of their prescription rather than their greater hepatotoxicity. However, some differences may be explained, at least in part, by the structural characteristics of certain molecules of quinolones. For example, the greater hepatotoxic potential of trovafloxacin may be due to its difluorophenyl side chain (shared with temafloxacin), but the specific cyclopropylamine moiety of the drug may also play an important role [6].

In the series reviewed, the main feature of the hepatic damage was the short latency and rapid onset of injury. Severe hepatotoxicity generally occurred within 14 days of the start of therapy and most cases occurred within 6 days. The reported hepatotoxic reactions showed a temporal relationship between the consumption of the culprit drug and the onset of the effects: up to 90% of the patients described in the reports had been taking fluoroquinolones for a period between 1 day and 3 months, and this time period can be considered to be "suggestive" in the causality assessment according to RUCAM. Dechallenge was always positive.

The occurrence of hepatotoxicity and the majority of fatal reports were significantly higher in patients over 65 years or older; 15 (42.8%) out of the 35 cases reviewed presented older age as a possible risk factor, while only one of our cases was older than 65 years. Although age is a risk factor for hepatotoxicity from some specific medications, which include erythromycin, halotan, nitrofurantoin, flucloxacillin, isoniazid and amoxicillin-clavulanate [43], the present observation may also reflect a differential fluoroquinolone usage related to age.

Both cytolytic and cholestatic patterns of liver injury have been reported with fluoroquinolones. Among the cases reviewed, the pattern of liver injury was predominantly hepatocellular (51.4%); cholestatic and mixed categories were evenly distributed (28.6% and 20.0%). Cytolytic pattern was also the main category of our three cases. The outcome of patients with predominantly hepatocellular and mixed injury was often severe (27.7% and 28.6% died respectively). Cholestatic cases tended to show less severe injury, but developed chronic liver injury more frequently. In contrast, all our patients had a self-limited, benign course.

In few of the cases reviewed here, the hepatotoxic reaction may have been related to concomitant medications, i.e. when the fluoroquinolone was associated with diclofenac [30], naproxen [22] or acetaminophen [20], since clear hepatotoxicity has been reported for these drugs [44, 45]. One other patient was also taking oral contraceptives [9], which has been associated with some cases of toxic hepatitis [46]. With the exception of these cases, in the other patients the hepatic damage could be attributed mainly to fluoroquinolones. None of our patients was taking any other drugs.

The pathophysiology of fluoroquinolone-related liver injury is still unclear. Possibly given the rarity of this complication of fluoroquinolone therapy, there have not been large pharmacogenetic studies that might aid better understanding of its mechanism(s). Based on the available clinicopathological observations, it appears likely that it is predominantly idiosyncratic [47] and not strictly dose-dependent. In most of the reported cases examined here, there was indeed a relatively short delay between the initiation of the drug and the development of liver injury. Also in our series, there was a close temporal relation between the use of the antibiotics and the onset of liver damage; 2 of our 3 cases developed symptoms while still taking the antibiotic.

Although the hepatotoxicity remains undefined, molecules generating reactive intermediates (e.g. temafloxacin and trovafloxacin) appear to be associated with a higher incidence of hepatotoxicity [48].

The frequent immunoallergic features that have been described on re-exposure and the lack of a common pattern of metabolism among the various fluoroquinolones might perhaps argue in favour of a hypersensitivity reaction. However, our cases did not show rash or fever; eosinophilia was uncommon, possibly because the pattern of referral of patients to our Unit often resulted in a delay, causing a normalisation of the eosinophil count.

Twelve out of 18 subjects with available liver histology showed increased eosinophils in the liver specimens. It has been postulated that quinolones with a 1-(2,4)-difluorophenyl group might carry an even greater risk of severe immune-mediated toxicities [49]. The available liver histology of our case 3 also showed increased eosinophils.

The immunoallergic phenotype would make it advisable for patients with hepatotoxicity from one fluoroquinolone to avoid other members of this class of antibiotics.

Overall, in the three cases observed by us, the temporal relation and short latency (median 2 days) between the use of ciprofloxacin or levofloxacin and liver damage, the fact that the patients were not taking other hepatotoxic drugs, the exclusion of other causes of hepatitis (viral infections, autoimmunity, alcohol etc.), and the presence of a compatible liver histology (case 3) supported the diagnosis of fluoroquinolone-associated liver injury. Dechallenge was positive in all cases; rechallenge was not performed. According to the RUCAM scale, our cases were classified to be "probable" or "highly probable". The Naranjo algorithm classified them as "possible" or "probable".

Of the 8 fluoroquinolones available in Italy during the study period, 4 (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin) were present in our review. Although our study did not include ofloxacin, it has been reported to cause hepatotoxicity with injury patterns similar to those already described [50–52]. Rises in total bilirubin and aminotransferases have occurred in some patients during prulifloxacin therapy. A clear association between this drug and hepatotoxicity has not been established; however, periodic monitoring of liver function is advisable in patients with pre-existing liver disease treated with this drug. There are no reports of cases of hepatotoxicity attributable to lomefloxacin or rufloxacin. Among the drugs considered here, the summaries of product characteristics (SPC) mention that hepatotoxicity is a rare adverse reaction of ciprofloxacin and levofloxacin related to their both oral and intravenous administration [8]. A review of the relative toxicities of moxifloxacin and other fluoroquinolones and antibacterials reported that the incidence of hepatotoxic reactions with moxifloxacin was not significantly different from those with other fluoroquinolones, and less than that reported for amoxicillin plus clavulanic acid [42]; however, an analysis by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) considered that such reactions were of sufficient concern that the use of moxifloxacin should be restricted. The CHMP strengthened warnings in product information by adding the statement “including fatal cases” [53].

Mild elevations of serum aminotransferase have been reported in 1 in 1,000 patients taking norfloxacin and acute hepatitis is very rare [38, 54–57]. Norfloxacin is widely used for prophylaxis of spontaneous bacterial peritonitis in cirrhotic patients and in cases of high elevations of aminotransferases in these patients the possible responsibility of norfloxacin treatment should be taken into account.

In addition, there are several other fluoroquinolones available outside Italy, some of them withdrawn from the market because of serious adverse reactions [6]. Gatifloxacin was approved in the USA and other countries, but not in Europe. It has recently been withdrawn, mainly owing to alterations in glucose homeostasis. However, it has also been implicated in several cases of hepatotoxicity, with 27 occurrences reported to the FDA (quoted in 11 cases as the most probable cause of death) [58]. Trovafloxacin was approved in the USA in 1998, but post-marketing surveillance promptly revealed serious hepatotoxicity [59]. In fact, 140 cases of serious hepatic injuries were reported within 2 years (with only 2.5 million patient exposures) from marketing [60]. Although approved in Europe, the drug was rapidly withdrawn before its actual commercial launch.

In conclusion, although fluoroquinolone-related hepatic injury occurs infrequently its consequences can be severe, causing prolonged jaundice, morbidity and acute liver failure resulting in transplant or death. Patients with fluoroquinolone-induced liver injury should be cautioned to avoid re-exposure to other members of the fluoroquinolone class. Because there are no established means of preventing fluoroquinolone-induced hepatotoxicity, it is important to prescribe these drugs for clear-cut indications only as well as to take a detailed history of possible drug allergies of the patient. Finally, physicians should be conscious and on the alert with reference to the possibility of such fluoroquinolone-induced adverse reactions and all cases should be reported to national pharmacovigilance systems whenever possible. In Italy, cases are reported to the Agenzia Italiana del Farmaco (http://www.agenziafarmaco.gov.it).

References

1. Desarro A, Desarro G (2001) Adverse reactions to fluoroquinolones. An overview on mechanistic aspects. Curr Med Chem 8:371–384
2. Lapi F, Tuccori M, Motola D et al (2010) Safety profile of the fluoroquinolones. Analysis of adverse drug reactions in relation to prescription data using four regional pharmacovigilance databases in Italy. Drug Saf 33:789–799
3. Mehlhorn AJ, Brown DA (2007) Safety concerns with fluoroquinolones. Ann Pharmacother 41:1859–1866
4. Gruppo di lavoro OsMed (2010) L’uso dei farmaci in Italia. Rapporto Nazionale. Roma: Il pensiero scientifico editore 2011
5. Polson JE (2007) Hepatotoxicity due to antibiotics. Clin Liver Dis 11:549–561
6. Andrade RJ, Tulkens PM (2011) Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother 66:1431–1446
7. George DK, Crawford DH (1996) Antibacterial-induced hepatotoxicity. Incidence, prevention and management. Drug Saf 15:79–85
8. Andrade RJ, Lucena MI, Fernandez MC et al (2005) Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 129:512–521
9. Nori S, Nebesio C, Brashear R et al (2004) Moxifloxacin-associated drug hypersensitivity syndrome with toxic epidermal necrolysis and fulminant hepatic failure. Arch Dermatol 140:1537–1538
10. Grassmick BK, Lehr VT, Sundareson AS (1992) Fulminant hepatic failure possibly related to ciprofloxacin. Ann Pharmacother 26:636–639
11. Fuchs S, Simon Z, Brezis M (1994) Fatal hepatic failure associated with ciprofloxacin. Lancet 343:738–739
12. Spahr L, Rubbia-Brandt L, Marinescu O et al (2001) Acute fatal hepatitis related to levofloxacin. J Hepatol 35:308–309
13. Thiim M, Friedman LS (2003) Hepatotoxicity of antibiotics and antifungals. Clin Liver Dis 7:381–399
14. Danan G, Benichou C (1993) 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 46:1323–1330
15. Naranjo CA, Busto U, Sellers EM et al (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239–245
16. García-Cortés M, Lucena MI, Pachkoria K, for the Spanish Group for the Study of Drug-induced Liver Disease (grupo de Estudio para las Hepatopatias Asociadas a Medicamentos, Geham) et al

(2008) Evaluation of Naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. Aliment Pharmacol Ther 27:780–789
17. Orman ES, Conjeevaram HS, Vuppalanchi R et al (2011) Clinical and histopathologic features of fluoroquinolone-induced liver injury. Clin Gastroenterol Hepatol 9:517–523
18. Alan C, Koçoğlu H, Ersay AR et al (2011) Unexpected severe hepatotoxicity of ciprofloxacine: two case reports. Drug Chem Toxicol 34:189–191
19. Titos-Arcos JC, Hallal H, Robles M et al (2011) Acute cholestatic hepatitis associated with levofloxacin. Gastroenterol Hepatol 34:369–370
20. Figueira-Coelho J, Pereira O, Picado B et al (2010) Acute hepatitis associated with the use of levofloxacin. Clin Ther 32:1733–1737
21. Cholongitas E, Georgousaki C, Spyrou S et al (2009) Ciprofloxacin-induced acute cholestatic hepatitis. Ann Hepatol 8:400–401
22. Carrascosa MF, Lucena MI, Andrade RJ et al (2009) Fatal acute hepatitis after sequential treatment with levofloxacin, doxycycline, and naproxen in a patient presenting with acute Mycoplasma pneumoniae infection. Clin Ther 31:1014–1019
23. García-Aparicio J, Herrero-Herrero JI (2010) Toxic hepatitis following sequential treatment with cotrimoxazol, levofloxacin, doxycycline and sertraline in a patient with a respiratory infection. Farm Hosp 34:152–154
24. Verma R, Dhamija R, Batts DH et al (2009) Moxifloxacin induced fatal hepatotoxicity in a 72-year-old man: a case report. Cases J 2:8063
25. Dichiara AJ, Atkinson M, Goodman Z et al (2008) Ciprofloxacin-induced acute cholestatic liver injury and associated renal failure. Case report and review. Minerva Gastroenterol Dietol 54:307–315
26. Bhagirath KM (2008) A case report of highly suspected ciprofloxacin-induced hepatotoxicity. Turk J Gastroenterol 19:204–206
27. Okan G, Yaylaci S, Peker O et al (2008) Vanishing bile duct and Stevens-Johnson syndrome associated with ciprofloxacin treated with tacrolimus. World J Gastroenterol 14:4697–4700
28. Coban S, Ceydilek B, Ekiz F et al (2005) Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. Ann Pharmacother 39:1737–1740
29. Zimpfer A, Propst A, Mikuz G et al (2004) Ciprofloxacin-induced acute liver injury: case report and review of literature. Virchows Arch 444:87–89
30. Goetz M, Galle PR, Schwarting A (2003) Non-fatal acute liver injury possibly related to high-dose ciprofloxacin. Eur J Clin Microbiol Infect Dis 22:294–296
31. Schwalm JD, Lee CH (2003) Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. CMAJ 168:847–848
32. Airey KJ, Koller E (2003) Acute hepatitis associated with levaquin in a patient with renal insufficiency taking amiodarone. CMAJ 14:169
33. Bataille L, Rahier J, Geubel A (2002) Delayed and prolonged cholestatic hepatitis with ductopenia after long-term ciprofloxacin therapy for Crohn's disease. J Hepatol 37:696–699
34. Soto S, López-Rosés L, Avila S et al (2002) Moxifloxacin-induced acute liver injury. Am J Gastroenterol 97:1853–1854
35. Contreras MA, Luna R, Mulero J et al (2001) Severe ciprofloxacin-induced acute hepatitis. Eur J Clin Microbiol Infect Dis 20:434–435
36. Karim A, Ahmed S, Rossoff LJ (2001) Possible levofloxacin-induced acute hepatocellular injury in a patient with chronic obstructive lung disease. Clin Infect Dis 33:2088–2090
37. Nakamae H, Hino M, Yamane T (2000) A case of rhabdomyolysis due to levofloxacin. Clin Drug Invest 20:203–205
38. Björnsson E, Olsson R (2000) Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. Am J Gastroenterol 95:3662–3663
39. Iannini PB (2007) The safety profile of moxifloxacin and other fluoroquinolones in special patient populations. Curr Med Res Opin 23:1403–1413
40. O'Donnell JA, Gelone SP (2000) Fluoroquinolones. Infect Dis Clin North Am 14:489–513
41. De Valle MB, Av Klinteberg V, Alem N et al (2006) Drug induced liver injury in a Swedish university hospital out-patient hepatology clinic. Aliment Pharmacol Ther 24:1187–1195
42. Van Bambeke F, Tulkens PM (2009) Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. Drug Saf 32:359–378
43. Chalasani N, Björnsson E (2010) Risk factors for idiosyncratic drug-induced liver injury. Gastroenterology 138:2246–2259
44. Aithal GP, Day CP (2007) Nonsteroidal anti-inflammatory drug induced hepatotoxicity. Clin Liver Dis 11:563–575
45. Larson AM (2007) Acetaminophen hepatotoxicity. Clin Liver Dis 11:525–548
46. Elouni B, Ben Salem C, Zamy M (2010) Cytolytic hepatitis possibly related to levonorgestrel/ethinylestradiol oral contraceptive use: 2 case reports. Ann Pharmacother 44:2035–2037
47. Wolfson JS, Hooper DC (1991) Overview of fluoroquinolone safety. Am J Med 91:153–161
48. Liu HH (2010) Safety profile of the fluoroquinolones. Focus on levofloxacin. Drug Saf 33:353–369
49. Owens RC, Ambrose PG (2005) Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 41 [Suppl 2]:S144–S157
50. Jones SE, Smith RH (1997) Quinolones may induce hepatitis. BMJ 314:869
51. Hautekeete ML, Kockx MM, Naegels S et al (1995) Cholestatic hepatitis related to quinolones: a report of two cases. J Hepatol 23:759–760
52. Blum A (1991) Ofloxacin-induced acute severe hepatitis. South Med J 84:1158
53. EMEA/CHMP (issued 24/07/08) European Medicines Agency recommends restricting the use of oral moxifloxacin-containing medicines. http://www.emea.europa.eu/pdfs/human/press/pr/38292708en.pdf
54. Lopez-Navidad A, Domingo P, Cadafalch J et al (1990) Norfloxacin-induced hepatotoxicity. J Hepatol 11:277–278
55. Davoren P, Mainstone K (1993) Norfloxacin-induced hepatitis. Med J Aust 159:423–426
56. Lucena MI, Andrade RJ, Sánchez-Martinez H et al (1998) Norfloxacin-induced cholestatic jaundice. Am J Gastroenterol 93:2309–2311
57. Romero-Gómez M, Suárez García E, Fernández MC (1999) Norfloxacin-induced acute cholestatic hepatitis in a patient with alcoholic liver cirrhosis. Am J Gastroenterol 94:2324–2325
58. Henann NE, Zambie MF (2001) Gatifloxacin-associated acute hepatitis. Pharmacotherapy 21:157–182
59. Ball P, Mandell L, Niki Y et al (1999) Comparative tolerability of the newer fluoroquinolone antibacterials. Drug Saf 21:407–421
60. Bertino J Jr, Fish D (2000) The safety profile of the fluoroquinolones. Clin Ther 22:798–817