Risk of Acute Liver Injury in a Cohort of Oral Antimicrobial Users

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CONFLICT OF INTEREST STATEMENT

Bayer Pharma AG provided funding to RTI Health Solutions to conduct this study. The contract between RTI Health Solutions and Bayer Pharma AG for the conduct of this study grants the research team all decisions regarding the content of the publication of the results (ClinicalTrials.gov Identifier: NCT01434173). No relationships to disclose.

BACKGROUND

- Liver injury (especially severe liver injury/liver failure) is uncommon; however, it is among the most frequent and important causes of drugs failing during clinical trials and being withdrawn from the market.[1] Many antimicrobials (AMs) are associated with acute liver injury (ALI), but few large, population-based studies have been reported.[2]
- Moxifloxacin is a synthetic fluoroquinolone; the oral formulation was approved in 1999 in Europe, the United States (US), and other markets. It is indicated to treat acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis, community-acquired pneumonia, skin infections, complicated intra-abdominal infections, and pelvic inflammatory disease.
- An unpublished Sanofi-Aventis–sponsored PharMetrics study[3] was presented to the Food and Drug Administration (FDA) in 2006 during an Advisory Committee review of telithromycin. The study reported an elevated risk of hospitalization with ALI after moxifloxacin dispensing compared with amoxicillin/clavulanic acid. In this study, patients on moxifloxacin were older and had more comorbidities than the comparison group. No case validation was conducted in the study.

OBJECTIVES

- Primary: (1) Estimate the incidence rates of hospitalization or emergency department visit for noninfectious ALI in adults during treatment with each study AM and during nonuse; (2) Estimate age- and sex-standardized incidence rate ratios (reference: nonuse); (3) Estimate adjusted incidence rate ratios (as odds ratios) in a nested, matched case-control study with incidence density sampling.
- Secondary: (1) Estimate incidence rates and rate ratios for severe ALI; (2) Estimate incidence rates and rate ratios for acute liver failure.

METHODS

Data Source/Study Population

- HealthCore, established in 1996, is a wholly owned subsidiary of WellPoint, Inc. (the largest health benefits company by medical membership in the US and an independent licensee of the Blue Cross and Blue Shield Association).
- The HealthCore Integrated Research Database (HIRD^{SM}) contains data since 2004 for all plans (since 2001 for some). A total of 31 million lives with both medical and pharmacy coverage were available for research as of June 2009. Most patients are aged < 65 years. Approximately one-third of those aged ≥ 65 years are in Medicare Advantage Plans. The HIRD^{SM} contains fully adjudicated paid medical (inpatient, emergency department, outpatient) and pharmacy claims.
- Clinical information was obtained through abstraction of inpatient and emergency department medical records.

Study Cohort

- Inclusion criteria:
  - Aged ≥ 18 years with both medical and pharmacy benefits
  - First claim for dispensing of a study AM from July 1, 2001, to March 31, 2009, after ≥ 6 months of continuous enrollment
- Exclusion criteria:
  - History of infectious hepatitis or HIV/AIDS
  - Chronic alcoholism or alcoholic cirrhosis
  - Pregnancy (temporary exclusion, 180 days before and after any claim for a pregnancy-related code)
- Patients with cancer or other hepatic, biliary, or pancreatic diseases were not excluded.
- Among patients aged < 65 years, new users of study AMs prescribed more commonly than moxifloxacin were randomly sampled to produce cohorts of similar size.
- Total study cohort was 1,299,056 patients.
- Follow-up continued until study event, death, exclusion, disenrollment, or end of study (October 2009).

Exposure

- Study AMs: amoxicillin, amoxicillin/clavulanic acid, cefuroxime, clarithromycin, doxycycline, levofloxacin, moxifloxacin, telithromycin
- Exposure categories: current (dispensed use + 30 days); recent (90 days after current use); or nonuse (90 days after recent use)

Case Identification

- Automated claims screening by ICD-9-CM codes: 570.xx (acute and subacute necrosis of liver); 572.2x (hepatic coma); 573.3x (hepatitis unspecified)
- Primary endpoint: ALI[4]
  - Alanine transaminase (ALT) > 2x upper limit of normal (ULN); or
  - Total bilirubin (TB) > 2x ULN; or
  - Aspartate transaminase (AST), alkaline phosphatase (ALP), and TB all > ULN, with one > 2x ULN
- Secondary endpoints (subgroups of patients with primary endpoint):
  - Severe ALI[5]: ALT ≥ 3x ULN and TB ≥ 2x ULN
  - Acute liver failure: ALI with increased prothrombin time or international normalized ratio (INR) > 2 (without anticoagulant exposure) and recorded diagnosis of encephalopathy

Case Validation[6]

- Hospital records were abstracted by a HIPAA-compliant third-party vendor for current/past clinical data, imaging studies, pathology reports, and liver test values. All information was blinded to patient and provider identities and study drugs.
- Liver test results were used to assign tentative case status.
- Abstractions were reviewed (blinded to exposure) by two physicians experienced in studying drug-induced liver injury.

Analysis

- The main analysis included all valid and uncertain cases. Secondary analyses included (1) valid cases only, (2) cases without other diagnoses that can cause liver tests abnormalities[7] ("restricted"), (3) severe ALI, and (4) liver failure.
- Incidence rates were standardized to age and sex distribution of nonuse person-time.
- Ten controls were selected at random from the risk set on the event date of each case. Controls were matched to cases on age (within groups shown in Table 1) and sex.
- Conditional logistic regression on nested, matched case-control data was adjusted for age; history of liver, biliary tract, or pancreatic disease; concurrent use of potentially hepatotoxic drugs (other than study AMs); Deyo-Charlson Comorbidity Index[8]; individual diagnosis components of Deyo-Charlson Comorbidity Index (Table 3); and measures of health care utilization during 6 months before event date (number of hospitalization days, outpatient visits, and unique prescription medications).
- Odds ratios from adjusted case-control analysis with incidence density sampling are estimates of adjusted incidence rate ratios.

Human Subjects Protection

- The study was conducted according to current pharmacoepidemiology research guidelines[9,10] and was granted exemption from informed consent requirements by the RTI International institutional review board.

RESULTS

- Among 715 potential cases, 312 (44%) were valid cases, 108 (15%) were not cases, and 295 (41%) were of uncertain status due to insufficient information.[6]
- Among 312 valid cases of ALI:
  - 221 (70.8%) had discharge diagnoses listed that can cause liver test abnormalities (e.g., cholecystitis, metastatic cancer, congestive heart failure, sepsis).
  - 63 (20.2%) had "hepatitis" (or "drug-induced hepatitis") listed, no evidence of infectious etiology, and no other discharge diagnoses that are known causes of liver test abnormalities ("restricted ALI").
  - 28 (9.0%) had no specific disease diagnoses listed that were relevant to liver test abnormalities.
  - 82 (26.3%) had severe ALI.
  - 11 (3.5%) had acute liver failure.
    - 5 had current or recent single use of levofloxacin, and none had current or recent single use of moxifloxacin.
    - None occurred during nonuse.
- 312 valid cases and 295 uncertain cases (total 607 cases) were combined for some analyses.
- Main results are shown for single current use and multiple current use categories only (with nonuse as reference exposure category).

Table 1. Study Cohort Characteristics by AM Exposure at Entry

Characteristic	AM (Number of Users)									
	Total (%)	Amoxicillin (%)	Amoxicillin/ Clav (%)	Cefuroxime (%)	Clarithromycin (%)	Doxycycline (%)	Levofloxacin (%)	Moxifloxacin (%)	Telithromycin (%)	Current Multiple Use (%)
	(N = 1,299,056)	(n = 166,888)	(n = 178,047)	(n = 151,238)	(n = 156,774)	(n = 176,794)	(n = 181,332)	(n = 176,934)	(n = 79,357)	(n = 31,692)
Age, years										
18-24	9	10	11	11	8	13	5	5	9	6
25-34	16	16	17	17	15	18	12	13	18	16
35-44	22	19	22	24	23	20	19	22	26	24
45-54	22	18	20	23	22	19	23	25	25	25
55-64	16	13	12	16	14	13	21	20	16	18
65-74	10	13	11	6	12	10	10	8	4	7
75-84	5	8	5	3	5	6	7	5	2	3
85+	2	2	2	1	1	2	3	2	1	1
Sex										
Male	44	42	46	39	45	44	44	44	43	50
Female	56	58	54	61	55	56	56	56	57	50

clav = clavulanic acid.

Note: Patients counted as being exposed to each study AM are those exposed to a single study AM at cohort entry. Patients with current use of more than one study AM at cohort entry are counted only in the column for current multiple use.

Table 2. ALI (607 Cases), Standardized Incidence Rates, per 100,000 Person-Years

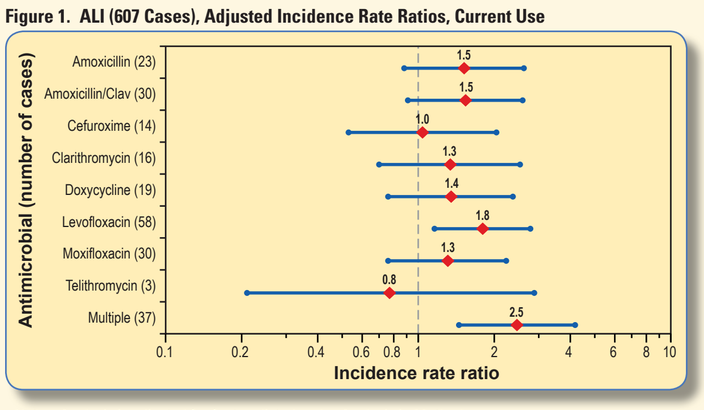
AM	Person-Years	Cases	Incidence Rate (95% CI)
Nonuse	350,873	123	35 (29-42)
Current single use			
Amoxicillin	44,555	23	51 (32-77)
Amoxicillin/Clav	35,529	30	86 (58-123)
Cefuroxime	21,456	14	70 (37-120)
Clarithromycin	25,593	16	64 (36-105)
Doxycycline	42,994	19	47 (28-73)
Levofloxacin	39,974	58	134 (101-175)
Moxifloxacin	24,901	30	116 (78-167)
Telithromycin	9,175	3	27 (5.5-83)
Current multiple use	15,915	37	235 (165-324)

CI = confidence interval.
Note: Incidence rates are standardized by age and sex.

Table 3. Characteristics of Cases (n = 607) and Controls (n = 6,070)

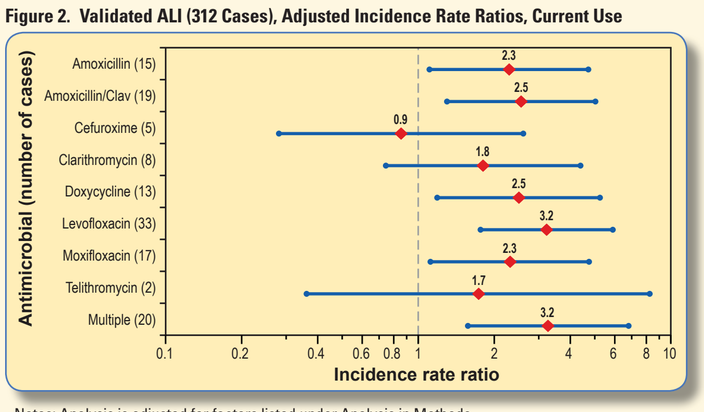
Characteristic	Cases n (%)	Controls n (%)
Sex		
Male	274 (45)	2,740 (45)
Female	333 (55)	3,330 (55)
Age, years		
18-24	23 (4)	230 (4)
25-34	48 (8)	480 (8)
35-44	78 (13)	780 (13)
45-54	129 (21)	1,290 (21)
55-64	128 (21)	1,280 (21)
65-74	99 (16)	990 (16)
75-84	77 (13)	770 (13)
85+	25 (4)	250 (4)
Comorbidity		
Myocardial infarction	73 (12)	194 (3)
Congestive heart failure	154 (25)	367 (6)
Peripheral vascular disease	71 (12)	257 (4)
Cerebrovascular disease	114 (19)	529 (9)
Dementia	15 (2)	69 (1)
Chronic pulmonary disease	233 (38)	1,298 (21)
Rheumatological disease	41 (7)	141 (2)
Peptic ulcer disease	42 (7)	112 (2)
Mild liver disease	28 (5)	11 (0)
Moderate to severe liver disease	17 (3)	1 (0)
Mild to moderate diabetes	153 (25)	775 (13)
Diabetes with complications	47 (8)	166 (3)
Hemiplegia or paraplegia	9 (1)	29 (0)
Moderate or severe renal disease	86 (14)	152 (3)
Malignancy	164 (27)	565 (9)
Metastatic solid tumor	62 (10)	111 (2)

Figure 1. ALI (607 Cases), Adjusted Incidence Rate Ratios, Current Use



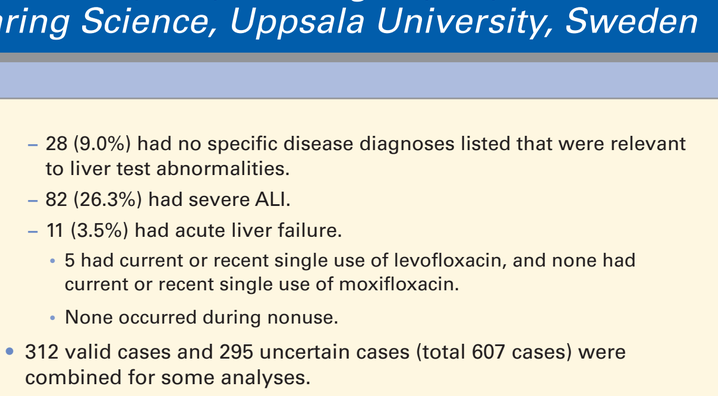
Notes: Analysis is adjusted for factors listed under Analysis in Methods.
Results for categories of recent use and of mixed current and recent use are not shown.

Figure 2. Validated ALI (312 Cases), Adjusted Incidence Rate Ratios, Current Use



Notes: Analysis is adjusted for factors listed under Analysis in Methods.
Results for categories of recent use and of mixed current and recent use are not shown.

Figure 3. Restricted ALI (63 Cases), Adjusted Incidence Rate Ratios, Current Use



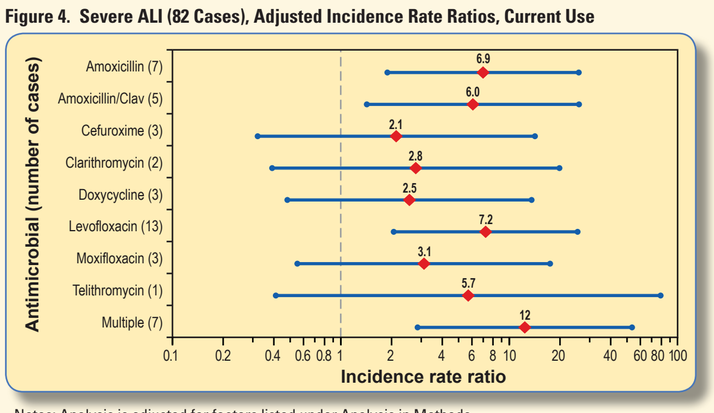
Notes: Analysis is adjusted for factors listed under Analysis in Methods.
Results for categories of recent use and of mixed current and recent use are not shown.
Scale differs from that in Figures 1 and 2.
Exact mid-P upper bound for doxycycline is based on the crude data.

Table 4. Severe ALI (82 Cases), Standardized Incidence Rates, per 100,000 Person-Years

AM	Person-Years	Cases	Incidence Rate (95% CI)
Nonuse	350,873	9	2.6 (1.2-4.9)
Current single use			
Amoxicillin	44,555	4	9.4 (2.5-24)
Amoxicillin/Clav	35,529	5	13 (4.2-31)
Cefuroxime	21,456	2	11 (1.2-41)
Clarithromycin	25,593	1	6.8 (0.2-31)
Doxycycline	42,994	3	7.4 (1.5-22)
Levofloxacin	39,974	10	23 (11-43)
Moxifloxacin	24,901	3	11 (2.2-32)
Telithromycin	9,175	1	8.9 (0.2-56)
Current multiple use	15,915	7	45 (18-92)

Note: Incidence rates are standardized by age and sex.

Figure 4. Severe ALI (82 Cases), Adjusted Incidence Rate Ratios, Current Use



Notes: Analysis is adjusted for factors listed under Analysis in Methods.
Results for categories of recent use and of mixed current and recent use are not shown.
Scale differs from that Figures 1 and 2.

CONCLUSIONS

- In a large study evaluating patients with a variety of common comorbidities in which cases were validated, we found modest elevations in the risk of noninfectious ALI associated with some AMs, but little evidence of any strong effect of commonly used AMs on the incidence of ALI. We found a comparatively high adjusted relative risk among current users of multiple study AMs. This finding is reminiscent of previous research reporting a higher risk of liver injury in patients exposed to multiple drugs.[11]
- Among current users of the individual study AMs, the highest incidence of liver injury was observed with levofloxacin; lower incidences were observed for moxifloxacin, amoxicillin/clavulanic acid, and the other study AMs. Recent use of AMs is associated with lower risk than current use (data not shown).
- Higher relative risks in the analysis restricted to valid cases than in the analysis that also includes uncertain cases is consistent with results representing causal associations.
- The HIRD^{SM} is a valuable resource for studies with outpatient drug exposures and clinical outcomes (such as ALI) requiring validation using hospital or emergency department records.

REFERENCES

Please see handout for a complete reference list.