Severe Hepatic Injury Following Antibiotic Use

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Conflict of interest, IRB, and GPP

- This study was funded in part by a research contract with Sanofi-Aventis
- This study was approved by the New England Institutional Review Board and the Privacy Board of New England
- We abided by the Guidelines for Good Pharmacoepidemiology Practices (GPP)

Objectives

- The primary objective of this study was to compare the risk of acute liver failure within 60 days of drug use among users of telithromycin compared to users of clarithromycin.
- The secondary objective was to compare the risk of severe hepatic injury, classified based on clinical criteria, among users of telithromycin compared to users of clarithromycin.

Data source: Ingenix Research Data Mart

- Administrative and Demographic Information
- Medical Claims
  - Inpatient hospital
  - Outpatient hospital
  - Emergency room
  - Physician's office
- Pharmacy Claims
  - Drug name
  - Dosage form
  - Drug strength
  - Fill date
  - Days of supply
- There were approximately 12 million enrolled persons in the database for 2005.

Methods: Cohort membership

- During the period from July 1, 2004 to December 31, 2005, we identified users of telithromycin and of clarithromycin.
- This study was limited to telithromycin and clarithromycin in order to take advantage of the i3 Aperio suite of programs.
- Patients were required to have
  - complete demographic and enrollment information, and
  - at least six months of continuous enrollment prior to their first dispensing of telithromycin or clarithromycin.
- The six-month baseline period, which included the date of first dispensing, was used to determine each patient's inclusion status and baseline covariates.

Methods

- Propensity score matched cohorts using greedy match algorithm
- Potential cases of liver injury were identified by the presence of either of the following in up to 1 year of follow-up:
  - ICD 570 – acute and subacute necrosis of liver
  - ICD 572.2 – hepatic coma
- Claims profiles of potential cases were reviewed
- Medical records abstracted for outcome adjudication

Outcome definition: Acute liver failure (ALF)

- The definition involved the following components to designate a case as ALF:
  - Acute onset;
  - Absence of underlying chronic active liver disease;
    - and
  - Meets Hy's Law laboratory criteria (see below);
    - and/or
  - Encephalopathy – any reported alterations in mental status
    - and/ or
  - Coagulopathy – abnormal coagulation (an increase in prothrombin time (PT) or an international normalized ratio (INR) > 2) in a patient not receiving anticoagulant medications.

Outcome definition: Hy's law

- Potential cases not meeting the ALF definition, where any degree of hepatocellular jaundice occurred, irrespective of severity or clinical symptoms, were classified as meeting Hy's Law [Navarro and Senior 2006] if the following conditions were met:
  - Serum alanine aminotransferase (ALT) levels greater than or equal to 3 times the upper limit of normal (ULN),
    - and
  - Direct bilirubin greater than 3 mg/dl,
    - and
  - Absence of alkaline phosphatase (AP) elevation.

Outcome definitions

- Alanine aminotransferase (ALT) levels greater than or equal to 10 times ULN
- ALT levels greater than or equal to 4 times ULN and less than 10 times ULN
- Other – available data in the chart did not meet the criteria above but the consulting clinician still considered the case representing severe hepatic injury without other causes.

Exposure definition

- Only cases with evidence of study drug use (telithromycin or clarithromycin) within 60 days of each outcome were retained for analysis
- We determined the most recently used study drug
- Based on the fill date and the days supplied from the dispensing records in the pharmacy claims, we determined amount of days treated and number of days elapsed since last study drug use

Data analysis

- As-matched – based on cohort of origin
- As-treated – based on number of dispensings of study drugs in matched cohorts
  - If exposure to both drugs occurred within 60 days of outcome then the outcome was counted in each study drug exposure category
- Nested case-control
  - Up to 1,000 controls selected, matched on propensity score and number of days of follow-up
  - Only controls with any study drug exposure in the 60 days prior were retained
  - Separate category of exposure to both drugs used

Results

- Between July 2004 and December 2005, there were:
  - 107,700 initiators of telithromycin
  - 202,903 initiators of clarithromycin
- We matched 102,660 (95.3%) telithromycin initiators to comparable clarithromycin initiators
- The cohorts were well-balanced with respect to a wide range of health care utilization and demographic characteristics, prior diagnoses and procedures, and drugs used.

Table 1 - Demographic characteristics

Demographics	Telithromycin (N=102,660) N	%	Clarithromycin (N=102,660) N	%
Age				
0 - 9	40	0.0	43	0.0
10 - 19	4,637	4.5	4,424	4.3
20 - 29	12,136	11.8	12,132	11.8
30 - 39	24,235	23.6	24,356	23.7
40 - 49	28,309	27.6	28,460	27.7
50 - 59	21,822	21.3	21,710	21.1
60 - 64	6,135	6.0	6,166	6.0
65 +	5,346	5.2	5,369	5.2
Gender				
Female	62,138	60.5	61,871	60.3
Male	40,522	39.5	40,789	39.7
Region				
Northeast	10,656	10.4	10,752	10.5
Midwest	26,238	25.6	26,121	25.4
South	56,635	55.2	56,758	55.3
West	9,131	8.9	9,029	8.8

Table 6a - Medical record abstraction results

Claims-based diagnosis (ICD-9)	Claims-based outcomes	Medical records attempted	Medical records abstracted	% abstracted	Accepted events	Acceptance rate
Hepatic failure (570)	68	64	56	88%	11	20%
Hepatic coma (572.2)	21	20	17	85%	1	6%
Both (570 and 572.2)	4	4	4	100%	4	100%
Overall	93	88	77	88%	16	21%

Table 6b - Reasons for exclusion of claims-based candidate outcomes

Reason for exclusion	Cohort of origin	
	Telithromycin	Clarithromycin
No LFTs or chart not obtained	17	17
Insufficient LFT elevation	4	4
Normal LFTs	4	5
Infectious hepatitis	4	2
Cirrhosis	3	2
Alcoholic hepatitis	2	1
Shock liver	1	2
Cholangiocarcinoma	1	0
Leukemia	1	0
Rhabdomyolysis	0	1
Acute cholecystitis	0	1
Total	37	35

Table 8 - Outcomes within 60 days of drug use, based on cohort of origin and most recent drug used

Outcome	Telithromycin Most Recent		Clarithromycin Most Recent	
	Telithromycin Initiators	Clarithromycin Initiators	Telithromycin Initiators	Clarithromycin Initiators
ALF	0	0	0	2
Hy's law	1	1	0	0
ALT ≥10 x ULN	2	1	0	0
ALT ≥4 and <10 x ULN	1	0	0	0
Other	1	0	0	0

Table 9 - Outcomes with use of both telithromycin and clarithromycin within 60 days, based on cohort of origin and sequence of drug use

Outcome	Telithromycin followed by Clarithromycin		Clarithromycin followed by Telithromycin	
	Telithromycin Initiators	Clarithromycin Initiators	Telithromycin Initiators	Clarithromycin Initiators
ALF	0	0	0	0
Hy's law	0	0	0	1
ALT ≥10 x ULN	0	0	1	1
ALT ≥4 and <10 x ULN	0	0	0	0
Other	0	0	0	0

Drug sequence within 60 days of outcome for patients with double exposure:

1) Clarithromycin initiator cohort: clarithromycin 500mg x 10 days, 11 days of no therapy, telithromycin 400mg x 5 days, 35 days of no therapy, then event -> Hy's Law

2) Telithromycin initiator cohort: clarithromycin 500mg x 10 days, 35 days of no therapy, telithromycin 400mg x 10 days, 4 days of no therapy, then event -> ALT > 10 and only study in-hospital death

3) Clarithromycin initiator cohort: clarithromycin 500mg x 10 days, 14 days of no therapy, telithromycin 400mg x 10 days, 21 days of no therapy, then event -> ALT > 10

Table 11 - Risk of each outcome within 60 days of drug use, based on cohort of origin

Outcome	Cohort of Origin	# of Events	Risk per 100,000 persons	95% CI	
ALF	Telithromycin	0	0.00	0.00	3.74
	Clarithromycin	2	1.95	0.53	7.10
Hy's law	Telithromycin	1	0.97	0.17	5.52
	Clarithromycin	1	0.97	0.17	5.52
ALT ≥10 x ULN	Telithromycin	2	1.95	0.53	7.10
	Clarithromycin	1	0.97	0.17	5.52
ALT ≥4 and <10 x ULN	Telithromycin	1	0.97	0.17	5.52
	Clarithromycin	0	0.00	0.00	3.74
Other	Telithromycin	1	0.97	0.17	5.52
	Clarithromycin	0	0.00	0.00	3.74
Any	Telithromycin	5	4.87	2.08	11.40
	Clarithromycin	4	3.90	1.52	10.02

Table 12 – Risk difference and relative risk of each outcome based on cohort of origin

Outcome	RD	95% CI		RR	95% CI	
ALF	-1.95	-4.65	0.75	0.00	0.00	5.32
Hy's law	0.00	-2.70	2.70	1.00	0.01	78.50
ALT ≥10 x ULN	0.97	-2.33	4.28	2.00	0.10	11.00
ALT ≥4 and <10 x ULN	0.97	-0.94	2.88	∞	0.03	∞
Other	0.97	-9.40	2.88	∞	0.03	∞
Any	0.97	-4.75	6.70	1.25	0.27	6.30

Note: Risk difference (RD) per 100,000 persons and relative risk (RR) of each outcome within 60 days of drug use, comparing telithromycin to clarithromycin, based on cohort of origin

Table 13 - Risk of each outcome within 60 days of drug use, based on the total number of dispensings per drug during follow-up

Total number of telithromycin dispensings: 127,808
Total number of clarithromycin dispensings: 132,119

Outcome	Drug used within 60 days	# of Events	Risk per 100,000 dispensings	95% CI	
ALF	Telithromycin	0	0.00	0.00	3.01
	Clarithromycin	2	1.51	0.42	5.52
Hy's law	Telithromycin	2	1.56	0.43	5.71
	Clarithromycin	1	0.76	0.13	4.29
ALT ≥10 x ULN	Telithromycin	3	2.35	0.80	6.90
	Clarithromycin	2	1.51	0.42	5.52
ALT ≥4 and <10 x ULN	Telithromycin	1	0.78	0.14	4.43
	Clarithromycin	0	0.00	0.00	2.91
Other	Telithromycin	1	0.78	0.14	4.43
	Clarithromycin	0	0.00	0.00	2.91
Any	Telithromycin	7	5.48	2.65	11.31
	Clarithromycin	5	3.78	1.62	8.86

Table 14 – Risk difference and relative risk of each outcome based on the total number of dispensings per drug during follow-up

Total number of telithromycin dispensings: 127,808
Total number of clarithromycin dispensings: 132,119

Outcome	RD	95% CI		RR	95% CI	
ALF	-1.51	-3.61	0.58	0.00	0.00	5.50
Hy's law	0.81	-1.82	3.44	2.07	0.11	121.97
ALT ≥10 x ULN	0.83	-2.55	4.22	1.55	0.18	18.56
ALT ≥4 and <10 x ULN	0.78	-0.75	2.32	∞	0.03	∞
Other	0.78	-0.75	2.32	∞	0.03	∞
Any	1.69	-3.55	6.93	1.45	0.40	5.78

Note: Risk difference (RD) per 100,000 dispensings and relative risk (RR) of each outcome within 60 days of drug use, comparing telithromycin to clarithromycin, based on the total number of dispensings per drug during the follow-up period

Table 15 - Nested case-control analysis of each outcome within 60 days of drug use

Outcome	Drug used within 60 days	# of Cases	# of Controls	OR	95% CI	
ALF	Both	0	2	0.00	0.00	730.40
	Telithromycin	0	515	0.00	0.00	1.97
	Clarithromycin	2	527	ref	-	-
Hy's law	Both	1	17	∞	0.00	∞
	Telithromycin	1	937	∞	0.00	∞
	Clarithromycin	0	974	ref	-	-
ALT ≥10 x ULN	Both	2	15	∞	0.00	∞
	Telithromycin	1	968	∞	0.00	∞
	Clarithromycin	0	994	ref	-	-
ALT ≥4 and <10 x ULN	Both	0	2	-	-	-
	Telithromycin	1	498	∞	0.00	∞
	Clarithromycin	0	500	ref	-	-
Other	Both	0	0	-	-	-
	Telithromycin	1	9	∞	0.00	∞
	Clarithromycin	0	29	ref	-	-
Any	Both	3	36	109.61	19.19	626.22
	Telithromycin	4	2927	2.90	0.51	16.51
	Clarithromycin	2	3024	ref	-	-

Note: The odds ratios and 95% confidence intervals for the combined outcome category of any liver injury were adjusted for the variable number of controls using conditional logistic regression.

Conclusions

- There were no cases of ALF among telithromycin users and 2 cases of ALF among clarithromycin users.
- The as-matched and as-treated analyses were comparable, with a 25% and 45% increase, respectively and with wide confidence bounds which include the null value, in telithromycin users for any severe hepatic injury outcome compared to clarithromycin users.
- In a secondary post-hoc nested case-control analysis separating out the effect of both drugs used within the 60-day period prior to the each outcome, there was a possible increase in severe liver injury overall with telithromycin use alone, and over a 100-fold increase when both study drugs were used, compared to clarithromycin alone.
- These study findings offer no support for an elevated risk of liver failure in recipients of telithromycin as compared to clarithromycin.
- This study points to an elevated risk of hepatic injury in users of clarithromycin and telithromycin in sequence, as compared to clarithromycin alone. This finding warrants further investigation.