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Drug Induced Liver Injury Caused by Intravenously Administered Medications: The Drug Induced Liver Injury Network (DILIN) Experience

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Abstract

Background and Aims—Idiosyncratic drug induced liver injury (DILI) can be caused by intravenous (IV) medications, but the characteristics of DILI caused by these agents are not known. The aim of this study is to characterize the clinical features of subjects with suspected DILI associated with IV agents enrolled into the DILIN Prospective Study.

Methods—Subjects with suspected DILI due to IV medications with probable, highly likely, or definite causality scores were eligible.

Results—Between 2004 and October 2010, 542 cases of DILI were adjudicated for causality, of which 32 were eligible for inclusion in this study. DILI was ascribed to a single IV agent in 27 and to multiple IV agents in 5 subjects. Antimicrobial agents (62%), anti-neoplastic agents (16%), and phenytoin (9%) were most commonly implicated. The pattern of liver injury was hepatocellular in 30%, mixed in 33%, and cholestatic in 37%. The peak ALT, AlkP, and total bilirubin were 686 ± 915 U/L, 623 ± 563 U/L, and 8.7 ± 10.3 mg/dL, respectively. The duration for ≥ 50% improvement from peak ALT, AlkP, and total bilirubin were 25 ± 37, 59 ± 69, and 20 ± 28 days respectively. DILI severity was mild in 37%, moderate in 47%, and severe in 13% and fatal in 3%, with no liver transplantation. Their causality was adjudicated as definite in 5, very likely in 17, and probable in 10 subjects. The frequency of chronic DILI was 13%.

Conclusion—Antimicrobial agents and anti-neoplastic are the most common IV agents to cause DILI. DILI ascribed to IV agents is relatively infrequent, but its outcomes are similar to those of the overall DILIN cohort.

Keywords

Drug induced liver injury; Hepatotoxicity; Intravenous; DILIN

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Introduction

Idiosyncratic drug-induced liver injury (DILI) is an unpredictable and rare event with an estimated incidence of 1 per 10,000 to 100,000 treated patients.[1-2] Although rare, it can be severe and life threatening, contributing to 13% of all cases of acute liver failure in the United States.[3] The majority of DILI cases published in the literature are due to agents administered orally, but in clinical practice it is not uncommon to encounter instances of acute liver injury potentially caused by agents that are administered intravenously (IV agents). Since IV agents may be administered at higher doses and may be used in different clinical circumstances than oral agents, it is possible that the phenotype and outcome of DILI caused by IV agents is different from that of liver injury caused by oral compounds.

The DILIN Prospective Study is an ongoing multicenter observational study that was initiated in 2004 to enroll adults and children with suspected DILI. A preliminary report described the clinical characteristics of first 300 patients enrolled into the DILIN Prospective Study.[4] Over 100 different medications and dietary supplements were associated with DILI, mainly antimicrobials (45%), central nervous system acting agents (15%) and non-steroidal anti-inflammatory agents (5%).[4] More than one agent was implicated in 20% of cases, liver enzyme abnormalities persisted for more than 6 months in 14% of cases, and overall mortality was 8%. Although some implicated agents in this report were administered intravenously, liver injury specifically related to IV agents was not characterized.

In this paper, we report the implicated agents, clinical characteristics, and outcomes of DILI associated with IV administered drugs in patients enrolled into the DILIN Prospective Study between September 2004 and October 2010.

Materials and Methods

Patients

This current study is based on subjects who were enrolled into the DILIN Prospective Study between September 2004 and October 2010 whose causality has been adjudicated. We studied episodes of probable, very likely or definite DILI where at least one implicated agent was administered intravenously and adjudicated as a probable, very likely or definite cause of DILI. The design of the DILIN Prospective Study has been previously described.[5]

Clinical Parameters

Enrolled patients had a baseline visit for clinical history, examination, and review of all biochemical, serologic, imaging and biopsy data, as well as undergoing necessary supplemental testing to exclude competing causes of liver injury. Patient demographics, comorbidities, social history, medication allergies, and concomitant medications were reviewed. Based on alanine aminotransferase (ALT) and alkaline phosphatase (AlkP) levels at presentation, the pattern of liver injury was categorized into hepatocellular, cholestatic, or mixed.[4] The interval between the administration of the implicated agent(s) and the onset of DILI was assessed. We also reviewed the health care setting (e.g., hospital, outpatient/ infusion center, or ambulatory surgery center) in which the implicated IV agent was administered. The time from DILI onset to peak liver biochemistries, as well as improvement from peak to 50% and to normal laboratory values were also determined. Patients were followed for at least 6 months, and if liver enzyme abnormalities persisted to that time point (protocol defined chronic DILI) they were seen in follow-up at 12 and 24 months after enrollment.

Causality and severity

According to previously described methods, the causality and severity scores were assessed for each enrolled patient.[6] The DILIN Causality scores ranged between 1 and 5; 1 “definite” (>95% probability), “very likely” (75-95% probability), “probable” (50-75% probability), “possible” (5-50%) and “unlikely” (<5% probability).[6] A DILIN causality score was also assigned to each implicated agent. Cases of “possible” or “unlikely” DILI, or where the IV agent was a “possible” or “unlikely” cause of DILI, were excluded. The DILIN severity scores ranged between 1 and 5; 1 mild, 2 moderate, 3 moderate and hospitalized, 4 severe, 5 fatal.[6]

Statistical analysis

Descriptive analysis included mean ± SD and percentages. Differences between groups were analyzed using Mann-Whitney and ANOVA tests for continuous variables, and the Chi-square for categorical variables. All analysis were performed using SAS statistical analysis software version 9.2 (Cary, NC), with a p-value of < 0.05 considered significant.

Results

During the study period, there were 55 subjects with suspected DILI with at least one of the implicated medications being an IV agent. Out of these, 32 subjects had suspected DILI due to an IV agent with causality score ≥ 3 (probably, highly likely or definite) and this constituted our study group (Figure 1).

Selected clinical characteristics of the study group are described in Table 1. Twenty seven patients (84%) had at least one co-morbid condition, and 11 (34%) had 4 or more. The implicated IV agent was administered in the hospital setting in 22 (69%) cases, in an outpatient infusion center in 5 (15.5%), and in an ambulatory surgical center in 5 (15.5%).

The characteristics of liver injury are described in Table 2. Latency ranged from 1 day to 14 weeks; it was ≤ 1 week in 9 (36%) and 2-4 weeks in 10 (40%) cases with single agents implicated. Most patients were symptomatic, and nausea, abdominal pain, itching and jaundice were the common symptoms. Selected laboratory test results are shown in Table 3. The pattern of liver injury was hepatocellular in 30%, mixed in 33.3%, and cholestatic in 36.7%. Total bilirubin and AlkP peaked later than ALT and aspartate aminotransferase (AST) after onset, and took longer to decline from their peak and to normalize.

Twenty-two patients (68.8%) were hospitalized. There was no difference in hospitalization rates in patients older or younger than 65 (65% and 78% respectively, P=0.7). Liver enzyme abnormalities persisted in 4 (12.5%) patients 6 months after onset of liver injury, i.e., had chronic DILI, and 4 (12.5%) patients died. One death was liver related in a patient with underlying malignancy. No patient underwent liver transplantation.

DILI was adjudicated as “definite” in 5 (15.6%), “very likely” in 17 (53.1%), and “probable” in 10 (31.3%) patients. DILI was ascribed to a single IV agent in 27 (84.4%) patients, and to two IV agents in 5 (15.6%) patients. The frequency of causality scores for the case as a whole and for the most implicated IV agent per case, and the RUCAM score the main implicated agent, and the severity scores are shown in Table 4.

The classes of the implicated IV agents were antimicrobials in 20 (62.5%) cases, anti-neoplastic agents in 5 (15.6%), central nervous system agents in 3 (9.4%), and cardiovascular agents in 2 (6.3%) (Table 5). Antimicrobials implicated included cephalosporins in 9 cases and fluoroquinolones in 7, but also included penicillins,

sulfonamides and macrolides. Anti-neoplastic agents, the 2nd largest class of implicated agents, agents, were similarly diverse and included immunomodulators in 3 cases.

IV agents were administered either daily over relatively short periods of time in 26 (81%) cases, (e.g., antibiotics and anti-epileptics) or intermittently over longer periods of time in 6 (19%) cases (e.g., anti-neoplastic agents and immunomodulators). The pattern of IV therapy was associated with differing settings of administration, with 81% of daily dosed IV agents being administered in the hospital setting and none in outpatient infusion centers, where as 83% of intermittently dosed IV agents were administered in outpatient infusion centers ($p < 0.001$). The mean duration of IV agent administration was 19 ± 17 days for daily vs. 48 ± 40 days for intermittently dosed IV agents ($p = 0.12$). The mean latency was shorter for daily (15 ± 12 days) vs. intermittently (47 ± 42 days) administered agents, but this did not reach statistical significance ($p = 0 .12$). Daily-administered IV agents presented less frequently with a hepatocellular injury pattern (21%) compared with intermittently dosed agents (67%) ($p = 0.09$). Aside from indication for IV agent use, all other patient and clinical characteristics, DILI severity and outcomes did not differ based on a daily vs. intermittent dosing pattern.

The characteristics of 17 episodes of DILI where daily-administered IV agents were given intravenously throughout were compared to 9 episodes of DILI where the IV agent was subsequently switched to oral route to complete the treatment course (Table 6). Although the pattern of liver injury did not differ, DILI due to IV followed by oral agents presented more frequently in younger female patients, and was associated with rash (60% vs. 18% respectively, $p=0.02$) and a greater frequency of eosinophilia. DILI cases due to IV followed by oral exposure were also associated with a trend towards higher aminotranseferases and more severe DILI, but their causality scores or overall outcomes were not different. None of the intermittently administered IV agents were available in oral form, and given their distinct duration of administration, latency and signature of injury, these 6 episodes of DILI were not included in this subgroup analysis.

Discussion

In this study, using data from a large multicenter prospective study, with uniform data collection and adjudication by consensus of an expert panel, we have described DILI caused by IV agents, that accounted for a relatively small proportion of the overall DILIN cohort at the time review (10% of cases). Thus, most DILI is related to orally administered agents.

An interesting finding was the difference in DILI due to daily vs. intermittently dosed IV agents. The shorter duration of exposure and shorter latency with daily-administered IV agents were not surprising. While it may be expected that DILI from an IV exposure with relatively short latency would be associated with a more hepatocellular injury pattern, and that DILI with chronic exposure would be associated with a cholestatic injury pattern, the converse was observed. This is likely explained by the class of agents involved. Daily administered agents were predominantly antimicrobials, of which cephalosporins were the most common agent group implicated. Cholestatic liver injury has been well described with cephalosporins, penicillins, sulfonamides and macrolides. Patients receiving IV antimicrobial agents were predominantly hospitalized with active infections, and sepsis too has been associated with cholestasis, which may have contributed to the injury pattern in some of those cases. Intermittently administered IV agents on the other hand were exclusively anti-neoplastic agents and immunomodulators. The longer half life of some of the latter agents and frequent underlying autoimmune disease in subjects receiving immunomodulators may have contributed to the longer latency and predominantly hepatocellular pattern.

In addition, the distinction between IV and oral administration of implicated agents was imprecise in 28% of patients in this study, who were exposed to the implicated agent both intravenously and orally prior to DILI onset. DILI due to IV and orally administered agents was associated with longer overall exposure and a trend towards more severe DILI, possibly as a result of this extended use. The increased incidence of rash and eosinophilia may be explained by the 3 cases of phenytoin-related DILI, which was given both IV and orally in all 4 cases, and is associated with these clinical features.[7] There was a trend towards younger age and a greater proportion of female gender in patients with IV and orally administered agent related DILI, factors that are associated with more frequent hepatocellular injury and more severe liver injury.[4] Although the frequency of hepatocellular injury was not different, these factors may have contributed to the trend of higher transaminases and more severe injury in patients with DILI after IV and oral exposure to the implicated agent.

As is the case with DILI in general,[4, 8] antimicrobials were the most frequently implicated class for IV DILI, however the sub-classes of implicated antimicrobials differed between the two groups. Cephalosporins and quinolones were the most common IV antimicrobials whereas amoxicillin/clavulanate, nitrofurantoin, isoniazid, and trimethoprim/sulfamethoxazole are the common oral antimicrobials to cause DILI.[4]

In order to understand whether IV DILI may have a unique phenotype (i.e., in comparison to DILI in general), we compared the characteristics of our current cohort to patients included in our earlier report of first 300 patients into the DILIN Prospective Study and the Spanish registry report on DILI in 461 patients (table 7).[4, 8] The present cohort of IV agent DILI represents a small subset of the DILIN cohort, whose characteristics are determined predominantly by DILI due to oral agents. Nevertheless, given the overlap in some cases of IV agent DILI in our study and the previously described DILI cohort, this comparison is strictly descriptive. There were no apparent differences in patient characteristics between the groups. DILI with IV agents was more frequently associated with antimicrobial agents, and presented with lower mean ALT and AST levels compared with the DILIN cohort, but relatively higher peak AlkP levels. Mirroring this, the DILI pattern with IV agents was less frequently hepatocellular than the DILIN cohort, but the frequency of cholestatic presentation was similar. Severity scores, development of chronic DILI and liver related mortality were similar. The mean duration of agent exposure was not reported in the DILI cohort, but mean IV agent exposure was shorter than mean agent exposure as reported by the Spanish registry study. The mean latency interval in IV agent cases was shorter than the mean latency in the DILIN and Spanish registry studies. Compared with the DILIN cohort, mean IV agent latency (20 days) was similar to that seen in patients with mild to moderate DILI (36 days) but shorter than in cases of severe DILI (66 days). In summary, DILI due to IV agents has a characteristic phenotype. IV related DILI is typically associated with antimicrobial agents, presents with brief agent exposure, shorter latency and less frequently with a hepatocellular pattern. All of these differences were more exaggerated when comparing continuously administered IV agents with the previously reported cohorts. This may reflect a selection bias for antimicrobials which are typically prescribed for limited periods of time and may be associated with shorter latency,[9] rather than a different signature of injury due to IV administration. DILI due to IV agents is associated with a similar distribution of severity of liver injury, and similar rates of chronic liver injury and liver related deaths compared with the overall DILIN cohort.

The proportion of IV agent cases adjudicated as less than probable DILI was 24%, compared with 13% for all agents in the DILIN cohort. The proportions of “definite” DILI were lower and “probable” DILI were greater with IV agents. This shift in likelihood scores raises the possibility that DILI due to IV agents may be more difficult to detect clinically. This may be

the result of clinically complex settings in which IV agents are typically administered, and reflected by the alternative causes of liver injury, predominated by viral infections, other drugs and/or sepsis, in the 14 cases that were enrolled on suspicion of DILI but adjudicated as less than probable DILI.

In summary, DILI with IV agents is associated with distinct classes of agents, unique clinical contexts of administration and associated injury patterns. DILI due to IV agents shares many characteristics with the broader spectrum of DILI. However, the complex clinical scenarios in which most IV agents are likely to be administered, such as in hospitalized patients receiving multiple medications, also likely limit the ability to differentiate DILI from other injury processes. Finally, the data suggest that increased vigilance and a high level of suspicion are likely required to identify cases of DILI due to IV agents.

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Abbreviations

ALT	alanine aminotransferase
AlkP	alkaline phosphatase
AST	aspartate aminotransferase
DILI	drug induced liver injury
DILIN	Drug-Induced Liver Injury Network
INR	international normalized ratio
IV	Intravenous
RUCAM	Roussel Uclaf Causality Assessment Method
ULN	upper limit of normal

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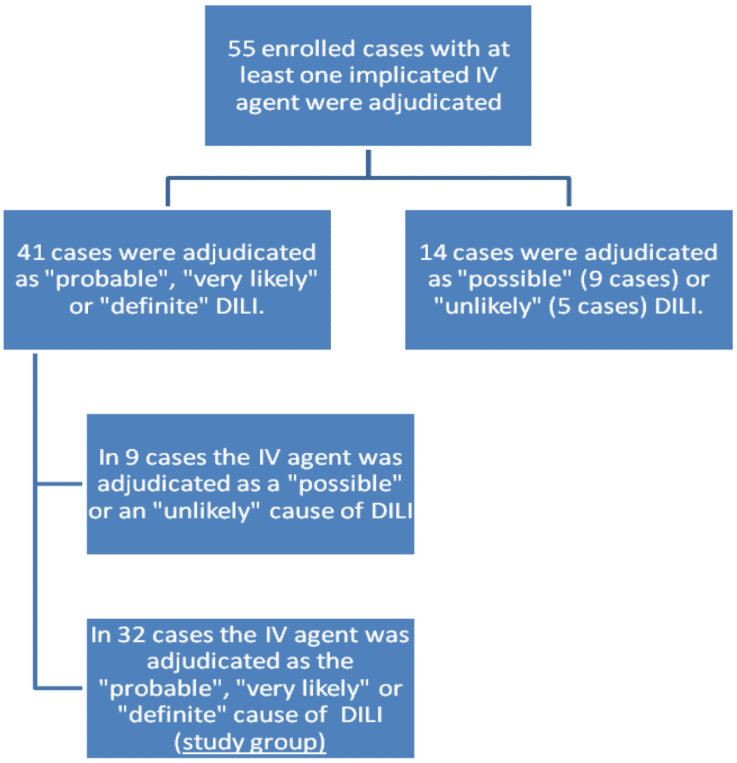

Figure 1.

A flow chart depicting the formation of the study cohort from cases with implicated IV agents enrolled during the period between 2003 and October 2010. The cause of liver injury in the 14 cases adjudicated as “possible” (9 cases) or “unlikely” (5 cases) DILI was acute hepatitis C infection in 3 cases, other liver disease in 3 cases, sepsis and biliary obstruction in 1 case each, unknown in 2 cases and other in 4 cases.

Table 1

Selected demographic and clinical features of the study cohort (N=32)

Age, mean ± SD *yrs*	51 ± 21
Proportion ≥ 65 yrs	9/32 (28%)
Females	16/32 (50%)
Self-reported race	
- Caucasian	28/31 (90.3%)
- Black	1/31 (3.2%)
- Other/Multiracial	2/31 (6.5%)
Body Mass Index, mean ± SD kg/m^2	26 ± 6.5
Prior Drug Allergies	14/32 (43.8%)
Alcohol Use	18/30 (60.0%)
Past Medical History:	
- Diabetes	10/32 (31.3%)
- Neurological Disease	7/32 (21.9%)
- Heart Disease	7/32 (21.9%)
- Renal Disease	4/32 (12.5%)
- Pulmonary Disease	11/32 (34.4%)
- Gastrointestinal Disease	14/32 (43.8%)
- Malignancy	9/32 (28.1%)
- Congestive Heart Failure:	2/32 (6.3%)
- Underlying liver disease	1/32 (3.1%)

Table 2
Selected clinical features at presentation (N=32)

Days from the IV agent start to earliest sign or symptom (mean ± SD)	9 ± 22
Days from IV agent start to onset (mean ± SD)	20 ± 22
Days from IV agent start date to DILI onset	
- ≤ 1 week	9/25 (36%)
- 2 to 4 weeks	10/25 (40%)
- 5 to 12 weeks	5/25 (20%)
- 13 to 24 weeks	1/25 (4%)
- >24 weeks	None
Signs and symptoms at onset	
- Jaundice	18/32 (56.3%)
- Itching	18/32 (56.3%)
- Nausea	17/32 (53.1%)
- Fever	16/32 (50%)
- Abdominal pain	15/32 (46.9%)
- Rash	9/32 (28.1%)
Extra-hepatic manifestations	
- Neutropenia	4/32 (12.5%)
- Thrombocytopenia	3/32 (9.4%)
- Stevens-Johnson syndrome	None
Number of concomitant drugs in 2 months prior to onset	
- 0-2	2/32 (6.3%)
- 3-5	4/32 (12.5%)
- > 5	26/32 (81.3%)

Table 3

Selected laboratory data at and following DILI onset (N=32, presented as mean± s.d)

	N=32
At protocol defined date of onset:	
- ALT (U/L)	499 ± 585
- AST (U/L)	414 ± 499
- AlkP (U/L)	365 ± 345
- Total Bilirubin (mg/Dl)	4.8 ± 6.5
- INR	1.1 ± 0.2
Pattern of Liver Injury	
- Cholestatic	11/30 (36.7%)
- Mixed	10/30 (33.3%)
- Hepatocellular	9/30 (30.0%)
Peak values:	
- ALT (U/L)	686 ± 915
- AST (U/L)	491 ± 488
- AlkP (U/L)	623 ± 563
- Total Bilirubin (mg/dL)	8.7 ± 10.3
- INR	1.4 ± 0.6
Times to Peak and Recovery (in days)	
ALT:	
- Onset to Peak	11 ± 26
- Peak to 50% Reduction	25± 37
- Peak to below ULN	106 ± 152
AST:	
- Onset to Peak	4 ± 6
- Peak to a 50% Reduction from Peak	8 ± 13
- Peak to below ULN	101 ± 163
AlkP:	
- Onset to Peak	31 ± 45
- Peak to a 50% Reduction from Peak	56 ± 69
- Peak to below ULN	123 ± 195
Total Bilirubin:	
- Onset to Peak	40 ± 88
- Peak to a 50% Reduction from Peak	20 ± 28
- Peak to < 2.5 mg/dL	41 ± 44
Eosinophils *	
- Absolute eosinophil (count/μL)	286 ± 407
- Eosinophil > 500/μL	4/17 (23.5%)

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AlkP: Alkaline Phosphatase; INR: International Normalized Ratio; ULN: Upper limit of normal

* Only 17 patients had a complete blood count within 2 weeks of onset to calculate eosinophil counts.

Table 4

Causality and Severity Scores

Causality Score for the Case as a Whole	
Definite	5/32 (15.6%)
Very Likely	17/32 (53.1%)
Probable	10/32 (31.3%)
Causality Score for the most implicated IV agents	
Definite	2/32 (6.3%)
Very Likely	17/32 (53.1%)
Probable	13/32 (40.6%)
RUCAM for the main implicated agent:	
Highly Probable (>8)	4/25 (16.0%)
Probable (6-8)	16/25 (64.0%)
Possible (3-5)	5/25 (20.0%)
Severity Score	
Mild	12/32 (37.5%)
Moderate	7/32 (21.9%)
Moderate-Hospitalized	8/32 (25.0%)
Severe	4/32 (12.5%)
Fatal	1/32 (3.1%)

Table 5

Implicated Intravenous Agents (N=32)

Antimicrobial agents	**n= 20 (62.5%)**
- Cefazolin	4
- Cefazolin and Clindamycin	1
- Ceftriaxone	2
- Ceftriaxone and Clindamycin	1
- Ceftriaxone and Levofloxacin	1
- Moxifloxacin	3
- Levofloxacin	2
- Ciprofloxacin and Moxifloxacin	1
- Oxacillin	2
- Piperacillin/Tazobactam	1
- Sulfamethoxazole/Trimethoprim	1
- Rifampicin	1
Anti-neoplastic agents	**n= 5 (15.6%)**
- Asparaginase	1
- Docetaxel	1
- Docetaxel and Carboplatin	1
- Bortezomib	1
- Interleukin 21	1
Central nervous system agents	**n=3 (9.4%)**
- Phenytoin	3
Other agents	**n=4 (12.5%)**
- Metoprolol	1
- Octreotide	1
- Infliximab	1
- Anti-thymocyte globulin	1

Table 6

Characteristics of DILI due to IV agents administered daily (Categorized into entirely IV or IV followed by oral administration)

	Entirely IV (n=17)	IV/Oral (n=9)	p-value
Age (mean ± s.d., yrs)	55 ± 20	42 ± 24	0.15
Female	35%	78%	0.10
BMI (mean ± s.d., kg/m^2)	26 ± 7	25 ± 7	0.5
Prior drug allergies	41%	44%	0.6
Alcohol use	63%	25%	0.2
Prior drug allergies	35%	50%	0.5
Setting of IV agent administration			
- Hospital	71%	100%	0.07
- Ambulatory surgical center	29%	None	
Symptomatic	77%	89%	0.4
Pattern of liver injury			
Cholestatic	44%	38%	0.6
Mixed	31%	50%	
Hepatocellular	25%	12%	
Laboratory values at presentation (mean ± s.d.)			
ALT (U/L)	287 ± 211	566 ± 383	0.02
AST (U/L)	259 ± 163	564 ± 403	0.18
AlkP (U/L)	317 ± 239	601 ± 515	0.10
Total bilirubin (mg/dL)	5.1 ± 6.6	5.4 ±7.7	0.8
Peak laboratory values (mean ± s.d.)			
ALT U/L	404 ± 281	649 ± 481	0.09
AST U/L	323 ± 186	519 ± 413	0.15
AlkP U/L	477 ± 387	938 ± 747	0.06
Total bilirubin mg/dL	8.6 ± 11.7	8.6 ± 8.5	0.9
Eosinophilia (> 500 per microliter)	7%	22%	0.046
Mean duration of implicated agent use: IV and oral combined (in days)	15 ± 12	26 ± 24	0.15
Mean latency (drug start to DILI onset in days)	14 ± 13	17 ± 10	0.4
Developed chronic DILI	12%	22%	0.6
Severity score (mean ± s.d.)	1.9 ± 0.8	2.7 ± 1.3	0.13
Causality score for the case (mean ± s.d.)	2.3 ± 0.7	1.9 ± 0.6	0.3
Causality score for the IV agent (mean ± s.d.)	2.5 ± 0.6	2.2 ± 0.4	0.13
RUCAM score for IV agent (mean ± s.d.)	7.3 ± 1.4	5.8 ± 2.5	0.10

Table 7

Selected clinical features of IV DILI compared to historic cohorts from DILIN and the Spanish registry¶

	IV agent DILI (N=32)	DILIN cohort[4] (N=300)	Spanish registry[8] (N=461)
Age (years)	51 ± 21	48 ± 18	53
Female (%)	50	60	49
Underlying liver disease (%)	3	5.7	4.7
Diabetes mellitus (%)	31	27	NA
Pattern of liver injury (%)			
- Cholestatic	36.7	23	NA
- Mixed	33.3	20	NA
- Hepatocellular	30	57	58
Laboratories at presentation			NA
- ALT (U/L)	499 ± 585	788 ± 967	
- AlkP (U/L)	365 ± 345	295 ± 272	
- Total bilirubin (mg/dL)	4.8 ± 6.5	6.3 ± 6.3	
- INR	1.1 ± 0.2	1.5 ±0.9	
Peak laboratory values			NA
- ALT (U/L)	686 ± 915	985 ± 1168	
- AlkP (U/L)	623 ± 563	390 ± 382	
- Total bilirubin (mg/dL)	8.7 ± 10.3	11.4 ± 10.2	
- INR	1.4 ± 0.6	1.6 ± 1.4	
Antimicrobial agents (%)	62	45	32
Duration of implicated agent use (days)	24 ± 25	NA	105 (95% CI: 63 - 146)
Latency (days)	20 ± 22	42 (20 - 117)	93
Hospitalized (%)	69	NA	53
Chronic DILI (%)	13	14	10
Severity score (%)			NA
Mild	37	27	
Moderate	20	19	
Moderate-hospitalized	26	33	
Severe	13	15	
Fatal	3	6	
Liver related death or liver transplantation (%)	3%	6%	7%
Overall mortality	13%	8%	5%
Overall case causality score			NA
- Definite	9.1%	32%	
- Very likely	30.9%	41%	

	IV agent DILI (N=32)	**DILIN cohort[4] (N=300)**	**Spanish registry[8] (N=461)**
- Probable	18.2%	14%	
- Possible	21.8%	10%	
- Unlikely	1.8% (of 55 adjudicated IV DILI cases)	3% (of 254 adjudicated cases)	