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ANTITUBERCULOSIS DRUG INDUCED LIVER INJURY: CLINICAL PROFILE AND OUTCOME OF VARIOUS REINTRODUCTION REGIMENS

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Abstract:

Background and Aims: Drug induced liver injury(DILI) is a challenging problem faced by clinicians. Lack of objective diagnostic test makes the diagnosis and management of DILI difficult. This study aims to study the clinical profile and reintroduction regimen outcomes in ATT DILI.

Methods:A Prospective Observational Studyonpatients with ATT induced hepatitis. A detailed historyof Antitubercular therapy,features of DILI and reintroduction regimenthat was initiated were noted. Clinical and biochemical parametersof all patients were analysed andfollowed till the end of ATT.

Results: In our study of50 patients, middle aged (30-39yrs) males(70%) were more prone for DILI. The median day of DILI occurrence was 15 days from ATT initiation,with the most common presenting symptom being anorexia (42%). Malnutrition (90%), HIVcoinfection (30%), concomitant ART medication, alcoholism(30%) were common associations. The most common pattern of DILIwas hepatocellular(32%) and cholestatic(32%)pattern. Out of the 50 patients, 14 patients were reintroduced with BTS regimen, 12 with ATS regimenand 12 were reintroduced with all drugs. It was observed that ATS regimen had a better outcome.($p = 0.0005$).

Conclusion: Study showed that middle aged males,malnourished,alcoholics, HIV co infected patients weremore prone for DILI . Hepatocellular and cholestatic patterns were most common ATT DILI patterns. ATS reintroduction regimen showed better outcome in our study however this needs to be further proved with a larger sample.

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Keywords: ATT; DILI;ATS; BTS.

Introduction

India accounts for one fourth of the global Tuberculosis (TB) burden. In 2020, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB[1].India has the highest burden of both TB and Multidrug resistant TB. Tuberculosis is a preventable, treatable and curable disease. With the usage of multiple drugs in the treatment, side-effects are bound to occur. The major side effects [2] include hepatitis, skin rash, deafness, dizziness,visual impairment, flu like syndrome, acute kidney injury,thrombocytopenia. Nearly 20% of the patients on Antitubercular therapy develop asymptomatic elevation of liver enzymes and the incidence of Antitubercular Drug Induced Liver Injury (DILI) varies between 2 to 28%[3].

Drug induced liver injury is a challenging problem faced by clinicians due to its wide range of presentation and culprit agents. There are two types of DILI noticed, one is Hepatocellular type ,other is Cholestatic type [4]. As of now two main guidelines are being followed for reintroduction of Antitubercular Therapy (ATT) after DILI, namely American Thoracic Society (ATS) guidelines and British Thoracic Society (BTS) guidelines. Presently RNTCP follows the BTS guidelines for reintroduction of ATT [5]. Lack of objective diagnostic test makes the diagnosis and management of DILI difficult. Once DILI occurs reintroduction of ATT becomes a even more challenging task for a physician.

Aims and objectives:

1.To study the clinical profile and the pattern of hepatotoxicity in ATT induced liver injury
2.To evaluate the outcome of various reintroduction regimens.

Materials and methodology:

Source of data:

Patientshospitalised at Bangalore Medical College and Research Institute (BMCRI) with first line ATT induced liver injury were included in the study.

Data collection:

Prospective Observational Study conducted at Victoria Hospital and Bowring & Lady Curzon Hospital attached to BMCRI. This study was conducted from November 2017 to May 2019, all patients satisfying the inclusion and exclusion criteria were included in the study.

All patients aged more than 18 years who were diagnosed with first line ATT induced DILI as per RNTCP criteria (AST/ALT >= 3 times ULN with nausea, vomiting, anorexia, jaundice, dark coloured urine or AST/ALT>5 ULN without symptoms) were recruited into the study. DILI patients with retroviral disease were also included in our study whereas patients with serological

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evidence of acute viral hepatitis, acute alcoholic hepatitis and pregnant women were excluded from the study group.

METHODOLOGY:

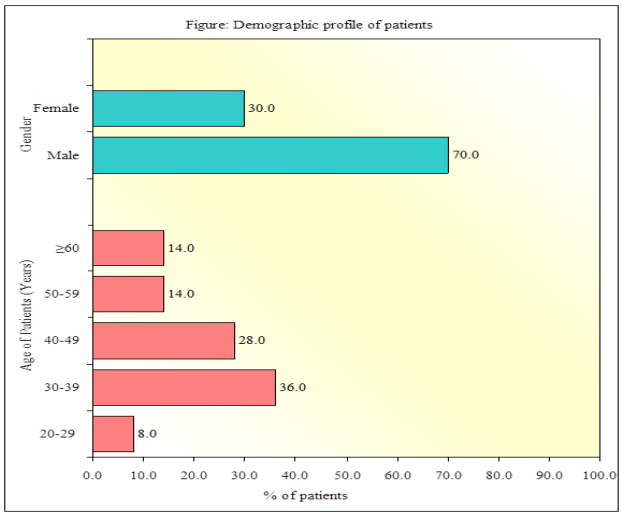
After obtaining ethical clearance and approval from the Institutional Ethics Committee of BMCRI a written consent was taken from all the patients. A detailed history including the sociodemographic profile,comorbidities,details of antitubercular therapy, the symptoms and signs of liver injury were noted. A modified ATT regimen consisting of ethambutol, fluoroquinolone and aminoglycoside was used till ALT/AST ≤2ULN after which thepatient was reintroduced to ATT in varied sequence (ATS regimen /BTS regimen /All drugs at once)as per the treating doctor's discretion. All the patients were followed till the end of tubercular therapy for any signs and symptoms of reoccurrence of liver injury and the outcome of DILI in each patient was noted at the completion of the treatment.

Statistical analysis: Qualitative variables for clinical profile was assessed by chi square test with continuity correction for all 2x2 tables.Comparisonof variables among different regimens was done with t test and Mann Whitney. p value <0.05 was considered statistically significant for all analysis.

Results:

50 patients with ATT induced liver injury were included in this study and a detailed clinical assessment was done and data entered in the proforma. In our study the age group distribution was from 20 years to 73 years with majority of the cases falling between 30-39years (36%). The mean age of the cohort being 43years. The study group comprised of 70% males and 30 % females(Figure 1). It was found that 15 patients i.e 30% were alcoholics and out of the 50 patients, 15 had retroviral disease of which 10 patients were receiving ART prior to the initiation of ATT.It was observed that most of the patients i.e 90% of them were malnourished at the time of diagnosis of DILI with low albumin, BMI and mid arm circumference (Table 1).

Figure 1. Demographic profile of patients



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Amongst the 50 patients 22 patients (42%) had anorexia as the first symptom of DILI followed by vomiting (18%), fatigue (8%), pain abdomen (8%) and 8% of the patients were asymptomatic with incidental detection of DILI. It was observed that only 6 % of DILI patients had jaundice as their first symptom recognition (Table 2). The study observation showed that patients developed DILI ranging from day 6 to 8 months post ATT initiation with the median day of liver injury occurrence being 15th day.

Table 1: Risk Factor Assessment

Parameters	**No of patients**	**% of patients**
Alcoholics		
No	35	**70%**
Yes	15	**30%**
HIV status		
HIV Negative	35	**70%**
HIV positive not on ART	5	**10%**
HIV positive on ART	10	20%
Nutrition		
Normal	5	10%
Malnourished	45	90%
Total	**50**	**100**

Analysis of the pattern of DILI revealed 32% to have hepatocellular type of DILI, 32% with cholestatic pattern, 20% with mixed pattern and 16 % had only raise in bilirubin with enzymes being normal as shown in Figure 2.

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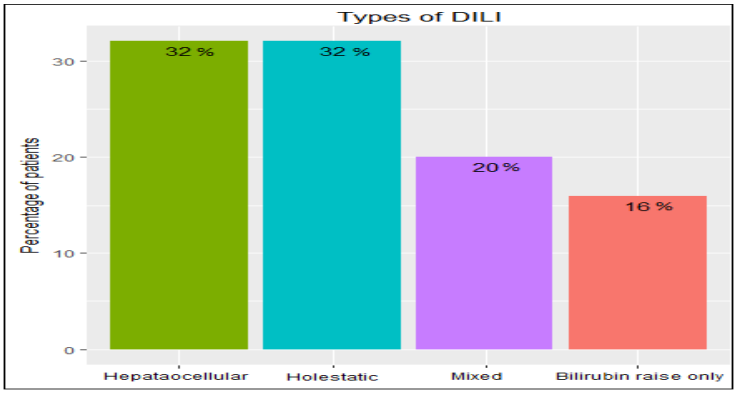
First symptom of DILI	No of patients	% of patients
Anorexia	22	42
Vomiting	7	18
Pain in abdomen	4	8
Fatigue	4	8
Incidentally detected	4	8
Jaundice	3	6
Pedal edema	2	4
Altered sensorium	2	4
Abdominal distention	1	2
Total	**50**	**100**

Table 2: Distribution of patients based on the presenting complaint of DILI

Figure 2 : Graphical representation of distribution of patients based on the pattern of DILI



Once the liver enzymes returned to less than 2 times the upper limit of normal clinicians reintroduced ATT as follows : 14patients i.e 28% had ATT reintroduction as per BTS guidelines , 12 patients as per ATS regimen , 12 patients had all 3 drugs(INH , Rifampicin , pyrazinamide) reintroduced at once and rest 12 patients did not receive reintroduction trial due to varied reasons like death (6), alternate diagnosis (1) , near completion of ATT treatment (1), clinician's decision-as patient was started with ATT based on clinical suspicion of tuberculosis (1), lost to follow up (3) (Table 3)

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Table 3: Distribution of patients based on the Reintroduction regimen followed

Regimen followed	No of patients	% of patients
BTS Regimen	14	28
ATS Regimen	12	24
All drug Regimen	12	24
No reintroduction	12	24
Total	**50**	**100**

Follow up of the patients and outcome analysis showed successful reintroduction of ATT in 25 out of 50 patients with only 4 patients having recurrence of DILI on reintroduction. In the rest of the 21 patients ,14 patients died during the follow up period, 2 patients were not given reintroduction trial (one had DILI at 8th month of ATT treatment, other one did not have tissue diagnosis of tuberculosis), 3 patients were lost during follow up period and 2 patients were found to have some other disease and an alternate diagnosis was considered(Figure 3).

Figure 3:Graphical representation of distribution of patients based on the outcome of DILI

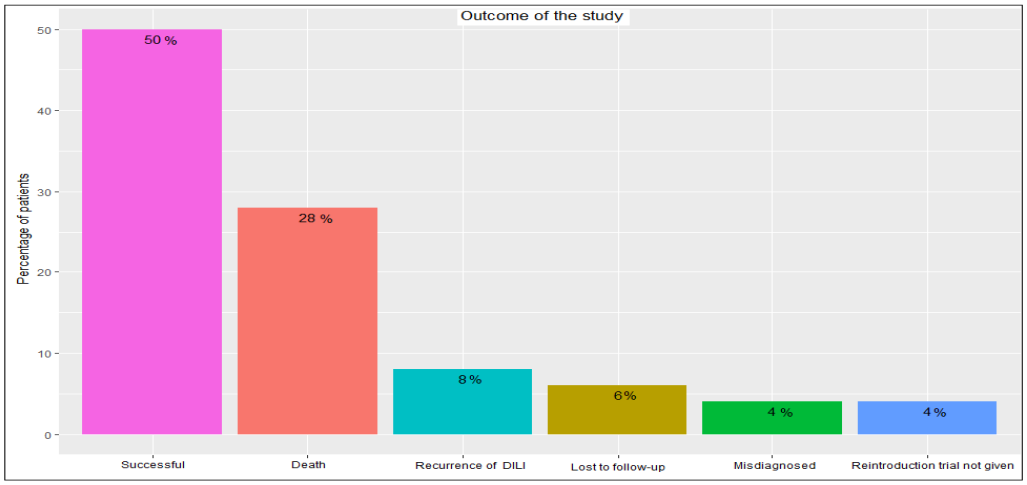

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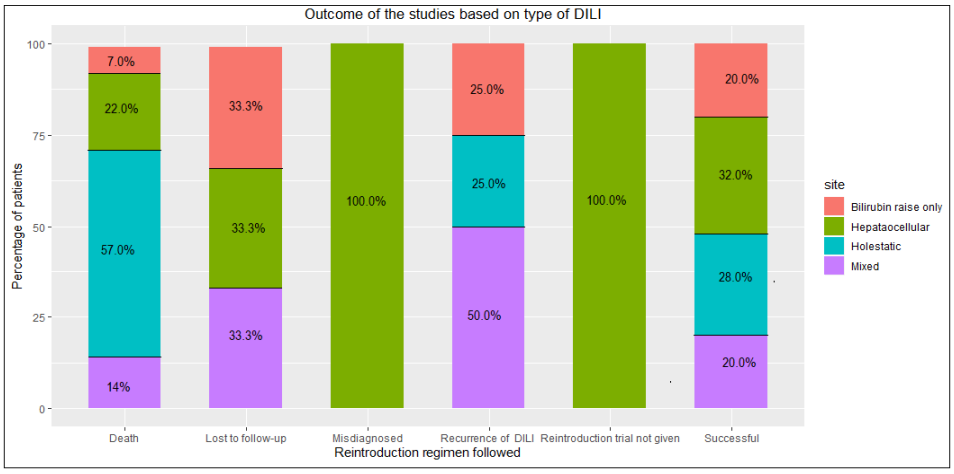
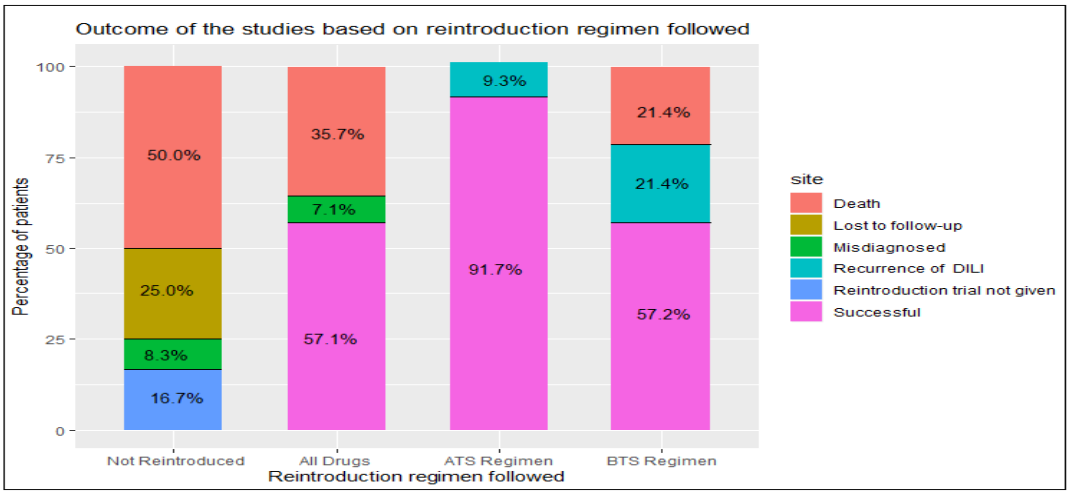
Figure 4: Graphical representation of outcome of DILI based on the pattern of DILI



Out of the 50 patients, 16 patients had hepatocellular pattern of DILI out of which 8 patients were successfully reintroduced with ATT. The rest of the 8 patients had varied outcomes as shown in the figure 4. Out of the 10 who received reintroduction – 4 had reintroduction with all 3 drugs, 5 had as per ATS regimen and one had as per BTS regimen. One patient who received BTS regimen died, all patients under ATS and All drug regimen had successful reintroductions.

Figure 5: Pictorial representation of outcome of DILI based on reintroduction regimen followed



16 patients had cholestatic DILI out of which 7 were successfully reintroduced with ATT, one had recurrence of DILI and half of the patients i.e 8 patients died during the follow up period. It was observed that out of the 14 patients who received reintroduction five patients were reintroduced with ATS, 5 had all drugs reintroduction at onceand 4 patients had BTS regimen. It

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was seen that 4 out of the 5 patients who got all drugs reintroduction died during follow up period and one died from BTS regimen.
10 patients had mixed pattern of DILI out of which half i.e 5 patients were reintroduced with ATT successfully.In this group 3 patients had ATS reintroduction with all being successful ,5 had BTS regimen reintroduction out of which 2 had recurrence of DILI with one death.Out of the 50, eight patients had only bilirubin raise with normal enzymes. Out of the 8 patients 5 had successful reintroduction of ATT. 4 patients received BTS regimen reintroduction amongst the 4 one had recurrence of DILI and the rest 3 received all drug regimen with one death. (Figure 4and 5)

Based on the reintroduction regimen followed for DILI patients, overall study outcome was examined. It was observed that the types of reintroduction regimen followed significantly affected the outcome of DILI patients at 99% confidence interval (P-value= 0.0005). Out of 25 (50%) patients with successful treatment, 8(32%), 6(24%) and 11(44%) had followed BTS regimen, all drugs and ATS regimen respectively. Recurrence of DILI was found in 4(8%) patients - 3(75%) who followed BTS regimen and 1 (25%) followed ATS regimen. Among the 14(28%) deaths seen during follow up, 6(42.9%) were not reintroduced to any regimen, 3(21.4%) were reintroduced to BTS regimen and 5(35.7%) were reintroduced to all drugs. There was no death among the patients who followed ATS regimen. With the above analysis there was a significant statistical difference in the outcome of DILI with ATS regimen showing a better outcome.

Discussion:

The present study was undertaken to study the clinical profile of ATT induced DILI patients and the outcome of various reintroduction regimens.

Observation of the clinical profile in our study revealed males(70%) to be more affected than females(30%). In the USPHS study[6], there was no overall difference between women and men in rates of probable isoniazid hepatotoxicity while study done by Devarbhavi et al[7,8] showed men to outnumber women in the incidence of TB DILI and women to at increased risk of severe liver injury . Most of the studies conducted so far showed higher prevalence of DILI in females compared to males but Indian study done in AIIMS Delhi[9] did not confirm these previous studies suggesting that females are more likely to have DILI just as our study. The median age of occurrence of DILI in this study was between 30 to 39 years of age. All age groups are at risk of DILI, Steele et al[10] observed hepatitis in 1-6.9% of children compared to 1.6 to 2.5% of adults taking INH and rifampicin combination, however Roy et al[11] noted that patients older than 35years are the 4 times increased risk to develop TB DILI. Montreal Chest Institute Canada 1990-1999[12] and study done at the All India Institute of Medical Sciences hospital, New Delhi, between 1996 and 2000[9]stated that advanced age had higher risk of DILI.It was also seen that in our study majority of the patients had malnutrition at the time of diagnosis of DILI. Singla et

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al[13] and Sharma et al[9] demonstrated that patients with low albumin had three fold higher risk of developing TB DILI.
Associated risk factor analysis showed that 30% of our patients were alcoholics. Consuming alcohol leads to depletion of glutathione and also under nourishment which leads to an increase in the risk of DILI as stated in Senousy et all study[14.]

Our study HIV positive patients receiving ART medications (20%) had double the occurrence of DILI compared to ones not on ART(10%). A study done at Ethiopia[15] assessed and compared the prevalence, severity and prognosis of anti-TBdrug induced hepatotoxicity in HIV positive and HIV negative tuberculosis (TB) patients in Ethiopia which concluded that clinical hepatotoxicity was significantly associated with HIV co-infection (p=0.002), concomitant drug intake (p=0.008), and decrease in CD4 count (p=0.001).

Symptomatology analysis of DILI revealed the most commonpresentation of DILI to be anorexia(42%) followed by vomiting(18%) , pain abdomen (8%) and fatigue(8%) , these findings were similar to the statement released by ATS on Hepatotoxicity of Antituberculosis Therapy[16] and study conducted at Shree Birendra Hospital, Nepal[17] which showed anorexia , nausea vomiting as the first symptoms of DILI and overt jaundice, dark urine, and clay-coloured stools being only later signs of clinical worsening.With respect to the pattern of DILI both hepatocellular (32%) and cholestatic pattern (32%) followed by mixed pattern(20%) of DILI were seen commonly in our study and there was no statistical difference in the outcome of DILI between the different patterns of DILI.

Various outcomes under individual reintroduction regimens in each pattern of DILI as mentioned in results were seen but the statistical significance of these observations cannot be commented on due to small sample size. As per a study conducted by Verma et al[18] the cholestatic pattern of hepatitis has the lowest mortality but has a small risk of protracted course leading to a longer time for normalization of liver tests. Additionally, cholestatic and mixed hepatitis pattern have a small but definite risk of evolution to chronicity. Reported mortality figures from the Spanish registry and the drug-induced liver injury network (USA) are 2% and 2.1% respectively for mixed hepatitis pattern; Contrastingly, two separate studies conducted by Andrade et al[19,] and Chalasani et al[20]the mortality for hepatocellular hepatitis pattern of DILI was 7% and 7.5% and for the cholestatic hepatitis pattern the mortality reported were 5% and 14.3% respectively.

In our study half of the patients had successful reintroduction of ATT without any recurrence of DILI. 4 patients (8%) had recurrence of DILI with 2 patients being misdiagnosed with tuberculosis and 3 patients being lost during follow up. It was seen that out of the 50 patients death was seen in 14 patients (28%), however all the 14 deaths cannot be directly attributed to

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just DILI because most of these patients had either extensive spread of tuberculosis or other comorbidities which could by itself lead to the death.

A study conducted by Tahaoglu et al[21] concluded that in patients with gradual reintroduction without pyrazinamide recurrence of DILI was 0 %, while 24% of patients with immediate, full-dose reintroduction of retreatment regimens with pyrazinamide experience recurrence. Most of the TB DILIwere successfully treated with regimens including isoniazid and rifampicin. Study by Sharma et al[22] showed the recurrence of DILI to be10.9%.

In our study it was observed that the type of reintroduction regimen followed significantly affected the outcome of DILI. It was seen that ATS regimen had a better outcome when compared to BTS and All drug regimen.

The study conducted by sharma el[22] showed the recurrence rate of hepatotoxicity was not significantly different between the 3 regimens(ATS, BTS, all drugs) followed. An article published in June 2019 -Comparison of sequential, incremental and concomitant reintroduction regimens of antitubercular therapy after initial episode of ATT hepatitis: a systematic review and network meta-analysis concluded that sequential and incremental reintroduction was better than concomitant reintroduction. The order of reintroduction of rifampicin and isoniazid does not seem to make any difference to the recurrence of ATT hepatitis.[23]

Conclusion:

Tuberculosis is a preventable, treatable and curable disease. Since multidrug therapy is the treatment for TB, side-effects are bound to occur. ATT induced liver injury is a challenging problem faced by clinicians due to its wide range of presentation and culprit agents. In the present study it was seen that middle age, males, malnutrition,alcoholics and HIV co infection were common associations with patients developing DILI during anti tubercular therapy.The median day of DILI development was 15 days from the day of initiation of ATT therefore testing liver function before starting ATT and atleast two weeks after ATT initiation would be a reasonable option in resource limited countries like ours.

Both hepatocellular pattern and cholestatic pattern of DILI were common in our study. Various regimens are being followed worldwide for reintroduction of ATT in ATT induced DILI. ATS regimen has shown to have a better outcome in our study, however this needs to be further proved by recruiting more patients and increasing the sample size.

An individual patient based designing of reintroduction regimen based on the pattern of DILI and comorbidities might be a better approach than a predefined protocol since varied mechanisms, patterns, genetic polymorphisms and responses are involved in ATT induced hepatotoxicity.

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Limitation of the study

The study included only 50 patients which is a small sample size and also there was non uniformity in the inclusion of pyrazinamide in the reintroduction regimens which could have altered the overall outcome of the DILI.

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