International Journal of Advances in Medicine
Giri RR et al. Int J Adv Med. 2022 Sep;9(9):951-954
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20222104

Case Report

Drug-induced liver injury after anti tuberculosis drugs administration, how to diagnose? a case report

Ray Ratnansari Giri, Ketut Suryana*

Department of Internal Medicine, Wangaya Regional Hospital, Bali, Indonesia

Received: 08 July 2022
Accepted: 30 July 2022

***Correspondence:**
Ketut Suryana,
E-mail: ketutsuryana@gmail.com

ABSTRACT

Drug-induced liver injury (DILI) is a liver injury caused by various drugs, herbs, or other xenobiotics, which causes abnormalities in liver tests or liver dysfunction in the absence of other causes of liver damage. The most common causative drugs are antituberculosis drugs (ATDs), anti-infective drugs, and natural herbal medicines. The diagnosis of DILI can be difficult due to the lack of specific signs, symptoms and tests and is partly a diagnosis based on exclusion. In this case report, we will discuss how to diagnosis DILI TB and causative assessment using RUCAM score. A male, 64 years old, has complained of weakness since 1 week ago and worsened since 1 day ago. The patient also felt persistent nausea for 1 week, so his eating and drinking decreased. Besides, he complained getting abdominal pain, especially in the upper right region and heartburn. The patient has been on first category of TB treatment since 20 days ago. Chest X-ray showed Lung TB with infiltrate in multiple cavities. Abdominal ultrasound showed no abnormality. The patient was discharged from our hospital after 6 days of hospitalization. DILI remains a diagnosis of exclusion based primarily on a detailed history and judicious use of blood tests, hepatobiliary imaging, and liver biopsy. The Roussel Uclaf causality assessment method (RUCAM) system is an assigning point for clinical, biochemical, serologic and radiologic features of liver injury. We use RUCAM score to make an assessment that show the likelihood of the hepatic injury due to a specific medication.

Keywords: DILI, Anti tuberculosis drugs, RUCAM score

INTRODUCTION

Drug-induced liver injury (DILI) is a liver injury caused by various drugs, herbs, or other xenobiotics, which causes abnormalities in liver tests or liver dysfunction in the absence of other causes of liver damage.[1] The estimated annual incidence rate of DILI is 13.9-24.0 per 100,000 population in worldwide. DILI is one of the leading causes of acute liver failure in the US.[1,2] In the West, the incidence of DILI is estimated to be 1-20 cases in 100,000 in general population. The severity of chemical-induced liver injury varies from on-specific changes in liver structure and function to acute liver failure, cirrhosis and liver cancer.[1,3]

The most common causative drugs of DILI are ATDs, anti-infective drugs, and natural herbal medicines.[4] Liver injury from anti-tuberculosis drugs (ATDILI) is still one of the most important side effects with the potential to cause liver failure and death.

DILI is a reaction that results in treatment changes or treatment being disrupted and has an impact on decreasing the effectiveness of treatment. In 2018, an estimated 10 million new cases of TB were reported in the world. In China, the prevalence of TB was 61 per 100,000 population and 2.6 per 100,000 people died from TB.[5] In India, TB is a major public health problem with an estimated prevalence of 256 per 100,000 population and 26 per 100,000 people dying from TB. The world health organization (WHO) declared TB a global public health emergency in 1993, when it was estimated that 7-8 million new cases and 1.3-1.6 million deaths occurred annually.[6]

Tuberculosis (TB) is a major global health problem despite the availability of highly effective treatments for decades. Among the first-line anti-TB drugs, isoniazid, rifampicin, and pyrazinamide are known to cause hepatotoxicity, but pyrazinamide is associated with a higher percentage of drug-induced liver toxicity compared with other drugs. Liver toxicity can lead to discontinuation of the drug, which can then lead to the development of multidrug resistant tuberculosis (MDR-TB).[2,7]

The diagnosis of DILI can be difficult because of the lack of specific signs, symptoms and tests and is partly a diagnosis based on exclusion.[7,8] In this case report, we will discuss how to diagnosis of DILI TB using RUCAM score.

CASE REPORT

A male, 64 years old, has complained of weakness since 1 week and worsened since 1 day ago. The patient also felt persistent nausea since 1 week ago, so his eating and drinking decreased. He complained getting abdominal pain, especially in the upper right region and heartburn since the last 3 days. Vomiting was occasionally happened while he was eating.

The patient complained of cough since about 3 months ago. It is a productive cough, and getting worse at night, without blood, accompanied by fever and cold sweat. The patient also complained of weight loss about 3 kgs since the last 3 months. There were no complaints of palpitations or shortness of breath.

The patient has been on first category of TB treatment (rifamficin, isoniazid, pyrazinamid, etambutol) since 20 days ago. There was no history of hepatitis, liver disorders, or other chronic diseases. The patient has a habit of smoking and rarely alcohol drinking since he was young. There's no history of hypotension, shock or ischemia before.

Physical examination showed a blood pressure 130/90 mmHg, pulse 80 times per minutes, respiratory rate 20 times per minutes, oxygen saturation 99% on room air, body temperature 36.3°C. Pupil remains normal isochor, no sign of anemia or icterus. Chest examination are normal. There was tenderness in the epigastric region and right hypochondrium. The spleen and liver were not palpable. Extremities and skin are normal.

Complete blood count revealed normal result (leukosit: 8.96 10^3/ul, Hb: 11.5 g/dl, Hct: 34.9%, MCV 84.1 fl, MCH 27.7 pg, MCHC 33.0 g/l, ratio neutrofill imfosit: 9.54. The liver function test are AST: 159 U/(H) ALT: 188 U/L (H) anti Hcv: negative; HbsAg: negative. ALP: 115 U/L (N) gamma GT 151 U/L, bilirubin total: 3.65 mg/dL, direct bilirubin: 3.6 mg/dl, albumin 2.2 g/dl, globulin 4.9 g/dl, ureum: 14 mg/dl, creatinine: 0.9 mg/dl.

Chest X-ray showed Lung Tb with infiltrate in multiple cavities in both lung fields and thickening of the upper left pleura with tracheal elevation to the left. Abdominal ultrasound showed no abnormality.

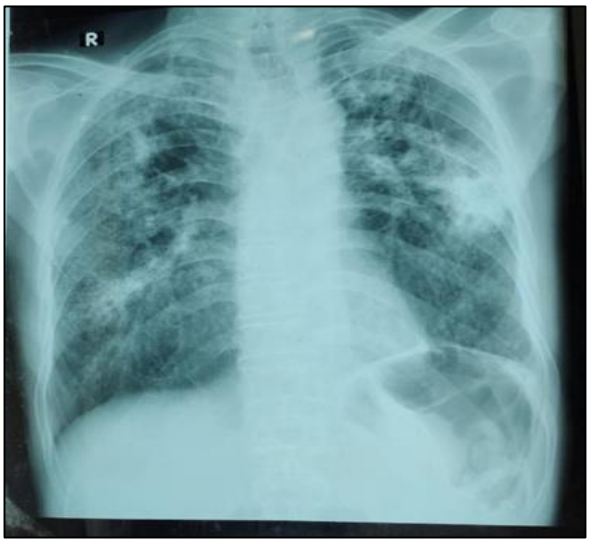

Figure 1: Chest X-ray showed lung TB with infiltrate in multiple cavities.

Then, we decided to stop medication of TB. During hospitalization, the patient was treated with cefoperazone 1 gram given every 12 hours, esomeprazole intravenous given every 24 hours. Ondansetron 4 mg given every 8 hours, N-acetylsistein 200 mg given every 8 hours. The patient was discharged from our hospital after 6 days of hospitalization.

Table 1: Evaluation of AST and ALT.

20/4/22	22/4/22	26/4/22	29/4/22, after re-administration of ATDs
AST: 159 U/l	AST: 84 U/l	AST: 49 U/l	AST: 93 U/l
ALT: 188 U/l	ALT: 75 U/l	ALT: 45 U/l	ALT: 73 U/l

DISCUSSION

DILI remains a diagnosis of exclusion based primarily on a detailed history and judicious use of blood tests, hepatobiliary imaging, and liver biopsy. Accurate history of medication exposure and onset of liver biochemistry abnormalities is very important.[7,8]

Acute liver injury is often detected and confirmed by liver biochemical blood tests. These generally include ALT, ALP, bilirubin, and albumin. Case definitions for DILI include one of the following thresholds: i) ≥5 ULN elevation in ALT, ii) ≥2 ULN elevation in ALP (particularly with accompanying elevations in concentrations of gamma-glutamyl transferase (GGT) in the absence of known bone pathology driving the rise in ALP level) or iii) ≥3 ULN elevation in ALT and

simultaneous elevation of TBL concentration exceeding 2 ULN.[7,8]

In this patient, the laboratory result is ALT: 188 U/L (H), total bilirubin: 3.65 mg/dl (H), gamma GT 151 U/L (H) albumin 2.2 g/dl (L) anti Hcv negative; HbsAgNegatif ALP:115 U/L (N). There is now wide consensus that minor increases in ALT or AST that could result from adaptive and reversible liver responses to the drug (i.e., statins), or preexisting liver disease (i.e., fatty liver) should not be classified as DILI.[7,8] The patient doesn't have history about liver disease or taking drug for dyslipidemia.

The RUCAM system is a mean of assigning points for clinical, biochemical, serologic and radiologic features of liver injury. We use RUCAM score to make an assessment that show the likelihood of the hepatic injury due to a specific medication.[7,8]

The differential diagnosis for acute hepatocellular injury includes acute viral hepatitis, AIH, ischemic liver injury, acute Budd-Chiari syndrome, and Wilson disease. The diagnosis of acute hepatitis C can be challenging because anti-hepatitis C virus (HCV) antibodies may be negative initially.[7,8]

First step in the RUCAM assessment is to know whether the hepatic injury is "hepatocellular", "mixed", or "cholestatic." by calculation of the "R ratio". The R ratio is calculated by dividing the alanine aminotransferase (ALT) by the alkaline phosphatase (Alk P), using multiples of the upper limit of the normal range for both values. The values used should be from the same day (or not more than 2 days apart).[7,8]

If the ALT value is more than twice the upper limit of the normal range (ULN) and the Alk P is normal, it should be considered hepatocellular and no need to calculate the R ratio. R ratio of >5 define a hepatocellular, <2 a cholestatic, and between a mixed pattern of DILI. The patient had an R ratio of 4.98, so we concluded that this patient had a hepatocellular injury.[7,8]

The total score consists of points for 8 separate factors in 7 categories that help define the "signature" of the drug induced liver injury. The interpretation of the final score is as follows: 0 or less indicate that the drug is "excluded" as a cause; 1 to 2 that it is "unlikely"; 3 to 5 "possible"; 6 to 8 "probable"; and greater than 8, as well as "highly probable".[7,8]

Time to onset

Patients with hepatocellular injury (R >5) receiving the medication for the first time are given 2 points if the time to onset is 5 to 90 days and they are still receiving the medication, but only 1 point if the time to onset is less than 5 or more than 90 days.[8] The patient feels nauseous and vomits every time he eats, after 20 days using anti-tuberculosis drugs. Patients also feel discomfort in his stomach.

Course

Then, after stopping the drug, we concern about the decrease of ALT. If ALT decrease >50% within 8 days (+3), decrease >50% within 30 days (+2), not applicable (+1), no information or decrease <50% after 30 days, decrease <50% after 30 days (-2) all situations (no point).[8] In this case, after stopping the drugs about 3 days, the ALT normal 49 U/l after 6 days. So, we decided to give 3 point (+3).

Risk factor

There are two categories in this score, we give one point (+1) if high consumption of alcohol or pregnancy presence and one point too if the age of patient ≥55 years (+1).[8] Age of this patient is 64 years old and has no history of high alcohol consumption before. We give score +1.

Concomitant drugs

There is no information of concomitant drugs (0) in this patient. The score is 0 if there is no information and getting worse if there is concomitant with drugs with clear evidence for its role (-3).

Exclusion of other cause of liver injury

The next step in assessing the RUCAM score is to exclude other causes of liver injury. Group 1 (HAV, HBV, HCV, Biliary obstruction by imaging, alcoholism (history of excessive intake and AST/ALT >2), history of hypotension, shock or ischemia within 2 weeks of onset). Group 2 (Complication of underlying disease, clinical features or serologic and virology test indicating CMV, EBV, or HSV). If all of group 1 and 2 ruled out (+2), 6 causes in group 1 (+1) 4 or 5 causes in group (0), less than 4 cause of group 1 ruled out (-2) or non-drug cause highly probable (-3).[7,8] We only can-do test exclusion for group 1 because of limitation of facility in our hospital, The result is: hepatitis (HBV and HCV) is negative and the result of abdominal ultrasonography is normal. There's no chronic liver disease or fatty liver. So, this patient gets the score +1.

The history of drugs hepatotoxicity

Step 6 is to find the previous information on hepatotoxicity of the drug: labeled (+2) published but not labeled (+1) or unknown (0). Studies have shown that multidrug regimens of ATDs (rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin) can cause adverse drug reactions in hepatology system (35.7%), the gastrointestinal tract (22%), the musculoskeletal system (19.5%), the skin and appendages (15.3%), the peripheral nervous systems (3%), the hematologic system (1.2%),

ototoxicity (1.2%), visual system (1.1%), and renal system (0.9%).[10]

Response to re-administration of the drug

Score 3 if there is a doubling of the ALT (in hepatocellular cases) or either the Alk P or total bilirubin doubles (in mixed or cholestatic cases) with the drug alone. One point is given if the drug is re-introduced during the acute injury and there is a doubling of the ALT, Alk P or bilirubin. Minus 2 points are assigned if there is no increase in ALT, Alk P or bilirubin to above the upper limit of normal with re-exposure to the agent after recovery from the initial injury. If the rechallenge or re-exposure are absence, we give no score (0).[8]

We start re-administration of drug after 3 days without any symptoms of DILI and ALT result is normal (45). Then, we check again after 3 days of re administration, and The ALT result is 73. So, we give 3 points.

The total score derived (ranging from -9 to +10) from the domain specific assessment classifies the event as highly probable (>8), probable (6-8), possible (3-5), unlikely (1-2) or excluded (≤0) according to its likelihood to be DILI. In this case, we conclude that the patient score is 8 (Highly Probable).

CONCLUSION

We presented a case report of a patient with TB DILI and how to use RUCAM score to diagnose and causality assessment. Although first-line anti-TB drugs are effective, liver toxicity can lead to discontinuation of the drug, which can then lead to the development of MDR-TB. DILI remains a diagnosis of exclusion based primarily on a detailed history and judicious use of blood tests, hepatobiliary imaging, and liver biopsy.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Suk KT, Kim DJ. Drug-induced liver injury: present and future. Clin Mole Hepatol. 2012;18:249-57.
2. Leise MD, Poterucha JJ, Talwalkar JA. Drug-Induced Liver Injury. Mayo Clin Proc. 2014;89(1):95-106.
3. Xinsheng G, Manautou JE. Molecular mechanisms underlying chemical liver injury. Expert Rev Mol Med. 2013;14:e4..
4. Shen T, Liu Y, Shang J, Xie Q, Li J, Yan M et al. Incidence and Etiology of Drug-Induced Liver Injury in Mainland China. Gastroenterology. 2019;156(8):2230-41.
5. Jiang F, Yan H, Liang L, Du J, Jin S, Yang S et al. Incidence and risk factors of anti-tuberculosis drug induced liver injury (DILI): Large cohort study involving 4652 Chinese adult tuberculosis patients. Live Int. 2021;00:1-11.
6. Vidyasagar R, Aithal GP. Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. J Clin Exp Hepatol. 2013;3(1):37-49.
7. Molla Y, Wubetu M, Dessie B. Anti-Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia. Hepatic Med Evidence Res. 2021;13:1-8.
8. European Association for the Study of the Liver. EASL Clinical Practice Guideline: Drug-Induced Liver Injury. J Hepatol. 2019;1-40.
9. Roussel Uclaf Causality Assessment Method (RUCAM) in drug Induced Liver Injury. LiverTox: Clinical and Research Information On Drug-Induced Liver Injury. 2019.
10. Aliasghar F, Sofian M. Adverse reaction to antituberculosis Drugs in Iranian Tuberculosis Patients. Tuberculosis Res Treat. 2014; 412893:1-6.

Cite this article as: Giri RR, Suryana K. Drug-induced liver injury after anti tuberculosis drugs administration, how to diagnose? a case report. Int J Adv Med 2022;9:951-4.