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(CASE REPORT)

A case report on Azathioprine induced hepatotoxicity

Mohamed Yasir. H [1,*], Reshma Babu [1], Dhanya Dharman [2] and Shaiju S Dharan [3]

[1] *Pharm D Intern, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram, Kerala, India.*
[2] *Associate Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram, Kerala, India.*
[3] *Principal/ HOD, Ezhuthachan college of pharmaceutical sciences, Marayamuttom, Thiruvananthapuram, Kerala, India.*

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Abstract

The most frequent cause of acute liver failure is drug induced liver damage. The lack of diagnostic testes or biomarkers, identification of DILI is difficult one. In most cases DILI was mild and reversible. Azathioprine, is a widely used immunosupressive agent had a nature of causing liver injury but rare. It basically presents with mild symptoms. Azathioprine can cause idiosyncratic liver injury, usually presented with juandice and fatigue and then linked to elevated liver enzymes. It is reversible and typically resolveson cessation of Azathioprine. This case focuses on Azathioprine's nature of hepatotoxicity. After the withdrawal of offending agent, it is resolved.

Keywords: DILI; Azathioprine; Corticosteroid; Hepatotoxicity

1. Introduction

Drug induced liver injury is a very frequently occurring phenomenon around the world. So many class of drugs are known to cause liver damage. Antibiotics, nonsteroidal anti-inflammatory medicines, and anticonvulsants are some of the commonly prescribed medications which cause liver injury. Acute liver failure has also been associated to herbal medications and supplements which contains kava, ephedra, skullcap, and pennyroyal.

Despite being helpful in lowering inflammation, the medication has a number of negative side effects, including immunological and bone marrow suppression, pancreatitis and very infrequently, liver damage. Despite widespread use of the medication, the frequency of hepatotoxicity with AZA looks rare based on the scant number of cases. Due to the fact that many of the conditions for which AZA is prescribed can independently produce hepatobiliary abnormalities and because hepatotoxicity may result in nonspecific gastrointestinal symptoms, it can be challenging to separate drug toxicity from a flare-up or complication of the main disease.

Azathioprine is an extensively used immunosuppressive agent. It is a FDA approved drug for the symptomatic treatment of Rheumatoid Arthritis (RA). Additionally, it has been approved as a complementary therapy for the prevention of kidney transplant rejection [1]. AZA is used off label to treat conditions such as inflammatory bowel disease, autoimmune hepatitis, multiple sclerosis, psoriasis, dermatitis, severe myasthenia gravia, lichen planus, ILD, bullous pemphigoid etc. Azathioprine is a purine analogue that undergoes conversion to its active metabolites, thioguanine (6-TGN) and mercaptopurine (6-MP), by the actions of the enzymes hypoxanthine-guanine phosphoribosyl transferase (HPRT) and thiopurine methyl transferase (TPMT). Purine synthesis is therefore halted. The metabolites of it prevent division by integrating with the DNA that is actively replicating [2]. The majority of AZA's immunosuppressive and toxic effects may also be mediated by its metabolites. The blood-brain barrier is not crossed by AZA, which is quickly absorbed through

* Corresponding author: Mohamed Yasir. H

the GI system. Its toxicity is increased with renal failure because of its liver metabolism and kidney-based excretion. Azathioprine is rarely associated with hepatotoxicity and its incidence varies from 1-10%.

2. Case report

A 28 year old man presented to the gastroenterology outpatient department with the complaints of fever, cough and breathing difficulty for past 4 days. He had no history of vomiting, abdominal pain, abdominal distention, dysuria or chest pain. No history of complaints in the past and also no family history of similar complaints was reported. He had a recent hospital admission with acute hepatitis, and on evaluation, HBV core IgM was positive, and he was treated with antivirals. But on further evaluation, the HBV viral load was negative, and his repeated LFT did not show any improvement; hence, antivirals were stopped. Prior to the commencement of jaundice, he had a history of azathioprine use from a dermatologist.

Table 1 Investigation Reports

INVESTIGATION	RESULT	
BLOOD RE	DAY 1	DAY 2
Hemoglobin	10 g/dl	11.8 g/dl
Total count	12740 cells/cumm	12020 cells/cumm
CRP	61.6 mg/L	41.2 mg/L
LFT		
Bilirubin [T]	19.3 mg/dl	8.50 mg/dl
Bilirubin [D]	7.17 mg/dl	4.90 mg/dl
ALT	255 U/L	188 U/L
AST	184 U/L	115 U/L
ALP	455 U/L	237 U/L
S. Albumin	2.7 g/dl	2.9 g/dl
Lipase	1895	
OTHERS		
BNP	8880	
D-Dimer	1298	
High sensitive Troponin I	1293	

The patient was found to be conscious, oriented and moderately built. Upon examination, there was pallor, icterus, bilateral pitting pedal edema whereas clubbing, cyanosis, lymphadenopathy were absent. On arrival, he had a blood pressure of 130/80 mmHg, a pulse rate of 126 breaths/min, and a respiratory rate of 28 cycles/min. He was tachypneic with a saturation of 70% at room air. Following the complaints, he was admitted to the medical ICU on NIV support. He was initially started on IV antibiotics (Inj. Meropenem) and other supportive medications.

On further evaluation, his routine lab investigation revealed hemoglobin of 10 gm/dl, raised CRP (306.9) and normal renal status. His liver function showed hyperbilirubinemia, raised liver enzymes with hypoalbuminemia and normal prothrombin time. Trop I and BNP were raised along with D-dimer. A cardiology opinion was requested in light of this and he was started on diuretic. Due to sepsis, an ID opinion was sought and he suggested to start an antiviral drug Oseltamivir [Fluvir]. As a result of the abnormal LFT and history of Azathioprine intake DILI was suspected. Patient was started on steroid pulse therapy as a trial for 3 days. Following the trial, a marked reduction in bilirubin level was showed in the repeated LFT. After a week, the patient become clinically better and stable. He was discharged in a stable state. His Bilirubin at the time of discharge was found to be 6.39 mg/dl. He was advised with medications such as TAB.

PREDNISOLONE 10 mg, TAB. FUROSEMIDE 40 mg, TAB. URSODEOXYCHOLIC ACID 300 mg and other supportive medications for 5 days

3. Discussion

Azathioprine is a frequently prescribed immunosuppressant agent linked with hepatotoxicity. Though the exact mechanism of injury is unknown, it may show that DILI from AZA can happen at any point during the course of treatment even with a consistent regimen. Azathioprine is a purine analogue that undergoes conversion to its active metabolites, thioguanine (6-TGN) and mercaptopurine (6-MP), by the actions of the enzymes hypoxanthine-guanine phosphoribosyl transferase (HPRT) and thiopurine methyl transferase (TPMT). Purine synthesis is therefore halted. The metabolites of it prevent division by integrating with the DNA [3]. Despite being helpful in lowering inflammation, the medication has a number of negative side effects, including immunological and bone marrow suppression, pancreatitis and very infrequently, liver damage. Despite widespread use of the medication, the frequency of hepatotoxicity with AZA looks rare based on the scant number of cases. Due to the fact that many of the conditions for which AZA is prescribed can independently produce hepatobiliary abnormalities and because hepatotoxicity may result in nonspecific gastrointestinal symptoms, it can be challenging to separate drug toxicity from a flare-up or complication of the main disease[4]. Our patient was presented with symptoms of fever, cough and breathing difficulty. He had no past comorbidities but had a history of taking Azathioprine for unknown reason. Intially it was diagnosed as juandice but further investigations shows abnormal liver function(elevated liver enzymes). From these evidrence the case was confirmed as drug induced liver injury due to Azathioprine. After the diagnosis corticosteriod therapy started that will shows marked decline of abnormal liver function. Liver supportivemedications also given for further management. After gradual progression the patient was discharged with oral corticosteroids and supportive medications.

According to Adverse drug monitoring, Naranjo probabaility scale shows that hepatotoxicity due to Azathioprine is classified as possible. The rapid onset of increase and decrease in liver enzymes after intiation and discontinuation suggest that Azathioprine was the exact reason for development of DILI[5]. The British Assosciation of Dermatologists states that monitoring liver enzymes with in the first week of Azathioprine should be considered for every 3 months.

4. Conclusion

Drug induced liver injury is one of the main liver dissease in world wide also it include prescription, Over the counter and herbal medicines. The exact mechanism and pathway behind the DILI was unclear. There is no laboratory testes or features to diagnose DILI. In most of the cases it was asymptomatic and shows mild elevation in liver enzymes. Majority of DILI was mild to moderate and improve after drug withdrawal. In some cases the patients have symptoms that are highly similar to other heaptic diseases. Rapid cessation of offending agent and supportive care are the important steps in management of DILI. Physicians should be aware about to monitor liver enzymes when intiating or taken Azathioprine or other medications that cause hepatotoxicity.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflict of interest to declare.

Statement of informed consent

Before taking this case the patient and their families were informed and informed consent was aquired.

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