ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS
Case Report

Drug-Induced Liver Injury from Vismodegib: A Case Report

Zehra Irshad*, Hina Shahid and Nwe Ni Than

Academic Clinical Fellow University Hospital Coventry and Warwickshire

***Corresponding Author**: Zehra Irshad, Academic Clinical Fellow University Hospital Coventry and Warwickshire.

Received: March 16, 2023; **Published:** March 28, 2023

Abstract

Vismodegib is a hedgehog pathway inhibitor; commonly used in patients with advanced basal cell carcinoma. Hepatotoxicity or drug induced liver injury (DILI) from vismodegib had been reported in literature but still regarded as a rare event. We reported a case of a patient presented with biopsy proven DILI that occurred two weeks after starting vismodegib.

Keywords: *Drug-Induced Liver Injury; Jaundice; Hepatotoxicity; Vismodegib*

Abbreviations

DILI: Drug Induced Liver Injury; BCC: Basal Cell Carcinoma; ALP: Alkaline Phosphate; ALT: Alanine Transaminase; GGT: Gamma Glutamyl-Transferase; HIV: Human Immunodeficiency Virus; CT: Computed Tomography; UDCA: Ursodeoxycholic Acid; CYP: Cytochrome

Introduction

Vismodegib is an approved treatment for locally advancing and metastatic basal cell carcinoma (BCC). This hedgehog pathway inhibitor is generally associated with adverse effects such as alopecia, muscle spasm, weight loss, asthenia and dysgeusia [1]. The most common reported adverse events are muscle spasms (53%) and dysgeusia or ageusia (49%) [2]. Drug induced liver injury (DILI) is still not recognised as a potential side effect of this drug despite several cases had been reported in the last decade regarding Vismodegib induced liver injury. Here, we report an interesting case of vismodegib associated hepatotoxicity.

Case Report

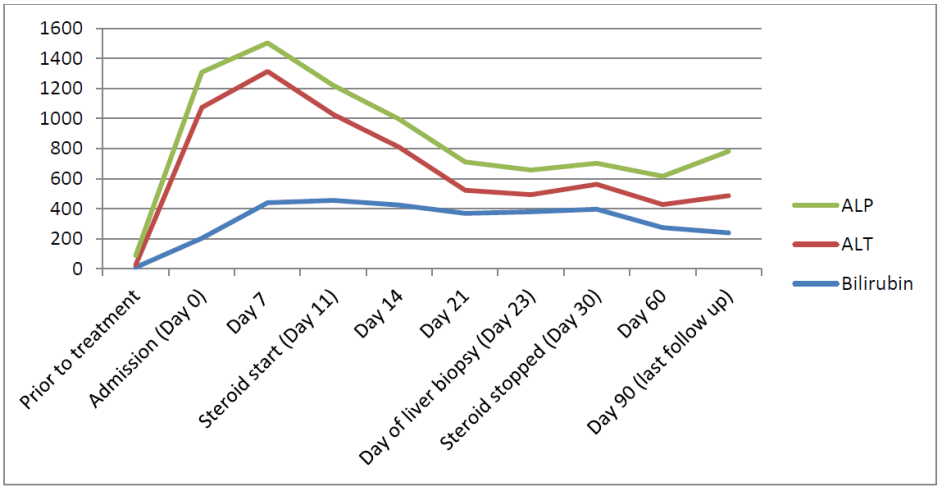
A 45-year-old Caucasian man with background of hypertension, learning disability and multiple basal cell carcinomas as part of Gorlin's syndrome presented with generally feeling unwell, jaundice, pruritus and lethargy. Two weeks prior to the admission, he was started on oral vismodegib 150 mg once daily for the treatment of BCC. His regular medications include candesartan 16 mg daily and indapamide 2.5 mg daily for hypertension. The metabolism of vismodegib can be decreased when combined with candesartan but the interaction is noted to be as minor. There is no interaction between indapamide and vismodegib.

There was no history of alcohol, smoking or illicit drug use. On admission, he was systemically well, and physical examination showed jaundice, conjunctival icterus and epigastric tenderness.

At admission, his blood investigations revealed deranged liver function tests and acute kidney injury with urea 18.4 mmol/L and creatinine 228 umol/L. Liver blood tests showed elevated alkaline phosphatase (ALP) 204 U/L, alanine transaminase (ALT) 835 U/L, total bilirubin 231 umol/L, gamma glutamyl-transferase (GGT) 504 U/l, INR 1.1, and albumin 43 g/l all of which were previously normal. His blood tests were closely monitored during admission. The peak value of total bilirubin was 483 umol/L at day 12 of the admission. The trend of the liver blood tests was shown in table 1 and figure 1.

	Liver blood tests				Renal blood tests	
	Bilirubin (umol/L)	**ALT (U/L)**	**ALP (U/L)**	**Albumin (g/L)**	**Urea (mmol/L)**	**Creatinine (umol/L)**
Prior to treatment	11	17	61	44	9.2	131
Admission (Day 0)	204	869	234	43	18.4	228
Day 7	440	872	190	36		
Steroid start (Day 11)	456	570	193	35		
Day 14	425	384	186	37		
Day 21	370	153	187	36		
Day of liver biopsy (Day 23)	379	114	164	34		
Steroid stopped (Day 30)	397	165	140	32		
Day 60	274	153	189	28		
Day 90 (last follow up)	240	247	295	31	6.1	84

Table 1: *The trends of blood tests during admission.*
ALT: Alanine Transaminase; ALP: Alkaline Transaminase.



ALP: Alkaline phosphatase; ALT: Alanine transaminase

Figure 1: *The trends of blood tests during admission.*

The inflammatory markers, amylase, immunology profile and full viral hepatitis screen including hepatitis A, E, cytomegalovirus, Epstein Barr virus, human immunodeficiency virus (HIV) screen were negative. Ultrasound abdomen was unremarkable. Computed tomography (CT) scan of the abdomen and pelvis with contrast showed normal liver texture with evidence of cholelithiasis without cholecystitis or biliary duct dilatation. Liver biopsy was performed due to worsening level of bilirubin which showed features of acute cholestatic hepatitis consistent with drug induced liver injury (DILI) (Figure 2). Vismodegib was stopped on admission.

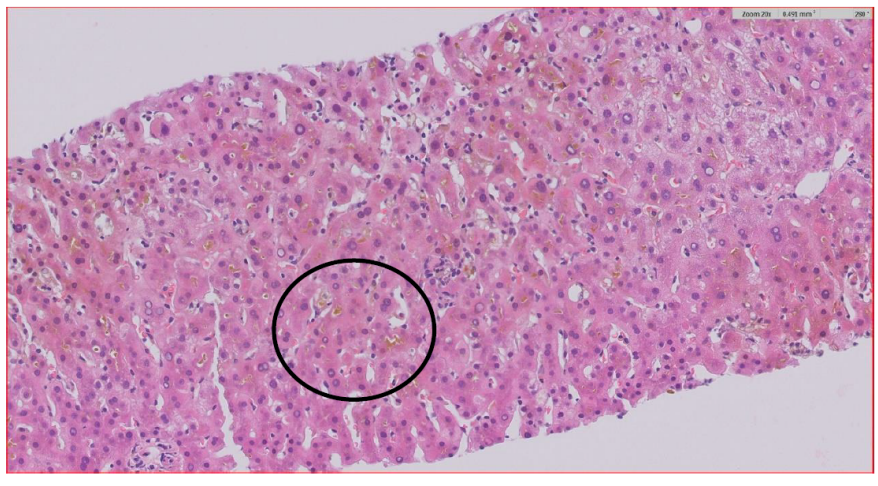


Figure 2: *Liver biopsy showed mild chronic inflammation predominantly lymphoid cells in the portal tract due to cholestasis (circle) consistent with drug induced liver injury.*

He was placed on intravenous fluids to resolve acute renal injury with strict monitoring of his intake and output. His usual medications were also stopped upon discussion with the renal team in view of his acute kidney injury. He was started on ursodeoxycholic acid (UDCA) and titrated up to 500 mg three times daily as per the body weight. He was also started on oral prednisolone (30 mg) once daily on day 11 after admission due to elevated bilirubin (456 umol/L). Steroid was discontinued after 3 weeks due to limited response with static bilirubin and ALT levels (See figure 1). He was discharged 6 weeks after admission with continuation of UDCA 1500 mg/day. Liver blood tests were monitored closed upon discharge in the outpatient clinic.

Discussion

The Hedgehog signalling pathway had been implicated in many types of cancer and proven to be a beneficial treatment target for cancer [2]. Vismodegib is a small molecule Hedgehog pathway inhibitor that had been approved for the treatment of locally advanced metastatic basal cell carcinoma [1]. The primary route of vismodegib elimination is via the liver through cytochrome p450 enzymes, including CYP3A4, 2C8, 2C9 and 2C19. Hence, it could potentially cause hepatic impairment [2,3]. The drug and its metabolites are primarily eliminated by the liver, with 82% of drug excreted in the faeces and 4.4% recovered in the urine [3].

One study showed that liver enzyme elevations were seen in 1.4% patients followed by cholestasis (0.3%), drug toxicity (0.3%) and hyper-bilirubinaemia (0.3%) [2]. Vismodegib had a long half-life (around 19 days) and the majority of the drug remained un-metabolised in plasma [2]. As a result, the effect can persist despite the discontinuation of the medication. The mechanism for vismodegib induced hepatotoxicity remains unclear. Factors that can increase susceptibility for hepatotoxicity are underlying non-alcoholic steatohepatitis, medication use, alcohol consumption and chronic liver disease [4].

Vestita., *et al*. [5] reported the case of vismodegib-related cholestatic liver injury which is similar to our case. The author hypothesized that the drug might have increased bile density, therefore promoting microlithiasis and causing cholestatic liver injury in those with pre-existing lithiasis or other predisposing conditions such as drugs favouring increased bile density. The patient in our case had cholelithiasis on the CT scan which may be the reason for slow progress in the improvement of the bilirubin.

Conclusion

DILI from Vismodegib is rare occurrence. So far, there had only been few cases reported in literature. It is important to have an awareness that Vismodegib can cause DILI/hepatotoxicity. Drug withdrawal is the initial step in the management. Considering of cholelithiasis is important since it can delay the resolution of DILI and jaundice.

Declaration

Our case was reported to medicines and healthcare products Regulatory Agency and the Yellow Card report ID is GB-MHRA-MED-202206122106282970-FVJKR.

Acknowledgements

We will like to acknowledge the histopathologists (Dr Neerudu and Dr Gopalakrishnan) for providing us with the histology image.

Conflict of Interest

None.

Funding Statement

No funding is acquired.

Ethic Approval

No ethic approval is required.

Consent

A written consent had been obtained from the patient.

Bibliography

1. De Perosanz-Lobo D., *et al*. "Hepatotoxicity Associated with Vismodegib: Could Dose Reduction Be an Effective Management?" *Dermatologic Surgery* 47.7 (2021): 1006-1007.
2. Ash MM and Jolly PS. "Cholestatic Hepatic Injury Associated with Vismodegib, Aspirin, and Naproxen Use: A Case Study and Review of Vismodegib Safety" (2015).
3. Bedi PS., *et al*. "Hepatotoxicity Associated with Vismodegib". *BMJ Case Reports* (2018).
4. Navarro VJ and Senior JR. "Drug-Related Hepatotoxicity". *New England Journal of Medicine* 20354.7 (2006): 731-739.
5. Vestita M., *et al*. "Vismodegib and risk of cholestatic injury: should we screen candidate patients?" *Clinical and Experimental Medicine* 17.3 (2017): 415-416.

Volume 6 Issue 4 April 2023