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(CASE REPORT)

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Nintedanib induced liver injury: A rare case report

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Abstract

Nintedanib (BIBF 1120) is a potent intracellular inhibitor of tyrosine kinase receptors, including vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors α and β, and non-receptors members of the Src family [1]. By binding competitively to the adenosine triphosphate sites of these receptors, Nintedanib blocks autophosphorylation and so inhibits the downstream intracellular signalling cascades necessary for the proliferation, migration and survival of endothelial cells, pericytes, and fibroblasts [2]. Nintedanib is approved in the European Union in combination with docetaxel for the treatment of Non- Small Cell Lung Cancer (NSCLC) of adenocarcinoma histology after first-line chemotherapy and for the treatment of Idiopathic Pulmonary Fibrosis (IPF) [3-5].We report a patient, who was admitted at Gastroenterology department with complaints of itching, yellowish discolouration of eyes, concentrated urine for 1 month & cough with shortness of breath for 3 days.He was taking treatment for Type II Diabetes Mellitus and Hypertension for past 5 & 8 years respectively. The patient also had a medical history of Interstitial Lung Disease (ILD) and was taking Cap Nintedanib for 1 month.

Keywords: BIBF 1120 (Tyrosine Kinase Inhibitor); ILD; IPF; LFT; DILI; VEGFR; NSCLC (Non-Small Cell Lung Cancer); GGT

1. Introduction

Nintedanib (BIBF 1120) is a potent, oral, small-molecule tyrosine kinase inhibitor, also known as triple angiokinase inhibitor, inhibiting three major signalling pathways involved in angiogenesis. Nintedanib targets proangiogenic and pro-fibrotic pathways mediated by the VEGFR family, as well as Src and Flt-3 kinases [6]. Drug Induced Liver Injury (DILI) is an uncommon occurrence with an estimated incidence of 14-19 cases per 1, 00,000 population. Nintedanib is the first choice medicine for patients with ILD. ILD is a common manifestation of systemic sclerosis and a leading cause of systemic sclerosis- related death [7]. ILD is characterized by chronic progressive fibrosis, which comprises a large and varied group of diseases that generally affect the interstitium, the connective tissue stroma that separates the epithelial and endothelial barriers in the lungs. ILDs may have a known cause, eg: they may be a manifestation of an autoimmune disease or a result of sensitization to an inhaled antigen. However, ILDs also include several diseases of unknown cause [8]. Idiopathic Pulmonary Fibrosis (IPF) is one of the most common types of ILD [9]. In this article, we report a rare case of Nintedanib induced liver injury. Patient had a medical history of Type II Diabetes Mellitus (5 Years), Hypertension (8 Years) and ILD (4 Years). The case was reported after obtaining consent from the patient and the treating physician. His own medicines were TAB METFORMIN 500mg 1-0-1, TAB BISOPROLOL 5mg 1-0-0 & CAP NINTEDANIB 150 mg 1-0-1.

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He had taken Nintedanib for 1 month and stopped the medicine after the incidence of itching and yellow discolouration of eyes and urine. He had no known drug allergies. The patient was dyspnoeic at the time of hospital admission.

2. Case report

A 62 years old male patient was presented with complaints of itching over the body, yellow discoloration of eyes, concentrated urine for 1 month & cough for past 3 days. He had a medical history of Type II Diabetes Mellitus (5 years), Systemic Hypertension (8 years) and ILD (4 years) and was on medical treatment with TAB METFORMIN 500mg 1-0-1, TAB BISOPROLOL 5mg 1-0-0 & CAP NINTEDANIB 150mg 1-0-1. He was advised to take CAP NINTEDANIB for 2 months. But he stopped the medicine after 1 month when the skin reaction occurs. At the time of admission the patient was conscious and oriented.

Admission examination showed: Normal temperature, 18 breathe/min respiratory rate, 77 beats/min pulse rate and 120/80 mmHg blood pressure. Elevated parameters include ESR, CRP which indicates the incidence of any form of infections. Other elevated parameters were liver enzymes and Gamma Glutamyl Transferases (GGT) and it was monitored (Table 1). HbA1c level was found to be raised. Serum sodium level (134mmol/L) was found to be slightly declined. INR levels were under normal limits. Patient had elevation in lipid profile also. USG of abdomen and pelvis showed Grade I fatty liver, mild prostatomegaly and intra-hepatic common bile duct.

Table 1 Monitored levels of Liver enzymes

Liver enzymes (mg/dL)	**DAY 1**	**DAY 5**	**DAY 8**
Total Bilirubin	14.65	10.99	7.77
Direct Bilirubin	11.39	8.15	8.04
Indirect Bilirubin	3.2	2.84	1.73
SGOT/ALT	79	62	43
SGPT/AST	172	130	90
Alkaline phosphatise	223	181	155
Total protein	6.3	6.3	6.1
Albumin	3.3	3.3	3.2
Globulin	3.1	3.0	2.9
Albumin-Globulin ratio	1.0	1.1	1.10
Gamma-Glutamyl Transferases (GGT)	392	101	94

The first step put forwarded by the physician was the drug withdrawal. He was treated with hepatoprotectants T URSODEOXYCHOLIC ACID 300mg PO BD,T ACETYL CYSTEINE 600mg PO BD, Antioxidants T GLUTATHIONE 500mg PO OD, Antihistamines T CETIRIZINE 10mg PO HS, Histamine blockers T RANITIDINE 150mg PO BD, Multivitamin supplement 30gm PO BD. For itching, CALAMIN LOTION 8% w/w L/A TDS was given for local application. Dyspnoea was managed by NEBULIZATION LEVOSALBUTAMOL & BUDESONIDE 0.63mg PN TDS & 0.5mg PN TDS respectively. His own medicines were continued during the hospitalization. He was clinically stable and discharged after 8 days of hospital stay. He was discharged with the following medicines (Table 2):

Table 2 Discharge medications

Sl no.	Brand name	Generic name	Dose	ROA & frequency	Duration
1	T UDILIV	URSODEOXY CHOLIC ACID	300 mg	PO 1-0-1	7 days
2	T MUCOMIX	ACTEYL CYSTEINE	600 mg	PO 1-0-0	
3	T HEPTAGON	MULTIVITAMIN	30 gm	PO 1-0-1	
4	T RABIUM	RABEPRAZOLE	20 mg	PO 1-0-0	
5	T ALERID	CETIRIZINE	10 mg	PO SOS	SOS
6	SYP AERODIL	AMBROXOL(15mg) GUAIFENESIN(50mg) TERBUTALINE(1.25mg)	5 ml	PO 1-1-1	7 days
7	BESVIL DPI	FLUTICASONE-VILANTEROL	100mcg/25mcg (1 puff)	PN 1-0-0	

3. Discussion

Idiosyncratic Drug-Induced Liver Injury (DILI) is an important cause of morbidity and mortality following drugs taken more than therapeutic doses [10]. Drugs can be harmful to the liver in a susceptible subject on the background of genetic and environmental factors. This accounts for modifications in the hepatic metabolism and excretion of the agent leading to cellular stress, direct cell death, activation of an adaptive immune response and a failure to adapt with progression to overt liver injury [11]. Here the patient was admitted for 8 days in the hospital. He was presented with chief complaints of itching, yellow discoloration of eyes, concentrated urine, cough and shortness of breath. He had taken Cap. NINTEDANIB 150mg PO 1-0-1 (1 month) for ILD. Liver Function test of the patient was elevated. After the withdrawal of the drug, patient became symptomatically stable and found subsequent reduction in his liver parameters.

Discontinuation of the drug is important in case of drug induced diseases. The occurence of DILI with Nintedanib was already identified in pivotal premarketing trials and initial spontaneous reporting data [12, 13]. Using Nintedanib for the treatment of ILD in patients with CLDs, including SSc-ILD, may have antifibrotic effects in organs other than the lungs. In conclusion, Nintedanib demonstrated antifibrotic and anti-inflammatory activity, showing therapeutic potential in the experiment mouse model of CCL4-induced hepatic fibrosis [14].

In a case report published by Marta Librero, Clara Heredia Carrasco, et al. presented an 88 years old male patient with complaints of weakness, weight loss, jaundice and pruritis without abdominal pain for 1 month. His ultrasound scan showed progressive cholestatic liver injury in the past months, whereas hyperbilirubinemia and mild coagulopathy at admission. The patient was diagnosed with ILD and started to take Cap. Nintedanib. Later the drug was withdrawn and progressive clinical and laboratory tests improvement was achieved[15]. In this case, the patient was effectively treated according to the standard treatment guidelines and became clinically stable.

4. Conclusion

Fibrosing ILDs with a progressive phenotype show commonalities both in clinical behaviour and in the pathogenic mechanism that drive their progression. Nintedanib is an approved treatment for IPF and has recently been shown to reduce the rate of progression of ILD in patients with SSc-ILD. Nintedanib based regimens are associated with a higher risk of high grade diarrhoea, elevate ALT and AST. Moreover, there is a proportional relationship between Nintedanib dose and the risk of elevated transaminases. Here the patient was presented with complaints of itching, yellowish eyes, concentrated urine for 1 month after the administration of Nintedanib for ILD. Liver function tests showed elevated levels. He had undergone USG of abdomen and pelvis and found Grade I fatty liver, mild prostatomegaly and dilated

intra-hepatic CBD. Cap. Nintedanib was stopped and started with hepatoprotectants, nutritional supplements, antioxidants, antihistamine, and body lotion for local application and bronchodilators for the ease of breathlessness.As the patient had past history of Type II Diabetes Mellitus, Systemic Hypertension, and ILD, his own medications were continued.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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