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Title: A case report of severe thrombocytopenia in hepatitis C patient treated with Eltrombopag from off label drug use to on label drug use

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A case report of severe thrombocytopenia in hepatitis C patient treated with Eltrombopag from off label drug use to on label drug use

Abstract

Introduction: Off-label drug use refers to drug use beyond the specifications authorized for marketing. Eltrombopag is a new thrombopoietin receptor agonist which was used successfully in this critical case of thrombocytopenia associated with hepatitis C infection before it becomes an approved drug for such cases.

Case presentations: A 56-year-old female with hepatitis C virus infection, she was treated with pegylated interferon α-2a and ribavirin, laboratory test results prior to therapy were within normal values. After four weeks of that treatment, the patient developed neutropenia, and severe thrombocytopenia. Hepatitis C virus treatment ceased many years till Eltrombopag used as Off-label drug use with episode of severe thrombocytopenia. Platelets count returned to normal level where triple therapy for HCV was used successfully.

Conclusion: Off label drug use must be used only as the best available drug, based on evidence from on-going multicentre trials. It could be life saving for some patients in critical situations. However, clinical use of eltrombopag confirmed later that it is a safe and effective drug for ITP or thrombocytopenia associated with Hepatitis C virus infection.

Keywords: Hepatitis C virus, thrombocytopenia, peginterferone, off label drug use

Introduction

In this case we used a new agent as an off label drug use (OLDU). It is always a matter of debate. OLDU has been used in this patient where the ethical methods followed literally and successfully in a patient with hepatitis C virus infection (HCV) which is known to result in thrombocytopenia, even in the absence of overt hepatic disease. This infection is considered a marker for severity of liver disease and may sometimes be the only manifestation of viral hepatitis. It is estimated that 160 million individuals worldwide have chronic HCV infection. Moreover, this infection has been associated with an increased risk of developing chronic immune thrombocytopenic purpura (ITP) [1]. HCV infection-induced thrombocytopenia has an underlying autoimmune mechanism similar to that of ITP. The virus binds to thrombocytes, resulting in the production of autoantibodies against thrombocyte membrane antigens. Over 90% of patients with chronic HCV infection develop high levels of IgG-associated thrombocytes called platelet-associated immunoglobulin G (PAIgG) [2]. The IgG antibodies react with specific glycoproteins on the thrombocyte membrane surface and label them for autoimmune destruction in the reticuloendothelial system [3]. High PAIgG levels are directly related with liver disease severity, suggesting that chronic HCV infection is associated with major changes in the immune system. Patients who underwent interferon-α and ribavirin therapy had significant adverse effects, including body aches, malaise in 60%, fever in 35%, anaphylaxis in 2%, thrombocytopenia in 15%, and granulocytopenia in 26% [4].

Off-label drug use (OLDU) refers to drug use for unlicensed indications, in terms of doses, preparation, patient population, or route of administration, beyond the specifications.
authorized for marketing[^3]. In the USA, OLDU implies the prescription of a drug that is not specified in the labelling approved by the USA Food and Drug Administration (FDA) [^6].

**Case report**

In 2002, a 56-year-old Kuwaiti female without a history of blood transfusion was diagnosed with chronic hepatitis C. The patient may have contracted the viral infection while administering insulin injections to a friend with chronic HCV. Virology studies revealed HCV genotype 1 infection. Polymerase chain reaction indicated an HCV-RNA viral load by Taqman was 785,000 IU/mL (lower limit <15 IU/mL). The histologic sections at that time showed the overall architecture is preserved. There was a portal and perportal fibrosis with occasional bridging. Mild to moderate portal inflammation, composed of mostly small lymphocytes, with focal interface hepatitis. Few plasma cells and histiocytes are noted with mild to moderate lobular inflammation and scattered acidophil bodies and minimal macrovesicular steatosis. No significant cholestasis, Mallory hyaline, ballooning degeneration or intranuclear/cytoplasmic inclusions. The central veins are unremarkable. Iron stain highlights few Kupffer cells with increase iron storage. Periodic acid–Schiff diastase (PAS-D) stain is negative for intracytoplasmic globules. Figure 1

In 2003, she was treated with pegylated interferon α-2a (Pegasys®, Hoffmann-La Roche Inc., NJ, USA) 180 µg per week and ribavirin 1000 mg daily. Laboratory test results prior to the therapy were as follows with the minimum and maximum normal values: white blood cell (WBC) count, 4 (4–10 x 10^9/L); hemoglobin (Hb) level, 14.1 g/L (12.0–15.0 g/L); platelet count, 167 x 10^9/L (150–410 x 10^9/L); international normalized ratio, 1.1; total protein level, 72 g/L (61–79 g/L); albumin level, 42 g/L (35–48 g/L); alkaline phosphatase (ALP) level, 66 IU/L (42–98 IU/L); alanine transaminase (ALT), 174 IU/L (10–42 IU/L); and thyroid-stimulating hormone, 4.01 mIU/L (0.43-4.1 mIU/L). The serum was negative for antinuclear antibodies, antimitochondrial antibodies and anti-smooth muscle antibodies. Quantitative assay indicated normal serum immunoglobulin levels. Abdominal ultrasound did not indicate any abnormality.

After four weeks of treatment with interferon, the patient developed neutropenia (WBC count, 2.9 x 10^9/L). She was then administered 300-µg GCSF a granulocyte colony-stimulating factor (Neupogen; Amgen Inc., CA, USA). She also developed severe thrombocytopenia (platelet count, 5 x 10^9/L) and underwent transfusion with 19 platelet units. A bone marrow biopsy revealed the presence of normal cellularity and normal differentiation of the three cell lineages, indicating neutropenia and thrombocytopenia due to peripheral destruction. Intravenous immunoglobulin 0.4 g/kg daily was administered for 5 days. There was good response to the treatment, and platelet count increased to 104 x 10^9/L. Because of severe thrombocytopenia, this patient was considered unsuitable for further interferon therapy. Treatment with peginterferon had probably caused the thrombocytopenia, and thus, treatment was discontinued for approximately seven years owing to the risk of thrombocytopenia recurrence. Between 2004 and 2010, her platelet count oscillated between 50 and 100 x 10^9/L.

In late 2010, the patient again presented with severe and progressive thrombocytopenia. At that time, her platelet count dropped from 72 to 17 x 10^9/L throughout the year. Thus, intravenous immunoglobulin was administered without adequate response: platelets only increased to 31 x 10^9/L and then dropped to 6 x 10^9/L after 7 days of treatment. She was referred again to the Hematology Outpatient Consultation Department. Eltrombopag 50 mg daily was administered off label because intravenous immunoglobulin became progressively less effective in this case. After 10 days of treatment, there was a very good response (Figure 2) platelet count increased to 250 x 10^9/L. The dose was then reduced to 25 mg daily. After 3 months of normal platelet count by continuous administration of eltrombopag 25 mg daily, the hepatologist considered the patient eligible for HCV infection treatment.
In 2011, HCV-RNA viral load by Taqman of 3141,000 IU/mL the patient received triple HCV infection therapy (interferon, ribavirin, and telaprevir). Her platelet count did not reduce while she was on eltrombopag as well as the triple therapy. However, after the triple therapy, she had serious complications presented hemolytic anemia and urticaria. One month later, she developed severe pneumonia with oxygen desaturation and required mechanic ventilation in intensive care unit for 10 days where eltrombopag was hold. During this period, her platelet count decreased once again to 76 x 10^9/L. However, once eltrombopag was resumed, her normal platelet count was re-established to normal values. The patient fully recovered from this complication and is currently leading a normal life with normal hematologic and normal serum chemistry parameters (Hb, WBC, platelet, ALT, AST, GGT, etc.). Even after 3.5 years, she is receiving eltrombopag treatment. In 2013, the patient’s platelet count reduced to 67 x 10^9/L owing to treatment cessation for two weeks; platelet count returned to 131 x 10^9/L once she resumed taking eltrombopag 25 mg daily. Figure 2.

On May 2013 HCV-RNA viral load by Taqman was not detected.

Discussion
Chronic HCV may be accompanied by variable levels of thrombocytopenia caused by different mechanisms, i.e., central and peripheral autoimmune mechanisms or drug-induced thrombocytopenia. An autoimmune mechanism was found in 85% of the cases. HCV infection can directly suppress the megakaryocyte production. Interferon treatment also has a direct myelosuppressive effect that could lead to thrombocytopenia [7]. A patient is considered eligible for HCV infection treatment if the platelet count is above 90 x 10^9/L [8]. In December 2012, eltrombopag was approved by the FDA for treatment of HCV infection-related thrombocytopenia. It is the first drug approved for ITP treatment in the patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins) [9]. Eltrombopag is also the first orally bioavailable drug in its class and is a thrombopoietin receptor agonist that induces increased proliferation and differentiation of human bone marrow progenitor cells into megakaryocytes and increased platelet production in the circulating. The development of a targeted thrombopoietin receptor agonist has great implications on the therapy of patients with diseases associated with decreased platelets [10]. Elnrombopag is found in medical trails to provide clinical benefits in other conditions in which thrombocytopenia can occur, such as post chemotherapy and myelodysplastic syndrome [11]. The patient did not refer or present any treatment-related adverse effects on hematology, coagulation, or clinical chemistry parameters during her treatment with eltrombopag. Reportedly, the adverse effects of eltrombopag were mild and only seen in a few patients; these effects include headache, nasopharyngitis, upper respiratory tract infection, fatigue, arthralgia, diarrhea, nausea, back pain, and urinary tract infection [12]. OLDU based on evidence obtained from controlled research trials is a useful medical tool. This case is an example of life saving treatment with OLDU, and this drug was approved after about two years for thrombocytopenia due to chronic HCV infection [13]. Currently, eltrombopag is use in adult HCV patients with chronic HCV infection for the treatment of thrombocytopenia when the degree of thrombocytopenia severity should be considered while maintaining optimal interferon-based therapy [14]. Platelets count with eltrombopag treatment should be adjusted to maintain platelets count around 100 x 10^9/L, to avoid the risk of portal vein thrombosis in a patient with liver disease [15].

Conclusion:
OLDU could be life saving for some patients in critical situations. Its use must be base evidence from on-going multicentre trials. OLDU must be the best available drug to be used. However, not all off label drugs become approved but the new thrombopoietin receptor agonist eltrombopag became approved effective drug for thrombocytopenia associated with HCV.

Abbreviations:
1-off label drug use (OLDU)
2- hepatitis C virus infection (HCV) 
3- immune thrombocytopenic purpura (ITP) 
4- platelet-associated immunoglobulin G (PAIgG) 

Consent
Written informed consent was obtained from the patients for publication of this manuscript. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of competing interests: I declare that I have no competing interests.

Authors’ Contributions
1- Hassan Al-Jafar: The treating haematologist and wrote the manuscript 
2- Jameela Al-Khaldi: The treating hepatologist, revised the manuscript and added references 
3- Ahmad Alduaij: The histopathologist reported the liver biopsy and wrote it in the manuscript and added references 
4- Khalifa Al-Banwan: revised the manuscripts and added references.

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Figure 1: Inflamed portal tract area with interface hepatitis, shows inflammatory cells beyond the limiting plate

Figure 2: Platelets levels during the treatment course