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Case report

Acute pancreatitis associated with boceprevir: a case report

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ABSTRACT

Approximately 170 million people are infected with hepatitis C, and the sustained virological response rate to treatment with pegylated interferon and ribavirin is 30–50%. In an attempt to improve the chances of cure, boceprevir is being added to therapy, but it is associated with an increased incidence of adverse events. We herein report a case of acute pancreatitis developed during treatment with pegylated interferon, ribavirin and boceprevir. Boceprevir was the most likely cause of drug-associated pancreatitis after the most common causes were ruled out, since this adverse event had not occurred when the patient had previously been exposed to pegylated interferon and ribavirin and there was no recurrence of the episode of pancreatitis when these two drugs were reintroduced. Acute pancreatitis is a rare adverse event associated with boceprevir therapy, but a potentially fatal event. Sequential determination of pancreatic enzymes should be considered during hepatitis C treatment with boceprevir.

Introduction

An estimated 170 million people worldwide are chronically infected with hepatitis C virus (HCV).[1] The sustained virological response (RVS) rate to combination treatment with pegylated interferon and ribavirin for HCV genotype 1 ranges from 30 to 50%.[2] In an attempt to improve the chances of cure, new drugs were developed and used in combination with pegylated interferon and ribavirin. One of the two recently approved direct-acting antiviral agents is boceprevir, a protease inhibitor that blocks viral replication by binding reversibly to the viral protease NS3.[3]

The addition of boceprevir to pegylated interferon and ribavirin increased the chance of a SVR (63–66% in treatment-naive patients and 52–75% in previously treated patients),[4,5] but it also was associated with an increased incidence of adverse events during treatment, especially anemia and dysgeusia.[4,5]

We report the case of a patient with acute pancreatitis associated with boceprevir therapy. Informed consent has been obtained.

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Case report

A 43-year-old white man was admitted to the Hepatitis Unit of the Federal University of São Paulo, Brazil, in May 1995 for the investigation of liver disease due to the finding of "chronic hepatitis caused by HCV" in an intraoperative liver biopsy obtained one month earlier. The patient had undergone cholecystectomy for symptomatic gallstones and reported no other comorbidities or surgeries. The patient had used illicit drugs in the past, has been smoking since he was 20 years old, and reported no alcohol abuse. The diagnosis of chronic hepatitis C was confirmed by the detection of HCV RNA. Re-examination of the liver biopsy classified the specimen as F1A2 according to the METAVIR scoring system. The patient received conventional interferon for six months until October 1996 and was considered a non-responder.

In 2006, genotype 1 was detected and analysis of a new percutaneous liver biopsy revealed F2A3. The patient received a second course of pegylated interferon alfa 2a (180 μg, subcutaneously, once a week) and ribavirin (1.0 g per day, orally) for 48 weeks and again did not respond to treatment.

In 2012, noninvasive examinations showed no evidence of advanced fibrosis and the patient started the third treatment with pegylated interferon alfa 2b (1.5 μg, subcutaneously, once a week), ribavirin (1.250 g per day, orally), and boceprevir (800 mg, orally, three times per day). The viral load at the beginning of treatment was 2,200,000 IU/mL (6.34 log) and boceprevir was administered after a 4-week lead-in period. The viral load remained at 2,360,000 IU/mL (6.37 log) after the lead-in period but was undetectable after 8 and 12 weeks of treatment and the patient presented only mild flu-like symptoms.

After 17 weeks of treatment (13 weeks on boceprevir), the patient was hospitalized with epigastric pain radiating to the back, nausea, and vomiting. The patient reported no alcohol consumption or use of other medications. Laboratory tests at admission showed hemoglobin 14 g/L, hematocrit 43, leukocytes 5700 mm^3, platelets 163,000 mm^3, amylase 1209 IU/mL (normal: up to 125 IU/mL), lipase 6462 IU/mL (normal: up to 60 IU/mL), aspartate aminotransferase 34 IU/mL (normal: up to 40 IU/mL), alanine aminotransferase 42 IU/mL (normal: up to 42 IU/mL), total Ca 9.0 mg/dL, ionized Ca 4.5 mg/dL, and triglycerides 195 mg/dL. Upper abdominal computed tomography only revealed absence of gallbladder (cholecystectomy). Nuclear magnetic resonance imaging of the upper abdomen showed a pancreas of normal size, with a zone of altered signal in the pancreatic head close to the papilla, measuring 1.5 cm.

The hypothesis of drug-associated pancreatitis was raised after the most common causes had been ruled out. Cholelithiasis and choledocholithiasis were excluded since the patient had undergone cholecystectomy in the past and the upper abdominal computed tomography did not reveal any change in the biliary tree. Alcohol associated pancreatitis was also ruled out since the patient denied alcohol consumption. Elevated calcium or triglycerides were not possible causes of pancreatitis, as both were within the normal range. Pegylated interferon, ribavirin and boceprevir were immediately discontinued and supportive care was initiated. The patient was discharged after two days with clinical improvement and amylase levels of 82 IU/mL.

On the follow-up visit to the outpatient clinic one week after discharge, the patient was asymptomatic and pancreatic enzyme levels were within the normal range, with amylase levels of 101 IU/mL and lipase levels of 101 IU/mL. On that occasion, pegylated interferon and ribavirin were reintroduced at the same doses as administered previously and the patient only developed mild flu-like symptoms. No symptoms suggestive of pancreatitis or new elevations of pancreatic enzymes were observed.

Treatment was discontinued at week 26 because HCV RNA had been detected at week 24 and the patient again was considered a non-responder. The patient remained asymptomatic six months after the end of treatment, without recurrence of pancreatitis.

Conclusion

This is the first report describing the association of acute pancreatitis and boceprevir. Recently, the first report describing drug-associated pancreatitis during triple therapy for hepatitis C with telaprevir was published,[6] indicating the need for constant monitoring of pancreatic enzymes during treatment with these new drugs.

In the present case, the patient was eligible for triple therapy since he had not responded to two previous treatments, one consisting of conventional interferon and the other of pegylated interferon plus ribavirin. In both treatments, the patient developed flu-like symptoms and mild anemia as adverse events.

During treatment with pegylated interferon, ribavirin and boceprevir, the patient was diagnosed with acute pancreatitis based on the criteria of the American College of Gastroenterology, which define the condition when two of three criteria are present: (1) abdominal pain characteristic of pancreatitis, (2) serum amylase and/or lipase $\geq 3\times$ upper limit of normal, and (3) computed tomography suggestive of acute pancreatitis.[7] The most common causes of acute pancreatitis, such as cholelithiasis, alcohol abuse, hypercalcemia and hypertriglyceridemia, were ruled out by tests performed on admission.

Drugs are less frequent causes of acute pancreatitis, responsible for 0.1%[8] to 5.3%.[9] The diagnosis of drug-induced pancreatitis requires the development of the condition during treatment with the suspected drug and the resolution of symptoms after discontinuation of the drug, an adequate criterion for the diagnosis of acute pancreatitis, and the absence of other common causes of pancreatitis.[10] According to the classification of Karchand Lasagna[11] published in 1975 and of Mallory and Kern[12] published in 1980, the association between a drug and acute pancreatitis is definite when there is recurrence of the adverse event after challenging with the suspected drug. The latter is rarely seen due to the fear of reappearance of a potentially serious adverse event. In most cases, the causal relationship is

classified as probable since the symptoms disappear after discontinuation of the drug, as observed in the present case.

Acute pancreatitis is a rare adverse event in registry studies of boceprevir. The SPRINT-2 study evaluated the efficacy and safety of boceprevir in treatment-naive patients with hepatitis C.[4] Acute pancreatitis was observed in one (<1%) of the 734 subjects exposed to the drug. In the RESPOND-2 study, which evaluated boceprevir for the retreatment of patients with hepatitis C, acute pancreatitis was observed in 2 (<1%) of the 323 patients who received boceprevir.[5]

In the present case, pancreatitis was most likely associated with boceprevir therapy since this adverse event had not occurred when the patient had previously been exposed to pegylated interferon and ribavirin. Pegylated interferon and ribavirin were reintroduced one week after clinical improvement and there was no recurrence of the episode of pancreatitis, lending support to the possibility that these drugs were not involved in the development of pancreatitis in this patient.

According to the Naranjo algorithm, which is used to estimate the probability of drug-induced adverse events,[13] boceprevir was a probable drug associated with pancreatitis in the present case. Another finding supporting the causal relationship between boceprevir and acute pancreatitis is the fact that the patient did not develop pancreatitis prior to the use of boceprevir or during the 6-month observation period after the end of treatment. Other less common causes of acute pancreatitis, such as biliary microlithiasis and autoimmune pancreatitis, could therefore be ruled out.

In conclusion, boceprevir has recently been introduced for the treatment of chronic hepatitis C, and will be used in a large number of patients. One of the side effects associated to this drug is acute pancreatitis which, although rare, is a potentially fatal event. We suggest that the sequential determination of pancreatic enzymes should be considered during hepatitis C treatment with boceprevir in order to allow for early diagnosis of acute pancreatitis.

Conflicts of interest

The authors declare no conflicts of interest.

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