CASE REPORT

# Protease Inhibitor-Induced Acute Pancreatitis in Post Liver Transplant Hepatitis C Patients

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**Abstract**

Drug induced pancreatitis (DIP) is a serious adverse effect of many commonly used drugs. Pegylated interferon (peg-IFN) and ribavirin used for treatment of chronic hepatitis C (CHC) infection and various protease inhibitors (PIs) such as indinavir, nelfinavir, ritonavir and saquinavir used for HIV infection have been reported to cause DIP; although the mechanism of pancreatitis is not well known. Recently, telaprevir and boceprevir are introduced for treatment of HCV genotype 1 infection along with peg-IFN and ribavirin. There are no reports of acute pancreatitis (AP) due to telaprevir and boceprevir in liver transplant setting. We managed two such cases; both were male with HCV genotype 1 infection, had living donor liver transplantation for hepatocellular cancer few years ago and stable on cyclosporine. Both developed AP a month after adding one of PI to their combination therapy. First patient had past history of partial response with peg-IFN and ribavirin and retreated with addition of telaprevir to combination therapy. Second patient received peg-IFN and ribavirin for 4 months and then boceprevir was added. Patients were managed conservatively, the culprit PI was stopped and they recovered. We used the Naranjo Probability Scale for Adverse Drug Events to estimate the probability that a drug was the cause of the acute pancreatitis. A score of 7 was calculated in both patients, indicating a probable adverse drug reaction. The algorithm devised by Trivedi et al to diagnose drug-induced pancreatitis was also used and confirmed that this was likely to be a drug reaction. There is adequate circumstantial evidence pointing to telaprevir and boceprevir as the cause of their acute pancreatitis. Further evidence is needed but in the meantime we would recommend routine monitoring of amylase levels for all patients on triple therapy and advise patients of potential symptoms for which they should seek medical advice.

**Key words:** Protease Inhibitor, Hepatitis C, Pancreatitis, Drug-induced, Transplant

## Introduction

Drug induced pancreatitis (DIP) is challenging to diagnose and hence under-reported. The incidence of DIP is difficult to determine, but is thought to be about 0.1-2%. There are many drugs implicated in DIP, including those used the anti-viral treatment (AVT) of chronic hepatitis C infection (CHC). Acute pancreatitis as a result of treatment with pegylated interferon (peg-IFN) and ribavirin for CHC is well recognized and previously reported in the literature (1-6). The mechanism for this is not well understood. There have been several published case reports of acute pancreatitis (AP) occurring with the addition of protease inhibitors (PI) to HIV regimes (7-9). Recently triple therapy, with the addition of a protease inhibitor (Telaprevir/bocepravir) to peg-IFN and Ribavirin, has been used to treat chronic hepatitis C (CHC) in the non-transplant and post liver transplant (LT) setting. Only one case of acute pancreatitis in this small cohort of patients has been published, occurring in a non-transplant patient (10). We report two cases of acute pancreatitis in patients on triple therapy post LT.

## Case 1

A 59-year-old male was admitted with a two day history of abdominal pain, vomiting, diarrhea and fever, 8 weeks into triple therapy for recurrent hepatitis C post liver transplant. He had undergone a living donor LT 6 years previously for hepatocellular carcinoma (HCC) on a background of hepatitis C cirrhosis (Genotype 1). He had received AVT twice, with peg-IFN and ribavirin, since transplant, with only a partial virological response. His maintenance immunosuppression was cyclosporine (Cys) and mycophenolate mofetil. He had commenced triple therapy (peg-IFN 180mcg weekly + ribavirin 400mg bid, reduced to 200mg bid + telaprevir 750mg tid) 2 months prior to admission and achieved a rapid viral response (RVR). Examination revealed abdominal tenderness. His amylase was 1211U/L and lipase 21500U/L, white cell count of $12.5x10^9$/L, glucose 5.0mmol/L, LDH 310U/L, AST 36U/L, calcium 1.48mmol/L, serum sodium 117mmol/L, serum creatinine 196 umol/L and bicarbonate 11mmol/L. Triglycerides and total cholesterol were normal. An abdominal CT scan showed mild peri-pancreatic inflammatory fat stranding only. The pancreas homogenously enhanced. The biliary system had a normal appearance. Anti-virals, including telaprevir, was stopped and he was managed with intravenous fluids, analgesia and meropenem. He improved with the above management, developed no associated complications and was discharged 12 days later.

## Case 2

A 61-year-old male was admitted with a one day history of abdominal pain and vomiting, 28 weeks into triple therapy for recurrent hepatitis C post liver transplant. He had undergone a living donor LT 4 years earlier for HCC on a background of hepatitis C cirrhosis (Genotype 1). His immunosuppression was Cys and prednisolone. He had commneced peg-IFN and ribavirin 4 months earlier and bocepravir 3 months earlier. His HCV RNA PCR was undetectable at 10 weeks. Examination revealed abdominal tenderness only. His amylase was 1507U/L and lipase 23000U/L, white cell count $5.3x10^9$/L, glucose 5.3mmol/L, AST 28U/L, calcium 2.04mmol/L, sodium 138mmol/L and creatinine 112umol/L. Triglycerides and total cholesterol were normal. An abdominal CT scan showed a mildly swollen pancreas, moderate peri-pancreatic fat stranding and previously known, stable biliary findings. Triple therapy was stopped and he was managed with intravenous fluids and analgesia. He developed no complications and was discharged home 7 days later.

## Discussion

We diagnosed two patients with acute pancreatitis on the basis of clinical symptoms, hyperamylasemia and CT findings. One patient had previously been treated with peg-IFN and ribavirin and the other had been on treatment for four months before developing acute pancreatitis. In both cases, their medications remained unchanged. Other similarities included sex, age group, living donors LT and HCC as an indication for transplant. They had resolution of their symptoms on stopping triple therapy and no other cause of acute pancreatitis was found after an extensive work-up. Neither patient has been re-challenged. Acute Pancreatitis with peg-IFN and ribavirin has been reported and an increase in incidence of acute pancreatitis was noted in the HIV population with introduction of PI's. The underlying mechanism is unclear. We contacted other centres in North American and Europe none had seen acute pancreatitis in their cohort of patients. We reported the cases to the drug manufacturers. Further evidence is needed but we would advise monitoring of amylase on triple therapy and patient education regarding symptoms.

We used the "Naranjo Probability Scale for Adverse Drug Events" to estimate the probability that a drug was the cause of the acute pancreatitis (11). A score of 7 was calculated in both patients, indicating a probable adverse drug reaction. The algorithm devised by Trivedi et al to diagnose drug-induced pancreatitis was also used and confirmed that this

was likely to be a drug reaction (12). Acute pancreatitis in relation to therapy with peg-IFN and Ribavirin is a rare, but well recognized occurrence. An increase in the incidence of pancreatitis in patients with HIV was noted in the early 2000's with the introduction of PI's such as indinavir, nelfinavir, ritonavir and saquinavir. The mechanism by which the combination of peg-IFN and Ribavirin increases the risk of acute pancreatitis is poorly understood. It is unlikely that Ribavirin alone causes acute pancreatitis, at the doses used in HCV treatment, but it theoretically raises the risk of pancreatitis by producing mitochondrial toxicity when co-administered with other drugs such as anti-retrovirals (13). There are however reports of acute pancreatitis with peg-IFN monotherapy for HCV (14). It has been postulated that peg-IFN could induce an autoimmune inflammation, leading to pancreatitis. PEG-IFN and PI's are known to cause hypertriglyceridemia, which may cause pancreatitis but there are documented cases of acute pancreatitis in patients on peg-IFN or PI's with normal triglyceride levels (9,15). It still remains unclear what the exact underlying mechanisms are.

10 cases of acute pancreatitis with Telaprevir have been reported to the FDA, 6 in patients receiving treatment for HCV. These cases have not been published in the literature. Currently the number of patients being treated with triple therapy for HCV, both in the non-transplant and post- transplant setting is too small to determine causality between triple therapy and increased susceptibility to acute pancreatitis. Further evidence is needed but in the meantime we would recommend routine monitoring of amylase levels for all patients on triple therapy and advise patients of potential symptoms for which they should seek medical advice.

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