A Case Report of Successful Peginterferon, Ribavirin, and Daclatasvir therapy for Recurrent Cholestatic Hepatitis C following Liver Retransplantation

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Abbreviations

Alk P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
DCV	Daclatasvir
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus infection
IFN	Interferon

LT	Liver transplant
MELD	Model for end stage liver disease
POD	Post-op day
SVR	Sustained virological response

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Abstract

Recurrent hepatitis C virus infection following liver transplantation can lead to accelerated allograft injury and fibrosis. The aim of this study is to report the first ever use of daclatasvir (BMS-790052), a potent orally administered NS5A replication complex inhibitor, in combination with peginterferonα and ribavirin in a liver transplant recipient. A 49 year old female developed severe recurrent HCV genotype 1b infection 4 months after transplant with severe cholestasis on biopsy and an HCV RNA of 10,000,000 IU/ml, alk phos of 1525 IU/ml, and total bilirubin of 8.4 mg/dl. Despite partial virological suppression with peginterferonα and ribavirin, progressive allograft failure ensued culminating in retransplantation at 9 months. At 3 months after the second transplant, daclatasvir 20 mg per day, peginterferonα2a 180 ug/ week and ribavirin 800 mg/ day were prescribed for early recurrent cholestatic HCV. Serum HCV RNA became undetectable at week 3 of treatment and remained undetectable during 24 weeks of triple therapy as well as during post-treatment follow-up. Daclatasvir was well-tolerated and the trough drug levels were within the targeted range throughout treatment. The cyclosporine trough levels were also stable during and after therapy. **Conclusion**: The lack of anticipated drug-drug interactions between daclatasvir and the calcineurin inhibitors coupled with its potent antiviral efficacy make this agent in combination with peginterferon and ribavirin an attractive antiviral regimen worthy of further study in liver transplant recipients with recurrent HCV.

Words= 229

Introduction

Liver failure and hepatocellular carcinoma (HCC) due to chronic hepatitis C virus (HCV) infection are the leading indications for liver transplantation (LT) in the United States (1). However, recurrence of HCV infection following LT is nearly universal and characterized by high serum HCV RNA levels and variable severity of allograft hepatitis (2, 3). The rate of fibrosis progression is greatly accelerated compared to non-transplant HCV patients with 10-30% developing cirrhosis within 5 years of transplant (4,5). The accelerated course of recurrent HCV infection is attributed, in part, to the use of potent immunosuppressants, treatment of acute rejection, and other donor and recipient factors. Not surprisingly, LT recipients with chronic HCV have a significantly lower 5-year survival compared to other recipients due to a higher rate of graft failure from recurrent disease (6,7).

Peginterferon (pegIFN) and ribavirin combination therapy are frequently used for selected LT recipients with recurrent HCV infection (8-10). In addition, several studies have shown that LT recipients who achieve a sustained virological response (SVR) have significantly improved survival compared to partial responders as well as untreated patients (11-13). However, many LT recipients are incapable of initiating interferon therapy due to pancytopenia, renal insufficiency, and/or other medical and psychiatric co-morbidities. In addition, antiviral response rates are lower in LT recipients compared to non-transplant patients (30% vs 45% SVR in genotype 1) due, in part, to the use of immunosuppressive agents and the need for more frequent antiviral medication dose reductions and/or early discontinuation (8-10). Therefore, better tolerated and more effective treatments for LT recipients with recurrent HCV are urgently needed. The direct acting antiviral agents, telaprevir and boceprevir, in combination with pegIFN and ribavirin were recently shown to significantly improve SVR rates in both treatment naïve and previously treated genotype 1 patients (14-17). However, both of these agents are contraindicated in LT recipients due to potentially severe and life-threatening drug-drug interactions with cyclosporine and tacrolimus as well as the lack of efficacy and safety data in this patient population (18, 19). Daclatasvir (BMS-790052; DCV, Bristol-Myers Squibb, Princeton, NJ) is an investigational oral NS5A replication complex inhibitor in development with demonstrated antiviral efficacy when combined with pegIFN and ribavirin in treatment naïve and previously treated patients with HCV genotypes 1 and 4 (20-25). In phase 2 clinical trials, DCV has been generally well tolerated in combination therapy with no unique adverse events identified to date. Furthermore, *In vitro* and *in vivo* testing suggests that DCV should not lead to any clinically significant drug-drug interactions when co-administered with other drugs that are metabolized by CYP3A4 such as cyclosporine, tacrolimus, and sirolimus (24). The aim of the current study is to report on the first successful use of a DAA, DCV, in combination with pegIFN and ribavirin in a LT recipient with severe, interferon-refractory cholestatic HCV infection.

Methods

Antiviral treatment regimen- An investigator initiated emergency IND (#109,999) was obtained from the United States Food and Drug Administration to provide antiviral treatment for this single patient with severe recurrent cholestatic HCV infection following LT. The treatment protocol included the use of

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DCV 20 mg per day (BMS, Princeton, NJ), peginterferonα2a 180 ug/week (Genetech, Nutley, NJ) and ribavirin 400 mg bid for 24 weeks. A reduced dose of DCV, 20 mg, was selected due to the potential for a theoretically mild drug-drug interaction with cyclosporine. Daclatasvir and cylosporine are substrates and inhibitors of CYP3A4 and P-glycoprotein, respectively; therefore, it was anticipated that the exposure of daclatasvir may be increased when concomitantly administered with cyclosporine. The patient was seen at weeks 0,1,2, 3, 4, 8, 12, 16, 20, and 24 as well as at follow-up weeks 12 and 24 at the University of Michigan Institute for Clinical and Health Research, Ann Arbor, MI. HCV RNA levels were tested using Roche Cobas Taqman (LLOD of 43 IU/ml) at weeks 0, 1, 2, 3, 4, 8, 12, 24 and follow-up weeks 12 and 24. Written informed consent was obtained from the patient after review and approval by the local Institutional Review Board.

Daclatasvir Pharmacokinetics- A morning blood sample was obtained at weeks 2, 4, 6, 8, and 12 to assess DCV trough levels using a validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) method (21). In addition, semi-intensive 6 hour pharmacokinetic sampling was performed at treatment week 2 to estimate the overall exposure and to determine the Cmax and Tmax values at steady state.

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Results

Initial pre- and post-transplant course- A 49 year-old female healthcare provider acquired HCV genotype 1b infection after an inadvertent needle stick in 1990. She was initially treated with interferon monotherapy without clearance and retreated with full dose pegIFN and ribavirin for 48 weeks in 2002 with suppression of HCV RNA to undetectable levels followed by post-treatment relapse. The patient also had a history of diabetes mellitus, hypertension, and a body mass index of 35 kg/m^2. Her Interleukin 28-B (IL28B) genotype at rs12979860 was CT. The patient progressed to decompensated cirrhosis with ascites, gastrointestinal bleeding, and encephalopathy and was listed for transplant with a model for end stage liver disease (MELD) score of 11. Following the diagnosis of a 2 cm HCC, she received a MELD upgrade to 22 points. While hospitalized with a MELD score of 32 on hemodialysis, she received a cadaveric liver transplant from a donor that was < 40 years old with a cold ischemia time of 9 hours. Induction immunosuppression consisted of basiliximab (Simulect, Novartis, East Hanover, NJ) on post-op days (POD) #1 and #4 as well as intra-operative steroids. She was discharged home on POD # 22 on cyclosporine, mycophenolate mofetil and prednisone with stable liver biochemistries.

At month 4 following her first LT, serum alkaline phosphatase (Alk P) was 1,525 IU/ml, bilirubin was 8.4 mg/dl and an HCV RNA level was 10.8 x 10^6 IU/ml. Evaluation for biliary strictures was negative and a liver biopsy showed intense pericentral cholestatic reaction with lymphocytic inflammation indicative of recurrent HCV (**Figure 1A**). As a result, pegIFNα2a 180 ug/week and ribavirin 1200 mg/day were initiated. At week 4 of antiviral therapy her bilirubin had increased to 17.9 mg/dl and a repeat liver biopsy demonstrated severe cholestatic HCV with perisinusoidal fibrosis. Although HCV RNA had declined to 3.2 x 10^3 IU/ml at treatment week 12, her cholestasis worsened with an Alk P of 1959 IU/ml and bilirubin of 36.8 mg/dl and antiviral therapy was discontinued due to her worsening clinical status (**Figure 2**).

The patient was subsequently hospitalized with severe encephalopathy requiring intubation and coagulopathy with an INR of 1.9. She underwent retransplantation with a MELD score of 36 while in the ICU. In this instance, a 19 year old cadaveric donor was utilized with a cold-ischemia time of only 7 hours. Initial immunosuppression consisted of cyclosporine, mycophenolate mofetil, and steroids. She was discharged home 4 weeks later on cyclosporine and prednisone and fully recovered. At week 12 following the second liver transplant, her Alk P had risen to 673 IU/ml with an ALT of 88 IU/ml and a total bilirubin of 1.4 mg/dl. A cholangiogram revealed no evidence of obstruction and the serum HCV RNA level was 4.0 x 10^6 IU/ml. Due to the diagnostic uncertainty, a liver biopsy was obtained that showed mild periportal and lobular hepatitis with a lymphocytic infiltrate (**Figure 1B**).

Daclatasvir in combination with pegIFN and ribavirin treatment- The patient was started on DCV 20 mg/day, pegIFNα2a 180 ug/ week and ribavirin 800 mg/day at week 12 after the second liver transplant due to the suspicion of early recurrent HCV infection with cholestatic features. Concomitant medications included cyclosporine 75 mg bid, prednisone 4 mg day, pantoprazole 40 mg/day, nifedipine 60 mg/ day, lasix 20 mg per day, ursodeoxycholic acid 600 mg per day, erythropoietin 20,000 units/week

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and atenolol 25 mg/day along with insulin and calcium with vitamin D. Serum HCV RNA became undetectable at week 3 of antiviral therapy with associated improvements in serum ALT and alk phos levels (**Figure 2**). At week 16 of antiviral therapy, the patient experienced an episode of herpes zoster reactivation that was successfully treated with valacyclovir over 4 weeks.

At treatment week 19, her serum ALT and Alk P levels increased to 99 and 517, respectively. A liver biopsy showed immune mediated allograft hepatitis with extensive plasma cell infiltration and hepatic necrosis. At that time, her ANA and anti-smooth muscle antibody were negative, quantitative immunoglobulin levels were normal, and her cyclosporine trough level was in the therapeutic range at 100 ng/ml. Since this was felt to be immune mediated allograft dysfunction due to interferon, the pegIFN dose was reduced to 135 ug/week and the prednisone dose was increased from 2 to 20 mg per day for the remainder of her treatment course.

After 24 weeks of triple antiviral therapy, an additional 4 weeks of pegIFN and ribavirin consolidation therapy were given.   Following cessation of the antiviral medications at week 28, her serum ALT was 82 and Alk P was 294 with a normal total bilirubin. At post-treatment weeks 12 and 24, her HCV RNA remained undetectable with a serum ALT of 50, Alk P of 220 IU/ml and total bilirubin of 0.6 mg/dl. At week 32 following treatment, the patient is feeling well with normal liver biochemistries while receiving cyclosporine 75 mg bid, prednisone 5 mg daily, and azathioprine 100 mg per day and HCV RNA remains undetectable.

Pharmacokinetic assessment: Plasma concentrations of DCV at treatment week 2 were 137, 102, 112, 218, 451 and 376 ng/mL at predose, 0.5, 1.0, 2.0, 4.0 and 6.0 hr post dose, respectively. Trough values at weeks 4, 6, 8, 12 and 24 were 129, 160, 270, 161, and 87 ng/mL, respectively.

Discussion

Recurrent HCV infection following LT can lead to accelerated allograft injury and fibrosis due to the high levels of HCV replication and ongoing suppression of the host immune response to viral antigens (4,5). Patients who receive monoclonal antibody induction therapy or who require treatment for acute rejection with pulse steroids are at particular risk for severe recurrent HCV infection as well as recipients of older donor allografts (7,27,28). Our patient developed severe recurrent cholestatic HCV infection within 4 months of her initial transplant in the absence of monoclonal antibody induction therapy and despite receiving a younger donor liver with a short cold-ischemia time. Despite minimizing her immunosuppression and early introduction of pegIFN and ribavirin combination therapy, the patient developed progressive and life-threatening cholestatic graft failure. The liver biopsies at months 4 and 5 showed classic features of severe cholestatic HCV infection (**Figure 1A)** (28, 29). This particular variant of recurrent HCV infection tends to occur within the first year of LT and is characterized by the development of inflammatory infiltrates, cholestasis, and hepatocyte ballooning that can frequently lead to early graft failure and premature death. Although there have been case reports of salvage antiviral therapy, most patients die of infection or progressive allograft failure (27).

Although prior data have shown poor outcomes with retransplanation in patients with severe recurrent HCV infection, a second transplant was offered to this patient due to her young age, excellent functional status and good general health (31,32). Fortunately, she had adequate physiological reserve to recover and was discharged home within 4 weeks of retransplantation. However, when the patient began to manifest early recurrent cholestasis with associated histological changes at 3 months following her 2nd transplant (**Figure 1B**), initiation of a potent DAA-based (DCV) antiviral therapy in combination with pegIFN and ribavirin was undertaken.

In comparison to her initial postLT treatment course, a rapid suppression of HCV RNA at week 3 was observed with associated improvements in serum ALT and Alk P levels while receiving DCV in combination with pegIFN and ribavirin (**Figure 2**). In addition, the HCV RNA remained undetectable throughout the 24 week course of triple antiviral treatment even though she had been previously treated 3 times without success. Furthermore, viral replication remained suppressed even despite an intensification in her immunosuppressive regimen due to allograft dysfunction at week 19 and an intentional reduction in the dose of pegIFN. We considered discontinuing all 3 antiviral agents at this point but wanted to complete a full 24 weeks of treatment in light of her prior lack of clearance with pegIFN and ribavirin. A reduced dose of 20 mg DCV was used throughout treatment in this patient due to the potential for cyclosporine to increase the plasma levels of daclatasvir. The plasma trough levels of DCV at weeks 2, 4, 8, 12, and 24 ranged from 87 to 270 ng/mL which is similar to what has been reported in non-immunosuppressed HCV patients receiving daclatasvir 60 mg per day (21). In addition, the observed Cmax of DCV of 451 ng/ml is similar to the values observed in non-transplant patients receiving a 30 mg once daily dose (21). The Tmax for the patient was 4 hours which is longer than the mean Tmax previously reported for non-transplant patients under fasting conditions but within the range observed when patients received DCV under fed conditions. Overall, the exposure observed for

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this subject is within the therapeutic range for DCV where safety and efficacy have been observed suggesting that cyclosporine did not have a clinically significant effect on DCV exposure.

Antiviral therapy was well tolerated in this LT recipient who was receiving concomitant cyclosporine, prednisone, and several other medications. The episode of herpes zoster at antiviral treatment week 19 was not felt to be related to the DCV study medication nor the pegIFN and ribavirin treatment since solid organ transplant recipients are known to be at increased risk for zoster reactivation (33-35). In addition, the zoster improved despite continued antiviral therapy. The other adverse event experienced by this patient of immune-mediated allograft hepatitis is being increasingly reported in LT recipients receiving interferon (8, 36, 37). Many HCV patients with immune-mediated hepatitis have detectable serum autoantibodies and develop a plasma cell rich infiltrate in the allograft which responds to increased immunosuppression. Some investigators speculate that immune-mediated hepatitis may be due to rapid suppression of HCV RNA and reflect an "Immune-reconstitution" syndrome as reported in HIV patients treated with anti-retroviral therapy (37). In support of this, Interferon therapy can promote HCV-specific CD4 and CD8 responses in the liver but additional prospective studies of viral kinetics and intrahepatic immune responses are needed (38). Hepatitis C patients with cholestasis and plasma cell hepatitis on their baseline biopsy or elevated alkaline phosphatase levels prior to antiviral therapy may be at particular risk for this complication (36,37). Other studies have suggested that virological responders to interferon therapy who experience improved liver function and metabolism of calcineurin inhibitors may be at increased risk of developing rejection during antiviral therapy (39,40). Although our understanding of this clinic-pathological entity is evolving, many patients improve with either a reduction or discontinuation of Interferon therapy or with an increase in their immunosuppression but cases of progressive hepatitis with graft failure and death have been reported (36). In the current patient, we were reluctant to stop the antiviral therapy in light of her progressive liver failure with her first transplant and rapid response to the 3-drug antiviral treatment. Therefore, the dose of pegIFN was reduced and the corticosteroid dose was increased to treat the immune-mediated allograft hepatitis. Fortunately, this patient was successfully supported through a full 24 week course of triple antiviral therapy and her liver biochemistries further improved during follow-up. In addition to being highly effective, DCV was not associated with any clinically significant drug-drug interactions in our patient. In particular, the trough levels of cylcosporine remained in the target range of 75 to 125 ng/ml during and after treatment.

In summary, we report the first successful use of a direct acting antiviral agent in combination with pegIFN and ribavirin in a LT recipient with severe, interferon refractory cholestatic HCV. Despite 3 prior attempts at antiviral therapy including a course of pegIFN and ribavirin after the first LT, the patient developed early cholestatic HCV after her second transplant. The rapid suppression of HCV RNA to undetectable levels within 3 weeks of initiating treatment with DCV and pegIFN and ribavirin along with the improved liver biochemistries suggest that effective antiviral therapy can lead to improved outcomes in these patients. In addition, the ability of this patient to remain suppressed despite the need to reduce the pegIFN dose and increase the dose of steroids is encouraging with regard to the potency and efficacy of DCV based combination antiviral therapy. Furthermore, the fact that only 24 weeks of triple antiviral therapy was required to achieve an SVR in this patient is also promising for

other genotype 1 LT recipients who frequently have difficulty tolerating 48 weeks of treatment. However, the optimal duration of triple antiviral therapy in HCV genotype 1a versus genotype 1b LT recipients requires further investigation. The favorable safety profile of DCV in combination with pegIFN and ribavirin observed in this patient and other studies including potentially minimal drug-drug interactions with the calcineurin inhibitors also make it an attractive agent to explore in future studies of LT recipients. Finally, it is hoped that if combination regimens of potent oral antiviral agents such as daclatasvir with other DAA classes such as NS3 protease inhibitors (asunaprevir or TMC435) or NS5B nucleoside polymerase inhibitors (INX-189 or GSI-7977) with or without ribavirin can be safely administered to non-transplant patients, many additional LT recipients with recurrent HCV will be able to be treated. However, additional prospective studies will be needed (41, 42).

Figure Legends

Figure 1. A) Severe cholestatic HCV infection at 4 months following liver transplant #1. The left side of the slide shows intense pericentral hepatocyte balloon degeneration. To the right is a portal tract with focal periportal cholestatic ductular proliferation and lymphocytic inflammation indicative of recurrent cholestatic hepatitis C (Hematoxylin and eosin stain, 200 x magnification). B) Recurrent hepatitis C infection at 3 months following liver transplant #2. On the right side of the slide, there is a central vein with normal pericentral hepatocytes without ballooning. To the left is a portal tract with moderate lymphocytic inflammation that is characteristic of early recurrent HCV infection. In the lobular parenchyma between the portal tract and central vein, there is mild inflammation with scattered sinusoidal lymphocytes and a single necrotic hepatocyte near the portal tract which are typical features of recurrent HCV infection.

Figure 2. Liver biochemistries and HCV RNA levels during antiviral therapy. At month 5 after LT #1, the patient was started on pegIFNα2a 180 ug/week and ribavirin 1200 mg/ day. Despite partial suppression of HCV RNA, the serum Alk P and bilirubin continued to rise and antiviral therapy was discontinued 12 weeks later. Following retransplantation, the serum alkaline phosphatase and total bilirubin nearly normalized but began to rise again with reemergence of HCV RNA. At month 4 after LT #2, the patient was started on DCV 20 mg per day, pegIFNα2a 180 ug/week and ribavirin 800 mg/day. Within 3 weeks of starting therapy, HCV RNA became undetectable with concomitant improvements in serum Alk P and bilirubin levels. After 24 weeks of triple therapy, the patient received an additional 4 weeks of pegIFN and ribavirin consolidation therapy. The patient remains well with undetectable HCV RNA at her last follow-up 32 weeks after completing treatment.
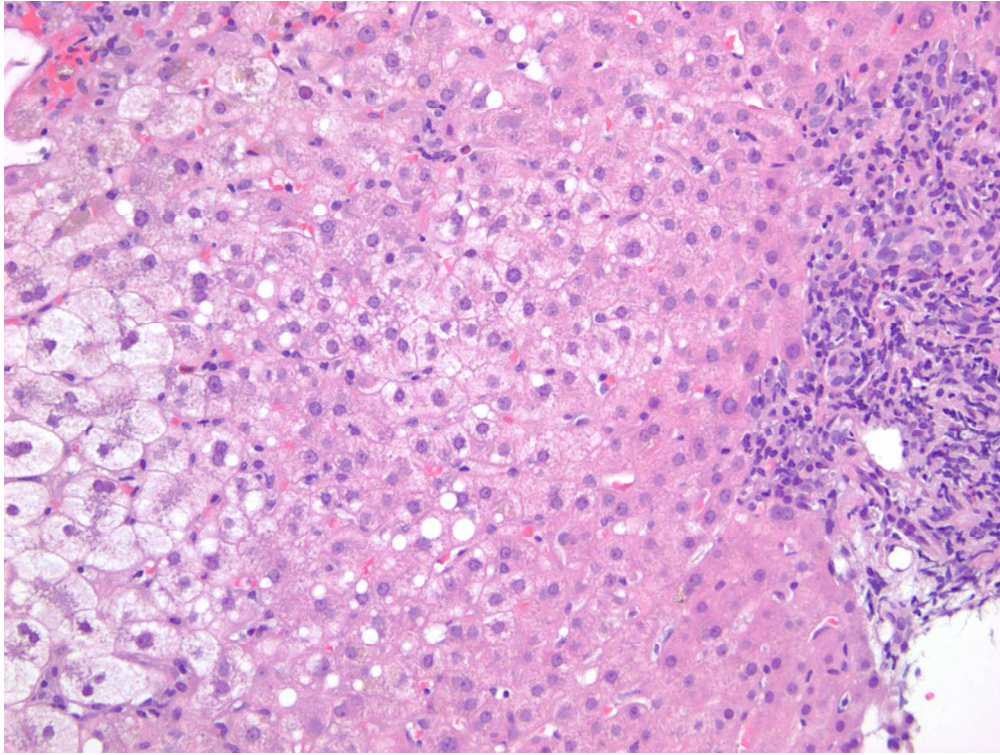
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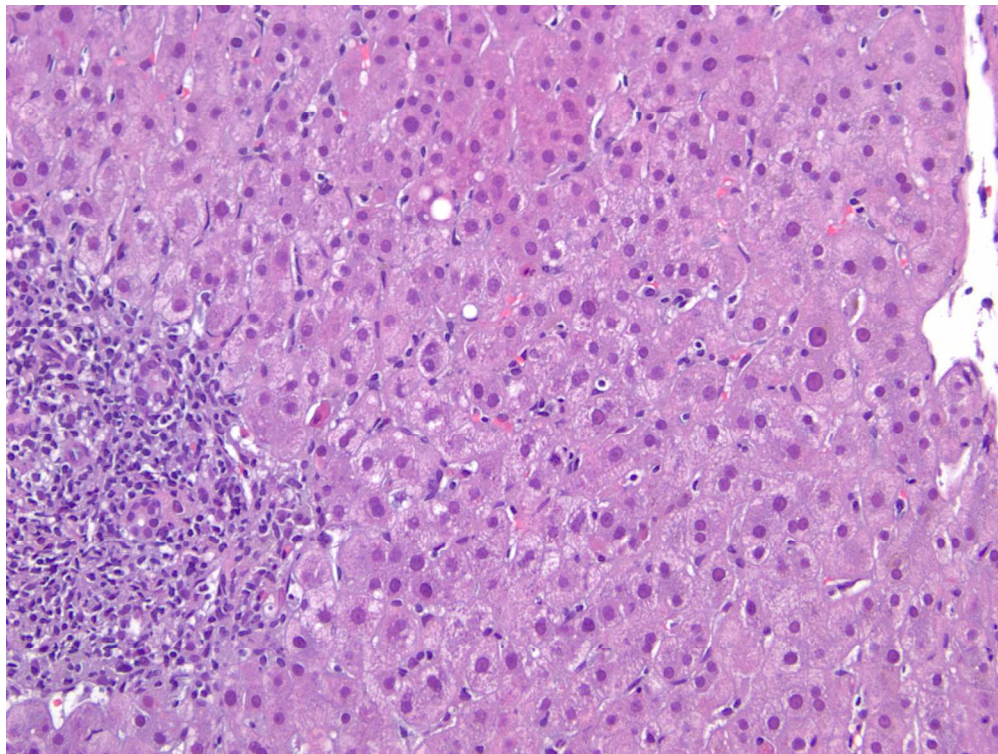
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in HCV genotype 1 infected null responders or patients ineligible/ intolerant to peginterferon/ribavirin (Abstract). J Hepatology 2012; 56.
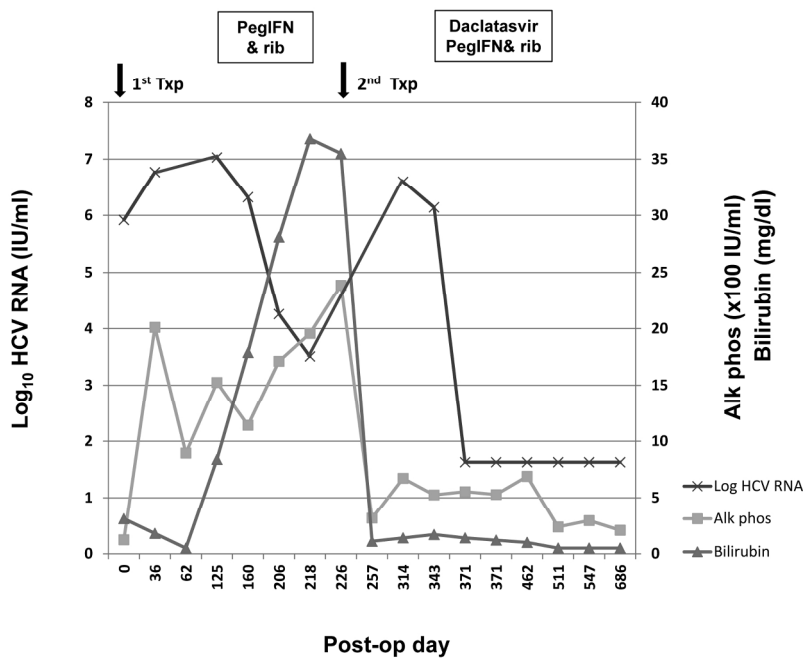
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