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Clinical decompensation after achieving SVR with sofosbuvir, daclatasvir and ribavirin in a patient with recurrent HCV post-liver transplant

To the Editor,

Recurrence of HCV post-liver transplant (LT) is associated with accelerated progression of fibrosis leading to cirrhosis in 20-54% of patients within 5 years post-LT [1]. Post-LT improvement in the inflammatory activity after achieving a sustained virological response (SVR) is well-established, but fibrosis regression/stabilization is less predictable after treatment with PegIFN/ribavirin. In one study, based on 29 patients who had reached a sustained virological response (SVR), fibrosis at 2 years improved by ≥1 Metavir stage in 27%, remained unchanged in 38%, and worsened in 35% despite viral clearance. After 3–5 years, the fibrosis stage had improved in 67%, remained unchanged in 13%, and worsened in 20% [2].

Though direct-acting antiviral agents (DAAs) are expected to change the management of HCV recurrence and decrease graft loss rates, at present there is little data on the impact of DAAs on fibrosis progression/regression post-LT. We describe a case of development of further clinical decompensation with variceal bleeding and ascites in a patient with recurrent HCV post-LT, despite achieving SVR with sofosbuvir, daclatasvir and ribavirin.

A 33-year old male with haemophilia A was transplanted in 2002 for HCV-genotype 3-related cirrhosis. Pre-LT he was treated with IFN monotherapy (1996) and combination of PegIFN and ribavirin (2000), without virological response. Donor age was 50 years old. Initial immunosuppression used was tacrolimus, azathioprine and tapered steroids for 3-6 months post-LT. Two episodes of moderate cellular rejection were treated with 3 doses of 1g methylprednisolone daily. One-year protocol liver biopsy showed Ishak stage 2 fibrosis, a collagen proportionate area (CPA) of 7% and a hepatic venous pressure gradient (HVPG) of 6 mmHg. Three years post-LT he was treated with PegIFN/ribavirin with a baseline viral load of $2x10^6$ IU/ml but the treatment was withdrawn 7 months later due to severe reaction at the injection site. He suffered decompensation 9 years post-LT, with a right-sided pleural effusion. A transjugular liver biopsy revealed a CPA of 16%, and a HVPG of 13mmHg. One year later (January 2012) he was commenced on sofosbuvir, PegIFN and ribavirin for 6 weeks and continued sofosbuvir and ribavirin for another 24 weeks. His HCV RNA was undetectable at the end of treatment. However, he relapsed shortly after the end of treatment (August 2012). On September 2013, he was re-treated with sofosbuvir 400mg, daclatasvir 60mg and ribavirin 400mg-800mg for 24 weeks and attained a SVR12 in May 2014. During the treatment, he developed no adverse events apart from fatigue, myalgia and insomnia treated with zopiclone; his haemoglobin levels remained stable at approximately 10.5 g/dL with no need for administration of erythropoietin. However, further decompensation occurred with variceal bleeding and gross ascites two months after achieving a SVR.

This case showed that despite the viral clearance and the SVR, a further hepatic decompensation occurred. We speculate that the initial relapse following sofosbuvir and PegIFN may have been detrimental and injurious to the liver. Direct-acting antiviral agents might not ameliorate fibrosis progression in all cases, since further decompensation occurred despite HCV eradication. Furthermore, there are studies suggesting mortality rates up to 25% in transplanted patients with recurrent HCV treated with sofosbuvir, daclatasvir ± ribavirin [3, 4]. Therefore, the antiviral treatment with DAAs post-LT should start early, before decompensation occurs; regimens and duration of therapy should be selected to minimise relapse in patients with advanced liver disease and, thus, to minimise adverse outcomes.

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Serum intestinal-fatty acid binding protein as a biomarker for refractory celiac disease

To the Editor,

Most celiac disease (CD) patients are treated successfully with a gluten free diet (GFD) [1]. A small fraction of adult onset CD patients become refractory to the GFD. Refractory celiac disease (RCD) type II patients, characterized by an aberrant intraepithelial lymphocyte population, are at risk to develop enteropathy associated T-cell lymphoma [2]. Early recognition of RCD and close monitoring of disease activity is of the utmost importance. Recently, we have shown that IgA antibodies against the luminal proteins pancreatic GP2 protein (GP2A) and Saccharomyces cerevisiae (ASCA) may aid in the diagnosis of RCDII. However, levels of these antibodies do not correlate with villous atrophy and are therefore not useful for the follow-up of RCDII patients [3, 4]. Furthermore, we have shown that intestinal fatty acid binding protein (I-FABP) levels relate to the severity of intestinal damage in uncomplicated celiac disease [5]. We therefore investigated whether serum I-FABP levels can be useful in the identification of RCDII patients and/or prediction of treatment response. I-FABP levels were determined using the previously described in-house enzyme-linked immunosorbent assay [5] and patient groups [3, 4]: controls (n=27), ACD patients (n=37), patients recovered on a GFD (n=33) and RCDII patients (n=16). Baseline I-FABP levels were higher in RCDII patients [870 (106-2234) pg/ml] compared to controls [229 (85-1338) pg/ml; p=0.001] and recovered CD patients (GFD: 170 [63-1572] pg/ml; p=0.003), and equalled the high levels of ACD patients [646 (113-3000) pg/ml] (Fig. 1a). A cross sectional analysis comparing I-FABP levels from CD patients with normal mucosa or only an increase in intraepithelial lymphocytes (IEL) or crypt hyperplasia (Marsh 0, I and II), with the I-FABP levels from patients with villous atrophy (Marsh IIIA-IIIC) showed a clear relation between increased I-FABP levels and villous atrophy (p<0.0001, Fig. 1b), confirming our previous data [5]. I-FABP levels did not significantly change upon treatment of RCDII patients (not shown).

As RCD patients had significantly higher I-FABP levels compared to patients that recovered histologically and serologically on a GFD, we tested whether I-FABP levels were able to distinguish RCD patients from patients recovered on a GFD. The ROC analysis based on data of RCD and GFD patients resulted in an area-under-the-curve (AUC) of 0.80 that was significantly different from 0.5 (p<0.0009). At a cut-off of 660 pg/ml the highest specificity (94%) was obtained with a sensitivity of 69%. As GP2A and ASCA may aid in the diagnosis of RCDII as well [4], we investigated whether a combination of tests leads to a higher sensitivity, without significant loss of specificity, for the identification of RCDII patients within patients on a GFD (negative for transglutaminase-2 auto-antibodies). When one out of two or three performed tests was positive, the sensitivity increased to 77%, while the specificity was 87% (AUC=0.83, p=0.0007). The best combination was the I-FABP with the GP2A test, showing a sensitivity of 80% and a specificity of 89% (AUC=0.82, p=0.02) when at least one of these tests was positive.

In conclusion, although not useful for treatment follow-up, I-FABP levels have the potential to serve as a serum marker for diagnosing RCDII, particularly in combination with GP2A.

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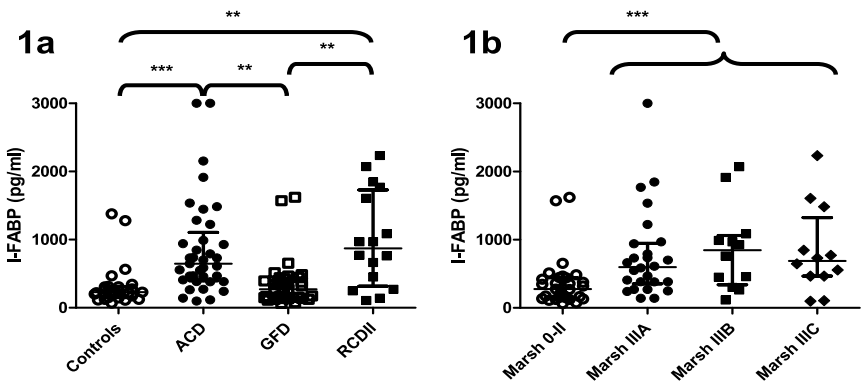

Fig. 1. Cross-sectional distribution of I-FABP levels. a) different patient groups are compared using Anova (Krukal-Wallis) p<0.0001, with Dunns post test **p≤0.005; ***p≤0.0005. b) Stratification of I-FABP levels according to Marsh classification in the CD (ACD, GFD and RCDII pre-treatment) groups; Anova (Krukal-Wallis) p<0.001. Marsh0-II vs Marsh IIIA-IIIC; Mann Whitney p<0.0001.

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Mesalamine-induced fever: an important reminder to prescribers

To the Editor,

A 64 year-old Caucasian man presented to the emergency department complaining of a 104°F (40°C) fever. Three weeks prior to the current admission, the patient was treated for a fever of up to 104°F in the emergency department. At this time the patient was treated with broad antibiotic coverage, but was discontinued within 48 hours of admission because he became afebrile with negative cultures.

Within 36 hours of discharge the patient's symptoms returned with a temperature of 103.5°F. Over the next few hours the symptoms improved with complete resolution of the fever within 48 hours of admission. In response to the patient's clinical improvement he was discharged and sent home with plans to follow up.

The following day the patient was again brought to the emergency department complaining of a fever of 103.5 °F. Upon questioning by the clinical pharmacist it was discovered that after the patient's colonoscopy nearly two months prior, the gastroenterologist had given the patient samples of Lialda® for the treatment of his colon ulcerations found at colonoscopy. Since this medication was not known on admission, it was not restarted while in the hospital. However, the patient explained that once he went home he did resume the mesalamine as a part of his usual routine. Since no other causes for the fever could be explained, the fevers were determined to be caused by the Lialda® samples and the patient was sent home with instructions to stop taking them and to return should the fever return. Follow up calls to the patient at one, two, and four weeks demonstrated no return of the fever.

Mesalamine induced fever was previously reported by Gonzalo et al. In their case, a patient with Crohn's disease was started on Claversal® for maintenance therapy. Five days after starting the therapy the patient presented with fever (40°C), headache, chest pain, myalgias and arthralgias [1]. Another more recent case was published by Slim et al., of a patient with ulcerative colitis who was being treated with mesalamine when he developed fever with rigors, myalgias, and anorexia [2]. When mesalamine was stopped the fever subsided. The patient was later re-challenged with rectal mesalamine and the fever returned.

Other cases of fever have been reported, but in all of the cases the fever was in addition to some other symptom that could have explained it [3-5].

Mesalamine is commonly used as a first line treatment. Therefore, it is important to remind practitioners of this infrequent yet significant adverse effect. The potential for this drug-induced fever should be considered in any patient where another good cause for his fever cannot be found. As in our case, missing this potential adverse effect led to three separate hospital admissions.

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