Glucose-6-phosphate dehydrogenase deficiency is associated with lower fibrosis score in non-progressive HBsAg-positive subjects

To the Editor,

Several studies have suggested a role for NADPH oxidases in the pathogenesis of liver fibrosis [1]. Availability of the substrate NADPH is in turn heavily dependent on the activity of the pentose phosphate pathway, whose key enzyme is glucose-6-phosphate dehydrogenase (G6PD).

Deficiency of G6PD is the most common enzymatic defect in humans worldwide. In Sardinia (Italy), the prevalence of males hemizygotes was reported to be 16.4%, while females heterozygotes are 20.6% [2]. Given the central role of this enzyme in the generation of NADPH, it appears reasonable to hypothesize that G6PD-deficient individuals might display a peculiar and distinct response during chronic liver disease leading to fibrosis.

In a first study, we identified two groups of patients, based on criteria recommended by the Italian Association for the Study of the Liver (AISF) [3]: those requiring antiviral therapy (PEG-IFN or nucleoside/nucleotide analogs) and those in whom the disease was qualified as non-progressive and did not require treatment [4]. Patients with fibrosis stage 3-4 and quantitative HBV DNA >2000 UI/ml were given antiviral therapy; those with fibrosis stage 0-1 were monitored over time but not treated; finally, patients with fibrosis stage 2, HBV DNA >2000 UI/ml and slightly elevated serum aminotransferase levels were treated with IFN only. Out of 31 patients, 15 showed signs of progressive disease and were given antiviral therapy, while 16 were non-progressive. Surprisingly, we noted that the prevalence of G6PD-deficient patients was higher than expected in the group of non-progressive patients (9/16, 56%), while it was within the expected range among patients requiring treatment (2/15, 13%).

We then conducted a follow-up study on the group of non-progressive patients. These patients do indeed offer the unique possibility to study the evolution of low intensity liver fibrosis in the absence of any interfering antiviral therapy. They were divided according to the G6PD status and their level of liver fibrosis was monitored over a 3-year period. Results are reported in Table I. The two groups of patients (14 G6PD normal and 19 G6PD-deficient) had comparable levels of serum ALT, AST, platelet counts, pseudocholinesterase (PCHE) and HBV-DNA. Liver fibrosis, as measured by TE, was generally mild and relatively stable over time in both groups of patients, as expected. However, the steady-state values were generally lower in G6PD-deficient patients, and the difference became statistically significant (p < 0.05) after 3 years of follow-up.

Surprisingly, no evidence is available so far on any possible role in fibrosis of the G6PD enzyme status, despite the high prevalence of G6PD deficiency worldwide.

Interestingly, treatment with dihydroepiandrosterone (DHEA), a known inhibitor of G6PD activity, exerted an antifibrotic effect in humans with idiopathic pulmonary fibrosis, whose baseline levels of DHEA were also low [5]. Most notably,

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<tr>
<td>G6PD-normal (14)*</td>
<td>6.0 ± 0.6 A a#</td>
<td>5.5 ± 0.5 A a</td>
<td>5.8 ± 0.7 A a</td>
<td>6.3 ± 0.5 A a</td>
</tr>
<tr>
<td>G6PD-deficient (19)*</td>
<td>4.7 ± 0.3 B a</td>
<td>4.9 ± 0.3 A a</td>
<td>4.5 ± 0.4 A a</td>
<td>4.3 ± 0.3 B a</td>
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* Number of patients enrolled in the follow-up; #Different capital letters indicate statistically significant differences (p < 0.05) between the two groups at the same time point in the follow-up. Different lowercase letters denote statistically significant differences (p < 0.05) within the same group of patients at different time points in the follow-up.
mortality for liver cirrhosis was reported to be substantially decreased in a cohort of Sardinian men expressing the G6PD deficient phenotype [6].

Our results are in line with the above indications and suggest a protective effect of G6PD deficiency in liver fibrosis.

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Sustained virological response after 4-week ritonavir-boosted paritaprevir, ombitasvir and dasabuvir treatment in a kidney transplant recipient

To the Editor,

Patients with chronic kidney disease (CKD) on hemodialysis have a high prevalence of hepatitis C virus (HCV) infection (up to 80%) [1]. Moreover, HCV infection significantly reduces patient and graft survival after kidney transplantation (KT) [2]. Until recently, treatment options in CKD patients were very limited. Interferon-based antiviral therapy was considered safe only before KT and mostly contraindicated after KT because of the risks of allograft dysfunction or rejection [2].

To date, only a few studies on the safety and efficacy of direct antiviral agents (DAAs) after KT have been performed. Rates of sustained virological response (SVR) up to 100% with a good safety profile were reported. However, careful monitoring of blood level of calcineurin inhibitors is recommended due to the drug-drug interactions and related adverse events [3].

We report the case of a 59-year-old male with KT, HCV infection, and compensated cirrhosis, who achieved SVR after only 28 days of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (Viekira Pak) plus ribavirin. He was a three-times KT patient and had never been treated with interferon due to his comorbidities.

In 2016, the patient was considered for treatment with DAAs. Virological examinations showed HCV genotype 1b, and HCV-RNA was 123,989 UI/ml. Other examinations showed compensated liver cirrhosis with evidence of mild portal hypertension. Renal function was mildly impaired (serum creatinine 1.59 mg/dL; eGFR 47 mL/min). He was on immunosuppressive therapy with tacrolimus, mycophenolate mofetil and prednisone. In April we started a 12-week treatment with Viekira Pak plus ribavirin. Two days after the initiation of the treatment, the patient complained of anxiety with insomnia and palpitation. Treatment with delorazepam was not effective. Ribavirin was then discontinued in attempt to improve tolerance. First blood examinations after one week showed signs of renal impairment (urea 130 mg/dl, creatinine 2.43 mg/dl), hyperuricemia (13.4 mg/dL) and, as expected, a significant increase in tacrolimus plasma levels despite its dose reduction (59 ng/ml; normal values 8-12). Eventually, after 28 days of therapy, he decided to interrupt the antiviral treatment mainly because of persistent anxiety and fatigue.

Unexpectedly, at the end of this short treatment and at subsequent controls (12 and 24 weeks), laboratory exams showed HCV-RNA under the limits of detection. Other hepatic and renal tests at the end of therapy were either normal or showed irrelevant changes. Tacrolimus plasma level had returned within normal range. As a result, despite a much shorter treatment than planned, the patient had achieved SVR.

We believe this represents the first case of a KT recipient who achieved SVR after 4 weeks of Viekira Pak plus ribavirin treatment. The achievement of a SVR after only 28 days of treatment was remarkable considering the reported low SVR rate with short duration therapy. The efficacy of a short course (4 weeks) treatment with DAAs has been evaluated only in a few sofosbuvir-based studies, but SVR rates were unsatisfactory (20-40%) [4].

In conclusion, the advent of new DAAs has led to a dramatic improvement in the management of HCV infection in special populations such as CKD patients and KT recipients even after very short treatment courses [5].

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Heller myotomy and endoscopic balloon dilation may be equally effective in the short- and long-term

To the Editor,

We read with great interest the recently published, well conducted meta-analysis of A. Illés et al. [1] which concludes that treatment of achalasia by laparoscopic Heller myotomy (LHM) is superior to endoscopic balloon dilation (EBD) in terms of efficacy. Achalasia is the most studied primary esophageal motor disorder. Because the etiology is unknown, treatment addresses the pathophysiological changes, i.e. the insufficient relaxation of the lower esophageal sphincter. The two established treatment methods are LHM and EBD, with peroral endoscopic myotomy (POEM) being the new kid on the block. Traditionally, LHM is considered to be superior to EBD regarding short and long term efficacy. The more extensive sectioning of the circular muscle layer of the esophago-gastric junction, distal esophagus and proximal stomach in comparison to the localised tearing during EBD makes it theoretically the method of choice for treatment. We retrospectively compared the two methods in our center over a period of 10 years (1999-2008) and LHM (61 patients) was also found to be superior regarding efficacy compared to EBD (51 patients) both in the short- (1 year) (92% vs 80%) and long-term (5 years) (80% vs 64%)(unpublished data), consistent with the results of the meta-analysis by A. Illés et al.

Achalasia being a rare and very heterogeneous disease in terms of symptom duration and response to treatment, many studies have addressed the issue of predictive factors for the success or failure and efficacy of the two treatment modalities. Most of them were single center studies, with a rather small number of patients. Moreover, some of the studies which compared the two methods were not randomised. As mentioned in the paper of Illés et al, the most well-known predictive factors of failure of EBD include young age, male sex, dilation with a small diameter balloon and a dilated esophagus. In some of the studies comparing LHM and EBD patient allocation to one of the two treatment methods was carried out, taking into account those predictive factors.

The fact that LHM and EBD may have similar short- and long-term success rates has been suggested as early as 2006 in a retrospective single center study published by Vela et al. [2]. In the European Achalasia Trial [3], which prospectively included a significant number of patients in both arms (EBD and LHM), although only the age criterion (cut-off 40 years) was used to stratify the patients before randomization, after a follow-up of 2 years there was no significant statistical difference in terms of efficacy between LHM and EBD (success rate 90% vs 86%). Moreover, at 5 year follow-up the results were comparable, with a therapeutic success rate of 84% for LHM, similar to that of EBD (82%), but with a need for additional dilations in 25% of patients in the EBD group [4]. Moreover, the economic evaluation of the same long term international multicenter trial was also in favour of EBD regardless of the economic system [5], consistent with other reports [6]. Therefore, the efficacy and cost-effectiveness results of these prospective, randomized, multicenter, long term, international data may represent the basis of a change of paradigm in the therapeutic approach of patients with achalasia, in that either of the two treatments can be proposed as an initial treatment.

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