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Arnaud Galbois[1,2,3,*]
Dominique Thabut[2,3,4]
[1]*AP-HP, Hôpital Saint-Antoine, Service de Réanimation Médicale, F-75012 Paris, France*
[2]*Université Pierre et Marie Curie (UPMC), Univ Paris 06, Sorbonne Universités, UMRS_938, CdR Saint-Antoine, F-75012 Paris, France*
[3]*INSERM, UMRS_893, CdR Saint-Antoine, F-75012 Paris, France*
[4]*AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service d'Hépato-gastroentérologie, Paris, France*
[*]*Service de Réanimation Médicale, Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75571 Paris Cedex 12, France. Tel.: +33 149282315; fax: +33 149282145*
E-mail address: galbois@gmail.com (A. Galbois)

Silibinin monotherapy prevents graft infection after orthotopic liver transplantation in a patient with chronic hepatitis C

To the Editor:

We read with great interest the letter by Neumann et al. [1] on the effect of Silibinin in preventing graft infection in a patient with cirrhosis due to chronic hepatitis C (HCV). We obtained the same result in a patient treated with intravenous (i.v.) Silibinin mono-therapy (Legalon SIL®, Rottapharm-Madaus).

In 1994, the 46-year-old male patient with beta-thalassemia was first diagnosed for HCV with mixed genotype 1a/4. Both genotypes were also present upon starting silibinin treatment and on the day of OLTx. In 1998, he was treated with 5 MU interferon three times a week and weight based ribavirin. Treatment was stopped due to failure to clear the virus after 24 weeks of treatment.

In 2009, he presented with end stage liver failure (Child–Pugh stage C, MELD 20). In the mean time, he had developed insulin dependent diabetes mellitus which is treated with insulin aspartate (Novomix 30 100 E/ml, Novo Nordisk Pharma GmbH; 16 IE-0-0/day). He was listed for orthotopic liver transplantation (OLT) on the 29th of October 2009. Based on our observation of the potent antiviral effects of Silibinin [2,3] a feasibility study was discussed in the transplant setting.

Accordingly, a patient placed first on the waiting list for OLT should receive i.v. Silibinin. In this patient a donor liver became available on day 15 of Silibinin mono-therapy. The data on virus concentrations, obtained pre and after OLT, are shown in Fig. 1. Baseline virus load was low (28.800 IU/ml) and decreased on intravenous Silibinin mono-therapy to 43 IU/ml on the day of OLTx. Due to a miscommunication between our outpatient center and the OLT-team, treatment was interrupted for 2 days after OLT and virus concentration increased to 115 IU/ml. Nevertheless, HCV-RNA levels decreased after resuming Silibinin-infusions to 30 IU/ml on day 6 and became unquantifiable (<15 IU/ml) on day 10, and undetectable on day 22 after OLT. Silibinin was stopped 25 days after OLT. During 5 months of follow-up, HCV-RNA levels remained undetectable.

The surgical procedure and post-operative phase went ahead without any complications. Immunosuppressive therapy included prednisolone and cyclosporine A. Like in the patient of Neumann et al. [1] bilirubin levels increased during treatment with Silibinin to a maximum of 17.15 mg/dl (on day 3 post OLT) but decreased continuously while the patient was still on Silibinin. The higher increase of bilirubin in our patient could be due to the longer administration of Silibinin combined with the post-operative phase. Aminotransferase levels reached nearly normal values (ASAT 39 U/l, ALAT 32 U/l) 4 days after starting Silibinin-infusions but increased again after OLT and reached normal levels within 4 weeks after OLT.

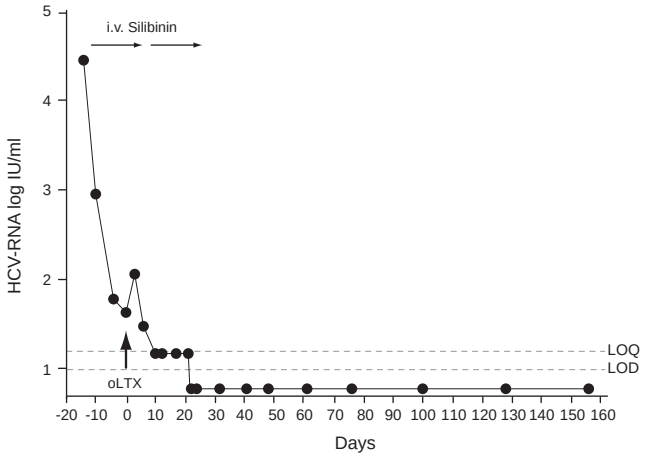

Fig. 1. HCV-kinetics during silibinin i.v. monotherapy. HCV RNA levels measured by real-time PCR (Cobas Taqman®, Roche Diagnostics, Pleasanton, CA).

While the goal to prevent graft infection was reached in both patients, the approaches were different. Neumann et al. [1] started Silibinin application 8 h after the anhepatic phase (while the viral load was 182 IU/ml). Our patient was pretreated with Silibinin for 15 days with an interruption of 2 days in the post-operative period. Previously, we have shown in a non-responders cohort that the interruption of Silibinin treatment over the week-end results in an increase in viral load [4]. The doses of Silibinin were slightly different. While Neumann et al. used a fixed dose of 1400 mg/day we applied 20 mg/kg body weight/day. The low baseline viral load may be a condition favoring the action of Silibinin.

These encouraging observations should lead to a prospective evaluation of i.v. Silibinin in this group of patients, having no medical alternatives to prevent graft infection. Studies are needed to find the best way to apply this concept in future (timing, duration, and optimal dose).

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Conflict of interest

All other authors have no financial disclosures to report.

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Sandra Beinhardt[1]
Susanne Rasoul-Rockenschaub[2]
Thomas Matthias Scherzer[1]
Peter Ferenci[1,*]
[1]*Internal Medicine III, Department of Gastroenterology and Hepatology, Medical University of Vienna, Austria*
[2]*Division of Transplantation, Department of Surgery, Medical University of Vienna, Austria*

[*]*Address: Internal Medicine III, Department of Gastroenterology and Hepatology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Tel.: +43 1404004745; fax: +43 1404004735*
E-mail address: peter.ferenci@meduniwien.ac.at (P. Ferenci)

Reply to the Letter to the Editor

Silibinin in hepatitis C related liver transplantation

Reply to Beinhardt et al.:

We congratulate Beinhardt et al. for their interesting paper about successful prevention of hepatitis C virus (HCV) reinfection by short-term administration of high-dose silibinin infusions before and after OLT [1]. Preventing HCV reinfection has an enormous impact on the long term outcome of liver transplantation. Since interferon alpha based treatment regimens are not tolerated early after OLT and also in most instances in the pre-transplant setting, silibinin mono therapy seems to be a promising treatment option – supported by its reasonable safety profile, as documented by its use in amanita-induced acute liver failure.

Success or failure of preventing re-infection with a short term silibinin mono therapy seems to depend mainly on the level of hepatitis C viremia at the time of OLT. The breakdown of hepatitis C viremia, usually seen during the anhepatic phase, works synergistically with the direct antiviral effect of silibinin infusion to support the prevention of re-infection.

As an additional mode of action, a direct inhibitory effect of silymarin components towards the viral entry into hepatocytes has been proposed *in vitro* [2].

In both cases, in ours [3] and the one reported by Beinhardt et al. [1], HCV RNA levels were low at the time of OLT and particularly after the anhepatic phase (range of 10^2 IU/ml). The approach reported here includes a silibinin treatment before OLT, hereby significantly lowering viremia in order to provide beneficial conditions for the successful prevention of re-infection. This might significantly enlarge the pool of patients benefiting from post-OLT silibinin infusions. However, since the exact timing of the transplantation is usually not feasible, a standardization of the reported procedure seems to be difficult and is probably only possible in the setting of living donor liver transplantation (LDLT).

Up to now little is known about the safety of high dose silibinin infusions in the setting of end stage chronic liver disease. In our hands patients with advanced cirrhosis showed a marked elevation of bilirubin (mainly indirect) in response to silibinin infusions – an observation that was not seen in patients with mild or moderate fibrosis. The clinical significance of this bilirubin elevation remains unclear. At the same time this finding is obviously affecting MELD-score depending organ allocation.

Clearly the potential of silibinin infusions in the peri-transplant period in HCV infected patients needs further evaluation. Studies should address several open questions as the optimal duration of treatment after OLT, the safety and effectiveness of silibinin infusions before OLT, and the potentially enhancing effect of adding ribavirin to silibinin infusions.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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