Successful prevention of hepatitis C virus (HCV) liver graft reinfection by silibinin mono-therapy

To the Editor:
Therapeutic measurements to control hepatitis C reinfection after orthotopic liver transplantation (OLT) still pose many problems and remain unsatisfactory [1]. While hepatitis C viremia decreases strongly during the anhepatic phase of OLT, initiation of viral replication does occur within hours or days [2,3]. At this early stage after OLT, i.e. once chronic HCV reinfection is established, the virologic response is often markedly reduced. Although specifically targeted antiviral therapeutic regimes for hepatitis C (STAT-C) are currently extensively studied, none of them have been tried in the post-OLT period treatment.

However, as recently described by Ferenci et al. [4], high dose intravenous silibinin (Legalon SIL®) can express potent antiviral activity. This effect was shown to be driven by direct inhibition of the viral RNA polymerase NS5B [5,6].

In this letter, we can report the first successful prevention of HCV reinfection after OLT by the administration of silibinin (1400 mg/d). This drug was applied immediately after OLT by daily infusions for 14 days.

At the time of OLT, the 57-year-old male patient exhibited a MELD Score of 23, Child-Pugh stage C liver cirrhosis, and a 25 mm hepatocellular carcinoma in the left lobe. HCV infection (genotype 3a) was first diagnosed in 1997 and three interferon-based treatment regimens – at last PegInterferon alpha and Ribavirin were given for 48 weeks 6 years before OLT – failed to induce a sustained virologic response (SVR). The anhepatic phase during OLT surgical procedures lasted 61 min and postoperative care transpired without complication after a short phase of renal insufficiency and haemodialysis treatment on day 1 and 2. Immunosuppressive therapy included methyl-prednisolone, mycophenolatmofetil, and belatacept. Aminotransferase levels reached normal values within 12 postoperative days. Bilirubin levels rose to a maximum of 9.5 mg/dl 7 days after OLT and showed a protracted mild elevation until 4 weeks later. The patient was discharged from the hospital 21 days after OLT.

The levels of HCV RNA 3 months prior to OLT were rather low (17.800 IU/ml), and further declined significantly during the anhepatic phase. Silibinin infusions were started 8 h after OLT. At this time HCV RNA levels measured 182 IU/ml, and dropped again to 127 IU/ml after 48 h (RNA levels measured directly after haemodialysis are not available). Already from day 3 onwards, HCV RNA levels were below <15 IU/ml and became undetectable at day 9. During follow-up HCV RNA remained negative when examined at day 14, 21, 66, 84, and 168 (Fig. 1).

This is the first report of the successful suppression of early HCV reinfection after OLT with a 14 day course of silibinin mono-therapy. This new treatment regimen thus induced an SVR, as after 6 months of follow-up, RNA for HCV was undetectable. Accordingly, liver histology 6 months after OLT did not show any cellular inflammation. Low pre-transplant HCV RNA levels may be taken as a favourable prognostic factor for the unexpected therapeutic efficiency of silibinin. Applying silibinin during the anhepatic phase or even in the days before transplant may expand the number of patients benefiting from this approach. This report may stimulate further trials and the concept of interferon-free HCV clearance induced by direct antivirals.

Conflicts of interest
The Authors have declared that they received funding from the drug companies involved in order to carry out their research in this manuscript.

References

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Combination of acarbose and ezetimibe prevents non-alcoholic fatty liver disease: A break of intestinal insulin resistance?

To the Editor:
We read with great interest the study by Nozaki and colleagues [1] that evaluated the effect of combination therapy of ezetimibe, an intestinal cholesterol adsorption inhibitor, and acarbose, an alpha glucosidase inhibitor, on the prevention of the high-fat diet induced, non-alcoholic fatty liver disease (NAFLD) in mice. In their study, the authors concluded that the combination of both drugs for 24 weeks significantly reduced steatosis, inflammation, and fibrosis in the liver of animals, compared to long-term monotherapy with either drug. Insulin resistance and liver steatosis are interlinked metabolic abnormalities, whose prevalence is rapidly increasing worldwide [2]. We absolutely agree that the effective pharmacological therapy for prevention or treatment of NAFLD does not exist today, and we thus acknowledge that the recent study by Nozaki and colleagues has paved the way towards a new therapeutic approach for the prevention and treatment of NAFLD. However, we have some concerns regarding this study and its conclusions, which are outlined as follows:

The authors use the high-fat diet which contains more than 57% of calories from fat and only 22.8% of carbohydrates to induce the NAFLD in animals. Despite the importance of impairment in the lipid metabolism and quantity of the dietary fat intake for the development of NAFLD [2], the high carbohydrate intake is also involved in the pathogens of NAFLD: first, the “soft drinks” without fat content were associated with hepatic steatosis independent of insulin resistance in humans [3]; second, dietary habits with high glycemic index were associated with liver steatosis [4]. Thus, the additional model using the high glycemic load were of interest for such experimental design. Another point is the action of the acarbose in the studied dietary conditions: the strong reduction of carbohydrate intake led to the diminished action of acarbose and promising effects for ezetimibe. Interestingly and surprisingly, the reduction of fasting glycemia and insulinemia under ezetimibe treatment was as pronounced as the effects of the antidiabetic drug acarbose. Based on the principal postprandial actions of both drugs, the data from oral stimulation tests, such as oral glucose loading or meal test, could be of great interest regarding the mechanisms of NAFLD prevention.

The major and very intriguing observation is the effect of the combination of acarbose and ezetimibe during the progression of NAFLD in the high-fat diet. The authors concluded two hypotheses in order to explain the observed effects: (i) the additive or multiplicative effects of both drugs on cholesterol reduction accompanying the inhibition of gut glucose absorption lead to the improvement of systemic insulin sensitivity and/or (ii) the promotion of lipid discharge from the liver and the β-oxidation of lipids in the liver.

Regarding the first hypothesis, after a 12-week high-dose acarbose treatment (300 mg/d), our data in humans showed no effects on whole body insulin sensitivity, measured in the euglycemic clamp, and no changes in body weight [5]. Moreover, we observed