Editorial

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Silibinin: An old drug in the high tech era of liver transplantation

Peter Ferenci*, Sandra Beinhardt

Internal Medicine 3, Gastroenterology and Hepatology, Medical University of Vienna, Austria

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HCV re-infection after liver transplantation is constant and accelerated in patients who are PCR-positive at the time of transplantation. Reinfection significantly impairs patient and graft survival [1]. At present, there are limited options available to prevent graft reinfection after transplantation or to successfully treat reinfected patients. Pretransplant antiviral combination therapy with (peg)interferon/ribavirin (PegIFN/RBV) is poorly tolerated and not very effective in patients infected with HCV genotype 1. In a prospective randomized controlled study, pretransplant treatment with PegIFN/RBV prevented post-transplant recurrence of HCV in 22% of a highly selected group of patients with HCV genotypes 1,4,6 [2]. Treatment after transplantation has also a limited efficacy and is associated with serious adverse effects. Currently, studies using triple therapy with PegIFN/RBV and a protease inhibitor (boceprevir or telaprevir) are ongoing, but again poor tolerance is a major issue.

Thus there is urgent medical need to develop safe and effective treatments for this group of patients. Two case reports indicated that therapy with intravenous silibinin (iv-SIL; Legalon SIL®, Rottapharm–Madaus) successfully eradicated the virus after transplantation [3,4]. Based on these encouraging observations, iv silibinin got EMA orphan drug designation for prevention of recurrent hepatitis C. Iv-SIL is a 1:1 mixture of silibinin A and silibinin B and is available as intravenous therapeutic agent for treatment of mushroom poisoning. However, acute liver failure related to mushroom (amanita or lepiota) poisoning is an uncommon condition and there is no definitive evidence that silibinin improves the outcome of these patients.

In 2008, the potent antiviral activity of iv-SIL against HCV was described [5] and confirmed by *in vitro* studies [6]. Silibinin inhibits the HCV NS5B polymerase activity directly [7] or by interfering with the binding of the RNA to this enzyme [8]. Furthermore, the mechanisms of the antiviral action of silibinin appear also to include blocking of virus entry, transmission, and secretion (for review see [9]).

In this issue of the *Journal*, 2 groups from Spain report their experience with iv-SIL in the transplant setting [10,11]. Both studies involved only a very small number of patients, but both included a control group: in the study performed in Madrid this was a historical control [10], while in the one performed in Barcelona, patients in the control group were treated with a placebo according to a prospective randomized, double-blind, placebo-controlled design [11].The Madrid group [10] started iv-SIL during the anhepatic phase and continued treatment for 21 days. In contrast, the Barcelona group [11] treated patients for up to 21 days prior transplantation, and continued or restarted the infusion for further 7 days after transplantation. Both studies confirmed the robust antiviral efficacy and the safety of iv silibinin in this difficult-to-treat patients, with the apparent lack of interaction with immunosuppressants, but not surprisingly, both approaches failed to eradicate the virus in a single patient, although quite a few had undetectable HCV RNA at the end of iv silibinin administration.

It is quite clear that giving an antiviral drug as monotherapy for just 21 days is not able to eradicate HCV. The so far shortest successful treatment in HCV genotype 1 patients having the *IL28B* CC genotype using peginterferon/ribavirin and telaprevir was 12 weeks [12]. Comparison with other published reports of iv silibinin (Table 1) shows that the best results in terms of SVR were obtained in patients in whom a low viral load was achieved by administering the drug before transplant and then continuing it for 3–4 weeks after transplant [4]. Taken together, the data published so far seem to indicate that HCV RNA levels below the level of quantification (LOQ) at the end of iv silibinin administration and SVR can be reached in 12/14 (85.7%) and 3/14 (21.4%) patients with a continuous pre-/post-transplant administration, respectively, while in patients receiving iv silibinin only after transplant, the same results could be achieved only in 6/35 (17.1%) and 2/35 (5.7%) patients, respectively (Table 1).

Studies in the transplant setting are difficult to design. The problems even increase if patients immediately prior to transplantation are involved. They are usually very sick and safety becomes the prime issue. Pretreating patients with iv-SIL is feasible and safe, but is limited by the need of daily infusions. The optimal timing for transplantation would be if the patient becomes HCV RNA undetectable, but the timing of transplantation depends

Keywords: silibinin; liver transplantation; hepatitis C.
Received 31 October 2012; received in revised form 17 November 2012; accepted 20 November 2012
☆ DOI of original articles: http://dx.doi.org/10.1016/j.jhep.2012.09.034, http://dx.doi.org/10.1016/j.jhep.2012.10.009.
* Corresponding author. Address: Klein. Abteilung für Gastroenterologie und Hepatologie, Univ. Klinik für Innere Medizin III, Medizinische Universität Wien, Waehringer Guertel 18–20, A 1090 Wien, Austria.
E-mail address: peter.ferenci@meduniwien.ac.at (P. Ferenci).

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Table 1. Cases treated with intravenous silibinin in the transplant setting.

Author, [Ref.]	Continuous pre/post-LTX			Pre-LTX and later post-LTX			Post-LTX			Pre-LTX only		
	n	HCV <LOQ at end of iv-SIL	SVR	n	HCV <LOQ at end of iv-SIL	SVR	n	HCV <LOQ at end of iv-SIL	SVR	n	HCV <LOQ at end of iv-SIL	SVR
Bárcena *et al.,* [10]							9	4	0			
Mariño *et al.,* [11]	4	4	0	4	1	0				3	1[&,§]	0
Eurich *et al.,* [16]							4	1	1			
Beinhardt *et al.,* [13]	10	8	3*,[#]				6	0	0	4	2[§]	1
Neumann *et al.,* [3]							1	1	1			
Aghemo *et al.,* [17]							1	0	0			
Rendina[$] *et al.,* [18]							14	0	0			
Total	14	12	3	4	1	0	35	6	2	7	3	1

iv-SIL, intravenous silibinin (20 mg/kg body weight/day); <LOQ = <15 IU/ml.
*Includes the case reported [4].
[#]One patient died 3 months after transplantation, she was HCV RNA negative.
[§]One patient died on the waiting list.
[$]Treated >1 year after LTX. (See above mentioned references for further information.)
[&]2 not transplanted.

on the availability of a donor organ, which is increasingly challenging in an era of donor organ shortage. Therefore, in some patients, infusion therapy had to be stopped before transplantation was performed.

In the Barcelona study, this was the case in 4 patients. Iv silibinin was restarted 7 to 38 days after the 21 days of silibinin administration. HCV below the level of quantification (LOQ) was achieved only in 1 of 4 of them in contrast to all of the 4 patients treated continuously. Similarly, in 3 patients treated pretransplant in our center, no liver was available when the targeted low or undetectable viral load was reached (updated from [13]). One patient even subsequently achieved SVR but died on the waiting list. Obviously the best approach would be to do the study at centers offering living donor transplantation. In such centers, treatment and transplantation can be scheduled exactly. A very important aspect in such a study would be to investigate the needed duration of silibinin monotherapy and/or the need for consecutive treatment with peginterferon/ribavirin, possibly in combination with a direct acting antiviral agent. It is conceivable that the optimization of the duration of treatment with iv-SIL, even after cadaveric donor transplantation (e.g., for at least 4 weeks) and/or combination therapy could improve the virological response by reducing viral load in the first weeks after transplantation. This may prevent, delay, or decrease the severity of recurrent hepatitis C, with favourable histological findings at 6–12 months [14]. This would represent *per se* a clinically relevant outcome.

So what do we learn from these studies? Iv-SIL is safe but by the currently used applications cannot prevent graft reinfection or eradicate HCV from the transplanted liver in most patients. At present there is no alternative of an interferon-free approach in the peritransplant setting and silibinin may be the ideal drug until safe and effective HCV RNA polymerase inhibitors with a high genetic barrier become available. Nevertheless, there is a need for improvements in treatment schedules before such a treatment can be recommended. Flushing the liver graft with a solution containing silibinin as it has been done to prevent oxidative damage to the liver [15] should be tested in order to determine if it helps prevent recurrence.

Conflict of interest

PF is a member of the global advisory boards of Roche, MSD, Vertex/Tibotec, Madaus–Rottapharm, Böhringer Ingelheim, Idenix, Gilead and Achillion.

He receives an unrestricted research grant from Roche Austria and MSD Austria.

References

[1] Roche B, Samuel D. Hepatitis C virus treatment pre- and post-liver transplantation. Liver International 2012;32:120–128.
[2] Everson GT, Terrault NA, Lok AS, Rodrigo DR, Brown Jr. RS, Saab S, et al. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis c after liver transplantation. Hepatology; in press. http://dx.doi.org/10.1002/hep.25976.
[3] Neumann UP, Biermer M, Eurich D, Neuhaus P, Berg T. Successful prevention of hepatitis C virus (HCV) liver graft reinfection by silibinin mono-therapy. J Hepatol 2010;52:951–952.
[4] Beinhardt S, Rasoul-Rockenschaub S, Scherzer TM, Ferenci P. Silibinin monotherapy prevents graft infection after orthotopic liver transplantation in a patient with chronic hepatitis C. J Hepatol 2011;54:590–591.
[5] Ferenci P, Scherzer TM, Kerschner H, et al. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. Gastroenterology 2008;135:1561–1567.
[6] Polyak SJ, Morishima C, Shuhart MC, et al. Inhibition of T-cell inflammatory cytokines, hepatocyte NF-kappaB signaling, and HCV infection by standardized Silymarin. Gastroenterology 2007;132:1925–1936.
[7] Ahmed-Belkacem A, Ahnou N, Barbotte L, et al. Silibinin and related compounds are direct inhibitors of hepatitis C virus RNA-dependent RNA polymerase. Gastroenterology 2010;138:1112–1122.
[8] Najera I, McCown M, Leveque V, et al. Silibinin inhibits HCV replication in vitro. J. Hepatol 2009;50:S346.
[9] Polyak S, Pawlotsky JM, Ferenci P. Hepatoprotective and antiviral functions of silymarin components in HCV infection. Hepatology; in press. http://dx.doi.org/10.1002/hep.26179.

[10] Barcena R, Moreno A, Rodriguez-Gandía MA, Albillos A, Arocena C, Blesa C et al. Safety and anti-HCV Effect of Prolonged Intravenous Silibinin in HCVGenotype 1 Subjects in the Immediate Liver Transplant Period. J Hepatol; in press.
[11] Mariño Z, Crespo G, D'Amato M, Brambilla N, Giacovelli G, Rovati L. Intravenous silibinin monotherapy shows significant antiviral activity in HCVinfected patients in the peri-transplantation period. J Hepatol; in press..
[12] Bronowicki JP, Hezode C, Bengtsson L, Pol S, Bourliére M, Serfaty L, et al. 100% SVR IN IL28B CC patients treated with 12 weeks of telaprevir, peginterferon and ribavirin in the PROVE2 trial. J Hepatol 2012;56:S430.
[13] Beinhardt S, Rasoul-Rockenschaub S, Maieron A, Scherzer T, Hofer H, Ferenci P. Intravenous Silibinin-therapy in patients with chronic hepatitis C in the transplant setting. J Hepatol 2012;56:S77.
[14] Ciccorossi P, Maina AM, Oliveri F, Petruccelli S, Leandro G, Colombatto P, et al. Viral load 1 week after liver transplantation, donor age and rejections correlate with the outcome of recurrent hepatitis C. Liver Int 2007;27:612–619.
[15] Rauen U, Reuters I, Fuchs A, de Groot H. Oxygen-Free Radical–Mediated Injury to Cultured Rat Hepatocytes During Cold Incubation in Preservation Solutions. Hepatology 1997;26:351–357.
[16] Eurich D, Bahra M, Berg T, Boas-Knoop S, Biermer M, Neuhaus R, et al. Treatment of hepatitis C-virus-reinfection after liver transplant with silibinin in nonresponders to pegylated interferon based therapy. Experimental and clinical transplantation : official journal of the Middle East Society for Organ. Transplantation 2011;9:1–6.
[17] Aghemo A, Bhoori S, De Nicola S, Mazzaferro V, Colombo M. Failure of intravenous silibinin monotherapy to prevent hepatitis C Genotype 2A liver graft reinfection. Hepat Mon 2012;12:411–444.
[18] Rendina M, D'Amato M, Castellaneta A, Castellaneta NM, Brambilla N, Giacovelli G, et al. Efficacy and safety of intravenous silibinin in patients with HCV recurrence on the graft after liver transplantation (LT): a prospective, randomized, double-blind, placebo-controlled pilot study. Hepatology 2012;56, Late breaker abstract AASLD 2012.