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File: ■ Milk Thistle (*Silybum marianum*)
■ Silibinin (Silybin)
■ Hepatitis C

HC 021022-402

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RE: Intravenous Silibinin Is Clinically Proven Effective in the Treatment for Chronic Hepatitis C Non-responsive to Standard Antiviral Combination Therapy

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. *Gastroenterol*. 2008;135(5):1561-1567.

Silymarin, a mixture of flavolignans extracted from milk thistle (*Silybum marianum*), appears to be effective in decreasing mortality in patients with cirrhosis.[1] The main component of silymarin is silibinin (silybin) in a 50:50 mixture of silybin A and silybin B; the remaining components are silydianin, silycristin, isosilybinA, isosilybinB, isosilycristin, and taxifolin. Silibinin is endowed with strong antioxidant and antifibrotic properties, making it a potentially useful drug for treatment of chronic liver diseases. In this clinical trial on patients with chronic hepatitis C, silibinin was postulated to improve the response to interferon in non-responders to pegylated interferon (PegIFN)/ribavirin (RBV) treatment, and was administered intravenously (SIL IV) to increase its concentration.

Patients with a liver biopsy within 2 years, at least 1 quantitative hepatitis C virus (HCV) RNA test within 6 months, and previous non-response (lack of a >2-log drop of viral load after 12 weeks of therapy and/or no achievement of an end-of-treatment response) to a full dose of PegIFN/RBV combination therapy, were included in the study. Sixteen patients received 10 mg/kg silibinin (Legalon® Sil; Madaus; Köln, Germany) daily, infused intravenously over 4 hours for 7 consecutive days. On day 1, blood was drawn for determination of oxidative stress parameters at baseline, every 30 minutes during the infusion, and 2 hours after the end of the infusion. On day 8, treatment was changed to 140 mg silymarin (Legalon) 3 times/day orally in combination with 180 µg/week PegIFNα-2a (PEGASYS®; Roche; Basel, Switzerland) and 1-1.2 g/day RBV (COPEGUS®; Roche).

After results indicated a substantial decline in viral load, a subsequent dose-finding study investigated the antiviral potency of silibinin: 20 patients received daily 5, 10, 15, or 20 mg/kg silibinin infused over 4 hours for 14 consecutive days. On day 8, 180 µg/week PegIFNα-2a and 1-1.2 g/day RBV were added to the treatment. After 2 weeks, patients received 280 mg silymarin (Legalon) orally 3 times daily. During the 14-day infusion

period, blood was obtained daily for determination of viral load. Responders at week 24 were offered to continue treatment for a further 48 weeks. After end of the infusion period, patients were tested after weeks 2 and 4, and then monthly until the end of therapy (week 24). Serum HCV RNA level was determined by TaqMan polymerase chain reaction (PCR) assay; reactive oxidative metabolites in blood were measured by d-ROMs test; antioxidants by BAP test. The primary outcome variable was the virologic response defined as the percentage of patients being PCR negative at end of treatment (week 24). Secondary efficacy variables were virologic response rates at week 12; safety and tolerability of treatment with PegIFN/RBV/silymarin; quality of life at baseline, week 24, week 48, week 72; and oxidative status after silibinin infusions.

Serum HCV RNA declined in all patients on SIL IV [baseline: 6.59 ± 0.53; day 8: 5.26 ± 0.81 log IU/mL (mean ± SD); $P < 0.001$] with a mean log decline of 1.32 ± 0.55 within 1 week. Alanine aminotransferase decreased from 162 ± 133 to 118 ± 107 U/L ($P = 0.004$). Three patients declined PegIFN/RBV combination therapy. In 11 of the remaining 13 patients, HCV RNA increased again after the end of the silibinin infusions, in spite of initiation of PegIFN/RBV therapy. At week 12, all patients were still HCV RNA positive, but 5 patients had a >2-log drop and continued treatment. None of them became HCV RNA negative at week 24; 1 patient had a 5.5-log drop and continued treatment. In the dose-finding study, viral load declined continuously: at t=7 the 5 mg/kg dose was marginally effective (n = 3; log drop, 0.55 ± 0.5), whereas the 10 mg/kg (n = 19; log drop, 1.41 ± 0.59), 15 mg/kg (n = 5; log drop, 2.11 ± 1.15), and 20 mg/kg daily doses (n = 9; log drop, 3.02 ± 1.01) led to a highly significant decrease in viral load ($P < 0.001$). After 1 week of combined silibinin and PegIFN/RBV therapy, viral load decreased further (log drop 5 mg/kg: 1.63 ± 0.78; 10 mg/kg: 4.16 ± 1.28; 15 mg/kg: 3.69 ± 1.29; 20 mg/kg: 4.8 ± -0.89; $P < 0.0001$).

This study demonstrated that intravenous silibinin is well tolerated and a potent antiviral agent in patients with chronic hepatitis C not responding to standard antiviral combination therapy. The daily intravenous administration represents a severe limitation in clinical practice, but oral administration seems not to reach the effective concentration levels in plasma/liver due to silibinin's poor oral bioavailability. The clinical use of silibinin/silymarin for treatment of chronic hepatitis C will depend on future studies addressing pharmacokinetics, mechanisms of action, drug interaction profiles, optimal dosage and alternative dosing routes.

—Silvia Giovanelli Ris

References

[1] Ferenci P, Dragosics B, Dittrich H, et al. Randomized controlled trial of Silymarin treatment in patients with cirrhosis of the liver. *J Hepatol*. 1989;9:105-113.

The American Botanical Council has chosen not to reprint the original article.