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Oral Silymarin for Chronic Hepatitis C - A Retrospective Analysis Comparing Three Dose Regimens

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Abstract: To investigate the effects of silymarin on aminotransferase levels in patients with chronic hepatitis C, a standardized treatment with 420mg, 840mg or 1260mg per day was performed in patients of our clinic, who were not eligible for treatment with pegylated interferon and ribavirin. Aminotransferase levels were determined before, at 3-6 week intervals during and at the end of treatment. Predefined inclusion criteria for the retrospective analysis were persistently elevated alanine aminotransferase (ALT) levels (at least 6 months prior to and at beginning of the treatment) and treatment duration of at least three weeks. Liver cirrhosis CHILD B or C, interferon therapy within the last three months before treatment with silymarin, alcohol use >30 g/d, coinfection with hepatitis B virus or other severe diseases were exclusion criteria. According to these criteria 40 patients (13 with 420mg, 20 with 840mg and 7 with 1260mg silymarin per day) were eligible for the analysis. The mean treatment period was 125 ± 78 days. ALT, aspartate aminotransferase and γ glutamyltransferase levels did not change significantly from baseline in any group and there were no differences between the treatment groups. Bilirubin and prothrombine time were normal in all but one patient and remained unchanged. Silymarin therapy had no side effects. Silymarin at the doses used, does not improve elevated aminotransferases in patients with chronic hepatitis C.

Key words: milk thistle, silybin, aminotransferase levels

Introduction

Standard therapy for the chronic hepatitis C with pegylated interferon alpha and ribavirin results in sustained response rates of about 50% in patients infected with genotype 1. Therefore, therapeutic alternatives are of major importance. Silymarin is one of the most frequently used 'liver support drugs' in Germany and the United States (Bean 2002, Schwabe and Paffrath 2004). Its pharmacological profile is well defined and studies in cell culture and animal models clearly show a hepatoprotective action with little or no toxicity (Schuppan et al. 1999, Saller et al. 2001). The efficacy in patients with chronic hepatitis C virus infection is unclear, however (Liu et al. 2001, Saller et al. 2001, Wellington and Jarvis 2001). Up to now, there is only one placebo controlled trial, which showed a significant reduction of aspartate aminotransferase (AST) and gamma glutamyltransferase (GGT) but not of alanine aminotransferase (ALT) levels of 240 mg silybin per day after one week of treatment (Buzzelli et al. 1993). There was no follow-up for more than one week. A retrospective study comparing patients treated with and without concomitant silymarin in parallel to interferon showed no differences in ALT levels (Barritta et al. 2001). There are, to our knowledge, no further studies about the efficacy of silymarin in HCV infected patients.

The dose of silymarin, recommended by the manufacturer (420 mg/d) and used in clinical studies (for review see Saller et al. 2001) is considerably lower than that shown to be protective in animal models (Agoston et al. 2003; Boigk et al. 1997; Mourelle et al. 1989; Tyutyulkova et al. 1983). Since silymarin is very well tolerable (Saller et al. 2001) we investigated the effects of silymarin at higher than the recommended doses.

Patients and Methods

Patients, Medication and Study Design

Between 1998 and 2003 patients who attended our outpatient clinic and were not eligible for combination therapy with pegylated interferon and ribavirin were treated with silymarin within an observational study. Silymarin was given as a commercially available extract (Legalon®, Madaus, Cologne, Germany) containing 140 mg silymarin (50% as silybin) per capsule. Legalon® is the most frequently used silymarin preparation in Germany and has a good bioavailability (Schulz et al. 1995). There were 3 prospectively planned treatment groups: group 1 received 3 x 140mg/day as recommended by the manufacturer, group 2 received 3 x 280mg/day and group 3 3 x 420mg/day. The allocation to the different groups by the physician was arbitrary. There was no sociodemographic or disease related criterion for the allocation. If, however, a patient had received any of the 3 treatments in the past, he did not receive the same treatment again. Follow up visits in intervals of 3-6 weeks were prospectively planned. At each visit aminotransferase levels, side effects and the compliance were documented. The treatment was stopped after 3 months, if no reduction of the ALT level or a subjective benefit had occurred.

Predefined inclusion criteria for the retrospective analysis were age between 25 and 85 years, persistently elevated ALT levels (>23 U/l) at least 6 months prior to and at beginning of the treatment and treatment duration of at least three weeks. Liver cirrhosis

CHILD B or C, interferon therapy within the last three months before treatment with silymarin, alcohol use >30 g/d, coinfection with hepatitis B virus, pregnancy, severe concomitant diseases (HIV, malignancies, autoimmune diseases etc.) or participation in a clinical trial were exclusion criteria. The main outcome parameter was the ALT level. Secondary parameters were AST, GGT, bilirubin and prothrombine time as well as side effects.

Statistical Analysis

All analyses were done on an intention-to-treat basis. This means that all patients who once had been included were analyzed regardless whether other medications were used or whether they complied with the treatment or not.

ALT, AST and GGT levels were modelled on the basis of generalized linear models (Diggle et al. 1994). Here, we assumed the treatment course to be linear in time and the serial correlation to be exponential in time. The respective baseline values were incorporated into the models as fixed factors. Group comparisons were based on appropriate F-Tests within these models. The results are presented as estimated values after 90 days of follow-up for a hypothetical patient who started with a baseline value of 50.

Results

Among 195 patients with chronic hepatitis C who attended our outpatient clinic between 1998 and 2003, 40 fulfilled the in- and exclusion criteria and were included into the analysis. The patient characteristics are shown in Table 1 and 2. 21/40 patients (group 1: 4/13, group 2: 13/20, group 3: 4/7) were interferon naive either because they had refused or because of contraindications. The mean duration of the HCV infection was 15 ± 9 years (group 1: 17 ± 8, group 2: 13 ± 9, group 3: 15 ± 7). All patients were infected with genotype 1, 25% had liver cirrhosis Child A.

The mean duration of therapy was 125 ± 78 days (Table 1) and the mean number of visits during the therapy in the three groups was 3.4, 3.4 and 3.6 respectively. The aminotransferase levels at the end of treatment and calculated for a baseline level of 50 U/l after 90 days treatment are shown in Table 2. There were no significant changes of the ALT, AST or GGT levels compared to the baseline and no significant differences between the groups (Table 2).

Table 1. Basic characteristics as absolute numbers or means ± standard deviation.

	Number of patients	Duration of treatment (days)	Patients age (years)	male/ female
Silymarin 420 mg	13	118 ± 86	59 ± 7	11/2
Silymarin 840 mg	20	134 ± 78	53 ± 13	12/8
Silymarin 1260 mg	7	111 ± 67	50 ± 16	4/3
Total	40	125 ± 78	55 ± 13	27/13

Table 2. Aminotransferase and γ-glutamyltransferase levels during treatment with Silymarin. Means ± standard deviations and estimated means and 95% confidence intervals for a treatment period of 90 days and a hypothesized baseline level of 50 U/l.

	Daily doses	Baseline	End of treatment	Estimated mean
ALT normal range < 23 U/l	420 mg*	91 ± 42	85 ± 51	52 (29 to 75)
	840 mg**	65 ± 32	58 ± 32	48 (26 to 69)
	1260 mg***	64 ± 26	61 ± 25	47 (19 to 76)
	Total****	73 ± 36	67 ± 39	49 (30 to 69)
AST normal range < 18 U/l	420 mg*	56 ± 23	53 ± 32	54 (39 to 68)
	840 mg**	39 ± 23	36 ± 19	54 (39 to 70)
	1260 mg***	34 ± 14	32 ± 15	52 (33 to 70)
	Total****	44 ± 23	40 ± 24	54 (41 to 67)
GGT normal range < 35 U/l	420 mg*	73 ± 59	69 ± 61	58 (39 to 78)
	840 mg**	55 ± 70	46 ± 50	44 (27 to 61)
	1260 mg***	47 ± 30	41 ± 36	49 (27 to 72)
	Total****	59 ± 60	53 ± 52	49 (34 to 64)

* n = 13, ** n = 20, ***n = 7, ****n = 40

No adverse events were reported in any of the 3 groups. Bilirubin and prothrombine time were normal in all but one patient (1.6 mg/dl). The bilirubin level of all patients was 0.7 ± 0.3 mg/dl and prothrombine time was 94 ± 7 %. There were no significant changes during therapy.

Discussion

Patients with chronic hepatitis C who were not eligible for the standard treatment were treated with 480, 840 or 1260mg silymarin per day to investigate, whether this treatment improves elevated aminotransferase levels. The follow up schedule was prospectively planned. The retrospective analysis demonstrates that aminotransferase levels didn't change during treatment with silymarin. Although this study had no control group, it can be concluded, that silymarin in the doses tested, can not be recommended to lower elevated aminotransferase levels in these patients.

The ALT is generally used in HCV infected patients to demonstrate a therapeutic response. It reflects to a certain extent the inflammatory activity in the liver (Lee et al. 2001, Pradat et al. 2002, Shiffman et al. 2000). We therefore used the ALT as the main outcome parameter.

Silymarin was investigated up to a dose of 1260 mg/d that is three times higher than the recommended daily dose. Therefore, the lack of efficacy of silymarin cannot be due to under dosing. Further, in patients treated for more than 90 days, because they subjectively felt a benefit, ALT levels did not change (data not shown).

The patients came to our clinic with the specific request for an alternative treatment and therefore were highly motivated. Furthermore, the patients´ compliance was documented at each visit. Therefore, noncompliance can be excluded as a cause for lack of efficacy. The standardized follow up schedule in intervals of 3-6 weeks, the determination of aminotransferase levels in the quality controlled central laboratory of the University Hospital Freiburg and the restriction to HCV infected patients with permanently elevated aminotransferase levels support the internal and external validity of our results. In our study we cannot assess the treatment effects on subjective benefits, because we did not document these data systematically. Furthermore, we cannot comment on antifibrotic or antiviral effects of the medications.

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