ONLINE EXPERT POSTER REVIEW AND DISCUSSION

Advances in Chronic Hepatitis C Management and Treatment

*Reporting From*

THE 62ND AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES ANNUAL MEETING

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# A Randomized, Placebo-Controlled Trial of Oral Silymarin (Milk Thistle) For Chronic Hepatitis C: Final Results of the SYNCH Multicenter Study

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***Abstract 228***

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## Silymarin for Hepatitis C Introduction

- Clinical studies have evaluated silymarin for the treatment of cirrhosis, alcoholic liver disease, and viral hepatitis
- The results have been inconsistent
- Previous studies have been confounded by:
  - Lack of well-defined efficacy endpoints
  - Inclusion of heterogeneous populations of patients with liver disease
  - Use of non-standardized silymarin preparations

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# Silymarin for Hepatitis C
# Dosing of Silymarin

- A standardized preparation of silymarin was used
  - Legalon® 140 (Rottapharm-Madaus)- Approved as a prescription drug in some countries in Europe and Asia
  - Customary oral dose is 140mg tid
- A phase I study identified doses to be used in this trial*
  - 3 to 5-fold higher than customary doses were chosen in order to provide highest likelihood of finding a therapeutic benefit
- Participants were randomized to receive silymarin (SM) or placebo for 24 weeks
  - 700 mg three times daily (5 capsules of SM tid)
  - 420 mg three times daily (3 caps of SM + 2 caps PLA tid)
  - Placebo (5 capsules of placebo tid)

* Hawke et al, 2010

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# Silymarin for Hepatitis C
# Efficacy Measurements

- Primary outcomes after 24 weeks of treatment:
  - Serum ALT < 45 IU (approximate ULN)

    **OR**
  - Serum ALT decline of at least 50% to < 65 IU (approximately 1.5X ULN)
- Multiple secondary outcomes:
  - Change in serum ALT and HCV RNA (Abbott RealTime HCV assay, Abbott Molecular)
  - Adverse events
  - Adherence (Medication cups returned/dispensed)
  - Quality of life instruments (CES-D, SF-36, CLDQ)
  - Silybin A pharmacokinetics

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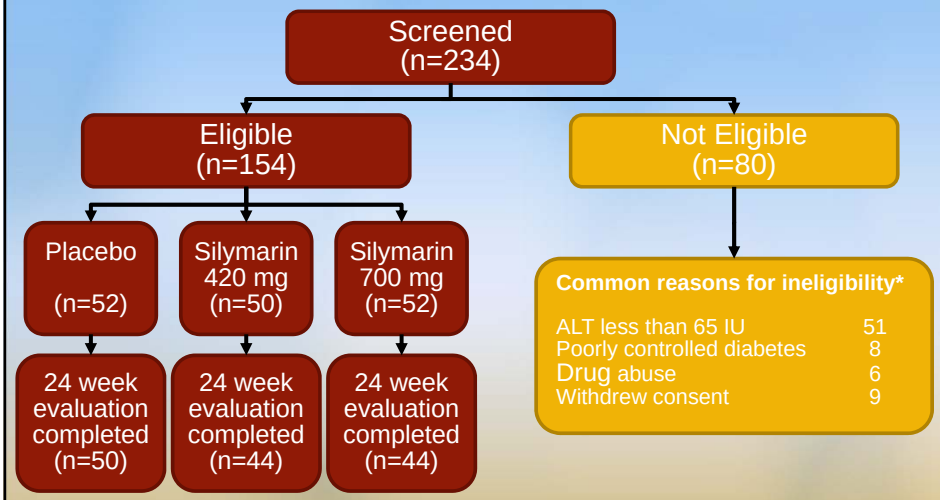
# Silymarin for Hepatitis C Participant Disposition




*May include >1 reason

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# Silymarin for Hepatitis C Participant Characteristics

| Characteristic | Placebo (n=52) | Silymarin 420Mg (n=50) | Silymarin 700 mg (n=52) | *P*-value |
|---|---|---|---|---|
| **Age (median)** | 56yrs | 54 yrs | 54 yrs | 0.31 |
| **Race** | | | | 0.08 |
| **White or Caucasian** | 45 (88%) | 36 (72%) | 33 (65%) | |
| **Black or African American** | 5 (10%) | 11 (22%) | 15 (29%) | |
| **Body mass index** | 29.1 | 28.5 | 30.2 | 0.29 |
| **History of diabetes** | 8 (15%) | 6 (12%) | 7 (14%) | 0.88 |
| **Platelets** | 180 | 173 | 177 | 0.98 |
| **Albumin (g/dl)** | 4.3 | 4.1 | 4.1 | 0.37 |
| **HCV Genotype 1** | 88% | 94% | 92% | 0.59 |
| **HCV RNA ($log_{10}$ IU)** | 6.4 | 6.1 | 6.3 | 0.18 |
| **Evidence of cirrhosis** | 11 (21%) | 14 (28%) | 18 (35%) | 0.31 |
| **History of any milk thistle use** | 46% | 44% | 42% | 0.92 |

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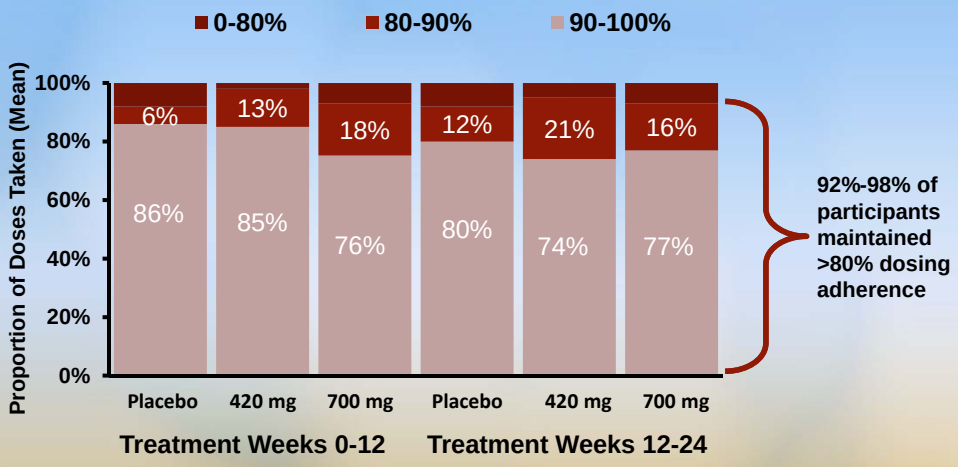
# Silymarin for Hepatitis C Adherence

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# Silymarin for Hepatitis C ITT Analysis of Primary Endpoints

| Endpoint | Placebo (n=52) | Silymarin 420 mg (n=50) | Silymarin 700mg (n=52) | *P*-value |
|---|---|---|---|---|
| **ALT ≤ 45 IU** | 1 (1.9%) | 2 (4%) | 2 (4%) | 0.8 |
| **Serum ALT decline of at least 50% to < 65 IU** | 2 (3.8%) | 1 (2%) | 2 (3.8%) | 0.8 |
| **Either of the above** | 2 (3.8%) | 2 (4%) | 2 (3.8%) | 1.0 |

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# Silymarin for Hepatitis C
# Analysis of Secondary Endpoints

| Endpoint* | Placebo | Silymarin 420 mg | Silymarin 700 mg | *P*-value |
|---|---|---|---|---|
| **Change in ALT (IU/L)** | -4.3 | -14.4 | -11.3 | 0.75 |
| **Change in HCV RNA ($log_{10}$ IU)** | 0.07 | -0.03 | 0.04 | 0.54 |
| | | | | |
| **Changes in Quality of Life** | | | | |
| **CESD score** | -0.26 | -0.73 | -0.41 (12.5)[M8] | 0.97 |
| **SF36 (Physical)** | -0.69 | -2.86 | -0.27 | 0.18 |
| **SF36 (Mental)** | 0.24 | 0.35 | -0.90 | 0.68 |
| **Chronic Liver Disease Questionnaire (CLDQ)** | 0.12 | -0.10 | -0.03 | 0.26 |

* Data provided as mean values

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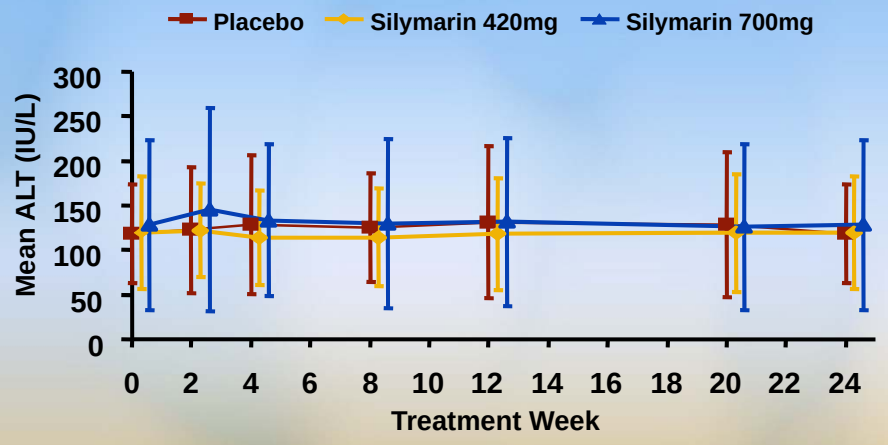
# Silymarin for Hepatitis C
# Serum ALT During Treatment*




* Analysis limited to those with complete ALT data (n=131)

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# Silymarin for Hepatitis C Adverse Events

| | Placebo (n) | Silymarin 420mg (n) | Silymarin 700mg (n) | *P* values* |
|---|---|---|---|---|
| **Adverse events*** | 34 | 31 | 29 | 0.84 |
| **Serious AEs** | 1 | 6** | 5 | 0.08 |
| | | | | |
| **Most common classes of AEs** | | | | |
| **Gastrointestinal** | 4 | 8 | 6 | 0.56 |
| **Musculoskeletal** | 4 | 2 | 3 | 0.70 |
| **Dermatologic** | 3 | 0 | 4 | 0.67 |
| **Infection** | 3 | 1 | 3 | 0.44 |
| **Physical Injury** | 1 | 1 | 3 | 0.65 |
| **Others** | 19 | 19 | 10 | 0.17 |

*Most AEs were mild-moderate
**One death by suicide 12 weeks post-treatment

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# Silymarin for Chronic HCV Summary

- This randomized, placebo-controlled, double-blinded study:
  - Administered a well-characterized silymarin product for a prolonged period
  - Focused on a specific liver disease
  - Enrolled a large cohort across 4 US centers
  - Had excellent adherence with study medication
  - Employed well-defined treatment outcomes
- There was no significant change in serum ALT activity in the silymarin treatment arms
- Similarly, symptom scores and quality of life measures were unchanged during silymarin treatment

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