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
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


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

Silymarin for Hepatitis C

Participant Disposition

- Screened (n=234)
- Eligible (n=154)
- Not Eligible (n=80)

Placebo (n=52)
- Silymarin 420 mg (n=50)
- Silymarin 700 mg (n=52)

- 24 week evaluation completed (n=50)
- 24 week evaluation completed (n=44)

Common reasons for ineligibility*
- ALT less than 65 IU 51
- Poorly controlled diabetes 8
- Drug abuse 6
- Withdrew consent 9

*May include >1 reason


Silymarin for Hepatitis C

Participant Characteristics

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

Silymarin for Hepatitis C
Adherence

92%-98% of participants maintained >80% dosing adherence

Proportion of Doses Taken (Mean)


Silymarin for Hepatitis C ITT
Analysis of Primary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=52)</th>
<th>Silymarin 420 mg (n=50)</th>
<th>Silymarin 700 mg (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT ≤ 45 IU</td>
<td>1 (1.9%)</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Serum ALT decline of at least 50% to &lt; 65 IU</td>
<td>2 (3.8%)</td>
<td>1 (2%)</td>
<td>2 (3.8%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Either of the above</td>
<td>2 (3.8%)</td>
<td>2 (4%)</td>
<td>2 (3.8%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Silymarin for Hepatitis C
Analysis of Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint*</th>
<th>Placebo</th>
<th>Silymarin 420 mg</th>
<th>Silymarin 700 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in ALT (IU/L)</td>
<td>-4.3</td>
<td>-14.4</td>
<td>-11.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Change in HCV RNA (log&lt;sub&gt;10&lt;/sub&gt; IU)</td>
<td>0.07</td>
<td>-0.03</td>
<td>0.04</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Changes in Quality of Life

| CESD score | -0.26 | -0.73 | -0.41 (12.5)<sup>M8</sup> | 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)

Silymarin for Hepatitis C

Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n)</th>
<th>Silymarin 420mg (n)</th>
<th>Silymarin 700mg (n)</th>
<th>P values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events*</td>
<td>34</td>
<td>31</td>
<td>29</td>
<td>0.84</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1</td>
<td>6**</td>
<td>5</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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


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