Available online at www.sciencedirect.com
ScienceDirect
Phytomedicine 16 (2009) 391–400
Phytomedicine
www.elsevier.de/phymed

A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis

Samer S. El-Kamary[a,*], Michelle D. Shardell[a], Mohamed Abdel-Hamid[b,f], Soheir Ismail[b], Mohamed El-Ateek[c], Mohamed Metwally[b,d], Nabiel Mikhail[b,g], Mohamed Hashem[a,b], Amr Mousa[b], Amr Aboul-Fotouh[e], Mohamed El-Kassas[b], Gamal Esmat[b,e], G. Thomas Strickland[a]

[a]*Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, 660 West Redwood Street, Howard Hall, Rm 103C, Baltimore, MD 21201, USA*
[b]*National Hepatology and Tropical Medicine Research Institute, Kasr Al-Aini St, Cairo, Egypt*
[c]*Tanta Fever Hospital, Tanta, Gharbeya Governorate, Egypt*
[d]*Banha Fever Hospital and Banha University Faculty of Medicine, Banha, Kaloubeya Governorate, Egypt*
[e]*Tropical Medicine Department, Cairo University Faculty of Medicine, Cairo, Egypt*
[f]*Minia University Faculty of Medicine, Minia, Egypt*
[g]*Assiut University, South Egypt Cancer Institute, Assiut, Egypt*

Abstract

Purpose: Milk thistle or its purified extract, silymarin (*Silybum marianum*), is widely used in treating acute or chronic hepatitis. Although silymarin is hepatoprotective in animal experiments and some human hepatotoxic exposures, its efficacy in ameliorating the symptoms of acute clinical hepatitis remains inconclusive. In this study, our purpose was to determine whether silymarin improves symptoms, signs and laboratory test results in patients with acute clinical hepatitis, regardless of etiology.

Methods: This is a randomized, placebo-controlled trial in which participants, treating physicians and data management staff were blinded to treatment group. The study was conducted at two fever hospitals in Tanta and Banha, Egypt where patients with symptoms compatible with acute clinical hepatitis and serum alanine aminotransferase (ALT) levels >2.5 times the upper limit of normal were enrolled. The intervention consisted of three times daily ingestion of either a standard recommended dose of 140 mg of silymarin (Legalon®, MADAUS GmbH, Cologne, Germany), or a vitamin placebo for four weeks with an additional four-week follow-up. The primary outcomes were symptoms and signs of acute hepatitis and results of liver function tests on days 2, 4 and 7 and weeks 2, 4, and 8. Side-effects and adverse events were ascertained by self-report.

Results: From July 2003 through October 2005, 105 eligible patients were enrolled after providing informed consent. No adverse events were noted and both silymarin and placebo were well tolerated. Patients randomized to the silymarin group had quicker resolution of symptoms related to biliary retention: dark urine ($p = 0.013$), jaundice ($p = 0.02$) and scleral icterus ($p = 0.043$). There was a reduction in indirect bilirubin among those assigned to silymarin ($p = 0.012$), but other variables including direct bilirubin, ALT and aspartate aminotransferase (AST) were not significantly reduced.

*Corresponding author. Tel.: +1 410 706 2228; fax: +1 410 706 8013.
E-mail address: selkamar@epi.umaryland.edu (S.S. El-Kamary).

0944-7113/$ - see front matter
doi:10.1016/j.phymed.2009.02.002

Conclusions: Patients receiving silymarin had earlier improvement in subjective and clinical markers of biliary excretion. Despite a modest sample size and multiple etiologies for acute clinical hepatitis, our results suggest that standard recommended doses of silymarin are safe and may be potentially effective in improving symptoms of acute clinical hepatitis despite lack of a detectable effect on biomarkers of the underlying hepatocellular inflammatory process.

Keywords: Hepatitis; Milk thistle; *Silybum marianum*; Silymarin; Randomized controlled trial; Egypt

Introduction

Acute hepatitis is a clinical syndrome with a presentation that can range from mild flu-like symptoms to severe fulminant hepatitis and is characterized by a triad of *impaired biliary excretion*, *hepatocellular liver damage* and *systemic effects of liver inflammation*. Acute viral hepatitis (AVH) is the commonest cause of acute hepatitis and infection with hepatitis viruses ranges from 20–40% in developed countries and 80–100% in developing countries (Corwin et al. 1996; Meky et al. 2006; Shepard et al. 2005).

No significant advances in managing acute symptomatic viral hepatitis have been developed since 1955 (Chalmers et al. 1955) where it was concluded that the best therapy was rest and a high-protein diet. Given that symptoms can last from a few weeks to several months, an effective intervention would permit early recovery and fewer days of work lost. In the absence of allopathic medications, homeopathic remedies such as milk thistle or its purified extract, silymarin, are used extensively (Jacobs et al. 2002; Luper 1998, 1999).

The botanical name for milk thistle is *Silybum marianum*. It is also referred to as holy thistle, Marian thistle, Mary thistle, Our Lady's thistle, St. Mary thistle, wild artichoke, Mariendistel (German), and Chardon-Marie (French). The seeds of milk thistle are the medicinal parts of the plant. The primary active constituent of milk thistle is silymarin, which is composed of four isomers: silybin, isosilybin, silychristin, and silydianin. In turn, silybin and isosilybin are both mixtures of two diastereomers, silybins A and B and isosilybins A and B, respectively (Lee and Liu 2003; Saller et al. 2001). Special formulations of silybin have been developed to enhance the bioavailability of the herbal product; these forms are sold under the names Legalon®, Silipide and Siliphos. Because of milk thistle's lipophilic nature, it is usually administered in capsule or tablet form rather than as an herbal tea.

Milk Thistle is widely used in Europe, United States, Egypt, and elsewhere for "liver support" (Luper 1998; Luper 1999; Mulrow et al. 2000; Saller et al. 2001). The German Commission E endorses its use as a supportive treatment for chronic inflammatory liver conditions and cirrhosis. Milk thistle/silymarin is thought to work via: (1) preventing entry of various toxins, e.g., alcohol, carbon tetrachloride and heavy metals, into hepatocytes; (2) stimulating protein synthesis with hepatocyte regeneration; (3) acting as a free-radical scavenger and antioxidant; and (4) modulating the immune response (Boigk et al. 1997; Deak et al. 1990; Muriel and Mourelle 1990; Pietrangelo et al. 1995). The hepatoprotective action of silymarin in fatal fulminant hepatic failure following *Amanita phalloides* mushroom poisoning is documented in experimental animals and humans even when given after exposure (Hruby et al. 1983; Vogel et al. 1984). Inconclusive results have been reported in a few randomized controlled trials (RCT), mostly on alcoholic liver disease, chronic hepatitis B (HBV) or hepatitis C (HCV) infections (Ball and Kowdley 2005; Jacobs et al. 2002; Mayer et al. 2005; Rambaldi et al. 2005; Strickland et al. 2005; Tanamly et al. 2004).

Since the therapeutic endpoint for acute hepatitis occurs in days or a few weeks as opposed to years in chronic hepatitis, we speculated that it would be an excellent model to evaluate safety and efficacy of silymarin.

Materials and methods

Design overview

We used a double blind, randomized, placebo-controlled trial to compare the effect of a standard recommended dose of silymarin with a placebo. This study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Institutional Review Boards at both the University of Maryland Baltimore and the Egyptian Ministry of Health & Population. All study participants provided informed consent.

Setting and participants

Symptomatic patients, thirteen years or older, were enrolled from Tanta and Banha Fever Hospitals in the Nile Delta where the incidence of acute viral hepatitis is high (Meky et al. 2006). Eligibility criteria included an alanine aminotransferase (ALT) level more than 2.5 times the upper limit of normal (>100 IU/l), with jaundice and/or scleral icterus and three or more of