Effectiveness and safety of orally administered silymarin (milk thistle) for Pegylated Interferon unresponsive chronic Delta Hepatitis patients

Mesut Aydin¹*, Erhan Ergin², Elif Tugba Tuncel², Yaren Dirik¹, Suat Ozluk³, Huseyin Guducuoglu³, Ahmet Cumhur Dulger⁴

¹ Yuzuncu Yil University Faculty of Medicine, Dept. of Gastroenterology, Van, TR
² Manisa State Hospital, Dept. of Gastroenterology, Manisa, TR
³ Yuzuncu Yil University Faculty of Medicine, Dept. of Microbiology, Van, TR
⁴ Giresun University Faculty of Medicine Dept. of Gastroenterology, Giresun, TR

* Corresponding Author: Mesut Aydin E-mail: gmstaydin@gmail.com

ABSTRACT

Objective: Silymarin is a natural extract from milk thistle (Silybum marianum), a natural herb that contains flavonoids. Silymarin also has anti-inflammatory properties and lipid peroxidation effects on human hepatocytes. It has also been used for the treatment of acute alpha-amanitin poisoning and chronic hepatitis C infection. Chronic Hepatitis D virus (HDV) infection is a severe health problem leading to fibrosis and hepatocellular carcinoma. Patients with chronic HDV infection can be treated with Peg-IFN with lower treatment success. Most patients with chronic HDV are unable or unwilling to use interferon (IFN)-based treatment due to liver cirrhosis. Our objective was to establish the long-term clinical outcomes with silymarin for interferon-experienced chronic HDV patients.

Materials and Methods: We studied ten patients from one centre with interferon who experienced chronic HDV, of which 8 had cirrhosis, and 2 had chronic hepatitis who received HDV treatment with silymarin 600 mg/day after a median period of 12 months. Information collected included demographic, clinical, virologic, and outcomes data. MELD and Child-Pugh (CP) scores were also obtained. Friedman test was used to evaluate the laboratory parameters during the study period.

Results: 10 chronic HDV patients (median age 54 yrs, six female, all of them previous null responders to Peg-IFN with mildly decompensated cirrhosis [CP 7 (range 6-11), MELD 11 (range 6-20)] were followed for 12 months from the start of silymarin 600 mg/day. There was no decomposition of both MELD and CP scores among patients at the end of therapy. In addition, no patients stopped silymarin treatment early due to side effects. At the end of treatment, there was no significant change in prothrombin time (p=0.949), AST (p=0.662) and AFP (p=0.983) levels and platelets counts (p=0.988) compared to the pre-treatment period (all p>0.005). Finally, HDV-RNA suppression was seen in all patients at the end of treatment (p=0.009).

Conclusions: In the light of the presented data, silymarin seems to be effective in treating chronic HDV infection. Further research is needed for validation. The study is ongoing with a collection of data on sustained viral response.

Keywords: Silymarin, Interferon therapy, Delta hepatitis

INTRODUCTION

Silymarin, an extract from the seed of the milk thistle plant (Silybum marianum [S. marianum]), is widely known for its hepatoprotective functions, mainly due to its anti-oxidative, anti-inflammatory, and immunomodulatory effects (1). The primary bioactive components of the extract consist of several flavonolignans (silybin, silychristin, silydianin, is silybin, and dehydrosilybin), and a few flavonoids, mainly taxifolin (2). The mixture of silybin A and silybin B (1:1) is also known as silibinin (C25H22O10, PubChem CID: 31553, Figure 1), which makes up the major active ingredient (roughly 50%) of silymarin (2,3).
Silymarin also has anti-inflammatory properties and lipid peroxidation effects on human hepatocytes. It has also been used for the treatment of acute alpha-amanitin poisoning and chronic hepatitis C infection.

Chronic Hepatitis D virus (HDV) infection is a serious health problem leading to fibrosis and hepatocellular carcinoma. Hepatitis D virus is a RNA virus that needs hepatitis B surface antigen for infection. That's why it doesn't cause infection on its own. He needs the hepatitis B virus for his infection. The main sensitive patients are chronic hepatitis B patients who become superinfected with this virus (4). Spreads parenterally like HBV in HDV (5).

HDV infection has been shown to worsen the natural course of underlying HBV infection. Hepatitis D is considered the most severe form of viral hepatitis in humans, accelerates progression to cirrhosis, and leads to earlier deterioration in liver function compared to the infection HBV alone. Approximately 5% of hepatitis B patients are infected with the hepatitis D virus (6).

Patients with chronic HDV infection can be treated with Peg-IFN therapy with lower treatment success. The majority of patients with chronic HDV are unable or unwilling to use Peg-IFN -based treatment due to liver cirrhosis. Recent studies have also documented the antiviral activities of silymarin and its derivatives against several viruses, including the flaviviruses (hepatitis C virus and dengue virus), togaviruses (Chikungunya virus and Mayaro virus), influenza virus, human immunodeficiency virus, and hepatitis B virus (7).

Silymarin acts as a free radical cleanser and modulates enzymes associated with the development of cellular damage, fibrosis, and cirrhosis.

These hepatoprotective effects have been observed in clinical trials in patients with alcoholic or non-alcoholic fatty liver disease, including patients with cirrhosis (8). At the same time, the intravenous form of Silybinin Amanita phalloides is used in fungal poisoning. Today, there is no direct effective antiviral agent for the hepatitis D virus. Interferon treatments currently used are the only treatment option for hepatitis D. However, both the serious side effects of interferons and the fact that their effectiveness around 30%, directs the researchers to new treatment modalities (9).

Although there are studies that report the positive effects of silymarin in patients with acute hepatitis, liver fat, and metabolic syndrome, there are no studies on the use of treatment in patients with unanswered hepatitis D. Our objective was to establish the long-term clinical outcomes with silymarin for interferon-experienced chronic HDV patients.

MATERIAL and METHODS

We studied ten patients from one center who experienced chronic HDV, of which 8 had cirrhosis, and 2 had chronic hepatitis who received HDV treatment with silymarin 600 mg/day after a median period of 12 months. Information collected included demographic, clinical, virologic, and outcomes data. MELD and Child-Pugh scores were also obtained. Friedman test was used to evaluate the laboratory parameters during the study period.

RESULTS

Ten chronic HDV patients (median age 54 yrs, six female, all of them previous null responders to Peg-IFN with mildly decompensated cirrhosis [Child Pugh 7 (range 6-11), MELD 11 (range 6-20)] were followed for 12 months from the start of silymarin 600 mg/day. There was no decompensation of both MELD and Child-Pugh scores among patients at the end of therapy. In addition, no patients stopped silymarin treatment early due to side effects. At the end of treatment, there was no significant change in prothrombin time (p= 0.949), AST (p=0.662), and AFP (p=0.983) levels and platelets counts (p=0.988) compared to the pre-treatment period (all p>0.005). Finally, HDV-RNA suppression was seen in all patients at the end of treatment (p=0.009).

Figure 1. Chemical structures of silibinin, the 1:1 mixture of silybin A and silybin B.

Figure 2. HDV RNA levels During 12 months of Silibinin IV Monotherapy and Subsequent Follow-up (HDV RNA Levels Measured by Abbott Real Time HDV Assay)
DISCUSSION

Hepatitis D virus is a defective virus that alone does not cause infection without hepatitis B virus. In patients affected by this virus, which is infected with hepatitis B virus, both the progression to cirrhosis is accelerated, and the risk of hepatocellular cancer increases.

In Western societies, it often leads to infection with hepatitis B virus in IV drug addicts and often individuals infected with Hepatitis C and HIV virus. While Delta hepatitis in the west has decreased to the degree that it almost forgets itself, it has become a major problem again in recent years with the increase in the flow of migrants to the west from the geographies where it is endemic. In this new wave, the disease is both more severe and faster to spread than before due to the fact that the patients are young populations compared to their predecessors (4).

There has been a search for new treatments due to the fact that there is no treatment option outside of interferon yet, and interferon is both limited in effectiveness and due to its frequent side effects. Silymarin preparation is an over-the-counter preparation that is recommended as a support treatment for various diseases. It is used in many liver and pancreatic disorders.

In a study conducted by Ferenci and his colleagues, they suggested that intravenously administered silymarin caused a decrease in viral load in hepatitis C patients who did not respond to Peg-IFN (10).

However, since no significant clinical effects were detected in many subsequent studies, intravenous silymarin therapy is not included in clinical practice in these patients. In a 2016 study on mice, Ni X. and his colleagues showed that silymarin causes intrahepatic lipid accumulation and positive effects on LDL, HDL, and Triglyceride lipid profiles. For this reason, silymarin is one of the promising treatments for non-alcoholic liver fat (11).

Song and his colleagues found that in alcoholic liver disease, silymarin had a positive effect on oxidative stress parameters and limited ALT growth (12). A 2017 report stated that silymarin in meta-analysis led to a minimal decrease in AST and ALT levels, but this decrease was not clinically significant (13).

In our study, AST decrease was observed but not statistically significant. What is interesting about our research is that it significantly reduces the level of HDV RNA. This result is promising for future treatment plans. These findings provide compelling evidence to explore the use of silymarin and derivatives in combination with existing antivirals as a potential treatment strategy, particularly for the treatment of chronic viral hepatitis.

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CONCLUSION

In the light of the presented data, silymarin seems to be effective in the treatment of chronic HDV infection. Further research is needed for validation. The study is ongoing with a collection of data on sustained viral response. Further research to improve the bioavailability, delivery, as well as elucidating the main mechanism of antiviral activity of silymarin and derivatives, could help to boost our understanding of these drugs and accelerate their development as hepatoprotective, antiviral agents.

REFERENCES