The Role of Ursodeoxycholic Acid in Acute Viral Hepatitis: an Evidence-based Case Report

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ABSTRAK

Tujuan: *mengetahui peran asam ursodeoksikolat terhadap hepatitis viral akut.* ***Metode:*** *melalui penelusuran literatur yang dilakukan di PubMed dan Cochrane Libarary sesuai dengan pertanyaan klinis. Setelah dilakukan penapisan dengan kriteria inklusi dan eksklusi, didapatkan satu meta analysis dan dua randomized controlled trials. Melalui telaah kritis, disimpulkan bahwa artikel tersebut memenuhi kriteria validitas dan relevansi.* ***Hasil:*** *artikel tersebut menemukan bahwa terdapat efek positif dari asam ursodeoksikolat terhadap aktivitas serum transaminase, dan indeks kolestasis, namun bukti yang didapatkan kurang memadai untuk menyokong ataupun menyanggah efek asam ursodeoksikolat terhadap perjalanan penyakit hepatitis virus akut maupun jumlah virus.* ***Kesimpulan:*** *dibutuhkan uji klinis dengan metode yang lebih baik untuk mendapatkan hasil yang baik dan dapat diterapkan dalam praktek klinis sehari-hari.*

Kata kunci: *asam ursodeoksikolat, hepatitis virus akut.*

ABSTRACT

Aim: *to review the role of ursodeoxycholic acid in acute viral hepatitis.* ***Methods:*** *following literature searching according to the clinical question on Pubmed and Cochrane Library. After filtered with our inclusion and exclusion criteria, one meta-analysis and two randomized clinical trials are obtained. Through critical appraisal, it was concluded that the articles meet the criteria for validity and relevance.* ***Results:*** *the article found that there is a positive effect of ursodeoxycholic acid on the activity of serum transaminases and cholestasis indexes. However, there is insufficient evidence to support or to refute effects of ursodeoxycholic acid on disease's course as well as the viral load.* ***Conclusion:*** *better method of clinical trials are needed to obtain a valid and applicable result for daily practice.*

Key words: *ursodeoxycholic acid, acute viral hepatitis.*

INTRODUCTION

Hepatitis is an inflammatory liver disease which has become a serious problem due to its wide spread and complications up to now. Acute viral hepatitis is generally caused by the Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis D Virus (HDV), Hepatitis E Virus (HEV), and Hepatitis non A-E virus. The clinical symptoms are generally similar, but may be vary from asymptomatic to fulminant.[1]

There is no exact data on the epidemiology of the prevalence of viral hepatitis around the world. As an illustration, the incidence of hepatitis A in 2007 in the United States is approximately 25,000 cases and the number of people with

hepatitis B in the world is around 350 million. The World Health Organization (WHO) reported that there are 4 million cases of acute hepatitis B each year with 25% of them being a carrier, and 1 million people died from chronic active hepatitis, cirrhosis or primary liver cancer.[2-3]

Management of acute viral hepatitis is supportive therapy, and in some cases requires administration of anti-viral agent. Cholestatic effect of ursodeoxycholic acid has been known and some studies have proven its use especially against chronic hepatitis with cholestatic, however, its role against acute viral hepatitis remains unclear.

CLINICAL PROBLEM

Male 22 years with chief complaint of yellow jaundice since 3 days, before admission. He complained a sense of weakness, nausea, loss of appetite, and sub-febrile fever about one week before. There are no history of drugs consumptions, previous history of jaundice, intravenous drug user, and free unprotected sexual contact. Physical examination found icteric sclera and mild hepatomegaly.

Patient was diagnosed as acute hepatitis and planned to take a hepatitis seromarker examination (anti-HAV, HbsAg, anti-HCV), liver function (AST/ALT, GGT, ALP, bilirubin), and abdominal USG. The results of the blood test are as follows: positive IgM anti-HAV, negative HbsAg and anti-HCV, AST/ALT: 256/532 IU/L, GGT 114 IU/L, ALP 233 IU/L, total/direct/indirect bilirubin: 4.4/3.4/1.0 mg/dL. Abdominal USG was not done due to financial problem. Patient was diagnosed as acute hepatitis A and advised to have bed rest, soft diet, and given domperidone 3x10 mg, curcuma 3x1 tab, ursodeoxycholic acid 3x1 cap, and revisited his doctor after 1 week.

During regular visit, patient's complaints are gradually decreased and had a good appetite. Jaundice had gradually disappeared. Laboratory examination of liver function are within normal limits and the patient was cured.

Clinical experience showed that therapy for acute viral hepatitis is generally supportive without giving ursodeoxycholic, but some studies have shown a positive effect on the use of ursodeoxycholic acid in chronic hepatitis. Thus, the proposed clinical questions is as follows: "Is there a role of ursodeoxycholic acid in acute viral hepatitis?"

METHODS

Literature search procedures to address the clinical problem is to trace online library using

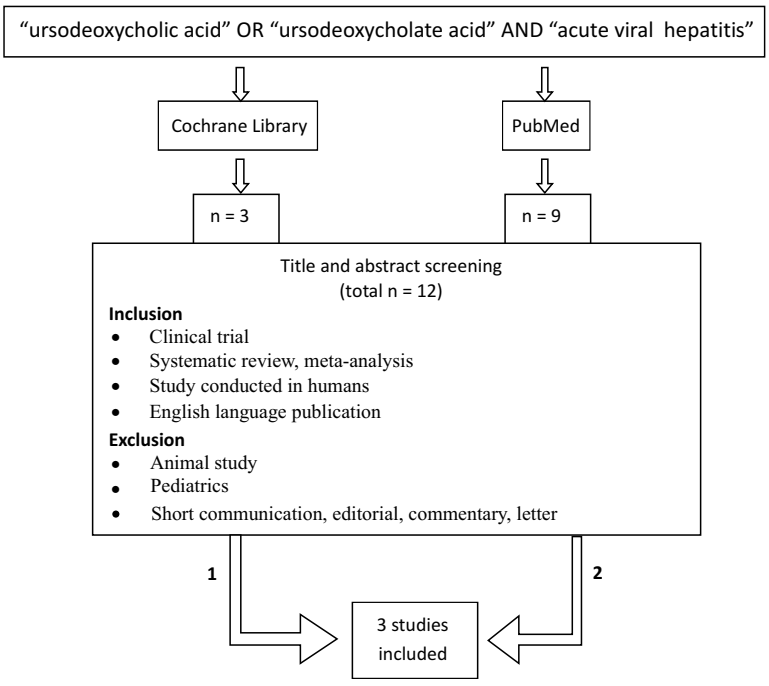

Figure 1. Flow chart of search strategy

Pubmed, Google Scholar, and Cohcrane Library. The keywords are "ursodeoxycholic acid" OR "ursodeoxycholate acid" AND "acute viral hepatitis".

By using this methods, 12 articles were obtained, the selection of title and abstract was conducted using inclusion and exclusion criteria as shown in the flowchart. Further research carried out manually on a list of relevant literature. Three articles which are relevant to the issue was found, which consists of 1 meta-analysis article and 2 clinical trial articles. After literature selection, critical appraisal was done using several spect based on Center of Evidence-Based Medicine, University of Oxford for therapy study.[4]

RESULTS

Chen et al.[5] reported the results of meta-analysis of 27 clinical trials where there is 1 clinical trial in acute hepatitis B with a reduced risk of HbsAg-positive at the end of therapy, HBV-DNA level, and improves transaminases significantly. The researcher concluded that ursodeoxycholic acid significantly improves transaminases activity in chronic hepatitis B and C, but there is no effect on viral clearance, and a randomized clinical trials with better methodological quality is needed.

Galsky et al.[6] observed 78 patients with acute hepatitis (59 patients with acute hepatitis B) which divided into 2 groups, and experimental group was given ursodeoxycholic acid and its development were followed until 12 months. The result showed there was a decrease in alanine aminotransferase, improved liver function significantly in experimental group. The author concluded that ursodeoxycholic acid has a positive effect on the disease course of acute hepatitis and may increase the clearance of hepatitis B virus, thus preventing chronic progression of the disease.

Fabris et al.[7] conducted a randomized clinical trial to evaluated the effects ursodeoxycholic acid (UDCA) administration on acute viral hepatitis-related cholestasis and the course of acute viral hepatitis. A total of 79 patients with acute viral hepatitis randomized to receive either UDCA for 3 weeks or no treatment. Author concluded that UDCA significantly improves cholestatic indices in patient with acute viral hepatitis, but it does not affect the course of the illness itself.

Table 1. Critical appraisal of the studies based on criteria by centre of evidence medicine University of Oxford

Author	Year	Validity							Relevance			
		Study design	Number of patients	Randomization	Similarity treatment and control	Comparable treatment	Intention-to-treat	Blinding	Domain	Determinant	Measurement of outcome	Levels of evidence
Galsky et al[6]	1999	RCT	78	+	+	+	+	+	+	+	+	2
Fabris et al[7]	1999	RCT	79	+	+	+	+	?	+	+	+	2

+ stated clearly in the article; - not being done; ? not stated clearly; *levels of evidence based on The Oxford Center of Evidence Based Medicine 2011

Table 2. Critical appraisal of a systematic review

Authors	Year	Validity					Level of evidence
		PICO	Appropriate searching	Relevant study included	Quality assessment of trials	Heterogenity	
Chen et al[5]	2003	+	+	+	+	+	2

Table 3. Results of all studies

Author	Results	Summary
Galsky et al[6]	1. Elevation of alanine aminotransferase persisted more frequently in the placebo group (all cases, p = 0.05; hepatitis B group, p = 0.03). 2. Presence of hepatitis B early antigen and hepatitis B virus DNA (polymerase chain reaction and hybridization) at 12 months of follow-up, was observed in 1 of 33 patients in the UDCA group and in 6 of 25 patients in the placebo group (p = 0.02).	Significant rate of decline of the alanine aminotransferase and considerable clearance rate of hepatitis B virus.
Fabris et al[7]	Decrease in liver enzymes and bilirubin: Statistically significant for cholestatic index - ALP (P<0.01) - Bilirubin (P<0.05) - GGT (P<0.01).	Significant improvement of cholestatic indices in patient with acute viral hepatitis.
Chen et al[5]	1. In 1 study UDCA for acute hepatitis B significantly reduced the risk of hepatitis B surface antigen positivity and serum HBV DNA level. 2. In 1 trial, UDCA for chronic hepatitis B significantly reduced the risk of having abnormal serum transaminase activities at the end of treatment. 3. 25 studies of chronic hepatitis C. Bile acids significantly decreased the risk of having abnormal serum alanine aminotransferase activity at the end of treatment (RR 0.82, 95% CI 0.76 to 0.90) and follow-up (RR 0.91, 95% CI 0.85 to 0.98).	Significant decrease in the risk of hepatitis B surface antigen positivity and serum HBV DNA level.

DISCUSSION

Acute viral hepatitis is an inflammation of liver cells caused by hepatitis virus with clinical symptoms that vary, from asymptomatic to fulminant. On physical examination, the general symptoms are jaundice, nausea, vomiting, and decreased appetite. Histologically, acute hepatitis has panlobular infiltration with mononuclear cells, liver cell necrosis, Kuppfer cell hyperplasia, and various degrees of cholestasis.

Additional investigations that can be done are viral serology marker examination such as anti-HAV, HbsAg, anti-HCV, and liver function examination such as AST/ALT, GGT, ALP, total/direct/indirect bilirubin. Abdominal USG can also be performed but it is not very necessary in acute hepatitis state, except in chronic hepatitis with acute exacerbation. Generally, non specific mild hepatomegaly is found.

Management for acute hepatitis are generally supportive and preventing further liver damage.[8]

In the state of acute hepatitis, cholestasis occurs in almost cases which probably caused by massive cytolysis, and increasing hepatic cell damage due to effects of hydrophobic bile salt detergent. At that state, liver uptake and secretion of bile acid is disrupted, resulting in intrahepatic accumulation of chenodeoxycholid (CDCA) and deoxycholid acid (DCA) which cause hepatic cell damage.[9]

Activities of bile salt can dissolve phospholipids and cholesterol, which are the main components of cellular membranes, but it can be prevented by administration of ursodeoxycholic acid. Several studies has reported the positive effects of ursodeoxycholic acid for the treatment of chronic liver disease with cholestasis because it acts as a cytoprotective, anti-apoptosis, membrane stabilizing, antioxidant and immune-modulator effects.

Protective effect of ursodeoxycholic acid is thought to exist from modification of bile acid by increasing hydrophilic fraction and membrane cell stabilization.[9-10] In addition, ursodeoxycholic acid increases the excretion of cytotoxic bile acid (CDCA, DCA) or by binding to hepatocyte or biliocyte membranes, thus preventing cell damage.[11]

Ursodeoxycholic acid therapy was originated from traditional Chinese medicine, where a "yutan" drug were made from bear's dried bile and used as hepatobilliary medicine.[10] In 1902, Hammarsten reported the content of bile acid on bear's bile and named it ursokoleinat.[12] In

1927, Shoda found its chemical element and named it ursodeoxycholate.[13] In 1936, Iwasaki found the chemical structure.[14] In 1975, Makino reported its use for bile stone dissolution.[15] In 1985, Leuschner found an improvement of liver function in active chronic hepatitis patient after administration of ursodeoxycholate acid for bile stone dissolution.[16] In 1987, Poupon reported the role of ursodeoxycholate for long-term treatment and has been effective in primary billiary cirrhosis.[17] Since then, there are numerous studies on role of ursodeoxycholic acid in liver disease, but the mechanism of action has not been clear until now.

Mechanism of ursodeoxycholate acid to liver via multiple interrelated pathways including alteration of bile acids storage, choleresis, immune-modulator, and cytoprotective. Role of cytoprotective effect in hepatic epithelium is to stabilize the structure of the cell and induction of subcellular anti-apoptotic pathways. **Figure 2** illustrates the working mechanism of ursodeoxycholic acid.

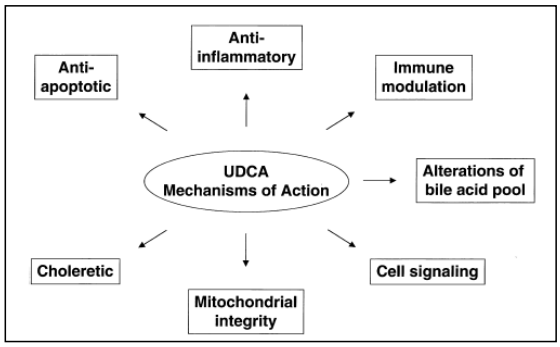

Figure 2. Mechanism of action of ursodeoxycholic acid[18]

Figure 2 illustrates about mechanism of action of ursodeoxycholate as a cytoprotective where ursodeoxycholate acid inhibits the dysfunction of mitochondria by inhibiting Fas-death receptor activation and preventing apoptosis by releasing C cytochrome.

From the existing research on the role of ursodeoxycholic acid, we analyzed 3 studies in this EBCR, two RCT and a meta-analysis that found favourable effects in acute viral hepatitis, mainly seen on the biochemical parameters. Two studies also showed reduced number of serum HBV DNA level at the end of the follow up in

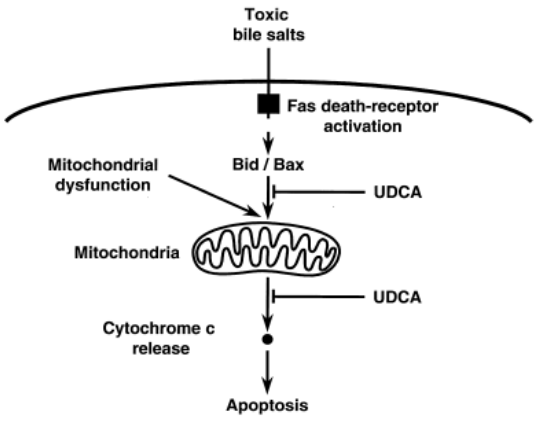

Figure 3. Cytoprotective effect of ursodeoxycholate acid (UDCA)[18]

group treated with UDCA versus placebo in acute viral hepatitis.

One study that is slightly different from another studies is done by Fabris et al.[7] This study found that UDCA treatment does not seem to affect the course of the disease. The different conclusions between these studies were explained by differences in determinants assessed. Interestingly, in this study they found a significantly higher reduction rate for GGT, ALP and blirubin serum levels, which was similar to that observed in cholestatic liver disease. However, the author emphasized that cholestasis that occurs during acute hepatitis is transient in the majority of case, and therefore it is not comparable to that reported in cholestatic liver disease and its usage rationalization still requires further research.

CONCLUSION

Based on the results and systematic review, it can be concluded that there are only a few research on the role of ursodeoxycholic acid in acute viral hepatitis and a clinical trial with good methodology is needed in order to make the result valid and applicable in clinical practice.

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