Combined use of ursodeoxycholic acid and Inchin-ko-to in jaundiced patients with primary biliary cirrhosis

Morikazu ONJI*, Takashi KIKUCHI, Kojiro MICHITAKA, Yoshimasa YAMASHITA and Yasuyuki OHTA

Third Department of Internal Medicine, Ehime University School of Medicine

(Received August 15, 1990. Accepted November 1, 1990.)

Abstract

There is currently no effective treatment available for jaundiced patients with primary biliary cirrhosis (PBC). We treated 3 jaundiced PBC patients with ursodeoxycholic acid (UDCA) in combination with Inchin-ko-to. Their combined use induced clinical and biochemical improvement, including a decrease of the bilirubin levels, in all 3 patients. On the other hand, neither UDCA nor Inchin-ko-to alone decreased serum bilirubin levels. These drugs were well tolerated and there was no side effects detected in this study. Because the presence of jaundice usually indicates a poor prognosis in patients with PBC, this regimen may well be worth using in the jaundiced patients with PBC in the future.

Key words primary biliary cirrhosis, UDCA, Inchin-ko-to (Intin-kô-tô), jaundice.

Abbreviation Inchin-ko-to, 茵蔯蒿湯 ; Inchin-gorei-san, 茵蔯五苓散 ; PBC, primary billiary cirrhosis ; a-PBC, asymptomatic PBC ; s-PBC, symptomatic PBC ; UDCA, ursodeoxycholic acid

Introduction

There is currently no effective treatment available for primary biliary cirrhosis (PBC), a chronic cholestatic disease characterized by destruction of the interlobular bile ducts, which eventually progresses to cirrhosis and often leads to death from liver failure.[1-3] In a recent study, Poupon *et al.* examined the effect of ursodeoxycholic acid (UDCA) on liver function in patients with PBC.[4] They found that in 15 patients with moderately severe disease, liver function tests improved significantly after 2 years of treatment. Side effects were clearly not a problem with UDCA treatment. Although there have been some trials of UDCA in patients with both asymptomatic and symptomatic PBC, most of the patients were in the early stages of PBC. Also, serum bilirubin levels did not improve in most of the patients, although other clinical and biochemical features of PBC improved during UDCA treatment.[5-10] The serum bilirubin level is one of the most important prognostic factors in patients with symptomatic PBC,[11,12] and there is a possibility that decreasing the serum bilirubin level with various agents can extend the lifespan of such patients.

We found that the combination of UDCA and Inchin-ko-to reduced serum bilirubin levels in the 3 patients with symptomatic PBC. Inchin-ko-to is a traditional Chinese medicinal preparation frequently used in hepatobiliary disease to increase bile flow.[13] This paper reports the results of a study to evaluate the effects of UDCA and Inchin-ko-to in jaundiced PBC patients.

Subjects and Methods

The subjects were 13 female patients with PBC. Their clinical, biochemical and histological data are shown in the Table I. The diagnosis of PBC was established by liver biopsy, and 9 patients were positive for anti-mitochondrial antibody by immunofluorescence. These patients had been previously treated with im-

*〒791-02 愛媛県温泉郡重信町志津川
愛媛大学医学部第3内科 恩地森一

Journal of Medical and Pharmaceutical Society for WAKAN-YAKU 7, 161−167, 1990

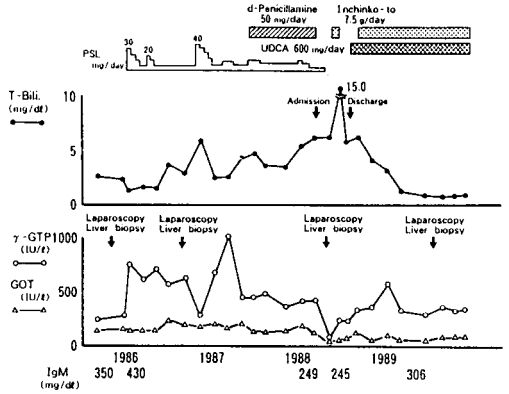

Fig. 1 Clinical course during the combined use of UDCA and Inchin-ko-to in case 11. Serum bilirubin decreased to within the normal range after starting the treatment. Histological improvement was confirmed by liver biopsy.

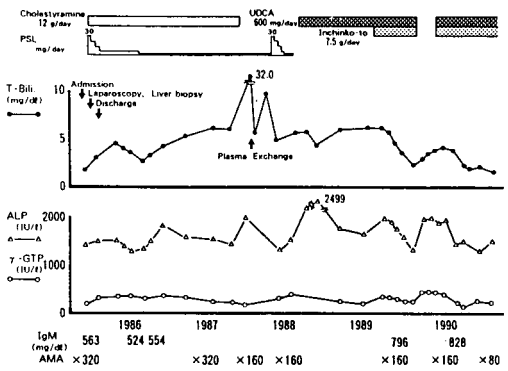

Fig. 2 Clinical course in case 12. Serum bilirubin and ALP levels fell during combined use of UDCA and Inchinko-to, and increased again transiently during interruption of therapy.

munosuppressive drugs and *d*-penicillamine without any success. At least 1 month prior to the treatment, all medications were discontinued.

UDCA (Tokyo Tanabe Co.) was given at a dose of 600 mg per day (six 200-mg capsules per day). Inchin-ko-to was supplied by Tsumura & Co. (Tokyo, Japan), and was given at a dose of 7.5 g per day. This is a traditional medicine composed of Sanshishi (Gardeniae Fructus), Daio (Rhei Rhizoma), and Inchin-ko (Artemisiae Capillaris Spica).

Student's paired *t*-test was used for all statistical analyses.

Results

Case Reports

Case 11

The patient was a 39-year-old woman who was admitted for the treatment of chronic cholestasis. She had suffered from pruritis and jaundice for more than 4 years. Prednisolone, *d*-penicillamine and cholestyramine had been administered without success. Physical examination showed moderate hepatosplenomegaly, jaundice, and xanthoma. Laboratory tests performed on admission revealed the following : total bilirubin, 6.2 mg/dl ; direct bilirubin, 5.0 mg/dl ; GOT, 127 IU/l ; GPT, 241 IU/l ; ALP, 683 IU/l (57 to 194) ; γ-GTP, 428 IU/l (0 to 31) ; ChE, 80 ChEU (73 to 150) ; ZTT, 5 U ; total cholesterol, 443 mg/dl ; Cu, 107 μg/dl (78 to 131) ; IgM, 222 mg/dl ; and erythrocyte sedimentation rate, 36 mm/h. Anti-mitochondrial antibody was negative. There was no evidence of extrahepatic obstruction of the biliary tract by ultrasonography, computed tomography, or endoscopic retrogade cholangiography. Laparoscopic examination revealed a diffusely cholestatic liver, with some mild gentle undulations which are specific for PBC.[14] Liver biopsy showed granuloma formation, chronic nonsuppurative destructive cholangitis (CNSDC), and bile pigment deposition.

Figure 1 outlines the clinical course and treatment regimen for this patient. The total bilirubin level decreased gradually, and fell to within the normal range 11 months after starting the combined use of UDCA and Inchin-ko-to, without any decrease of the γ-GTP level. Pruritus diminished and disappeared 6 months after the initiation of therapy. She was admitted again in August 1989 for laparoscopy. Physical examination showed that her xanthoma had diminished in size and number in comparison with the first admission. Laboratory investigations at the second admission showed the following data : total bilirubin, 1.0 mg/dl ; direct bilirubin, 0.5 mg/dl ;

Table I Summary of the clinical data of 13 patients with primary biliary cirrhosis.

Case Number	Sex	Age	a or s	AMA	Scheuer's Classification	Drug
1	M	66	a	160	II	UDCA alone
2	F	66	a	160	II	UDCA alone
3	F	66	a	320	I	UDCA alone
4	F	59	a	80	II	UDCA alone
5	F	58	a	320	I	UDCA alone
6	F	59	a	<20	II	UDCA alone
7	F	65	s	<20	I	UDCA alone
8	F	52	a	160	III	UDCA alone
9	F	59	a	160	I	UDCA alone
10	F	68	s	320	II	Inchinko-to
11	F	39	s	<20	III	UDCA, Inchinko-to
12	F	49	s	320	II	UDCA, Inchinko to
13	F	40	s	<20	II	UDCA, Inchinko-to

a : asymstomatic PBC, s : symptomatic PBC.

GOT, 64 IU/l ; GPT, 90 IU/l ; ALP, 859 IU/l ; γ-GTP, 275 IU/l ; ChE, 99 ChEU ; ZTT, 6 U ; total cholesterol, 407 mg/dl ; total bile acids, 54 μM (1.1 − 6.1) ; ESR, 60 mm/hr ; Cu ; 166 μg/dl ; IgM ; 391 mg/dl, and AMA ; negative< ×20. There was no change seen at laparoscopy except for resolution of the cholestasis. Liver biopsy specimen showed a decrease of the mononuclear cell infiltration in the portal tracts and the disappearance of bile plugs.

Case 12

The patient was a 49-year-old female. She initially presented to a local doctor with epigastric pain due to gastric ulcer, and abnormal liver function test results suggesting chronic cholestasis were detected incidentally. She complained of mild pruritus. A routine physical examination revealed moderate hepatosplenomegaly. Laboratory tests on admission showed the following : total bilirubin, 2.0 mg/dl ; direct bilirubin, 1.2 mg/dl ; GOT, 67 IU/l ; GPT, 78 IU/l ; ALP, 1403 IU/l ; γ-GTP, 227 IU/l ; ChE, 74 ChEU ; ZTT, 9 U ; total cholesterol, 342 mg/dl ; Cu, 185 ; ESR, 75 mm/hr, IgM, 544 mg/dl ; and total bile acids, 156 μM. Anti-mitochondrial antibody was positive (×320). The biliary tract was normal according to the findings of endoscopic retrograde cholangiography, abdominal ultrasound, and computed tomography. There were many gentle undulations of the liver seen on laparoscopy. Liver biopsy revealed stage II disease of Scheuer's classification with CNSDC and a decreased number of intralobular bile ducts.

Prednisolone and cholestyramine were administered for more than 2 years without success. In August 1987, plasma exchange was performed due to an abrupt increase of the serum bilirubin level. Laboratory test results before the initiation of UDCA therapy were as follows : total bilirubin, 4.3 mg/dl ; direct bilirubin, 3.3 mg/dl ; GOT, 69 IU/l ; GPT, 75 IU/l ; ALP, 1225 IU/l ; γ-GTP, 612 IU/l ; ZTT, 19 U ; cholesterol, 403 mg/dl. The bilirubin and ALP levels did not change during UDCA administration, but the combined use of UDCA and Inchin-ko-to induced a fall of both bilirubin and ALP levels. The laboratory data in September 1989 showed considerable improvement : total bilirubin 2.4 mg/dl, direct bilirubin 2.0 mg/dl, GOT, 44 IU/l, GPT, 39 IU/l, ALP, 1324 IU/l, γ-GTP, 203 IU/l, total cholesterol 292 mg/dl, total bile acids 57.1 μM. When the use of UDCA and Inchin-ko-to was ceased for 2 months, the bilirubin and ALP levels increased transiently.

Case 13

The patient was 38-year-old female who was admitted in August 1988 with jaundice and pruritus that had persisted for more than 6 months.

Physical examination showed mild jaundice, moderate hepatosplenomegaly, skin pigmentation, and excoriations. Laboratory investgations revealed the following : total bilirubin, 3.4 mg/dl ; direct bilirubin, 2.0 mg/dl ; GOT, 58 IU/l ; GPT, 87 IU/l ; ALP, 494 IU/l ; γ-GTP, 140 IU/l ; ChE, 68 ChEU ; ZTT, 15 U ; total cholesterol, 224 mg/dl, Cu 176 μg/dl ; IgM, 336 mg/dl ; and anti-mitochondrial antibody $< \times 20$ (negative). Extrahepatic obstruction was ruled out by endoscopic retrograde cholangiography, abdominal ultrasound and computed tomography. Some gentle undulations of the liver were observed at laparoscopy. Liver biopsy specimen showed stage III disease of Scheuer's classification with CNSDC and a decreased number of intralobular bile ducts.

We tried *d*-penicillamine therapy, but this had to be discontinued due to an allergic reaction (skin eruptions and leucopenia). Inchin-gorei-san was then given for 8 months without achieving any decrease of the bilirubin levels. UDCA was next given (from October 1988), and Inchin-ko-to was added from May 1989. Serum bilirubin levels fell gradually during the combined use of UDCA and Inchin-ko-to (Fig. 3), and her pruritus subsided gradually. Liver function tests before the combination regimen showed the following data : total bilirubin, 3.1 mg/dl ; direct bilirubin, 2.0 mg/dl ; GOT, 54 IU/l, GPT, 83 IU/l ; ALP, 544 IU/l ; γ-GTP, 150 IU/l ; and total cholesterol, 260 mg/dl. The same tests after combination therapy revealed slight improvement, as follows : total bilirubin, 2.2 mg/dl ; direct bilirubin, 1.4 mg/dl ; GOT, 42 IU/l ; GPT, 66 IU/l ; ALP, 572 IU/l ; γ-GTP, 139 IU/l ; total cholesterol 254 mg/dl.

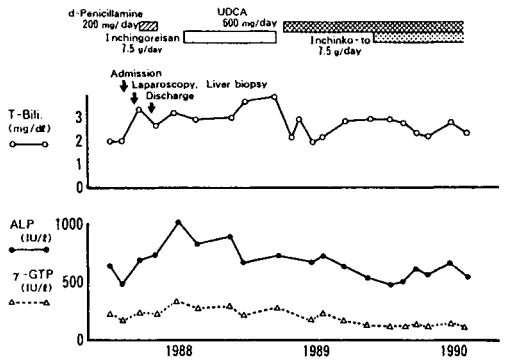

Fig. 3 Clinical course in case 13. The serum bilirubin level decreased transiently following administration of UDCA alone, but then returned to the same level as before therapy. The combined use of UDCA and Inchin-ko-to decreased the serum bilirubin level gradually.

Use of UDCA alone

The changes of liver function test results during the administration of UDCA alone are shown in Figs. 4 to 7. Serum bilirubin levels did not change in the 3 patients with symptomatic PBC, as shown in Fig. 4. GPT levels decreased after 1 month of UDCA administration in 7 of 10 cases, but the fall was not significant. ALP and γ-GTP levels decreased significantly after one month of UDCA in patients with asymptomatic PBC, and continued to decrease up to 3 months after starting UDCA, but fell no further from the 4th month.

Use of Inchin-ko-to alone

Inchin-ko-to alone was given to 3 patients with asymptomatic PBC. There were no marked changes in any liver function test results during the administration of Inchin-ko-to alone, as shown in Fig. 8.

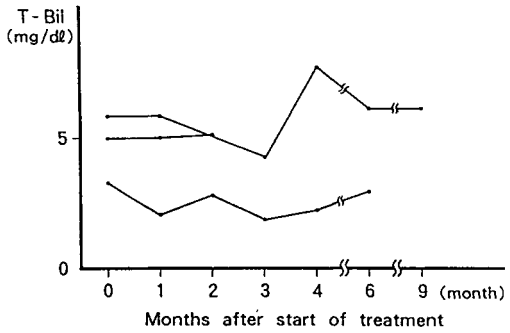

Fig. 4 Serum bilirubin levels during the use of UDCA alone in jaundiced PBC patients. The serum bilirubin levels in 3 patients before and at one month after treatment were 5.0 mg/dl (before), 5.1 mg/dl, (after) ; 3.4 mg/dl, 3.2 mg/dl ; 5.8 mg/dl. 5.9 mg/dl, respectively. The serum bilirubin level did not decrease during treatment.

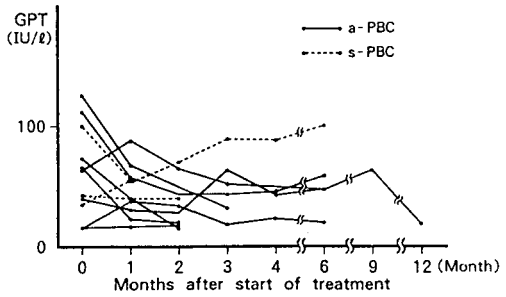

Fig. 5 Serum GPT levels during the administration of UDCA alone. There was no significant difference between before (mean±one standard deviation, 65.6±36.8 IU/l) and after treatment (47.2±20.5), but the levels decreased at one month of UDCA therapy in 7 of 11 cases.

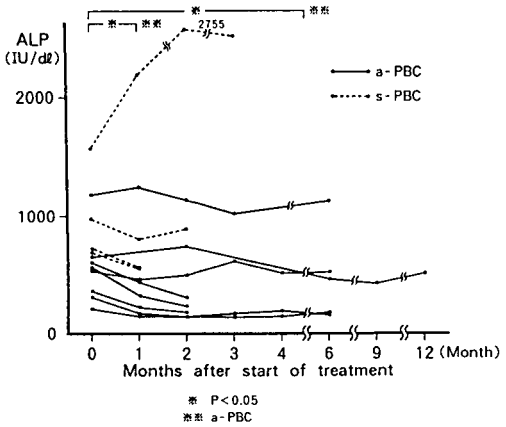

Fig. 6 Serum ALP levels during the administration of UDCA alone. The serum ALP levels decreased significatly 1 month after starting UDCA administration in patients with asymptomatic PBC.

Discussion

The combined use of UDCA and Inchin-ko-to induced clinical and biochemical improvement, especially a decrease of the serum bilirubin level, in all three patients with symptomatic PBC that we treated. No other therapeutic agents, including corticosteroids, azathioprine, *d*-penicillamine, chlorambucil and colchicine, have proved convincingly effective for PBC in previous trials.[1-3] Recently, Poupon *et al.* reported that UDCA produces a considerable clinical and biochemical improvement in patients with PBC.[4] It has been

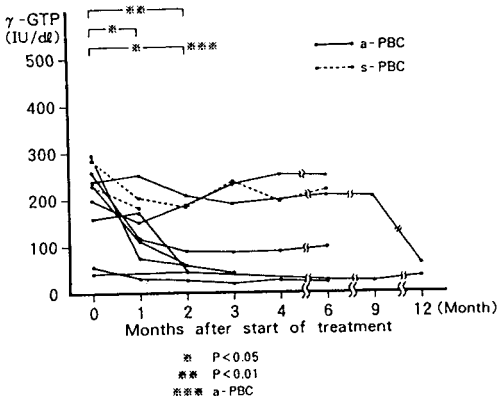

Fig. 7 Serum γ-GTP levels during the administration of UDCA alone. The serum γ-GTP levels decreased significatly 1 and 2 month after starting UDCA administration in patients with PBC.

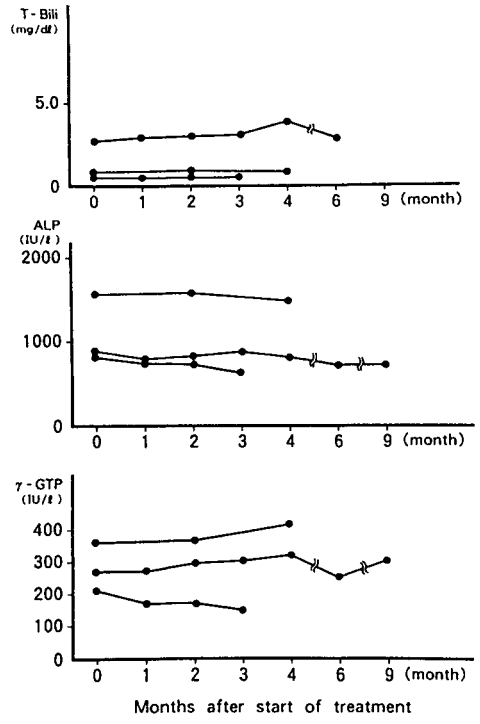

Fig. 8 Serum bilirubin, GPT, ALP and γ-GTP levels during the use of Inchin-ko-to. There were no marked changes in any of the liver function tests.

suggested that, despite the relatively well-preserved synthesis of chenodeoxycholic acid, impaired hepatic secretion of this endogenous bile acid may

lead to its accumulation in the liver and contribute to the development of cirrhosis. The retention of large quantities of chenodeoxychlic acid and cholic acid in the liver and in the systemic circulation may promote hepatic injury and cirrhosis.[15,16] It has been shown that the administration of high doses of taurocholic acid and taurochenodeoxycholic acid can cause hepatocyte injury and cholestasis in the rat,[17] and that UDCA acid may be beneficial in preventing this.[18,19] Then, the main rationale for the use of UDCA is to induce quantitative changes in the bile acid pool.[20] In addition, UDCA apparently has some other beneficial actions, *e.g.*, its choleretic properties,[21-23] cytoprotective effect,[24] and ability to increase hepatic blood flow.[25] Most of the patients studied in previous trials were in the early stages of PBC. Although UDCA had many beneficial effects in these patients, it did not decrease serum bilirubin levels in most of the subjects studied previously. This limitation of UDCA was also reaffirmed in present study (Fig. 4). It has previously been reported that serum bilirubin levels can determine the length of survival of patients with PBC.[11,12] Thus, in the treatment of PBC, it would seen desirable to use UDCA together with an agent that decreases serum bilirubin levels. This study shows that Inchin-ko-to may be a candidate for combined use with UDCA.

Inchin-ko-to is a traditional Chinese medication, which is composed of Sanshishi (Gardeniae), Daio (Rhei Rhizoma) and Inchin-ko (Artemisiae Capillaris Spica). It appears to have many beneficial actions in liver desease, one of which is increasing bile flow in the rat.[13] It also induces the improvement of cholestasis in patients with acute cholestasis. There are many uncertainties about its actions which require future investigation.

For both UDCA and Inchin-ko-to, significant toxicity or side effects have been reported, although occasional diarrhea has been noted. In our patients, the drug was well tolerated and there were no side effects.

We must emphasise that our study was not a controlled randomised double - blind trial. Although our results suggest that long-term treatment with UDCA and Inchin-ko-to is a safe and effective regimen for symptomatic PBC, this must be confirmed in a future randomised double-blind trial.

和文抄録

原発生胆汁性肝硬変（PBC）に対してウルソデオキシコール酸（UDCA）の投与が行われているが，症候性PBC（s-PBC）における減黄効果についての検討は乏しい。UDCAと茵蔯蒿湯との併用により減黄例を経験したので報告する。対象は臨床像と肝生検により診断しえた症候性PBC 4例と無症候性PBC 9例である。UDCAは1日600 mgを，茵蔯蒿湯は1日7.5 gを経口的に投与した。UDCA単独投与では，γ-GTP，ALP，GPTには低下傾向が，特にa-PBCで認められたが，血清ビリルビン値は変化しなかった。一方，茵蔯蒿湯単独投与でも肝機能検査には変化を認めなかった。s-PBC 3例にUDCAと茵蔯蒿湯を併用したところ，全例で血清ビリルビン値は低下し，2例で掻痒感の軽減を認めた。症候性PBCに対しUDCAと茵蔯蒿湯を併用することにより減黄する症例のあることが明らかとなった。

References

1) James, S.P.: Primary biliary cirrhosis. *N. Engl. J. Med.* **312**, 1055-1057, 1985.
2) James, O.F.W.: D-penicillamine for primary biliary cirrhosis. *Gut* **26**, 109-113, 1985.
3) Roll, J.A.: A new treatment for primary biliary cirrhosis ? *Gastroenterology* **89**, 1195-1199, 1985.
4) Poupon, R., Chretien, Y., Poupon, R.E., Ballet, F., Calmus, R. and Darnis, F.: Is ursodeoxycholic acid ah effective treatment for primary biliary cirrhosis ? *Lancet* **II**, 834-836, 1987.
5) Fisher, M.M. and Paradine, M.E.: Influence of ursodeoxycholic acid (UDCA) on biochemical parameters in cholestatic liver disease (Abstract). *Gastroenterology*, 1725, 1986.
6) Wada, T., Koga, Y., Yoshitake, M., Asou, S., Koujiro, R., Arikata, T., Mukouzaka, S., Abe, H. and Tanikawa, H.: Effects of ursodeoxycholic acid on primary biliary cirrhosis. *Rinsyo to Kenkyu* **64**, 2590-2594, 1987.
7) Leuschner, U., Fischer, H., Kurtz, W., Guldutuna, S., Hubner, K., Hellstern, A., Gatzen, M. and Leuschner, M.: Ursodeoxycholic acid in primary biliary cirrhosis : Results of a controlled double-blind trial. *Gastro-*

enterology **97**, 1268-1274, 1989.

8) Basteson, M.C. : Ursodeoxycholic acid (UDCA) for primary biliary cirrhosis (PBC). International Lugano symposium on Biliary Physiology and Diseases : Strategies for the treatment of hepatobiliary diseases. *Falk Symposium* **53**, 17, 1989.

9) Breuer, N., Zotz, R., Sprunken, A. and Goebell, H. : Ursodeoxycholic acid in the treatment of primary biliary cirrhosis and primary sclerosing cholangitis. International Lugano symposium on Biliary Physiology and Diseases : Strategies for the treatment of hepatobiliary diseases. *Falk Symposium* **53**, 20, 1989.

10) Osuga, T., Matsuzaki, Y., Tanaka, N., Aikawa, T., Shoda, J., Doi, M. and Nakano, M. : A new treatment of primary biliary cirrhosis with ursodeoxycholic acid. International Lugano symposium on Biliary Physiology and Diseases : Strategies for the treatment of hepatobiliary diseases. *Falk Symposium* **53**, 24, 1989.

11) Shapiro, J.M., Smith, H. and Schaffner, F. : Serum bilirubin : A prognostic factor in primary biliary cirrhosis. *Gut* **20**, 137-140, 1979.

12) Sasaki, H., Inoue, K., Higuchi, K., Yasuyama, T., Koyata, H., Kuroki, T., Yamamoto, S. and Ichida, F. : Primary biliary cirrhosis in Japan : National survey by the Subcommittee on Autoimmune Hepatitis. *Gastroenterologia Japonica* **20**, 475-485, 1985.

13) Sakagami, Y., Mizoguchi, Y., Miyajima, K., Yamamoto, S., Takeda, S., Aburada, M. and Morisawa, S. : Effects of the chinese prescription "Inchin-ko-to" on intrahepatic cholestasis induced by the cholestatic factor. *Japanese J. Gastroenterol.* **82**, 2608-2612, 1985.

14) Onji, M., Yamashita, Y., Kato, T., Kondo, H., Bandou, N., Horiike, N. and Ohta, Y. : Laparoscopic histopathological analysis of "gentle undulation" findings observed in patients with primary biliary cirrhosis. *Endoscopy* **19**, 17-19, 1987.

15) Scaffner F, Bacchin P.G, Huntterer F, *et al.* : Mechanism of cholestasis. 4. Structural and biochemical changes in the liver and serum in rats after bile duct ligation. *Gastroenterology* **60**, 888-897, 1971.

16) Palmer, R.H. : Bile acids, liver injury and liver diseases. *Arch. Intern. Med.* **130**, 606-617, 1972.

17) Hertz, R., Paumgartner, G., Preisig, R. : Inhibition of bile formation by high doses of taurocholate in the perfused rat liver. *Scand. J. Gastroenterol.* **11**, 741-746, 1976.

18) Kitani, K., Ohta, M. and Kanai, S. : Tauroursodeoxycholate prevents biliary excretion of proteins induced by taurocholate and taurochenodeoxycholate in the rat (Abstract). *Hepatology* **3**, 810, 1983.

19) Kanai, S. and Kitani, K. : Glycoursodeoxycholate is as effective as tauroursodeoxycholate in preventing the taurocholate induced cholastasis in the rat (Abstract). *Hepatology* **3**, : 811, 1983.

20) Batta, A.K., Salen, G., Arora, R., Shefer, S., Tint, G.S., Abroon, J., Eskreis, D. and Katz, S. : Effect of ursodeoxycholic acid on bile acid metabolism in primary biliary cirrhosis. *Hepatology* **10**, 414-419, 1989.

21) Kurtz, W., Leuschner, U. and Langhans, G. : Ursodeoxycholic acid (UDCA) improves hepatic bile acid extraction in the rat. *J. of Hepatol.* **1** (Suppl. 2), 270, 1985.

22) Kitani, S. and Kanai, S. : Effect of ursodeoxycholate on the bile flow in the rat. *Life Science* **31**, 1973-1985, 1982.

23) Kanai, S. and Kitani, K. : Glycoursodeoxycholate is as effective as tauroursodeoxycholate in preventing taurocholate induced cholestasis in the rat. *Res. Commun. Chem. Pathol. and Pharmacol.* **42**, 423-4430, 1983.

24) Koga, Y. : Anti-cholestatic and cytoprotective properties of ursodeoxycholic acid-Studies in vivo and vitro. *Acta hepatologica* **28**, 1597-1604, 1987.

25) Miyaji, K., Akiyama, T., Ito, M., Hosokawa, T. and Shimaji, Y. : Effect of ursodeoxycholic acid on liver function in chronic liver diseases. *Rinsyou to Kenkyu* **53**, 1395-1403, 1976.