



Ursodeoxycholic Acid Therapy in Patients with Primary Biliary Cholangitis with Limited Liver Transplantation Availability

Yazmín Karel Melchor-Mendoza,^{*,**,*} Braulio Martínez-Benítez,^{*}
Aline Mina-Hawat,^{**} Gustavo Rodríguez-Leal,^{**} Ximena Duque,^{**} Segundo Moran-Villota^{***}

^{*} Social Service and Department of Pathology, National Institute of Medical Sciences and Nutrition "Salvador Zubirán", Mexico City.

^{**} Laboratory of Gastro-Hepatology Research, Hospital of Pediatrics, National Medical Center XXI Century, Mexican Institute of Social Security, Mexico.

^{***} Medica Sur Clinic Foundation, Mexico.

ABSTRACT

Introduction. There is little information on survival rates of patients with primary biliary cholangitis (PBC) in developing countries. This is particularly true in Latin America, where the number of liver transplants performed remains extremely low for patients with advanced liver disease who fulfill criteria for liver transplantation. The goal of this study was to compare survival rate of patients with PBC in developing countries who were treated with ursodeoxycholic acid (UDCA) versus survival of patients who received other treatments (OT) without UDCA, prescribed before the UDCA era. **Material and methods.** A retrospective study was performed, including records of 78 patients with PBC in the liver unit in a third level referral hospital in Mexico City. Patients were followed for five years from initial diagnosis until death related to liver disease or to the end of the study. Patients received UDCA (15 mg/kg/per day) (n = 41) or OT (n = 37) before introduction of UDCA in Mexico. **Results.** Response to treatment was higher in the group that received UDCA. In the five years of follow-up, survival rates were significantly higher in the UDCA group than in the OT group. The hazard ratio of death was higher in the OT group vs. UDCA group, HR 8.78 (95% CI, 2.52-30.61); Mayo Risk Score and gender were independently associated with the risk of death. **Conclusions.** The study confirms that the use of UDCA in countries with a limited liver transplant program increases survival in comparison to other treatments used before the introduction of UDCA.

Key words. Ursodeoxycholic acid. Primary biliary cholangitis. Latin America. Survival rates.

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by progressive destruction of intrahepatic bile ducts, which may lead to biliary cirrhosis, portal inflammation, and liver failure.^{1,2} Ursodeoxycholic acid (UDCA) is the only drug approved by the U.S. Food and Drug Administration to treat PBC, with a recommended dosage of 13-15 mg/kg/day.¹⁻³ The use of obeticholic acid is on the horizon.⁴

It has been suggested that UDCA treatment improved the serum liver test results, slowed the histological progress, and improved patients' survival without an or-

thotropic liver transplant.^{5,6} However, the effect of UDCA on survival is still controversial.^{7,8}

At present, studies on PBC have mostly been carried out in Asia, Europe, Australia, and North America, in developed countries with liver transplant programs for PBC.^{2,5-8} However, there is little information about PBC in Latin America. Currently, there are no studies in Mexico or other countries in Latin America that evaluate the medium-term effect of UDCA treatment on survival of patients with PBC.

The aim of this study was to compare survival rates of patients in developing countries with PBC using UDCA versus survival rates of patients who received other drugs (OT) prescribed before the UDCA era.

MATERIAL AND METHODS

Patients

A retrospective study was performed in the Department of Pathology of the National Institute of Medical Sciences and Nutrition Salvador Zubiran in Mexico City, included patients diagnosed with PBC between 1971 and 2011. All patients who were included had histological and biochemical evidence of cholestasis based mainly on nonsuppurative destructive cholangitis and destruction of interlobular bile ducts, alkaline phosphatase (ALP) elevation at least 1.5 times the upper limit normal (ULN), and presence of positive antimitochondrial antibody (AMA). Exclusion criteria were features suggestive of other coexistent liver diseases, including overlap syndrome, alcoholic liver disease, a positive serological test for hepatitis B or C, non-alcoholic steatohepatitis, and hepatocellular carcinoma. The histological stage was assessed using Ludwig criteria: portal hepatitis, bile duct abnormalities, or both are present (stage 1), Periportal fibrosis is present, with or without periportal inflammation (stage 2), bridging fibrosis or necrosis or both (stage 3), and cirrhosis (stage 4).⁹

The following parameters were obtained from medical records: age, gender, associated diseases, symptoms, and liver function test [serum bilirubin levels, albumin, prothrombin time, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST)]. Results of liver function tests were recorded at baseline, one month and one year after starting the treatment. The cut-off points used were: ALP 120 U/L as the upper limit of normal (ULN), 35 U/L for AST and ALT, and 1.0 mg/dL for bilirubin. The lower limit of normal (LLN) for albumin was 3.5 g/dL.¹⁰ Patients had received UDCA (15 mg/kg/per day) since 1992 and before other drugs (OT) as colchicine (n = 28), cholestyramine (n = 18), penicillamine (n = 7), azathioprine (n = 5), or prednisolone (n = 13), at standard doses. In some cases, patients received more than one drug.

Ethical aspects

This study was approved by the Ethics Board of the National Institute of Medical Sciences and Nutrition Salvador Zubiran, Mexico City, Mexico. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

Statistical analyses

In descriptive analyses, data are expressed as means \pm standard deviation, and percentages. Categorical variables

were compared by χ^2 test among both groups and continuous variables by Student t-test. A paired t test was used to compare means before and after one month of treatment. The biochemical response to UDCA or OT was evaluated by comparing proportion of treatment response at one month and at one year after treatment, according to Barcelona criteria (decrease in ALP > 40% of the baseline level or normal level), Paris criteria (ALP level \leq 3 ULN, together with AST level \leq 2 ULN and a normal bilirubin level), Rotterdam criteria (normal bilirubin and albumin concentrations when one or both parameters were abnormal before treatment, or normal bilirubin or albumin concentrations after treatment when both were abnormal at entry), and Toronto criteria (ALP level < 1.76 ULN).^{2,11}

Survival analysis was used: The follow-up started from the date at histological diagnosis of PBC, time zero (t0), and the end point was liver-related death. Time at event was calculated. Patients who did not present the event was censored at the end of the study, also was censored patients who died from causes unrelated to liver failure and patients that were lost at follow-up; also were censored patients referred for liver transplantation at the moment of OLT. Liver-related death was defined as death due to liver failure or death occurring within two months of an episode of variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatic encephalopathy.¹²

Probabilities of survival were estimated by the Kaplan-Meier method. For the univariate analyses, we compared the survival functions of categorical variables using the log-rank test. To compare survival by continuous variables, Cox proportional hazard regression model with one only variable was used.

Multivariate analysis to evaluate the associations between treatments received and the survival function of patients with CBP was done using Cox proportional-hazard risk regression models. Variables with p value less than 0.20 at univariate analysis were included in the multivariable analyses; and in the final model, variables statistically associated with the risk of death or important confounder variables were included.¹³ Model assumptions and good fit were tested. The analysis was performed using the statistical software STATA (version 12.0, STATA Corporation, College Station, TX, USA).

RESULTS

Baseline characteristics

A total of 78 patients matched by age and sex were included: 41 in the UDCA Group and 37 in the OT Group. When comparing the baseline characteristics of the treatment groups (Table 1), a higher concentration of bilirubin

Table 1. Baseline characteristics of the patients in this study.

Characteristic	UDCA Group (n = 41)	OT Group (n = 37)
Age (years)	46.2 ± 9.81	45.6 ± 12.3
Female gender, n(%)	38 (92.7)	35 (94.6)
ALP(ULN)	5.2 ± 3.7	4.0 ± 4.5
Albumin (LLN)	1.0 ± 0.1	1.0 ± 0.2
Bilirubin (ULN)	3.0 ± 3.2	5.0 ± 5.4
AST (ULN)	3.2 ± 1.6	3.2 ± 2.8
ALT (ULN)	3.1 ± 2.0	3.1 ± 2.8
Creatinine (mg/dL)	0.7 ± 0.2	0.6 ± 0.2
Child-Pugh index	6.3 ± 1.0	6.8 ± 1.7
A	20 (48.8)	17 (46.0)
B	16 (39.0)	17 (46.0)
C	5 (12.2)	3 (8.0)
Mayo Risk Score	5.9 ± 1.8	6.8 ± 1.9
Ludwig Histological stage		
I	16 (39.0)	14 (37.8)
II	11 (26.8)	8 (21.6)
III	9 (22.0)	5 (13.5)
IV	5 (12.2)	10 (27.0)

Data are expressed as means ± standard deviation. ALP: alkaline phosphate. ULN: Upper limit of normal. AST: aspartate aminotransferase. ALT: alanine aminotransferase. LLN: lower limit of normal. UDCA: ursodeoxycholic acid and other drugs. OT: other drugs.

and higher Mayo Risk Score were found in the OT group and respect liver damage, in UDCA group fibrosis (n = 20/41) and cirrhosis (n = 5/41) ; and in OT group fibrosis (n = 13/38) and cirrhosis (n=10/38) was found.

Treatment response

After one month of treatment, an intragroup comparison of UDCA group showed a significant reduction in ALP, total bilirubin, AST, and ALT concentration; no difference with statistical significance was observed in the OT group (Table 2). Furthermore, when comparisons after one month post-treatment between groups were done, total bilirubin (ULN) was statistically different; it was higher in the OT group (2.1 ± 2.3 vs. 5.7 ± 6.0 , $p = 0.007$).

Table 3 shows the treatment response at one month and at one year post-treatment in light of the different criteria commonly used to evaluate treatment response in CBP patients. For all criteria, a higher percentage of response was observed in the UDCA group compared to the OT group. Nevertheless, this difference was statistically significant only after one year of the treatment, according to Toronto and Rotterdam criteria.

Table 2. Biochemical indicators of hepatic function before and after one month of treatment.

Variable	UDCA Group (n = 41)			OT Group (n = 37)		
	Baseline	One month post-treatment	Value p ^a	Baseline	One month post-treatment	Value p ^a
ALP (ULN)	5.1 ± 3.7	3.7 ± 2.4	0.005	3.9 ± 4.5	3.4 ± 2.2	0.330
Albumin (LLN)	1.0 ± 0.1	1.0 ± 0.1	0.997	1.0 ± 0.2	1.0 ± 0.2	0.479
Bilirubin (ULN)	3.0 ± 3.3	2.1 ± 2.3	0.014	4.8 ± 5.4	5.7 ± 6.0 ^b	0.276
AST (ULN)	3.2 ± 1.6	2.4 ± 1.2	0.004	2.4 ± 1.0	2.8 ± 1.8	0.229
ALT (ULN)	3.1 ± 2.0	2.3 ± 1.3	0.011	3.1 ± 3.1	2.5 ± 1.6	0.299

Data are expressed as means ± standard deviation. ALP: alkaline phosphate Upper limit of normal (ULN) = 120 U/L, albumin lower limit of normal (LLN) = 3.5 g/dL, aspartate aminotransferase (AST) (ULN = 35 U/L), alanine aminotransferase (ALT) (ULN = 35 U/L), bilirubin (ULN = 1.0 mg/dL). ^a Paired t test.

^b Student t test, $p < 0.05$.

Table 3. Treatment response according to different criteria.

Criteria	At 1 month n (%)			At 1 year n (%)		
	UDCA group	OT group	p value	UDCA group	OT group	p value
Paris ^a	8 (20.0)	2 (6.7)	0.171	8 (20.5)	1 (4.0)	0.078
Barcelona ^b	10 (25.6)	5 (13.9)	0.204	14 (35.9)	6 (21.4)	0.202
Toronto ^c	19 (47.5)	9 (29.0)	0.114	19 (47.5)	6 (23.1)	0.046
Rotterdam ^d	15 (37.5)	7 (20.0)	0.097	20 (51.3)	7 (21.1)	0.009

^a ALP ≤ 3ULN and AST ≤ 2 ULN and normal total bilirubin. ^b ALP minor to 40% of baseline ALP. ^c ALT < 1.76 ULN. ^d Normal total bilirubin or normal albumin if the two had abnormal value at baseline or normal total bilirubin and normal albumin if only one of two was abnormal at baseline.

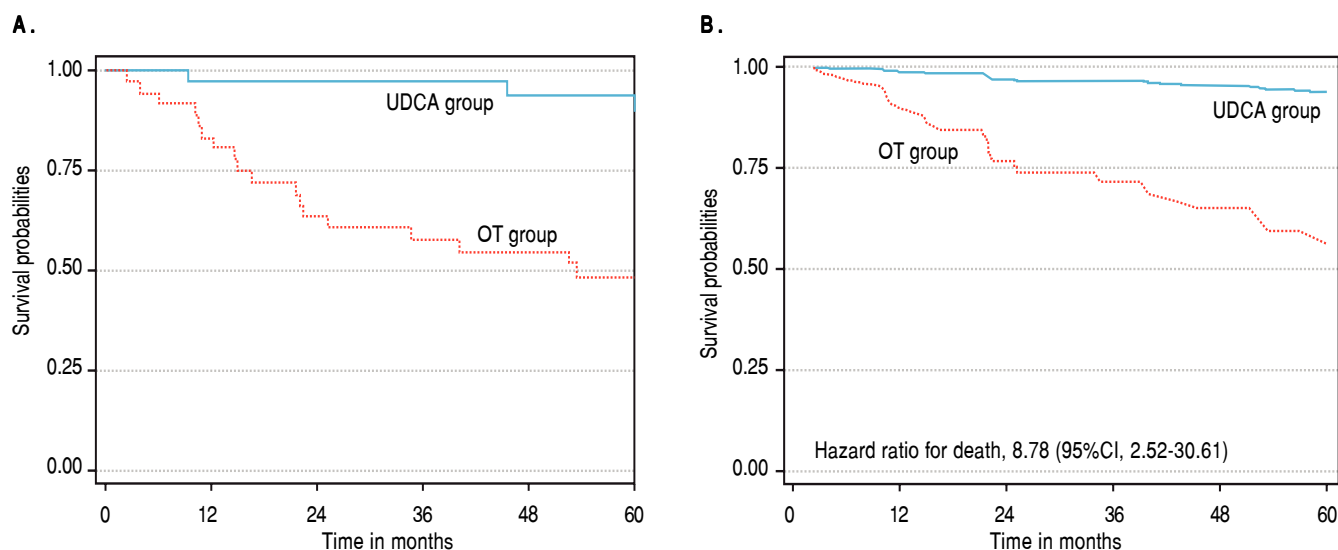


Figure 1. **A.** Survival probabilities estimates by Kaplan-Meier method, in five years of follow-up of CBP patients treated with UDCA and others drugs vs. OT without UDCA. **B.** Adjusted survival curves obtained from a Cox Proportional Hazard Model by treatment (OT vs. UDCA) and letting Mayo Score Risk be the mean value (6.3) and female gender.

Table 4. Risks factors associated with mortality at five years of follow-up in patients with PBC. Multivariate analyses, Cox, proportional hazard model.

Variable	Hazard Ratio ^a	95% CI	p value
Other treatment vs. UDCA treatment	8.78	2.52-30.61	0.001
Baseline Mayo Risk Score ^b	1.68	1.26-2.24	0.000

^aHazard Ratio, adjusted by gender. ^bLetting Mayo Score Risk be centred at the mean value (6.3).

Survival probability

During the follow-up period, 21 patients died from liver-related disease. In the UDCA group, three patients died, while in the OT group 18 died. The survival probability at one year was 0.97 (95% CI, 0.83-0.99) in the UDCA group and 0.83 (95% CI, 0.67-0.92) in the OT group; and the survival probabilities at 5 years were 0.89 (95% CI, 0.70-0.96) in the UDCA group and 0.49 (95% CI, 0.31-0.64) in the OT group, $p < 0.001$ (Figure 1A).

In univariate analysis, gender, total bilirubin (ULN), alanine aminotransferase (ULN), score Child-Pugh, histologic stage (IV vs. I to III), and Mayo Risk Score were factors related to risk of death ($p < 0.20$). In multivariate analyses, treatment, gender, and Mayo Risk Score were associated with risk of death; the HR of the group in the OT treatment vs. patients in the UDCA group was 8.78 (95% CI, 2.52-30.61), $p = 0.001$; patients that received OT died at a rate 8.78 times higher than those patients that received treatment with UDCA, where the Mayo Risk Score and the gender are held constants. In the same way, for each increase of one point in the Mayo Risk Score, the rate of

death for liver disease was higher by 68% after adjustment by treatment group and by gender (Table 4, Figure 1B). Figure 1B shows the difference in survival probabilities to females with 6.3 points in Mayor Risk Score treated with UDCA or OT.

DISCUSSION

Results suggest UDCA treatment as an optimum choice for patients with PBC not suitable for a liver transplant and considering the higher survival probability after five years with UDCA compared to those in the OT group (0.89 vs. 0.49).

Results of this study confirm UDCA as proper treatment for patients with PBC in countries where liver transplants are still limited. Treatment response at one month and at one year of treatment was better in patients treated with UDCA.

In Mexico, patients with histological diagnosis of PBC between 1972 and 1992 showed low probability of survival, 0.75, 0.44, and 0.13 at 1, 5, and 7 years.¹⁴ These probabilities are lower than those reported in other countries.^{5,11,12,15-17}

But survival probabilities at 5 years, 0.89, found in the present study in patients admitted at a third level referral hospital in Mexico City between 1992 and 2011 and treated with UDCA are similar to survival probabilities reported at 5 years by Zhang, *et al.*, 0.86,² ter Borg, *et al.*, 0.87¹⁸ and Kuiper, *et al.*, 0.90,¹² in patients treated with UDCA. Differences in the grade of liver damage, treatment received, and number of patients included could explain differences in survival probabilities. In the studies of the Mexican population, patients treated before 1992 were treated with drugs other than UDCA.

Treatment with 10-15 mg/kg/day UDCA *vs.* a placebo has been evaluated in various clinical essays,¹⁹⁻²⁵ but not all studies report UDCA as beneficial for treating PBC.^{7,8} In the present study, results show a survival difference between the UDCA and OT group.

Different prognostic factors with an impact on survival of PBC patients have been described: degree of hepatic damage at time of diagnostic; serum bilirubin higher than 1.57 mg/dL; serum albumin concentration lower than 3.8 mg/dL; and lack of response to UDCA treatment.^{15,16,26} In present study, UDCA treatment, gender, and Mayo Risk Score had impacts on the mortality of PBC patients. These findings are consistent with other reports.^{2,15,16}

Before the UDCA era, the main reason for hepatic transplants in the United States was PBC. In the last few decades, the number of patients with PBC who require hepatic transplants has diminished by 20%.²⁷ According to U.S. statistics, PBC patients are now the sixth choice for suggested hepatic transplants.²⁸

The use of UDCA therapy to slow histological progression has a greater impact in Latin America because hepatic transplant program development there is very heterogeneous. Presently, hepatic transplants are only performed in 13 of the 19 countries of Latin America.^{29,30}

In some countries, like Mexico, the programs are still being developed and it is exceptional to find a hepatic transplant program more than 10 years old that fulfills all necessary quality criteria. Therefore, it is hard to compare Latin American statistics to European or North American programs. It is necessary to continue to do research that will allow us to better typify PBC patients in Latin American countries and their response to UDCA treatment and to continue to assess the need, benefits, and risks of subjecting PBC patients to liver transplants.

Limitations of our study are related to patient data collected retrospectively; however, selection and recall biases were minimized because information about diagnoses and drug treatment was taken from clinical records.

The study suggests that the use of UDCA improves survival in patients with PBC in Mexico. Further randomized controlled studies should be conducted to evaluate the effect of UDCA therapy on the natural history,

clinical manifestation, and prognosis of patients with PBC in Latin America.

ABBREVIATIONS

- **95% CI:** 95% confidence interval.
- **ALP:** alkaline phosphatase.
- **ALT:** alanine aminotransferase.
- **AMA:** antimitochondrial antibody.
- **AST:** Aspartate aminotransferase.
- **HR:** hazard ratio.
- **LLN:** lower limit of normal.
- **OLT:** orthotopic liver transplantation.
- **OT:** other treatments.
- **PBC:** primary biliary cirrhosis.
- **UDCA:** ursodeoxycholic acid.
- **ULN:** upper limit normal.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

REFERENCES

1. Czul F, Peyton A, Levy C. Primary biliary cirrhosis: therapeutic advances. *Clin Liver Dis* 2013; 17: 229-42.
2. Zhang LN, Shi TY, Shi XH, Wang L, Yang YJ, Liu B, Gao LX, et al. Early biochemical response to ursodeoxycholic acid and long-term prognosis of primary biliary cirrhosis: results of a 14-year cohort study. *Hepatology* 2013; 58: 264-72.
3. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *Hepatology* 2009; 50: 291-308.
4. Corpechot C. Primary biliary cirrhosis beyond ursodeoxycholic acid. *Semin Liver Dis* 2016; 36: 15-26.
5. Corpechot C, Carrat F, Bonnard AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. *Hepatology* 2000; 32: 1196-9.
6. Corpechot C, Abenavoli L, Rabahi N, Chrétien Y, Andréani T, Johanet C, Chazouillères O, et al., et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008; 48: 871-7.
7. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gludd C. Ursodeoxycholic acid for primary biliary cirrhosis. *Cochrane Database Syst Rev* 2012; Dec 12: CD000551. DOI: 10.1002/14651858.CD000551.pub3.
8. Chan CW, Gunsar F, Feudjo M, Rigamonti C, Vlachogiannakos J, Carpenter JR, Burroughs AK, et al. Long-term ursodeoxycholic acid therapy for primary biliary cirrhosis: a follow-up to 12 years. *Aliment Pharmacol Ther* 2005; 21: 217-26.
9. Ludwig J, Dickson ER, McDonald GS. Staging of chronic non-suppurative destructive cholangitis (syndrome of primary biliary cirrhosis). *Virchows Arch A Pathol Anat Histol* 1978; 379: 103-12.
10. Kratz A, Feraro M, Sluss PM, Lewandrowski KB. Laboratory reference values. *N Engl J Med* 2004; 351: 1548-63.
11. Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *J Hepatol* 2011; 55: 1361-7.

12. Kuiper EMM, Hansen BE, de Vries RA, den Ouden-Muller JW, van Ditzhuijsen TJM, Haagsma EB, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. *Gastroenterology* 2009; 136: 1281-7.
13. Hosmer D, Lemeshow S, Susanne M. Applied Survival Analysis. Regression Modeling of Time-to-Event data. Second Edition. John Wiley & Sons, Inc. Hoboken; New Jersey. USA: 2008.
14. Morán S, Rodríguez-Leal G, Marín-López E, Arista J, Poo JL, Vargas-Vorackova F, Kershenobich D, et al. Cirrosis biliar primaria: características clínicas y supervivencia en la población mexicana. *Rev Gastroenterol Mex* 1996; 61: 212-19.
15. Floreani A, Caroli D, Variola A, Rizzotto ER, Antoniazzi S, Chiaramonte M, Cazzagon N, et al. A 35-year follow-up of a large cohort of patients with primary biliary cirrhosis seen at a single centre. *Liver Int* 2011; 31: 361-8.
16. Poupon RE, Bonnard AM, Chrétien Y, Poupon R. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. *Hepatology* 1999; 29: 1668-71.
17. Papastergiou V, Tsochatzis EA, Rodríguez-Peralvarez M, Thalassinou E, Pieri G, Manousou P, Germani G, et al. Biochemical criteria at 1 year are not robust indicators of response to ursodeoxycholic acid in early primary biliary cirrhosis: results from a 29-year cohort study. *Aliment Pharmacol Ther* 2013; 38: 1354-64.
18. ter Borg PC, Schalm SW, Hansen BE, van Buuren HR, Dutch PBC Study Group. Prognosis of ursodeoxycholic acid-treated patients with primary biliary cirrhosis: results of a 10-yr cohort study involving 297 patients. *Am J Gastroenterol* 2006; 101: 2044-50.
19. Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology* 2006; 130: 715-20.
20. Combes B, Carithers RL Jr, Maddrey WC, Lin D, McDonald MF, Wheeler DE, Eigenbrodt EH, et al. A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1995; 22: 759-66.
21. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. *N Engl J Med* 1991; 324: 1548-54.
22. Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, Michieletti P, et al. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology* 1994; 19: 1149-56.
23. Lindor KD, Dickson ER, Balducci WP, Jorgensen RA, Ludwig J, Murtaugh PA, Harrison JM, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. *Gastroenterology* 1994; 106: 1284-90.
24. Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, Lindor KD, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. *Hepatology* 2005; 42: 1194-202.
25. Shi TY, Zhang LN, Chen H, Wang L, Shen M, Zhang X, Zhang FC. Risk factors for hepatic decompensation in patients with primary biliary cirrhosis. *World J Gastroenterol* 2013; 19: 1111-18.
26. Azemoto N, Kumagi T, Abe M, Konishi I, Matsuura B, Hiasa Y, Onji M. Biochemical response to ursodeoxycholic acid predicts long-term outcome in Japanese patients with primary biliary cirrhosis. *Hepatol Res* 2011; 41: 310-17.
27. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ, American Association for Study of Liver Diseases. Primary biliary cirrhosis. *Hepatology* 2009; 50: 291-308.
28. Crosignani A, Battezzati PM, Invernizzi P, Selmi C, Prina E, Podda M. Clinical features and management of primary biliary cirrhosis. *World J Gastroenterol* 2008; 14: 3313-27.
29. Garcia VD, Garcia CD, Santiago-Delpin EA. Organ transplants in Latin America. *Transplant Proc* 2003; 35: 1673-74.
30. Hepp J, Innocenti FA. Liver transplantation in Latin America: current status. *Transplant Proc* 2004; 36: 1667-8.

Correspondence and reprint request:

Braulio Martínez-Benítez, M.D.

Department of Pathology, National Institute of

Medical Sciences and Nutrition "Salvador Zubirán", Mexico City.

Vasco de Quiroga, No. 15, Belisario Domínguez Sección XVI,

Tlalpan, 14080 Mexico City, Mexico.

E-mail: braulioimb77@yahoo.com.mx