ANNALS of Hepatology

ORIGINAL ARTICLE

January-February, Vol. 11 No.1, 2012: 100-106

Effect of cirrhosis at baseline on the outcome of type 1 autoimmune hepatitis

Graciela Landeira,* Silvia Morise,** Eduardo Fassio,*
Margarita Ramonet,** Estela Álvarez,*** Patricia Caglio,** Cristina Longo,* Nora Domínguez*

* Liver Unit, Hospital Nacional Profesor Alejandro Posadas, El Palomar, Provincia de Buenos Aires, Argentina.
** Pediatric Liver Unit, Hospital Nacional Profesor Alejandro Posadas, El Palomar, Provincia de Buenos Aires, Argentina.
*** Pathology Service, Hospital Nacional Profesor Alejandro Posadas, El Palomar, Provincia de Buenos Aires, Argentina.

ABSTRACT

Material and methods. With the aim of analyzing the influence of presence of cirrhosis at baseline on the outcome, we revised the evolution of a cohort of patients with type 1 autoimmune hepatitis, prospectively followed at a single hospital. 139 patients (113 females, 26 males), median age 45.7 years, interquartile range 13-59 years, were followed-up for a median period of 58 months (interquartile range 27-106). **Results.** At baseline, 55 patients had cirrhosis and they were significantly older, had lower prothrombin activity and serum albumin than patients without cirrhosis. In contrast, patients without cirrhosis had significantly higher bilirubin, AST and ALT levels at diagnosis time. There was no significant difference in the follow-up time between patients with and without cirrhosis at baseline and either in the percentage of patients receiving immunosupresor treatment (80 *vs*. 91%, respectively) or in the response to therapy (complete response in 82 *vs*. 95%, respectively). However, patients with cirrhosis had a significantly lower probability of remaining free of cirrhosis complications (49.1% at 102 months, 95%CI, 35.5-67.9% *vs*. 86.7%, 95%CI, 77.1%-97.5%, respectively) (p = 0.0000) and a significantly lower overall survival at 120 months (67.1%, 95%CI, 51.3-87.6 *vs*. 94.4%, 95%CI, 86.9-100%, respectively) (p = 0.003) than those without cirrhosis at presentation. **Conclusion.** Patients with type 1 autoimmune hepatitis and cirrhosis at presentation have a lower survival than those without cirrhosis despite a similar response to treatment.

Key words. Prognosis in autoimmune hepatitis. Survival of autoimmune hepatitis. Autoimmune cirrhosis. Cirrhosis complications. Liver mortality.

INTRODUCTION

Autoimmune hepatitis (AIH) is a relapsing chronic liver disease of unknown etiology that appears in genetically predisposed individuals. It is characterized by a female predominance, elevated aminotransferases, hypergammaglobulinemia, circulating autoantibodies, interfase hepatitis on the liver biopsy and a good response to immunosuppressive therapy.[1,2]

An expert panel, the International Autoimmune Hepatitis Group (IAHG) has published 2 reports containing descriptive criteria for the diagnosis[3,4] and a scoring system to consider patients as having a definite or probable AIH, according to the final revised score.[4] More recently, the IAHG has proposed simplified criteria for the diagnosis,[5] but these are not massively used yet. The efficacy of immunosuppressive treatment (IST) and its impact on the natural history in severe clinical forms of AIH have been recognized for decades based on the results of randomized clinical trials performed many years ago.[6-10] However, despite the long time past since the first descriptions of the disease, some particular aspects still persist unclear regarding natural history. There is a controversy about the evolution of patients who already present a cirrhotic stage early in the diagnosis time. This is a common situation, observed in 30-40% of patients.[11] Some years ago, Roberts, *et al.*, from the Mayo Clinic in Rochester, USA, analyzed the response to steroid treatment in type 1 AIH and reported that rates of remission, re-

Correspondence and reprint request: Dr. Eduardo Fassio
Belgrano 1.102, Ramos Mejía
Provincia de Buenos Aires, Argentina
Ph.: 54 11 4659-8731
E-mail: efassio@intramed.net

Manuscript received: April 21, 2011.
Manuscript accepted: October 03, 2011.

lapse after drug withdrawal and treatment failure were comparable in patients with and without cirrhosis at baseline.[12] More importantly, they found that ten-year survival was not different between those with and without cirrhosis at entry. This concept has been sustained since then in reviews by Dr Czaja from Rochester;[2] has not been discussed in the last AASLD practice guidelines[13] and only recently was challenged by the findings by Feld, *et al.*, from Toronto University, in Canada, who observed that patients with cirrhosis at baseline had a lower 10-year survival than those without cirrhosis at presentation.[14]

Our hospital harbors 2 Liver Units: one Pediatric and one Adult Liver Unit, working as tertiary Hepatology centers. Thus, we have been able to follow prospectively a large series of AIH patients. In this study, we revised one single-center large cohort of type 1 autoimmune hepatitis patients to analyze the influence of cirrhosis at baseline on the evolution and survival.

MATERIAL AND METHODS

Between 1981 and December 2004, 200 patients were given a diagnosis of AIH at the Hospital Nacional Profesor Alejandro Posadas. Six patients were seropositive for anti-LKM_1 antibodies and were excluded from the analysis because it has been claimed that prognosis of type 2 AIH might be different than type 1 AIH.[15] The other patients were positive for anti-nuclear antibodies (ANA) and/or anti-smooth muscle antibodies (ASMA) and/or anti-neutrophil cytoplasmic antibodies (ANCA) and they were considered for the study and their charts were reviewed. Patients who were positive for anti-mitocondrial antibodies as well were considered as having an overlapping syndrome and excluded from the analysis. Patients who had been diagnosed before 1993 were re-evaluated and only those who fulfilled the descriptive criteria of the IAHG.[3] were included. Since 1993 and later on, we have confirmed the diagnoses of AIH based on the reports of the IAHG.[3,4] Patients who had been lost to the follow-up or whose outcome (alive, death or liver transplant) were unknown, were contacted by phone or conventional mail (some patients had been referred to our hospital for the diagnostic work-up since other provinces and they are being followed-up at present at their cities by the referring doctors). Those patients who could not be contacted were excluded from further analysis. 139 type 1 AIH patients are in active follow-up or their final outcome is well known and they constitute the population of our study (Table 1).

Table 1. Clinical, biochemical and histological characteristics at the presentation of 139 patients with type 1 autoimmune hepatitis.

Variable	
Age (years)*	46 (13-59)
Female/male gender (n)	113/26
Total bilirubin (mg/dL)*	3.4 (1.2-8.0)
AST (IU/L x ULN)*	8.8 (3.8-26.0)
Prothrombine activity (%)*	64 (48-83)
Albumin (g/dL)*	3.27 (2.8-3.7)
Gamma globulin (g/dL)*	3.0 (2.1-4.3)
Extrahepatic manifestations (%)	27.0
Cirrhosis (%)	45.8
Acute hepatitis-like onset (%)	49
Chronic onset (%)	35
Cirrhosis complications onset (%)	16

*Median (interquartile range). **UNL:** Upper limit of normal.

All the patients were studied for HBsAg by enzyme linked immunosorbent assay (ELISA) and were negative. All the patients were studied for anti-HCV using second or third generation ELISA and 4 of them were positive. All of them were persistently seronegative for HCV RNA by semi-automated PCR (Cobas Amplicor HCV 2.0®, Roche Molecular Systems). They were treated with IST and a complete response was observed in all of them.

All the histological examinations were performed by the same pathologist (E.A.). Since 1995, the semiquantitative evaluation of the inflammatory activity (grading) and fibrosis (staging) was done using the Ishak classification.[16] All the liver biopsy specimens studied before 1995, originally analyzed through the Knodell score,[17] were re-evaluated and classified according to Ishak system. Presence of cirrhosis was confirmed by standard histological criteria or, in patients with persistent coagulopathy that did not ameliorate with IST and therefore, liver biopsy was contraindicated, by unequivocal imaging diagnosis.

IST was indicated to those patients who presented necroinflammatory activity at the diagnosis time: increase of AST/ALT levels more than 2-fold the upper normal limit plus hypergammaglobulinemia and moderate to severe interfase hepatitis in the liver biopsy. Patients who did not show inflammatory activity at presentation (normal aminotransferases, portal hepatitis or mild periportal hepatitis in the liver biopsy) were not given IST. Initial treatment consisted of prednisone monotherapy or a combination of prednisone and azathioprine in the usual doses,[2] followed by the tapering of corticosteroids in

the usual period until reaching the maintenance dose. After obtaining the remission, we did not indicate steroid withdrawal but maintain patients with the lowest dose able to sustain them without presenting a relapse (usually 4-10 mg/day of prednisone alone or in combination with 50 mg/day of azathioprine). This low-dose prednisone schedule was maintained indefinitely.

Complete response and relapse were defined according to IAHG criteria.[4] Complete response is defined as marked improvement of symptoms and return of serum AST or ALT, bilirubin and immunoglobulin values completely to normal within 1 year and sustained for at least a further 6 months on maintenance therapy (or at least 50% improvement of all liver test results during the first month of treatment, with AST or ALT levels continuing to fall to less than twice the upper normal limit within 6 months during any reductions toward maintenance therapy), or a liver biopsy specimen at some time during this period showing at most minimal activity. Relapse is defined as an increase in serum AST or ALT levels of greater than twice the upper normal limit or a liver biopsy showing active disease, with or without reappearance of symptoms, after a complete response as defined above.

During follow-up, patients underwent a clinical and laboratory (including AST, ALT, bilirubin, albumin, prothrombin time and activity, immunoglobulins) control every 3-6 months. Cirrhotic patients underwent an abdominal ultrasonography and α-feto protein level assessment every 6 months and an upper endoscopy at baseline for screening of esophageal varices.

For the analysis of our aim, patients were separated in 2 groups: presence or absence of cirrhosis at the diagnosis time. The end points were:

- Occurrence of cirrhosis complications during the follow-up: ascites, hemorrhage associated with portal hypertension, portosystemic encephalopathy and bacterial infections. Events like ascites or encephalopathy that were present in the clinical onset and were eliminated with the IST were not considered.
- Overall survival.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Although this is a retrospective analysis of prospectively collected data, an informed consent had been obtained from each patient in the time of liver biopsy and all the data were used in a confidential manner.

Statistical analysis

Variables were described using measures of central tendency (median and mean) and variability (interquartile range, standard deviation, minimal and maximal values) for continuous level parameters; and using percentages for categorical level parameters. Quantitative variables were compared between cirrhosis and non cirrhosis groups using Wilcoxon rank-sum test and qualitative variables, using difference of two binomial proportions. Survival curves for both groups, patients with and without cirrhosis at presentation, were calculated using Kaplan-Meir method and were compared by log-rank test. A p value < 0.05 was considered as statistically significant.

RESULTS

Characteristics of patients at baseline

Table 1 shows the main clinical, biochemical and histological features at presentation time in the 139 patients with type 1 AIH. Gender was female in 113 patients, male in 26 (female:male ratio, 4.3). Median age was 45.7 years old (minimal age 2, maximal age 79), with a bimodal distribution (Figure 1). Immunological extrahepatic manifestations were found at the diagnosis time or during the follow-up in 37 out of 139 patients (27%). The more frequent extrahepatic diseases were thyroiditis in 10 patients, reumatoid arthritis in 6, vasculitis in 5, autoimmune thrombocytopenic purpura in 4, systemic lupus erythematosus in 3.

At presentation time, liver biopsies were performed in 100 out of 139 patients, and median stage (according to Ishak classification) was 4 (interquar-

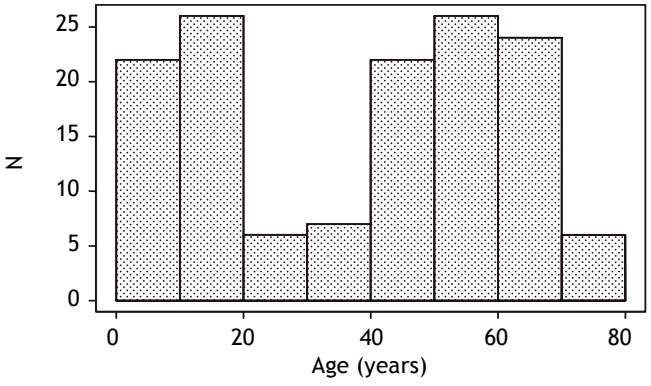

Figure 1. *Age distribution at diagnosis time in a series of 139 patients with type 1 autoimmune hepatitis.*

tile range 3-5), cirrhosis being shown in 35. Among the 39 patients in whom liver biopsies could not be taken (usually because of coagulopathy), imaging methods inequivocally showed features of cirrhosis in 20 of them. Therefore, among 120 patients in whom this result could be evaluated, 55 (45.8%) presented a cirrhotic stage at presentation and 65 did not. In the other 19 patients, a liver biopsy could not be performed and the imaging methods did not show unequivocal signs of cirrhosis.

Outcomes after immunosuppressive treatment

The median follow-up was 57.7 months (minimal 0.4, maximal 231.9 months, interquartile range 27.2 to 105.9 months). IST was given to 118 out of 139 patients (85%) and a complete response was obtained in 91%, a partial response in 4% and treatment failure was observed in 5%. During follow-up, 20 patients presented a relapse, mostly (n = 15) associated with a treatment withdrawal (decided by the patients and against the medical indication). In the other 5 cases, relapses were associated with postpartum period in 2 and reductions of IST doses in 3 other patients. During follow-up, 36 patients presented one or more cirrhosis complications (ascites in 21, severe infections like bacteremia or spontaneous bacterial peritonitis in 19, encephalopathy in 16, upper digestive bleeding related to portal hypertension in 11). Eighteen patients died, 10 because of non liver related deaths, 8 because of liver related deaths. Eight patients underwent a liver transplantation, because of cirrhosis complications and/or irreversible hepatic failure. The survival for the whole group of 139 type 1 AIH patients was 81.7% at 120 months (95% CI, 72.7%-91.8%) (Figure 2).

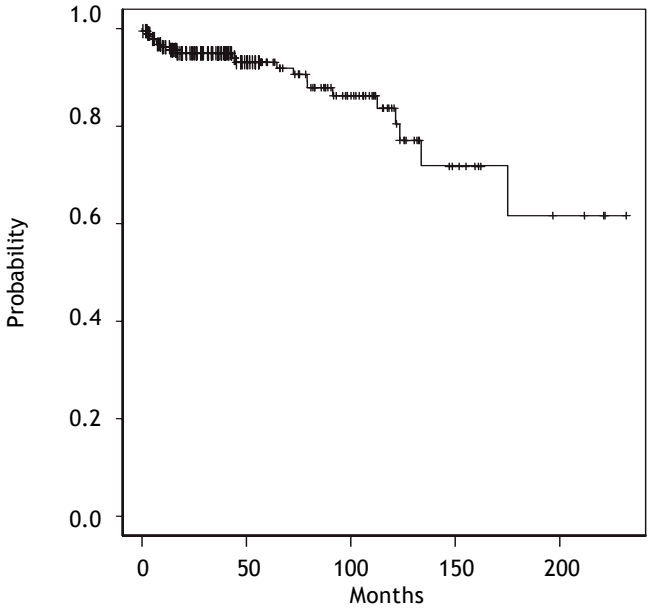

Figure 2. *Overall survival for the whole group of 139 patients with type 1 autoimmune hepatitis. Survival was 81.7% at 120 months (95% CI, 72.7-91.8%).*

Table 2 shows the basal clinical and biochemical features of patients with presence or absence of cirrhosis at diagnosis time. Patients with cirrhosis were significantly older than those without cirrhosis [median age (interquartile range) 50.1 (29.2-79.5) years old *vs.* 32.4 (10.8-49.2) years old, respectively] (p = 0.0002). Prothrombin activity and serum albumin were significantly lower in patients with cirrhosis than in those without cirrhosis at baseline (Table 2). In contrast, bilirubin, AST and ALT levels were significantly higher in patients without cirrhosis than in those with cirrhosis (Table 2), probably due to a slightly higher proportion of patients showing an acute hepatitis-like presentation in the group without cirrhosis.

There was no significant difference in the follow-up time between patients with and without cirrhosis at baseline [median (minimal-maximal) 56.2 months (0.4-231.9) *vs.* 66.2 months (5.4-196.7), respectively] (NS) and either in the proportion of patients receiving IST or in the response to treatment (Table 2).

Complications of cirrhosis and survival

During follow-up, 27 out of 55 patients with cirrhosis at presentation and 7 out of 65 patients without cirrhosis had cirrhosis complications. The probability of remaining free of cirrhosis complications was significantly lower in patients with cirrhosis at baseline (49.1% at 102 months, 95% CI, 35.5-67.9%) than in those without cirrhosis at presentation (86.7% at 102 months, 95% CI, 77.1%-97.5%) (p = 0.0000) (Figure 3).

During follow-up, 13 out of 55 patients with cirrhosis at presentation and 2 out of 65 patients without cirrhosis died (5 and 2 patients, respectively, due to liver related events). The other 3 deaths occurred in the subgroup of 19 patients where we could not define presence or absence of cirrhosis (one death due to a liver event). The figure 4 shows that patients with cirrhosis at diagnosis time had a significantly lower survival at 120 months than those without cirrhosis at presentation (67.1%, 95% CI, 51.3-87.6% *vs.* 94.4%, 95% CI, 86.9-100%, respectively) (p = 0.003).

Table 2. Baseline characteristics and treatment result of patients with type 1 AIH according to presence or absence of cirrhosis at presentation.†

	Cirrhosis (n = 55)	No cirrosis (n 65)	p
Age (years)*	50.1 (29.2-79.5)	32.4 (10.8-49.2)	0.0002
Female/male gender (n)	45/10	50/15	NS
Total bilirubin (mg/dL)*	2.4 (1.2-4.7)	4.3 (0.9-10.6)	0.0171
AST (IU/L x ULN)*	5.7 (2.1-11.4)	13.2 (4.9-32.9)	0.0016
ALT (IU/L x ULN)*	4.8 (2.0-9.8)	10.9 (4.1-39.2)	0.0002
Prothrombin activity (%)*	63.0 (42.5-76.0)	70.0 (54.5-90.5)	0.0124
Albumin (g/dL)*	3.2 (2.6-3.6)	3.5 (3.1-3.7)	0.0098
Clinical onset (acute/chronic/CC) (%)	40/38/22	61/35/4	NS
Indication of IST (%)	80	90.8	NS
Complete response to IST (%)	82	94.7	NS

†Analyzed in 120 patients. *Median values (interquartile range). **AIH:** Autoimmune hepatitis. **ULN:** Upper limit of normal. **CC:** Cirrhosis complications. **IST:** Immunosuppressive treatment. NS: not significant.

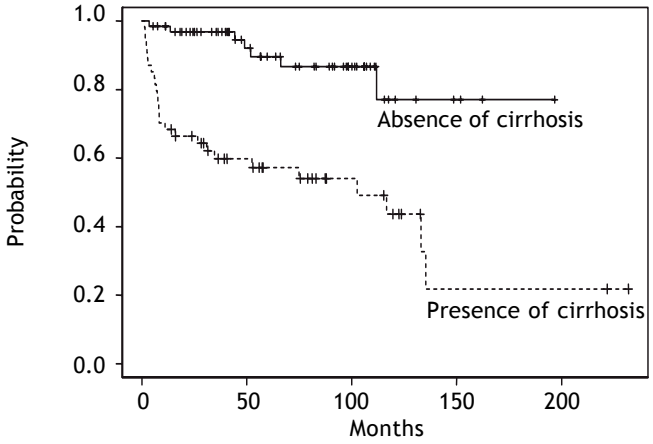

***Figure 3**. The probability of remaining free of cirrhosis complications was significantly lower in patients with type 1 autoimmune hepatitis and cirrhosis at baseline (49.1% at 102 months, 95% CI, 35.5-67.9%) than in those without cirrhosis (86.7% at 102 months, 95% CI, 77.1-97.5%) (p = 0.0000).*

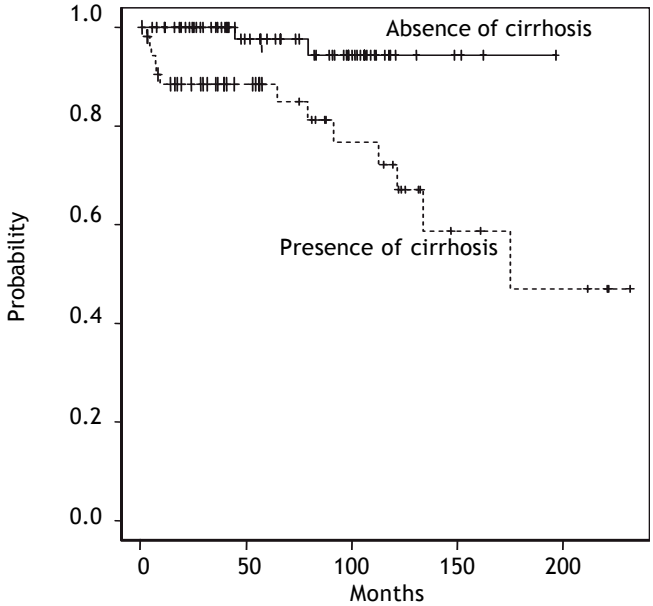

***Figure 4**. Overall survival was significantly lower in patients with type 1 autoimmune hepatitis and cirrhosis at diagnosis time than in those without cirrhosis (67.1%, 95%CI, 51.3-87.6%* vs. *94.4%, 95%CI, 86.9-100%, respectively, at 120 months) (p = 0.003). Red line: presence of cirrhosis. Green line: absence of cirrhosis.*

DISCUSSION

In this retrospective analysis of a large series of type 1 autoimmune hepatitis patients prospectively followed in a single center, we found that presence of cirrhosis at presentation did influence the evolution and prognosis, being associated with a higher incidence of decompensation and a lower survival.

Our population of type 1 AIH patients shows clinical, demographic, biochemical and histological features that are similar to those described in the international literature, with a female predominance (female:male ratio 4.3:1), immunological extrahepatic manifestations in 27%, median AST levels 9 times above the ULN, median gamma globulin levels 3.0 gr/dL and acute hepatitis-like presentation in 49%. The characteristics of our hospital harboring a Pediatric and an adult Liver Units gives us the possibility of studying the whole spectrum of type 1 AIH patients and we confirmed a bimodal age distribution, with one peak in the first 2 decades of life and another peak in the 6th and 7th decades (Figure 1). The percentage of patients receiving IST (85%), the response to therapy (complete response in 91%) and the

global survival [93.1% at 60 months (95% CI, 0.89-0.97) and 80.4% at 120 months (95% CI, 0.71-0.92)] were also comparable to previous studies.[2,18]

We do not have a clear explanation for the discrepancy in the long term outcome among patients with autoimmune hepatitis and cirrhosis at presentation in the Mayo Clinic report[12] and the other two, the Toronto group study[14] and ours. The 3 studies analyzed a large population of AIH patients (n = 128, 125 and 139, respectively). All the patients had a type 1 AIH in the Mayo Clinic study and ours, while there were only 5 cases of type 2 AIH included in the Toronto study. The criteria for indicating IST, the definitions for response to treatment and percentages of responses observed were similar as well in the 3 hospitals. Among the subgroup of cirrhotic patients at baseline, a complete response to treatment was found in 78% of them by Roberts, *et al.* in the Mayo study,[12] and in 82% of them by us. More recently, the Mayo Clinic group has published that patients who presented more than one relapse episode during follow-up had a poor prognosis, associated with more frequent hepatic deaths or need for transplantation.[19] This finding does not explain the lower survival observed among our cirrhotic patients, because we do not indicate treatment withdrawal (as Dr Czaja group usually does[2,12]). As a consequence, only a minority of our patients (n = 20) has presented relapses (mostly only one episode).

One variable that is very difficult to analyze in these retrospective studies is the level of aminotransferases during the long-term follow-up. A recent study from Japan has shown that elevated serum alanine aminotransferase levels (≥ 40 IU/L) during the follow-up period were associated with progression to decompensated cirrhosis;[20] and a previous one had found that the inability to have consistently normal aminotransferases during remission was associated with cirrhosis development.[21] The definition of complete response according to the IAHG report included these 2 possibilities: persistently normal AST or ALT values; or aminotransferase values less than twice the upper normal limit during reductions in steroid doses in the maintenance therapy.[4] This subtle difference in the response to treatment has not been analyzed in the 3 retrospective studies that we are comparing. Therefore, further prospective studies should be performed to address if the long term outcome is better in cirrhotic HAI patients who achieve completely normal AST and ALT values during IST than in those who show aminotransferase values less than twice the UNL.

The percentage of ten-year survival that we found in our cirrhotic patients (67.1%, 95% CI, 51.3-87.6%) is comparable to that described by Feld, *et al.*, in Toronto (61.9%, 95% CI, 44.9%-78.9%).[14] Furthermore, percentages of ten-year survival were also very similar among noncirrhotic patients from our study and the Canadian study (94.4%, 95% CI, 86.9-100%, and 94.0%, 95% CI, 87.4-100%, respectively). Finally, a recently published Swedish multicentric study also concluded that cirrhosis at diagnosis was associated with worse outcome and the overall survival in the AIH cohort was significantly lower compared to an age- and gender-matched population from Sweden, 15 years after the diagnosis.[22]

CONCLUSION

In spite of patients with autoimmune hepatitis and cirrhosis show similar patterns of response to immunosupresive treatment than those without cirrhosis, their long-term prognosis seems to be worse. These findings should be further investigated in prospective studies and especially addressing subtle differences in the response to maintenance therapy (completely normal *vs.* mildly elevated aminotransferases).

ABBREVIATIONS

- **AST:** aspartate aminotransferase.
- **ALT:** alanine aminotransferase.
- **CI:** confidence intervals.
- **AIH:** autoimmune hepatitis.
- **IAHG:** International Autoimmune Hepatitis Group.
- **IST:** immunosuppressive treatment.
- **ANA:** anti-nuclear antibodies.
- **ASMA:** anti-smooth muscle antibodies.
- **ANCA:** anti-neutrophil cytoplasmic antibodies.
- **ELISA:** enzyme linked immunosorbent assay.
- **PCR:** polymerase chain reaction.
- **NS:** not significant.
- **ULN:** upper limits of normal.

DISCLOSURE OF INTEREST

None of the authors have received any financial support or grants for the realization of the study.

REFERENCES

1. McFarlane IG. Definition and classification of autoimmune hepatitis. *Semin Liver Dis* 2002; 22: 317-24.

2. Czaja AJ. Treatment of autoimmune hepatitis. *Semin Liver Dis* 2002; 22: 365-77.
3. Johnson PJ, McFarlane IG, convenors, on behalf of the panel. Meeting Report: International Autoimmune Hepatitis Group. *Hepatology* 1993; 18: 998-1005.
4. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cançado EL, Chapman RW, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999; 31: 929-38.
5. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, et al. Simplified criteria for the diagnosis of autoinmune hepatitis. *Hepatology* 2008; 48: 169-76.
6. Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q J Med* 1971; 40: 159-85.
7. Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. *Lancet* 1973; 1: 735-7.
8. Soloway RD, Summerskill WHJ, Bagentoss AH, Geall MG, Gitnick GL, Elveback LR, Schoenfield LJ. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatment and early prognosis. *Gastroenterology* 1972; 63: 820-33.
9. Wright EC, Seef LB, Berk PD, Jones EA, Plotz PH. Treatment of chronic active hepatitis. An analysis of three controlled trials. *Gastroenterology* 1977; 73: 1422-30.
10. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. *Gut* 1980; 21: 78-83.
11. Heneghan MA, McFarlane IG. Current and novel immunosupresive therapy for autoimmune hepatitis. *Hepatology* 2002; 35: 7-13.
12. Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. *Gastroenterology* 1996; 110: 848-57.
13. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; 51: 2193-213.
14. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. *Hepatology* 2005; 42: 53-62.
15. Homberg JC, Abuaf N, Bernard O, Islam S, Alvarez F, Khalil SH, Poupon R, et al. Chronic active hepatitis associated with antiliver/kidney microsome antibody type 1: a second type of "autoimmune" hepatitis. *Hepatology* 1987; 7: 1333-9.
16. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; 22: 696-9.
17. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981; 1: 431-5.
18. Czaja AJ, Carpenter HA. Distinctive clinical phenotype and treatment outcome of type 1 autoimmune hepatitis in the elderly. *Hepatology* 2006; 43: 532-8.
19. Montano-Loza AJ, Carpenter HA, Czaja AJ. Consequences of treatment withdrawal in type 1 autoimmune hepatitis. *Liver Int* 2007; 507-15.
20. Miyake Y, Iwasaki Y, Terada R, Takagi S, Okamaoto R, Ikeda H, Sakai N, et al. Persistent normalization of serum alanine aminotransferase levels improves the prognosis of type 1 autoimmune hepatitis. *J Hepatol* 2005; 43: 951-7.
21. Verma S, Gunuwan B, Mendler M, Govindrajan S, Redeker A. Factors predicting relapse and poor outcome in type 1 autoimmune hepatitis: role of cirrhosis development, patterns of transaminases during remission, and plasma cell activity in the liver biopsy. *Am J Gastroenterol* 2004; 99: 1510-6.
22. Werner M, Wallerstedt S, Lindgren S, Almer S, Björnsson E, Bergquist A, Prytz H, et al. Characteristics and long-term outcome of patients with autoimmune hepatitis related to the initial treatment response. *Scand J Gastroenterol* 2010; 45: 457-67.