Digestive and Liver Disease 43 (2011) 309–313

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Alkaline phosphatase normalization is associated with better prognosis in primary sclerosing cholangitis

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ARTICLE INFO

Article history:
Received 3 October 2010
Accepted 8 December 2010
Available online 19 January 2011

Keywords:
Alkaline phosphatase
Primary sclerosing cholangitis
Ursodeoxycholic acid

ABSTRACT

Background: Primary sclerosing cholangitis results in elevated but fluctuating serum alkaline phosphatase levels that occasionally return to normal.
Aims: To investigate the frequency of normalization of alkaline phosphatase in newly diagnosed primary sclerosing cholangitis patients and the subsequent clinical outcomes.
Methods: Records of newly diagnosed primary sclerosing cholangitis patients were examined retrospectively for laboratory values and clinical end points (cholangiocarcinoma, liver transplantation and death) within 10 years of diagnosis. Data from a recent prospective ursodeoxycholic acid treatment trial were also studied.
Results: Eighty-seven patients met the inclusion criteria. Normalization of alkaline phosphatase was seen in 35 (40%) patients. Five (14%) patients with normalization reached an end point whereas 17 (33%) of the patients with persistent elevation reached an end point ($P = 0.02$). Ursodeoxycholic acid was used similarly by both groups. When the investigative criteria were applied to a prospective trial, there was again a significant relationship between normalization of alkaline phosphatase and survival in patients receiving ursodeoxycholic acid ($P < 0.01$) and the placebo group ($P = 0.02$).
Conclusions: Serum alkaline phosphatase was found to normalize in a high proportion of newly diagnosed primary sclerosing cholangitis patients. This was significantly associated with a better prognosis in a retrospective cohort and when data from a prospective treatment trial was evaluated.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic liver disease. It is characterized by fibrosis of the intrahepatic and extrahepatic biliary tree leading to bile duct strictures in the absence of other causes [1]. PSC currently has a median survival of approximately 17 years after diagnosis, primarily due to progression to end-stage liver disease [2]. Medical therapy has proven disappointing, with no currently available agents shown to improve survival. Liver transplantation is the only treatment option to improve long-term prognosis, with 10-year survival rates of 70% after transplant [3]. As such, natural history models have been developed and validated in order to predict prognosis of individual patients. The model developed at the Mayo Clinic incorporates age, bilirubin, albumin, aspartate aminotransferase (AST) and history of variceal bleeding [4].

Ursodeoxycholic acid (UDCA) has been studied extensively for use in PSC and primary biliary cirrhosis (PBC). UDCA therapy has been correlated with improved 10-year survival in PBC [5]. Recent work has shown that PBC patients with a biochemical response to UDCA, usually defined as a reduction in the alkaline phosphatase (ALP) level, have higher survival rates than non-responders [6,7]. This improvement in survival has not been reported in PSC, despite UDCA improving laboratory values including ALP [8]. This has been consistent at varying dosing levels [9,10].

Persistent elevation of ALP is the laboratory finding that often prompts the investigations that result in the diagnosis of PSC, especially in the setting of inflammatory bowel disease. As such, it is routinely measured during clinical follow up and generally remains abnormal [11]; however it will occasionally normalize spontaneously [12,13]. It was unclear if this was meaningful in regards to prognosis. The aim of this study was to determine the frequency of

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1590-8658/$36.00
doi:10.1016/j.dld.2010.12.008

normalization of ALP in patients with PSC and investigate whether this is associated with liver transplant-free survival.

2. Methods

After approval from the appropriate institutional review board, electronic medical records from the Mayo Clinic in Rochester, MN were retrospectively reviewed for all patients coded for the first time with a diagnosis of "sclerosing cholangitis" from January 1, 1997 to December 31, 2001. Only patients that received a new diagnosis of PSC at our centre within the time period and had at least 1 year of clinical follow-up were considered eligible for inclusion. The criteria used to diagnose PSC were the presence of cholestatic liver disease and characteristic findings of biliary duct dilatation and narrowing on a cholangiographic investigation that was reviewed by a radiologist or gastroenterologist at our institution. Other causes of elevated serum ALP and sclerosing cholangitis were excluded at the time of diagnosis.

Exclusion criteria included age less than 18 years at diagnosis, a previous diagnosis of a chronic liver disease or a prior liver transplant, evidence of cholangiocarcinoma or need for liver transplantation within 1 year of diagnosis and death prior to 1 year of follow-up.

The data compiled from the medical record included gender, age at diagnosis, cholangiogram results and whether stricture dilatation was performed, liver biopsy at diagnosis and the corresponding Ludwig stage [14] if one was performed, concomitant inflammatory bowel disease and presence of symptoms attributable to PSC (pruritus, abdominal pain and fatigue severe enough to limit activities). Laboratory values performed at our institution were also collected; this included serum ALP, AST, total bilirubin, albumin and international normalized ratio (INR). The use of UDCA and the highest dosing level in mg/kg were recorded. End points considered were the development of cholangiocarcinoma, liver transplantation or death if they occurred within 10-years after the initial diagnosis. Times to end point were calculated from the date of the diagnostic cholangiogram to the date of the procedure that diagnosed the cholangiocarcinoma, the date of the liver transplant procedure or the date of death.

ALP levels were compared to the upper limits of normal (ULN) for all laboratory testing performed in the study period and calculated as a ratio. ALP was considered to be persistently abnormal if the levels were continuously greater than a ratio of 1 and considered to normalize if there were one or more values with a ratio of 1 or less.

These criteria were also applied to data collected in a recent PSC treatment trial [10]. This was a prospective, double-blinded trial of high-dose UDCA (28–30 mg/kg/day). Liver enzymes were assessed every 3 months over 3 years in a standardized fashion. Similar primary endpoints were utilized as in the current study, with the additional consideration of development of varices and progression to cirrhosis as clinical endpoints.

2.1. Statistics

Median and inter-quartile range was calculated for all initial characteristics and laboratory values of the included patients. When presented, median values are followed by the inter-quartile range parenthetically unless otherwise noted. As the ULN for ALP varied due to a change in assays during the study period, all values presented were calculated as a ratio with the test result compared to ULN. For comparison of baseline characteristics and biochemical values, Pearson chi-square tests were used for binomial values and Wilcoxon rank-sum tests were used for continuous variables where appropriate.

Event-free survival was estimated by the Kaplan–Meier method and compared between the group with normalization of ALP levels and the group with persistently abnormal levels using the Wilcoxon log-rank test. Data on patients that did not reach an end point were censored at the time of their last follow-up visit or 10-years after their diagnosis, dependent on which was earlier. Kaplan–Meier analysis was also used to determine time to ALP normalization and compared between the group that received UDCA and the group that did not using the Wilcoxon log-rank test. Cox proportional-hazards regression modelling was performed to evaluate covariates (initial levels of ALP, AST, total bilirubin and Mayo risk score) that may have influenced time until endpoint or normalization as indicated. Initial biopsy scores were not included in this analysis as the data were not available for more than 10% of patients. The association between normalization and survival in the UDCA treatment trial data was assessed statistically using Fischer's exact test.

All statistical testing was done at the conventional two-tailed level of 0.05.

3. Results

A total of 87 patients met the inclusion criteria and were incorporated in the study. The clinical features and biochemical findings of the patient population at the time of entry are included in Table 1. The median follow-up time was 7.3 years (4.5–8.9). A total of 22 (25%) reached a clinical end point within the study period, with 5 (6%) developing cholangiocarcinoma, 10 (11%) undergoing a liver transplant and 7 (8%) dying without cholangiocarcinoma or transplantation.

Normalization of ALP was observed in 35 (40%) of the patients. The median time to normalization was 1.03 years (0.35–3.95). There were no significant differences in sex, age, concomitant inflammatory bowel disease or the presence of symptoms due to PSC between the groups (Table 2). Twenty-five (71%) of those that normalized had 3 or more serum ALP assays within normal range during their follow-up period, with a median of 5 (2–12). Six of the patients that normalized had persistently normal ALP values during the remainder of their follow-up period, with a median of 4 assays (4–7) over a median of 3.5 years (2.4–5.1).

Table 1
Clinical characteristics and initial laboratory values of the study population. Alkaline phosphatase results are shown as a ratio compared to upper limit of normal range for each assay. Normal ranges for laboratory values were: aspartate aminotransferase 8–48 U/L, total bilirubin 0.1–1 mg/dL, international normalized ratio 0.9–1.2 and albumin 3.5–5 g/dL.

	Patients $n = 87$
Male sex, *n* (%)	64 (74)
Follow-up years[a]	7.3 (4.5–8.9)
Age at diagnosis[a]	44 (33–52)
Symptomatic at diagnosis, *n* (%)	37 (43)
Inflammatory bowel disease, *n* (%)	66 (76)
Biopsy at diagnosis, *n* (%)	65 (75)
Biopsy stage[a]	2 (1–3)
Laboratory values at diagnosis	
Alkaline phosphatase (ULN ratio)[a]	2.8 (1.8–4.6)
AST (U/L)[a]	74 (44.5–125)
Total bilirubin (mg/dL)[a]	1.1 (0.7–1.8)
INR[a]	1 (0.9–1)
Albumin (g/dL)[a]	4 (3.7–4.3)
Initial MELD score[a]	8 (7–10.5)
Initial Mayo risk score[a]	0.12 (0–0.84)

AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; ULN, upper limit of normal.

[a] Median with inter-quartile range included parenthetically.