Research Article

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The independent effects of fatigue and UDCA therapy on mortality in primary biliary cirrhosis: Results of a 9 year follow-up

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Background & Aims: Long-term outcome in primary biliary cirrhosis (PBC) remains unclear. Whilst response to ursodeoxycholic acid (UDCA) is associated with good outcome, this effect is not universal. Early data from our group have suggested that one factor associated with a poorer outcome in PBC is fatigue. The aim of this study was to explore the inter-relationship between UDCA use, response, and fatigue in determining outcome over 9 years in a unique, comprehensive patient cohort.

Methods: Longitudinal prospective study of a geographically-defined complete cohort of PBC patients in North-East England and matched community controls.

Results: Survival to death or transplant was significantly lower in PBC patients than in the case–control population (88/136 (65%) v 114/136 84% (p <0.001 by log-rank test), with better survival in UDCA responders (defined using the Paris criteria) than in patients not treated with UDCA at study outset. Compared to the whole control group survival was reduced in PBC patients fatigued at study outset but not in those without fatigue (p <0.0001); an effect independent of the beneficial effect of UDCA response and of conventional parameters of liver disease severity. UDCA responders without fatigue at the study outset had a 9 year survival which was identical to controls. Patients without fatigue at the study outset who developed fatigue during follow-up had significantly worse survival than patients who remained without fatigue throughout (p <0.05). Fatigued controls had worse survival than non-fatigued controls (p = 0.05).

Conclusions: Survival in a comprehensive cohort of PBC patients is substantially reduced compared with case-matched community controls. Development of fatigue and non-treatment with UDCA were specifically (and independently) associated with increased risk of death in PBC.

Keywords: Fatigue; Outcomes research; Quality of life; Liver cirrhosis; Biliary.
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Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; FIS, Fatigue Impact Scale.

Introduction

Recent studies of the epidemiology of the autoimmune liver disease primary biliary cirrhosis (PBC) have identified a significantly increased mortality rate over long-term follow-up when compared to relevant population data [1,2]. Two independent, broadly-based, population studies from the UK put the standardised mortality ratio (SMR) at between 2.7 and 2.9, suggesting that, historically at least (the follow-up for the patients in these studies dates as far back as the 1970s) the increased risk to life associated with PBC is substantial. It is now widely accepted that long-term treatment with ursodeoxycholic acid (UDCA) is associated with significant reduction in liver-related mortality in PBC patients and therefore plays an important role in the reduction of the mortality burden [3,4]. One of the less predictable observations of the long-term study of the epidemiology of PBC in North-Eastern England was that a significant proportion of the increased mortality risk resulted from non-liver causes, suggesting that PBC patients may be at increased risk of death from causes not apparently directly related to the development of advanced liver disease and its associated complications [1].

At present it is unclear what factors are responsible for increased non-liver-related mortality in PBC. Additional studies, performed in the large cohorts demonstrating increased SMR, have shown that increases in malignant disease, myocardial infarction, and stroke are not responsible (hepato-cellular carcinoma is seen at an increased rate in the PBC population but even at this increased rate does not substantially influence overall survival) [2,5–8]. In 2006 we reported the 4 year follow-up of a discrete, geographically-defined, cohort of PBC patients originally identified in order to determine the prevalence and severity of fatigue in PBC [9–11]. Base-line study of this complete and representative patient cohort had demonstrated significantly higher levels of fatigue in PBC patients than in closely-matched community controls and that the degree of that fatigue was unrelated to the severity of underlying liver disease. The 4 year follow-up suggested that the degree of fatigue at study outset was associated with the subsequent risk of death. In the current study we report the 9-year follow-up of this important patient cohort, and explore the relationship between symptom onset, symptom severity, response to UDCA therapy (a concept not established at the interim follow-up point), and risk of death in PBC.

Subjects and Methods

Study subjects

The original study cohort consisted of those patients (n = 136) attending the Newcastle PBC clinic who resided within the geographical area NE1-NE25 (Newcastle-upon-Tyne and surrounding suburbs). This geographical area was chosen to reflect local referral patterns in order to ensure that the study cohort was complete, consisting, as it did, of a comprehensive cross-section of PBC patients. This approach allowed us to identify a fully representative PBC population not subjected to confounding referral bias which might occur using a whole cohort approach (in addition to local referrals our service takes specialist referrals from all over the UK) [12,13]. In the original description of this cohort, fatigue severity was assessed using the Fatigue Impact Scale (FIS) [14], a measure fully validated for use in PBC [15]. Extended clinical information available for the patients at study outset, including UDCA usage and liver biochemical parameters, has been outlined previously [9,10]. The study controls were identified prospectively from primary physician age- and sex-registers and were fully matched (in each case the non-PBC patient of the same sex closest in age to the index PBC patient was invited to participate). This approach led to a very high degree of matching for sex, age, and location of residence (with implications for socio-economic class). The median FIS for the PBC population in the base-line study was 40 (maximum possible 160). For the purposes of follow-up (in an interim follow-up published in 2006 and in the current study) presence of fatigue was defined as FIS >40 (median value at baseline assessment for the whole PBC population) at the appropriate assessment point. PBC patients with an FIS $\geqslant$40 at the study outset were defined as the "with fatigue group" and FIS <40 the "without fatigue group" [9].

For the current follow-up study, PBC patients were sent a comprehensive symptom and health assessment tool including FIS. Use of this symptom assessment tool is now a routine part of the clinical management of patients within our PBC clinical service [16]. Where patients had died, comprehensive additional information regarding clinical events prior to death was gathered from hospital records, primary health care records, and death certificates to supplement the study documentation. Using a previously adopted approach for cause of death assignation, [1] an independent investigator (AA-R), blinded as to the fatigue status of the patient, examined all case documentation for each patient who died and independently ascribed the principal cause of death. Anonymised information regarding survival status, but not follow-up symptom severity or cause of death, was available for the community controls. Ethical approval for this study was granted by the local research ethics committee.

Statistical analysis

Survival following the original cohort study was assessed using Kaplan–Meier analysis and the impact of individual parameters assessed using the Log-Rank test. Independence of the parameters impacting on survival was assessed using Cox survival regression. Comparisons of biological parameters between groups was performed with parametric and non-parametric t-test as appropriate for the nature of the population value distributions. Proportions of patients in relevant sub-groups were compared using Fishers Exact Test.

Results

The original PBC cohort consisted of 136 patients, 93 of whom were alive at the 9 year follow-up point; 78 of the survivors (84%) participated in a symptom follow-up study. Complete follow-up data sets to the censor point (date of death or transplant or full clinical information at the censor point) were therefore available on 89% of the original cohort, survival only data were available on the remaining 11% (none of the non-participating patients had undergone transplantation during the follow-up period). Survival data only were available on the community controls. Survival over 9 years of follow-up was significantly lower in the PBC patient cohort (43 deaths (32%)) than in the control cohort (22 deaths (16%), p <0.005, Fig. 1A). A further six patients underwent liver transplantation during the follow-up period, all for prognostic reasons in the context of advanced disease rather than for the treatment of symptoms. One of the transplanted

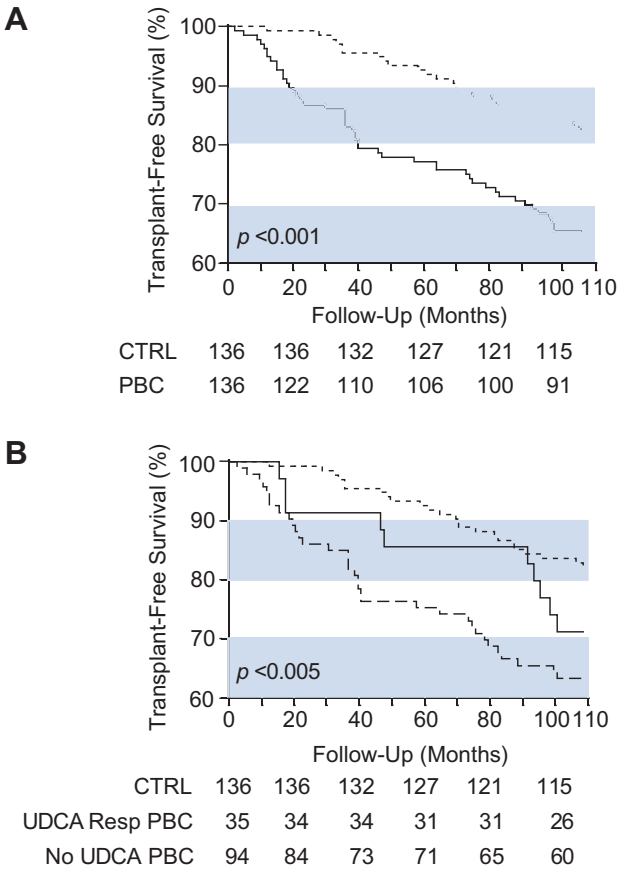

Fig. 1. Impact of diagnosis of PBC and UDCA treatment on survival. Survival to death or transplantation over 9 years of follow-up for (A) the full geographically-defined PBC patient cohort (solid line) and the case controls (dotted line) first reported in 2000 [9], (B) UDCA responders as defined by the Paris criteria (solid line) [3], and UDCA-untreated patients in 2000 (broken line) in comparison with the case control group. Comparison is by the log-rank test.

patients died (in the peri-operative period). A total of 48 patients (35%) therefore reached the primary study end-point of death or transplantation (p <0.0005 vs controls).

In 2000, 42 of the patients in the study had received UDCA therapy for at least 1 year (median dose of UDCA 600 mg (range 300–1200 mg). The relatively low doses of UDCA being received by patients reflected then current practice. Of the 42 stable UDCA recipients, 35 (83%) would fall into the category of UDCA responders using the recently defined Paris criteria [3]. Survival to death or transplant in UDCA responders in 2000 was not statistically different from the community control population (Fig. 1B). Survival to death or transplant in the UDCA-untreated group was, in comparison, significantly impaired compared with controls. In this cohort the number of UDCA non-responders was low (7) precluding meaningful analysis of the impact of UDCA non-response (as opposed to non-treatment with UDCA) on their survival. No UDCA-responding patient required transplantation during the study follow-up period.

The 4 year follow-up of this cohort had suggested that the "with fatigue PBC patient group" (FIS >40) at study outset had significantly reduced survival compared with the "without fatigue group" (FIS <40). Initially, therefore, we re-assessed survival patterns over 9 years of follow-up in relation to base-line fatigue