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Long term outcome and response to therapy of primary biliary cirrhosis—autoimmune hepatitis overlap syndrome☆

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See Editorial, pages 251–252

***Background/Aims*: Whether primary biliary cirrhosis (PBC)—autoimmune hepatitis (AIH) overlap syndrome requires immunosuppressive therapy in addition to ursodeoxycholic acid (UDCA) is a controversial issue.**

***Methods*: Seventeen patients with simultaneous form of strictly defined overlap were followed for 7.5 years. First-line treatment was UDCA alone (UDCA) in 11 and combination of immunosuppressors and UDCA (UDCA + IS) in 6.**

***Results*: Characteristics at presentation were not significantly different between the 2 groups. In the UDCA + IS group (f-up 7.3 years), biochemical response in terms of AIH features (ALT < 2ULN and IgG < 16 g/L) was achieved in 4/6 and fibrosis did not progress. In the UDCA group, biochemical response was observed in three patients together with stable or decreased fibrosis (f-up 4.5 years) whereas the eight others were non-responders with increased fibrosis in four (f-up 1.6 years). Seven of these eight patients subsequently received combined therapy for 3 years. Biochemical response was obtained in 6/7 and no further increase of fibrosis was demonstrated. Overall, fibrosis progression in non-cirrhotic patients occurred more frequently under UDCA monotherapy (4/8) than under combined therapy (0/6) ($P = 0.04$).**

***Conclusions*: Combination of UDCA and immunosuppressors appears to be the best therapeutic option for strictly defined PBC-AIH overlap syndrome.**

***Keywords*: Primary biliary cirrhosis; Autoimmune hepatitis; Autoimmunity; Overlap syndrome; Ursodeoxycholic acid; Corticosteroids**

1. Introduction

Primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH) are classically viewed as distinct liver diseases. However, patients presenting with clinical, biochemical, serological, and/or histological features reminiscent of both diseases, either simultaneously or consecutively, have been repeatedly recognised [1–5]. The term overlap syndrome is used to describe these settings [6–10]. Unfortunately, lack of universal agreement on what precisely constitutes a PBC-AIH overlap syndrome has generated considerable confusion in the literature. In 1998,

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we proposed strict diagnosis criteria and found an overlap syndrome prevalence of 9% in a large series of PBC patients [8]. It is generally assumed that these criteria provide a diagnostic template that can be consistently applied [11] allowing to address the numerous questions raised by the PBC-AIH overlap syndrome. Treatment is one of the unresolved issues and whether overlap syndrome requires immunosuppressive therapy in addition to ursodeoxycholic acid (UDCA) remains controversial. On one hand, our preliminary findings [8] and those of Lohse et al. [9] have suggested that adjunction of immunosuppressive therapy was beneficial and tragic consequences of a missed opportunity of instituting immunosuppressive therapy in patients with PBC-AIH overlap syndrome have occasionally been reported [12]. On the other hand, Joshi et al. found that response to UDCA therapy in strictly defined PBC-AIH overlap syndrome patients was similar to patients with PBC without features of AIH [13].

Randomized controlled trials are the best way to address therapeutic issues. However, such trials are virtually unfeasible in a restricted subgroup of a relatively rare disease. Despite their obvious limitations, retrospective non-randomized studies may provide useful information in this context. Thus, to further clarify the optimal management of this subgroup of PBC, we report here our detailed experience of the long-term outcome (median follow-up longer than 7 years) of patients with simultaneous variant of PBC-AIH overlap syndrome treated with different regimen, i.e. UDCA alone or combination of UDCA and immunosuppressors, with a special emphasis on AIH biochemical response and fibrosis progression.

2. Patients and methods

2.1. Study population

Charts of the 190 patients with PBC who consecutively presented at our Liver Unit from 1982 to 2001 and who had a minimum follow-up of 1.5 years were reviewed. Patients with overlap syndrome were identified according to the criteria we proposed in 1998 [8]. PBC-AIH overlap syndrome was strictly defined by the association of PBC and AIH. For diagnosis of each disease, presence of at least 2 of the 3 accepted criteria was required. PBC criteria were the following: (1) alkaline phosphatase (AP) levels at least two times the upper limit of normal values (ULN) or γ glutamyltranspeptidase (GGT) levels at least five times the ULN, (2) a positive test for antimitochondrial antibodies (AMA), (3) a liver biopsy specimen showing florid bile duct lesions. AIH criteria were the following: (1) alanine aminotransferase (ALT) levels at least five times the ULN, (2) serum immunoglobulin G (IgG) levels at least two times the ULN or a positive test for smooth muscle antibodies (ASMA), (3) a liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis. In addition, AIH score was determined [14].

Only simultaneous forms of overlap syndrome were considered because consecutive forms are less frequent and raise different diagnostic and therapeutic issues.

According to these criteria, 17 patients (8.9%), including the 11 patients we described in 1998 [8], had a simultaneous form of PBC-AIH overlap syndrome among our PBC population. Data from laboratory or other diagnostic investigations were obtained at the initial and at follow-up visits (usually twice a year) after the initiation of therapy.

2.2. Study design (see Fig. 1)

Median follow-up was 7.5 years [2.0–13.5]. Initial management has been individually decided by the physician in charge of the patient. Because the optimal type of treatment was not known, the managing physician was free to decide whether he will treat first with UDCA monotherapy (13–15 mg/kg/day in divided doses given with meals) (UDCA group) or with combination of UDCA (13–15 mg/kg/day) and immunosuppressors (IS + UDCA group). Immunosuppression regimen was corticosteroid based. Initial dose of predniso(lo)ne was 0.5 mg/kg/day and then progressively tapered when ALT levels were decreased by more than 50%; secondarily and according to the usual guidelines for treatment of AIH, azathioprine or mycophenolate mofetil was added as a corticosteroid sparing agent in most patients. Complete biochemical response of the AIH component was defined by ALT levels lower than twice the ULN [15] and IgG levels lower than 16 g/L. A combined treatment was subsequently proposed to the patients of the UDCA group who did not respond after at least 6 months of UDCA monotherapy (Fig. 1). Liver biopsy was performed in case of incomplete biochemical response and systematically after at least 2 years of follow-up.

2.3. Histopathological assessment

A special attention was paid to activity of chronic hepatitis. As previously done by us and others in PBC [8,16] we used the METAVIR score [17,18] which is based on lobular and interface inflammation to evaluate inflammatory activity from 0 to 3 (A0, no histological activity; A1, mild activity; A2, moderate activity; A3, severe activity). Fibrosis was also graded by using the METAVIR score on a five point scale: 0, no fibrosis; 1, portal fibrosis without septa; 2, few septa; 3, numerous septa without cirrhosis; 4, cirrhosis. Liver tissue specimen was reviewed by a single pathologist (D.W). Progression of fibrosis was defined by an increase of at least one unit of the fibrosis score.

2.4. Statistics

Quantitative data were expressed as median-range. Comparisons were made by using non-parametric tests: the Mann–Whitney rank sum test and the Wilcoxon rank sum test for paired data. Ratios were compared by using the chi-square (χ^2) test. Differences with a P value <0.05 were considered significant.

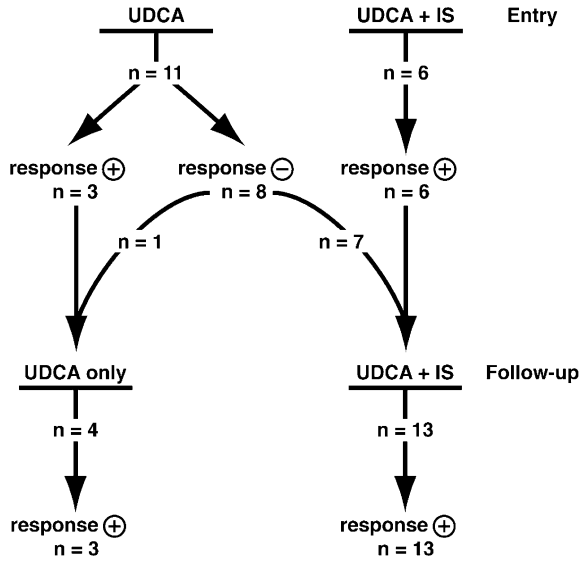

Fig. 1. Treatment regimen [UDCA alone (UDCA) or UDCA and immunosuppressors (UDCA + IS)] and biochemical response defined by ALT levels lower than twice the upper normal limit.