Management options for patients with primary biliary cirrhosis (PBC) who have progressive disease despite treatment with ursodeoxycholic acid (UDCA) remain unsettled. Indeed, a 2009 guideline issued by the American Association for the Study of Liver Diseases did not specify criteria by which such patients should be identified or treatment approaches that should be considered [1,2]. In contrast to the favorable prognosis in patients who respond biochemically and histologically to UDCA, non responders (approximately 30—40% of patients treated with UDCA) remain at risk for development of liver failure [3]. As a result, more than 300 patients with PBC continue to be added to the transplant waiting list in the United States each year [4].

The study by Rabahi et al. published in this issue of Gastroentérologie Clinique et Biologique (Clinics and Research in Hepatology and Gastroenterology) adds to a small number of provocative reports suggesting that it is possible to identify PBC patients with progressive disease despite UDCA and offer them adjuvant therapy that may reduce the rate of disease progression [5].

The investigators identified 15 patients who had well defined PBC and who had responded inadequately to at least 12 months of treatment with UDCA (13–15 mg/kg/d). An inadequate response was defined as persistent elevation of alkaline phosphatase above 250 U/L (normal < 110 U/L), or AST > 70 IU (normal < 35) or total serum bilirubin > 17 micromol/L with conjugated bilirubin > 7 micromol/L, and moderate or severe lymphocytic interface hepatitis on repeat liver biopsy. Patients with cirrhosis and bilirubin levels greater than 51 micromol/L were excluded.

The study group represented approximately 10% of their overall PBC population. As the authors note, the cohort had distinctive clinical characteristics compared with patients with classical PBC. They tended to be younger (average age 42), often had pruritus (80% patients) and had marked inflammation on liver biopsy (100% had moderate to severe lymphocytic hepatitis). None of the patients had serologic features suggesting that they had autoimmune hepatitis or overlap syndrome.

Patients were treated with budesonide (6 mg/d) and mycophenolate mofetil (1.5 g/d) in addition to UDCA. All patients received supplemental calcium, vitamin D, a bisphosphonate and rifampin, if they had disturbing pruritus. Patients were seen at three to six month intervals and had repeat liver biopsies after three years. Biopsies were read by one pathologist who had no knowledge of the patient’s laboratory data or clinical status. Patients also underwent yearly transient elastography (Fibroscan, Echosens, Paris).

After three years of follow-up, six of the 15 patients (41%) achieved complete normalization of liver biochemical tests while seven others (47%) had significant improvement compared with baseline. The proportion of patients with moderate to severe necro-inflammatory activity (A2—A3 using the Metavir system) decreased significantly from 100 to 30% while the proportion of patients with moderate to severe fibrosis (F2—F3 using the Metavir system) decreased significantly from 80 to 40%. The authors reported that the average liver stiffness value after three years (7.2 kPa) excluded the presence of extensive fibrosis or cirrhosis, although they did not report yearly changes in individual patients.
No adverse effects of treatment were observed. There were no overt signs of hypercorticoidism and bone density in the femoral neck and lumbar spine was unchanged after three years.

A number of earlier reports have described experience with adjuvant therapy in patients with an inadequate response to UDCA. Agents that have been evaluated include budesonide [6], colchicine [7], methotrexate [8,9], moexipril [10], mycophenolate mofetil [11,12], tetrathiomolybdate [13], and silymarin [14]. All of these were short-term trials and most were observational. As a result, none has established a benefit on long-term outcomes such as development of cirrhosis or transplant-free survival. Results on surrogate and intermediate markers (such as liver biochemical tests and histologic changes) have been mixed and correlation of these measures to long-term clinical outcomes is imperfect. Thus, at present, the role of adjuvant therapy is unproven.

Despite these limitations, the clinical course of the 15 patients described in the present report provides tantalizing support for the ability to identify a subset of patients with PBC who benefit from combined therapy with UDCA, mycophenolate mofetil and budesonide. The concordant benefits on liver biochemical tests and liver histology are difficult to explain away solely as an artifact of random effects or sampling variability on liver biopsy. Liver disease in these patients appears to have improved. While unproven, we believe that they are better off than having been left on UDCA until progressive liver disease would have left liver transplantation as the only option.

As the authors point out, it is not clear whether we can expect randomized controlled trials evaluating long-term outcomes to provide clarity on the benefits and safety of adjuvant therapy. Such studies would be difficult to conduct since most patients with PBC respond well to treatment with UDCA and have normal survival for at least 20 years [3]. Nevertheless, enthusiasm for adjuvant approaches must be tempered by the small number of patients, the short duration of follow-up, and potential for side-effects. Although no side effects were reported in the current study, mycophenolate mofetil has a number of known adverse effects including gastrointestinal upset, bone marrow suppression, a risk of congenital malformations and potentially infections and neoplasia.

Further studies clarifying subgroups of patients with PBC who might respond to adjuvant therapy would be helpful. Much more controversial is what should be done now for patients who seem to be progressing to liver transplantation despite UDCA. Patients should be managed on an individual basis, ideally in a center of excellence and in a clinical study. We advocate a repeat liver biopsy to document histologic activity and fibrosis progression. Despite the risks of a liver biopsy and the potential for sampling variation, liver biopsies continue to provide valuable insight into histologic disease activity and fibrosis progression to guide management.

We believe it is reasonable to offer a trial of adjuvant therapy to patients with histologic deterioration and persistently abnormal liver biochemical test after advising them of the risks and uncertain benefits. For many years, our group has added colchicine and methotrexate to UDCA [7,9] but the combination approach described in the current report has the advantage of using drugs that are familiar to most hepatologists. We follow patients with serial liver biochemical tests and repeat a liver biopsy depending upon the clinical and biochemical response. We stop adjuvant therapy in patients who do not appear to be responding.

Until further data are available, the optimal approach to the recognition and management of UDCA non responders will remain unclear. The current report should provide strong encouragement for efforts to identify subsets of patients with PBC who are at risk for progressive disease and who might benefit from additional therapy.

References


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