Remission with ursodeoxycholic acid of type 1 autoimmune hepatitis resistant to azathioprine and steroids

Jean-Charles DUCLOS-VALLÉE (1), Vincent DI MARTINO (2), Alain CAZIER (3), Eric BALLOT (4), Catherine JOHANET (5), Ana Maria YAMAMOTO (5), Jean-François EMILE (6), Catherine GUETTIER (6), Pierre COUTAREL (7), Jean-François CADRANEL (7)


SUMMARY
Combination therapy with steroids and azathioprine is the reference treatment for autoimmune hepatitis, but potential adverse effects are numerous and intolerance can occur. We report a patient with a well-documented type 1 autoimmune hepatitis intolerant to corticosteroids and azathioprine therapy, in whom eight years of ursodeoxycholic acid monotherapy was associated with biochemical and histological remission.

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utoimmune hepatitis is a liver disease of unknown etiology often affecting young women. It is a chronic hepatitis characterized by hypergammaglobulinemia and serum autoantibodies, and is unrelated to viral infection, hepatotoxic drugs or hereditary disorders. The natural outcome is generally poor, with cirrhosis at presentation in 50 to 90% of patients [1].

The preferred treatment includes corticosteroids and azathioprine [1]. Remission is achieved in over 70% of cases and long-term treatment with azathioprine, with or without prednisolone, can prevent relapse [2, 3]. However, severe adverse effects occur in about 10% of patients treated with combination therapy, and in 44% of patients treated with high dose prednisone monotherapy [3-5]. For patients with drug toxicity or intolerance, a dose reduction or drug discontinuation may be necessary. Numerous second-line agents which have been used include cyclosporine, 6-mercaptopurine and tacrolimus [6-10].

Ursodeoxycholic acid is the 7α-hydroxy epimer of chenodeoxycholic acid and has been reported to yield improvements in liver dysfunction due to cholestatic liver diseases, with few if any adverse effects. Ursodeoxycholic acid is now the reference therapy for primary biliary cirrhosis [11, 12].

Ursodeoxycholic acid has rarely been tested in autoimmune hepatitis, although preliminary reports suggest that it might be effective [13-17].

We report a case of well-documented typical type 1 autoimmune hepatitis in a patient intolerant to corticosteroid and azathioprine combination therapy, in whom long-term remission was obtained during ursodeoxycholic acid monotherapy.

Case report

In September 1992, a 37-year-old woman weighing 60 kg was admitted for fatigue associated with elevated serum alanine aminotransferase (ALT) activity (25 times the upper limit of normal (ULN)). Serum alkaline phosphatase and gamma-glutamyl transpeptidase levels were within the normal range. Type 1 autoimmune hepatitis was diagnosed on the basis of: (1) hypergammaglobulinemia at 30 g/L, (2) positive antinuclear antibodies (ANA) and antimitochondrial antibodies were not detected. Histologically, the interlobular and septal bile ducts were normal, there was neither steatosis nor iron overload. Her HLA phenotype was A2/32 B27 Bw4 Cw2/w7 and DR4/4. Her score for diagnosis of autoimmune hepatitis was 16 (definite autoimmune hepatitis). Immunosuppressive therapy with corticosteroids (30 mg per day) and azathioprine (100 mg per day) was administered. Steroids were gradually reduced to a dose of 3 mg per day and were stopped in March 1994. One month later, despite continued azathioprine therapy, a relapse occurred with an increase in serum ALT (3 ULN); steroids (30 mg per day) were promptly reintroduced, leading to rapid recovery; the dose was gradually reduced to 2.5 mg per day and then stopped in December 1994 (figure 2).

Reprints: J.-C. DUCLOS-VALLÉE, Centre Hépato-Biliaire and UPRES 3541, Hôpital Paul Brousse, 14 avenue Paul Vaillant Couturier, 94804 Villejuif. E-mail: jean-charles.duclos-vallee@pbr.ap-hop-paris.fr
Because of intolerance (nausea and rash), azathioprine was stopped in April 1995. In June 1995, a new flare-up of autoimmune hepatitis occurred (serum ALT 7.3 ULN), and the patient refused corticosteroids. She was prescribed ursodeoxycholic acid 800 mg daily. A significant improvement in clinical and biochemical parameters was noted in September 1995, and the serum ALT level returned to normal in November 1995 (figure 2).

A second liver biopsy was performed in September 1997, 15 months after the outset of ursodeoxycholic acid monotherapy. Histological examination showed marked improvement of the portal inflammatory infiltrate and the degree of fibrosis in the portal tract with persistent mild to moderate chronic (interface and lobular) hepatitis. No histological features of cholangitis suggestive of primary biliary cirrhosis or overlap syndrome were present (figure 3). Ursodeoxycholic acid was stopped. In March 1998, a new increase in serum ALT occurred (2.5 ULN). Prescription of 1000 mg/d ursodeoxycholic acid rapidly led to normalization of serum ALT values. In March 1999, the ursodeoxycholic acid dose was reduced to 600 mg daily. A subsequent slight increase in serum ALT (1.6 ULN) was controlled by increasing the ursodeoxycholic acid regimen to 800 mg daily. Moreover, gamma-globulin levels were found to be within the normal range. From this date until December 2003, liver tests remained within the normal range (figure 3). The patient refused any additional liver biopsy. However, several non invasive markers of liver fibrosis ie: apoliprotein A1 1.3 g/L (1.2-1.7), hyaluronic acid 40 \( \mu \)g/L (< 75 \( \mu \)g/L), \( \alpha \)2 macroglobulin 2 g/L (1.6-4), prothrombin index 80% and platelet count 180 000/mm3 were within the normal range [18].

**Discussion**

We describe a complete biochemical and histological remission of type 1 autoimmune hepatitis in a middle-aged woman during ursodeoxycholic acid therapy. The diagnosis of type 1 autoimmune hepatitis in this patient was unequivocal. Concomitant primary biliary cirrhosis or overlap syndrome was ruled out by liver test results (elevated serum ALT and normal serum alkaline phosphatase and gamma-glutamyltranspeptidase at diagno-

![Fig. 1. – HES X 200: Histological features at diagnosis: portal tracts are enlarged with a lymphoplasmocytic inflammatory infiltrate (A). Portal tract fibrosis is present without bridging fibrosis. In the lobular tract, a moderate chronic inflammatory component is present and lobular hepatitis is present (B).](image)

**Fig. 1.** – HES X 200: Description histologique au moment du diagnostic : les espaces portes sont élargis par un infiltrat inflammatoire lymphoplasmocytaire (A). Une fibrose portale est présente sans fibrose en pont. Dans le lobule, une hépatite modérée d’interface est présente.

![Fig. 2. – Changes in biochemical liver test results, immunological parameters and histological features during UDCA therapy. SMA: anti-smooth muscle antibodies. ULN: upper limit of normal. UDCA: ursodeoxycholic acid.](image)

**Fig. 2.** – Changes in biochemical liver test results, immunological parameters and histological features during UDCA therapy.


UDCA: ursodeoxycholic acid.
sosis), serum antimitochondrial and anti-gp210 antibody negativity and the absence of bile duct injury or ductopenia on histological examination of the liver [19]. The efficacy of ursodeoxycholic acid on this patient's autoimmune hepatitis is strongly suggested by the following observations: 1) successful control of relapse following steroid withdrawal, 2) successful control of a post-ursodeoxycholic acid relapse by ursodeoxycholic acid reintroduction, and 3) successful control of a relapse following a reduction in the ursodeoxycholic acid regimen by a slight dose increment.

Ursodeoxycholic acid therapy has led to improvements in many liver diseases, particularly primary biliary cirrhosis [11, 12, 21-23]. Data on ursodeoxycholic acid in autoimmune hepatitis are controversial. In a Japanese study of eight patients, levels of serum transaminases and immunological markers (serum IgG, g-globulin, anti-smooth muscle antibodies) fell during ursodeoxycholic acid therapy at doses of 11.5-11.8 mg/kg [17]. Moreover, in 4 patients who underwent liver biopsy after one year on therapy, there was an improvement in necrotic-inflammatory lesions but not in fibrosis. Interestingly, in one patient, serum ALT again increased after ursodeoxycholic acid withdrawal. All eight patients had mild type autoimmune hepatitis with few symptoms [17]. In a recent study by Czaja et al. [23] of a small cohort of patients, short term ursodeoxycholic acid therapy improved serum aspartate aminotransferase levels but did not improve the liver histology or facilitate steroid tapering or withdrawal. One explanation for these discrepancies may be differences in HLA-DR haplotypes. In the Japanese study, ursodeoxycholic acid induced a strong response in patients with the HLA-DR4 phenotype. This was also our patient's phenotype. In Czaja's study report, and in the series by Nakamura et al. [16], the histological recovery observed during ursodeoxycholic acid therapy was most marked when liver damage was initially mild (absence of septal fibrosis). To our knowledge, ursodeoxycholic acid has never been reported to improve severe autoimmune hepatitis. Another factor favoring response to ursodeoxycholic acid is the HLA-DR4 haplotype.

In conclusion, this case report suggests that ursodeoxycholic acid could significantly improve autoimmune hepatitis, and might be particularly useful in case of resistance or intolerance to conventional therapies, or as a first-line treatment of mild to moderate liver injury due to autoimmune hepatitis. Its possible efficacy in combination with steroids and/or azathioprine remains to be determined. The factors influencing the response to ursodeoxycholic acid in autoimmune hepatitis need to be clearly identified.

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REFERENCES


