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 (4), 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.

RÉSUMÉ

Obtention d’une rémission grâce à l’acide ursodésoxycholique chez une malade atteinte d’hépatite auto-immune de type 1 et résistante à l’azathioprine et à la corticothérapie

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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 anti-smooth muscle antibodies (1:1000 by immunofluorescence on unfixed 4 mm cryostat sections of rat liver, stomach and kidney), (3) periportal necroinflammatory lesions with lymphoplasmocytic infiltrate and mild portal fibrosis (figure 1) and (4) no other cause of liver disease. The patient did not consume alcohol or drugs, and had no markers of hepatitis A, B or C, cytomegalovirus or Epstein-Barr virus infection, Wilson’s disease, α1-antitrypsin deficiency, or hemochromatosis. Serum antimitochondrial antibodies were not detected. Histologically, the interlobular and septal bile ducts were normal, and 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).
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 μg/L (< 75 μg/L), α2 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 gammaglutamytranspeptidase 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 interface and lobular hepatitis is present (B).

*HESX200 : Description histologique au moment du diagnostic : les espaces portes sont élargis par un infiltrat 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.


UDCA: ursodeoxycholic acid.

*Evolution des paramètres biochimiques, immunologiques et histologiques sous traitement par acide ursodesoxycholique.*

SMA : anticorps anti-muscles lisses ; ULN : N X la valeur normale.

UDCA : acide ursodesoxycholique.
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 necroinflammatory 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 haplotype. This was also our patient's phenotype. In Czaja's study a high proportion of patients were HLA-DR17, which is associated with a poorer outcome [23-25].

The pathogenesis of autoimmune hepatitis probably involves cellular immune-mediated cytotoxicity. A virus, drug or environmental toxin might be the triggering factor, or the disease might occur spontaneously with the emergence or the persistence of “forbidden clones” and loss of self-tolerance. The trigger may induce high levels of cytokines, which may regulate peptide presentation via MHC class I molecules and induce MHC class II molecule expression on hepatocytes [26]. The well-documented beneficial effect of ursodeoxycholic acid in primary biliary cirrhosis involves direct cytoprotection [26]. However, ursodeoxycholic acid also has other effects, such as protection of mitochondrial function, hypercholesterolemia and immunomodulation. In autoimmune hepatitis, ursodeoxycholic acid might reduce MHC class I antigen expression on hepatocytes, thereby inhibiting the immune-mediated liver cell damage by suppressing the interaction between antigen-presenting cells and T helper lymphocytes, and the subsequent activation of cytotoxic T lymphocytes. In the present casereport, 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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