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

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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 remission 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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La combinaison thérapeutique d’une corticothérapie et d’azathioprine est le traitement de référence de l’hépatite auto-immune. Toutefois les effets secondaires sont nombreux et une mauvaise tolérance peut survenir. Nous rapportons le cas d’une malade atteinte d’hépatite auto-immune de type 1 qui a présenté une intolerance majeure à la corticothérapie et à l’azathioprine et, qui après 8 ans d’un traitement par acide ursodésoxycholique est en remission clinique, biologique et histologique.

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 interfascicular and septal bile ducts were normal, and there was neither steatosis nor iron overload. Her HLA phenotype was A2, A2, 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 \( \mu \)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 gammaglutamyltranspeptidase at diagno-
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La bile acide ursodéhydrocholique a d’autres effets, tels que la protection cellulaire [26]. Cependant, la bile acide ursodéhydrocholique n’a jamais été rapportée à améliorer la hépatite auto-immune. Une autre cause favorisant la réponse à la bile acide ursodéhydrocholique dans la hépatite auto-immune est le haploïde HLA-DR4.

En conclusion, ce cas rapporté suggère que la bile acide ursodéhydrocholique pourrait significativement améliorer la hépatite auto-immune, et pourraient être particulièrement utiles en cas de résistance ou d’intolérance à des thérapies conventionnelles, ou comme traitement de première ligne des hépatites modérées à sévères. Les facteurs influençant la réponse à la bile acide ursodéhydrocholique dans la hépatite auto-immune nécessitent d'être clairement identifiés.

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**REFERENCES**


