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Ursodeoxycholic acid can be used as a steroid-tapering drug in the treatment of autoimmune hepatitis

Ursodeoksikolik asit otoimmün hepatit tedavisinde steroid dozunu azaltmada kullanılabilir

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Bacground/aims: *Corticosteroids are the drug of choice for the treatment of autoimmune hepatitis . Azathioprine is also prescribed to allow a decreased dosage of corticosteroids and to provide more efficient immunosuppression. Almost 20-40 % of patients with autoimmune hepatitis do not respond to the standard treatment regimen or require higher doses of corticosteroids for a longer period of time. Due to its immunomodulatory effects, ursodeoxycholic acid is thought to contribute to autoimmune hepatitis treatment. This study investigated the efficacy of ursodeoxycholic acid administration in the treatment of patients with autoimmune hepatitis type 1, who were resistant to standard corticosteroid treatment.* ***Methods:*** *Between 1997 and 1999, 23 patients were diagnosed as autoimmune hepatitis type 1 in Ege University Hospital. Corticosteroids and/or azathioprine treatment were administered to all patients (four male and 19 female, mean age 42±12 years). Ursodeoxycholic acid (750 mg./day) was added to the treatment of seven (20%) of these patients (three male and four female, mean age 43±7 years) whose ALT values had not returned to normal levels by the end of the sixth month or whose corticosteroid dose could not be decreased to 15 mg/ day or less.* ***Results:*** *Pre-treatment ALT and AST values of the patients who were prescribed ursodeoxycholic acid were 130.8±72.0 U/l and 126.1±96.6 U/l respectively. After three months of ursodeoxycholic acid administration, ALT values of all patients were found to be normal. Sufficient remission was provided with prednisolone dosages of 10 mg/day or less.* ***Conclusions:*** *Ursodeoxycholic acid should be considered as a supplementary treatment for patients with autoimmune hepatitis type 1 who require high-dosage steroid treatment or do not respond to corticosteroid treatment. Randomized studies with placebo controls are needed in order to obtain more accurate results.*

Key words: Autoimmune hepatitis, ursodeoxycholic acid.

Amaç: *Kortikosteroidler otoimmün hepatit tedavisinde kullanılan ilaçlardandır. Azathioprin de daha etkili immünosüpresyon sağlamak ve kortikosteroidler dozunu azaltmak amacıyla kullanılmaktadır. Otoimmün hepatit olguların %20-40'ında standard tedavi rejimine yanıt alınamaz ya da uzun süreli yüksek doz kortikosteroidler tedavi vermek gerekebilir. Ursodeoksikolik asit bir miktar immünomodülatör etkiye sahip olduğundan otoimmün hepatit tedavisine katkıda bulunabileceği düşünülebilir. Biz, standard kortikosteroidler tedasine dirençli otoimmün hepatit tip 1 olgularda ursodeoksikolik asit etkinliğini araştırdık.* ***Yöntem:*** *Eylül 1997- Eylül 1999 tarihleri arasında Ege Üniversitesi Tıp Fakültesi Hepatoloji kliniğinde 23 olguya otoimmün hepatit tip 1 tanısı koyduk. Tüm olgulara (4 erkek ve 19 kadın, ortalama yaş 42±12) kortikosteroidler ve/veya azathioprin tedavisi uygulandı. Kortikosteroidler tedavisi 15 mg/gün altına indirilemeyen veya 6. ayın sonunda ALT düzeyi normale inmeyen 7 olguya (3 erkek ve 4 kadın, ortalama yaş 43±7) almakta oldukları tedaviye ek olarak ursodeoksikolik asit (750 mg/gün) verildi.* ***Bulgular:*** *Ursodeoksikolik asit eklenen olguların tedavi öncesi ortalama AST ve ALT değerleri sırasıyla 130.8±72.0 U/l ve 126.1±96.6 U/l idi. Ursodeoksikolik asit tedaviye eklendikten 3 ay sonra olguların tümünde ALT değerleri normal bulundu. Prednisolon 10 mg/gün veya altındaki dozlar ile yeterli remisyon sağlandı.* ***Sonuç:*** *Kortikosteroidler tedaviye yanıt alınmayan veya yüksek doz kortikosteroidler tedavi kullanılmak zorunda kalınan otoimmün hepatit tip 1 tanılı olgularda ursodeoksikolik asitin tedaviye eklenmesi düşünülmelidir. Bu konu ile ilgili olarak daha gerçekçi sonuçlar çıkarmak için plasebo kontrollü randomize çalışmalara gereksinim vardır.*

Anahtar kelimeler: Otoimmün hepatit, ursodeoksikolik asit.

INTRODUCTION

Autoimmune hepatitis is a chronic, progressive and necro inflammatory disease, which is mostly observed among young and middle-aged women. Although the different types of disease are characterized by different autoantibodies, the role of these autoantibodies in clinical presentation is not known. The clinical appearance and prognosis of autoimmune hepatitis and its response to treatment shows great inter-individual differ-

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ences (1), as is the case in other autoimmune diseases. The standard treatment for the disease is based on corticostreoids (CS). Azathioprine (AZT) is also included in the standard treatment with the aim of decreasing the corticosteroid dosage and providing more efficient immunosuppression. Although 60-80% of patients respond to standard treatment, a percentage (20-40 %) require higher doses of CS for a longer period of time or do not respond to the treatment at all (1-4). Due to the known side-effects of both CS and AZT, alternative medications are needed to replace these agents or at least to be able to decrease their doses, especially in patients who are resistant to standard treatment.

Ursodeoxycholic acid (UDCA), a hydrophilic biliary acid, has started to be used more widely in the treatment of many chronic liver diseases, especially in cholestatic liver diseases (5, 6). In cholestatic cases, it is thought that it protects the liver by replacing hydrophobic biliary acids (7). It has also been reported to suppress the production of immune globins G, M and A, decrease HLA Class I and II antigen expression, decrease the production of IL-2, IL-4 and interferon-gamma (8-10). These immunomodulatory effects are considered to provide a great contribution to the positive effect of cholestatic liver disease treatment, especially in primary biliary cirrhosis (PBC).

This study investigated the efficacy of supplementary UDCA administration in addition to CS in the treatment of patients with autoimmune hepatitis type 1 (AIH1), who resisted standard CS treatment or whose CS dosage could not be decreased.

MATERIALS AND METHODS

Between September 1987 and September 1999, 23 patients were diagnosed as AIH1. Criteria for the diagnosis of AIH1 where those of the International Autoimmune Hepatitis Group (11): i) a liver biopsy with findings of chronic hepatitis, ii) negative viral hepatitis markers (HBs Ag, anti HCV), iii) exclusion of metabolic liver diseases (alpha-1-antitripsin, seruloplasmin, iron, iron binding capacity and ferritin levels were normal), iv) no history of alcohol and hepatotoxic medications, v) antinuclear antibody (ANA) and/or anti smooth muscle antibody (ASMA) positivity (titer of at least 1/80), vi) any abnormality in serum transaminases, vii) elevation of serum gamma globulin concentiations. Patients with i) findings of biliary duct pathology with biopsy suggesting primary biliary cirrhosis, ii)alkaline phosphatase level two times higher than the upper normal limit and iii) anti mitochondrial antibody positivity were excluded to avoid possibility of an "overlap syndrome".

All 23 patients received CS based treatment. Six patients (Group 1) had CS only; prednisonolono 60 mg/day was prescribed initially, with the dose tapering planned (15 mg decrease every week to 15 mg/day at fourth week). After the fourth week, it was planned to continue prednisolone 15 mg/day until ALT values decreased to normal levels. The remaining 17 patients (Group 2) received combined prednisolone and AZT treatment. (AZT 50 mg/day + prednisolone 30 mg/day during the first week, 20 mg/day during the second week and then 15 mg/day). It was planned to continue treatment until ALT values decrease to normal levels.

Serum transaminase levels were monitored on alternate weeks.

The ALT values of two patients in group-1 and five patients in group-2 did not return to normal levels, so the prednisolone dosage could not be decreased to 15 mg /day after six months of therapy. The treatment of these patients therefore continued by adding UDCA 750 mg/day (morning 250 mg, evening 500 mg). If ALT levels decreased to normal levels, the steroid dosage was planned to be decreased gradually by 2.5 mg. every two weeks. Following three months of UDCA therapy, prednisolone dose and transimanase values were evaluated.

The study received approval of the local ethics committee and was conducted in accordance with the Helsinki declaration of 1975.

RESULTS

Among the 23 autoimmune hepatitis type 1 (four male, 19 female, mean age 42±12 years) who received treatment, pre-treatment values were found to be as follows: ALT: 165±213 U/l, AST: 161±238 U/l, gamma globulin: 3.42±0.74 gr/dl, total bilirubin: 1.02±0.9 mg/dl, alkaline phosphatase: 198.0±80.1 U/l (normal <249).

Sixteen (76%) of the 23 patients responded to simple CS or CS + AZT treatment, whilst seven patients (24%) did not respond (three male, four female, mean age 43±7 years) and these patients were also prescribed UDCA. Their pre-treatment

Table 1. Patient demographics, ALT values, pre- and post-treatment CS doses of the patients who had additional UDCA treatment.

Patients	*Age*	*Sex*	*Therapy prior to UDCA mg/day*	*ALT Before - After UDCA*	*After UDCA* Pred mg/day*	*Pretreatment histology*
A.K.	39	F	Prednisolone 20	116 - 36	5	CAH Stage 3
A.S.	40	F	Prednisolone 15	72 - 40	5	CAH Stage 2
K.Ö.	42	F	Prednisolone.20+AZT 50	146 - 38	2.5	Cirrhosis+ CAH
M.K.	54	M	Prednisolone.20+AZT 50	73 - 42	5	CAH Stage 2
G.Y.	38	F	Prednisolone.20+AZT 50	247 - 38	7.5	CAH Stage 3
A.S.	44	M	Prednisolone.30+AZT 50	129 - 37	7.5	CAH Stage 2
M.A.	38	M	Prednisolone.20+AZT 100	82 - 26	5	CAH Stage 2

*6th month, Prd: Prednisolone, AZT: Azathioprine, UDCA: Ursodeoxycholic acid, CAH: Chronic active hepatitis.

values were as follows: ALT: 130±72 U/l, AST: 126±96 U/l, gamma globulin: 3.32±0.46 g/dl, total bilirubin: 1.01±0.7 mg/dl, alkaline phosphatase: 290±80 U/l. There was no significant difference in pre-treatment serum biochemistry values between responder and non-responder groups. Patient demographics, pre- and post-UDCA treatment serum biochemistry results and prednisolone doses in the UDCA treated group are shown in Table 1.

Serum transaminase levels decreased to normal values in all patients after UDCA treatment and during follow-up (range 3-12 months, median eight months) continued to be normal.

No significant side effect was observed during the UDCA treatment, except for dyspeptic complaints, which could also be attributed to prednisolone,

Mean prednisolone doses for maintainence therapy among group-1 and group-2 patients were 8.0±2.1 mg/day, and 4.6±1.7 mg/day, respectively.

DISCUSSION

Although the immunological mechanisms responsible for liver damage are not clear, it is thought that both cellular and humoral mechanisms are involved during the course of AIH in immunologically predisposed individuals.

Corticosteroids inhibit the production of interleukin 2 (IL-2), which is known to be an important cytokine in the process of lymphocyte activation and proliferation. IL-1 and IL-6 mediated monocyte production and lymphocyte activation and proliferation is also inhibited by CS. Azathioprine, an anti-metabolite, is a pro-drug that prevents B- and T-lymphocyte production and inhibits RNA synthesis.

The efficacy of prednisolone (alone or in combination with AZT) in the treatment of AIH has been reported. In many controlled clinical studies, it is said that classical treatment protocols provide a clinical and biochemical resolution in up to 80% of patients Czaja et al. reported that 13% of cases showed partial response and 9% did not respond to standard CS + AZT treatment at all (4).

For the patients who fail to respond to these standard treatment protocols, apart from higher doses of CS and/or AZT for longer periods of time, other medications, such as methotrexate, cyclosporin and tacrolimus, have been suggested (2, 12, 13). However, all of these medications may have many potent and serious side effects and thus alternative treatment options are needed.

Apart from its cytoprotective, cholerectic effects, ursodeoxycholic acid (UDCA) decreases HLA expression and cytokine production. It is known to be effective in the treatment of various chronic liver diseases, especially in PBC (14, 15). We studied the effect of supplementary UDCA in the treatment of autoimmune hepatitis type-1 which is resistant to the standard treatment of CS and AZT.

It was observed that UDCA lowered serum transaminase levels in each case and was effective in allowing a decrease in the CS dosage. However, there was no significant difference in gamma globulin values. Since follow-up liver biopsy was not performed, it is unclear whether any histopathological improvement accompanied biochemical recovery.

In accordance with our findings, Nakamura et al reported a significant decrease in serum ALT, AST, gamma globulin levels and also ANA and/or ASMA titration following two year UDCA treatment (600 mg/day) in patients with autoimmune hepatitis type-1 (16). They also observed an improvement in the inflammation score on histopathologic examination of follow-up liver biopsies.

In conclusion, UDCA may be regarded as a supplementary treatment for patients with type I autoimmune hepatitis who do not respond to standard CS and AZT treatment or require higher doses of CS and AZT. Since the number of cases in this study was limited and follow liver biopsies were not performed, randomized studies with larger numbers of cases, placebo controls and fallow are required.

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