Methotrexate For The Treatment of Primary Biliary Cirhosis

PRİMER BİLİYER SİROZ TEDAVİSİNDE METHOTREXATE

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SUMMARY

77»© aim of this study was to *evaluate ttis efficacy of methotrexate (MTX) for the treatment of primary biliary cirrhosis (PBC). We included 10 female patients (mean age: 47.8±9,6 years) with symptomutlc PBC, Pretreatmeni serum IgM concentrations (mean: 678.1 ±332,4 mg/dl) and alkaline phosphatase (AP) levels (mean: 14.3\6 BLu) elevated in all patients. Six of them were antimitochondrial antibody (AMA) positive. Seven patients with histological stage /' disease and three patients with stage III were assigned to receive per oral MTX (15 mg/week) for 6-24 months. Clinical examination and determination of biochemical variables were repeated every two months. Six of seven patients under MTX therapy over 12 months were free of itching. We observed statistically significant reductions in IgM and AP and increase in albumin after six months period of therapy (p<0.05). Cholesterol was significantly (p<0,0u/ reduced by 12th month. Changes in aminotransferases, bilirubin, triglyceride and protrombin time values were Insignificant. Three patients became AMA negative. Liver histology improved in one patient and was stable in three, at 12 th month. There was no significant clinical and hemathological side effects.*

We concluded that MTX may be effective for the treatment of PBC,

Key Words: **Primary** biliary cirrhosis, Methotrexate

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ÖZET

Bu çalışma, primer biyiler siroz (PBS) tedavisinde methotrexate (MTX)'in etkinliğini değerlendirmek amacıyla planlandı. Çalışmaya, semptom atik PBS'lu 10 kadın hasta (yaş ort:47.8±9.6 yıl) dahil edildi. Tedavi öncesi vakaların tümünde IgM (ort:678.1 ±332.4 mg/dl) ve alkalen fosfataz (ort: 14.3+6 BLu) yüksekti, altısında ise antimltokondrial antikor (AMA) pozitifti. Histolojik olarak yedi vaka evre II'de, üçü evre IH'de idi. Hastalara ağız yolu ile 15 mg/hafta MTX. 6 24 ay süreyle verildi. İki aylık aralıklarla fizik muayene, hemogram ve biyoşimik tetkikleri tekrarlandı. Kaşıntı ve halsizlik şikayetlerinde, altıncı ayda belir gin düzelmeler oldu. Oniki aylık tedaviyi tamamlayan yedi hastanın altısında, kaşıntı tamamen kayboldu. Altıncı aydan itibaren IgM ve alkalen fosfataz değerlerinde anlamlı düşmeler, albuminde ise yükselme gözlendi (p<0.05). Kolesterol, 12. ayda anlamlı derecede (p<0.05) azaldı. Buna karşıklık aminotransferazlar, bilirubin, trigliserid ve protrombin zamanındaki değişiklikler anlamsızdı. Üç vakada AMA negatif leşti. Onikinci ayda, karaciğer histolojisi bir vakada iyileşti, üç vakada aynı kaldı. Hastalarda, Haca bağlı klinik ve hematolojik bir yan etki ortaya çıkmadı.

Sonuç olarak, MTX'in PBS'un tedavisinde etkili olabı leceği kanaatine varıldı.

Anahtar Kelimeler: Primer bıliyer siroz, Methotrexate

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Primary biliary cirrhosis is chronic, progressive, cholestatic liver disease with unknown etiology, though, the primary lesion is thought to be related to immune mechanisms **(1,2).** Cirrhosis and portal hypertension with their related complications and grave prognosis slowly develops in a patient which is typically middle aged woman who initially has fatigue, itching and jaun dice **(3).**

Liver translantation is the only therapeutic choice for end-stage disease (4). There is no totally effective medical treatment for the underlying disorder yet. Drug trials conducted for medical treatment of PBC includes penicillamine, prednisolone, azathioprine, chlorambucil,

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cochicine, cyclosporine and ursodiol (5). Recently Kaplan and his collagues applied to their four patients with PBC low dose oral pulse MTX therapy and obtained clinical, biochemical and histological improvements (6). We planned to evaluate the efficacy of MTX theraphy in PBC.

MATERIAL AND METHODS

Ten female patients (mean age: 47.8:9.6 years, range: 32-63 years) with PBC, admitted to Istanbul Medical Faculty, Gstioenterohepatology department, were included in this study. PBC was diagnosed with the presence of clinical and histopathological features compatible with a diagnosis of PBC, elevated serum AP and IgM levels, a positive test for AMA and exclusion of extrahepatic cholestasis by mean of percutane transhepatic cholangiography or ultrasonography (7). All patients were symptomatic (mean duration of symp toms: 1.8+0.9 years). Pretreatment symptoms were graded by givoen one to five points. Mean itching and fatigue scores were 4i 1 and 3.4±1, respectively. Jaundice was positive in five patients. Skin pigmentation was determined in five, xanthtelesma in three of them (Table 1). Hepatomegaly was more pronounced than splenomegaly in all cases. Patients were free of any other immunosuppressive durg or colchicine and D-penicillamine at the entry of the trial, for at least three months. Cholestyramine was withdrawn 15 days before the beginning of the trial to evaluate basal complaint scores truely.

At entry to the tiiai, in additon to the clinical examination, serum levels of bilirubin, AP, aspartate and alanine aminotransferases (AST and ALT), cholesterol, triglyceride, protein electrophoresis and blood counts were determined with standait methods and otoanalysers. Immunoglobulins were assayed by radial immunodiffusion, AMA by immunofluorescense microscopy, and protrombin time by Quick method. While AMA was positive in six patients, serum AP (range: 7.3-25 BLu) and IgM levels (range: 392-1290 mg/dl) were elevated in all of them. Liver biopsy specimens were obtained at entry and evaluated according to preaccepted criteria (8). Histological analysis revealed stage II disease in seven, stage Ill disease In three patients. On endoscopic evaluation, grade I and grade II esophageal varices were determined in two patients, respectively.

Table 1. Clinical features of patients with primary biliary cirrhosis

Mean age (±SD yr)	47.8±9.6
Female/Male	10/—
Duration of symptoms (±SDyr)	1.8±0.9
Fatigue	10
Itching	10
Icter	5
Associsfsd di>?QtiSOS	
Sjogren's sydrome	1
Psoriasis	1

Ascites was absent in all. Sjogren's syndrome in one patient and psoriasis in another accompanied to PBC.

Methotrexate, 15 mg per week, in three divided doses, and polyvitamin preparates were applied to all patients. Cholestyramine usage was prohibited unless strongly needed.

The clinical examination and laboratory tests were repeated in every two months and symptom scores were noted. Follow-up liver biopsies were performed at 12 months in three patients and 15 months in one patient.

Informed consent was obtained from each patient before the study. Quantitative data were compared with paired t-test. A p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

1. Methotrexate was given to patients for 6-24 months. Seven patients completed one year of theraphy (mean 12.3+4.9 months).

2. Physical examination did not revealed any change throughout the trial duration. The skin lesions of patient with psoriasis cleared rapidly after MTX administration.

3. Itching and fatigue began to improve after fourth month and improvement was correlated with the duration of the therapy. The difference between pre and posttreatment symptom scores was statistically significant ($p<0.05$). Six of seven patients who completed a year on treatment were free of itching. The seventh patient with ongoing itching had stage Ill disease and repeat liver biopsy showed no improvement and her jaundice was progressed. MTX was withrawn, ursodiol was tried.

4. Changes in serum AP (Figure 1), IgM and albumin were statistically significant after sixth month ($p<0.05$, $p<0.01$ and $p<0.05$, respectively). Changes in cholesterol levels were unsigniflcantly at sixth month. Serum AP, IgM and cholesterol levels in seven patients who completed a year under treatment were significantly decreased when compared with pretreatment levels ($p<0.05$). Mean albumin concentration was significantly increased ($p<0.05$). There was no signifi-

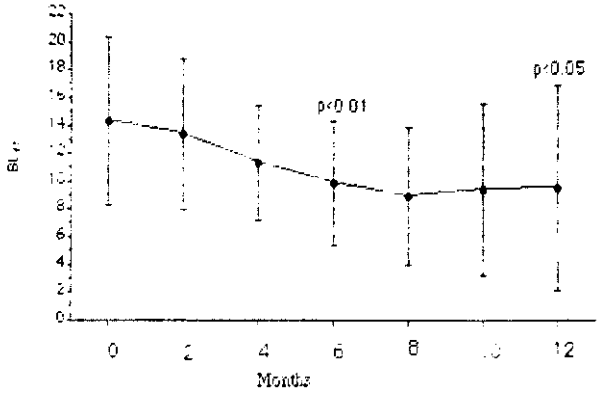

Figure 1. Changes in mean alkaline phosphatase levels of patients with PBC during methotrexate administration.

Table 2. Changes in the laboratory findings of patients in response to methotrexate

	BASAL A	6th month B	12th month C
No of patients	10	10	7
lgM(±SDmg/dl)*	678.1 ±332	459±43.4	438±59.8
AP (±SD BLu)"	14,3±6	9.7+4.7	9.5±7.4
T.Bil.(±SDmg/dl)	3.1+3.3	3.5±3.5	2.4±3,3
AST(±SD RFÜ)	125i61 2	121.7±75	108.2±47
ALT (±SD RFÜ)	133±67.5	130±90.4	129±90.6
Cholesterol(±SDmg/dl)***	3803-227	294.3±97.9	301+169.8
Triglyceride (+SDmg/dl)	185±117.9	165.6±109	138+80.9
Albumin (±SDg/dl)**"	3.38±0.3	3.72±0.5	3.84+0.4
Prot.time (±SD seconds over control)	1.9±0.6	1.5+1.1	1.4+1.1

*A-B: p<0.05 " A - B i p<0.01 "*A-C:p<0.05
* « - - ' " '* "A-C:p<0.05 **"A-BveA-C:p<0.05

cant difference between sixth month and 12th month values (Table 2). Three of six patients with AMA positive serology became negative at 12th month.

5. Changes in serum AST, ALT, bilirubin, triglyceride and in prothrombin times were not statistically significant despite a trend to decrease in serum bilirubin and triglyceride levels (Table 2).

6. Liver biopsy* specimens were obtained in four patients (one in stage Ⅲ and three in stage Ⅱ) who completed a year under MTX treatment. Inflammation was receded in one stage II disease whose serum AP was normalized at 12th month. There was no significant histologic improvement in three other patients.

7. One of the patients, 32 years old, stage Ⅲ female whose AP raised from 25 to 25.8 BLu and serum bilirubin from 7.8 to 9.6 mg/dl with a histology showing no improvement was thought to be liver transplant candidate and MTX was withrawn, ursodiol was started.

8. There was no significant clinical or hematological side effects related to MTX during the study period.

DISCUSSION

The primary lesion in PBC is attributable to an attack of cytotoxic T-lymphocytes on antigens of the interlobular and septal bile duct epithelium (9). The defective T-supressor ceil function facilitates this reaction (10). It seems innocent to use immunosuppressive drugs for treatment of PBC in view of this hypothesis of pathogenesis. Prednisolone (11), penicillamine (12), azathioprine (13), chlorambucil (14), colchicine (15), cyclosporlne (16) are among the immunosuppressive or immunomodulating drugs so far evaluated in controlled or uncontrolled trials for their therapeutic efficacy. Evidence that hepatic lesions in chronic cholestatic diseases can result from intracellular accumulation of toxic bile acids lead to use of ursodiol for modifying the composition of the endogenous bile acid pool (17). Most of these drugs, especially cyclosponne and ursodiol show some degree of efficacy. But, insufficient potency and high toxicity of so far mentioned drugs warrant further research on this field.

Methotrexate is a folic acid antagonist with antiinflamatuary and immunosuppressive properties. Per oral, lowe-dose, pulse therapy with MTX is a well-established approach to the treatment of rheumatoid arteritis and psoriasis (18). Initially, MTX had been administered for treatment of PBC by Kaplan and his collagues (6), Afterward, their favourable results were supported by studies of Achord et al (comprising four patients) (19) and Kaplan et al (covering nine patients) (20). Early results achieved indicate that patients with stage IV disease and/or serum bilirubin exceeding four mg/dl are unresponsive to MTX therapy (21). Asymptomatic patients with stage I disease are reported to have a normal life expectancy and, hence, should not be enrolled in clinical trials (22). Consequently, our study included smptomatic patients with stage II and Ⅲ disease.

A significant improvement in clinical (IgM, AP, albumin) variables were noted during the second or third month of therapy. In Kaplan's series, two of the seven patients who fullfilled one year MTX therapy showed total response with normalization of clinical and biochemical variables (20). Liver biopsy obtained from one of these patients displayed regression of inflammatory activity. The short-term goal of medical treatment of PBC is to achieve clinical (disappearance of fatigue and pruritus) and biochemical (normalization of bilirubin, AST, IgM and AP less than 1.5 times the upper limit of normal) remission (23). This target was accomplished in our two patients. An elevated serum bilirubin and a decreased serum albumin level is a poor prognostic sign in PBC (24). Mean serum albumin concentrations were significantly increased in our patients. Furthermore, mean 22 percent decrease was observed in serum bilirubin levels at 12th month, although not statistically significant. We obtained complete clinical and partial biochemical remission in our eight patients. Histologic progression was arrested in three and regressed in one of them. Seven of nine pa-

tients in Kaplan's series clinically, biochemically and histologically improved (20).

Low weekly doses of MTX induce anti-inflammatory action by inhibiting interleukin-I synthesis (25). The efficacy in PBC is related to this property of MTX (20). Major side effects include nause, vomiting, stomatitis, diarrhea, bone marrow supression, interstitial pneumonitis and hepatotoxicity (18). Liver toxicity ranges from asymptomatic transaminase elevations to hepatocellular carcinoma. Meta-analysis of liver biopsies of 636 rheumatoid arthlritic or psoriatic patients treated with MTX revealed fibrosis and/or cirrhosis in five percent (26). Age, alcohol consumption, total accumulative dose of over 1.5 g increase hepatotoxicity (27). Liver biopsy should be done when total accumulative dose of MTX is over 1.5-2 g. The hepatotoxicity of long-term MTX treatment in patients with pre-existing chronic liver disease is as yet unknown.

In conclusion, the administration of low weekly doses of MTX is a promising approach to the treatment of PBC, but safety and suitability for long-term use needs further trials.

REFERENCES

1. James SP, Hoofnagle JH, Strober W, Jones EA. Primary biliary cirrhosis: a model autoimmune disease. Ann Intern Med 1983; 99:500-12.

2. Manns MP, Bremm A, Schenider PM, et al. HLA DRw8 and complement C4 deficiency as risk factors in primary biliary cirrhosis. Gastroenterology 1991; 101:1367-73.

3. Kaplan MM. Primary biliary cirrhosis. N Engl J Med 1987; 316:521-8.

4. Markus BH, Dickson ER, Grambsch PM, et al. Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med 1989; 320:1709-13.

5. Kaplan MM. Treatment of primary biliary cirrhosis. Semin Liver Dis1989; 9:138-43.

6. Kaplan MM, Knox TA, Arora S. Primary bilary cirrhosis treated with low-dose oral pulse methotrexate. Ann Intern Med 1988; 109:429-31.

7. Sherlock S. Disease of the liver and biliary system. 8th ed, Oxford: Blackwell, 1989:273-88.

8. Vierling JM. Primary biliary cirrhosis. In: Zakim D, Boyer TD, (eds). Hepatology a textbook of liver disease. Vol 2, 2nd ed. Philadelphia:WB Saunders, 1990:1158-1205.

9. Sprengler U, Pope GR, Hoffman RM, et al. Differential expression of MHC class II subregion products on bile duct epithelial cells and hepatocytes in patients with primary biliary cirrhosis. Hepatology 1988; 8:459-6.

10. James SP, Elson CO, Jones EA, Strober W. Abnormal regulation of immunoglobulin synthesis in vitro in primary biliary cirrhosis. Gastroenterology 1980; 79:242-54.

11. Mitchison HC, Bassendine MF, Malcolm AJ, Watson AJ, Record CO, James OFW. A pilot, double-blind controlled l-year trial of prednisolone treatment in primary biliary cirrhosis: hepatic improvement but greater bone loss. Hepatology 1989; 10:420-29.

12. Bodenheimer HC, Schaffner F, Sternlieb J, Klion FM, Vernace S, Pezzulo J. A prospective clinical trial of D-penicillamine in the treatment of primary biliary cirrhosis. Hepatology 1985; 5:1139-42.

13. Christensen E, Neuberger J, Crowe J, et al. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis. Gastroenterology 1985; 89:1084-91.

14. Hoofnagle JH, Davis GL, Schafer DF, et al. Randomized trial of chlorambucil for primary biliary cirrhosis. Gastroenterology 1986; 91:1327-34.

15. Zifroni A, Schaffner F. Long-term follow-up of patients with primary biliary cirrhosis on colchicine therapy. Hepatology 1991; 14:990-93.

16. Wiesner RH, Ludwig J, Lindor KD, et al. A controlled trial of cyclosporine in the treatment of primary biliary cirrhosis. N Engl J Med 1990; 322:1419-24.

17. Poupon R, Poupon RE, Calmus Y, et al. Is ursodeoxycholic acid an effective treatment for primary biliary cirrhosis? Lancet 1987; i:834-36.

18. Weiblatt WE. Methotrexate. In: Kelley WN, ed. Textbook of rheumatology. 3rd ed, Philadelphia: W-B Saunders, 1989: 833-44.

19. Achord JL, Jackson MS. Low dose pulse methotrexate (MTX) in primary biliary cirrhosis (PBC). Am J Gastroenterol 1990; 85:1245 (abstract).

20. Kaplan MM, Knox TA. Treatment of primary biliary cirrhosis with low-dose weekly methotrexate. Gastroenterology 1991; 101:1332-38,

21. Kaplan MM, Knox TA. Methotrexate improves symptoms and biochemical tests in pre-cirrhotic primary biliary cirrhosis (PBC). Gastroenterology 1989; 96:A612 (abstract).

22. Nyberg A, Loot L. Primary biliary cirrhosis: clinical features and outcome, with special reference to asymptomatic disease. Scand J Gastroenterol 1989; 24:57-64.

23. Beukers R, Schalm SW. Immunosupressive therapy for primary biliary cirrhosis. J Hepatol 1992; 14:1-6.

24. Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histological features in asymptomatic and symptomatic primary biliary cirrhosis. N Engl J Med 1983; 308:1-7.

25. Van de Kerkhof PCM, Bauer FW, Maassen-de Grood RM: Methotrexate inhibits the leukotriene B4 induced intraepidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1985; 113:251 a-55a.

26. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med 1991;90:711-16.

27. Gilbert SC, Klintmalm G, Menter A, Silverman A. Methotrexate-induced cirrhosis requiring liver transplantation in three patients with psoriasis. A word of caution in light of the expanding use of this "steroid-sparing" agent. Arch Intern Med 1990; 150: 889-91.

28. Hoofnagle JH, Bergasa NV, Methotrexate therapy of primary biliary cirrhosis: promising but worrisome (editorial). Gastroenterology 1991; 101:1440-42.