The Effectiveness of Ursodeoxycholic Acid (UDCA) ın the Treatment of Autoimmune Liver Diseases

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***Özet:* OTOİMMÜN KRONİK KARACİĞER HASTALIKLARIN TEDAVİSİNDE URSODEOKSİKOLİK ASİTİN ETKİNLİĞİ**

Ursodeoksikolik asit (UDKA) karaciğer fonksiyon testlerine olumlu etkisi nedeniyle Primer Bilier Siroz (PBS) ve Primer Sklerozan Kolanjit (PSK) gibi kolestatik karaciğer hastalıklarında önerilen bir hidrofilik tersiyer safra asididir. Bu çalışmada 6 PBS, 2 PSK ve 2 otoimmün ktonik aktif hepatitli (oKAH) toplam 10 otoimmün kronik karaciğer hastasında UDKA etkinliğini araştırdık. Hastalar klinik ve biyokimyasal parametrelerle izlendi. 7 olguda (%70) karaciğer fonksiyon testlerinde düzelme, klinik ve biyokimyasal tam cevap, 3 olguda (%30), kısmi (relatif) iyileşme görüldü. Sonuçlar ursodeoksikolik asidin bu grup hastaların tedavisinde alternatif, uygun bir seçenek olduğu görüşünü desteklemekteydi.

Anahtar kelimeler: Safra asitleri (tersiyer), ursodeksikolik asit (URSO), kolestatik karaciğer hastalığı (tedavi), primer bilier siroz (PBS), primer sklerozan kolanjit (PSK), otoimmün hepatit.

Summary: *Ursodeoxycholic acid (UDCA) improves liver function tests in patients with cholestatic liver disease, like primary biliary cirrhosis (PBC), autoimmune chronic active hepatitis (aCAH) and primary sclerosing cholangitis (PSC). In this study we investigated the effects of UDCA in 10 patients with autoimmune chronic liver diseases (6 patients with PBC, 2 patients with PSC, and 2 patients with autoimmune chronic hepatitis). The patients received UDCA at doses of 10 mg/kg body weight/day. This treatment lead to improvement of biochemical parameters and clinical state in a period of 3-6 months in 7 patients (70%) and there was partial response in 3 patients (in this study histological response to treatment was not included). In conclusion we can say that UDCA proved to be the best alternative drug for autoimmune cholestatic liver disease.*

Key words: URSO or UDCA (ursodeoxycholic acid), bile acids, cholestatic liver disease, PBC, PSC, aCAH.

Autoimmune liver diseases included in this study, namely Primary Biliary Cirrhosis (PBC), autoimmune Chronic Active Hepatitis (aCAH) and Primary Sclerosing Cholangitis (PSC) are characterised by polyclonal hypergammaglobulinemia, circulatory antibodies, predilaction to females and inflammatory cell infiltration in the liver-predominantly T-cells (1). Although the etiopathogenesis of these disordersis not well determined, particularly in PSC, immune system pathologies have been reported (2).

The association of PSC with inflammatory bowel diseases and saccular dilatation of the biliary system either intra or extrahepatic are the main features of the disease. Recently, antineutrophilic antibodies have been introduced into clinical practice and are very specific and sensitive for PSC. Since intrahepatic cholestasis is the common clinical feature of these disorders, pruritus, jaundice and weakness are the main complaints encountered. Hyperbilirubinemia, elevated serum levels of ALT, AST and ALP are the major laboratory findings. In diagnosis and differential diagnosis, the viral markers, liver enzymes, bilirubin levels and autoantibodies including antinuclear, antimitochondrial and antismooth muscle antibodies should be tested. Abdominal ultrasonography (to estimate the dimensions of the liver and spleen etc.), liver biopsy, endoscopic retrograde cholangiopancreatography (ERCP) are the essential tools to reach a correct diagnosis.

In this disease group, there is no completely effective treatment modality and liver transplan-

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Table I: The clinical specifities of patients.

No of patiens		Age Average: 44.5	Sex	Diagnosis	Auto antibodies	Another drugs	Follow up Months
1	MH	(55)	F	PBC	ANA(+)	-	12
2	VÖ	(49)	F	PBC	ANA (+) AMA (+)	Cyclosporin	36
3	YY	(56)	F	PBC	ANA (+) AMA (+) ANTI DNA (+)	- Corticosteroid	30
4	ST	(51)	F	PBC	AMA (+)	-	48
5	NG	(46)	F	PBC	AMA (-) ANTI DNA (-)	Corticosteroid -	12
6	EH	(30)	F	PBC	ANA (+)	-	24
7	ZB	(44)	F	PSC	-	Corticosterozoid	19
8	SÖ	(40)	F	PSC	-	Azathiopurine	4
9	NT	(33)	F	ACAH	ANA AMA (+) ANTI MUSCLE	Corticosteroid	18 18
10	NG	(28)	F	ACAH	ANA (+) AMA (+)		24

tation seems to be the final procedure. Penicillamine-D, colchicine, methotrexate and cyclosporine have been used in the treatment (1-10).

Leuschren et al. had reported in 1985 11 that UDCA improved the liver function tests in chronic liver diseases. After this observation, this tertiary, hydrophilic bile acid was started to be used broadly in the treatment of PBC, PSC and autoimmune chronic hepatitis 12-14. We used UDCA in ten patients with autoimmune liver diseases and tried to evaluate the effectiveness of the durg with the liver function tests and clinical findings during the therapy.

MATERIAL AND METHOD

10 patinets, 6 with PBC, 2 with PSC and 2 with aCAH were included in the study. All of them were female and the average age was 44.5 years (range: 30-56). The diagnosis was made by liver needle biopsy, liver function tests, ERCP, abdominal ultrasonography, clinical findings and the presence of autoantibodies such as ANA, ASMA, AMA and IgM levels.

All the patients were given UDCA 10 mg./kg./day p.o in the morning as a single dose and were followed-up in three month intervals.

RESULTS

Table I shows the clinical spesificities of ten patients. Figure I demonstrates the levels of IgM. Figure 2,3,4 and 5 reveal the levels of ALP, ALT, AST and bilirubin before and after the treatment. In seven patients all the biochemical parameters returned to normal levels at the end of

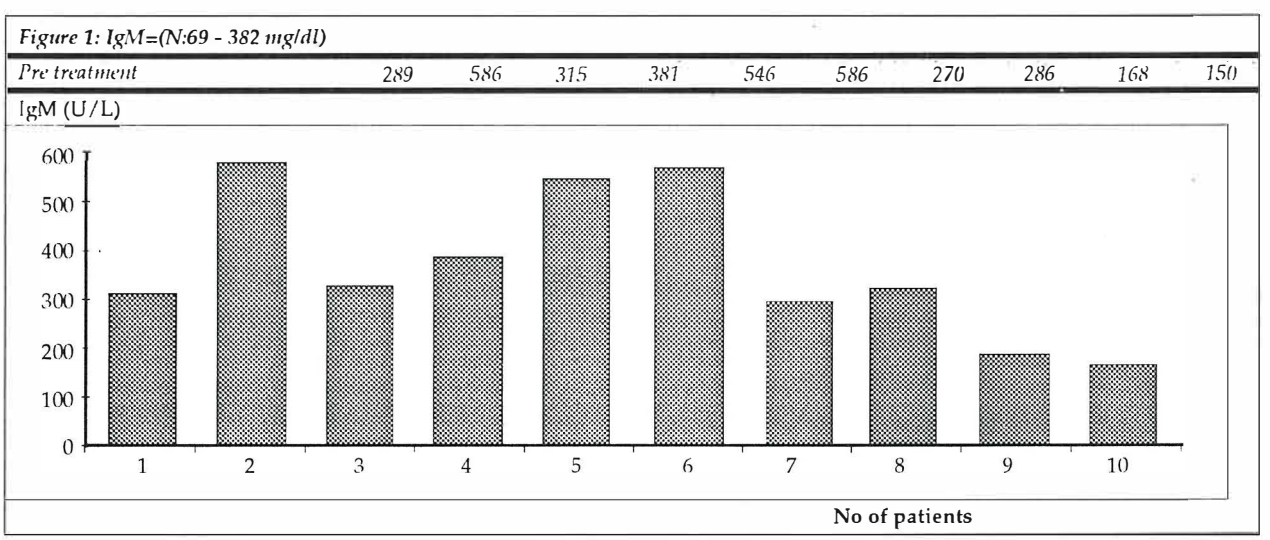
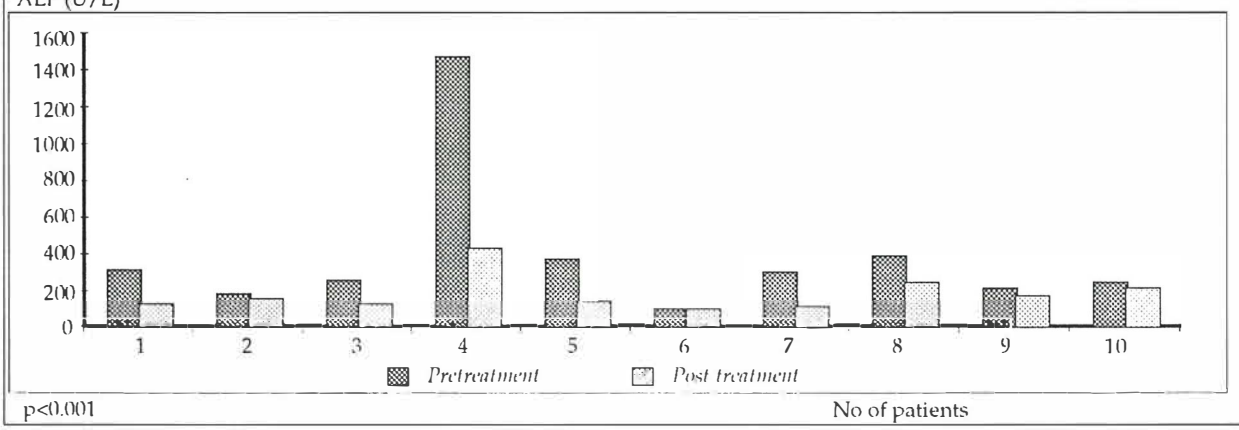


Figure 2 : Alkalen Phospatase ALP (41 - 133 u/dl)

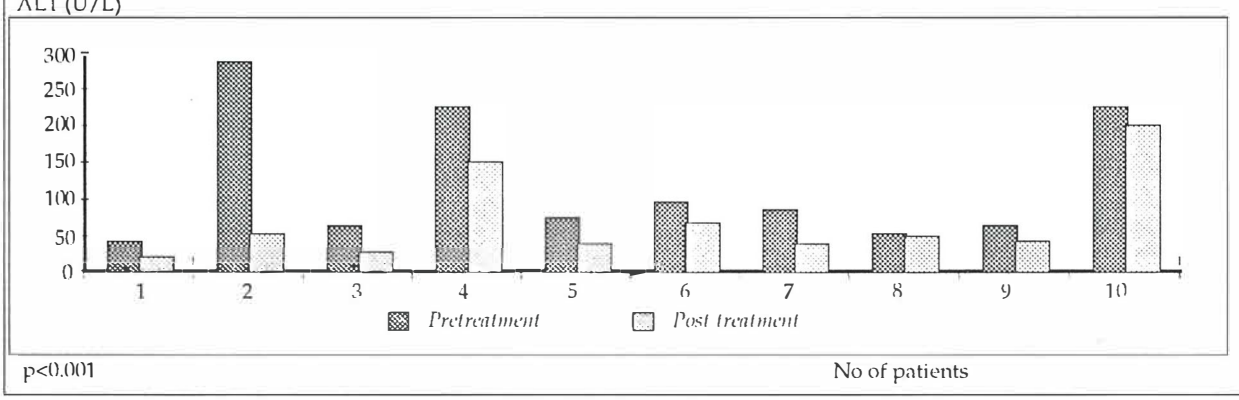
Pre treatment	299	202	242	1492	351	110	269	334	190	193
Post treatment	126	172	137	389	141	106	96	193	133	172



p<0.001 No of patients

Figure 3: ALT (N:2 - 54 u/dl)

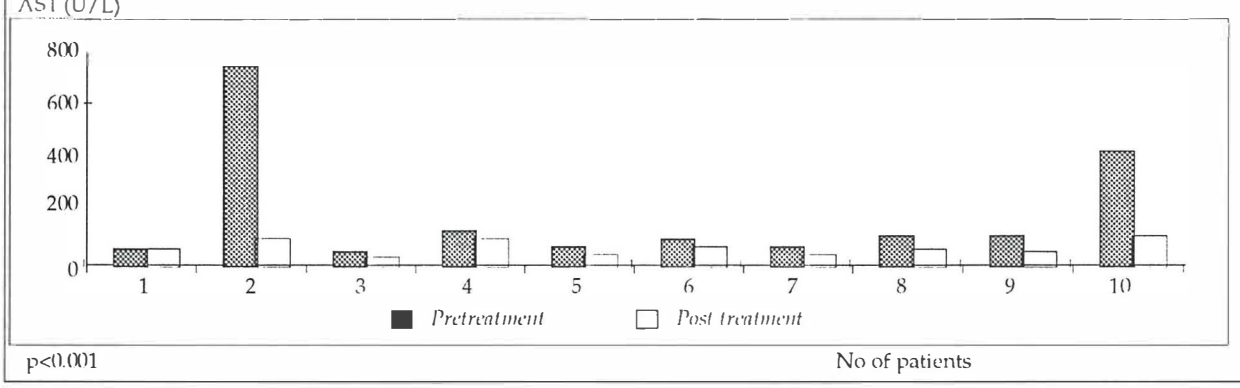
Pre treatment	39	296	63	226	73	91	79	53	58	236
Post treatment	16	49	28	153	38	66	37	49	40	197



p<0.001 No of patients

Figure 4: AST (N: 7 - 39 u/dl)

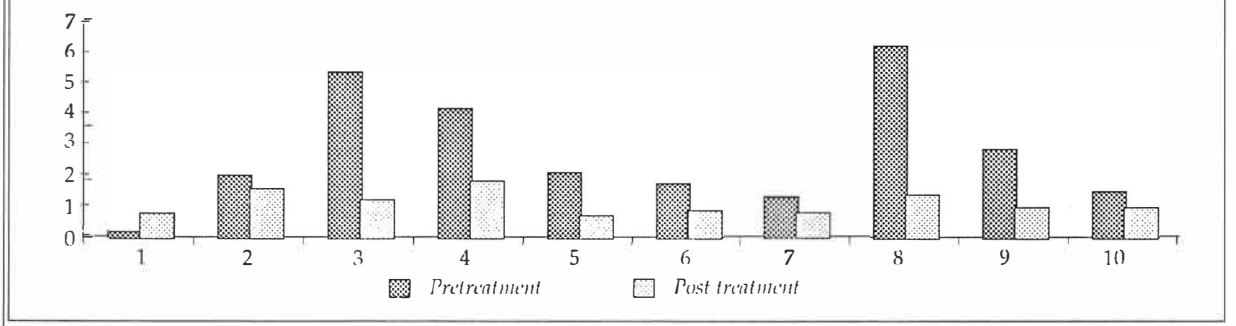
Pre treatment	44	740	40	139	66	101	63	103	105	515
Post treatment	38	84	17	105	30	55	25	47	24	100



p<0.001 No of patients

Figure 5 : Total Bilirubin (N : 0.1 - 1.2 mg/dl)

Pre treatment	0.1	2	5.4	4.3	2.1	1.5	1.2	6.3	3	1.7
Post treatment	0.9	1.5	1.2	1.9	0.7	0.9	0.6	1.2	1	1



p<0.001 No of patients

six months of treatment. In these patients, in addition to the improvement of liver function tests, clinical healing such as disappearence of pruritus and weakness has also been established. In the remainding three patients, the liver function tests improved partially but did not returne to the normal levels. We accepted these three patients as partial responders. Figure 6 shows the duration of the follow-up and the results of the treatment.

İn one patient, ERCP was repeated after one year of therapy and it was closer to normal.

The results were evaluated according to Wilcoxon-Matched-Pairs Signed-Ranks test. The difference of ALT, AST, ALP and total bilirubin levels before and after the treatment was statistically significant ($p<0.005$).

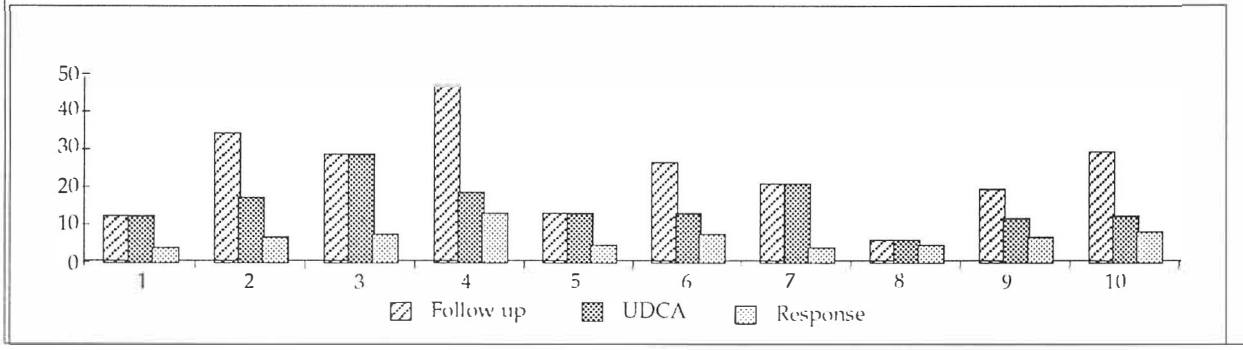
Discussion

The beneficial effect of UDCA on the liver function tests of cholestatic patients was observed by chance and thereafter this drug was used in such disorders (11-14). The mechanism of action of the drug is that it prevents the accumulation of toxic bile acids in the liver and it acts on the immune system.

UDCA has also been used in PSC, aCAH, cystic fibrosis and PBC with success. The recent studies documented that it reduced the liver enzyme levels 30-70% compared to the initial levels(17).

Figure 6 : The response of the treatment with UDCA in patients and follow up months

Follow up (Months)	12	36	30	48	12	24	19	4	18	24
UDCA (Treatment)	12	18	30	18	12	12	19	4	10	10
Response	2	6	6	12	3	6	2	3	5	6



In this study all the patients were followed up for more than 12 months except one. Our results of clinical and biochemical parameters correlated well with the literature (11,21-23). The disappearence or decrease of pruritus was evaluated in favour of clinical healing 10. In some studies, it has been reported that liver histology might not be a good criterion in evaluating the response rate of UDCA treatment(21-23). Thus we considered clinical and laboratory improvement in evaluating the effectiveness of the drug.

Conclusion

UDCA is an alternative way of treatment in cholestatic liver diseases. It can be used for a long time without severe side effects. Biochemical parameters and clinical improvement should be the determinant factos in discontiniuation of the drug. UDCA can prolong the period of time to liver tarnsplantation and can allow the patient to lead a better life and to be in a better condition for the operation.

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