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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Bezafibrate for the treatment of primary sclerosing cholangitis

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Abstract
Background It is known that bezafibrate decreases serum alkaline phosphatase (ALP) in patients with hyperlipidemia, and the efficacy of this drug for the treatment of primary biliary cirrhosis has been confirmed. However, there has been little evidence of its efficacy for the treatment of primary sclerosing cholangitis (PSC).
Methods Bezafibrate (400 mg/day) was orally administered to 7 consecutive patients with PSC, and we analyzed their clinical features and the drug efficacy in terms of the effect on hepatobiliary enzymes, including ALP, gamma-glutamyl transpeptidase (γ-GTP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) after 6 months. The latest hepatobiliary enzyme levels were also evaluated.
Results In 3 patients (effective group), the levels of all hepatobiliary enzymes had decreased after 6 months. Mean ALP had decreased to approximately 40% of the baseline in this group. The efficacy of bezafibrate was observed for a long period (range, 8–27 months) in these 3 patients. There seemed to be no definite association between the efficacy of bezafibrate and the clinical features in the short term.
Conclusions This study showed that bezafibrate could lower the levels of hepatobiliary enzymes in about half of a cohort of patients with PSC.

Keywords Primary sclerosing cholangitis · Drug therapy · Bezafibrate

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic inflammatory cholestatic liver disease of unknown etiology, characterized by chronic inflammation and obliterative fibrosis of the intra- and extra-hepatic biliary tree [1]. The disease is slowly progressive, even in asymptomatic patients, usually leading to biliary cirrhosis and its complications over a 10–15-year period [2]. Although ursodeoxycholic acid (UDCA) is widely used for PSC patients and UDCA can lead to improvements in serum hepatobiliary enzymes [3], a randomized controlled trial in which 198 patients were enrolled demonstrated no effect of UDCA on symptoms, quality of life, or transplant-free survival [4]. Corticosteroids are also used in some PSC patients, but corticosteroids do not seem to be effective in typical PSC and have considerable risks in this population (osteoporosis, increased susceptibility to infection) [3]. Currently, there is no medical treatment for PSC with enough evidence to show a delay in disease progression, and new therapy is needed.

Bezafibrate is a commonly used medication for hyperlipidemia, and reduction in serum alkaline phosphatase (ALP) was initially shown as a well-documented side effect of fibric acid derivatives [5]. It was reported that bezafibrate decreased serum hepatobiliary enzymes in hyperlipidemic patients without any liver diseases [6]. Subsequently, bezafibrate was first used for the treatment of primary biliary

cirrhosis (PBC) in 1999, and it was demonstrated that this drug had the beneficial effect of lowering hepatobiliary enzyme levels [7]. Although PBC and PSC are different disease entities, cholestasis finally causes cirrhosis in both diseases. Bezafibrate was later used for the treatment of PSC, and a beneficial effect was reported in 2002 [8]. Until now, only 7 cases of PSC treated with bezafibrate have been reported in the English-language literature, from 2 groups [9, 10]. These studies reported limited numbers of cases with a beneficial effect, and information about patient characteristics was not clarified. In the present study, we report our experience of 7 consecutive patients with PSC treated with bezafibrate (including cases in which the treatment was ineffective); we also examined factors associated with the efficacy of bezafibrate.

Methods

In this study the findings in seven patients with PSC who were treated with bezafibrate and followed at the University of Tokyo Hospital or the Japanese Red Cross Medical Center between November 2006 and June 2008 were analyzed retrospectively. We used diagnostic criteria published from the Mayo Clinic in 2003 [11], but excluded patients with sclerosing cholangitis with autoimmune pancreatitis (AIP) who fulfilled the diagnostic criteria of AIP proposed by the Mayo Clinic [12] or the revised criteria of the Japan Pancreas Society [13]. Clinical features and laboratory data were reviewed from medical records. Other medications used for PSC during the period of administration of bezafibrate were also reviewed.

Bezafibrate was administered orally twice a day, for a total dose of 400 mg/day. Changes in the levels of ALP, gamma-glutamyl transpeptidase (γ-GTP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were evaluated. In order to assess the efficacy of bezafibrate for reducing the serum enzyme levels, a reduction index (RI) was calculated: RI = postadministration serum level/preadministration serum level. The primary endpoint of the study was the RI for each hepatobiliary enzyme after 6 months of bezafibrate administration. The secondary endpoint was the latest RI for ALP in the observation period as of February 2009.

Informed consent was obtained orally from each patient before administering bezafibrate.

Results

All patients were followed for at least 6 months after the introduction of bezafibrate. The clinical features of the patients at the time of the introduction of bezafibrate are summarized in Table 1. There were 3 men and 4 women.

Table 1 Baseline characteristics

	Age/sex	Age of at onset (years)	Duration of disease (months)	Other medications				Plt (10^9/L)	PT-INR	Alb (g/dL)	ALP (IU/L)	γ-GTP (IU/L)	AST (IU/L)	ALT (IU/L)	T. bil (mg/dL)	T. chol (mg/dL)	TG (mg/dL)	Child-Pugh class
				UDCA (mg)	PSL (mg)	UC	CCA											
Case 1	34/F	33	16	600	–	+	–	281	1.25	4.2	877	481	83	167	0.9	166	71	A
Case 2	80/F	80	6	–	–	–	–	218	1.14	3.6	315	179	38	27	0.5	177	98	A
Case 3	73/M	69	48	600	–	–	+	258	1.05	3.3	507	155	58	41	2	201	158	B
Case 4	58/M	57	18	900	–	–	–	324	1.05	2.7	1072	277	70	62	2.8	294	132	B
Case 5	31/M	30	19	600	–	–	–	270	0.94	4.8	295	214	30	49	0.6	–	–	A
Case 6	35/F	32	39	600	–	–	–	286	0.91	4.3	438	126	27	42	0.7	212	58	A
Case 7	69/F	61	97	900	6	–	–	310	0.89	3.4	1077	227	48	67	2.2	191	–	B

UDCA ursodeoxycholic acid, *PSL* prednisolone, *UC* ulcerative colitis, *CCA* cholangiocarcinoma, *Plt* platelets, *PT* prothrombin time

Alb albumin, *ALP* alkaline phosphatase, *γ-GTP* Gamma-glutamyl transpeptidase, *AST* aspartate aminotransferase

ALT alanine aminotransferase, *T. bil* total bilirubin, *T. chol* total cholesterol, *TG* triglyceride

The mean age at onset was 52 years (range, 30–80 years). The mean duration of the disease was 35 months (range, 6–97 months). In Case 6, bezafibrate was stopped after 3 months because of the rapid elevation of hepatobiliary enzymes, and UDCA was then administered. In Case 1, UDCA was added after 4 months of bezafibrate administration. In Cases 3–5, and 7, bezafibrate was added to UDCA treatment. Overall, UDCA was used in 6 patients.

Changes in hepatobiliary enzyme levels during the administration of bezafibrate are shown in Table 2, and these changes, expressed as the RIs, are shown in Fig. 1. In the patients overall, the mean RIs for ALP, γ-GTP, AST, and ALT after 6 months were 0.69, 0.83, 1.35, and 0.95, respectively. In Cases 1–3, the RIs for all hepatobiliary enzymes were below 1.0 after 6 months of bezafibrate administration; therefore, we considered bezafibrate was effective in these patients. The mean RIs for ALP, γ-GTP, AST, and ALT after 6 months were 0.41, 0.38, 0.49, and 0.30, respectively, in this effective group; also, improvements in each hepatobiliary enzyme level had been achieved after 3 months of bezafibrate administration in this group.

Table 2 Changes in hepatobiliary enzymes enzyme levels in each patient

	Time (months)		
	0	3	6
ALP (IU/L)			
Case 1	877	275	134
Case 2	315	126	132
Case 3	507	294	336
Case 4	1072	1040	806
Case 5	295	190	215
Case 6	438	594	446
Case 7	1077	972	1204
γ-GTP (IU/L)			
Case 1	481	248	66
Case 2	179	28	26
Case 3	155	130	131
Case 4	277	654	532
Case 5	214	81	189
Case 6	126	206	109
Case 7	227	218	227
AST (IU/L)			
Case 1	83	43	34
Case 2	38	20	21
Case 3	58	29	30
Case 4	70	251	268
Case 5	30	25	47
Case 6	27	39	22
Case 7	48	72	86
ALT (IU/L)			
Case 1	167	41	29
Case 2	27	11	9
Case 3	41	16	16
Case 4	62	181	156
Case 5	49	38	59
Case 6	42	63	36
Case 7	67	78	78

The latest RIs for ALP are shown in Table 3. The maximum observation period was 27 months. In the effective group, the RIs were below 1.0 even after a long period of bezafibrate administration. In Cases 4, 5, and 7, whose ALP decreased slightly after 3 or/and 6 months, bezafibrate was continued thereafter; however, the ALP increased again in all 3 patients. In Case 6, UDCA was administered for 8 months after bezafibrate discontinuation, and the latest RIs for ALP, γ-GTP, AST, and ALP were 0.97, 0.80, 0.78, and 0.69, respectively.

Bezafibrate was administered as the first medication in 3 patients (Cases 1, 2, and 6), and the effect of bezafibrate as a single-agent therapy was assessable in these patients. The RIs for ALP in each of these patients after 3 months of bezafibrate monotherapy were 0.31, 0.40, and 1.36 (mean, 0.69). In Case 2, bezafibrate monotherapy was continued for 17 months, and the latest RI for ALP was 0.49.

As for liver function, the Child-Pugh class was A in 4 patients and B in 3 (Table 1). Bezafibrate was effective in 2 of the 4 patients with Child A class liver function, and in 1 of the 3 patients with Child B class liver function. There seemed to be no association between the efficacy of bezafibrate and the Child-Pugh class. There were no remarkable changes in platelet counts, prothrombin time (PT)-INR, albumin, or total bilirubin during the treatment with bezafibrate (data not shown).

Discussion

In the present study, bezafibrate was administered to 7 consecutive patients with PSC, and improvements in the levels of all hepatobiliary enzymes were observed in 3 patients (43%). Bezafibrate was not effective in all the patients, although only effective cases were described in the previous reports [9, 10]. In the effective group in the present study, the effect of bezafibrate was observed rapidly, in 1 month, and lasted for a long period (Table 3). Meanwhile, in the ineffective group, except for Case 6, the RIs for ALP did not fall below 1.0 after 9–26 months of administration. The mid- to long-term effect of bezafibrate may be predicted from laboratory data after 6 months' administration. The levels of hepatobiliary enzymes were normalized after 6 months in 2 patients in our effective group. Porayko et al. showed in their study that

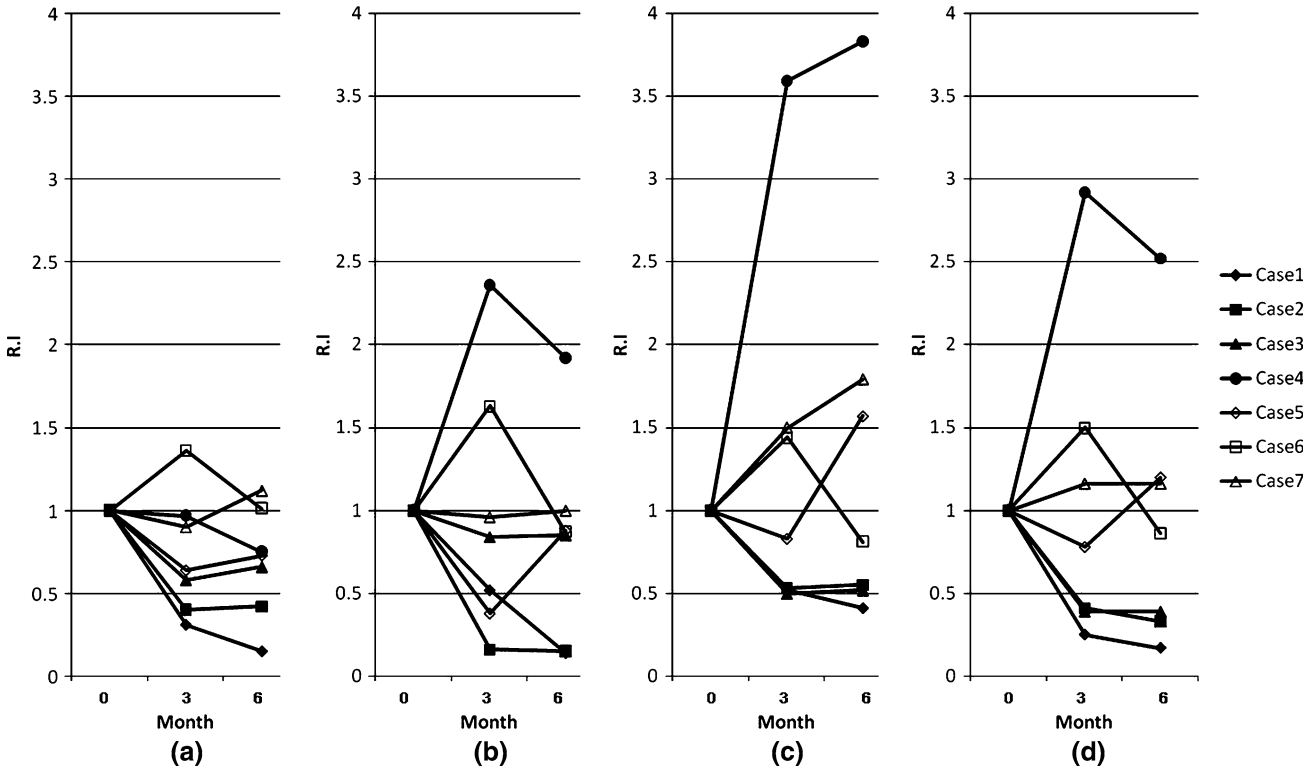

Fig. 1 Changes in hepatobiliary enzyme levels in each patient. Reduction indexes for **a** alkaline phosphatase, **b** gamma-glutamyl transpeptidase, **c** aspartate aminotransferase, and **d** alanine aminotransferase

Table 3 The latest reduction index values of alkaline phosphatase

	Observation period (months)	RI
Effective group		
Case 1	27	0.15
Case 2	17	0.49
Case 3	8	0.55
Ineffective group		
Case 4	26	1.22
Case 5	18	1.26
Case 6	11	0.97
Case 7	9	1.24

RI reduction index

asymptomatic PSC patients with comparatively high levels of AST or ALP had short survival times [2]. Thus, bezafibrate, which can lower the levels of AST and ALP in some patients with PSC, may delay disease progression.

Assessment of the effect of bezafibrate as single-agent therapy was possible in 3 patients in our study. The mean RI for ALP after 3 months of bezafibrate monotherapy in these 3 patients was 0.69. The RIs for ALP with UDCA monotherapy for PSC at standard doses were reported to be 0.53–0.75 in previous trials [14–16]. Bezafibrate monotherapy may have a beneficial effect similar to that of UDCA.

As for combination therapy of bezafibrate and UDCA, 3 of 4 patients in the present study for whom bezafibrate was added to UDCA therapy did not show a definite beneficial effect, although 2 of 3 patients in whom bezafibrate was administered prior to UDCA therapy showed a beneficial effect. This may mean that the use of bezafibrate for patients who are refractory to UDCA is not effective. However, it should be considered that bezafibrate plus UDCA therapy was administered in patients with Child B class liver function in the present study. From the viewpoint of drug therapy for PSC, UDCA eventually decreased the level of all hepatobiliary enzymes in Case 6, a patient with Child A class liver function. Overall, drug therapy was effective in 3 of our 4 patients with Child A class liver function, and in 1 of 3 with Child B class liver function. In patients without cirrhosis, it was reported that bezafibrate had an additional effect in UDCA-resistant PBC patients [17]. Similarly, oral vancomycin was reported to be effective in children with noncirrhotic PSC [18]. Thus, it is possible that drug therapy for both PSC and PBC may be more effective in patients with better liver function.

It has been reported that Japanese patients with PSC can be categorized into 2 groups [19, 20], distinguished according to age at onset, but there seemed to be no association between the efficacy of bezafibrate and the age at onset in the present study.

It is not clear from our study whether bezafibrate is useful for improving the prognosis of PSC, because the study was retrospective, the sample size was small, and the follow-up period was limited. There was no defined study protocol because of the retrospective nature of this study. We could not describe the long-term effect of bezafibrate and could not analyze statistically the factors associated with the efficacy of bezafibrate. However, our report may be noteworthy in that the number of cases in our study was the same as the total number previously reported, and in that we reported the possibility of predicting the long-term effect of bezafibrate from the laboratory data 6 months after the initiation of its administration. Moreover, we discussed the relationship between the effectiveness of bezafibrate and liver function for the first time, albeit in a nonstatistical way.

In conclusion, bezafibrate can lower levels of hepatobiliary enzymes, especially as the first medical therapy in PSC. Further studies with a larger subset of patients and a long-term follow-up period are needed to evaluate the effect of this agent on the prognosis of PSC and to determine the prognostic factors for its efficacy.

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