Chapter 19
Bezafibrate Treatment of Primary Biliary Cirrhosis

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Abstract Hepatologists commonly encounter difficulty in treating patients with primary biliary cirrhosis (PBC) who are refractory to ursodeoxycholic acid (UDCA). Even when UDCA treatment is initiated in the early stages of the disease, approximately 20–30 % of patients show persistently abnormal levels of hepatobiliary enzymes and undergo a progressive course, eventually leading to the icteric stage or liver transplantation. Several reports, mainly from Japan, have shown the beneficial effect of the fibric acid bezafibrate in UDCA-resistant patients. According to both case studies and pilot studies, bezafibrate lowers the biliary enzyme levels below the upper limit of the normal range in 60–70 % of patients who respond poorly to UDCA alone. Interestingly, IgM also decreases in a parallel manner with biliary enzymes. The main putative mechanisms of bezafibrate involve increased output of phosphatidylcholine into the bile through the upregulation of multidrug resistance protein 3 (MDR3) P-glycoprotein and a consequent reduction in the cytotoxicity of hydrophobic bile acids. Fenofibrate, another fibric acid derivative, demonstrates equivalent clinical efficacy to bezafibrate with a similar molecular mechanism. More than a dozen reports regarding the efficacy of fibrates, along with an understanding of the molecular basis of bile acid metabolism, produce the expectation that large-scale, randomized clinical trials would demonstrate the full impact of bezafibrate on cholestasis.

Keywords Bezafibrate • MDR3 • Phosphatidylcholine

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19.1 Introduction

Ursodeoxycholic acid (UDCA) replaces the cytotoxic hydrophobic bile acids that accumulate during endogenous bile acid recycling under cholestatic conditions and alleviates bile duct damage by virtue of its hydrophilic properties. It has been widely used throughout the world since the early 1990s as the first choice of treatment for primary biliary cirrhosis (PBC) [1].

Long-term monotherapy with UDCA appears sufficient for approximately 60–70 % of patients with early-stage PBC [2–4]. However, according to data from the Japanese national survey on PBC, 20–30 % of UDCA-treated asymptomatic patients continued to exhibit abnormal biochemical parameters and progressed to the icteric stage [5]. Long-term observational data from Europe also suggests that the survival rate of PBC patients treated with UDCA alone was statistically lower than that of sex- and age-matched controls [6]. Therefore, there is still a need for additional therapeutic approaches, particularly in patients refractory to UDCA.

Since a Japanese group first reported the efficacy of bezafibrate in non-cirrhotic patients with PBC in 1999 [7], a growing body of case reports and pilot studies has demonstrated that bezafibrate or a combination therapy of UDCA with bezafibrate is effective in patients who have shown incomplete responses to UDCA alone [8–17]. Most of these reports, however, are of insufficient study size and relatively short observation periods. Now that UDCA-bezafibrate combination therapy has been shown to be effective, at least in improving biochemical parameters and lowering IgM levels, it is expected to represent a new therapeutic option for improving the prognosis of PBC. Recent understanding at the molecular level of bile acid metabolism supports this contention. One of the putative mechanisms by which bezafibrate alleviates cholestasis is believed to be through the increased expression of phosphatidylcholine-specific flippase (multidrug resistance protein 3 (MDR3) in humans, mdr2 in mice, also called ABCB4) on canalicular membranes. This lipid transporter increases phosphatidylcholine output into the bile, thereby forming micelles with and reducing the cytotoxicity of the bile acids.

The initial pathological event of PBC is thought to be autoimmune destruction of bile duct epithelial cells. As bile duct damage advances, cholestasis plays a more important role in tissue damage than autoimmunity. Thus, when designing a strategy for the treatment of PBC, detoxification of the accumulated bile acids should be the major objective. Although the actions of bezafibrate and UDCA are not specific [14, 18] for PBC, they should be important agents for lessening the harmful effects of organic detergents on cells, thereby preventing further disease progression in PBC patients.

In this chapter, we discuss and review the following issues: the putative mechanisms of bezafibrate treatment, clinical studies from Japan regarding bezafibrate treatment of PBC, and our experience in the medical treatment of 89 PBC patients.

19.2 Mechanism of Action of Bezafibrate on Cholestasis (Fig. 19.1)

19.2.1 History of Fibrate and Cholestasis

Fibrate has a long history in Japan, with clofibrate first approved for hyperlipidemia in 1965 and bezafibrate approved in 1991. A large-scale clinical trial revealed that long-term bezafibrate treatment reduced the risk of cardiovascular events in patients with hyperlipidemia without major side effects [19] and bezafibrate has been widely used in Japan ever since.

The potential role of fibrate therapy in cholestasis was first suggested in 1993. Day et al. reported that bezafibrate reduced serum alkaline phosphatase (ALP) activity in patients with hyperlipidemia and prevented cholestasis. The authors speculated that the benefits were due to reduced hepatic ALP production [20]. Although some clinical researchers considered using bezafibrate to treat cholestatic liver diseases, the idea was never tested because the underlying mechanisms and clinical significance of lowering ALP activity were not well understood.

Recently, membrane transporters along the enterohepatic bile acid recycling route (present on hepatocytes, biliary epithelial cells, and enterocytes) and their regulation by the nuclear receptors PPARα and farnesoid X receptor (FXR) have

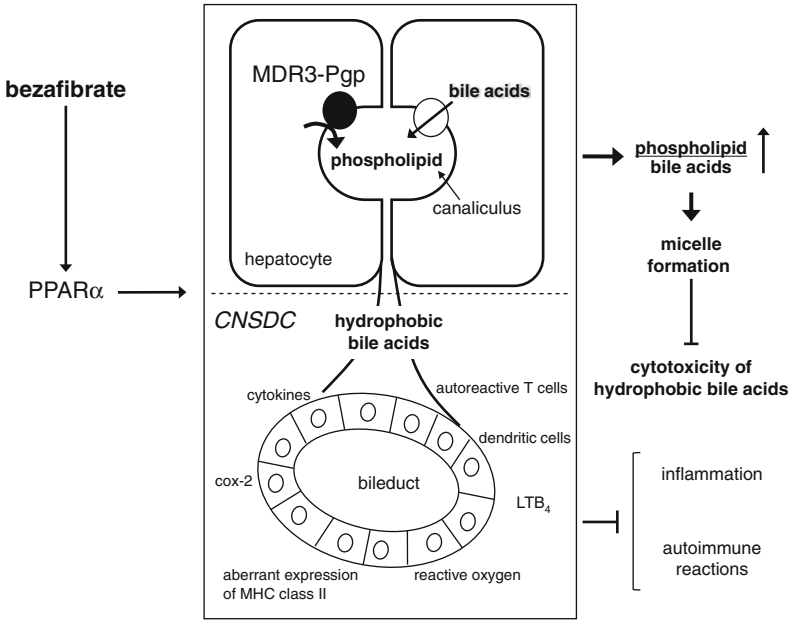

Fig. 19.1 A schematic summary of putative mechanisms of bezafibrate in treatment of PBC

been thoroughly investigated. Accordingly, our understanding of the pathological changes associated with bile formation has been enhanced, enabling the extrapolation of the putative mechanisms underlying the anti-cholestatic effects of bezafibrate [21, 22].

19.2.2 Cytoprotective Properties of Phospholipids

Bile acids are recycled several times a day, with a total amount of bile acid production of up to 20 g/day. The cells bordering the route of the bile stream are continuously exposed to harmful concentrations of hydrophobic bile acids. Therefore, these cells are equipped with several different cytoprotective mechanisms that prevent bile salt-induced toxicity. The concentration of bile acids in hepatocytes is mainly controlled by FXR, which either activates the expression of the *BSEP* (bile salt export pump, ABCB11) and *MRP2* (multidrug resistance-associated protein 2, cMOAT, ABCC2) genes or represses the *NTCP* (sodium-taurocholate cotransporting polypeptide), *OATP* (organic anion transporting polypeptides), and *CYP7A1* (cholesterol 7alpha-hydroxylase) genes [21, 22]. On the other hand, non-hepatocytes possess other protective mechanisms. HCO_3^- secretion, regulated by anion exchanger 2 (AE2) [23], maintains pH levels higher than the pK_a of bile salt monomers (the so-called HCO_3^- umbrella hypothesis). In addition, in large bile ducts, membrane-bound and secreted mucins provide a protective coating for cholangiocytes. However, the most important mechanism is the formation of mixed micelles of bile salts and phospholipids in the extracellular environment of the bile. Under physiological conditions, the ratio of bile acids to phospholipids is maintained at benign levels by the coordinated regulation of the nuclear receptors PPARα and FXR. There are many reports that emphasize the importance of this mechanism.

In mammals, phosphatidylcholine (PC) biosynthesis is completely dependent on phosphatidylethanolamine *N*-methyltransferase (PEMT). When *Pemt*$^{-/-}$ mice were fed a choline-deficient diet, hepatic PC decreased by 50 % and mice died within 5 days because of the complete absence of PC in the bile. On the other hand, animals with a double knockout of *Pemt* and *mdr2*, the gene for PC-specific flippase, survived more than 90 days. The double knockout mice adapted to choline deprivation via various recycling mechanisms, including the induction of phospholipase A2, choline kinase, and phosphocholine cytidylyltransferase, as well as the suppression of choline oxidase [24].

Tsuboi et al. described the cytoprotective effects of lecithin against bile salt-induced bile duct damage in vitro. Immortalized mouse cholangiocytes were cocultured with various hydrophobic bile acids to induce cellular apoptosis. Addition of lecithin inhibited bile acid-induced apoptosis in a concentration-dependent manner, accompanied by enhanced multidrug resistance-associated protein 3 (*MRP3*) expression and suppression of apical sodium-dependent bile salt transporter (*ASBT*) [25].

These findings indicate that bile phospholipid provides physiological protection of cells from damage by hydrophobic bile acids by virtue of micelle formation as

well as by the possible alteration of membrane transporter expression. Furthermore, hereditary abnormalities in transporter genes, or cholestasis caused by acquired factors, result in the deterioration of these cytoprotective mechanisms [22].

19.2.3 MDR3 Controls Phospholipid Concentration in the Bile

In humans, biliary phospholipids are transported into the bile via MDR3 P-glycoprotein (also called phosphatidylcholine flippase), which is equivalent to rodent *mdr2* P-glycoprotein. Mice with homozygous disruption of the *mdr2* gene completely lack phospholipids in the bile and develop portal inflammation, ductular proliferation, hepatocyte degeneration, and fibrosis [26]. deVree et al. identified mutations in the *MDR3* gene in patients with progressive familial intrahepatic cholestasis (PFIC) type 3 [27], which shows similar hepatic histological characteristics to that of *mdr2* knockout mice.

It should be noted that these pathological features are similar to those found in PBC liver. Recent advances in basic research clarified that hereditary abnormalities in ATP-binding cassette transporters are related to a broad spectrum of cholestatic liver diseases such as PFIC, benign recurrent intrahepatic cholestasis, and intrahepatic cholestasis of pregnancy [22]. Although the role of genetic impairment or variation in such ATP-binding cassette transporters in the pathogenesis of PBC is not clear, recent data suggest that such variation might be related to PBC disease severity or susceptibility.

Interestingly, no abnormalities were found in *mdr2*(+/−) heterozygous mice, even though the maximal phospholipid output in these mice is reduced to 60 % of that observed in (+/+) mice [26]. Similarly, *MDR3* (+/−) human subjects do not appear to have liver disorders. The mother of a patient with PFIC3, who is thought to be heterozygous for mutant *MDR3*, developed recurrent cholestasis during pregnancy [27]. Presumably, an unknown pregnancy-related mechanism decreased the phospholipid/bile acid ratio. These observations lead to the speculation that a phospholipid output of 60 % of normal is sufficient to counteract the detergent action of the bile acids, and increasing the amount of phospholipid output could represent a therapeutic strategy for cholestatic liver disease.

19.2.4 Bezafibrate Upregulates MDR3 Expression and PC Output into the Bile

These data prompted us to speculate that fibrate could have therapeutic benefits on cholestatic liver diseases, because one of the most important actions of fibrate is the augmentation of MDR3 expression via PPARα and the subsequent increased

phospholipid output into the bile [28]. Therefore, bezafibrate is expected to increase the phospholipid concentration in the bile and restore the phospholipid/bile acid ratio to harmless levels. Direct evidence was reported recently indicating that bezafibrate induces MDR3-Pgp expression in cultured human hepatocytes and humanized liver in chimeric mice [29], with expression levels of MDR3 in PBC liver reported to be unchanged or not deficient [30–32]. To date, there are no reports of genetic abnormalities in MDR3 or bile acid transporter genes, and a recent genome-wide association study comparing PBC patients and normal subjects did not identify PBC-specific SNPs in those genes [33]. Therefore an imbalance of the phospholipid/bile acid ratio is thought to be mainly due to the accumulation of bile salts in cholestasis rather than congenital genetic abnormalities. Furthermore, bezafibrate may induce further upregulation of MDR3 expression to compensate for the excess levels of hydrophobic bile acids in the cholestatic environment.

Recently, Honda et al. reported a novel mechanism for bezafibrate using DPX2 cells, a derivative of the Hep2 cell line, which suggests that bezafibrate is capable of acting as a dual agonist of PPARs (α, δ, γ) and PXR and modulates their target genes, resulting in the upregulation of CYP3A4, downregulation of CYP7A1, and enhancement of canalicular MDR3, MDR1, and MRP2 expression [17]. Although further studies are required, their study breaks new ground in the elucidation of the precise molecular mechanisms of bezafibrate and may lead to the development of new therapeutic agents.

19.2.5 Bile Salt Transporters and Fibrate

Under cholestatic conditions, MRP3 and MRP4 become important as alternative basolateral transporters for bile acid efflux. Bezafibrate may upregulate these export transporters to eliminate toxic bile salts, and it has been reported that clofibrate alters the expression of these transporters in mice [34]. Another potential beneficial effect of bezafibrate on the enterohepatic circulation of bile salts is the regulation of ileal bile acid-binding protein (I-BABP) expression. I-BABP acts as a bile acid carrier and contributes, together with the liver fatty acid-binding protein (FABP), to the regulation of bile acid metabolism. Bezafibrate has been shown to upregulate the expression of I-BABP in human intestine-derived Caco-2 cells [35].

There has been almost no data regarding the effects of bezafibrate on FXR. When PPARα knockout mice were administered bezafibrate, CYP7A1 expression was suppressed and BSEP expression was enhanced [36]. Because these expression profiles are consistent with FXR activation, it is expected that bezafibrate could influence signaling networks involving nuclear receptors and transcription factors.

19.2.6 Anti-inflammatory Effects of Fibrate

Fibrates, including bezafibrate, are capable of acting as ligands of PPARα. PPARα plays a pivotal role in mitochondrial energy metabolism and the maintenance of cellular homeostasis. PPARα also regulates leukotriene B_4 (LTB_4) inactivation, which determines the extent and duration of inflammation [37].

In smooth muscle cells in human atherosclerotic lesions, PPARα inhibits interleukin-1-induced production of interleukin-6 and prostaglandin and the expression of cyclooxygenase 2 (Cox2) [38]. This observation is interesting because Cox2 is reported to be expressed in PBC biliary epithelial cells [39].

PPARα plays an important role in immunological reactions, such as MHC expression and antigen presentation in dendritic cells. Aberrant expression of MHC class II on biliary epithelial cells is one of the most important phenomena in the pathogenesis of PBC [40]. Bezafibrate may have certain effects on autoimmune reactions involved in chronic non-suppurative destructive cholangitis (CNSDC) of PBC.

Oxidative stress is considered to be another important mechanism in bile duct damage in PBC. Inoue reported that rat liver Cu^{2+},Zn^{2+}-superoxide dismutase (SOD) gene expression was enhanced by bezafibrate administration, which was correlated with the expression of PPARα mRNA level [41]. Consequently, bezafibrate may have an antioxidant effect in liver inflammation. Recent study showed that bezafibrate improved oxidative stress, hepatic stellate cell activation, and fibrogenesis in murine nonalcoholic steatohepatitis model and directly inhibited hepatic fibrogenic response induced by TGF-β1 in vitro [42].

The above findings suggest the possibility that bezafibrate may contribute to the attenuation of inflammation or autoimmune reactions in the PBC liver through PPARα activation.

19.3 Pilot Studies Examining the Effectiveness of Bezafibrate on PBC (Table 19.1)

The first study that suggested the effectiveness and putative mechanism of bezafibrate on PBC originated from Japan in 1999 [7], and more than a dozen case studies and pilot studies [8–17] have been subsequently reported. Most of these studies were from Japan and no reports were from the USA, probably because bezafibrate has not been approved for use by the FDA.

Overall, the reports concur on the beneficial effects of bezafibrate on the improvement of biochemical changes, including levels of ALP, abnormal γ-glutamyltransferase (GGT), aminotransferases, cholesterol, and immunoglobulin M (IgM), as well as the manifestation of cholestasis. In most studies, biliary enzymes were reduced to 50–70 % of the pretreatment levels. Most interestingly, as reported in all eight studies that included UDCA-resistant patients, bezafibrate

Table 19.1 Summary of prospective clinical studies and case series testing the efficacy of bezafibrate in patients with primary biliary cirrhosis

			Number of patients			Treatment outcome of additional BF or BF alone								
Author (year)	Study design	Study duration	UDCA	UDCA + BF	BF	UDCA resistant	ALP	GGT	ALT	Bil	IgM	cho	TG	Pruritis	Fatigue
Randomized controlled trials															
Nakai (2000) [12]	Single center	12 months	13	10	0	23	↓*1*2	↓*2	→	→	↓*1*2	NS	NS		
Kurihara (2000) [11]	Single center	12 months	12	0	12	0	↓*1*2	↓*1*2	↓*1*2	NS	↓*1*2	NS	NS		
Kanda (2003) [10]	Single center	6 months	11	11	0	22	↓*1	↓*1	→	→	↓	→	NS	↓	NS
Itakura (2004) [9][a]	Single center, crossover design	6 months	7	9	0	0	↓*1	↓	↓	→	↓	→	→		
Iwasaki (2008) [8]	Multicenter	52 weeks	25	20	0	0	↓*2	↓*2	↓*2	→	↓*2	↓*2	↓*2		
	Multicenter	52 weeks	10	12	0	22	↓*2	↓*2	↓*2	→	↓*2	↓*2	↓*2		
Pilot studies and case series															
Iwasaki (1999) [7]		12–21 months	0	7	4	9	↓	↓	NS	NS	↓	NS	NS	↓	↓
Ohmoto (2001) [13]		12 months	0	10	0	10	↓	↓	↓	NS	↓	NS	NS	Symptoms were improved in all patients	
Akbar (2005) [16]		12 months	0	10	6	10	↓*2	↓*2	NS	→	↓*2	↓*2	NS		
Kita (2006) [14]		6< months	0	12	0	12	↓*2	↓*2	↓	NS	↓*2	NS	NS		
Takeuchi (2011) [15]		6< months	22	15	0	12	↓*1	↓*1	→	→	↓*1	↓*2	↓*2		
Honda (2013) [17]		3 months	0	19			↓*2	↓*2	↓*2	NS	↓*2	↓*2	↓*2		

UDCA ursodeoxycholic acid, *BF* bezafibrate, *1 significant compared to UDCA alone, *2 significant compared to the data before treatment

[a]The data from the first period of the crossover trial

appears to show a beneficial effect in patients who have been refractory to previous UDCA monotherapy.

Three studies showed that the IgM lowering effect of bezafibrate was significantly stronger than that of UDCA. Four studies evaluated bezafibrate monotherapy and reported its effectiveness in PBC patients in improving hepatobiliary enzymes and IgM. As for symptoms, such as malaise and pruritus, three studies using bezafibrate and UDCA combination therapy reported improvement of symptoms.

A UDCA dose of 600 mg/day was used in all of the Japanese studies. This standard dose in Japan is thought to be subtherapeutic compared to the typical recommended dose of 13–15 mg/kg/day used in other countries. Therefore, it is difficult to precisely compare the Japanese data with those from European countries or the USA with respect to UDCA therapy.

Although the great majority of these studies used biliary enzyme levels as a measurement of treatment effects, the definition of refractoriness or resistance to UDCA therapy is not consistent. Most of the definitions of suboptimal biochemical responses to UDCA proposed in European countries use ALP levels [2, 3, 43], and the most recent study from France reported that ALP <1.5 times the normal upper limit after adequate UDCA treatment is the biochemical criterion used to identify early-stage PBC patients who are at very low risk of long-term development of liver failure [44]. The Ehime group analyzed the Japanese population and proposed that abnormal GGT, or inadequate decreases in GGT following UDCA treatment, should be a more important criterion for determining treatment outcomes [45]. Taking these studies into consideration, satisfactory improvement of biliary enzymes could be considered as a good prognostic marker.

Results from these pilot studies are encouraging, because in all studies bezafibrate improved or normalized biliary enzyme levels, which are surrogate markers of prognosis in patients with PBC. However, a long-term, large-scale, multicenter randomized control study using international unified criteria is definitely required to prove the genuine efficacy of bezafibrate as an additive treatment for PBC. Indeed, the systematic review of six trials with 151 Japanese patients by Cochrane showed only a possible beneficial effect of bezafibrate on hepatic biochemical data compared with the control group. Furthermore, this study did not demonstrate an effect of bezafibrate, versus no intervention, on mortality, liver-related morbidity, adverse events, and pruritus, because of several limitations and a high risk of bias [46].

19.4 Bezafibrate in Clinical Practice

Bezafibrate is recommended for all PBC patients that have been refractory to UDCA alone. Although several definitions of a suboptimal biochemical response to UDCA are proposed [2, 3, 43], in clinical practice all patients with abnormal biliary enzyme levels, in spite of adequate UDCA therapy, deserve consideration for additive therapy with bezafibrate. In our experience, almost all patients with early-stage

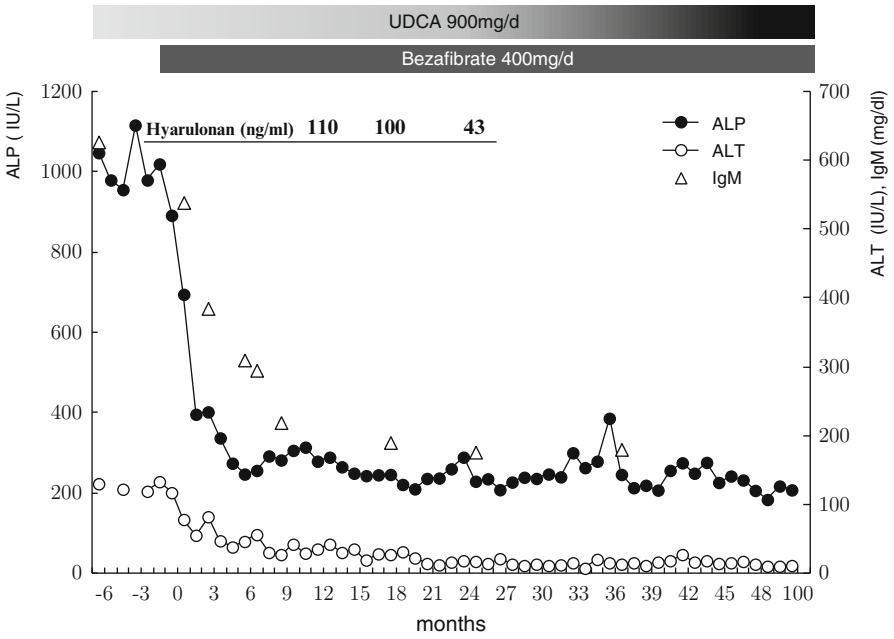

Fig. 19.2 Clinical course of 56 years of male patients with stage II PBC. After addition of bezafibrate to 900 mg/day of UDCA, hepatobiliary enzymes and IgM were normalized within 6 months and were maintained under the upper limit of normal range until the age of 74, except 19 weeks of bezafibrate discontinuation at the age of 68 (identical to the second case of Fig. 19.3). Needle biopsy at the age of 74 in 2014 revealed progression of disappearance of interlobular bile ducts, but inflammation in portal area has been improved and no bridging fibrosis was observed. In total, his histological stage remained in stage III

PBC exhibited good responses to bezafibrate, but no or little biochemical improvement was observed in patients with advanced disease. Careful attention may be required for patients with diminished hepatic functional reserve because exacerbation of ALT was observed after bezafibrate administration in two icteric patients.

The standard dose of bezafibrate is 400 mg/day, usually administered twice a day. In patients with serum creatinine >1.5 g/dL, the dose should be reduced to 100–200 mg/day. Coadministration with UDCA is recommended because the pharmacological mechanisms of these drugs are different and complementary to each other, with possible additive or even synergistic effects. In particular, for patients with high biliary enzymes or high-grade histological inflammation, it is recommended to initiate UDCA and bezafibrate simultaneously or to evaluate the effectiveness of UDCA for 3–6 months after commencing UDCA treatment, since these patients are at a high risk of developing cirrhosis.

When bezafibrate is effective, biliary enzymes and transaminase rapidly decline by 3–6 months, frequently reaching levels near or below the upper normal range. The typical clinical course of the patient is shown in the figure (Fig. 19.2). IgM also decreases in a parallel manner with biliary enzymes.

Bezafibrate is usually well tolerated, but rhabdomyolysis or renal dysfunction can occur. Careful attention is necessary, especially in the elderly and patients with renal dysfunction. Concomitant use of statins should be avoided, because of an increased risk of rhabdomyolysis or myopathy.

Fenofibrate is another fibric acid used for the treatment of PBC. In 2002, Ohira reported on the efficacy of fenofibrate comparable to that of bezafibrate in patients with PBC [47]. Since then, similar results have been obtained in four other studies. The hypothesized mechanism is the same as for bezafibrate, and upregulation of MDR3/ABCB4 by way of PPARα has also been demonstrated in rats [48]. Comparison of individual fibric acid derivatives, in terms of efficacy and adverse events in the treatment of PBC, should be a topic for future research.

19.5 Response to UDCA Monotherapy and UDCA/ Bezafibrate Combination Therapy: Single-Center Results from 89 Patients [49]

19.5.1 Single-Center Results of Medical Treatment of 89 PBC Patients

Eighty-nine patients with anicteric (total bilirubin, <2.0 mg/dL) PBC were analyzed retrospectively. All patients were diagnosed based on biochemical and histological findings as having definite PBC, and UDCA monotherapy was initiated from 1995 to 2004 at Kochi Medical School. In 28 of 89 patients (31 %), hepatobiliary enzymes did not return to the normal limit following at least 6 months of UDCA administration, after which bezafibrate adjunct therapy was started. In 19 (67.9 %; 10 stage I, 4 stage II, 4 stage III, and 1 stage IV) of these 28 UDCA-resistant patients, hepatobiliary enzymes improved to below normal limits following coadministration of bezafibrate and have remained within normal limits for an extended period of time. Of the three patients who underwent serial liver biopsies, two patients showed histological improvement in portal inflammation and fibrosis. The nine patients (32.1 %; 4 stage I, 4 stage II, and 1 stage IV) who did not have a complete response to combination therapy exhibited disease progression. Among them, one died of liver failure and two had to undergo liver transplantation.

19.5.2 Predictive Factors Related to Responsiveness to Adjunct Bezafibrate

To explore the factors that influenced the efficacy of combination therapy with UDCA (600 mg/day) and bezafibrate (400 mg/day), we analyzed the patients' clinical, biochemical, and immunological parameters. When the responder group

was compared with the nonresponder group using univariate analysis, serum bilirubin (group of complete response to bezafibrate, 0.59 ± 0.17 mg/dL, vs group of incomplete response to bezafibrate, 1.05 ± 0.42 mg/dL; $p = 0.0004$), aspartate aminotransferase (AST)(group of complete response, 47.2 ± 22.4 IU/L, vs group of incomplete response, 66.3 ± 13.1 IU/L; $p = 0.03$), and GGT levels (group of complete response, 118 ± 66.3 IU/L, vs group of incomplete response, 354 ± 252 IU/L; $p = 0.0007$) were found to be significantly associated with responsiveness to adjunct therapy with bezafibrate. Subsequent multivariate analysis, however, revealed that none of the factors was significantly related to responsiveness to the addition of bezafibrate. This is likely due to the small patient size.

19.5.3 Discontinuation of Bezafibrate Resulted in Exacerbation of Biochemical Findings

Of the 19 patients who had been refractory to prior UDCA monotherapy and responded completely to adjunct bezafibrate with long-term biochemical normalization, bezafibrate was discontinued and reverted to UDCA monotherapy in five patients. The duration of combination therapy with UDCA and bezafibrate ranged from 5 to 12 years. Several weeks after discontinuation of bezafibrate, biochemical rebound was observed in all five patients and bezafibrate treatment was restarted. Renormalization of biochemical data was observed in all patients in response to the resumption of bezafibrate treatment (Fig. 19.3).

Overall, UDCA was effective in terms of normalization of biochemical data in about two thirds of patients with anicteric PBC, which was largely consistent with other reports. Among the remainder of UDCA-resistant patients, two thirds responded to bezafibrate. Although the number of patients is small and histological evaluation is lacking, our observation strongly suggests that bezafibrate is indispensable for maintaining biochemical parameters within the normal range in a cohort of patients who are refractory to UDCA.

On the other hand, it is reasonable to speculate that an underlying inflammatory process in the bile duct, which is likely to be autoimmune in nature, remains active in patients with normal biochemical parameters during UDCA and bezafibrate combination therapy, because withdrawal of bezafibrate produces an immediate biochemical rebound even in the patient with >12 years of treatment.

19.6 Conclusions and Outlook

PBC has two aspects of the disease process, the first being liver-specific autoimmunity and the other being cholestasis. Although many studies have been conducted since the discovery of the anti-mitochondrial antibody, the significance

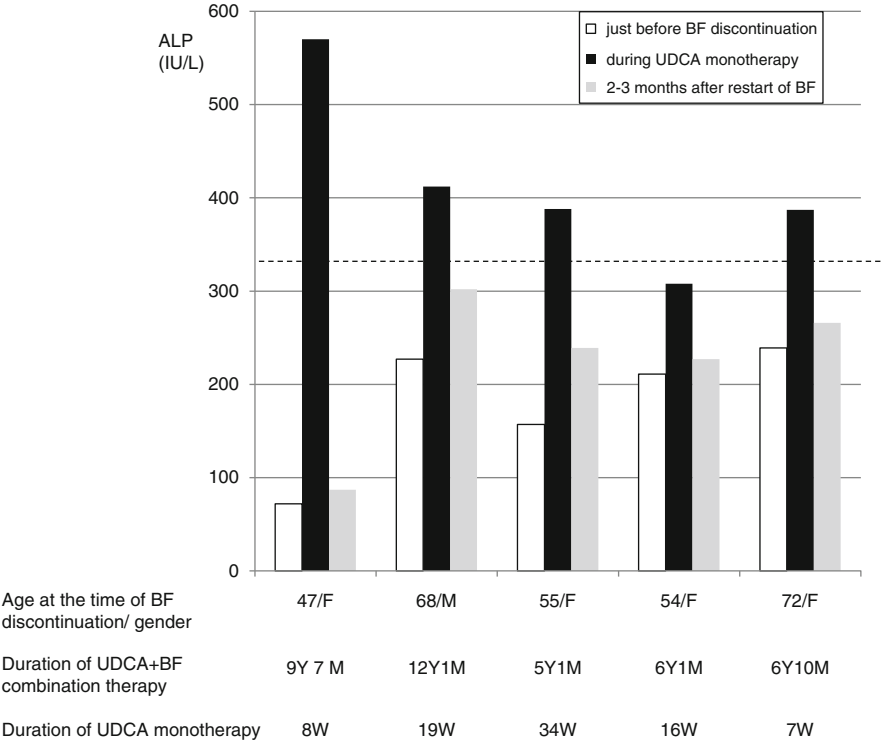

Fig. 19.3 Discontinuation of bezafibrate resulted in exacerbation of ALP and renormalization was observed in all patients in response to resumption of bezafibrate treatment. The *dotted line* indicates the upper limit of normal range. *BF* bezafibrate, *UDCA* ursodeoxycholic acid

and relationship of this antibody to PBC pathology remains unknown. An autoimmune process is probably the initial event that is important for the development of this disease. However, subsequent cholestasis modifies the disease pathology, obscures the elucidation of the disease mechanism, and complicates therapeutic strategies. Although clinical trials involving several immunosuppressants targeting autoimmunity have been conducted, most of these trials failed or could not demonstrate beneficial effects in PBC.

To date, accumulating knowledge of the molecular basis of bile acid metabolism has provided insight into the pathophysiology of cholestasis and clues for therapeutic approaches. In fact, several novel therapeutic approaches are under investigation, such as agonists for FXR and the G protein-coupled bile acid receptor TGR5 [50, 51]. Bezafibrate already has greater than a decade of history in clinical and basic research as a PPARα ligand and therapeutic agent for PBC. Large-scale, prospective, multicenter randomized controlled trials are definitely required to evaluate the full impact of bezafibrate on cholestasis, as noted by others [52, 53].

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