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Transition from Conventional Drugs to Promising Drugs for Primary Biliary Cholangitis

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Abstract

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a chronic cholestatic liver disease characterized by chronic, non-suppurative, destructive cholangitis that eventually leads to cholestasis, fibrosis, cirrhosis and subsequent hepatic failure and death if left untreated. The only available therapeutic agent for PBC is ursodeoxycholic acid (UDCA), which has been demonstrated to delay the development of fibrosis as well as improve patient survival without the need for liver transplantation. However, not all patients achieve a complete biochemical response to UDCA.

Fibrate is a fibric acid derivative used in the treatment of hypercholesterolemia and hyperglyceridemia, and it has been incidentally noted to cause a decrease in serum liver biochemical markers. The proposed mechanism of action of fibric acid derivatives involves regulation of the expression of various kinds of lipids and proteins, as well as cell proliferation, through the activation of peroxisome proliferator-activated receptor-α. Obeticholic acid, a first-in-class alternative farnesoid X receptor agonist, is a semi-synthetic bile acid analogue of 6α-ethyl-chenodeoxycholic acid that is nearly 100-fold more potent than chenodeoxycholic acid. The efficacy of both fibrate and beticholic acid in addition to UDCA in asymptomatic PBC patients who did not respond well to UDCA alone has been confirmed. Further progress in the study of newer drugs that are effective for symptomatic PBC patients is expected in the future.

Keywords: Primary biliary cholangitis; Fibrate; Histology; Therapy

Ursodeoxycholic Acid

The first known available therapeutic agent for primary biliary cholangitis (PBC) is ursodeoxycholic acid (UDCA), which has been demonstrated to delay the development of fibrosis as well as improve survival in patients without the need for liver transplantation [1-3]. The optimal dosage of UDCA is 13-15mg/kg/day and it is the standardized treatment for PBC. However, not all patients achieve a complete biochemical response to UDCA, and 10-20% will progress to cirrhosis or require liver transplantation. The most important merits of UDCA are lower costs and few adverse effects.

Budesonide

Budesonide is a glucocorticoid receptor/pregnane X receptor (PXR) agonist. Combination therapy of budesonide and UDCA was able to ameliorate the plasma biochemical index of hepatic function and hepatic histology, particularly in PBC patients with hepatic fibrosis, whereas the treatment effeciveness of UDCA alone was principally seen in laboratory results [4].

Methotrexate

In patients who responded inadequately to UDCA, methotrexate noticeably improves hepatic enzyme tests and hepatic histology [5]. However, of the immunosuppressive drugs that have been tested for the treatment of PBC, azathioprine, cyclosporine and methotrexate were not found to improve patient survival [6,7].

Fibrates

Fibrate is a fibric acid derivative used in the treatment of hypercholesterolemia and hyperglyceridemia that has been incidentally noted to cause a decrease in the levels of serum liver biochemical markers. The proposed mechanism of action of fibric acid derivatives involves the regulation of cell proliferation and the expression level of various lipids and proteins via the activation of peroxisome proliferator-activated receptor (PPAR)-α [8-10]. Therefore, fibric acid is referred to as a "PPAR-α agonist". Bezafibrate activates all three isoforms of human PPAR (PPAR-α, PPAR-δ, and PPAR-γ) at similar concentrations (i.e., 50, 20 and 60

μM, respectively) [11,12]. Therefore, the term "pan-PPAR" agonist is a more accurate description of bezafibrate. On the other hand, fenofibrate has been confirmed to exhibit a stronger binding activity for PPAR-α than bezafibrate [12]. Hence, fenofibrate is referred to as a "PPAR-α-selective" agonist [11].

There are scarce data regarding the biochemical effects of fenofibrate in patients with PBC [11,13-19]. Moreover, the long-term biochemical effects of fenofibrate on PBC are unknown. As for histological studies of PBC patients treated with UDCA or UDCA plus fibrate, Angulo et al. [7] reported that long-term UDCA therapy for 6.5 years in 16 PBC patients resulted in eight cases of "no change/improvement" histologically and eight cases of "worse" findings, although the difference was not significant between the UDCA group and the control group (50% vs. 71%) [20]. In addition, Yano et al. reported that clear histological improvements were not observed in their study despite a dramatic biochemical response in patients treated with bezafibrate plus UDCA for PBC [21]. Recently, it was confirmed that the use of fenofibrate plus UDCA treatment for asymptomatic PBC leads to histological improvements as well as reductions in the levels of ALT, ALP, γGTP and IgM [22]. In the study, there was no apparent tendency for fenofibrate to cause elevation of the levels of total bilirubin, transaminase or creatinine. In addition, no patients experienced adverse effects, such as rhabdomyolysis, miosis or increased serum creatinine phosphokinase levels [22].

Obeticholic Acid

Obeticholic acid (OCA) is a semi-synthetic bile acid analogue of 6α-ethyl-chenodeoxycholic acid that is nearly 100-fold more potent than chenodeoxycholic acid (CDCA) and is a powerful first-in-class alternative FXR agonist derived from primary human bile acid CDCA, the natural endogenous FXR agonist. A randomized, controlled clinical trial showed that treatment with OCA observably decreased the serum concentrations of γ-GTP, ALP and ALT in PBC patients who had an inadequate response to UDCA, in comparison with placebo [23]. OCA is so expensive that improving cost-effectiveness could be a challenge.

Newer drug expectations and appropriate timing of administration of drugs

The efficacy of UDCA, fibrate or other medicines for symptomatic PBC patients has not been confirmed. Newer drugs that are effective for symptomatic PBC patients are clearly needed. Moreover, the use of drugs is expected to be categorized according to the stage of PBC and response to drugs could be predictive of the outcomes of PBC.

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