First-and Second-Line Therapies for Primary Biliary Cholangitis

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Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by the progressive destruction of the intrahepatic bile ducts. Currently, the first line drug for PBC is ursodeoxycholic acid characterized by anti-apoptotic, anti-inflammatory and protective actions on cholangiocytes.

liver ursodeoxycholicacid obeticholic acid cholestasis

1. Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by the progressive destruction of the intrahepatic bile ducts and progression, if not treated, to fibrosis and cirrhosis [1][2][3]. PBC predominantly affects women over the age of 40 (woman/man rate of 9–10:1). Recent epidemiological data point to an increase in cases in men (woman/man rate of 2–3:1) [4]. The disease is characterized by a yearly incidence and prevalence rate of 0.33–5.8/100.000 and 1.91–40.2/100.000 individuals, respectively [4][5][6]. Most of the affected subjects are asymptomatic throughout the initial phase of the disease, which is often diagnosed by chance following an increase in alkaline phosphatase (ALP). Diagnosis is made when at least two of the following criteria are met: (1) positivity for antimitochondrial antibodies (AMA), (2) increase in ALP, (3) chronic non-suppurative cholangitis of small and medium caliber bile ducts [7][8].

Although the etiopathogenesis of PBC is still uncertain, multifactoriality represents a crucial element in the onset of the pathology. The development of PBC has been linked to genetic predisposition of the affected subjects. In particular, PBC susceptibility has been shown to be associated with polymorphisms in the Human Leucocyte Antigen (HLA) region especially in the alleles DRB1*08, DRB1*11, DRB1*14, DPB1*03:01 and DQB1 [9][10][11][12].

One of the determining factors is the loss of tolerance for the PDC-E2 autoantigen (component E2 of pyruvate dehydrogenase complex). It seems that PDC-E2 plays a fundamental role in activating Th1 cells response through interleukin (IL)-12. T cells start producing interferon (INF)-γ and tumor necrosis factor (TNF)-α, which trigger a cytotoxic action. In addition, IL-4 activates B cells causing the release of AMA, which promote senescence and apoptosis of bile epithelial cells (BEC) [13][14][15]. In addition, another element contributing to the onset of PBC is the presence of a defective “bicarbonate umbrella”. This “bicarbonate umbrella” is essential for protection against the accumulation of bile acids and their cytotoxic effects. In PBC, the impairment of this protective “umbrella” increases the sensitivity of cholangiocytes to bile acids, which accumulate in the BEC generating reactive oxygen species thus further promoting senescence and apoptosis [14].

2. The First-and Second-Line Therapies for PBC

The first-line pharmacological treatment in PBC patients is ursodeoxycholic acid (UDCA), and in those with inadequate response to UDCA treatment, the FXR agonist OCA, which represents the second-line treatment for PBC, is used. Despite the therapeutic efficacy of UDCA and OCA, interesting pharmacological alternatives are being evaluated as reported below.

2.1. UDCA

UDCA represents the first line therapy in the treatment of PBC, and for a long time, it has been the only drug approved by the Food and Drug Administration (FDA) for this syndrome [16]. Therapy with UDCA involves long-term treatment with a dose of 13–15 mg/kg/day [17]. UDCA can be administered as a single oral dose, and in case of poor tolerability, the dose can be divided [14]. UDCA owes its effectiveness in the treatment of PBC, to a series of effects such as the protective action on cholangiocytes, anti-apoptotic and anti-inflammatory activities and a post-translational stimulation of synthesis of liver export pumps [1][2]. Indeed, it has been shown that one of the protective mechanisms of UDCA against cholestasis is the disposal of accumulated bile acids. However, the secretory capacity of the hepatocytes is closely related to the presence of transport proteins in the canalicular membrane. In this regard, UDCA induces an increase in expression for bile salt export pumps (BSEP), proteins associated with multi-drug resistance (MDR3) and multidrug resistance associated protein 4 (MRP4) thus facilitating the elimination of bile acids [18][19][20]. Furthermore, timely diagnosis and early treatment with UDCA delay the progression of PBC. In particular, it was found that treatment with UDCA of PBC patients at advanced stages (extensive liver fibrosis) led to a considerably reduced rate of disease progression. Moreover, after 4 years of therapy, an arrest in the initial state of the syndrome has been observed in 76% of cases. Despite the high efficacy demonstrated by UDCA therapy, about 40% of the subjects do not benefit from its use [2]. In this case, the combined regimen, UDCA plus OCA, has been proposed.

2.2. OCA

OCA is a semisynthetic derivative of chenodeoxycholic acid (CDCA) and represents a second-line therapy in case of non-responsiveness to UDCA [1][16][17]. OCA is an FXR agonist with 100 times higher affinity for the receptor with respect to CDCA, the endogenous ligand [16]. FXR is a member of the nuclear receptor superfamily, comprising endocrine, metabolic and orphan receptors [21]. FXR is highly expressed in the liver, gallbladder, intestines and kidneys [22][23]. In particular, upon activation, FXR regulates the synthesis, excretion, transport, absorption and metabolism of bile acids [24]. Furthermore, OCA increases the expression of fibroblast growth factor 19 (FGF-19) thus leading to a reduction in the synthesis of biliary acids. In the ileum, OCA reduces the reabsorption of biliary acids by down-regulating the apical transporter (apical sodium dependent bile acid transporter or ABST) [16]. OCA, unlike UDCA that interacts at a post-transcriptional level, acts directly on the synthesis, absorption and secretion of bile acids [14].The efficacy of OCA was assessed in the POISE study, a double-blind phase 3 study of 12-month duration [25]. In this study, 217 patients with inadequate response to UDCA were divided into three groups and were treated with OCA, respectively, with a daily dose of 10 mg, 5 mg with an adjustment to 10 mg when applicable, or with placebo in addition to UDCA treatment (13–15mg/kg/day). The primary end point, represented by an ALP level

of less than 1.67 × upper limit normal, occurred in 46% of patients in 5–10 mg OCA treatment and in 47% of those in 10 mg OCA treatment compared to 10% in the placebo group. In addition, improvements in cholestasis, hepatocellular damage, inflammation and apoptosis were observed. The most commonly observed side effect was pruritus, noted in 56% of the 5–10 mg group and 68% of the 10mg group versus 38% of the placebo group. Currently, in the clinical setting, OCA is used in combination with UDCA in subjects who do not respond to UDCA treatment alone; this combination allows to reduce the incidence of liver complications [2]. OCA is considered as a safe treatment, albeit itching is the more common side effect [26].

Other therapies, and in particulr for patients with advanced fibrosis should are now under evaluation. However, in PBC patients with decompensated cirrhosis, medical treatment is unlikely to significantly impact the course of disease, and the unknown risk of second-line therapies in these patients should give with caution.

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