Obeticholic Acid for the treatment of Primary Biliary Cholangitis.

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Primary Biliary Cholangitis, previously known as Primary Biliary Cirrhosis, is a disease mainly affecting women in their fifth to seventh decades of life. In many patients the disease may progress faster toward cirrhosis and its complications. Ursodeoxycholic acid (UDCA) is the only treatment available today, but even if effective in counteracting the disease progression for the majority of patients, in approximately 40% is not able to decrease effectively the alkaline phosphatase, a surrogate marker of disease activity. Obeticholic acid (OCA) is an analogue of chenodeoxycholic acid (CDCA), where the addition of an ethyl group provides a strong affinity for the nuclear farnesoid X receptor (FXR). This receptor is actively involved in the regulation of bile acids metabolism, inhibiting their production, increasing their excretion and reducing liver and intestinal reabsorption. OCA has a 100 times higher affinity for FXR than CDCA, and plays a different mechanism of action from UDCA, whose primary activity is the dilution of the endogenous bile. Based on the results of two phase II studies and one phase III study (POISE), OCA received a conditional approval by EMA and it is now available in Italy. In the phase II 747202 study, OCA in combination with UDCA was proven to reduce ALP by 20-25% in a non dose-dependent fashion after a 12 week treatment. The reduction of ALP is clinically and statistically significant even after two weeks of treatment, reaches a peak after 6 months and then stabilizes. In the POISE study, a composite primary endpoint based on ALP<1.67 + ALP reduction of at least by 15% from baseline and total bilirubin (TB) lower than or equal to the Upper Limit of Normal (ULN) at 12 months was evaluated. The secondary endpoints were the reductions of biochemical markers: ALP, AST, bilirubin and GGT. The primary endpoint was reached by 46 to 47% of patients taking OCA, with an earlier effect in the OCA 10mg treatment arm. ALP, AST and GGT reached their lowest levels after three months and then remained stable for the whole study period, as it was seen in phase II studies. Furthermore, a reduction of ALP by at least 15% was reported in 77% of patients. The main adverse event was pruritus but, this symptom decreased over time and reached the same level as at baseline after six months. In substance, OCA represents a significant advance in the treatment of PBC.