Falk Workshop

Targeted Therapies in Hepatology

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Falk Workshop

TARGETED THERAPIES IN HEPATOLOGY

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N.P. Malek, Tübingen (Germany)
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Another challenge for personalized therapy: Efficacy of therapeutic influence on Peroxisome Proliferator Activated Receptor-gamma is determined by PPARG Pro12Ala gene polymorphism

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Introduction: Multiple studies showed that Peroxisome Proliferator Activated Receptor-gamma – NR1C3 (PPARG) plays an important role in various biological processes including lipid and glucose metabolism. PPARG agonists have been used in treatment of different metabolic disorders and non-alcoholic steatohepatitis (NASH) decreasing steatosis, inflammation, and fibrosis.
The aim of the study was to clarify the perspectives for individualized therapy with thiazolidinediones.

Methods: 249 patients with hypertension, dyslipidemia, metabolic syndrome participated in the study. Among them 50 patients with NASH were selected to form study group. PPARG agonist Pioglitazone administered 30 mg daily during 50–51 weeks. Genetic polymorphism (Pro12, Pro12Ala, Ala12Ala) of PPARG gene determined by PCR. Genotypes were: Pro12 (n = 32, 64.0%); Pro12Ala (n = 14, 28.0%); Ala12 (n = 4, 8.0%) Liver biopsies performed prior and after study.

Results: Pioglitazone improved glycemic control and glucose tolerance ($p < 0.001$), normalized liver aminotransferase levels as it decreased AST by 42.1 ± 1.17% $p = 0.014$; ALT by 57.5 ± 1.37%, $p < 0.001$; decreased hepatic fat by 54.6 ± 2.09%, $p < 0.001$; and increased hepatic insulin sensitivity by 48.5 ± 1.63% $p = 0.006$. Administration of pioglitazone caused improvement in histologic findings with regard to steatosis, ballooning necrosis, and inflammation. In 4 (8%) Ala12 patients no reliable changes were observed, except glycemic control and glucose tolerance.
Reduction in fibrosis did not change significantly. Statistically insignificant weight gain and mild lower-extremity edema developed in 2 subjects with Pro12Ala genotype, no other side effects were observed.

Discussion/Conclusion: Administration of thiazolidinediones leads to metabolic and histologic improvement in most patients with NASH. However, individual response may be affected by Pro12Ala polymorphism of PPARG gene. This study shows that carriers of Ala genotype whilst comparatively rare among NASH patients are much less sensitive to PPARG agonists' therapy.

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