PHARMACOGENETICS OF SOFOSBUVIR , A NEW ANTI-HCV DRUG: A PRELIMINARY STUDY.

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New anti-HCV drugs have increased the probability to achieve the sustained virological response: sofosbuvir is a potent nucleotide nonstructural 5B polymerase inhibitor and it is a P-glycoprotein (encoded by ABCB1 gene) and BCRP (encoded by ABCG2 gene) substrate.

Concerning older anti-HCV therapies, pharmacogenetics had a great impact: for example IL28B polymorphisms association with ribavirin therapy outcome.

We investigated if variants (SNPs) in genes encoding transporters and their regulation (ABCB1, ABCG2 and HNF4 α), related to sofosbuvir metabolism and elimination, were associated with sofosbuvir and its main metabolite (GS-331007) plasma concentrations at 1 month of therapy.

Allelic discrimination was performed through real-time PCR, whereas plasma concentrations were evaluated through liquid chromatography.

119 patients were analyzed. Sofosbuvir concentration resulted undetectable, because it was prevalently converted in its GS-311007 metabolite.

ABCB1 2677G>T (p=0.044, figure 1.) and HNF4 α 975C>G (p=0.049, figure 2.) SNPs were associated with GS-331007 metabolite plasma concentrations: ABCB1 2677GG genotype patients showed levels of 260 ng/mL, whereas patients with GT/TT genotypes had concentrations of 345 ng/mL. Considering HNF4 α C>G polymorphism, CC genotype patients had GS-331007 concentrations of 366 ng/mL, whereas GC/CC genotypes had 270.5 ng/mL.

In linear multivariate analysis (table 1.), stiffness, insulin resistance, baseline hemoglobin and hematocrit, and SNPs in ABCB1 gene (3435 CT/TT and 1236 TT genotypes) were considered predictors of GS-331007 metabolite concentrations at one month of therapy.

This is the first and preliminary analysis focusing on sofosbuvir pharmacogenetics, showing that this discipline could still have a role in the era of new anti-HCV therapies.

Further studies analyzing a bigger cohort are required.