OI-A-3

ER-ALPHA AND ER-BETA GENOTYPES PREDICT TAMOXIFEN EFFECTS ON SERUM LIPIDS IN BREAST CANCER PATIENTS. M. I. Rehman, MD, A. Bermes, BSc, K. Lee, MD, PhD, T. Skaar, PhD, M. Arefayene, L. Li, PhD, V. Stearns, MD, D. A. Flockhart, MD, PhD, D. F. Hayes, MD, Indiana University School of Medicine, Sungkyunkwan University School of Medicine, John Hopkins, University of Michigan, Indianapolis, IN.

Therapy with tamoxifen has been shown to be associated with favorable changes in lipid profile. We examined the relationship between genetic polymorphisms in estrogen receptor genes (ER-alpha and ER-beta) and serum lipid profile in 82 women who were prescribed tamoxifen (20mg/day). The fasting serum lipid profiles were evaluated before starting tamoxifen therapy and at the end of four months of treatment. Pvu II and Xba I RFLPs were used to identify the IVS1-401 and IVS1-354 polymorphisms of ER-alpha. Genotyping for the ER-beta single nucleotide polymorphism located in 3′ UTR (dbSNP ID: rs4986938) was performed by a TaqMan assay. After four months of tamoxifen therapy all women had significantly lower LDL-cholesterol compared to baseline and the effect appeared more pronounced in postmenopausal women ($p=0.03$ and <0.0001 for pre- and postmenopausal women respectively). In the postmenopausal women, those with ER-alpha IVS1-401 C/C genotype had significantly lower total and LDL-cholesterol when compared to those with C/T and T/T genotypes ($p= 0.014$ and 0.017 for total cholesterol and LDL-cholesterol respectively). In the subgroup of postmenopausal women with ER-alpha IVS1-401 C/C genotype, those carrying ER-beta G/G genotype (dbSNP ID: rs4986938) had the most augmented response of LDL-cholesterol to tamoxifen therapy when compared to other groups ($p=0.03$). This pattern of genotypes may identify a group of women most likely to experience cardiovascular benefits from tamoxifen.

OI-A-4

ARG389GLY BETA-1 ADRENERGIC RECEPTOR POLYMORPHISM AND LEFT VENTRICULAR REMODELING CHANGES TO BETA-BLOCKER THERAPY. S. G. Terra, PharmD, K. K. Hamilton, MD, D. F. Pauly, MD, PhD, C. R. Lee, PharmD, J. Patterson, PharmD, K. F. Adams, Jr, MD, R. S. Schofield, MD, J. A. Hill, MD, J. M. Aranda, MD, H. N. Yarandi, PhD, J. A. Johnson, PharmD, University of Florida, University of North Carolina, Gainesville, FL.

The β_1-adrenergic receptor (β_1AR) contains a common functional polymorphism at codon 389 (Arg389Gly). In vitro studies indicate that Arg389 has greater basal and agonist stimulated adenylyl cyclase activity. We hypothesized that the Arg389Gly polymorphism was associated with left ventricular (LV) remodeling changes to a β-blocker. We prospectively enrolled 47 β-blocker naïve patients with ischemic or non-ischemic heart failure (HF). Patients received metoprolol CR/XL (MXL) 12.5-25 mg/d, titrated q 2 weeks (as tolerated) up to 200 mg/d or highest tolerated dose over 8 weeks. Patients completed a 2D echocardiogram at baseline and at the end of study, which occurred 3 months after attainment of highest tolerated MXL dose during titration. An ANCOVA with baseline measures and MXL dose as covariates was used to compare changes in ejection fraction (EF), LV end-diastolic and end-systolic diameters (LVEDD and LVESD, respectively), between genotypes. The % of patients with non-ischemic HF, HF duration, and heart rate reduction was similar between genotypes. The final MXL dose was 136 mg/d for Arg389Arg and 103 mg/d for Gly389 carriers. Gly389 carriers experienced progressive ventricular dilatation reflected by increases in LVEDD and LVESD, while patients with the Arg389Arg genotype had an attenuation of LV remodeling. The difference in LVEDD was statistically significant between groups. In conclusion, the codon 389 genotype is associated with LV remodeling changes from β-blocker therapy.

	Arg389Arg (n=20)		Gly389 Carriers (n=27)		
	Baseline	Final	Baseline	Final	P*
EF (%)	24 ± 6	29 ± 11	22 ± 8	23 ± 11	0.15
LVEDD (mm)	62 ± 12	61 ± 11	63 ± 9	66 ± 9	0.01
LVESD (mm)	53 ± 11	51 ± 13	54 ± 10	56 ± 12	0.12

*For comparison of change from baseline between genotypes.
Means ± SD.

OI-B-1

LACK OF DEVELOPMENT OF ACUTE TOLERANCE (AT) TO INTRAVENOUS (IV) ETHANOL (ETH) IN THE ELDERLY. P. W. Slattum, PharmD, PhD, V. A. Ramchandani, PhD, J. Venitz, MD, PhD, Virginia Commonwealth University, National Institute on Alcohol Abuse and Alcoholism, Richmond, VA.

AT is defined as a decrease in effect with prolonged exposure during the time course of a single dose. Development of AT to the perception of intoxication has been reported after ETH administration in young persons. Since the elderly have less CNS reserve, it is hypothesized that they will not develop AT to the same degree as the young. This study was designed to evaluate AT development in the elderly. Eight men (mean age 72.4 yr; range 70-82 yr) and 7 women (mean age 74.9 yr; range 69-88 yr) underwent pharmacokinetic (PK) screening to determine individual PK characteristics and estimate ETH doses to achieve and sustain serum ETH concentrations (SEC) at a target of 1000 mg/L. Later, they received a 1-hr IV ETH infusion to achieve target SEC, followed by a 5-hr IV ETH infusion to maintain target SEC. SEC was measured by TDx/TDxFlx. The pharmacodynamic (PD) effect was measured by a subject-rated impairment (SRI) scale and number vigilance speed (NVS). The degree of AT was estimated using PK-PD modeling. Vd_{ss} was lower in the elderly (males 0.38 L/kg; females 0.36 L/kg) than reported for the young, supporting earlier findings. AT to SRI was noted in only 4 of 15 elderly compared to 14 of 16 young volunteers studied in the same laboratory. NVS showed no AT; sensitivity was similar to the young, but baseline performance was lower in the elderly. The elderly appear to develop AT to the subjective effects of ETH to a lesser degree/at a slower rate than the young.