LBOVI-A-1

DOES PRIOR TREATMENT FOR OVERACTIVE BLADDER AFFECT QUALITY OF LIFE OUTCOMES WITH TRANSDERMAL OXYBUTYNIN? RESULTS FROM THE MATRIX STUDY. R. P. Goldberg, MD, MPH, N. V. Dahl, PharmD, Evanston Continence Center, Watson Laboratories, Evanston, IL.

BACKGROUND/AIMS: Treatment history may impact perceived effectiveness of antimuscarinic therapy for overactive bladder (OAB). This analysis of the Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin (MATRIX) compares quality of life (QOL) in treatment-experienced vs -naive patients.

METHODS: MATRIX, an open-label, multicenter prospective trial, evaluated adults with OAB treated with transdermal oxybutynin 3.9 mg/d (Oxytrol®, Watson Pharma, Corona, CA) for ≤6 mos. Study population included 3 predefined patient groups: treatment naive (n=973), recently discontinued (therapy stopped 0-29 days prior; n=785), lapsed (no therapy ≥30 days; n=566). King's Health Questionnaire® (KHQ) was used to evaluate QOL. P values based on ANCOVA.

RESULTS: MATRIX enrolled 2878 patients (mean age 62.5y±14.8y; 87% women). At baseline, 46% had OAB symptoms ≥4y; 57% had prior oral OAB treatment (32% of whom with multiple drugs), predominantly extended-release tolterodine or oxybutynin. Baseline differences in impairment were seen between groups ($P<.0001$) in 5 of 10 KHQ domains (trend for increasing severity: naive < recently discontinued < lapsed). At study end, all KHQ domains except general health perception showed significant improvement ($P<.0001$). Magnitude of response was similar between groups in 6 domains, with greater improvement among lapsed and naive patients in 4 domains.

CONCLUSIONS: OAB patients benefit from transdermal oxybutynin, regardless of treatment history.

LBOVI-A-2

USING PHARMGENIX™ RATS TO DETECT TACRINE HEPATOTOXICITY. Y. A. Harrington, MS, S. K. Korb, BS, N. V. Cozzi, PhD, S. H. Nye, PhD, A. L. Wittenburg, BS, H. J. Vernon, BS, D. L. Evans, MS, J. A. O'Connor, MS, L. H. Lapczynski, BS, A. J. Dahly-Vernon, PhD, J. F. Baye, BS, R. J. Roman, PhD, H. J. Jacob, PhD, PhysioGenix, Inc., Wauwatosa, WI.

BACKGROUND/AIMS: Over 90% of drug candidates fail in clinical trials, incurring high costs to the pharmaceutical industry. To address this problem, PhysioGenix has developed a novel combinatorial breeding strategy, the PharmGenix™ panel, to capture greater genetic diversity within the rat genome and allow for preclinical drug screening. Tacrine, which causes hepatotoxicity in a small percentage of the human population, was tested to demonstrate the utility of this panel.

METHODS: A single dose of tacrine (35 mg/kg) was administered to each of six hybrid PharmGenix™ strains, CD-IGS and CDF strains. Rats were euthanized twenty-four hours later and serum analyzed for alanine transaminase (ALT) and aspartate transaminase (AST) levels, indicators of hepatotoxicity.

RESULTS: Tacrine did not significantly elevate ALT levels in CD-IGS or CDF, however, the PharmGenix™ panel showed significant ALT elevations in five of the six strains, ranging from 111% to 142% of control values. CD-IGS and CDF exhibited increases in AST levels of 82% and 174%, respectively, while the PharmGenix ™ rats showed much higher AST levels, ranging between 621% and 1069% of control values in four of the six strains.

CONCLUSIONS: The ability to detect significant AST and ALT elevations in the PharmGenix™ panel, but not in CD-IGS or CDF, suggests a genetic component underlies the development of tacrine toxicity and may have alerted the pharmaceutical industry to toxicity currently seen in a small percentage of the human population.

LBOVI-A-3

IDENTIFICATION OF SKIN BIOMARKERS FOLLOWING TESTOSTERONE ADMINISTRATION IN POSTMENOPAUSAL WOMEN. S. A. Stoch, W. K. Tanaka, D. A. Hilliard, D. L. Chappell, V. R. Modur, R. L. Phillips, P. Deutsch, S. Abbi, T. M. Crumley, J. L. Miller, S. Lyle, B. L. Schapiro, K. M. Gottesdiener, J. A. Wagner, Merck & Co., Inc., University of Massachusetts, Michigan Dermpath, Rahway, NJ.

BACKGROUND/AIMS: To pilot a pharmacodynamic (PD) model of short-term androgen administration that may be used to predict long-term effects of androgen administration in postmenopausal women. The study was specifically designed to identify biomarkers that evaluate early skin response to exogenous androgens. The clinical consequences of androgen administration include hirsutism and acne. Skin biopsies were performed to document morphological changes in the pilosebaceous unit (PSU) and gene expression changes (Taqman and microarray). Functional skin response was gauged by measuring sebum excretion rates (SER).

METHODS: A double-blind, randomized, placebo-controlled, parallel-group study was conducted in 36 healthy postmenopausal female subjects to identify early biomarkers of androgen administration. Subjects were randomized to receive either 2.5 mg of transdermal testosterone gel (TTG; AndroGel®), 300 μg of TTGtransdermal testosterone gel, or placebo gel, daily for 6 weeks in a 1:1:1 ratio. Skin biopsies were performed to document morphological changes in the pilosebaceous unit (PSU) and gene expression changes (Taqman and microarray). Five-mm skin punch biopsies were obtained from the back of subjects at baseline, after 6 weeks of treatment, and 4 weeks post treatment. Biopsies were analyzed for histological changes characterized by total sebaceous gland volume and sebocyte cell size. Skin biopsies were also analyzed for molecular skin changes using skin Taqman/microarray assays. Measurements of sebum excretion rates (SER) were obtained at baseline and after 6 weeks of treatment.

RESULTS: Six weeks of treatment with the 2.5-mg TTGdose of AndroGel® increased sebaceous gland volume on average by 42% (p=0.0410) and sebum excretion rateSER by 52% (p=0.0021) relative to placebo. Microarray and Taqman analyses on skin samples also demonstrated changes in the 2.5-mg TTG AndroGel® group. Histological and molecular findings were noted to be reversible 4 weeks after discontinuing therapy.

Analysis of Total Sebaceous Gland Volume (10^6 μm^3) at Week 6

		Mean (SD)		% Change from Baseline		
Treatment	**N**	**Baseline**	**Week 6**	**Mean (SD)**	**LS Mean**	**95% CI**
Placebo	13	19.58 (32.51)	24.00 (32.27)	4.42 (33.53)	4.42	(−21.79, 30.63)
300 ug TTG	13	37.20 (39.16)	45.59 (47.20)	8.40 (51.97)	8.40	(−17.81, 34.61)
2.5 mg TTG	10	31.93 (36.34)	77.91 (71.76)	45.98 (53.01)	45.98	(16.10, 75.87)

Analysis Results for SER at Week 6

		Geometric Mean (CV)		% Change from Baseline		
Treatment	**N**	**Baseline**	**Week 6**	**Geometric Mean (CV)**	**Geometric LS Mean†**	**95% CI‡**
Placebo	13	0.67 (0.52)	0.67 (0.51)	−0.14 (0.29)	−0.14	(18.22, −15.65)
300 ug TTG	12	0.81 (0.55)	0.89 (0.56)	10.80 (0.38)	10.80	(32.08, 7.05)
2.5 mg TTG	10	0.82 (0.43)	1.24 (0.42)	52.09 (0.22)	52.09	(84.37, 25.46)

CONCLUSIONS: TTG treatment is associated with marked increases in sebaceous gland volume and SER, consistent with side effects including hirsutism and acne. Biomarkers sufficiently robust to support using to test for androgen-mediated skin effects in postmenopausal women were identified.