EARLY-PHASE DEVELOPMENT OF SALIVARY PROANGIOGENIC CYTOKINES AS BIOMARKERS IN LEUKOPLAKIA CLINICAL TRIALS. Nelson L. Rhodus, Eva Szabo, Beverly Wuertz, Kate Cole, Joe Rohrer, and Frank Ondrey, University of Minnesota, Minneapolis, MN, USA.

Objectives. A significant emphasis has recently developed as to the potential utility of minimally or noninvasive surrogate end points in head and neck cancer clinical trials. Consequently, biomarkers analysis in saliva is an attractive area of investigation in oral cancer. Our laboratory (and others) has demonstrated the upregulation of NF-κB-dependent cytokines (IL-6, IL-8, VEGF) in squamous cell carcinoma (SCC) cell lines, animal models and oral cavity fluids from patients. The goal of this study was to quantify 3 NF-κB-dependent cytokines (IL-6, IL-8, VEGF) in the saliva (and other oral fluids) of patients undergoing clinical trials for the intervention of oral leukoplakia.

Material and Methods. Twenty-one patients with oral leukoplakia (biopsy-proven moderate-severe epithelial dysplasia) were enrolled, examined, and their lesions measured. We collected whole unstimulated saliva, along with an isotonic saline rinse and serum. IL-6, IL-8, and VEGF were analyzed in triplicate by ELISA (by methods which we have previously reported). The patients were then enrolled in a 12-week clinical trial of a ppar-gamma agonist for treatment of the leukoplakia.

Results. The results indicated up to a 10-fold increase in saliva as compared with serum for all 3 cytokines. IL-6 was considerably lower than IL-8 or VEGF and comparable with levels in cell lines, IL-8 and VEGF were coordinate significantly upregulated in saliva (P < .0001). There were modest correlations between the cytokine levels and lesion size (P < .05).

Conclusions. We conclude that these NF-κB-dependent cytokines (IL-6, IL-8, VEGF) are produced in oral SCC and preneoplastic leukoplakia and therefore found in the local milieu (saliva and fluids). The correlative science between SCC cell lines and saliva in oral leukoplakia strengthens the case for further use of these biomarkers in oral carcinogenesis studies and lesion monitoring in clinical trials.

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Objectives. High-dose melphalan followed by an ASCT is standard initial therapy for MM. Oral mucositis is a potentially severe complication of this treatment. We hypothesized that obesity and renal insufficiency modulate the pharmacokinetics of melphalan and, therefore, affects the severity of oral mucositis.

Methods. Thirty-nine patients with MM undergoing high-dose melphalan followed by ASCT were evaluated. Patients received melphalan on day –2 at a dose of 200 mg/m² and ASCT on day 0. We assessed body composition using DXA and renal function using 24-hour urine creatinine clearance. We assessed toxicity on day +7 using the OMAS. We also assessed patient-reported symptom scores using the MDQ periodically during the first month.

Results. The median age was 55 years (range 37-70) and 59% were male. The median percentage body fat as measured by DXA was 31% (range 15%-53%), and the median GFR was 105 mL/min (range 28-194). In a multivariable linear regression model, including percent body fat, weight, GFR, and actual melphalan dose, we observed a correlation between OMAS score and percent body fat. In a similar multivariable model, including percent body fat, weight, GFR, and actual melphalan dose, we observed a correlation between MDQ score and percent body fat.

Conclusions. More obese patients, as measured by percent body fat, have more severe oral mucositis after high-dose melphalan, independent of melphalan dose, weight, and renal function.

HIGH CONCENTRATION OF MINOCYCLINE RINSES FOR CONTROLLING RECURRENT APHTHOUS STOMATITIS. Noam Yarom, Keren Zelig, and Meir Gorsky, Sheba Medical Center, Tel Hashomer, Israel.

Objectives. In previous studies, we demonstrated the beneficial effect of minocycline 0.2% mouthwash on symptoms associated with recurrent aphthous stomatitis (RAS) when compared with those of placebo or tetracycline. The purpose of this study was to compare the efficacy of 2 different concentrations of minocycline water solution mouthwashes on the symptoms associated with RAS.

Methods. The study was designed as a prospective, randomized, double-blind, crossover study. Twenty-nine RAS patients who fulfilled the entry criteria were enrolled using minocycline mouthwashes of 2 different concentrations: 0.2% and 0.5%. The patients were randomly instructed to use 5 mL of minocycline water solution mouthwashes 4 times a day, initiating the treatment at the point of the prodromal symptoms of aphthous ulcers. A washout period of 4 weeks was needed before using the other concentration. The intensity of symptoms, using the visual analog scale of 0 to 10, and adverse reactions were recorded by each individual at the end of each day of treatment.

Results. Of 21 patients who experienced RAS during the study period, only 14 experienced 2 episodes and completed the whole protocol of the study. The intensity of pain associated with RAS was significantly lower when the higher minocycline concentration was used, reaching a level of statistical significance as soon as the fourth day of treatment (P = .017). The mean duration of RAS-associated pain was significantly shorter (4.07 vs 5.64 days; P = .02) and healed sooner (5.64 vs 6.85 days; P = .011) when the higher concentration was used. No adverse reactions were reported by the patients.

Conclusions. The higher concentration of minocycline mouthwash (0.5%) is significantly more efficient for controlling RAS than the 0.2% concentration, as tested in our previous studies.

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AZITHROMYCIN TREATMENT OF DRUG-INDUCED GINGIVAL HYPERPLASIA IN RENAL TRANSPLANT PATIENTS. Nayer Abo El Saad, Una El-Shinnawi, and Adel Bakr, Mansoura University, Mansoura, Egypt.

**Objectives.** The objective of the study were to evaluate and compare the efficacy of azithromycin therapy in reducing drug-induced gingival hyperplasia as an adjunctive therapy in renal transplant patients (RTP) under cyclosporine (CsA) and those under tacrolimus (Tcr) therapy.

**Methods.** A total 570 patients were screened from the outpatient Renal Transplant Clinic of the Nephrology Centre, Mansoura University, Egypt. Those patients had received kidney transplants between February 1992 and July 2009. Seventy-five kidney transplant recipients (48 men, 27 women) diagnosed to have early to moderate gingival overgrowth with stable allograft function entered the study. These patients had been taking either CsA or Tcr for more than 6 months. The patients were randomized equally into 3 groups. Two groups had received 500 mg azithromycin for 5 days, given at baseline only, whereas the control group received placebo in addition to the oral hygiene program. The clinical periodontal parameters were assessed and included the plaque index, bleeding on probing index, the gingival overgrowth index, and the probing depth. They were evaluated at the baseline and at follow-up time (1, 3, 6 months).

**Results.** At baseline, all groups were similar in the clinical parameters with no statistically significant difference (P > .05). At follow-up time intervals, all groups showed improvement over baseline measurements; however, both groups who received azithromycin showed more favorable results manifested by reduction of gingival bleeding and the depth of gingival sulci; however, this improvement was more in the CsA group than the Tcr group and the difference was statistically significant (P < .05).

**Conclusions.** Azithromycin is an effective therapeutic tool in the management of drug-induced gingival overgrowth, as it is conservative, well tolerated, and rapidly effective with minimal side effects; especially in renal transplant patients under cyclosporine therapy.

SKELETAL BIODISTRIBUTION OF FLUORESCENTLY LABELED BISPHOSPHONATE IS ANATOMIC SITE-DEPENDENT. Demin Wen, Ellis Golub, Sunday O. Akintoye, University of Pennsylvania, Philadelphia, PA.

**Objectives.** Long-term administration of bisphosphonates has been associated with bisphosphonate-related jaw osteonecrosis (ONJ). A potential etiologic factor is disproportionate concentration of bisphosphonate in the jaws, but it is unclear if regional biodistribution and bioavailability of bisphosphonates is site-dependent. We tested in rats the hypothesis that skeletal biodistribution and release of pamidronate (a nitrogen-containing bisphosphonate) is anatomic site-dependent.

**Methods.** Four NIH-Foxn1nu rats received tail vein injection of 80 nmol/kg body weight of fluorescently tagged pamidronate (OsteoSense®680) followed by optical imaging after 24 hours. After the rats were killed, individual bone parts were recovered and rescaned using similar in vivo imaging parameters. Bound bisphosphonate in bone parts was desorbed using sequential EDTA decalcification. Bisphosphonate signal intensity per unit area normalized to adjacent background intensity was expressed as relative fluorescence units (RFUs) after defining specific regions of interest (ROIs) correlating with bone sections subjected to bisphosphonate desorption. Recovered labeled bisphosphonate was measured with a fluorometer, whereas calcium released in solution was measured with an atomic absorption spectrophotometer. Mean site-specific RFU was correlated with bisphosphonate and calcium amounts from corresponding bone sections. Skeletal site differences of ROIs were analyzed and compared based on oral, axial, and appendicular regions. Data expressed as mean ± standard deviation were analyzed by 1-way ANOVA followed by Dunn-Sidak post hoc multiple comparisons with statistical significance set at P < .05.

**Results.** Bisphosphonate signal intensity was similar in oral and appendicular bones but lower in axial bones; however, liberation of hydroxyapatite-bound bisphosphonate following sequential EDTA decalcification resulted in significantly higher bisphosphonate release from oral bones relative to axial and appendicular sites (P < .05).

**Conclusions.** This study demonstrated regional site disparity in rat skeletal uptake and release of bisphosphonate in oral, axial, and appendicular bones that suggest possible preferential bisphosphonate uptake in the jawbone.

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**Objectives.** RAS is a painful condition of unknown etiology affecting over 2.5 billion individuals worldwide. Because vitamin deficiencies have been implicated as a possible cause of RAS, we hypothesized that vitamin supplementation may be beneficial. The goal of this study was to examine the effects of daily multivitamin supplementation on incidence and duration of RAS episodes.

**Methods.** Adult patients with idiopathic minor RAS were randomized to daily multivitamin (n = 83) or placebo (n = 77) for 1 year. The active medication contained 100% of the reference daily intake (RDI) of the essential vitamins. Subjects recorded onset and duration of RAS episodes, mouth pain, normalcy of diet, and treatment compliance in study diaries. Subjects were asked to come in for study visits at baseline, at 6 and 12 months, and during RAS episodes for verification. Number of new RAS episodes was compared between the 2 groups using an analysis of covariance (ANCOVA) with treatment as the factor and length of study participation as the covariate. Duration of RAS episodes was compared using a linear mixed model with treatment as the factor and duration in days as the dependent variable.

**Results.** There was no significant difference in the mean number of new RAS episodes between the multivitamin (4.06 episodes) and placebo (4.27 episodes) arms during the study period.