OR24-03

Aldosterone is produced by adrenocortical zona glomerulosa (AZG) cells in response to hyperkalemia or angiotensin II (AngII) acting through its type I receptors (AT_1Rs). AT_1R is a G protein-coupled receptor (GPCR) that induces aldosterone synthesis and secretion via both G proteins and the GPCR adapter proteins βarrestins. AZG cells express all three subtypes of β-adrenergic receptor (AR) and respond to catecholamines by producing aldosterone. Being GPCRs, both activated βARs and AT_1Rs are phosphorylated by GPCR-kinases (GRKs), followed by βarrestin binding to initiate G protein-independent signaling. Herein, we investigated whether the major adrenal GRKs, GRK2 and GRK5, are involved in catecholaminergic regulation of AngII-dependent aldosterone production. We used the human AZG cell line H295R, in which we measured aldosterone secretion via ELISA and synthesis via real-time PCR for steroidogenic acute regulatory (StAR) protein and CYP11B2 (aldosterone synthase) mRNA levels. Isoproterenol (Iso, a βAR full agonist) treatment significantly augmented AngII-dependent aldosterone synthesis (2.2+0.8-fold CYP11B2 & 1.6+0.5-fold StAR mRNA inductions over AngII alone; $p<0.05$, n=4), as well as secretion (2.3+0.8-fold of vehicle with Iso; 3.2+1.1-fold of vehicle with AngII; 7.4+1.1-fold of vehicle with Iso+AngII, $p<0.05$ vs. either agent alone; n=5) in H295R cells. Importantly, GRK2, but not the other major GRK isoform expressed in human adrenals GRK5, was indispensable for the catecholamine-mediated enhancement of aldosterone production in response to AngII in H295R cells. Specifically, GRK2 inhibition with the small molecule Cmpd101 abolished Iso effects on AngII-induced aldosterone synthesis and secretion (Iso+AngII-induced aldosterone secretion: 8.1+2.3-fold of vehicle without Cmpd101; 2.8+0.8-fold of vehicle with Cmpd101; $p<0.05$, n=5). In contrast, GRK5 knockout via CRISPR/Cas9 did not affect the synergism between isoproterenol and AngII in stimulating aldosterone production. Mechanistically, βAR-activated GRK2, but not GRK5, phosphorylated and activated the Ca^{2+}-activated chloride channel anoctamine-1 (ANO1), also known as transmembrane member (TMEM)16A, ultimately increasing aldosterone production in H295R cells (Iso+10^{-6} M $[Ca^{2+}]$-induced ANO1 activity of Cmpd101-pretreated cells: 55+15 % of non-Cmpd101-pretreated cells; $p<0.05$, n=5). AngII alone failed to stimulate GRK2 in H295R cells. In conclusion, GRK2 mediates a βAR-AT_1R signaling crosstalk at the level of ANO1 activation, which results in enhanced aldosterone production in H295R cells. This finding suggests that adrenal GRK2 may be a molecular link connecting the sympathetic nervous and renin-angiotensin systems in the adrenal cortex and that GRK2 inhibition might be therapeutically advantageous for aldosterone suppression.

Bone and Mineral Metabolism

OSTEOPOROSIS AND VITAMIN D

Romosozumab Treatment Lowers the Incidence of New Vertebral Fractures Across All Fracture Severity Grades Among Postmenopausal Women with Osteoporosis

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Vertebral fractures (VFx) are the most common type of fracture in postmenopausal osteoporosis (PMO). VFx are generally classified using the Genant grading system as mild (grade 1), moderate (grade 2), or severe (grade 3) according to their degree of compression visualized on spinal x-rays. Regardless of their severity, VFx are associated with significant morbidity and carry the highest subsequent fracture rate of any fragility fracture. We assessed the incidence of new VFx by Genant severity grade in the romosozumab (Romo) vs placebo (Pbo) or alendronate (ALN) arms of the FRAME and ARCH studies, respectively.

In FRAME, 7,180 women with PMO were randomized 1:1 to receive monthly Romo 210 mg or Pbo for 12 months followed by biannual denosumab (DMAb) 60 mg (Romo→DMAb or Pbo→DMAb) for 12 months. In ARCH, 4,093 women with PMO and ≥ 1 fracture were randomized 1:1 to receive monthly Romo 210 mg or weekly oral ALN 70 mg for 12 months followed by ALN 70 mg (Romo→ALN or ALN→ALN) for ≥ 12 months. Throughout both studies, lateral radiographs of the spine were assessed for the presence and severity (mild, moderate, or severe) of VFx using the Genant grading at baseline and after 12 and 24 months of treatment.

The incidence of new VFx was significantly lower among patients who received Romo during the 12-month double-blind treatment phase in both studies. Over 12 months, the incidence of new VFx was 0.5% Romo vs 1.8% Pbo ($P<0.001$) in FRAME and 3.2% Romo vs 5.0% ALN ($P=0.008$) in ARCH. Over 24 months, the incidence of new VFx was 0.6% Romo→DMAb vs 2.5% Pbo→DMAb ($P<0.001$) in FRAME and 4.1% Romo→ALN vs 8.0% ALN→ALN ($P<0.001$) in ARCH. Fewer new VFx were observed in the Romo arm of both studies across all fracture severity grades. Specifically, in FRAME, the incidence of mild VFx was 0.2% Romo vs 0.4% Pbo over 12 months and 0.2% Romo→DMAb vs 0.6% Pbo→DMAb over 24 months; the incidence of moderate VFx was 0.1% Romo vs 0.9% Pbo over 12 months and 0.2% Romo→DMAb vs 1.4% Pbo→DMAb over 24 months; and the incidence of severe VFx was 0.2% Romo vs 0.5% Pbo over 12 months and 0.2% Romo→DMAb vs 0.6% Pbo→DMAb over 24 months. Similarly, in ARCH, the incidence of mild VFx was 0.5% Romo vs 1.0% ALN over 12 months and 0.4% Romo→ALN vs 1.4% ALN→ALN over 24 months; the incidence of moderate VFx was 1.3% Romo vs 2.1% ALN over 12 months and 1.8% Romo→ALN vs 3.4% ALN→ALN over 24 months; and the incidence of severe VFx was 1.5% Romo vs 1.9% ALN over 12 months and 1.9% Romo→ALN vs 3.3% ALN→ALN over 24 months. In conclusion, Romo administered over 12 months to women with PMO resulted in reductions in VFx across all fracture severity grades compared with Pbo and standard-of-care

ALN. The treatment effect of Romo continued after patients transitioned to an antiresorptive agent. These data will help to foster treatment decisions in postmenopausal women at high risk for VFx.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

The Content of Serum Clusterin in Patients with Diabetic Macular Edema Depending on the Kind of Glucose Lowering Therapy

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MON-668

Relevance. Insight into the pathophysiology of diabetic macular edema (DME) has led to novel treatments, including anti-VEGF, corticosteroid-based treatment strategies and novel therapies, such as a clusterin blood retina barrier (BRB) cytoprotection. It has been shown the protective effect of clusterin on oxidative stress-induced cell death and its emerging roles in reduction of both BRB breakdown and neural retina damage. **Goal.** To assess the content of serum clusterin in patients with type 2 diabetes (T2D) and diabetic macular edema depending on the type of glucose lowering therapy. **Material and methods.** This study was conducted in 82 patients with T2D and DME. The average age of patients was 65.25 ± 10.85 years (±SD) [25; 84], the average duration of diabetes was 14.0 ± 7.05 years (±SD) [1; 35], the average level of HbA1c was 8.40 ± 1.58% (±SD). The criteria for inclusion in the open study was voluntary informed consent, age 18 years and more, the presence of T2DM. Non-inclusion criteria were the presence of endocrine diseases, which can lead to type 2 diabetes, T1D, acute infectious diseases, cancer, decompensation of comorbid pathology, mental disorders, antipsychotics, antidepressants, neurodegenerative diseases of the central nervous system, proteinuria, damage to the optic nerve, glaucoma and mature cataracts. 43 patients received oral glucose lowering drugs (OGLD: sulfonylureas, biguanides), 39 patients received insulin therapy. All patients had instrumental ophthalmological examinations. The concentration of serum clusterin was measured by «Human Clusterin ELISA» kits. Statistical analysis was performed by one-way ANOVA analysis. **Results.** A study of level variability of blood clusterin in patients with DME showed its dependence from the type of glucose lowering therapy. Comparison of mean values of strum clusterin in patients with DME and T2DM revealed the following statistically significant differences: OGLD 87,08 ± 3,15 mcg/ml [95% CI 82,63 - 91,54 mcg/ml]; insulin therapy 74,79±2,98 mcg/ml [95% CI 70,58 - 78,99 mcg/ml] (p=0,006). Apparently, clusterin is involved in the pathogenesis of DME and may have a potential in reducing of the pathogenic effect of diabetes on the neurovascular unit. The data obtained make it possible to discuss the neuroprotective role of clusterin in DME with the use of voiced oral hypoglycemic drugs, which usually prescribe for patients with mild form of T2D or for the patients with moderate severity T2D (i. e. at the initial stages of development of diabetes). **Conclusion.** Against the background of glucose lowering drugs in patients with type 2 diabetes and diabetic macular edema statistically significant (p=0,006) increases the content of serum clusterin compared to insulin therapy.

Bone and Mineral Metabolism

CLINICAL ASPECTS OF OSTEOPOROSIS AND VITAMIN D ACTION

Efficacy and Safety of Romosozumab vs Alendronate Is Similar Across Different Levels of Renal Function Among Postmenopausal Women with Osteoporosis

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MON-378

Postmenopausal women with osteoporosis may also have renal insufficiency. We conducted a post hoc analysis of the ARCH study to determine the efficacy and safety of romosozumab (Romo) vs alendronate (ALN) among patients with different levels of baseline renal function.

In ARCH, 4,093 postmenopausal women, 55–90 years old, were randomized 1:1 to receive monthly subcutaneous Romo 210 mg or weekly oral ALN 70 mg for 12 months (double-blind phase [DBP]). Eligible patients had a bone mineral density (BMD) T score of ≤ –2.5 at the total hip (TH) or femoral neck (FN) and either ≥ 1 moderate/severe vertebral fracture (VFx) or ≥ 2 mild VFx; or a T score of ≤ –2.0 at the TH or FN and either ≥ 2 moderate/severe VFx or an Fx of the proximal femur sustained 3–24 months before randomization. Pts were excluded for significantly impaired renal function (eGFR < 35 mL/min/1.73 m^2, calculated using the MDRD equation). For the current analysis, patients were categorized by baseline eGFR: normal renal function (eGFR ≥ 90), mild renal insufficiency (eGFR 60–89), or moderate renal insufficiency (eGFR 30–59). The least squares mean (LSM) % change from baseline in BMD at the lumbar spine (LS), TH, and FN; incidence of new VFx; incidence of adverse events (AEs); and changes in renal function were assessed for each eGFR category at month 12 of the DBP.

At baseline, 15% of patients had eGFR ≥ 90, 60% had eGFR 60–89, 24% had eGFR 30–59, and 0.3% had eGFR 15–29. In the overall patient population, LSM % change (95% CI) from baseline in BMD (Romo vs ALN) was 13.7% (13.4–14.0) vs 5.0% (4.7–5.2) for LS, 6.2% (5.9–6.4) vs 2.8% (2.7–3.0) for TH, and 4.9% (4.7–5.2) vs 1.7% (1.5–2.0) for FN ($P < 0.001$ at each site). Changes in BMD were similar irrespective of baseline eGFR. Among patients with eGFR ≥ 90, eGFR 60–89, and eGFR 30–59, the incidence of new