CYP11A1 inhibition as a therapeutic approach for the treatment of castration resistant prostate cancer

R. Oksala, K. Räsänen, M. Karimaa, R. Riikonen, M. Ramela, P. Vehmaan-Kreula, O. Simola, P. Rummakko, G. Wohlfahrt and M.V.J. Mustonen

Background
Androgen receptor (AR) signaling plays a vital role in PC tumor growth and progression. Approximately half of the men with castration-resistant prostate cancer (CRPC) respond initially to abiraterone or enzalutamide, but most the patients develop a resistance within one to two years, however majority of tumors have still high AR expression and persistent AR activity (1). The expression of steroidalogenic gene transcripts is changed in patients with CRPC, indicating altered steroid synthesis profile. Several precursor steroids, like progesterone (P) testosterone (T) and dihydrotestosterone (DHT) and their derivatives, which bind and activate AR, can be synthesized in adrenal glands and de novo in tumors. Increased P levels in patients treated CYP17A1 inhibitors have been speculated to be one of the resistance mechanisms in CRPC, especially via mutated androgen receptor (2, 3).

ODM-208 is a novel, oral, non-steroidal and selective inhibitor of CYP11A1 enzyme (cytchome p450sc), which suppresses the synthesis of all steroid hormones and precursors that could be potential AR ligands and is therefore expected to be effective agent in CRPC.

Methods
Inhibition of CYP11A1 in vitro: The inhibition of CYP11A1 was studied in vitro by measuring the conversion of 3H-labeled substrate, [24,25-3H]-cholesterol, into its 3H-labeled product, isocaproic aldehyde (IARA) in NCI-H295R cells, that originate from a hormonally active adrenocortical carcinoma, and further analyzing Preg and T formation by ELISA in the same cell line.

VCAp CRPC xenografts: Tumor growth inhibition was studied using androgen dependent VCAp cells, which were subcutaneously grafted to intact male nude mice. When tumor volumes reached on average 200 mm³, mice were castrated. After regrowth of the tumors, the oral treatment with ODM-208 (20 mg/kg or 30 mg/kg b.i.d.) alone or as combination with Prednisone (0.6 mg/kg q.d.) was started and continued 42 days. Full length AR (AR-FL) and AR-V7 were analyzed from the tumors by western blot. In addition key enzymes of androgen biosynthesis, CYP17A1, AKR1C3, SRD5A1 were quantified by qPCR. At the end of the xenograft study, key steroid hormone concentrations, progesterone (P), corticosterone (C) and testosterone (T) were analyzed from plasma and target tissues with LS-MS/MS.

Conclusions
ODM-208 is a novel nonsteroidal inhibitor of CYP11A1 which is a key regulator on steroidsogenesis. ODM-208 has similar effects as ORX+ADX in CRPC VCAp model (4, 5). • Efficient inhibition of steroid hormone production both in adrenals and VCAp tumors, even during continuous ACTH stimulation • Consistent activity throughout species • No increase observed in IARA or AR-V7 protein levels in CRPC VCAp tumors • Promising antitumor activity in preclinical CRPC model ODM-208 has potential for being an effective treatment option for the patients with CRPC. Clinical trial in metastatic CRPC is ongoing (NCT04354645).

References

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E-mail to: riikka.oksala@orionpharma.com

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