Publication

OBE022, an Oral and Selective Prostaglandin $F_{2\alpha}$ Receptor Antagonist as an Effective and Safe Modality for the Treatment of Preterm Labor.

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Abstract

Preterm birth is the major challenge in obstetrics, affecting ~10% of pregnancies. Pan-prostaglandin synthesis inhibitors [nonsteroidal anti-inflammatory drugs (NSAIDs)] prevent preterm labor and prolong pregnancy but raise concerns about fetal renal and cardiovascular safety. We conducted preclinical studies examining the tocolytic effect and fetal safety of the oral prodrug candidate OBE022 [(S)-2-amino-3-methyl-butyric acid (S)-3-{[(S)-3-(biphenyl-4-sulfonyl)-thiazolidine-2-carbonyl]-amino}-3-(4-fluoro-phenyl)-propyl ester] and its parent OBE002 [(S)-3-(biphenyl-4-sulfonyl)-thiazolidine-2-carboxylic acid [(S)-1-(4-fluoro-phenyl)-3-hydroxy-propyl]-amide], both potent and highly selective antagonist of the contractile prostaglandin F2α (PGF2α) receptor (FP). Efficacy of OBE022 and OBE002, alone and in combination with other tocolytics, was assessed in human tissues and pregnant animal models for inhibition of uterine contraction and delay of parturition. Selective safety of OBE022 and/or OBE002, compared with NSAID indomethacin, was assessed on renal function, closure of the ductus arteriosus, and inhibition of platelet aggregation. In in vitro studies, OBE002 inhibited spontaneous, oxytocin- and PGF2α -induced human myometrial contractions alone and was more effective in combination with atosiban or nifedipine. In in vivo studies, OBE022 and OBE002 reduced spontaneous contractions in near-term pregnant rats. In pregnant mice, OBE022 delayed RU486 [(8S,11R,13S,14S,17S)-11-[4-(dimethylamino)phenyl]-17-hydroxy-13-methyl-17-prop-1-ynyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one] -induced parturition and exerted synergistic effects in combination with nifedipine. OBE022 and/or OBE002 did not show the fetal side effects of ductus arteriosus constriction, impairment of kidney function, or inhibition of platelet aggregation observed with indomethacin. Orally active OBE022 and OBE002 exhibits potent tocolytic effects on human tissues ex vivo and animal models in vivo without causing the adverse fetal side effects seen with indomethacin. Selectively targeting the FP receptor in combination with existing tocolytics may be an effective strategy for preventing or delaying preterm delivery.