Administration of anti-RANKL antibody to pregnant mice results in impaired development of mammary gland and death of newborns

Nobuhiro Sakai¹, Nobuaki Okamatsu^{1,2,3}, Akiko Karakawa¹, Masahiro Chatani¹, Takako Negishi-Koga¹, Yuji Kiuchi³, Masamichi Takami¹

¹Department of Pharmacology, School of Dentistry, Showa University, Japan, ²Department of Orthopaedic Surgery, School of Medicine, Showa University, Japan, ³Department of Pharmacology, School of Medicine, Showa University, Japan

[Aim] Recently, the number of patients with osteoporosis and bone metastases from solid tumor during pregnancy is increasing, but drug treatment is not proactively done. Denosumab, a fully human monoclonal antibody that neutralizes receptor activator of nuclear factor- κ B ligand (RANKL) and blocks bone resorption by osteoclasts, is currently administered to patients with osteoporosis and bone metastasis of cancer. However, it is unclear how blocking RANKL activity affects pregnant mothers and their newborns. In this study, we injected an anti-mouse-RANKL antibody into mice and analyzed the mothers and newborns, including bones and mammary glands. [Methods] We injected an anti-mouse-RANKL antibody (OYC1[®], 5 mg/kg) into mother mice on gestation day 7. After birth, we analyzed the mothers and newborns including bones by micro-computed tomography. And further, mammary glands were analyzed by histomorphometry. [Results] Mothers injected with the anti-RANKL antibody had increased bone mass compared with the control mothers, although osteoclast number and serum level of TRAP5b, a bone-resorption marker in serum, were increased at the end of pregnancy. Consistent with this, anti-RANKL antibody injected mothers displayed impaired mammary gland development. Newborn mice exposed to the antibody in utero were normally born with increased bone mass, but they died within 48 hours after birth. All newborns were found to have no milk in their stomachs, suggesting that they died due to a maternal defect in lactation. However, fostering by healthy surrogate mothers rescued only 33% of antibody-exposed newborns, suggesting that neonatal lethality was due, at least in part, to an intrinsic defect in newborns. [Conclusions] Anti-RANKL antibody administration during pregnancy results in not only an undesirable increase in bone mass, but also has harmful effects on newborn survival.