INTRODUCTION:
Steroid-induced osteonecrosis (ON) is known to occur in patients who received corticosteroids for the treatment of such underlying diseases as systemic lupus erythematosus, nephrotic syndrome and after renal transplantation. Since patients with steroid-induced ON are generally young-aged, the ultimate goal is the prevention of the development of ON.

Several possible factors in the pathogenesis of ON have been suggested based on both human and animal studies, including coagulation abnormalities and hyperlipidemia. Human studies demonstrate that vascular occlusion may occur as a result of mechanical interruption by thrombi or lipid emboli in nutrient vessels (1). In a rabbit model of ON, hyperlipidemia associated with abnormal thrombophilic coagulopathy and bone marrow fat-cell packing was linked to the development of ON (2-4). Recently, the effect of lipid-lowering agents (probucol, statin) on prevention of steroid-induced ON in rabbits.

MATERIALS AND METHODS:
We utilized a rabbit model of steroid-induced ON in this study (2). This experiment was reviewed by the Committee on the Ethics of Animal Experiment in Faculty of Medicine, Kyushu University.

Sixty-five adult male Japanese rabbits, weighing 3.5-4.2 kg, were intramuscularly injected once with 20 mg/kg of methylprednisolone acetate into the right gluteus medius muscle. These rabbits were divided into two groups, pitavastatin group (PS group, n=35), and control group (CTR group, n=30).

Pitavastatin, 0.7 mg/kg body weight per day, was intravenously administered once daily for 4 weeks from 2 week before the corticosteroid injection till 2 weeks after the injection. Two weeks after the corticosteroid injection, both femora and humeri were histopathologically examined for the presence of ON and the sizes of the bone marrow fat cells were examined morphologically, as previously described (3).

Blood samples were collected from all rabbits equally through the transcutaneous cephalic vein. The levels of total cholesterol in the PS group were significantly lower than those in the CTR group (p<0.05). The average sizes of bone marrow fat cells were significantly smaller in the PS group (56.6±10.0 μm) than those in the CTR group (60.0±4.0 μm) (p<0.01).

RESULTS:
The incidence of ON in the CTR group was 21/30 (70%), while that in the PS group was 13/35 (37%) (Figure 1). The incidence of ON in the PS group was significantly lower than that in the CTR group (p<0.05).

The levels of total cholesterol in the PS group were significantly lower than those in the CTR group (p<0.05) (2). The average sizes of bone marrow fat cells were significantly smaller in the PS group (56.6±10.0 μm) than those in the CTR group (60.0±4.0 μm) (p<0.01).

The levels of total cholesterol in the PS group were significantly lower (p<0.01) than those in the CTR group throughout the experimental period (Figure 2A). The LDL cholesterol levels in the PS group remained significantly lower than those in the CTR group at all the time points tested (p<0.01, Figure 2B).

However, we did not observe any significant differences in the plasma lipid levels (VLDL, triglycerides) between the PS and CTR groups.

DISCUSSION AND CONCLUSION:
In a recent study, pitavastatin has been reported to have not only the LDL-lowering effect, but also the anti-atherogenic effects, such as the improvement of endothelial cells, anti-inflammatory effect and anti-oxidative effect. These various effects have been received much attention for the inhibition of early cardiac events (8). In this study, the lipid-lowering effect as well as the anti-atherogenic effects may have been prevented the formation of the thrombi or lipid emboli in blood vessels, which resulted in the prevention of ON in steroid-treated rabbits.

In summary, our current study showed that, in a rabbit model of steroid-induced ON, pitavastatin, a new HMG-CoA reductase inhibitors, significantly prevented the development of ON.

REFERENCES: