

Editorial

Clopidogrel: a drug with potential to prevent steroid-induced osteonecrosis?

What is the evidence?

Clopidogrel is an anti-platelet drug that has been widely used to prevent strokes and heart attacks in persons at high risk. In a study reported in this issue of *Rheumatology*, Yamaguchi *et al.* [1] investigated whether clopidogrel prevented steroid-induced osteonecrosis (ON) in rabbits. Thirty-three animals received clopidogrel (5 mg/kg of body weight) mixed with normal saline (5 ml/kg/day) orally once daily for 3 weeks, while 30 control animals were given normal saline [1]. One week after the initial administration, all rabbits were injected i.m. with single-dose methylprednisolone acetate (20 mg/kg) for 2 weeks to induce ON. Clopidogrel significantly reduced the incidence of ON (48.5 vs 73.3%) and significantly inhibited platelet aggregation. The data presented indicate that platelet aggregation may be involved in steroid-induced ON and clopidogrel can prevent this in experimental rabbits.

Although the pathogenesis of ON remains unclear, corticosteroid use has been reported as a major predisposing factor. In a rabbit model, Iwakiri *et al.* [2] reported that a single high dose (20 mg/kg) of i.m. methylprednisolone injection induced 83% incidence of multifocal ON 3 weeks later. With the same model, Kuribayashi *et al.* [3] reported a 70% incidence in the femur, which was detected by histology after 4 weeks. In Yamaguchi *et al.*'s study [1], the incidence of ON in the femur of the control group was 73.3% as early as 2 weeks after steroid administration; similar observations were also noted by Yamamoto's group [4]. However, Takao *et al.* [5] found only bone marrow necrosis without ON 1, 3, 6 and 9 weeks after induction; thus, consistent effects of methylprednisolone could not be precisely observed even in the same model.

In human beings, ON is defined by the presence of diffuse and empty lacunae or pyknotic nuclei of osteocytes within the bone trabeculae, accompanied by necrosis of the surrounding bone marrow cells, which is followed by a reparative process and is often complicated by articular collapse [6]. In rabbits, previous studies have shown that the osteonecrotic lesion was neither concentrated at the femoral head nor any progression to articular collapse. These results implied that there was no ideal model for ON.

Investigators have suggested multifactorial pathogenesis of steroid-induced ON. In Yamaguchi's study, after clopidogrel administration, nearly 25% (73.3 minus 48.5%) of rabbits were spared ON, indicating effective inhibition of platelet aggregation; there were no

differences in triglycerides and total cholesterol levels between clopidogrel-treated and control groups [1]. As for pathogenesis, the 48.5% incidence of ON was not related to platelet aggregation factors, which further supports the premise of multifactorial pathogenesis of steroid-induced ON. Therefore, the role of clopidogrel in preventing ON could be clarified by further statistical analysis of platelet aggregation assay to test the differences in the platelet aggregation threshold index between those positive for ON and those negative within the antiplatelet-treated group, or by giving clopidogrel in the initial 3 weeks and then suspending it in the subsequent 3 weeks.

Methylprednisolone can have individual effects. In this study, 8 of the 30 control rabbits (27%) were not sensitive to steroid-induced ON [1], which is similar to other results. This observation could be explained by genetic factors interacting with certain risk factors that play an important role in establishing whether a subject will develop ON. Cui *et al.* [7] reported that corticosteroids produced adipogenesis and stimulated expression of the fat-specific gene, *422(aP2)*, after long-term high-dose administration in rabbits. Corticosteroids may direct bone marrow stromal cells into the adipocytic pathway, which is the opposite of the osteoblastic pathway, and the altered function of bone marrow stromal cells can be responsible for the pathogenesis of ON [8]. Therefore, the challenge for clinicians is to distinguish whether the absence of genetic factors or the effects of clopidogrel determine that the individual will not develop ON.

Clopidogrel is a pro-drug, which is converted to an active metabolite that selectively blocks adenosine diphosphate (ADP)-dependent platelet activation and aggregation [9]. Clopidogrel bisulphate was reported to be more effective than aspirin in reducing heart attacks, with fewer gastric side-effects and less intestinal bleeding. The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) study showed significant reductions in overt gastrointestinal haemorrhages with a combination of omeprazole and clopidogrel compared with clopidogrel alone [10]. Therefore, the major concern to clinicians for the use of clopidogrel is to weigh the side-effects and benefits for patients.

Clearly, more research is needed to explore the pathogenesis of steroid-induced ON, to establish an ideal animal model and to study the use of drugs to treat or prevent ON before they are clinically used. Following the thorough investigation by Yamaguchi's research group,

I would hope that clopidogrel might eventually prove to be a safe and effective preventive alternative to steroid-induced ON.

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