Treatment of glucocorticoid-induced osteoporosis in rheumatoid arthritis patients with alfacalcidol versus risedronate.

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Introduction
Rheumatoid arthritis (RA) patients are, as a consequence of their disease and its treatment, believed to have an increased risk for osteoporosis. As inhibitors of bone resorption, bisphosphonates are becoming widely used in the management of postmenopausal and glucocorticoid-induced osteoporosis (GIO). Also vitamin D and calcium therapy has been used for the treatment of GIO. However, there was no head-to-head comparison of these two medicines for the treatment of GIO. The aim of our study was to evaluate the efficacy of the active metabolic alfacalcidol compared with the risedronate in patients with RA receiving glucocorticoids.

Materials and Methods
The trial was performed as a prospective randomized controlled study. We studied Japanese postmenopausal women with RA who required long-term (>6 months) treatment with oral glucocorticoids at an average daily dose of at least 2.5 mg prednisolone. Patients continued taking their usual medications for RA. All patients provided informed consent and the protocol was approved by the local ethics committee. Patients were randomly assigned to receive either daily 1 mg alfacalcidol (n=20, age; 65.3 ± 6.9 y, average total amount of prednisolone; 2654.5 mg) or daily 2.5 mg risedronate (n=20, age; 64.6 ± 11.2 y, average total amount of prednisolone; 4334.4 mg) without calcium supplementation.

The primary efficacy endpoint was the mean percent change from baseline at the third year in bone mineral density (BMD) at the lumbar spine. Additional efficacy endpoints included changes in total BMD and bone metabolic markers (urinary type I collagen N-telopeptide; NTx and bone specific alkaline phosphatase; BAP), rate of vertebral and non-vertebral fractures, and adherence rate of medications. BMD was measured by dual-energy X-ray absorptiometry (BMD-1, Hitachi, Japan). At 6-month intervals, routine laboratory examinations including bone metabolic markers and lateral X-ray studies of the thoracic and lumbar spine were performed. Patients were interviewed for adverse events and an endoscopy was requested for all patients with moderate-to-severe upper gastrointestinal adverse events. Here we show the result at the first year.

Results
The two groups were alike in age range, average initial BMD at lumbar spine (alfacalcidol; 0.867 ± 0.246, risedronate; 0.787 ± 0.159 g/cm2), total BMD (alfacalcidol; 0.900 ± 0.095, risedronate; 0.850 ± 0.074 g/cm2), and levels of NTx (alfacalcidol; 52.1 ± 25.0, risedronate; 77.3 ± 27.3 nMBCE/mMCre). During the 1-year study we found a small but significant (p<0.05) increase of total BMD in group alfacalcidol and no significant changes at lumbar spine. In risedronate group, there were no significant changes at both sites. NTx, a bone resorption marker, dramatically decreased in risedronate group (-39.4%, p<0.01) but increased in alfacalcidol group (+24.9%, not significant). The adverse events (epigastric discomfort) were observed on four patients in risedronate group and pathologic abnormalities (gastric ulcer) were found in two patients. There was no severe or moderate adverse event in alfacalcidol group. The adherence rates of medication in risedronate and alfacalcidol groups were 75% and 92%, respectively. Only one vertebral fracture was observed in alfacalcidol group at early phase of the study and no fracture in risedronate group.

Discussion
The community-based studies have confirmed that women with RA have lower bone mass and that the deficit in bone mass varies by steroid use. The precise pathophysiology of GIO is uncertain. However, taking into account that intestinal calcium malabsorption and secondary hyperparathyroidism are important pathogenetic mechanisms in GIO, there has always been a high interest in vitamin D and its metabolites for prevention and treatment of GIO. In large placebo-controlled studies, bisphosphonates have shown the dramatic therapeutic effects for several types of osteoporosis but in all studies calcium and vitamin D were supplemented in both control and intervention groups. Taking together with our result, which has several limitations (small size, short period, without calcium supplementation), alfacalcidol is superior to risedronate in the treatment of GIO in RA patients.

![NTX (nMBCE/mMCre)](image_url)

![BAP (U/l)](image_url)