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Marked increase in bone formation markers after cinacalcet treatment by mechanisms distinct from hungry bone syndrome in a hemodialysis patient

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Running title: Cinacalcet may promote bone formation

Abstract

A 59-year-old female who was on dialysis due to diabetic nephropathy was referred to our hospital for severe hyperparathyroidism refractory to intravenous vitamin D receptor activator treatment. With subsequent cinacalcet hydrochloride treatment, parathyroid hormone (PTH) levels were only slightly suppressed. However, progressive increases were observed in serum alkaline phosphatase (ALP) and bone-specific alkaline phosphatase (BAP) levels with mild hypocalcemia. Bone biopsy, obtained immediately before surgical parathyroidectomy after three months of cinacalcet treatment, revealed no disappearance of osteoclasts. These data suggest that cinacalcet hydrochloride treatment may induce marked promotion of bone formation by mechanisms distinct from hungry bone syndrome that usually develops after parathyroidectomy.

Keywords: bone formation; cinacalcet hydrochloride; secondary hyperparathyroidism

Background

Cinacalcet hydrochloride is a new class of drugs for the treatment of severe secondary hyperparathyroidism in hemodialysis patients. It has also been reported that successful suppression of parathyroid hormone (PTH) levels results in a decrease in serum markers for bone formation [1, 2].

Here, we report a case of a dialysis patient presenting with severe hyperparathyroidism, who was treated with cinacalcet hydrochloride. Without significant suppression or further increases in PTH levels, marked and progressive increases in serum markers for bone formation were observed. Bone histology did not support the development of hungry bone syndrome, as was presumed in previous cases.

Case report

A 59-year-old female with diabetic nephropathy was referred to our hospital for bone pain. She was on dialysis therapy three times a week for nine years. She had severe hyperparathyroidism (whole PTH level, 904 pg/mL; normal, 9–39 pg/mL) with a single enlarged parathyroid gland (16 mm × 15 mm × 19 mm). Although intensive intravenous vitamin D receptor activator (VDRA) treatments were performed several years ago, secondary hyperparathyroidism progressed. The dose of vitamin D was decreased because of concomitant hypercalcemia. Although 22-oxacalcitriol (OCT) was administered at a dose of 2.5 µg twice a month since January 2007, OCT was stopped in August 2007. Because of the

progression of secondary hyperparathyroidism, OCT was started again at a dose of 10 µg once a week since October 2007. However, OCT was stopped in February 2008. Although calcium carbonate was administered at a dose of 1.5 g/day, no phosphate binder was administered since January 2007.

While planning a surgical parathyroidectomy which was scheduled to be conducted in near future, cinacalcet hydrochloride was started at a dose of 25 mg per day and was finally increased to 75 mg per day. Cinacalcet hydrochloride therapy induced a mild decrease in the patient's serum calcium and phosphate levels. PTH levels also decreased slightly, whereas serum alkaline phosphatase (ALP) levels (normal: 109–321 IU/L) increased significantly and progressively after the start of cinacalcet treatment, as shown in Figure 1. Serum bone-specific alkaline phosphatase (BAP) levels also significantly increased from 295 U/L to 995 U/L (normal: 9.6–35.4 U/L) during the therapy. The patient had no evidence of bone fracture by X-ray imaging. There was no difference in bone scintigraphies obtained before and after three months of initiating cinacalcet therapy. On the other hand, serum bone resorption marker type I collagen cross-linked N-telopeptide (NTx) levels were significantly high (1058.4 nmolBCE/L; normal, 10.7–20.4 nmolBCE/L) after three months of initiating cinacalcet therapy.

We performed surgical parathyroidectomy three months after the start of cinacalcet treatment. During the operation, an iliac bone biopsy was performed before removing the parathyroid tissue to identify the cause of elevation of serum ALP and BAP levels. The bone

biopsy specimen demonstrated osteitis fibrosa (fibrosis volume/tissue volume 21.4%) and defective mineralization (osteoid volume/bone volume 29.1%) (Figure 2A). With regard to bone formation parameters, osteoblast surface/bone surface (BS) increased (25.3%). Bone formation rate (BFR)/BS also increased to $0.094 \text{ m}^3/\text{m}^2/\text{year}$ (normal: $0.015 \pm 0.008 \text{ m}^3/\text{m}^2/\text{year}$). However, we could not measure BFR precisely due to blurred tetracycline labels. Multinucleated osteoclasts resorbing mineralized bone were observed, in contrast to the mechanisms observed in hungry bone syndrome after parathyroidectomy (Figure 2B). Staining for aluminum was negative and she has never been treated with aluminum gels.

After parathyroidectomy, serum PTH levels decreased immediately to levels below the detection limit. In addition, the patient reported the disappearance of bone pain. Serum ALP levels decreased slowly and returned to a normal range at 6 months after parathyroidectomy.

Discussion

Cinacalcet hydrochloride reduces serum PTH levels by direct action on calcium-sensing receptor in parathyroid, thereby decreasing bone formation markers in hemodialysis patients [1, 2]. Nevertheless, in a recent report of a clinical trial, it has been shown that serum BAP levels increase at early time after the start of cinacalcet treatment [2, 3]. This temporary increase of BAP was assumed to be a result of hungry bone syndrome without bone biopsy. Although development of hungry bone syndrome by cinacalcet was reported previously in two reports [4, 5], the authors failed to describe the changes in bone formation markers after

the administration of cinacalcet. Typical hungry bone syndrome develops after surgical parathyroidectomy and is characterized by hypocalcemia and a temporary increase in bone formation. According to another recent report, osteoclasts disappear immediately after parathyroidectomy [6]. Bone histology of this particular case did not support the development of hungry bone syndrome seen after parathyroidectomy.

In the present case, neither progression of hyperparathyroidism nor the sudden decrease of PTH level, as in spontaneous infarction, were observed during cinacalcet treatment. We could not find any evidence of bone fracture by X-ray or in changes of bone scintigraphies. Although we could not completely rule out the possibility of microfractures, we hypothesized that bone formation is possibly enhanced as a result of cinacalcet treatment by unknown mechanisms. We failed to demonstrate the pathomechanism of bone biopsy clearly because of the bone biopsy specimen only at the end of cinacalcet treatment and not prior to treatment.

Cinacalcet reduces serum PTH levels maximally around 2 to 4 h after administration. Therefore, cinacalcet induces daily fluctuation of serum PTH levels, which differs from VDRA treatments. As reported previously, PTH (1–34) has different effects on bone mass when administrated by intermittent injections or by continuous infusion [7]. Furthermore, it has been suggested that intermittent decreases in serum PTH levels by oral administration of calcimimetics have an anabolic-like effect on the bones, whereas continuous suppression of PTH by calcimimetics infusion does not have a similar effect [8]. Therefore, we conclude that daily fluctuations of PTH, as induced by cinacalcet treatment, may have promoted bone

formation.

Osteoblasts express calcium-sensing receptors. It has been shown that high extracellular ionized calcium concentration stimulation induces mitogenic action of osteoblasts via calcium-sensing receptors [9]. However, the calcium-sensing receptor in osteoblasts may be different from parathyroid [10]. Therefore, further studies will be necessary to clarify whether cinacalcet has direct effects on osteoblast.

The bone histology in our case also showed defective mineralization. Hypovitaminosis D probably induced defective mineralization because serum vitamin D levels at bone biopsy were low (1,25(OH)₂D₃ level, 5.6 pg/mL; normal, 20–60 pg/mL: 25(OH)D₃ level, 21 ng/mL; normal, 7–41 ng/mL). However, since hypovitaminosis D may be recognized before the start of cinacalcet treatment, the significance of hypovitaminosis D for bone formation markers in this case is unclear.

In summary, we have reported a case with marked increase of serum markers for bone formation due to cinacalcet treatment. The mechanism responsible for bone formation was distinct from hungry bone syndrome. We concluded that the fluctuation of PTH levels may have promoted bone formation.

References

1. Malluche HH, Monier-Faugere MC, Wang G, et al. An assessment of cinacalcet HCl effects on bone histology in dialysis patients with secondary hyperparathyroidism. *Clin Nephrol* 2008; 69: 269-278
2. Fukagawa M, Yumita S, Akizawa T et al. Cinacalcet (KRN1493) effectively decreases the serum intact PTH level with favorable control of the serum phosphorus and calcium levels in Japanese dialysis patients. *Nephrol Dial Transplant* 2008; 23: 328–335
3. Shigematsu T, Akizawa T, Uchida E et al. Long-term cinacalcet HCl treatment improved bone metabolism in Japanese hemodialysis patients with secondary hyperparathyroidism. *Am J Nephrol* 2009; 29: 230–236
4. Nowack R, Wachtler P. Hypophosphatemia and hungry bone syndrome in a dialysis patient with secondary hyperparathyroidism treated with cinacalcet—proposal for an improved monitoring. *Clin Lab* 2006; 52: 583–587
5. Lazar ES, Stankus N. Cinacalcet-induced hungry bone syndrome. *Semin Dial* 2007; 20: 83–85
6. Yajima A, Ogawa Y, Takahashi HE, Tominaga Y, Inou T, Otsubo O. Changes of bone remodeling immediately after parathyroidectomy for secondary hyperparathyroidism. *Am J Kidney Dis* 2003; 42: 729–738
7. Chen P, Satterwhite JH, Licata AA et al. Early changes in biochemical markers of bone formation predict BMD response to teriparatide in postmenopausal women with

- osteoporosis. *J Bone Miner Res* 2005; 20: 962–970
8. Ishii H, Wada M, Furuya Y, Nagano N, Nemeth EF, Fox J. Daily intermittent decreases in serum levels of parathyroid hormone have an anabolic-like action on the bones of uremic rats with low-turnover bone and osteomalacia. *Bone* 2000; 26: 175–182
9. Chattopadhyay N, Yano S, Tfelt-Hansen J et al. Mitogenic action of calcium-sensing receptor on rat calvarial osteoblasts. *Endocrinology* 2004; 145: 3451–3462
10. Pi M, Quarles LD. Osteoblast calcium-sensing receptor has characteristics of ANF/7TM receptors. *J Cell Biochem* 2005; 95: 1081–1092

Figure legends

Figure 1

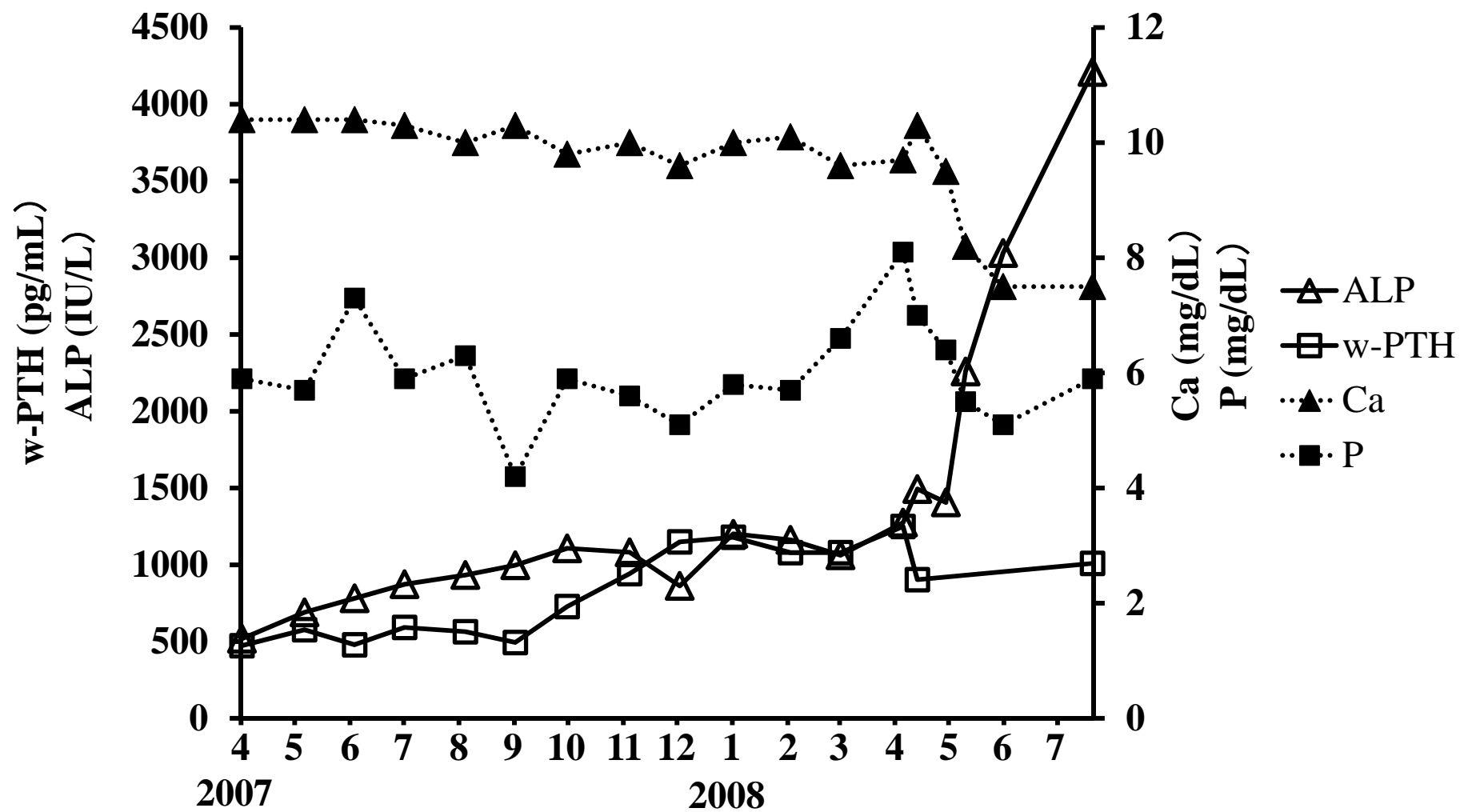
Change of serum ALP, PTH, calcium, and phosphate levels before and after the administration of cinacalcet hydrochloride.

Figure 2

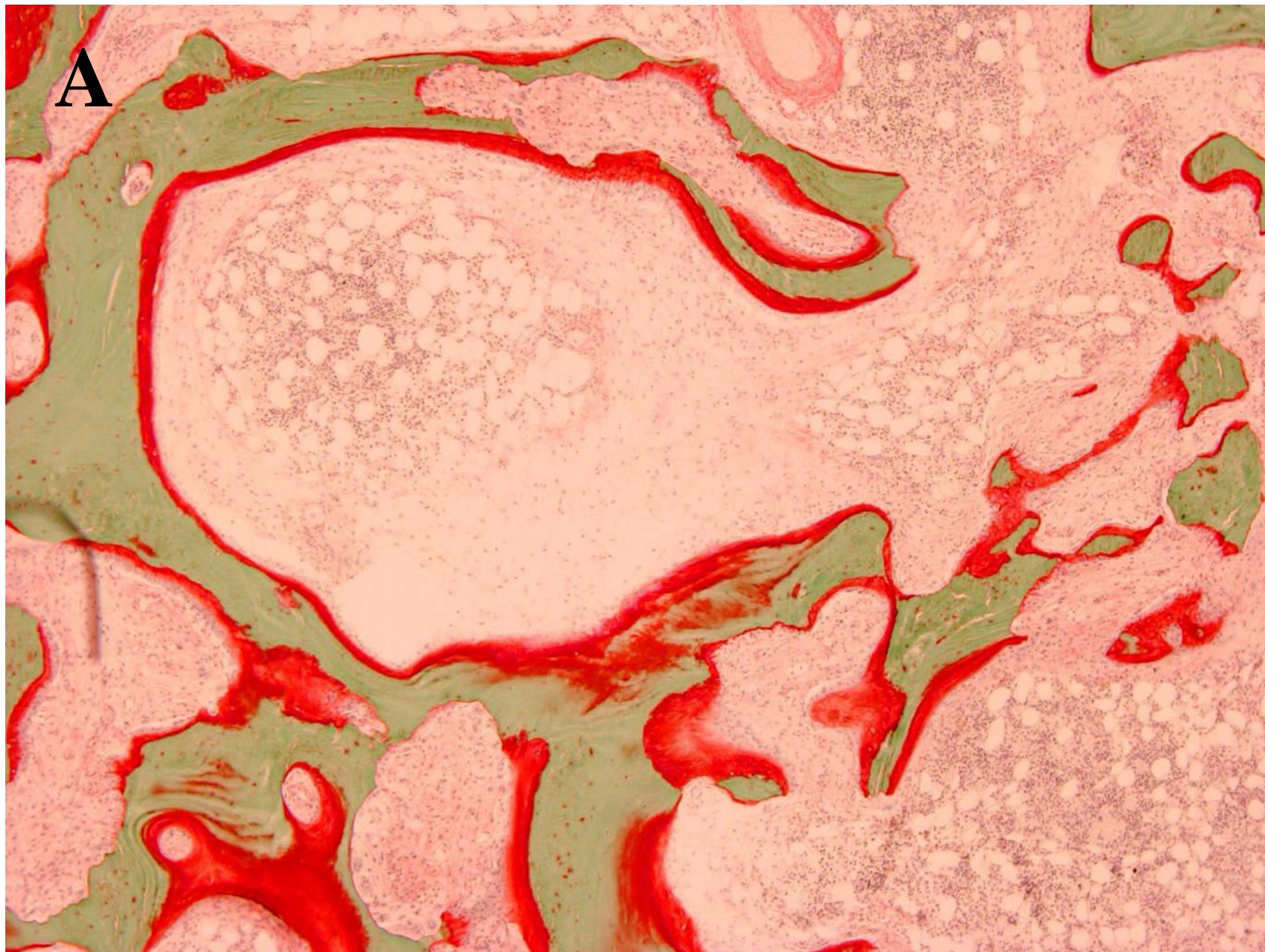
(A) Increased collagen fibres and fraction of trabecular surface covered by osteoid. (Villanueva–Goldner stain, 40×) (B) Multinucleated osteoclasts (arrows) resorbing mineralized bone. (Villanueva–Goldner stain, 200×)

22-oxacalcitriol

cinacalcet HCl



A



B

