The Effect of Paricalcitol on Osteoprotegerin Production by Human Peripheral Blood Mononuclear Cells

THEODOROS ELEFTHERIADIS, GEORGIA ANTONIADI, VASSILIOS LIAKOPOULOS and GRAMMATI GALAKTIDOU

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To the Editor:

It has been known for years that the ratio of receptor activator of nuclear factor-kB ligand (RANKL) relative to its decoy receptor, osteoprotegerin (OPG), controls osteoclastogenesis. Under normal conditions the main source of RANKL and OPG is the osteoblast. Osteoblasts express on their surface RANKL that induces the formation of osteoclasts from their precursors as well as their survival and activation. OPG is also produced and then secreted by the osteoblasts, but it inhibits osteoclast formation by binding to RANKL and preventing binding to its receptor RANK on the surface of the osteoclasts’ precursors1. However, a recent study suggests that both B and T lymphocytes also play a significant role in basal bone turnover, since T cells help B cells to produce 65% of total OPG in bone marrow in mice2. In inflammatory diseases the participation of activated lymphocytes in pathological bone erosion is established3.

Vitamin D promotes osteoclastogenesis through RANKL upregulation and OPG downregulation in the osteoblasts4-5. In vitro experiments, in the absence of inflammatory stimuli, have shown that 1,25-dihydroxyvitamin D3 initially downregulates OPG by accelerating the degradation of OPG mRNA and by transrepressing the OPG gene through its activating protein-1 (AP-1) binding site. But later the OPG gene becomes insensitive to suppressed OPG production mediated by 1,25-dihydroxyvitamin D3. Importantly, experimental data and clinical observations confirmed that vitamin D has immunomodulatory/antiinflammatory properties6. Epidemiological studies have shown an inverse relation between serum levels of vitamin D and the occurrence or severity of various inflammatory bone erosive diseases. Rheumatoid arthritis is the best example7,8.

Under inflammatory conditions vitamin D exerts osteolysis in part due to downregulation of OPG. Recently, we have shown that the vitamin D analog paricalcitol has antiinflammatory properties, since it reduces both basal and lipopolysaccharide (LPS)-induced TNF-α and IL-8 production by the peripheral blood mononuclear cells (PBMC)9. Additionally, paricalcitol is less calcemic than vitamin D10, which allows its administration in higher doses. In this context, its use for attenuating inflammation in chronic inflammatory diseases could be limited due to its possible detrimental osteotropic factors as well as their survival and activation. OPG is also produced and then secreted by the osteblasts, but it inhibits osteoclast formation by binding to RANKL and preventing binding to its receptor RANK on the surface of the osteoclasts’ precursors. However, a recent study suggests that both B and T lymphocytes also play a significant role in basal bone turnover, since T cells help B cells to produce 65% of total OPG in bone marrow in mice. In inflammatory diseases the participation of activated lymphocytes in pathological bone erosion is established.

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In clinical practice, the main obstacle for vitamin D administration as an immunomodulatory/antiinflammatory agent is that at high doses it provokes hypercalcemia. Paricalcitol is a vitamin D analog that is safe, since it has been used for years in the treatment of secondary hyperparathyroidism in hemodialysis patients11 and, importantly, it is less calcemic10. It has antiinflammatory properties as well. In our study, paricalcitol did not decrease OPG production by the LPS-treated PBMC, indicating that under inflammatory conditions paricalcitol may not promote osteoclastogenesis. This feature of paricalcitol, along with its antiinflammatory properties and the less calcemic action, indicate that paricalcitol may have an advantage over vitamin D regarding its possible therapeutic role in inflammatory diseases characterized by pathological bone erosion.

THEODOROS ELEFHERIADIS, MD, PhD, Research Institute, Theagenion Anticancer Hospital, Thessaloniki, and Department of Nephrology, General Hospital of Serres, Serres; GEORGIA ANTONIADI, MD, PhD, Department of Nephrology, General Hospital of Serres; VASSILIOS LIAKOPoulos, MD, PhD, Department of Nephrology, University Hospital of Thessaly, Larissa; GRAMMATI GALAKTIDOU, MD, PhD, Research Institute, Theagenion Anticancer Hospital, Thessaloniki, Greece. Address reprint requests to Dr. T. Eleftheriadis, Department of Nephrology, General Hospital of Serres, 3rd km Serres-Drama, 62100 Serres, Greece. E-mail: teleftheriadis@yahoo.com

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