# New Therapeutic Targets in the Treatment of Osteoporosis

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When one is planning an editorial referring to in the treatment of osteoporosis a classical phrase comes to mind: "In the last few years the advances in the diagnosis and treatment of this illness have been notable and there has been development of new drugs with a marked anti-fracture capacity." Well, it's true. In fact, only 2 decades ago it was considered that osteoporosis was an inevitable process associated to aging, densitometry was starting its widespread use, and the available drugs were limited to calcium, vitamin D, estrogens, and calcitonin, with the experimental use of fluoride salts in certain centers. In the context of the development of research, both basic and clinical, the risk factors for fracture and low mass have been identified, the abnormalities in mineral density, but also the bone microarchitecture and in a parallel form, there has been development of new drugs. The biphosphonates have been the drug class most developed, since the initial etidronate administered in intervals to the recent ibandronate, passing through alendronate and risedronate. What's more, there has been development of other classes of drugs such as raloxifen, selective estrogen receptor modulator, with its known extraskeletal effects. All of them belong to the group of anti-resorptive or anticatabolic to drugs, whose main mechanism is to reduce the frequency of activation of remodeling units, with a diminished osteoclast activity and later of the osteoblasts, and a stabilization of the bone microarchitecture. In the last 2 years, another class of drugs, the osteoforming or anabolics with teriparatide (PTH 1-34) as its exponent. These drugs not only stimulate the bone remodeling with its predominant formation, but, apart from that, modified bone microarchitecture, which gives the skeleton more resistance.[1] On the road between anticatabolic and anabolic we can find the strontium ranelate, which acts through a yet unknown mechanism. Although previously cited drugs reduce the relative risk of fractures due to fragility in postmenopausal women with a low bone mass. It is important to emphasize that the capacity to reduce the relative risk of vertebral fracture, the most common osteoporotic fracture, is significant in all the cases when compared to placebo, but with different magnitudes that vary between 21% and 65%.[2-5] Nonetheless, their efficacy is more variable in the reduction of the relative risk of non-spinal fractures, including the most serious of all, femoral fracture.[2-5] Therefore, today we have at hand anticatabolic and anabolic drugs with which a marked reduction in the risk of fractures obtained, which is the object of the treatment. But it is interesting to note that these results have been obtained in the "ideal" circumstances of clinical trials, and their everyday efficacy (efficacy in day-to-day practice) is more important and the results are more uncertain.[5] In the last few years, a low compliance to osteoporosis treatment has been noted, situated around 50% for daily biphosphonates and not surpassing 70% when the drug is administered weekly. Even more, lower compliance rates have been suggested, as in a recent study were only around a third of the patients had a good adherence to daily treatment and less than half the weekly formulations.[6] But this is a problem that not only happens in drugs with special conditions (such as taking it with an empty stomach), but with other drugs such as estrogen, raloxifen, and calcium supplements, that don't require these conditions. Therefore, one of the main objectives of new treatments has been to facilitate adherence apart from equaling or incrementing their efficacy in the reduction of this fracture risk. With these objectives, there has been development of monthly oral biphosphonates such as ibandronate[7] or yearly intravenous administration such as zolindronic acid, which is the most potent biphosphonate and is in the late phases of evaluation for osteoporosis efficacy and security.[8] But not only is there development of new bisphosphonates, there is a wider market for anabolic drugs with the imminent introduction of PTH (1-84) for its application in postmenopausal women with a high risk of fracture.[9] On the other hand, in the last few years there have been great advances in the identification of the mechanisms involved in the regulation of bone remodeling. Several members of the receptor and ligand family for tumor necrosis factor alpha (TNF) and osteoprotegerin (OPG), the activated receptor of nuclear factor kB (RANK) and its ligand (RANKL) have been described. OPG, which is a protein synthesized by

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osteoblastic lineage cells, has a potent inhibitory activity of osteoclastogenesis and RANKL, which is a transmembrane ligand expressed by osteoblastic cells, joins RANK, which is a transmembrane receptor localized on osteoclast precursors. The joining of RANKL-RANK activates proliferation and differentiation of osteoclasts, while the OPG-RANKL union would have been inhibiting effect.[10] From this knowledge, a new drug has been developed, denosumab, also known as AMG-162, which is a monoclonal human antibody that links with great affinity to RANKL and inhibits its action. Preliminary results indicate that it's subcutaneous administration every 6 months increases bone mineral density and diminishes resorption in postmenopausal women with a low bone mass.[11] Parallel to the advance in the pharmacological treatment of osteoporosis, there have been advances in the treatment of secondary pain due to recent spinal fracture. In this sense, new, sequentially administered analgesic drugs have been developed as well as two particular procedures, vertebroplasty and kyphoplasty, for the treatment of patients with intense and the non-remitting spinal pains.[12] With both these procedures the pain disappears or improves rapidly in an elevated percentage of patients. But, due to their recent introduction and the scarcity of adequately designed trials that compared them to classical treatment of analgesics and rest, studies are needed to analyze in a strict form their advantages and complications in the short and long term. It is evident that the development of new drugs for the treatment of osteoporosis is progressive and opens the field to new possibilities of therapy based on different mechanisms of action. But it is also important to know the mechanisms better on the long-term safety of the drugs that are used today, in an illness that is chronic.[13,14] To that effect, clinical studies are being done to evaluate the efficacy and security of the drugs in the long-term[14] and in their sequential administration, and noninvasive techniques are being perfected to analyze a micro structure and resistance of bone.[15] To finalize, I would like to emphasize that in 2006 we have numerous drugs with a good efficacy profile, new drugs that theoretically will improve over the the current ones and an ample potential for research. For the moment, the physician must evaluate and treat the patient based on the knowledge of the available drugs, on common sense and on the "state-of-the-art."

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