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Recombinant Full-Length Parathyroid Hormone (1-84)
A Viewpoint by James Whitfield

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The key to the demonstration of the osteogenicity of parathyroid hormone (PTH) in osteoporotic humans was the chemical synthesis of an affordable PTH fragment, PTH(1-34), in 1974.[1] This peptide, teriparatide, now made by recombinant technology and approved by the US FDA for the treatment of osteoporosis in November 2002,[2] became the first true bone-anabolic drug, instead of just another of the many anticatabolics (i.e. antiresorptives) to reach the market for treating osteoporosis.

During the late 1980s, a recombinant human full-length PTH (PTH[1-84]) was developed. PTH(1-84) has been approved for use in postmenopausal women with osteoporosis in the EU, although the FDA has delayed approval in the US because of concerns with an injection device used in the US and the incidence of hypercalcaemia.[3]

For a physician to choose PTH(1-84) instead of teriparatide, it would have to be more effective osteogenically and significantly less able to cause hypercalcaemia at the recommended dose than teriparatide. Moreover, it should have the same or greater chance to be formulated in the near future for non-injectable, preferably oral, delivery.

From the excellent summary of the properties of PTH(1-84) by Moen and Scott, it appears that PTH(1-84) has not yet been compared with teriparitide in randomised clinical trials; therefore, conclusions can not yet be drawn regarding the relative efficacy and tolerability of the two agents.

Despite the recent excitement about the discovery of a receptor for the C-terminal region of PTH(1-84) [the CPTHR receptor], in addition to the PTHR1 receptor for the N-terminal region, it appears that this has not given the PTHR1/CPTHR-targeting full-length protein any osteogenic advantage over the only PTHR1-targeting N-terminal fragments in rats. Indeed, Whitfield and colleagues[4,5] reported that PTH(1-84) was no more osteogenic in ovariectomised rats than the radically C-terminally truncated, but still potently osteogenic, hPTH(1-31)NH_2. Clinical data are therefore awaited with interest.

Of note, Vahle and colleagues[6] have reported that the carcinogenicity of teriparatide in Fischer 344 rats is completely separable from osteogenicity on the basis of dose and duration of treatment. In other words, there is a dose of teriparatide that is osteogenic but not carcinogenic.[6] It appears there is not yet an equivalent peer-reviewed detailed analysis of the carcinogenicity of PTH(1-84) in Fischer rats.

In conclusion, on the basis of currently available clinical evidence, it is too soon to say whether PTH(1-84) can compete with teriparatide or the promising smaller N-terminal fragments that apparently do not cause hypercalcaemia and may even be orally deliverable.[2,7] However, for deciding which PTH to use for treating osteoporosis or one of the many other emerging uses of these peptides it would be useful to have a single, continuously updatable publication on the lines of Moen and Scott's article which includes the properties of all PTHs as they emerge from their clinical trials. ▲

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