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NEWS

Calcitonin therapy: is the story coming to an end?

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European Medicines Agency says physicians should no longer use the drug to treat osteoporosis, because of an association with a small increase in cancer risk

Clinicians who treat postmenopausal osteoporosis today have a number of proven therapeutic agents at their disposal, but this wasn't always the case in the bone field. Just two decades ago, doctors could offer their patients only estrogen—or calcitonin. Filling the pre-bisphosphonate era treatment gap, calcitonin would become a huge commercial success: in 1992, more than 900 million US dollars' worth of calcitonin was sold worldwide. Even 10 years later, more than 4 million prescriptions for Miacalcin, a salmon calcitonin nasal spray, were dispensed just in the US alone. If sales are the guide, calcitonin was a blockbuster drug in its day.

In 2012, the landscape of osteoporosis treatment looks dramatically different. Having long been overshadowed by bisphosphonates, which were first approved for clinical use in the mid-1990s, calcitonin now represents only a sliver of the market for osteoporosis medications; in many regions, including the US, it has been many years since calcitonin played a meaningful role in the clinic. Considering this greatly diminished presence, it is perhaps unsurprising that a July 2012 recommendation by the European Medicines Agency (EMA) that physicians no longer use calcitonin to treat osteoporosis met with little attention at the time.[1] After conducting a risk–benefit review of available clinical data, the EMA's Committee for Medicinal Products for Human Use (CHMP) found a small but significant increase in cancer incidence in patients taking calcitonin-containing medicines for osteoporosis or osteoarthritis.

What is the bone field to make of this news? Osteoporosis experts told *BoneKEy* that the evidence linking calcitonin to cancer is weak. Regardless, as more powerful drugs have long been available to treat osteoporosis, they say the loss of calcitonin from the therapeutic armamentarium will have little impact. In fact, as an osteoporosis therapy, calcitonin has always had many skeptics. The drug never found a secure spot in clinical practice, owing its commercial success more to the lack of availability of other osteoporosis agents rather than to evidence of efficacy. Still, if it will soon be time to write calcitonin's epitaph, it would be unfair for that statement to focus solely on efficacy. From a historical vantage point, the clinical development of calcitonin was an important stepping stone for the bone field on the path towards more powerful osteoporosis drugs and better-designed clinical trials. However, it is from the basic science perspective that calcitonin's influence has been most deeply felt. Calcitonin was the first paradigm of a bone resorption inhibitor, and it stimulated much fruitful laboratory research, by some of the bone field's most respected investigators, into bone biology and peptide biology. Yet, even in that light, calcitonin is still somewhat of an enigma: 50 years after its discovery, calcitonin's exact physiological role in humans remains unclear.

The Discovery of a New Hormone in the Early '60s Leads to a New Drug by the Early '70s

Calcitonin was discovered in 1961, by Harold Copp and colleagues[2], as a hormone that lowered blood calcium levels. Although calcitonin was initially thought to originate from the parathyroid gland, shortly after Copp's discovery two groups—one led by Iain MacIntyre in London, the other by Paul Munson in Boston—would show that the thyroid gland was calcitonin's true source. MacIntyre and co-workers reported the amino acid structure of human calcitonin in the late '60s, and work in that decade also identified calcitonin as an inhibitor of bone resorption.

'There was tremendous interest in calcitonin in the 1960s,' said Jack Martin, who spent a significant part of his research career investigating calcitonin, including work undertaken with MacIntyre on calcitonin's mechanism of action. It did not take long for the bone field to recognize the clinical implications of calcitonin's discovery. 'Very quickly the idea developed that if calcitonin was an inhibitor of bone resorption, it should be helpful in diseases characterized by increased bone resorption, such as osteoporosis and Paget's disease,' said Dr Martin, an emeritus professor of medicine at St Vincent's Institute of Medical Research in Fitzroy, Australia.

Hopes for a new drug were first realized in 1973, which saw the introduction of an injectable version of calcitonin i nto Europe, and then in 1984, when the Food and Drug Administration approved that formulation in the US for the treatment of postmenopausal osteoporosis. However, clinical use of injectable calcitonin was short-lived, in large part because of adverse effects that resulted in poor compliance

and patient acceptance of the drug. That outcome was not the end of calcitonin, but rather only a temporary setback, as a nasal formulation of calcitonin would be invented by Moise Azria at Sandoz (which would later merge with Ciba-Geigy to form Novartis) in Basel, Switzerland. In the 1980s, nasal calcitonin was tested in clinical studies by Jean-Yves Reginster and others and would receive approval for treatment of postmenopausal osteoporosis in Europe in 1987, and in the US in 1995. It was the nasal version of calcitonin that would achieve great commercial success throughout the world.

'What is really important to understand is that the '80s and early '90s were an era where for postmenopausal women with osteoporosis, there were only two therapeutic options: hormone replacement therapy or calcitonin,' said Donato Agnusdei, currently Director of Medical External Relations at Eli Lilly in Italy. An assistant professor of medicine at the University of Siena during calcitonin's ascent, Dr Agnusdei saw the growth in calcitonin use firsthand during his many years as a practicing physician treating osteoporosis in Italy, where calcitonin would become extremely popular. Owing to the dearth of other treatments, 'the advent of calcitonin for the treatment of postmenopausal osteoporosis was absolutely critical' for the bone field, said Dr Agnusdei, who published numerous studies of calcitonin beginning in the late 1980s.

Calcitonin would come to have a particularly large role in southern European countries like Italy, Spain, and Greece, where hormone therapy replacement was seldom used; generous insurance reimbursement also had a key role in increasing utilization of the drug. Calcitonin would also become widely used in Latin American countries, especially Mexico and Brazil, in Middle East regions, and in Asia as well. However, Dr Agnusdei emphasized that calcitonin's most important role was to bring attention to a hitherto neglected and misunderstood disease. 'Calcitonin was the major factor in increasing awareness among postmenopausal women, and among the general population, about osteoporosis, which up to that time had been considered mainly as an unavoidable consequence of aging,' he said.

The PROOF Study

Despite the extensive uptake of nasal calcitonin throughout the world, fracture efficacy data in support of the drug were lacking, as had been the case for injectable calcitonin (in the latter instance, a number of small studies were underpowered to assess fracture as an endpoint). That changed in 2000, with publication of the Prevent Recurrence of Osteoporotic Fractures (PROOF) study.[3] PROOF was a 5-year, double-blind, randomized controlled trial that examined the effects of nasal spray salmon calcitonin in 1255 postmenopausal women with established osteoporosis, who received 100, 200 or 400 International Units (IU) of the drug. Results from the entire study cohort indicated a relative risk reduction in new vertebral fractures of 33% in the 200-IU calcitonin group compared with placebo, and a 36% relative risk reduction in a subgroup of women with one to five prevalent vertebral fractures at study enrollment. However, no significant effects on vertebral fractures were observed at the 100-IU or 400-IU doses, nor was there a consistent reduction in non-vertebral fractures across doses.

'The data were inconsistent,' acknowledged Charles Chesnut, lead author of the PROOF study, in an interview with *BoneKEy*. 'I believe very strongly there was an effect of 200 units in reducing the risk of fracture, but I couldn't explain why there was no dose-response,' said Dr Chesnut, a professor of radiology and medicine, and an adjunct professor of orthopedics, at the University of Washington Medical Center in Seattle. At the time the PROOF results were published, critics of the study also pointed to other shortcomings of the trial, including a high dropout rate; only partial blinding of doctors and patients to bone density testing results that were revealed during the course of the study; poor communication between Novartis, the study sponsor that ran the trial, and the expert clinical investigators seeing study participants; and a study population that was too widely dispersed, with a large number of study sites each including only a small number of subjects.[4]

The PROOF study, though, was the first large, multicenter clinical trial designed to assess fracture risk reduction with an osteoporosis drug, and the benefit of hindsight suggests that PROOF's conduct and design should not be judged too harshly. 'None of us really understood how to best go about designing those kinds of trials. We had no experience, so it was a lot of guesswork, ' said Michael McClung, Founding Director of the Oregon Osteoporosis Center in Portland who has been involved with many of the bone field's seminal clinical trials of osteoporosis drugs, including as an investigator in the PROOF study. From this historical perspective, the PROOF study of calcitonin appears in a much more favorable light, as a first step in the bone field's path towards better-designed clinical trials.

Nonetheless, the fracture effect at only the middle dose of the drug in PROOF meant that calcitonin would never become widely accepted as an osteoporosis drug. 'The lack of a dose-response pretty much doomed calcitonin' as an osteoporosis therapy that would be well received by the majority of leading osteoporosis physicians, Dr Chesnut told *BoneKEy*. But, even before the PROOF results appeared, it was already too late for calcitonin. Clinical data were already available supporting the antifracture efficacy of alendronate, which had been approved for osteoporosis treatment in 1995, and even if the PROOF results had been more compelling, bisphosphonates had already established themselves as first-line treatment for osteoporosis, leaving little room for a mild inhibitor of bone resorption. In fact, from a clinical perspective, calcitonin exerted its most significant impact not in osteoporosis but in Paget's disease. As the first drug to make a real difference in that condition, calcitonin would spur investigators to seek even more effective antiresorptive approaches. In addition, calcitonin administered intravenously at high doses was the first agent developed to treat hypercalcemia of malignancy; there, calcitonin's calcium-lowering effects likely resulted mostly from calciuric effects via the kidney, rather than through an antiresorptive mechanism.

At Least It Was Safe—and Still Is?

Although experts have always doubted calcitonin's efficacy as an osteoporosis treatment, few worried that calcitonin, which has a long and enviable track record of safety, could actually do harm. Consequently, investigators were astonished to learn of

the CHMP's findings. 'I was really surprised to hear of the association' between calcitonin and an increased incidence of cancer, said George Lyritis, an emeritus professor at the University of Athens who has studied the analgesic effect of nasal and injectable calcitonin. Dr Lyritis said that in the numerous prospective randomized trials of calcitonin with which he has been involved, there was never any indication of such a link, though he notes his studies were short-term investigations ranging from a couple of weeks up to a year.

After preliminary findings from two osteoarthritis studies of an unlicensed oral calcitonin medication suggested a possible association with prostate cancer in men, the CHMP initiated a review of available clinical data on calcitonin, including data from trials of osteoporosis and osteoarthritis, and from a variety of sources, including companies that market calcitonin. The CHMP reported a small but statistically significant increase in the absolute risk of cancer occurrence ranging from 0.7% with oral calcitonin to 2.4% with nasal calcitonin, in patients using the drug long-term, compared with placebo. Because of this finding, when considered along with the limited benefit of calcitonin in decreasing vertebral fracture risk in postmenopausal osteoporosis, the CMHP recommended that calcitonin no longer be used to treat postmenopausal osteoporosis. Furthermore, though it concluded that the benefit of using calcitonin still outweighed the risk in the treatment of Paget's disease in those who cannot be treated with alternative treatments, in prevention of acute bone loss due to sudden immobilization, which can occur, for instance, in patients with recent osteoporotic fractures, and in the treatment of hypercalcemia caused by cancer, the CHMP said that even in those cases, calcitonin should be given only for the shortest possible time, at the smallest effective dose. After the CHMP's recommendation in July, a company authorized to market calcitonin appealed the CHMP decision in September, but the CHMP then reaffirmed its original recommendation in mid-November.

Experts say that the evidence linking calcitonin to cancer is not compelling. 'I felt their [CHMP's] analysis was subject to bias and that they did not do a consistent, thorough analysis of the data,' according to Dr Chesnut, who said he has seen some of the data provided to the CHMP. 'The data are not enough to convince me of any association between calcitonin and malignancy, and I have no cause for concern, either as a researcher or as a clinician,' he said. Other experts who spoke to *BoneKEy* expressed similar views. One primary criticism they have is that clinical studies of calcitonin did not prospectively report cancer cases, but rather only reported cancer as an adverse event. The data also have other flaws. For instance, a meta-analysis[5] of 13 randomized controlled trials of nasal calcitonin in osteoporosis patients found an increased risk of any malignancy in those taking nasal calcitonin compared with placebo, but the increased risk—an odds ratio of 1.61—was accompanied by wide 95% confidence intervals (1.11–2.34); those results were reported in abstract form by Novartis at the 2012 Annual Meeting of the American Society for Bone and Mineral Research (ASBMR). Nor can anyone think of a plausible mechanism by which calcitonin could cause cancer. 'There is a very substantial literature investigating calcitonin responsiveness of cancer cells, most of it *in vitro*, and not indicating any credible way in which calcitonin might actually cause cancer,' said Dr Martin, who has made numerous contributions to that literature.

The Future of Calcitonin

To some in the osteoporosis field, calcitonin's removal from the market has been long overdue, not because of any link to cancer, but simply because calcitonin just doesn't work very well for osteoporosis in an era when more powerful bisphosphonates and other drugs like denosumab do. 'My reaction when I first heard [of the link between calcitonin and cancer] was that this is finally an opportunity to have an ineffective drug removed from the market without having to say it was ineffective,' said Dr McClung, who noted that in the US, many primary care physicians and geriatricians still use the drug for osteoporosis under the assumption that it is effective. 'It would not disturb me if calcitonin was no longer on the list of approved drugs in the US for osteoporosis,' said Dr McClung, who added that the quality of the data linking calcitonin to cancer is unconvincing. The FDA is currently conducting its own review of calcitonin.

There is widespread recognition that, as an antiresorptive, calcitonin fares poorly in comparison to more powerful agents. However, some maintain that calcitonin could still have an important role as an analgesic in patients with acute pain from vertebral fractures, particularly in those who cannot tolerate other pain medications such as opiates; physicians have used calcitonin for that purpose over the years. In addition, Dr Chesnut noted that calcitonin could still be useful in osteoporosis patients who do not want to take newer drugs like denosumab and who may be concerned about rare events like atypical fractures and osteonecrosis of the jaw that have been associated with bisphosphonate use.

From a clinical perspective, one open question is what the CHMP's findings mean for ongoing efforts to develop a new oral formulation of the drug. A US company, Tarsa Therapeutics, is developing such a version. In results presented in abstract form at the 2012 Annual Meeting of the ASBMR,[6] the company found no carcinogenicity signal after reviewing safety data from the two clinical trials of its formulation that have been conducted to date. In a written statement provided to *BoneKEy*, Tarsa said it is in ongoing discussions with the FDA regarding its plans to submit a New Drug Application to the agency in 2013.

Regardless, at the least, nasal calcitonin's chapter in the story of osteoporosis treatments appears to be drawing to a close. However, on the basic science side, Dr Martin says that calcitonin is here to stay. Interestingly, calcitonin's exact physiological role in human skeletal biology remains unclear even 50 years after the hormone's discovery. Indeed, there is no discernible effect on bone when calcitonin levels are very high, as occurs, for instance, in cases of medullary carcinoma of the thyroid, nor are there clear skeletal effects when calcitonin levels are very low, as happens in patients who have had their thyroid gland removed. Still, past and ongoing work looking at calcitonin and calcitonin receptor knockout mice has started to more precisely elucidate calcitonin's functioning, with the evidence suggesting that the hormone may act physiologically as an inhibitor of bone formation.[7] 'Calcitonin may still be a hormone in search of a function, but we're actually getting somewhere with these mouse studies now, and I suspect that the next few years will tell us a great deal more about calcitonin's

function,' Dr Martin said. By the time that happens, though, calcitonin as an osteoporosis therapy will have come—and very likely gone.

Conflict of Interest

The author declares no conflict of interest.

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