

SHOTS TO GROW BONE: PARATHYROID HORMONE 1-34 ANALOGUES ARE PROMISING BONE REGENERATIVE AGENTS

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Summary

Arguably, methods to induce bone healing, growth, and strengthening are among the most important recent advances in musculoskeletal medicine. If an equally effective strategy for cartilage restoration was possible, many problems presenting to orthopedic surgeons would be solved.

The osteoanabolic bone-forming drugs based on parathyroid hormone (1-34), Forteo® (Eli Lilly and Company, Indianapolis, IN) and Tymlos® (Radius Health, Waltham, MA), are highly effective daily injections without serious side effects or complications. They are Food and Drug Administration (FDA) cleared for treating osteoporosis but are considered as second-line agents because of their high cost. Despite only two published randomized trials and without an FDA clearance, Tymlos and Forteo are becoming mainstream options in the nonsurgical treatment of fracture nonunion.

Both Forteo and Tymlos are synthetic analogues of naturally occurring parathyroid hormone (PTH). They are universally effective in making more and stronger bone. I have used Forteo or Tymlos in 472 patients. 86 of 88 nonunions went on to heal and 46 fresh fractures healed in half or less than the expected normal healing time. Another 157 patients with periprosthetic bone loss with osteolysis from arthritis or prior failed implants were treated for 4 to 12 months and there have been no revisions for prosthetic loosening. Thirty percent of patients had a failed previous revision procedure, but no patient treated with Forteo or Tymlos has required re-revision. There

were 181 patients with poor bone quality who requested hip resurfacing surgery that were treated with Forteo or Tymlos. None has experienced failure of osseointegration of the implant or femoral neck fracture. It is predicted, but not proven, that protection with osteoanabolic medications will increase the reliability of hip resurfacing even in patients with poor bone quality. No patient had a significant complication from these osteoanabolic bone medications.

Introduction

Poor bone health is an important challenge to maintaining an active life. Bone loss occurs naturally with aging and with several health conditions. Aging causes a progressive functional and biological loss of bone viability and increase in vulnerability. Arthritis causes localized bone loss in young and otherwise healthy individuals. The bone loss occurs because of the chronic inflammation of the joint but can also occur as pressurized joint fluid insinuates itself into the bone structure that is no longer protected by cartilage.

Bone can regenerate after injury through a series of well-orchestrated biological steps that signal hormones to initiate new bone formation. Regeneration is not rejuvenation, but they are similar processes. Bone-forming medications are a form of tissue regeneration but in a young patient with localized bone loss, the process rejuvenates the bone to match the condition of the remainder of the patient's skeleton.

Fractures are also a major cause of loss of function in both young and old patients. Fracture healing needs to be complete and rapid to restore the individual to full activity. Approximately 5% of fractures experience complications in healing and 15% take several months to heal. Surgical fixation has been used for most major fractures to allow earlier function. All the classical operations in orthopedic surgery have likely been explored. The last several years have seen improvements in orthopedic surgical procedures for the patient's benefit, such as computer/robotic assistance, materials advances, and less invasive techniques and methods. The next important advance, however, is putting the control of bone regeneration in the surgeon's and patients' hands.

History

Marshall Urist, MD (1914-2001) was a pioneer in understanding bone healing. I met him during my residency and got to know him well through the Association of Bone and Joint Surgeons. In addition to his clinical and laboratory research, he was the editor of the journal *Clinical Orthopaedics and Related Research* for 28 years. Dr. Urist developed bone morphogenic protein (BMP)¹, which has been very helpful in promoting fracture healing and spinal fusions. It can also stimulate antibody formation. However, it requires surgery to implant and is very expensive, making it a valuable but not a practical and complete option to promote bone healing.

Stimulating the body to form bone naturally with hormones has been an interest of mine for 30 years. Growth hormone promotes bone formation.² In 1992, I established that growth hormone is metabolized directly in bone.³ Local rather than oral administration avoids any systemic concerns of growth hormone administration. In 1990, I demonstrated that the drug L-Dopa can also encourage fracture healing. This was a cheaper and indirect way to activate the hormonal axis.⁴ However, the effect was not strong enough and L-Dopa had several side effects. Locally applied pharmacologic therapies are attractive to accelerate bone healing.

Systemic agents have been more controversial. However, because they are effective and not intrusive, there is a rapidly growing acceptance of systemic metabolic therapies. Yet, the cost of \$1800/month for Tymlos or \$3600/month for Forteo is the main reason for their limited use.

Parathyroid Hormone

In 1999, PTH emerged as a candidate hormone to stimulate bone healing. Parathyroid hormone is a naturally occurring 84 amino acid polypeptide.^{5,6} The function of PTH is to increase serum calcium levels in response to hypocalcemia. In addition to this classical effect, the terminal 34 amino acid fragment of PTH has been shown to increase bone mass and bone strength, and reduce bone loss.^{7,8} Parathyroid hormone can be made in recombinant form and it has been used to encourage the healing of fresh fractures, fracture nonunions, and implant osseointegration. It is given as a daily 100 mcg subcutaneous injection.

FORTEO®

Forteo (Teriparatide) is a recombinant form of the 34 amino acid terminal PTH fragment. It is manufactured using a genetically modified strain of *Escherichia Coli* and is supplied as a solution for daily 20 mcg subcutaneous injection. It has been marketed by Eli Lilly since 2002⁹⁻¹¹ and is a multibillion-dollar product for this pharmaceutical giant.

TYMLOS®

Tymlos (Abaloparatide) is a 34 amino acid analog of PTH receptor protein. It works as an anabolic agent for bone through selective activation of the PTH receptor expressed in osteoblasts and osteocytes. Abaloparatide has been marketed since 2017 by Radius. It is given daily as an 80-mcg subcutaneous injection. There are plans for development of a transdermal Tymlos patch.¹²

During the pre-release clinical trials for both Forteo and Tymlos, I provided support and had access to the data collected from enrolled

patients. In the combined trials, 2604 patients were followed. Overall, 34% reported some type of adverse side effect symptom, such as headache, ringing in the ears, skin rashes, constipation, and hallucinations. In the placebo injection arm of the trials (saline injection), 32% of patients reported side effects. There were no serious side effects in either the treatment or placebo group. Reports of different symptoms occur in up to one-third of patients in most placebo studies. More than 2% of patients report nausea, headache, fatigue, upper abdominal pain, and vertigo attributed to PTH (1-34) hormones (both Tymlos and Forteo). However, these side effects tend to be limited and have not resulted in any patients being unable to take the medications.

Contraindications

Paget's disease of bone is a contraindication for anabolic bone agents. Paget's disease is a rare bone disease occurring primarily in elderly white males. Paget's disease causes bone pain, deformity, and bone overgrowth. Multiple myeloma and all other bone cancer conditions are also contraindications. Skeletally immature individuals should not be given PTH or its analogues, as osteogenic cancers are risks. Laboratory studies have shown that rodents such as rats continue to have bone growth throughout their lifecycle. Rats typically die of dementia before reaching skeletal maturity. There is a dose- and time-dependent increase in the incidence of osteogenic sarcoma in rodents receiving any anabolic bone stimulation. There are **no** human reports of osteogenic sarcoma related to PTH supplements. There is no increase in the incidence of **ANY** type of cancer in patients treated with PTH analogues. The incidence of cancer is not zero. It is the same in treated and untreated patients is the same. There is no expected increased risk, since patients with either primary or secondary hyperparathyroidism have elevated PTH levels but no increase in cancer of any type. Parathyroid hormone supplements should also not be provided to individuals with hyperparathyroidism. Hyperparathyroidism can result from parathyroid adenomas or, occasionally, from renal failure.

Dose

Bone regenerative medications are given daily by a painless subcutaneous injection with a microneedle. The Tymlos dose is 80 mcg and Forteo is 20 mcg. Patients with fractures receive treatment until fracture healing occurs, which can range from 6 weeks to 6 months. Treatment for implant osseointegration is given for 4 months and for bone loss it is typically given for a year. No patient is treated for more than 2 years. Patients are also treated with vitamin D3 2000 IU and calcium 1200 mg.

Food and Drug Administration

Tymlos and Forteo are both approved for treatment of osteoporosis. This encompasses postmenopausal females, glucocorticoid-induced osteoporosis, and males with hypogonadal or idiopathic osteoporosis who are at high risk of fracture. Tymlos and Forteo are not FDA cleared for fracture healing, treatment of nonunion, or for osseointegration of implants. There is no FDA clearance for localized bone loss around joints or dental applications.

Tymlos or Forteo?

Forteo has been used since 2002 but Tymlos only since 2017. There is only one human study comparing the effectiveness of the two drugs. This study showed more bone formation around the hip with Tymlos and the two drugs performed identically in all other respects.¹² Tymlos is typically one-half the cost of Forteo.

Literature and Clinical Effectiveness

The serum levels of PTH rise within 30 minutes of administration of PTH or its analogues. The PTH level returns to normal within a few hours. The bone histology shows decreased adipocytes and decreased angiogenesis in addition to the new bone formation. This always occurs in all patients. Normal healing time of a humeral fracture even in the elderly with poor bone quality has been reported in patients receiving Forteo.¹³ The effects of PTH analogues continue for several months or years after a

course of treatment, and the levels of procollagen-1 as a marker for bone healing remain elevated for up to 5 months after treatment.¹⁴

Two randomized human trials have been performed for Tymlos and Forteo.^{7,12} There are many anecdotal reports of their use for fracture healing in the odontoid process of the spine, thoracic and lumbar vertebrae, sternum, tibia, femur, humerus, radius, and metatarsals.^{8,12,15-19} One study reported that 141 of 145 (93%) of chronic nonunited fractures healed with anabolic bone medications.¹¹ All reports except for one hip fracture study have shown reduced time to fracture union, faster functional recovery, and no major side effects with the medication. One study of 78 patients with femoral neck fractures showed no overall benefit in functional recovery but there were no complications. The study was closed early due to recruiting and methodological difficulties.¹⁰ The largest study of 8644 enrollees showed a 56% reduction in the incidence of hip fracture in patients receiving PTH 1-34.²⁰

My Results

Periprosthetic Bone Loss

As with almost all other studies of PTH analogues, my patients were not randomized or controlled. This series is a clinical observational study. All patients provided their informed consent. These patients took the anabolic bone-forming medications based on their own choice and their ability and willingness to accept uncertainty of results and any side effects. They also assumed any risk and all the cost. There were 56 patients with periprosthetic bone loss in the study who were treated with daily injections for 4 - 14 months. All 56 patients had increased bone mass (along with resolution of subchondral cyst formation when present). No complications have occurred.

Joint Implant Osseointegration

Modern joint replacement implants become permanently fixed to the skeleton by bone growth into the porous surface of the implant. This process of



osseointegration is the basis for the success of orthopedic and dental implants. One-hundred one patients were treated to assist implant osseointegration (Fig. 1) (90 were hip implants, 10 were total knee implants, and 1 was a shoulder implant). All implants progressed to full osseointegration.

Fig. 1a. This anteroposterior (AP) pelvis radiograph shows a 56-year-old woman with bilateral failed total hip replacements (THR) with acetabular bone loss and implant loosening.

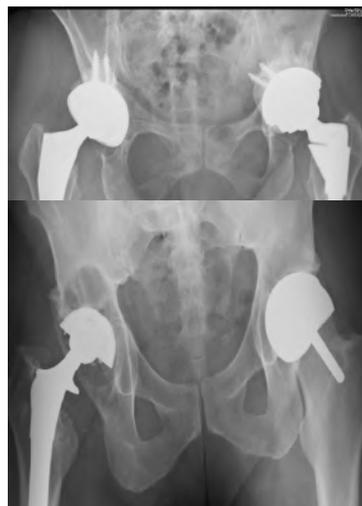


Fig. 1b. This radiograph following bilateral revision surgery and 7 months of daily Forteo injections shows that both acetabular components have osseointegrated.

Fig. 2a. This AP pelvis radiograph shows a 55-year-old man with severe osteolysis from polyethylene wear in his right hip. He had a THR at age 32 and two prior revisions procedures failed. On the left is a well-functioning hip resurfacing implant placed 22 yrs. before.



Fig. 2b. After a revision and allograft, the acetabular component did not osseointegrate.



Fig. 2c. There is much less osteolysis after 1 year of daily Forteo injections and a successful third acetabular revision procedure. Modest bone loss remains with an osseointegrated femoral prosthesis. This patient returned to an athletic lifestyle

There were 61 acetabular revisions (Fig. 2). No patient required supplemental (secondary) surgery for failure of osseointegration after treatment. The time to complete union ranged from 12 - 49 weeks. Patients were treated from 8 - 56 weeks.

I also sometimes treat patients with localized bone loss during surgery by harvesting endothelial progenitor cells (EPCs) from the pelvis and injecting these cells directly into the areas of bone loss. This procedure, combined with the osteoanabolic medication, is the most powerful bone rejuvenation technique available.

It is not completely known how long osteoanabolic medications should be taken to create additional bone but so far no patient has taken medication for more than a year. Full restoration has occurred by then. Also, it is not clear how long before surgery is optimal. The range is 6 weeks to 6 months.

Nonunion

Eighty-eight patients with fracture non-unions were treated with Forteo (n=61) and Tymlos (n=27). There were 14 humerus fractures, 4 clavicle fractures, 3 forearm fractures, 12 femoral fractures, 14 tibial fractures, 8 ankle fractures, 11 wrist fractures, 19 spine fractures and 3 pelvic fractures (Fig. 3).



Fig. 3a. Forearm radiograph of a 78-year-old woman with a 2-year history of a nonunion of the radius and ulna despite internal fixation, bone grafting, and ultrasound stimulation.

Fig. 3b. These radiographs shows healing after 4 months of daily injections of Tymlos.



All fractures showed no sign of union or progress toward union for a minimum of 3 months prior to treatment. Eighty-six of the 88 fractures (98%) progressed to union after treatment. The time to union ranged from 6 - 22 weeks.

Accelerated Healing of Fresh Fractures

Forty-six patients took Forteo or Tymlos for fresh extremity fractures. There were 12 hand/wrist fractures, 11 foot/ankle, 10 tibia, 10 humerus, and 3 clavicle fractures. All fractures healed in an average of 4 - 6 weeks compared to 8 - 12 weeks predicted for the same fracture in a healthy adult. Clinical improvement with reduced pain and feeling of stability occurred in average of 2.5 weeks (range, 10 - 30 days). Patients received the injections from 4 - 12 weeks (Fig. 4).



Fig. 4a. AP



Fig. 4b. Lateral

The AP and lateral radiographs show a tibial fracture in a 56-year-old woman with juvenile rheumatoid arthritis. She had taken steroids for many years and has a minimally displaced fracture of her distal tibial shaft. There was no trauma and she has a total knee replacement and an auto fused ankle.



Fig. 4c. AP



Fig. 4d. Lateral

The AP and lateral radiographs after 6 weeks of daily Forteo injections show full healing of her tibial fracture.

Protection for Hip Resurfacing Patients

One-hundred eighty-one patients who were at risk for failure of their hip resurfacing procedure due to poor bone quality at presentation were treated with Tymlos or Forteo. The most effective injection strategy begins 6 weeks prior to surgery and continues for 7 months after surgery. All treated patients had successful outcomes with no femoral neck fractures, osteonecrosis, or failures of osseointegration. In this high-risk group the expected failure would be 7 cases compared to the observed 0. The anti-fracture benefit is clear and compelling, yet the cost has been the barrier to a full recommendation for all hip resurfacing patients to take the medication. Forteo and Tymlos may be more effective in building bone around the hip. (Fig. 5).

Fig. 5a. This AP pelvis radiograph of a 33-year-old man shows severe arthritis with periprosthetic bone loss and subchondral cyst formation.



Fig. 5b. This AP pelvis radiograph of the same patient shows increased bone formation and involution of the cysts following bilateral hip resurfacing and daily injections of Tymlos for 4 months.

We also treat these patients by harvesting EPCs from the patient's pelvis and injecting them into the femoral neck and areas of acetabular bone loss during the resurfacing surgery.

Blood tests

P1NP (N-terminal propeptide of type 1 collagen) is a measure of bone formation. It is a useful marker as it reliably increases with during fracture healing and returns to normal with fracture union. It also increases in response to anabolic bone forming medications. CTX (C-terminal telopeptide of type 1 collagen) is a measure of bone resorption and reflects the activity of osteoclasts. It is used to determine if the increasing bone mass is due to anti-resorptive rather than bone forming effects.

The PTH level increased by a mean of 109% above base line at one month. The PTH level continued to increase to 176% of baseline by 12 months. The P1NP increased by a mean of 148% compared to baseline at one month and peaked at 200% at 6 months. P1NP was 174% of baseline at 8 months and was 121% of baseline 4 months after discontinuation of treatment. CTX remained at baseline at one month, 12 months and 4 months after treatment. CTX increased to 116% of baseline at 8 months. The increase in bone formation as measured by the increase in P1NP without a significant increase in CTX confirms that the increased bone mass was due to anabolic rather than anti-resorptive effects. The continued increase after treatment indicates there is a trailing effect to the bone formation following completion of the anabolic drug administration.

Conclusions

Forteo and Tymlos are made of the bone-forming terminal component of PTH (1-34) and are FDA-approved for use for osteoporosis. Forteo and Tymlos “turn on” normal bone healing within 30 minutes of administration. Research and clinical studies show they increase bone mass and prevent fractures. They also improve fracture callus formation, bone mineral content formation, and healing time of fractures. Forteo and Tymlos are increasingly common options in the conservative treatment of fracture nonunion and, occasionally,

fresh fractures. Recent promising uses of Forteo and Tymlos have been to recover periprosthetic bone loss related to the pretreatment joint disease or osteolysis related to a failed prior implant. Both Tymlos and Forteo are expensive but they are safe and effective. They are suitable for most patients in need of additional bone formation.

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