Currently available agents improve bone mineral density (BMD) values on their own in monotherapy but may not completely restore microarchitecture and the patient may continue to sustain fragility fractures. Current monotherapies can only address either increased bone resorption or decreased bone formation. In this setting, combination therapy with antiresorptive and anabolic agents appears to be a promising option. A 49-year-old premenopausal woman presented with severe low backache associated with significant height loss. Evaluation elsewhere revealed severe osteoporosis, which prompted treatment with three doses of parenteral zoledronate 4 mg annually, followed by oral alendronate 70 mg once weekly for 7 years. However, her symptoms persisted despite treatment, and investigations done at our center confirmed severe osteoporosis, with multiple vertebral compression fractures. She was initiated on teriparatide therapy but despite 1 year of treatment, there was persistent height loss. In addition, there was a marked elevation of bone resorption, which prompted us to add denosumab which was administered subcutaneously every 6 months. On follow-up, there was marked relief from pain, no further decrease in height, and progressive improvement in BMD, and bone turnover markers were noted. A dual therapy with anabolic agent teriparatide and antiresorptive agent denosumab for osteoporosis may be a viable option in individuals with severe osteoporosis who do not respond well to a single agent.

Keywords: Denosumab, fractures, severe osteoporosis, teriparatide

### INTRODUCTION

Osteoporosis is a common skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, which predisposes affected individuals to an increased risk of fragility fractures. Nowadays, various drugs including antiresorptives and anabolic agents are available for the treatment of osteoporosis. Monotherapy with either of these agents increases bone mineral density (BMD) but may not result in complete restoration of normal BMD. Conventional treatment approaches reduce fracture risk but do not eliminate it totally. Combination therapy with antiresorptives and anabolic agents has been proposed as an alternative to overcome the limitations of monotherapy. It has been reported that concomitant teriparatide and denosumab therapy increases BMD to a greater extent than that with either agent alone, and the gains in BMD are more than what has been reported with any other currently available therapy. Here, we report a case of severe idiopathic osteoporosis treated effectively with such combination therapy.

### CASE REPORT

A 49-year-old premenopausal woman was referred to the endocrinology outpatient department with severe low backache and a 10 cm height loss over the preceding 10 years (from 160 to 150 cm). Evaluation at her center confirmed severe osteoporosis, with multiple vertebral compression fractures. She was initiated on teriparatide therapy but despite 1 year of treatment, there was persistent height loss. In addition, there was a marked elevation of bone resorption, which prompted us to add denosumab which was administered subcutaneously every 6 months. On follow-up, there was marked relief from pain, no further decrease in height, and progressive improvement in BMD, and bone turnover markers were noted. A dual therapy with anabolic agent teriparatide and antiresorptive agent denosumab for osteoporosis may be a viable option in individuals with severe osteoporosis who do not respond well to a single agent.
hometown revealed severe osteoporosis, for which she had received three doses of parenteral zoledronate annually, followed by oral alendronate 70 mg once weekly for 7 years. There was no history suggestive of secondary osteoporosis or long bone fractures. There was no history of similar disease in first-degree relatives.

On examination, she was obese with a body mass index (BMI) of 31.6 kg/m² and height of 150 cm [Figure 1]. Systemic examination was unremarkable except for kyphoscoliosis. On biochemical evaluation of blood bone mineral parameters, she was found to have an albumin corrected calcium of 8.9 (N: 8.3–10.4) mg/dL, fasting phosphorus of 3.1 (2.5–4.6) mg/dL, 25 OH Vitamin D level of 29 (>30) ng/mL, and parathormone (PTH) of 26 (8–50) pg/mL. Bone turnover markers were suppressed at the time of presentation (alkaline phosphatase [ALP] 49 (40–125) U/L, P1NP 17.7 [15.1–58.3] ng/ml, CTX 103 [137–573] pg/mL) [Figure 2]. X-ray of the thoracic and lumbar spine showed multiple vertebral compression fractures [Figure 3]. Genetic screening for osteogenesis imperfecta was negative. Dual-energy X-ray absorptiometry scan (DXA) showed osteopenia at the neck of the femur and lumbar spine. The BMD at the neck of the femur and lumbar spine were 0.684 and 0.825 g/cm², respectively. In view of suppressed bone turnover markers and ongoing height loss, she was initiated on subcutaneous teriparatide at a dose of 20 μg daily in addition to 1000 mg of elemental calcium and cholecalciferol 1000 IU/day. However, despite 1 year of treatment, there was further height loss of 2 cm (150 to 148 cm). Even though lumbar spine BMD increased by 4.24%, there was a BMD loss of 7.3% at the neck of the femur.

Due to ongoing height loss and elevated levels of bone turnover markers (ALP 125 [40–125] U/L, P1NP 457 [15.1–58.3] ng/ml, and CTX 1381 [137–573] pg/mL) at the end of 1 year of anabolic therapy, denosumab (receptor activator of nuclear factor κB ligand [RANKL] inhibitor antiresorptive agent) subcutaneously at a dose of 60 mg at 6 monthly intervals was added. Subsequent to the first dose of denosumab added to her ongoing therapy with teriparatide, she had marked improvement in symptoms and no further height loss was recorded thereafter.

Three months after initiation of denosumab therapy continued along with teriparatide, alkaline phosphatase, P1NP, and beta crosslaps levels were 83 U/L, 110 ng/mL, and 451 pg/mL, respectively. BMD at the neck of femur and L1–L4 were 0.680 and 0.934 g/cm², respectively, after 6 months of initiation of denosumab [Figure 4]. Bone formation markers were not improved with the combination therapy; however, there was improvement in BMD. Combination therapy resulted in marked symptomatic improvement, with no further height loss. The plan is to continue the combination therapy (teriparatide and denosumab) for a total duration of 2 years and thereafter to give denosumab or bisphosphonates.

**DISCUSSION**

Currently available agents improve BMD values, but monotherapy alone may not completely restore microarchitecture and the patient may continue to sustain fragility fractures. In this setting, combination therapy with antiresorptive agents such as denosumab and anabolic agent teriparatide appears to be a promising option.

Currently available antosteoporosis medications can be classified into either antiresorptive agents or anabolic agents based on their mechanism of action. Antiresorptive agents include drugs such as bisphosphonates and the RANKL inhibitor denosumab. Anabolic agents include the full-length molecule parathyroid hormone [PTH- (1–84)] and teriparatide [PTH- (1–34)]. Although conventional monotherapy increases BMD and reduces fracture risk, at times to improve treatment efficacy, combination therapy using antiresorptive denosumab and anabolic agent teriparatide has been proposed.[2]

Combination therapy with anabolic agent teriparatide and bisphosphonates was initially thought to be a promising approach, but their combination was not shown to be consistently superior to monotherapy.[3,4] However, the denosumab and teriparatide administration (DATA) study reported that 2 years of concomitant teriparatide and denosumab therapy increases spine and hip BMD more than with either medication alone and more than what has been reported with any other currently available.

![Figure 1: Patient at presentation with a height of 150 cm](image-url)
therapy.[5] DATA-high resolution peripheral quantitative computed tomography study demonstrated that 2 years of combined teriparatide and denosumab improves bone microarchitecture and estimated strength more than the individual treatments, particularly in the cortical bone.[6] Thus, the denosumab-teriparatide combination therapy emerges as a potential treatment option particularly in patients at high risk of fracture.[2]

The patient presented in this report was initiated on teriparatide due to suppressed bone turnover, persistent pain, and continued height loss despite prior bisphosphonate therapy. Following teriparatide administration, there was minimal improvement in pain, with the continuation of height loss. Concomitant administration of denosumab with the continuation of teriparatide resulted in a dramatic improvement in symptoms, a halt in height loss, and a gradual improvement in BMD.

In subjects with severe osteoporosis, where there is continuing bone loss, combined treatment with bone anabolic agent teriparatide and antiresorptive denosumab helps in preserving the bone mass accrued by teriparatide therapy alone and thereby halts the progression of osteoporosis.

**Informed consent**

Informed consent was obtained from the patient for publishing this report.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.
Conflicts of interest
There are no conflicts of interest.

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