

Chapter 150

Emerging Vistas in Osteoporosis Treatment: Newer Bisphosphonates and Biologics

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INTRODUCTION

Osteoporosis literally means HOLES IN BONES. It is the most common metabolic bone disease which affects both sexes and all races. It is a global problem which most of the time goes unrecognized and untreated.

History

It is a disease of antiquity. In 1820, G.C.F.M. Lobstein coined the term OSTEOPOROSIS based on appearance of affected tissue (porous bone). In 1940 Fuller Albright defined the clinical syndrome of osteoporosis mainly in postmenopausal women.

Definition

The current consensus definition of Osteoporosis is "a systematic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures"¹.

World Health Organization (Definition)

A bone mineral density ≥ 2.5 standard deviation below the young normal mean.

Epidemiology

By above definition, 10 million people in US have osteoporosis, Third National Health And Nutrition Examination Survey (NHANES III) data estimates 13-18% of women over age 50 have osteoporosis and an additional 37-50% have low bone mass at hip. It results

in 350000 hip fractures alone each year in US. Because the elderly population is growing worldwide the annual number of fractures is expected to double by 2025. 20% of white postmenopausal women had osteoporosis at femoral neck². Fractures are more frequent in women than in men, more in Caucasians than other races. The common sites of fracture are hip, forearm and spine.

With dramatic growth of elderly population the number of osteoporotic fracture will increase unless the cost effective control programs are implemented

In India

Osteoporosis now is considered as a major healthcare problem in India with an estimated 50% of healthy women and 36% men over 50 years of age having low bone mass. Occurrence of osteoporosis is 10 years earlier in Indian than people in the west³. Analysis reveals that 29.9% of women and 24.3% of men between the age of 20-79 years have low bone mass.

The observations of the study suggest that there is higher prevalence of low bone mass in the Indian population compared to western population⁴.

In another study the hip fractures occur at a relatively earlier age in Indian males and females compared to their western counterparts. A higher male to females ratio suggest that Indian males are at a higher risk for hip fracture. With the increase in life expectancy osteoporosis has become a formidable public health problem in India and a multidisciplinary approach is needed⁵.

Every Standard Deviation (SD) of decrease in Bone Mineral Density (BMD) increases fracture risk two to threefold. Over 10 year period, 18% of 65 years old

women with osteoporosis will experience a fracture, increasing to 33% among those with BMDs more than four SDs below the peak mean. The lifetime hip fracture risk for a 50 years old woman is nearly 15%. The one year mortality after hip fracture is 20% among those less than 70 years old, 30% for ages 70-79 years and 40% in those greater than 80 years old⁶.

RISK FACTORS

Non-modifiable

- History of fracture as an adult
- Presence of fracture (especially of hip) in first degree relative
- White
- Advanced age
- Dementia and frailty
- Immobilization

Modifiable

- Alcohol and tobacco use
- Low body weight (<127 lbs for white, <100 lbs for Asian)
- Premature menopause
- History of amenorrhea
- Low dietary calcium intake
- Frequent falls and poor eyesight
- Low level of physical activity
- Use of glucocorticoids
- Vitamin D deficiency
- Caffeine intake

Various causes of osteoporosis

Primary osteoporosis	Bone marrow disorders
Juvenile	Multiple myeloma and related disorders
Idiopathic (Young adults)	
Involuntary osteoporosis	Systemic mastocytosis
• Type I (Postmenopausal)	
Type II (Senile)	Disseminated carcinoma
Endocrine Disease	Connective tissue diseases
Hypogonadism	Osteogenesis imperfecta
Ovarian agenesis	Homocystinuria
Glucocorticoid excess	Ehlers-Danlos syndrome
Hyperthyroidism	Marfan's syndrome
Hyperparathyroidism	

Diabetes mellitus (?)

Gastrointestinal diseases	Miscellaneous causes
Subtotal gastrectomy	Immobilization
Malabsorption syndromes	Chronic obstructive disease
Chronic obstructive jaundice	
Primary biliary cirrhosis	Chronic alcoholism
Severe malnutrition	Rheumatoid arthritis (?)
	Chronic heparin administration
	Chronic administration of Anticonvulsant drugs (?)

Pathogenesis

Bone is metabolically active throughout life. After skeletal growth is complete, remodeling of both cortical and trabecular bone continues. Cortical bone is replaced at a lower rate (H² 2% per annum) than trabecular bone (H² 10% per annum).

The pathogenesis of Osteoporosis reflects complex interplay among genetic, metabolic and environmental factors that determine, bone growth, peak bone mass, calcium homeostasis, bone loss. These factors are influenced by aging, physical inactivity, sex hormone deficiency and nutritional status.

Bone loss in osteoporosis results from an imbalance between the two components of the bone renewal process- bone resorption and bone formation. This is the fundamental basis of osteoporosis.

Postmenopausal bone loss is the single most important cause of bone loss. Rate of loss is greatest early after the menopause. Loss from different bone sites occurs at different ages and at different rates. Low calcium intake is associated with osteoporosis

Genetic basis: Genetic factors that regulate skeletal development include CBFA1 gene for osteoblast differentiation and Receptor Activator of Nuclear Factor κ B (RANK)/RANK-ligand system for osteoclasts. 50% of peak bone mass is determined by genetic factors. The production of cytokines such as IL -1, TNF α , and IL -6 can potentially enhance bone resorption which can be suppressed by physiological doses of estrogens⁷.

A functional polymorphism affecting an Sp1 binding site has been identified in the collagen type 1 α 1 gene that predicts osteoporotic fracture independent of bone mass by influencing collagen regulation and bone quality⁸.

Table 1: Characterization of the two main types of involutional osteoporosis

	<i>Type I</i>	<i>Type II</i>
Age	51-75 yrs	>70
Sex Ratio	6:1	2:1
Type of bone loss	Mainly cancellous	Cancellous and cortical
Rate of bone loss	Accelerated	Not accelerated
Fracture site	Vertebrae(crush) and distal radius	Vertebrae (multiple wedge), hip
Parathyroid function	Decreased	Increased
Calcium absorption	Decreased	Decreased
Estrogen effects	Mainly skeletal	Mainly extraskkeletal
Main causes	Menopause and individual predisposing factors	Factors related to ageing, Late effects of estrogen deficiency

Mechanical loading induce prostaglandin synthesis, increased nitric oxide production and later increases Insulin like Growth Factors (IGF), changes in aminoacid transporters and eventually increases in new bone formation

Bone Markers

Bone turnover markers can be used to predict the rate of postmenopausal bone loss and the occurrence of osteoporotic fracture. They may have a role in monitoring the efficacy of treatment.

<i>Bone formation</i>	<i>Bone resorption</i>
• Alkaline phosphatase (bone specific)	N-telopeptide (NTX)-urine/serum
• Osteocalcin	C - telopeptide (CTX)-urine/serum
• Procollagen I extension peptide (serum)	Deoxypyridinoline-urine

Clinical Features

It includes wrist fractures, persistent hand pain, hip fractures, vertebral fractures, back pain which may be acute and chronic, hyperkyphosis, Loss of spinal mobility, height loss and decreased lung function.

Management

- PRIMARY – reducing fracture risk in patients with no fracture history but with low T score below -2.5.
- SECONDARY – reducing fracture risk in patients with fracture history

All those with osteoporosis should have a diagnostic evaluation including a careful history, physical exami-

nation, and laboratory investigations to exclude the other conditions that mimic osteoporosis, to elucidate secondary causes of osteoporosis and to identify contributory factors and comorbid conditions.

Investigations of Fracture or Bone Pain

- X-ray of affected part
- Full blood count
- ESR
- Serum calcium, alkaline phosphatase, serum creatinine, albumin
- Serum testosterone and SHBG in men
- Isotope bone scan
- CT scan or MRI
- Liver function test
- Serum protein electrophoresis
- Thyroid function test
- Urine for bence Jones protein
- PSA in men with vertebral fracture

Investigations of Bone Densitometry

- There are different options for bone density assessment.
- Radiographic techniques
- Single energy densitometry
- Dual energy densitometry (DXA scan)
- Quantitative computed tomography
- Quantitative ultrasound

Who Should Receive a BMD Test?

In 1998 National Osteoporosis Foundation (NOF) created guidelines for the use and interpretation of BMD measurements⁹.

- Post menopausal women under the age of 65 and have one or more additional risk factors for osteoporosis (besides menopause).
- Aged 65 and older regardless of additional risk factors.
- Present with fractures.
- Are considering therapy for osteoporosis, if BMD testing would facilitate the decision.
- Have been on HRT for prolonged periods.
- Men/women with low trauma fracture.
- Patient taking 5 mg/day of prednisone for more than 3 months.
- Men 65 years and older with risk factors such as alcoholism or hypogonadism or radiographic evidence of bone loss.

Goals of Therapy

- Prevention of fractures
- Optimization of skeletal development and maximization of peak bone mass at skeletal maturity
- Prevention of age related and secondary causes of bone loss
- Preservation of the structural integrity of the skeleton
- Improvement in quality of life
- Decreases in morbidity and mortality.

TREATMENT OPTIONS

Non-Pharmacological Interventions

Physical Exercise is of benefit for the well being and general health of every person. Mechanical loading of the skeleton is one of the mechanism by which bone remains physiologically intact as it is an important signal for bone remodeling. Bone mass increases in response to increased load. Evaluating current and life time effects on exercise retrospectively indicates higher total and hip BMD in persons exercising. Exercise programs increases bone mass by few % in the post menopausal and elderly women¹⁰.

The impact exercise confirmed a 0.9-1.6% non significant net gain in spine or femoral neck bone density compared to 1.0-1.2% from non impact exercise in pre- and post-menopausal women.

The physical activity gives only small percentage increase in bones and its significantly contributes to an anti-fracture effect to improve the balance and coordinates the muscle strength. The prospective studies indicates that it is possible to increase the muscle strength in the elderly and to improve balance with a concomitant decrease in number of falls through regular exercise. Physical activities like aerobic, weight bearing,

and resistance exercise lead to increase in bone mineral density of spine.

Other life style changes includes *avoidance of smoking*, reducing alcohol intake, using *hip protectors* to minimize trauma to hip during a fall and *fall prevention*.

PHARMACOLOGICAL INTERVENTIONS

Antiresorptive Agents: Calcium, Estrogen, Calcitonin, Vitamin D, and Bisphosphonates.

Bone formation stimulating agents: Fluoride, Calcitonin, Androgens, Growth hormone, and Parathyroid hormone (PTH).

General Therapeutic Measures

Acute back pain responds to analgesics, heat, and gentle massage to alleviate muscle spasm. Sometime a brief period of bed rest is required. Chronic back pain often is caused by spinal deformity and thus is difficult to relieve completely.

Calcium: The goals of therapy for Osteoporosis are to reduce bone resorption and to enhance bone formation. Weight bearing exercise increases muscle strength & may stabilize or modestly increase bone density. If calcium intake and absorption are insufficient to balance the daily calcium losses, bone loss ensues.

Table 2: Optimal calcium requirements recommended by the National Institute of Health Consensus panel

Age Group	Optimal Daily Intake of Calcium (mg.)
Infants	
Birth-6 month	400
6 mo-1 Yr	600
Children	
1 – 5 Yr	800
6 – 10 Yr	800 – 1200
Adolescents, young adults	
11 – 24 Yrs	1200 – 1500
Men	
25 -65 Yr	1000
Older than 65 Yr	1500
Women	
25 -50 Yr	1000
Older than 50 Yr (Postmenopausal)	
On estrogens	1000
Not on estrogens	1500
Older than 65 Yr	1500
Pregnant and nursing	1200 – 1500

In the absence of kidney stones or and underlying disorder of calcium metabolism, these calcium intakes

are safe. It is well tolerated and inexpensive. To prevent negative calcium balance, premenopausal women require 1000mg and postmenopausal women 1500 mg of total elemental calcium daily. Children have increasing calcium requirements during adolescence. Calcium acts by decreasing parathyroid hormones secretion..

Vitamin-D: Vitamin-D preparations have been used in osteoporosis. Because calcium absorption is impaired and serum levels of $1,25(\text{OH})_2\text{D}$ are marginally low. Subclinical vitamin-D deficiency is associated with secondary hyperparathyroidism and is common in elderly women. In these women low dose of vitamin-D combined with calcium supplements is useful in maintaining bone masses and decreasing incidence of hip fractures. Oral administration of calcitriol also may increase intestinal calcium absorption, suppress bone resorption and prevent bone loss in postmenopausal osteoporosis.

Bisphosphonates (Anti-Resorptive Agents)

Bisphosphonates are anti-resorptive drugs that are adsorbed to bone crystals. These drug also impair mineralization after long use. Modification of the side chains of etidronate results in the development of variety of compounds with differing potency to inhibit Bone resorption.

Bisphosphonate therapy has become the preferred treatment option to reduce the risk of spine and hip fractures in men and women with involution and glucocorticoid induced osteoporosis. They act on bone by binding to the hydroxyapatite and inhibiting osteoclasts.

Nitrogen containing Bisphosphonate inhibit farnesyl pyrophosphatase and other distal steps in the intracellular mevalonate pathway. As a consequence the post translational modification by prenylation of important intracellular regulatory proteins such as Ras and Rho is impaired, causing the inhibition of recruitment or differentiation of osteoclast precursors, alteration of cytoskeleton, decreased acid production and decreased production of lysosomal enzymes and prostaglandins, and increased apoptosis^{11,12}.

Non nitrogen containing Bisphosphonates are metabolized in the cell into cytotoxic ATP analogues.

They are poorly absorbed from gastrointestinal tract. Only about 0.5-5% of a given dose is absorbed. The absorption of bisphosphonates is inhibited by food intake, coffee, juice antacids, calcium salts or iron. Bisphosphonates are contraindicated in patients with renal dysfunction.

The plasma half life of bisphosphonates is very short and drug is displaced into the bone tissue within 30 min to 2 hours where as the half life of bisphosphonates deposited in bone is probably upto 10 years or more.

The 3 bisphosphonates currently licensed in the UK for the treatment of osteoporosis are the most commonly used drugs for treating this condition. These are Alendronate, Risedronate and cyclical Etidronate. It is estimated that these drugs account for 57% of all prescriptions for Osteoporosis.

Nitrogen Containing

- Alendronate, Risedronate, Ibandronate, Zoledronic acid.

Non Nitrogen Containing

- Etidronate, Clodronate, Tiludronate

Etidronate

Was the first licensed bisphosphonate for treatment of osteoporosis. Taken cyclically 400 mg for 2 weeks every 3 months (over dosage may cause mineralization defect). It significantly lower number of vertebral fractures were seen compared to placebo (Danish study). Patient on etidronate appear to have fewer non vertebral fractures compared to patient not treated.

Alendronate

Second generation bisphosphonate. First bisphosphonate for which a clear anti fracture effect was seen in large RCT. A reduction in vertebral deformities of about 50% and prevention of non vertebral fracture has been demonstrated. Fracture Intervention Trial (FIT1) demonstrated a significant reduction in the number of new radiographic and clinical vertebral fractures, significant reduction of hip and wrist fractures in women with bone density below the WHO threshold for osteoporosis who were treated with Alendronate for 3 years¹³.

Most efficient in reducing fracture in those at highest risk of new fractures by having a prevalent vertebral fractures or bone density confirming osteoporosis,. Treatment of women at lower risk appears less beneficial. Bone density increases at all sites during treatment with mean increase over three yrs is about 6% in lumbar spine, 4-4.5% in femoral neck and 4.5-5.0% in the total hip measure. A significant 50-65% decrease of bone markers, particularly resorption marker NTx is evident after 6-8 weeks of therapy¹⁴.

Available as 10 mg tab daily which has been linked with GI side effects (esophageal erosions). A 70 mg weekly dosing regimen is now available with lower risk of GI events. Over 10 years the therapeutic effects are sustained and the drug is well tolerated, discontinuation of Alendronate leads to a gradual loss on bone mass.

Risedronate

Third generation bisphosphonate. 1000 fold higher potency than etidronate. Prevent vertebral and nonvertebral fractures. Number of radio graphically diagnosed vertebral fracture was reduced by 41% and nonvertebral fracture by 39% in a 3 year Randomised Control Trial (RCT) of 2458 postmenopausal women with one or more prevalent radiographic vertebral deformities.¹⁵

49% reduction in hip fracture was evident only in women with low bone density while no effect was seen in the group of very elderly women aged 80-89 included only on risk factors alone. Points out that low bone density is a major determinant for clinical effect of anti resorptive agents. A 35 mg weekly dosing regimen is available now which produces 4-6% increase in spinal and femoral bone mass after 3 yrs of treatment.

Ibandronate

Given as 150 mg monthly or 2.5 mg daily (oral). IV Ibandronate (2 mg) once every 3 months dose dependently increased lumbar spine and femur BMD in postmenopausal women with or without osteoporosis¹⁶.

Once monthly oral Ibandronate is at least as effective as daily treatment¹⁷.

Lumbar spine BMD increased by 2.4%, 3.5%, 3.7%, and 5.2% after 1 yr treatment with IV Ibandronate 0.25, 0.50, 1.0, 2.0 mg respectively. Greatest BMD changes occurred in those who had osteopenia at base line (T score -2.5 to -1). It has been shown to reduce vertebral but not peripheral fractures, it is not yet licensed for use in England.

Other bisphosphonates used off label include intravenous Pamidronate and Zlendronate.

Intravenous pamidronate has not been put through any controlled trial and its intravenous use can cause prolonged hypocalcemia in those with vitamin D deficiency as well as leading to an acute phase response with myalgias and flu like illness during the first dose.

Intravenous Zolendronate has been shown to support bone resorption and improve BMD in postmenopausal women for as long as one year after a single dose. Currently it is undergoing phase 3 trial to assess its ability to reduce osteoporotic fractures.

One of the major problems with bisphosphonates has been compliance - with one study demonstrating 20% non-compliance within 6 months of starting bisphosphonates. There is some evidence that the availability of the once weekly preparation has improved compliance.

Adverse Effects of Bisphosphonates

It includes esophagitis, ulcers and erosion, slight increase in bone pain and transient hypocalcemia. GI side effects can be reduced if the drugs are taken in an upright position with a glass of water. To aid the absorption of the drug, they need to be taken 30 minutes before the administration of any food and on empty stomach. When used with aminoglycosides there is an increased risk of hypocalcemia.

Hormone Replacement Therapy (HRT)

Estrogen Replacement Therapy (ERT) involves use of estrogens only in patients who had hysterectomy. HRT — Combinations of estrogens and progestins (medroxy progesterone acetate) — endometrial hyperplasia and carcinoma are prevented when unopposed estrogen is replaced with the combination because the latter does not permit continuous endometrial stimulation.

PEPI (postmenopausal estrogen/progestin intervention) established the efficacy of various HRT or ERT regimens to prevent postmenopausal bone loss at hip and spine based on DXA scan after 36 months of therapy. Showed +3 to 5% increase in lumbar spine BMD and 1.7% increase in hip BMD¹⁸.

Regimens Available

- Conjugated equine estrogen 0.3, 0.625, 0.9 mg.
- Medroxyprogesterone acetate /day 1.25, 2.5 or 5.0 mg
- Transdermal estradiol 100 microgram on day 1-21+medroxyprogesterone acetate on days 11-31
- Micronized estradiol 0.5mg per day +progestins.

Selective Estrogen Receptor Modulator (Serm)- Raloxifene

It acts like estrogen agonists or antagonists depending on the specific target tissues.

It was developed with the goal of capitalizing on the benefits of estrogen in bone and eliminating or diminishing the impact of estrogen like compounds on cardiovascular and breast cancer risks.

The Multiple Outcomes of Raloxifene Evaluation (MORE) study was designed to assess the efficacy of raloxifene in postmenopausal women

After 3 years of treatment the occurrence of vertebral fractures was significantly reduced by 45% (60 mg dose) and 40% (120 mg dose) in groups 1 patients (BMD at Lumbar spine / Femoral neck < -2.5) and by 30% (60 mg dose) and 50% (120 mg dose) in group 2 patients (Had reduced BMD and e'' 1 moderate or severe vertebral fractures) compared with the placebo group¹⁹.

The overall incidence of nonvertebral fractures (ankle, hip, wrist) was unchanged with raloxifene therapy and there was no significant impact on hip fractures,

It was not associated with an increased risk of endometrial carcinoma, vaginal bleeding or mastalgia.

Venous thromboembolic events were increased and were recorded in 1% patients compared with 0.3% women receiving placebo.

Additional adverse events that were increased in women taking raloxifene included hot flashes, leg cramps, edema, and a flu like syndrome.

TIBOLONE

A synthetic steroid with estrogenic, androgenic and gestagenic properties which acts by binding to estrogen receptors. Two years treatment in early postmenopausal women has shown a bone density response similar to that of ERT but no data on fracture prevention is available²⁰.

CALCITONIN

A biological agent for osteoporosis

It binds to receptors on osteoclasts and this interaction inhibits osteoclast-mediated bone resorption. Availability of nasal calcitonin is about 25% or less of the administered dose.

Effective in reducing bone loss in early menopausal period in spine (trabecular bone) than cortical bone (hip and radius). A nasal spray is approved for the treatment of postmenopausal osteoporosis (200u/d) but not for prevention.

The PROOF (Prevent Recurrence of Osteoporotic Fractures) trial established the efficacy of this agent by comparing the 3 different doses of calcitonin (100, 200, 400 IU/d). All patients received 1000mg elemental calcium and 400 IU vitamin D daily. After 5 yrs of therapy, nasal spray calcitonin (200Iu/d) induced +1.0 to 1.5% increases in lumbar spine BMD that were accompanied by a 33% reduction in new spinal fractures compared with placebo²¹.

Adverse events included nasal irritation.

Strontium Ranelate

Composed of Ranelic acid and two atoms of nonradioactive Strontium. Increases bone formation by osteoblast precursor replication and collagen synthesis. Reduces bone resorption by decreasing osteoclast differentiation and resorbing activity. It is said to have dual action and in a randomized-trial reduced the risk of vertebral fracture by 40%. However non-vertebral fracture reduction was only observed in a post hoc analysis of a small group of women.

Measured mean BMD increased by 4% per year at lumbar spine and 2% per year at femoral neck reaching 13-15% and 5-7% respectively after 3 years²².

No dosage adjustment is required in relation to age. Not recommended for patients with severe renal failure (Cr clearance below 30 ml/min).

No dosage adjustment is required in patients with hepatic impairment.

Safety not established in pregnancy, lactation and in children.

Other Substrates – Fluoride

It is a potent anabolic agent which acts directly on osteoblasts by altering intracellular signal transduction. In a 4 yr placebo controlled randomized trial using Na fluoride at the dosage of 25 mg bid, a 4.8 % increase in lumbar spine bone mass and a 2.4 % increase in femoral neck hip bone density were noted and there was a decrease in vertebral fracture rate.

Terriparatide (Recombinant PTH)

Terriparatide (synthetic parathyroid hormone 1-34) first anabolic agent approved for treatment of postmenopausal osteoporosis. Stimulates bone remodelling by increasing bone formation. In Randomised Control Trial in postmenopausal women with osteoporosis terriparatide given intermittently increased BMD by 10-14% and femoral neck by 3-5%. Vertebral and non vertebral fractures are reduced by 65 and 50% respectively²³.

Trial was stopped because of concern about the development of osteosarcoma in rats treated. In UK treatment is limited to 18 months and USA 20 months.

Current recommendation is that terriparatide should be used in moderate to severe osteoporosis which in UK has been defined as failure of bisphosphonates to prevent fracture and bone loss in people with significantly reduced T score Or have multiple risk factors for fractures.

It is well tolerated except mild asymptomatic hypercalcemia. Should not be used in patients with Paget's disease of bone, unexplained elevations of alkaline phosphatase, pediatric patients or young adults with open epiphysis and patients with prior radiation therapy involving the skeleton, patients with history of hypercalcemia, hyperparathyroidism.

NOVEL THERAPIES

Increasing knowledge of mechanisms regulating bone cell activity provides potential sources for new therapeutic strategies. Unique ability of osteoclasts to dissolve and degrade bone tissue includes production of numerous substances both for mineral dissolution and enzymatic degradation of matrix. The degradation of matrix is mediated by cathepsin K, an osteoclast protease which appears to specifically act on bone collagen.

Deletion of cathepsin K gene results in an osteopetrotic bone in mice. An inhibitor of cathepsin K may therefore have potential use as an anti-resorptive drug.

Most cytokines are implicated as enhancers of osteoclast activity and subsequently bone resorption. Blockage of cytokine activity has already gained success with the anti-TNF- α treatment of Rheumatoid arthritis (RA), which may have additional effects on bone turnover since TNF- α has been shown to be one of the most important cytokines modifying bone resorption. Bone resorption markers significantly decrease in patients with RA treated with Infliximab²⁴.

This may allow for development of inhibitors to other bone active cytokines, such as IL-1 or IL-6. Identification of factors acting on receptors for osteoclast attachment or function, such as $\alpha_v\alpha_3$ integrin, RANKL (receptor activator of nuclear factor κ B ligand) or the soluble ligand osteoprotegerin may be fertile ground for development of antagonists. Clinical testing of osteoprotegerin indicates a positive effect on bone density in postmenopausal women²⁵.

Denosumab (the RANK ligand inhibitor) treatment for 24 months in postmenopausal women led to both continued, significant increase in BMD and sustained, significant reductions in bone turnover markers from base line compared with placebo²⁶.

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