Osteoporosis, Treatment Options and Their Impact

Chandrashekaran Girish* and Karri Sowjanya

Abstract

Osteoporosis, often considered as the silent disease poses serious socio-medical issues and its incidence in recent years has increased manifolds in the developing and developed countries. Though many effective pharmacological agents are widely available, adverse effects are quite troublesome with a majority of them. So, it is necessary to thrive for newer drugs having better efficacy with few adverse effects. This review mainly tries to look into such new drugs along with existing pharmacological agents approved by the United States Food and Drug Administration (US FDA) to treat osteoporosis; and those under pipeline like cathepsin K inhibitors and anti-sclerostin antibodies. The main goal concerned with the management of osteoporosis is to increase bone mineral density and prevent the progression of bone loss thereby reducing the incidence and fracture risk. The high costs involved with some of the existing and upcoming drugs have limited their usage to selective patients with a high chance of fracture risk and to those failing to show any response to the first-line agents. To improve the therapeutic choices, further studies are to be conducted with the newer agents and some other drugs that are already approved in places like Europe and are yet to be approved by FDA. A continuous research on plant derivatives may further help to discover newer agents, thereby creating more opportunities for treating osteoporosis.

Abbreviations: RANKL- receptor activator of NF-κβ ligand, CE- Conjugated estrogens, SERM’s- Selective estrogen receptor modulators, FDA- Food and Drug Administration, ABL- Abaloparatide, PTHrP- Parathyroid hormone related protein, HRT- Hormone replacement therapy, EMA- European Medical Agency, CaSR- Calcium sensing receptors, LRP5/6 - Lipoprotein receptor-related protein, Dvl - Disheveled GSK3β- Glycogen synthase kinase 3β

Introduction

Osteoporosis (means porous bone), one of the metabolic disorders of bone is characterised by a reduced bone mass with deterioration of the bone micro architecture. It can predispose to fractures as the fragile nature of the bone is often increased (1). It is often considered as a “silent disease” as it progresses rapidly without any appreciable symptoms till a fracture occurs either spontaneously or traumatically. It is also shown to have a marked
public health burden due to its association with high morbidity and mortality thereby increasing the economic cost (2). The annual burden of osteoporosis worldwide is around 200 million, of which the US accounts for 1.5 million cases. The major economic burden is due to vertebral and non-vertebral fractures as they require a high expense to treat and often have detrimental consequences. Following a hip fracture, the risk of deaths is one in four in the consecutive year (3).

**WHO (World Health Organisation) definition of osteoporosis:**

WHO has defined osteoporosis based on the "measurement of bone mineral density (BMD) at the hip or lumbar spine by dual energy X-ray absorptiometry (DXA) and T-score" as shown in Table I (4).

\[
T\text{-}score = \frac{\text{Patients BMD} - \text{Mean BMD (reference population)}}{\text{Standard deviation (SD)}}
\]

T-score is used for postmenopausal women and men ≥ 50 years. A score of ≥ -1.0 is normal, -1.0 to -2.5 as osteopenia (low bone mass), ≥ -2.5 as osteoporosis and ≥ -2.5 with one or more fractures as severe or established osteoporosis (4).

However, to diagnose osteoporosis in children, premenopausal women and men < 50 years, International Society for Clinical Densitometry (ISCD) has recommended the usage of race or ethnic adjusted Z-scores instead of T-scores (4).

\[
Z\text{-}score = \frac{\text{Bone mineral density} - \text{Mean bone mineral density (reference population)}}{\text{Standard deviation (SD)}}
\]

- ≤ -2.0 "below the expected range for age"
- > -2.0 "within the expected range for age"

**Etiopathogenesis:**

The etiology of osteoporosis is multifactorial, some of which include the lifestyle factors, genetic, gastrointestinal, haematological, rheumatologic and neurological disorders and a few medications which are shown in Table II (4).

<table>
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<th>Table I: WHO Classification- Bone mineral density (BMD).</th>
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<tr>
<td><strong>Classification</strong></td>
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<tr>
<td>Normal</td>
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<tr>
<td>Osteopenia</td>
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<tr>
<td>Osteoporosis</td>
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<td>Severe or established osteoporosis</td>
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<table>
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<th>Table II: Etiology of osteoporosis.</th>
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<tr>
<td><strong>Lifestyle factors</strong></td>
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<tr>
<td><strong>Genetic disorders</strong></td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td><strong>Hematologic</strong></td>
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<tr>
<td><strong>Rheumatologic</strong></td>
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<tr>
<td><strong>Neurological</strong></td>
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<tr>
<td><strong>Medications</strong></td>
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</table>

To understand the pathogenesis of osteoporosis, an aspect of bone remodelling (bone turnover) comes into picture. It is the replacement of an old bone with a new bone and includes four phases – bone resorption, reversal, formation and mineralisation. However, the main underlying factor is because of an imbalance between bone formation and resorption that can lead to fractures as shown in Fig. 1 (5).

**Available treatment options for osteoporosis:**

The treatment options available for osteoporosis include the following –

1. **Non-pharmacologic treatment:**
   - Lifestyle modifications: Calcium & Vitamin-D through diet
   - Physical activity
   - Smoking cessation; limited alcohol & caffeine intake

2. **Pharmacologic treatment:**
   a) Anti-resorptive drugs:
Bisphosphonates (BP’s) – Alendronate, Ibandronate, Zoledronate

RANKL (receptor activator of NF-κβ ligand) antibody – Denosumab

Estrogen replacement – Conjugated estrogens (CE)

Selective estrogen receptor modulators (SERM’s) – Raloxifene, Bazedoxifene

Calcitonin

An outline of the mechanism of anti-resorptive drugs, in general, is shown in Fig. 2.

b) Anabolic drugs: Parathyroid hormone (PTH) peptides – Teriparatide (6)

Non-pharmacologic treatment:

Lifestyle modifications do have an impact on the maintenance of bone health. Some of these include adequate intake of calcium (1000–1200 mg/day) and vitamin D (600-800 IU/day), weight bearing exercises (at least 30 minutes/day), avoiding high alcohol intake (≥ 2 servings/day), avoiding or quitting smoking, decreasing intake of caffeine and by providing moral, emotional and psychological support by health care providers and family members. Meta-analyses were performed in osteoporotic women who received calcium and Vitamin-D supplementation. One of these studies revealed that vitamin D alone was not effective in reducing the risk of fractures. However, another meta-analysis showed that there is a decrease in the risk of fractures at both vertebral as well as non-vertebral sites. Though the results are often conflicting; overall, it was found that adequate supplementation of calcium and vitamin-D can promote bone health by preventing the bone loss to a certain extent in osteoporotic patients (6).

Pharmacologic treatment:

Newer FDA (Food and Drug Administration) approved drugs (2013 – 2017):

The drugs approved include - abaloparatide, conjugated estrogens/bazedoxifene.
Abaloparatide: (ABL), (Brand name: Tymlos), 2017

It is a potent & selective synthetic analog of parathyroid hormone related protein (PTHrP), 1-34 indicated to treat postmenopausal osteoporotic women with high fracture risk. It is given as 80 µg subcutaneously in the periumbilical region once daily with a prefilled pen containing 30 doses. It causes activation of the cyclic AMP signalling pathway in target cells thereby exerting its anabolic effect on bone. The most common ADR’s include orthostatic hypotension, hypercalcemia, hypercalciuria, urolithiasis and some others like headache, nausea, dizziness, palpitations, vertigo, abdominal pain (7). Preclinical studies: Abaloparatide (ABL) when given at different doses of 5 and 20 µg/kg for 6 weeks increased BMD in ovariectomised (OVX) rats in a dose dependent manner. However, an evidence of bone cancer (osteosarcoma) is seen on long term usage, hence the label comes with black box warning (8). Some of the clinical studies which had shown a remarkable benefit with ABL are mentioned in Table III below (10).

Conjugated estrogens (CE)/bazedoxifene, (Brand name: Duavee), 2013

CE are extracted from the pregnant mares urine after purification and blending with sodium salts. Bazedoxifene is a selective estrogen receptor modulator (SERM), acting both as an estrogen agonist/antagonist. FDA has approved it for preventing postmenopausal osteoporosis and to treat vasomotor symptoms of menopause. Conjugated estrogen (CE)/bazedoxifene is available at 0.45 mg/20 mg tablet once daily. It acts by mimicking the favourable effects of estrogens; but simultaneously blocks estrogen in tissues where it might be harmful. Thus, CE with bazedoxifeneexerts a composite effect which is specific to each organ. The side effects include

Fig.2: Mechanism of action of cathepsin K inhibitors and anti-resorptive drugs on bone.
TABLE III: Overview of clinical trials and their findings associated with recently FDA approved osteoporotic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Description</th>
<th>Study population and duration</th>
<th>Intervention</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Abaloparatide (ABL)</td>
<td><strong>ACTIVE</strong> (Abaloparatide Comparator Trial In Vertebral Endpoints), Phase 3 trial</td>
<td>Postmenopausal women (50-85 years) Duration: 18 months</td>
<td>80 µg s.c ABL or a similar placebo, Open label active comparator: Teriperatide 20 µg s.c daily</td>
<td>Increased BMD with decreased fractures; rapid action with positive safety profile compared to teriperatide (10)</td>
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<td><strong>ACTIV Extend trial, open label single group assignment trial</strong></td>
<td>Recruited 1200 patients from ACTIVE trial and followed for next 6 months Duration: 25 months</td>
<td>70 mg/week alendronate along with calcium and Vitamin-D supplementation</td>
<td>ABL group showed an increased BMD with a significant reduction in vertebral and non-vertebral fractures (10)</td>
</tr>
<tr>
<td>CE/bazedoxifene</td>
<td><strong>(SMART) trials 1-5</strong>: Selective Estrogen, Menopause, and Response to Therapy, Phase 3 trials</td>
<td>Postmenopausal women</td>
<td>CE/Bazedoxifene at different doses or a similar placebo</td>
<td>SMART 1 &amp; 4 trials showed that CE/Bazedoxifene ↑BMD at hip and lumbar spine significantly compared to placebo Other trials: improvement in menopausal symptoms like vulvovaginal atrophy and other breast density assessment parameters (13)</td>
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muscle spasms, oropharyngeal pain, dyspepsia, nausea, diarrhea, abdominal pain, dizziness, neck pain (11). **Preclinical studies**: In a study conducted in OVX monkeys, up to 25 mg/kg/day of bazedoxifene was given for 18 months; and it helped in preserving the bone mass and its associated strength (12). The major breakthrough clinical studies with CE/bazedoxifene that led to its approval are listed in Table III below (13).

**FDA approved drugs from 1995–2012:**

**Denosumab (Brand name: Prolia, Xgeva), 2010**

RANKL inhibitor was approved by FDA to treat postmenopausal osteoporosis with fracture risk, in men with non-metastatic prostatic cancer receiving androgen deprivation therapy, and in breast cancer women receiving adjuvant aromatase inhibitor therapy. Normally, RANKL activates a receptor present on osteoclasts called RANK that causes bone resorption; denosumab acts by inhibiting this activation. It is administered subcutaneously 60 mg every 6 months in the arm or abdomen with a single use prefilled syringe. Daily supplementation of calcium 1000 mg and Vitamin-D 400 IU is advised routinely. The side effects include musculoskeletal pain, dermatological reactions, hypercholesterolemia and osteonecrosis of the jaw (14).

**Raloxifene hydrochloride, (Brand name: Evista), 2007**

It is an estrogen agonist or antagonist (SERM) indicated for the prevention and treatment of osteoporosis in postmenopausal women and to reduce their risk of invasive breast cancer. It acts dually by activation of estrogenic pathways, and by inhibiting them in tissues where it might be harmful. It is administered as 60 mg tablet once daily. Side effects include leg cramps, hot flushes, flu syndrome, and peripheral edema (15).

**Zoledronic acid, (Brand name: Reclast), 2007**

A bisphosphonate compound indicated for the prevention and treatment of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, to enhance the bone mass in osteoporotic men and to treat Paget’s disease of bone (men and women). It acts on farnesyl pyrophosphate synthase (enzyme present on osteoclasts) and prevent bone resorption. It is administered as an infusion of 5 mg in 100 mL for a minimum period of 15 minutes along with routine calcium and Vitamin-D supplementation. Adverse reactions include renal impairment, atypical femoral fractures and osteonecrosis of jaw (16).

**Ibandronate, (Brand name: Boniva), 2005**

A bisphosphonate indicated to treat postmenopausal
osteoporosis. It acts on osteoclasts and inhibits bone resorption. It is given as 3 mg intravenously every 3 months. ADRs include muscle, joint & bone pain, osteonecrosis of the jaw, atypical femoral fractures (17).

**Conjugated estrogens, (Brand name: Premarin), 2003**

It is indicated for the prevention of postmenopausal osteoporosis, to treat advanced androgen dependent carcinoma of the prostate and in the treatment of vulvar and vaginal atrophy. It acts by retarding postmenopausal bone loss and is given 0.625 mg daily or cyclical regimens (25 days on drug & 5 days off drug). ADRs include cardiovascular events, breast cancer and venous thromboembolism (18).

**Teriperatide, (Brand name: Forteo), 2002**

A recombinant human parathyroid hormone analogue (1-34) approved to treat postmenopausal osteoporotic women with a high risk for fracture, in men with primary or hypogonadal osteoporosis with high fracture risk and glucocorticoid-induced osteoporosis. It preferentially acts on osteoblasts over osteoclasts by acting on cortical and trabecular surfaces stimulating bone formation. It is given 20 µg subcutaneously once daily. The adverse drug reactions include arthralgia, urolithiasis and orthostatic hypotension (19).

**Estradiol transdermal patch, (Brand name: Alora), 2002**

This patch is available at different doses like 0.025, 0.05, 0.075 and 0.1 mg of estradiol per day. The reason behind the development of this patch is its increased potency when compared to estrone and estriol. The benefit of having a transdermal patch over oral therapy is that – the target therapeutic concentrations in plasma are attained at a lesser dose by a patch. The BMD was markedly increased in comparison to placebo when treated for two years (20).


These include Estradiol / Norethindrone acetate tablets (Activella 1/0.5, 0.5/1), 2000; estradiol transdermal patch, (Climara patch), 1999; Esterified estrogens, (Estratab 0.3 mg), 1998; Raloxifene, (Evista), 1997; Alendronate sodium, (Fosamax), 1995; Calcitonin-salmon nasal spray, (Miacalcin), 1995; CE/MPA tablets, (Prempo and Premphase), 1995.

Some of the important clinical trials with currently approved FDA drugs (1995-2012) are listed in Table IV.

**Off-label drugs used for osteoporosis:**

a) Calcitriol: It is an synthetic Vitamin-D analogue that promotes calcium absorption. It was approved by FDA for the management of hypocalcemia and metabolic bone disease in renal dialysis patients (4).

b) Genistein: Anisoflavone phytoestrogen marketed and approved by FDA as a medical food ("Fosteum", brand name). It acts by increasing the osteoblastic factors like bone alkaline phosphatases (B-ALP) and decreasing osteoclastic factors like collagen C-telopeptide (4, 27). Several clinical trials were conducted, however, they revealed conflicting results. Some trials had demonstrated an increase in bone mineral density (at femoral neck) and B-ALP time-dependently (28) and act as anti-resorptive agents (29); and few others showed that it failed to prevent bone loss or menopausal symptoms (30). Also, it was found that its potency is comparatively less when compared to bisphosphonates like risedronate (29).

c) Bisphosphonates: These include etidronate, pamidronate and tiludronate which are approved by FDA for treatment in Paget’s disease and hypercalcemia of malignancy. However, their role in osteoporosis needs to be established.

d) PTH(1-84): This is found to decrease the fracture risk when administered at 100 µg/day. It was approved in Europe and some other countries but not yet by the FDA.

e) Sodium fluoride (NaF): Acts by revitalizing the formation of new bone, however, its role in
TABLE IV: Overview of clinical trials and their findings associated with some of the FDA approved osteoporotic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Study population and duration</th>
<th>Intervention</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Denosumab</td>
<td>FREEDOM Trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months), phase 3 trial</td>
<td>Postmenopausal osteoporotic women Duration: 3 years</td>
<td>Denosumab 60 mg s.c or a similar placebo (once in 6 months)</td>
<td>Significant reduction of new radiographic vertebral fractures, hip &amp; non-vertebral fractures with denosumab (21)</td>
</tr>
<tr>
<td></td>
<td>FREEDOM Extension Trial</td>
<td>Recruted patients from FREEDOM trial and group received denosumab 60 mg s.c.</td>
<td>Denosumab and placebo group received denosumab 60 mg s.c.</td>
<td>Assessed long term safety and sustained efficacy fracture incidence was low and BMD was maintained with no marked ↑ in adverse effects (22)</td>
</tr>
<tr>
<td>Raloxifene hydrochloride</td>
<td>MORE Trial (Multiple Outcomes of Raloxifene Evaluation), phase 3 trial</td>
<td>Postmenopausal osteoporotic women Duration: 3 years</td>
<td>Raloxifene (30, 60, 150 mg/day) or placebo along with daily calcium and Vitamin-D supplementation</td>
<td>Raloxifene maintained BMD, prevented onset of new vertebral fractures; and the lipid profile was improved (23)</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>HORIZON Trial (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly)</td>
<td>Postmenopausal osteoporotic women Duration: 3 years</td>
<td>Zoledronic acid, 5 mg in comparison to placebo along with routine calcium and Vit-D supplementation</td>
<td>Marked improvement in assessed parameters (↑ fracture risk, ↑ BMD) with a good safety profile (24)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>ESTHER Trial (Efficacy and Safety of 12 months BonvivaTHERapy), phase 3 trial</td>
<td>Postmenopausal osteoporotic women Duration: 2 years</td>
<td>Ibandronate, 150 mg orally every month along with calcium 500 mg &amp; Vit-D 400 IU</td>
<td>Good tolerability and safety profile with marked improvement in BMD; and excellent compliance to treatment (25)</td>
</tr>
<tr>
<td>Conjugated estrogen (CE)</td>
<td>HOPE Trial (Health, Osteoporosis, Progestin, Estrogen)</td>
<td>Postmenopausal osteoporotic women Duration: 2 years</td>
<td>Premarin (0.625, 0.45, 3 mg) or placebo or a combination of CE + medroxyprogesterone acetate (MPA) along with daily calcium supplementation of 600 mg</td>
<td>BMD increased at spine, femoral neck and trochanter region in estrogen and combination group with no associated change in the body composition (26).</td>
</tr>
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</table>

...decreasing fracture risk is controversial and conflicting.

f) Tibolone: Estrogen like agent which is tissue specific and was approved by Europe to prevent postmenopausal osteoporosis but not yet by FDA (4).

Alternatives to treat osteoporosis:

Traditional methods are available for many centuries for the treatment of bone loss and its associated fracture risk by isolating the active compounds from several plant parts like seeds, roots, leaves, flowers. They act in different ways - they are a rich source of calcium, act on the gastrointestinal tract and promote calcium absorption or decrease the release of pro-inflammatory cytokines that lead to bone loss. The plant products which are found useful include:

a) *Allium cepa* and *Allium sativum* (stem-useful part), act by decreasing bone resorption b) *Cnidiummonnieri* (Coumarins, fruit is found useful), act by decreasing osteoclast formation c) *Anemarrhenasphodeloides* (rhizome) act by increasing bone formation d) *Curculigoorchioides* (rhizome) act by increasing osteoblast proliferation and decreasing bone resorption. Fatty acid supplementation is also found helpful in reducing bone loss and it acts by enhancing calcium absorption and also causes down regulation of osteoclastogenesis, pro-inflammatory cytokines and prostaglandins. These include n-3 alpha linoleic acid (Perilla oil), α-linoleic acid, linoleic acid (Flaxseed oil, Hemp oil), omega-3 essential fatty acids, docosahexanoic acid & eicosapentanoic acid (Salmon oil), omega-3 essential fatty acids (Cod liver oil) (5).

Recent developments: Drugs awaiting FDA approval:

a) Anti-resorptive agents:
• Cathepsin K inhibitors – ONO-5334, Odanacatib
• Strontium ranelate

b) Anabolic agents:
• Anti-sclerostin antibodies – Romosozumab, Blosozumab

c) Combination therapies:
• Anti-resorptive & anabolic agents – BP’s + PTH, SERM’s + PTH
• Two antiresorptive agents – BP’s + HRT (hormone replacement therapy), BP’s + SERM’s

Among the above mentioned newer drugs awaiting approval, anti-resorptive agents have shown to increase the BMD and decrease the fracture risk. However, anabolic agents and combination therapies are only found to increase the BMD lacking clear cut evidence regarding a decrease in fracture risk (6).

Cathepsin K inhibitors:
Cathepsin is a lysosomal cysteine protease which causes collagen degradation in different tissues. There are different types of cathepsins like cathepsin B, L, S, K. However, cathepsin K is specific to bone whereas the other types of cathepsin degrade collagen in tissues like skin and lung. The idea behind developing this class of drugs started from a rare disorder named pycnodysostosis which is autosomal recessive. The patients suffering from this disorder have a mutation in cathepsin K gene leading to an increased bone mass. So, the cathepsin K inhibitors prevented the adverse effects of collagen degradation in tissues like bone. It also promotes bone formation with the help of clastokines (secretory products of osteoclasts) as shown in Fig. 2 (35).

Cathepsin K inhibitors act on osteoclasts of bone thereby releasing clastokines which help in the differentiation of osteoblasts and promote bone formation. These drugs are under different phases of clinical trial to develop them as a treatment strategy for the treatment of osteoporosis; and some of which are listed in Table V.

Strontium ranelate (Brand name: Protelos):
It was approved by European Medicines Agency (EMA) to treat postmenopausal osteoporotic women with a high risk of hip and vertebral fractures, and intolerant to other pharmacological agents. Though

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<tr>
<td>ONO-5334</td>
<td>OCEAN Trial, phase 3 trial</td>
<td>Postmenopausal osteoporotic women (55-75 years)</td>
<td>ONO-5334 with one of the three different doses (50, 100, 150 mg daily) or alendronate (70 mg/week) or placebo</td>
<td>ONO-5334 and alendronate showed an increase in BMD significantly in a dose dependent manner at hip, lumbar spine, and femoral neck when compared to placebo, and no serious adverse events were reported (36)</td>
</tr>
<tr>
<td>Odanacatib</td>
<td>LOFT (Long-Term Odanacatib Fracture Trial), phase 3 trial</td>
<td>Postmenopausal osteoporotic women ≥65 years with a T-score ≥-2.5 at the total hip (TH) or femoral neck (FN) or with a prior vertebral fracture on radiography and a T-score ≥-1.5 at TH or FN</td>
<td>Odanacatib or placebo, 50 mg once weekly for 5 years along with calcium 1200 mg/day and weekly Vit-D supplementation of 5600 IU</td>
<td>Interim analysis: odanacatib showed significant and robust increase in BMD with decreased risk of fractures. Study was extended for next 5 years and shifted to open labelodanolacatib: a significant increase in cardiovascular events were recorded. This led to removal of drug from FDA regulatory process in 2016 after a long time of 12 years spent for clinical development (34, 37).</td>
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the mechanism of how it acts is not completely understood, it had a beneficial effect on bone formation with mild anti-resorptive effect. It acts on the calcium sensing receptors (CaSR) thereby inhibiting the function of osteoclasts and promoting the activity of osteoblasts increasing the BMD and decreasing the fracture risk. It also has an indirect action on proliferation and differentiation of osteoblasts. Strontium replaces the calcium ions in hydroxyapatite crystals and increasing the BMD. The adverse reactions include myocardial infarction and other cardiovascular events, venous thromboembolism, gastrointestinal discomfort, seizures. The EMA has made strict regulations regarding its usage only in osteoporotic men or women with high risk of fractures and prohibited in those with heart or other circulatory problems as it is associated with an increased risk of serious heart attacks (6).

Anti-sclerostin antibodies:

Sclerostin, primarily produced by osteocytes is a 190-kDa glycoprotein encoded by SOST gene. Canonical Wnt/β-catenin signalling pathway is an important mediator in bone formation. Wnt interacts with its lipoprotein receptor related protein, LRP5/6 and its co-receptor Frizzled resulting in activation of Disheveled (Dvl), an intracellular protein which inhibits glycogen synthase kinase 3β (GSK3β). This results in the survival of β-catenin which is then translocated into the nucleus thereby promoting gene transcription as shown in Fig. 3. This leads to growth and proliferation, maturation, differentiation, functioning

![Fig. 3: Wnt/β-catenin signalling pathway.](image-url)
and death of osteoblasts and chondrocytes (35).

Wnt binds to its receptor and helps in the movement of intracellular $\beta$-catenin into the nucleus thereby regulating gene transcription and promoting bone formation.

Abbreviations: LRP5/6 - lipoprotein receptor related protein 5/6; Dvl - Disheveled; GSK3$\beta$ - glycogen synthase kinase 3$eta$

Sclerostin acts by inhibiting the Wnt/$\beta$-catenin signalling pathway thereby preventing the interaction between Wnt and LRP5/6. The idea of developing anti-sclerostin antibodies started after the occurrence of two rare autosomal recessive disorders namely sclerosteosis and van Buchem disease. These disorders have a SOST gene mutation leading to the loss of sclerostin resulting in an increased bone mass and decreased risk of fractures. Anti-sclerostin antibodies bind to sclerostin and facilitate Wnt-LRP5/6 interaction thereby activating the pathway (35). The drugs in this class include romosozumab and blosozumab.

**Romosozumab**

It is an anti-sclerostin antibody; the safety and efficacy of which was demonstrated in a phase 3 trial, FRAME trial (Fracture Study in Postmenopausal Women with Osteoporosis). The efficacy data is shown in Table IV; and the most common adverse reactions reported in this trial include cardiovascular events, osteoarthritis, hyperostosis, osteonecrosis of jaw, and atypical femoral fractures. The underlying mechanism of romosozumab is attributed to the increased bone formation and decreased bone resorption (35).

**Blookozumab:**

Blookozumab, a humanised monoclonal antibody acts similarly like romosozumab by increasing bone formation and decreasing bone resorption (36). The efficacy data is listed in Table IV. However, the exact duration for which it has to be taken is not yet understood and further studies are needed to conclude its duration of action. In a phase 2 trial, the serum markers associated with bone formation declined within 3 months in the follow-up period and completely returned to baseline by the end of one year post-treatment. The adverse events reported were almost the same in both the groups. These results support the usage of blosozumab as an anabolic agent in the treatment of osteoporosis (37).

However, the long term safety concern is a debate and the company that developed this drug finds it difficult to manufacture subcutaneous formulation of this preparation. So, they again reverted its development from phase 2 to phase 1 to carry on with further investigations taking the necessary concerns into account (36).

Some of the clinical trials linked with anti-sclerostin antibodies are listed in Table VI.

**Conclusion:**

Osteoporosis, a major socio-economic issue worldwide is characterised by increased risk of fractures and hospitalisations, thereby impairing the quality of life. Currently, bisphosphonates remain to

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<tbody>
<tr>
<td>Romosozumab</td>
<td><strong>FRAME Trial</strong> (Fracture Study</td>
<td>Postmenopausal osteoporotic women Duration:</td>
<td>Romosozumab 210 mg or placebo s.c once</td>
<td>Decrease in vertebral fractures with romosozumab compared to placebo after 12 and 24 months; BMD significantly increased at hip and spine (35)</td>
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<td></td>
<td>in Postmenopausal Women with</td>
<td>24 months</td>
<td>a month followed by denosumab 60 mg s.c</td>
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<td></td>
<td>Osteoporosis) phase 3 trial</td>
<td></td>
<td>every 6 months for the next 12 months</td>
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<tr>
<td>Blosozumab</td>
<td><strong>Phase 2 trial</strong></td>
<td>Postmenopausal osteoporotic women Duration:</td>
<td>Blosozumabs, c at different doses of 180</td>
<td>Pronounced increase in BMD (hip and spine); however it declined when followed for another one year post-treatment (37)</td>
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<td></td>
<td></td>
<td>52 weeks; follow-up for next 52 weeks</td>
<td>180 mg and 270 mg once every two weeks</td>
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<td>and a similar placebo along with calcium</td>
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<td>and Vitamin D</td>
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**TABLE VI: An overview of clinical trials and their findings with anti-sclerostin antibodies.**
be the first-line treatment option due to their notable efficacy in both prevention and treatment of osteoporosis. However, their safety issues on long term usage is concerning. Also, there are several constraints linked with the usage of other available anti-resorptive (CE’s, SERM’s, etc) and anabolic agents (PTH peptides). One of them is the occurrence of adverse effects (hot flushes, peripheral edema) on their long term usage. Besides this, their efficacy in non-vertebral fractures and in eliminating the risk of fractures is limited. Hence, there is a necessity to thrive for newer drugs with increased efficacy & less adverse effects, for which clinical trials should be conducted on a large scale for a sufficient duration. Other newer drugs in the pipeline include cathepsin K inhibitors and anti-sclerostin antibodies that promote osteoblast differentiation and bone formation. Though there is no complete cure for the treatment of osteoporosis, steps can be taken to prevent, slow down or stop its progression. Some of these measures include lifestyle and dietary modifications, weight bearing exercise along with calcium and vitamin D supplementation.

References

9. Reginster JY, Al Daghrı NM, Bruyere O. Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) confirms that abaloparatide is a valuable addition to the armamentarium against osteoporosis. Expert Opin Pharmacother 2017; 18: 1811–1813.


