Bone Targeted Drug Delivery Systems: Osteoporosis

R. Prasanthi & T. Mamatha*

Department of Quality Assurance, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, Telangana, India

tmamathasnvpmv@gmail.com

1.Introduction

Drugs used to treat bone diseases that are administered systemically frequently have poor drug absorption in the tissue they are intended to treat, the potential for systemic toxicity, and poor therapeutic outcomes. Numerous micro- and nano-sized drug carriers have been created in order to get around these restrictions and treat bone pathologies that have a particular affinity for bone. A targeted drug delivery system that can bind to bone and release therapeutics exactly where it is needed can be formed by functionalizing drug carriers with bone mineral seekers (BMS). Drugs that are aimed to the site of action can improve efficacy while also lowering toxicity. A specific cell type or the entire skeletal system are the two general targeting moieties that are used to create drugs that target the bones. The majority of drugs that target bones have an affinity for hydroxyapatite, which makes up a significant portion of the bone matrix and contains a significant amount of positively charged Ca^{2+} (1-3).

Common bone diseases include osteoporosis (OP), Paget's disease, osteoarthritis (OA), osteosarcoma (OS), and osteomyelitis. Different bone diseases are listed below.

1.1. Bone Metastases

Cancer cells can spread to a bone through a process known as bone metastasis. In almost all cases, cancer can "metastasize" (spread) to the bones. Breast and prostate cancer, however, are two cancers that are particularly likely to spread to the bones. It is a common site of metastasis, particularly for prostate and breast cancer, but less frequently for primary cancer, particularly in adults. It is the main factor interfering with natural bone remodelling. There are three different types of bone metastasis: osteolytic, osteoblastic, and mixed.

1.2. Osteosarcoma

The most common type of bone sarcoma, which mostly affects patients between the ages of 10 and 20 and is characterised by the production of osteoid and bone by malignant spindle cells. Chemotherapy is a current treatment requirement. Early OS treatment focuses on amputation, which harms patients physically and mentally. The current treatment paradigm for OS, thanks to advancements in medicine, consists of preoperative neoadjuvant chemotherapy, surgical resection, and postoperative adjuvant chemotherapy. This disease's 5-year survival rate increased from 20% to about 60%.

2. Osteoporosis

Osteoporosis, a common bone disease that increases bone fragility and fracture susceptibility, is characterised by low bone mass and micro architectural deterioration of bone tissue as frequent symptoms. The two types of OP—primary and secondary—can be categorised based on their aetiologies. Primary OP, which includes old age and post-menopause, is the more prevalent type. In the case of postmenopausal osteoporosis, which is primarily brought on by oestrogen deficiency, bone loss and high conversion osteoporosis result from more bone resorption than bone formation. In order to maintain bone mineral density, oestrogen is frequently used.

2.1. Osteomyelitis

Osteomyelitis is an infection or inflammation of the bones that is more common in the elderly, diabetics, children, and residents of Third World nations. A bone can become infected by an infection that has spread from nearby tissue or through the bloodstream. If a wound makes the bone vulnerable to germs, infections can also start inside the bone itself.

2.2. Bone Regeneration

In response to injury, bone can repair itself, but this requires certain biological processes called bone induction and conduction that involve a variety of cell types and intracellular and extracellular molecular signalling pathways (4).

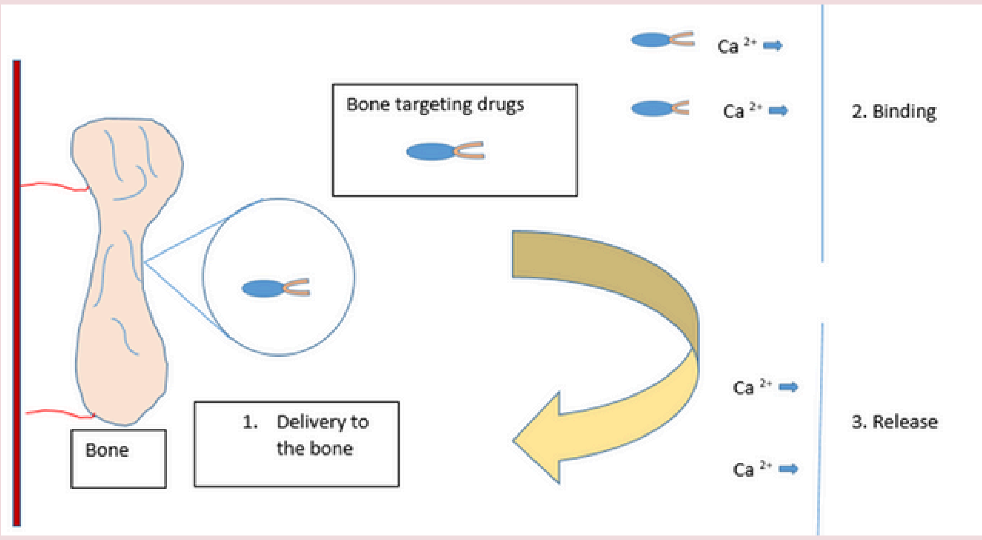

Figure 1: Bone targeting drugs

3. Osteoporosis- treatment options

3.1. Diagnosis

Osteoporosis is a bone disorder that raises a person's risk of fracture by reducing bone strength, bone microarchitecture, and/or bone mineralization. Men are also diagnosed with osteoporosis, making up about one in five people with the condition despite it typically being associated with women (5).

Bone mineral density (BMD) measurements, particularly in the hip and lumbar spine using the dual-energy x-ray absorptiometry (DXA) device or the occurrence of nontraumatic hip or vertebral fractures are used as the gold standard for diagnosing osteoporosis (6). Monitoring BMD is advised by the National Osteoporosis Foundation (NOF) one to two years after treatment begins and then every two years after thereafter (7).

For the treatment of bone diseases, a number of systems are used from the wide range of nanotechnology-based drug delivery methods. Tetracyclines, bisphosphonates, aspartic acid, and aptamers are just a few of the many bone-targeting ligands that have been produced and used to deliver anti-tumour medications specifically to the bone. The mechanism of action of bone targeting drugs is given in figure 1. In order to actively target bone metastasizing prostate cancer and breast cancer, respectively, antibodies to the human epidermal growth factor receptor 2 (HER2) and the prostate-specific membrane antigen (PSMA) are used (8).

3.2. Non-pharmacological Treatment

Adequate calcium and vitamin D intake, weight-bearing exercise, quitting smoking, limiting alcohol and caffeine consumption, and fall prevention techniques are all part of non-pharmacological management of osteoporosis. High dietary calcium intake may reduce the risk of kidney stones, whereas high calcium supplementation may increase the risk. In order to meet calcium needs, it is advised to increase dietary calcium intake before beginning calcium supplements (9).

3.3. Pharmacological Treatment

Treatment suggestions are based on a variety of factors, including gender, the likelihood of fracture, and additional risk factors like coexisting illnesses or medications. Drugs used to treat osteoporosis fall into one of two categories:

Antiresorptive - Antiresorptive drugs primarily slow down bone resorption, whereas anabolic drugs promote bone formation at the expense of bone resorption. Examples include bisphosphonates, oestrogens, oestrogen agonists/antagonists, calcitonin, and denosumab.

Anabolic – Teriparatide, abaloparatide (Tymos) and anti-remodeling medicines romosozumab (sclerostin antibody)

According to AACE/ACE guidelines (American Association of Clinical Endocrinologists/ American College of Endocrinology), alendronate, risedronate, zoledronic acid, and denosumab are the first-line treatments for the majority of patients who are at high risk of fracture. Teriparatide, denosumab, or zoledronic acid are advised for those who cannot use oral therapy and are at a high risk of fracture. (10).

Patients with osteopenia or low bone mass and a history of fragility fractures at the hip or spine, patients with a T-score of 2.5 or less in the lumbar spine, femoral neck, total hip, or 33% radius, or patients with a T-score between 1.0 and 2.5 if the FRAX (Fracture Risk Assessment Tool) 10-year probability for a major osteoporotic fracture is greater than 20%, or patients with a hip fracture should all begin taking medication. Diagnosis and treatment initiation are made by the NOF and Endocrine Society (11).

There are numerous formulations of bisphosphonates. Oral tablets of alendronate, risedronate, and ibandronate are readily available. In particular, two studies found that the delayed-release formulation of risedronate is not inferior to the immediate release. (12). Zoledronic acid and ibandronate are available as IV injections. Denosumab is available as an injectable formulation in either a prefilled syringe or a single-use vial subcutaneously (13).

3.4. Hormonal Therapies

Drugs in the oestrogen antagonist/agonist class are also referred to as selective estrogen receptor modulators (SERMs). An EAA (Essential amino acids) known as raloxifene exhibits both agonistic and antagonistic effects on estrogenic pathways. Raloxifene increases BMD by reducing bone resorption and bone turnover in the bone. Additionally, it has estrogen-antagonistic effects on uterine and breast tissue. Once daily dosage of Duavee tablets, which contain 0.45 mg of conjugated oestrogens and 20 mg of bazedoxifene. Careful consideration should be exercised despite the fact that it has the same boxed warnings, precautions, and contraindications as other estrogen-containing medications because it has a clinical role in therapy for the prevention of osteoporosis with the additional indication of treating vasomotor symptoms. (14). Testosterone therapy and calcitonin also helps in the treatment of osteoporosis.

3.5. Parathyroid Hormone Analogues

Teriparatide (20 mcg SC once daily in the thigh or abdomen), a recombinant human PTH (parathyroid hormone) analogue, is the first anabolic treatment approved for osteoporosis. Abaloparatide is the second recombinant human PTH (recommended dose is 80 mcg SC once daily into the periumbilical region of the abdomen) for osteoporosis treatment (15).

3.6. Emerging Therapies and Investigational Drugs

A monoclonal antibody that has been humanised and inhibits sclerostin is called romozumab. Sclerostatin is a protein that osteoclasts secrete in the skeletal tissue to prevent osteoblasts from proliferating and performing their normal functions, thereby reducing bone formation. Romosozumab induces a rapid increase in the marker of bone formation procollagen type I N-terminal propeptide (P1NP), which is followed by a slow decrease towards baseline levels, after 9 months of treatment. Blosozumab and BPS804 are two antisclerostin monoclonal antibodies currently under development and testing. The third generation of SERMs includes lasofoxifene (16).

4. Conclusion

There has been a lot of focus on the increasing incidences of bone diseases. More fractures are caused by osteoporosis each year, which is a global concern. A significant financial burden on health care systems will result from the anticipated rise in doctor visits, hospital stays, and nursing home admissions related to osteoporotic fractures. In light of age, gender, and other risk factors, screening is crucial. The first-line and most economical treatment for osteoporosis continues to be bisphosphonates, but there is growing worry about their long-term safety. We can soon anticipate drugs that treat osteoporosis using novel mechanisms. Osteoporosis is preventable with proper management of diet, lifestyle, and fall prevention interventions, despite the importance of appropriate BMD screening and medication treatment.

5 References

1. Rotman SG, Grijpma DW, Richards RG, Moriarty TF, Eglin D, Guillaume O. Drug delivery systems functionalized with bone mineral seeking agents for bone targeted therapeutics. J Control Release. 2018;269:88-99.
2. Stapleton M, Sawamoto K, Alméciga-Díaz CJ, Mackenzie WG, Mason RW, Orii T et al. Development of bone targeting drugs. Int J Mol Sci. 2017;18(7):1345.
3. Katsumi H, Yamashita S, Morishita M, Yamamoto A. Bone-targeted drug delivery systems and strategies for treatment of bone metastasis. Chem Pharm Bull (Tokyo). 2020;68(7):560-6.
4. Chen Y, Wu X, Li J, Jiang Y, Xu K, Su J. Bone-targeted nanoparticle drug delivery system: an emerging strategy for bone-related disease. Front Pharmacol. 2022;13:909408.
5. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465-75.
6. Cosman F, de Beur S, LeBoff M, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359-81. Erratum in: Osteoporos Int. 2015;26(7):2045-7.
7. Berry SD, Samelson EJ, Pencina MJ, McLean RR, Cupples LA, Broe KE, et al. Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture. JAMA. 2013;310(12):1256-62.
8. Chindamo G, Sapino S, Peira E, Chirio D, Gonzalez MC, Gallarate M. Bone diseases: current approach and future perspectives in drug delivery systems for bone targeted therapeutics. Nanomaterials (Basel). 2020 May 1;10(5):875.
9. National Institutes of Health Office of Dietary Supplements. Calcium: dietary supplement fact sheet, November 17, 2016.
10. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology: clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2016. Endocr Pract. 2016;22;Suppl 4:S1-S42.
11. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(6):1802-22.
12. McClung MR, Miller PD, Brown JP, Zanchetta J, Bolognese MA, Benhamou CL, et al. Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet. Osteoporos Int. 2012;23(1):267-76.
13. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.
14. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344(19):1434-41.
15. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of abaloparatide vs. placebo on new vertebral fractures in postmonopausal women with osteoporosis, a randamized clinical trial. JAMA. 2016;316(7):722-33.
16. Vasiliadis ES, Evangelopoulos DS, Kaspiris A, Benetos IS, Vlachos C, Pneumaticos SG. The Role of Sclerostin in Bone Diseases. J Clin Med. 2022; 11(3):806.