Wishing everyone a very Happy New Year 2023

DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Eighth, Oct– Dec 2022

Dear Readers,
The purpose of this bulletin is to disseminate some important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights drug agents for osteoporosis, recent drug approvals, few recent potential research and latest monoclonal antibodies nomenclature guidelines. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

World Osteoporosis Day: 20 Oct 2022; Theme: Step *Up For Bone Health*

Drug agents for osteoporosis: A glimpse

- Osteoclasts (OCs) and osteoblasts (OBs) play a very important role in bone remodeling.
- Multiple factors are involved in the differentiation, activation and survival of OCs including receptor activator of NF-κB ligand (RANKL), a molecule produced by different types of cells including osteoblasts (OBs), OCs, bone marrow stromal cells, lymphocytes, etc.
- In an acidic microenvironment formed by the sealing zone of OCs, cathepsin K degrade non-mineral components of bone such as collagen type I (Col-I). The attachment of OCs on bone surface is mediated by integrins, mainly αvβ3.
- Mature OBs produce osteoid consisting of Col-I and non-collagenous proteins. Mineralization of osteoid ensues and osteoblasts are embedded in bone, referred to as osteocytes (OCT. While OCTs were thought to be quiescent cells, several lines of evidence suggest they are active participants of bone metabolism. They can perceive mechanical loading signal and be regulated by hormones to coordinate coupling processes of formation and resorption mediated by OCs and OBs. In addition, OCTs are the major source of sclerostin, a potent inhibitor of Wingless-related integration site (Wnt) signaling pathway.

Anti-Resorptive Drugs

Anti-resorptive agents such as bisphosphonates, estrogen and denosumab, have been proven effective in some patients.

- **Bisphosphonates** like alendronate, ibandronate etc. are commonly used agents for primary and secondary osteoporosis to increase bone marrow density (BMD), but may affect the flexibility of bone, causing atypical subtrochanteric fractures and osteonecrosis of jaw, particularly, for those who will have dental procedures in the near future.
- **Estrogen replacement therapy** may increase cardiovascular events, venous thromboembolism and breast cancer. While selective estrogen receptor modulators (SERMs) have a reduced risk of breast cancer, their efficacy is lower than estrogen.
- **Denosumab** is a fully human IgG2 monoclonal antibody (mAb) against the ligand of the RANK receptors on the surface of osteoclast precursors (RANKL). Binding of RANKL to RANK activates multiple signaling pathways. The binding of TNF receptor-associated factors (TRAFs) to specific sites in the cytoplasmic domain of RANK is crucial for differentiation and survival of OCs. Osteoprotegerin (OPG), a decoy receptor, may compete with RANKL for the binding to RANK. Clinical trials have shown that in the first year, it may reduce the risk of vertebral and non-vertebral fractures. While prolonged treatment leads to continuous increase of BMD, the risk of infection also increases.

Reference: UpToDate

The Pill Box Quiz: 08

Instructions:
Scan the QR code to access the quiz.

SCAN ME

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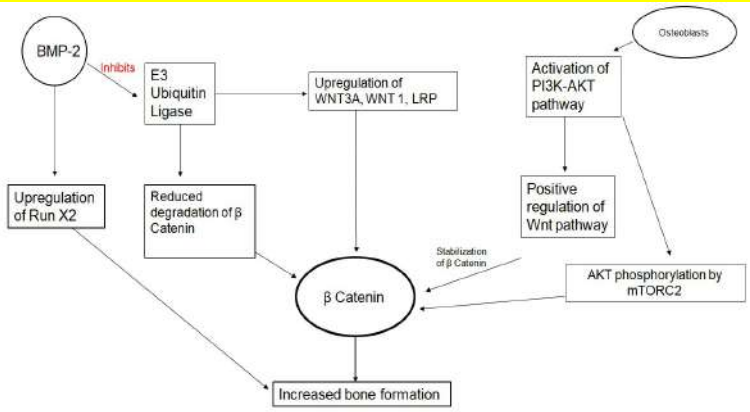
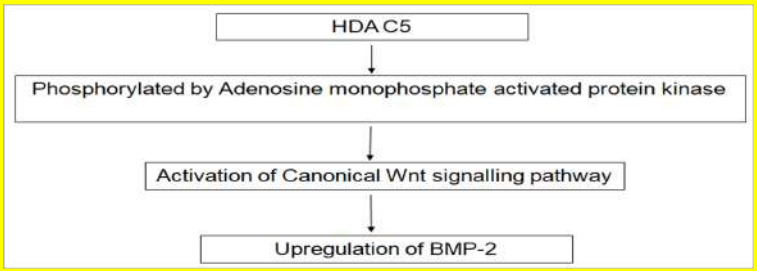
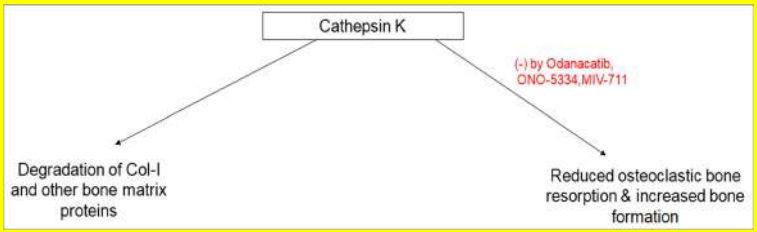
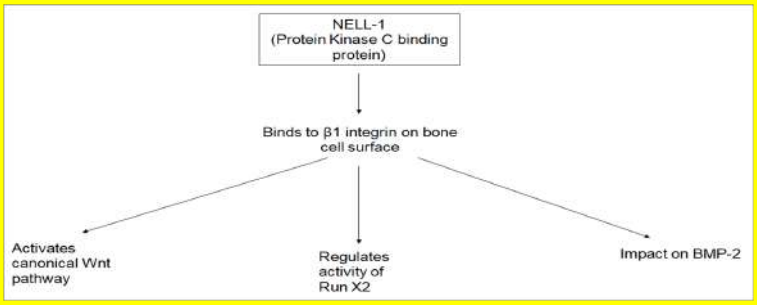
Newer drug targets for osteoporosis

Interaction of Wnt Pathway With Other Signaling Pathways and potential drug targets









- Bone morphogenetic proteins-2 (BMPs-2) of transforming growth factor beta (TGF-β) super family up-regulates the expression of Runt-related transcription factor 2 (RUNX2) through Suppressor of Mothers against Decapentaplegic (SMAD) pathway, leading to enhanced bone formation. BMP-2 also inhibits the activity of E3 ubiquitin ligase to prevent degradation of β-catenin and up-regulates the expression of WNT3A, WNT1, and low density lipoprotein receptor-related protein (LRP), which causes accumulation of β-catenin and activation of Wnt signaling pathway, thereby, increasing bone formation.
- Phosphatidylinositol-3 kinase- Ak strain transforming (PI3K-AKT) pathway regulates Wnt by stabilizing β-catenin and deactivating GSK3β. AKT form a complex with BMP-2 and regulate OB differentiation and endochondral ossification. AKT phosphorylation by upstream kinase mammalian target of rapamycin (mTORC2) may cause accumulation of β-catenin both in cytoplasm and nucleus.
- Adenosine Monophosphate Activated Protein kinase phosphorylates HDAC5, activate Wnt and up-regulate the expression of BMP-2.
- Protein kinase C-binding protein NELL-1 bind to β1-integrin on the surface of bone cells and activates canonical Wnt pathway.

-Preclinical studies have been performed to test the effect of mAb to DKK1. DKK1 is a prototypic Wnt signaling inhibitor that binds to and antagonizes the function of LRP. It improved BMD improvement in ovariectomized (OVX) rodents, whereas only a minimal improvement was observed in OVX monkeys. Notably, a bispecific antibody directed at both sclerostin and DKK1 has been generated and shown a more significant BMD improvement than mono-antibody in OVX rats. Concern: Off-target effects of DKK1 inhibitors in non-skeletal tissues, no clinical trials are currently going on.

-Lithium, a GSK3β inhibitor, can activate Wnt-β-catenin pathway. Lithium chloride (LiCl) stimulated bone formation, but did not affect bone resorption in mice. A newly-developed GSK3β inhibitor rapidly increased the number of OBs and decreased the number of OCs, resulting in a significant increase in bone volume, trabecular number and trabecular thickness. LY294002, an inhibitor of phosphatidylinositol-3-kinase-protein kinase B (PI3K-AKT) signaling pathway, can inhibit OC differentiation. Concern: both LiCl and LY294002 are highly toxic at conventional doses.

-miRNA-based therapies targeting secreted frizzled-related proteins (sFRPs), an antagonist of Wnt pathway, may become novel approach to treat osteoporosis in future.

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Anti-resorptive Drugs Under development

Drug Targets Inhibiting Bone Resorption

-**Cathepsin K inhibitors**: Cathepsin K, the primary cysteine protease secreted by mature OCs, is involved in the degradation of Col-I and other bone matrix proteins. Inhibiting cathepsin K decreased osteoclastic bone resorption and increased bone formation in animal studies. Selective cathepsin inhibitors, such as Odanacatib , ONO-5334 and MIV-711 , have been shown to reduce bone resorption and continuously increased BMD in multiple studies.
Concern: Cathepsin K deficiency may disrupt the blood-brain barrier via AKT-mTOR-VEGF signaling, causing neurological deficits and neuron apoptosis leading to the adverse events, especially stroke. Other concern is the rapid loss of functions after cessation of treatment. Further development is restricted due to potential adverse effect.

-**Chloride channel-7 (ClC-7) inhibitor**: ClC-7 and cathepsin K coexists and works synergistically in the ruffled border of OCs. Damage of ClC-7 results in severe OP, possibly due to the defect in bone degradation caused by the inability to acidify the sealing zone. N53736, a CIC-7 inhibitor, showed a long-term anti-resorptive effect in ovariectomized (OVX) rats.

-**Integrin αvβ3 antagonists**: αvβ3 integrin mediates the attachment of OCs onto bone matrix proteins. In different animal models of induced osteoporosis, αvβ3 integrin antagonists such as L-000845704 and HSA-ARLDDL significantly increase the BMD. In addition, a dual-specific protein, macrophage colony-stimulating factor (M-CSFRGD), may bind to and inhibit both c-FMS and αvβ3 integrin.

Drugs related to wnt signaling pathway

- **Romosozumab**, a humanized antibody that neutralizes sclerostin, has been approved by the FDA for OP treatment. It significantly increases BMD and decreases new vertebral and non-vertebral fractures but did not improve the fracture-healing-related outcomes of hip fractures. A recent study showed that romosozumab induced a transient bone formation in the first 2 months and a sustained suppression of bone resorption for up to 12 months. Sustainable BMD gains can be achieved by sequential therapy with romosozumab followed by denosumab.

Concern: Not recommended for patients with a previous myocardial infarction or other cardiovascular events because of potential adverse effects. Sclerostin is expressed in aortic vascular smooth muscle and can inhibit angiotensin II-induced atherosclerosis. Systemic blockade of sclerostin may affect the remodeling process in the cardiovascular system. The treatment duration of romosozumab should be no longer than 12 months.

- **Blosozumab**, another mAb against sclerostin, has shown to be well-tolerated and increased BMD in dose-dependent manner in completed phase 1 and phase 2 trials. Phase 3 results are awaited.

Non-wnt related anabolic drugs

-**Teriparatide (a recombinant human PTH 1–34)** may enhance bone formation by promoting osteoblast differentiation and functions. Intermittent administration of teriparatide stimulates bone formation on cancellous, endosteal, and periosteal surfaces. Its effects on cortical bone vary at different sites.
- Randomised controlled trials shown a higher efficacy of teriparatide than risedronate in reducing the fracture risk in vertebral and non-vertebral sites.
- **Abaloparatide**, a synthetic analogue of PTHrP, has a higher efficacy in the increment of BMD and lower incidence of hypercalcaemia than Teriparatide. It has higher affinity to PTH1R and is able to specifically stimulate osteogenesis.
- Abaloparatide is superior to Teriparatide and Alendronate with regard to the reduction of fracture risks.
-Although no increased risk of osteosarcoma is observed in patients, laboratory studies have shown a dose-dependent increase of osteosarcoma in rats treated with either Teriparatide or Abaloparatide.

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Monoclonal Antibodies: Nomenclature mystery

Monoclonal antibodies (mAbs) are the largest class of biological products in clinical use. They comprise a large variety of different structures, from small fragments to intact, modified, or unmodified immunoglobulins, all of which contain an antigen binding domain. Appropriate nomenclature for all pharmaceutical substances including mAbs is important for clinical development, licensing, prescribing, pharmacovigilance, and identification of counterfeits. The WHO International Nonproprietary Names (INN) Programme implemented a mAb nomenclature scheme in 1991, using the stem -mab to identify this group. The suffix is preceded by an infix that indicates the target class. The new INN mAb nomenclature scheme was approved and adopted by the WHO at the 73rd INN Consultation held in October 2021, and the radical decision was made to discontinue the use of the well-known stem *-mab* in naming new antibody-based drugs and going forward, to replace it with four new stems: *-tug, -bart, -mig*, and *-ment* as shown below.

Group 1 -**tug** for unmodified immunoglobulins

Group 2 -**bart** for antibody artificial

Group 3 -**mig** for multi-immunoglobulin

Group 4 -**ment** for fragment

Infixes: The mechanisms of monoclonal antibodies are complex, may be different for different indications and might not be completely understood during development. Therefore, the infix is assigned according to the proposed known mode of action at the time of the INN request.

Infix	Definition
-ami-	serum amyloid protein (SAP)/ amyloidosis (presubstem)
-ba-	bacterial
-ci-	cardiovascular
-de-	metabolic or endocrine pathways
-eni-	enzyme inhibition
-fung-	fungal
-gro-	skeletal muscle mass related growth factors and receptors (presubstem)1 -ki- cytokine and cyto kine receptor2 -ler- allergen

Infix	Definition
-sto-	immunostimulatory
-pru-	immunosuppressive
-ne-	neural
-os-	bone
-ta-	tumour
-toxa-	toxin
-vet-	veterinary use (sub-stem)
-vi-	viral

Reference: New INN mAb nomenclature scheme, WHO, 2021

Four letter suffixes after a drug name are intended to make it easier for health care providers to distinguish between biologic medications made by different manufacturers. By distinguishing between the different manufacturers, the FDA intends to be better able to monitor the safety of these products..eg. Trastuzumab-anns, trastuzumab-dkst, trastuzumab-dttb, trastuzumab-pkrb, trastuzumab-qyyp.

- All new monoclonal antibody-drug applications being named based on the antibody part, using the four new stems, and with the conjugated drug name as the second word .
- Monoclonal antibodies as component of fusion proteins are given suffix *-fusp* for fusion protein . e.g. *tebentafusp*
- Monoclonal antibodies as components of substances for cell based gene therapy: These substances do not follow the INN monoclonal antibody nomenclature scheme, instead they follow the INN nomenclature scheme for substances for cell-based gene therapy. A two-word name is given to these substances, in which the first word is identified with the suffix *-gene* and refers to the gene component, and the second word is identified with the suffix *-cel* and refers to the cell component.

The next time you encounter a prescription for XYZ-i-mAb, follow Shakespeare's work. Don't "deny thy father and refuse thy name," but embrace that "a rose by any other name would smell as sweet."

New Drugs Corner

Mosunetuzumab-axgb
MOA: Bispecific CD20-directed CD3 T-cell engager
Indication: To treat adults with relapsed or refractory follicular lymphoma, a type of non-Hodgkin lymphoma

Lenacapavir
MOA: Capsid inhibitors
Indication: To treat adults with HIV whose HIV infections cannot be successfully treated with other available treatments due to resistance, intolerance, or safety considerations

Adagrasib
MOA: Inhibitor of the RAS GTPase family
Indication: For the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA approved test, who have received at least one prior systemic therapy

Olutasidenib
MOA: Isocitrate dehydrogenase-1 (IDH1) inhibitor
Indication: For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test

Teplizumab-mzwv
MOA: CD3-directed antibody
Indication: To delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients aged 8 years and older with Stage 2 T1D

Mirvetuximab soravtansine-gynx
MOA: Folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate
Indication: For the treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens

Teclistamab-cqyv
MOA: Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager
Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody

Tremelimumab
MOA: Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody
Indication: For the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) in combination with durvalumab

Futibatinib
MOA: Kinase inhibitor
Indication: For the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements

Reference: USFDA

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Potential research in pharmacology & drug discovery

When it comes to harvesting energy, some guts do it better than others

Everyone has a unique composition of gut bacteria – shaped by genetics, environment, lifestyle, and diet. Gut bacteria in the colon serve to break down food parts that our body's digestive enzymes can't, e.g., dietary fiber. Humans can be divided into three groups based on the presence and abundance of three main groups of bacteria that most of us have: B-type (Bacteroides), R-type (Ruminococcaceae), and P-type (Prevotella). In this study, participants were divided into three groups based on the composition of their gut microbes. The so-called B-type composition (dominated by Bacteroides bacteria) were more effective at extracting nutrients from food and was observed in 40 percent of the participants. The researchers also observed that the group with less energy in their stool weighed more than the other groups. This study confirms earlier studies in mice where it was found that germ-free mice that received gut microbes from obese donors gained more weight compared to mice that received gut microbes from lean donors, despite being fed the same diet. The fact that our gut bacteria are great at extracting energy from food is basically a good thing, as the bacteria's metabolism of food provides extra energy in the form of short-chain fatty acids , which our body can use as energy-supplying fuel. But if we consume more than we burn, the extra energy provided by the intestinal bacteria may increase the risk of obesity over time.

Reference: Boekhorst, J., Venlet, N., Procházková, N.et al.Stool energy density is positively correlated to intestinal transit time and related to microbial enterotypes.Microbiome.10, 223 (2022).

New combination of drugs may lead to improved treatment of cervical cancer

Despite advances in screening, early diagnosis, and prevention through HPV vaccination, cervical cancer remains the second-leading cause of cancer-related death in women between ages 20 and 39. Most treatment regimens used for cervical cancer involve the platinum-based chemotherapy drug cisplatin in combination with other drugs. But tumours can become resistant to cisplatin and necessitate the use of alternative drug combinations that may improve treatment outcomes. PARP inhibitors (PARPi) like olaparib and niraparib, which block the repair of DNA damage in cancer cells, were recently approved by the FDA as cancer therapeutics, particularly for gynaecological cancers. The researchers found that the combination of cisplatin and PARP inhibitors is more effective at restricting some cervical cancer cells' growth than either used alone. Using cell lines that represent different types of cervical cancer, including adenocarcinoma, epidermoid, and squamous, the researchers tested the cells' growth and survival in response to treatment with PARPi, cisplatin, or a combination of the two. The researchers showed that the combination of PARPi and cisplatin does not kill these cells simply by blocking the repair of damaged DNA in cancer cells but also stimulated the expression of genes whose proteins inhibit the cell cycle, block the growth and division of cells, and promote apoptosis. This mechanism was independent of PARPi's role in enhancing DNA damage in cancer cells.

Reference: Gupte, R.,*et al. (2022) Combinatorial Treatment with PARP-1 Inhibitors and Cisplatin Attenuates Cervical Cancer Growth through Fos-Driven Changes in Gene Expression.Molecular Cancer Research.*

Higher dose of new antimalarial drug reduces disease recurrence by 85%

Tafenoquine is the first newly approved anti-relapse drug with advantage of single dose, unlike primaquine (the current treatment) which needs to be taken daily for 7–14 days. Like primaquine, the conversion of tafenoquine into oxidative metabolites was responsible for its antimalarial activity. The study suggests that the current 300 mg adult dose of tafenoquine reduces recurrent vivax malaria infection by 70%, whereas increasing it to 450 mg would reduce recurrence by 85%. They found that each additional mg/kg of tafenoquine substantially reduced the chance of having a recurrent vivax malaria infection within four months. For example, increasing the dose from 3mg/kg to 4mg/kg reduces the proportion of patients with a recurrent infection from ~30% to 20%. This association between tafenoquine dose and the proportion relapsing was seen in patients from Asia, Africa and the Americas. The results of the study provides strong evidence that the currently recommended adult dose of tafenoquine is insufficient for radical cure in all adults. Getting the dose right is critical. The efficacy, tolerability and safety of increased doses should be evaluated in prospective studies.

Reference: Watson, J.A.,*et al.(2022) The clinical pharmacology of tafenoquine in the radical cure of Plasmodium vivax malaria: An individual patient data meta-analysis.eLife.*