Review Article

Therapeutic Dimensions of Bisphosphonates: A Clinical Update

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Abstract

Bisphosphonates (BPs) are a commonly used class of drugs for the treatment of bone disorders. An extensive review of BPs with their clinical efficacy and safety profile is unavailable. This study aimed to review the available literature on BPs, summarize their role in clinical therapy, and emphasize their safety profile. Authors reviewed the existing literature using the Google Scholar, PubMed, and Micromedex databases and analyzed the collected articles. BPs are the preferred medication for osteoporosis and other similar conditions owing to their efficient antiosteoclastic activity. Few of them are available in oral dosage forms; hence, they are patient-friendly. The mechanism of action, common adverse effects and their clinical applications, precautions and warnings pertaining to the route of administration, and safety profiles have been discussed in this manuscript. The common adverse effects are majorly related to the gastrointestinal, cardiovascular, and endocrine system. Upon chronic usage, patients may experience serious problems like osteonecrosis of the jaw and atypical bone fractures. Although BPs are effective and safe, they may cause GI adverse effects and rare cases of osteonecrosis. Patient counseling could prove beneficial in early identification and prevention of the adverse effects associated with BPs.

Keywords: *Bisphosphonates, clinical efficacy, dosage regimen, osteoporosis, safety profile, treatment outcome*

Introduction

Bisphosphonates (BPs) are synthetic pyrophosphate analogs.[1] They are commonly used as drugs for treating multiple conditions majorly related to the bones owing to their antiresorptive properties. Based on their chemical nature, they are subdivided into three classes, namely, without ammonia, with ammonia, and with the heterocyclic ring.[2] Considering the route of administration, they are also classified as oral and parenteral BPs.[3] The commonly available BPs include alendronate, clodronic acid, etidronate, ibandronate, olpadronate, risedronate, tiludronate, and zoledronate. The presence of nitrogen-containing group adds to the potency of the drugs.[4] This class of drugs became popular because of the safety concerns raised about estrogen-containing drugs that posed threats related to carcinomas.[5] The major advantage of this class of drugs is that they only act on the bones that undergo resorptive changes, and hence they do not show any concentration-related systemic effects.[6] In addition to these advantages, BP therapy is cost-effective when compared with the other available options for osteoporosis management.[7] The overall tolerability and safety of BP therapy is considered reasonable, and the major adverse effects include gastrointestinal (GI) disorder (observed with oral BPs) and bone necrosis (generally observed with parenteral BPs).[8] However, these adverse effects can be tackled by the appropriate selection of patient and drug, adequate dosage titration, and patient counseling. In this study, the researchers review the existing literature on BPs, emphasizing their clinical efficacy, safety profile, and patient counseling aspects.

Chemistry of bisphosphonates

BPs are chemically inorganic pyrophosphate compounds formed as a result of replacing the oxygen atom by a carbon atom. The P-C-P moiety thus formed is resistant to hydrolysis. Being a highly stable moiety, the central carbon atom acts as a binding site for the two additional substituents (R^1 and R^2). Of

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them, R^1 is preferentially a hydroxy group, which allows the compound to be a powerful tridentate ligand of calcium (bone hook), whereas R^2 is responsible for the antiresorptive potency. BPs are divided into two categories based on their chemical structure and mechanism of action, namely, nonnitrogen containing (those that normally get incorporated into the nonhydrolysable cytotoxic adenosine triphosphate [ATP] analogs) and nitrogen containing (those that inhibit the farnesyl pyrophosphate synthase [FPPS], a key enzyme in the mevalonate pathway).[9] In general, BPs bind to the hydroxyapatite structures of the bone mineral, thereby exhibiting antiresorptive activity.[10] Two phosphonates ($-PO_3$) groups share a covalent bond with the carbon atom and become "bisphosphonate." The long side chain ($-R_2$) of the BPs determines their chemical properties, the mode of action, and the strength. The short-side chain ($-R_1$), known as the "hook," influences the chemical properties and kinetics of BPs.[11]

Pharmacokinetics of bisphosphonates

The pharmacokinetic profiles of BPs are mentioned in Table 1.[12,13]

US FDA-approved indications: The United States Food and Drug Administration (US FDA)-approved indications for BPs are listed in Table 2.[12,13]

Non-US FDA-approved indications: The non-US FDA-approved indications of BPs are listed in Table 3.[12]

The dosage regimen of BPs: The various dosage regimens of BPs are as listed in Table 4.[12,13]

Clinical applications of bisphosphonates

Osteoporosis

Osteoporosis is a skeletal disorder characterized by the weakening of bone leading to risk of fracture, which is highly prevalent in postmenopausal women. This condition is a "silent disease" and progresses without symptoms until a fracture occurs. BPs are recommended as a first-line approach to hormone replacement therapy (HRT) in postmenopausal osteoporosis.[14,15]

Osteoporosis can be caused by various reasons; the primary cause is because of the depletion of hormones (estrogen depletion in women in the postmenopausal state and androgen depletion in elderly men).[16,17] In particular, because of the imbalance in bone remodeling after menopause (decreased estrogen), the osteoclastic activity predominates the osteoblastic activity. BPs are antiosteoclastic agents, which suppress the osteoclastic formation and aid in increasing or maintaining the bone mineral density (BMD) in the long term.[18,19] Among the BPs, oral alendronate therapy benefits by decreasing the hip, vertebral, and wrist fractures.[20,21] Zoledronate therapy aids in effectively decreasing the risk of vertebral fractures compared with that of hip fractures. Risedronate is also known to be more effective in the reduction of vertebral fractures than in the reduction of hip fractures.[22]

Osteoporosis in Crohn's disease

Crohn's disease is an inflammatory bowel disease (IBD) that affects the gastrointestinal tract (GIT) anywhere from the mouth to anus, majorly affecting the lower part of GIT—small intestine and ileum. It is an immune-related disease triggered by pathogenic bacterial infections caused by *Mycobacterium*, *Pseudomonas*, *Listeria*, and others. It is an unregulated inflammatory condition that aids in tissue destruction. Individuals chronically suffering from Crohn's disease manifest rectal bleeding, weight loss, fever, arthritis, and osteoporosis. In such patients, osteoporosis may majorly result from two reasons, which are anemia of chronic disease or anemia because of deficiency of B12, folate, and iron, with the latter being more common.[23,24] In general, the disease results in poor absorption of calcium and vitamin D from the affected part. Crohn's disease increases the risk of osteoporosis,[25] and these individuals are at increased risk of bone fractures.[26] Moreover, the long-term usage of corticosteroids (prednisone or cortisone), as a part of Crohn's disease management, can also cause osteoporosis.[27] Crohn's disease cases associated with osteoporosis can be treated with intravenous (IV) risedronate, alendronate, pamidronate, or ibandronate. The treatment should also be accompanied by calcium and vitamin D supplementation.[28,29]

Osteoporosis in male hypogonadism

Similar to estrogen depletion in females, the gradual depletion of testosterone in elderly males also leads to osteoporosis, namely, secondary osteoporosis (primary osteoporosis is age-related, also known as "senile osteoporosis," [>70 years] or idiopathic osteoporosis [<70 years]).[30] In general, male osteoporosis is linked with hip fractures,[31,32] and vertebral fractures[33] are higher in men than in women. Testosterone depletion is the prime factor for the onset of osteoporosis in males; other mutual risk factors, such as genetics and lifestyle choices (e.g., immobilization, tobacco usage, and excess alcohol consumption), as well as specific risk factors (e.g., long-term corticosteroid medication), exacerbate the condition. Secondary osteoporosis in men is caused due to glucocorticoids, hypogonadism, alcohol intake, smoking, GI disease, hypercalciuria, and immobilization.[34] BPs, such as alendronate, ibandronate, and risedronate, are effective in treating osteoporosis in males. Alendronate as an oral medicine on a daily or weekly basis is prescribed for osteoporosis due to secondary causes, such as

Table 1: Pharmacokinetics of bisphosphonates[12,13]

Bisphosphonate	Absorption	Distribution	Metabolism	Excretion	Elimination half life
Alendronate	Bioavailability: 0.7% (women), 0.59% (men) Effect of food: significantly decreased the bioavailability	Vd: 2576 L Protein binding: approximately 78%	None	Fecal: minimal Renal: approximately 50% Dialyzable: no	1.9 h (plasma); greater than 10 years (terminal half-life)
Clodronate	Bioavailability (oral): 1%–2%—poor absorption because of high water solubility and nearly complete ionization at pH 7.4 in the stomach	Vd: 15–30 L Protein binding: 36% Bone: 20%–25%	None	Fecal: 5% Renal clearance (rate): 6–7 L/h Renal (IV): 58%–80% Total body clearance: 6–8 L/h	2–13 h
Etidronate	Bioavailability: approximately 3%	None	None	Fecal: unchanged Renal: approximately half the dose within 24 h	165 days
Ibandronate	Bioavailability (oral): 0.6% Effect of food: (oral), 90% reduction in bioavailability	Vd: 90 L Protein binding: (IV), 86%; (oral), 85.7%–99.5%	None	Fecal: (oral), unabsorbed drug is eliminated Renal: 50%–60% of absorbed dose Dialyzable: yes	(IV) 4.6–25.5 h, dose dependent Postmenopausal women: (oral), 37–157 h, dose dependent
Pamidronate	Bioavailability (oral): 0.3%–3%	None	None	Renal clearance rate: 49–74 mL/min Dialyzable: yes	28 h
Risedronate	Bioavailability (oral): 0.63% (immediate-release): 1 h (delayed-release): approximately 3 h Effect of food: reduced by 30%–55%	Vd: 13.8 L/kg Protein binding: 24%	None	Fecal: unabsorbed portion unchanged Renal (oral): approximately 50% unchanged Renal (IV): 85% unchanged Renal clearance: 105 mL/min Total body clearance: 122 mL/min	561 h, osteopenic postmenopausal women
Tiludronate	Bioavailability: 6% ± 2% Effect of food: reduced bioavailability by 90% with or 2 h after breakfast	Protein binding: approximately 90%	None	Renal (IV): approximately 60% as unchanged drug Dialyzable: no	Patients with Paget's disease: (IV), approximately 150 h Renal insufficiency: approximately 205 h
Zoledronic acid	Oral: Human oral absorption data for zoledronic acid are unavailable	Protein binding 28%–53%	None	Renal clearance (rate): 3.7±2 L/h, (0–24 h) dose independent Renal excretion: 39% ± 16% (±SD) unchanged	146 h

Vd=Volume of distribution, SD=Standard deviation

corticosteroid use, androgen deprivation therapy (ADT), rheumatologic disorders, and hypogonadism.[35]

Corticosteroid-induced osteoporosis

Glucocorticoids possess anti-inflammatory and immunosuppressive effects and are majorly prescribed to treat patients with asthma and rheumatoid arthritis (RA), as well as organ (kidney) transplant patients. Bone loss is one of the noticeable adverse effects of these medications.[36] The most commonly affected bones are ribs and vertebrae.[37,38] Apart from bone loss, the inflammatory suppressive function of corticosteroids can cause muscle weakness or immobility, decreased calcium absorption, depleted testosterone levels, or a combination of any of them.[39]

Table 2: US FDA-approved indications of bisphosphonates[12]

Drug	US FDA-Approved indications
Alendronate	Osteoporosis, osteoporosis because of corticosteroids, Paget's disease, postmenopausal osteoporosis, postmenopausal osteoporosis prophylaxis
Clodronate	Not approved
Etidronate	Heterotopic ossification, hypercalcemia of malignancy, Paget's disease
Ibandronate	Postmenopausal osteoporosis, postmenopausal osteoporosis prophylaxis
Olpadronate	Not approved
Pamidronate	Bone metastasis; osteolytic, associated with metastatic breast cancer or multiple myeloma; hypercalcemia of malignancy (moderate–severe), with adequate hydration; Paget's disease (moderate–severe)
Risedronate	Osteoporosis in male, osteoporosis because of corticosteroids, osteoporosis because of corticosteroid (prophylaxis), Paget's disease, postmenopausal osteoporosis, postmenopausal osteoporosis prophylaxis
Tiludronate	Paget's disease
Zoledronic acid	Bone metastasis - Solid tumor, hypercalcemia of malignancy
	Multiple myeloma, osteoporosis in men, osteoporosis secondary prophylaxis in patients with recent low-trauma hip fracture, osteoporosis because of corticosteroids (treatment and prophylaxis), Paget's disease, postmenopausal osteoporosis, postmenopausal osteoporosis (prophylaxis)
In addition to the aforementioned indications, few nonFDA approved indications also exist	

US FDA=United States Food and Drug Administration

Table 3: Non-US FDA-approved indications of bisphosphonates[12]

Drug	Non-US FDA approved indications
Alendronate	Antiviral drug adverse reaction, drug-induced osteoporosis (adjunct), arthroplasty of knee, bone necrosis, complex regional pain syndrome (type I), Crohn's disease (osteoporosis), cystic fibrosis of the lung (osteopenia), fibrous dysplasia of bone, growth hormone deficiency (osteoporosis), hypercalcemia of malignancy, juvenile idiopathic generalized osteoporosis, male hypogonadism (osteoporosis), OI
Clodronate	Bone metastasis, complex regional pain syndrome type I, Gorham's disease, hypercalcemia of malignancy, multiple myeloma, myelofibrosis, OI, osteopenia (prophylaxis), osteoporosis, osteoradionecrosis, Paget's disease, primary hyperparathyroidism
Etidronate	Hypercalcemia of malignancy, oral maintenance therapy, osteoporosis
Ibandronate	Bone metastasis, a disorder related to transplantation (osteoporosis), hypercalcemia of malignancy, multiple myeloma
Olpadronate	Bone metastasis, OI, Paget's disease
Pamidronate	Calcinosis, cancer pain, Charcot's arthropathy, complex regional pain syndrome type I
	Cystic fibrosis (osteoporosis), disorder of joint of spine, disorder related to transplantation (osteoporosis), drug-induced osteoporosis (prophylaxis - Gonad regulating hormone adverse reaction), fibrous dysplasia of bone, hypercalcemia associated with tamoxifen-induced tumor flare, hypercalcemia because of hyperthyroidism, hypercalcemia - Metabolic bone disease, hyperparathyroidism, hypertrophic osteoarthropathy, pulmonary Langerhans cell histiocytosis (PLCH), malignant bone pain associated with metastatic prostate cancer, OI, osteopenia (acute); Prophylaxis—total replacement of hip
	Osteopenia - Tetraplegic cerebral palsy, osteoporosis, children osteoporosis because of corticosteroid, postmenopausal osteoporosis, transient osteoporosis
Risedronate	Decreased BMD in IBD, hypercalcemia of malignancy, IBD in remission, postmenopausal osteoporosis, OI, mild osteopenia, in breast cancer survivors as an prophylaxis
	Osteopenia, secondary to ADT in patients with prostate cancer (prophylaxis), primary hyperparathyroidism
Zoledronic acid	Monoclonal gammopathy of uncertain significance, with osteopenia or osteoporosis, osteopenia, secondary to ADT in prostate cancer patients; prophylaxis, osteopenia, secondary to hormone therapy in breast cancer patients; prophylaxis, osteopenia, secondary to ovarian dysfunction induced by adjuvant chemotherapy in premenopausal women with early-stage breast cancer (prophylaxis)

OI=Osteogenesis imperfecta, BMD=Bone mineral density, IBD=Inflammatory bowel disease, ADT=Androgen-deprivation therapy

Patients on long-term corticosteroid therapy are advised to undergo BMD test.[40]

BPs reduces bone loss in patients consuming glucocorticoids for a long time. Alendronate followed by risedronate are effective agent to prevent and treat bone loss, whereas pamidronate and ibandronate are less efficient.[41] Along with BPs, adequate calcium and vitamin D supplements are also important for treatment.[28,42]

Table 4: Dosage regimen of bisphosphonates[12,13]

Drug	Indication	Dosage regimen
Alendronate	Paget's disease	40 mg orally once daily for 6 months
	Male hypogonadism - Osteoporosis	10 mg orally once daily or 70 mg orally once a week Calcium supplements are added
	Osteoporosis because of corticosteroid	5 mg orally once daily 35 mg once a week
	Postmenopausal osteoporosis	10 mg orally once daily or 70 mg orally once in a week Calcium and vitamin D supplements are added
	Prevention of osteoporosis in postmenopausal women	5 mg orally once daily or 35 mg once a week
Clodronate	Hypercalcemia of malignancy	1500 mg over 2 or more hours in a single dosage
		300 mg daily for 5 consecutive days (IV)
		375 mg/h (subcutaneous)
		800–3200 mg daily (oral)
	Multiple myeloma	900 mg clodronic acid every other week for at least 18–24 months (IV)
		1600 or 2400 mg/day reduced skeletal complications (new osteolytic lesions and vertebral fractures after the first year)
	Paget's disease	300 mg daily for 5 days for 6 months
		800–1600 mg daily for 6 months
	Primary hyperparathyroidism	300 mg infused over 2 h at the end of 5 consecutive hemodialysis sessions (IV)
		800 mg twice daily and 1–3.2 g daily (single daily dose) 800–1600 mg for 2–3 months (oral)
Etidronate	Hypercalcemia of malignancy	30 mg/kg (standard dose is 7.5 mg/kg/day for 3 days)
	Total hip replacement	20 mg/kg/day orally for 1 month before and 3 months after surgery was used (oral)
	Spinal cord injuries	
		20 mg/kg/day orally for 2 weeks followed by 10 mg/kg/day for 10 weeks was used (oral)
	Hypercalcemia of malignancy	20 mg/kg/day for 30 days (as oral maintenance therapy)
	Osteoporosis	Cyclical oral etidronate therapy (90-day cycle), 400 mg daily for 14 days followed by calcium supplementation of 500 mg (elemental calcium) daily for the remaining 76 days showed increase BMD in patients with osteoporosis
	Paget's disease	5–10 mg/kg/day for the duration of therapy not to exceed 6 months
		Absorption is affected by the presence of food, mineral supplements, and antacids (e.g., any food or supplement containing metal salts - calcium, iron, magnesium, and aluminum). Etidronate should be administered with fruit juice or water 2 h before or after a meal or a supplement (containing a metal salt)
Ibandronate	Hypercalcemia of malignancy	A dose of 2 mg infused over 2 h is effective (IV)
	Postmenopausal osteoporosis	2 mg every 2 months OR 3 mg infusion 15–30 s every 3 months (IV)
		2.5 mg per day or 20 mg per week or 150 mg orally once monthly 60 mins before first food or drink (except water) of the day or any other medication or supplements, such as calcium, antacids, or vitamins. Swallow the ibandronate tablet whole with 6–8 ounces of plain water while standing or sitting in an upright position
Olpodronate	Prostate cancer patients with skeletal metastases	4 mg per day for 5 consecutive days diluted in normal saline infuse for 4 h (IV) followed by 100 mg twice daily for 3 months (oral)
		Oral olpadronate was administered 30–60 mins before a meal

Contd...

Table 4: Contd...

Drug	Indication	Dosage regimen
Pamidronate	Bone metastasis associated with	90 mg every 3–4 weeks 2 h infusion monitor creatinine levels (IV)
	Metastatic breast cancer	
	Multiple Myeloma	Treatment should be withheld for renal failure risk patients with normal baseline creatinine
		If increase of 0.5 mg/dL
		If an increase of 1 mg/dL
		90 mg over 4 h per month. If dehydration or marked Bence Jones proteinuria is present, the patient should receive adequate hydration before receiving pamidronate (IV)
	Hypercalcemia of malignancy (moderate–severe) - serum calcium of 12–13.5 mg/dL	60–90 mg as a single IV infusion over at least 2–24 h, with adequate hydration (IV)
		1200 mg daily (in 3 divided doses) each given for a period of 6 days (oral)
	Paget's disease (moderate–severe)	30 mg/day administered as a 4 h infusion for 3 consecutive days (total dose 90 mg) (IV)
	Postmenopausal osteoporosis	150 and 300 mg daily have demonstrated efficacy (oral)
	Subcutaneous route	90 mg diluted in 375–1000 mL infusion over 12–24 h
Risedronate	Osteopenia, secondary to ADT in patients with prostate cancer; prophylaxis	Dosage: 35 mg orally once weekly, with supplemental calcium and vitamin D
	Osteoporosis, male	35 mg per week, given with 6–8 ounces of water at least 30 mins prior to the first food or drink of the day Supplemental calcium and vitamin D can be added (oral)
	Osteoporosis because of corticosteroid	5 mg once daily with 6–8 ounces of water at least 30 mins prior to the first food or drink of the day. Supplemental calcium and vitamin D can be added as an oral preparation
	Paget's disease	30 mg once daily for 2 months. Retreatment may be considered following posttreatment observation of at least 2 months. For retreatment, dose and duration of therapy are the same as for the initial course. Take immediate-release risedronate sodium with 6–8 ounces of water at least 30 mins prior to the first food or drink of the day. Supplemental calcium and vitamin D can be added (oral)
	Postmenopausal osteoporosis	Delayed-release tablets
		Dose: 35 mg orally once weekly with 4 ounces of water in the morning immediately following breakfast; supplement with calcium and Vitamin D
		Immediate-release tablets
		Dose: Daily 5 mg taken once orally or 35 mg orally once weekly with 6–8 ounces of water at least 30 mins prior to the first food or drink of the day; alternatively, one 75 mg tablet may be taken orally on 2 consecutive days (total of two 75 mg tablets each month), or one 150 mg tablet orally once a month
		Supplemental calcium and vitamin D: if dietary intake is inadequate
		Immediate-release tablets with calcium carbonate tablets
		Dose: Risedronate sodium immediate-release tablet 35 mg orally once a week on day 1 of 7-day treatment cycle with 6–8 ounces of water at least 30 mins prior to the first food or drink of the day and calcium carbonate 1250 mg (equivalent to 500 mg elemental calcium) orally once daily with food on each of the remaining 6 days of the week (days 2–7 of 7-day treatment cycle)
	IBD	5 mg daily or 35 mg orally once a week with supplemental calcium vitamin D3 (oral)
	(decreased BMD)	

Contd...

Table 4: Contd...

Drug	Indication	Dosage regimen
Tiludronate	Paget's disease	400 mg daily for 3 months. After completing 3 months of therapy, an additional 3 months is necessary to assess response to therapy (oral)
Zolendronate	Bone metastasis - Solid tumor	4 mg infused over 15 mins every 3–4 weeks; optimal duration of therapy is unknown (FDA dosage)
		Administration every 12 weeks was not inferior to every 4 weeks for 2 years (off-label dosage) (IV) along with supplemental calcium and vitamin D can be added (oral)
	Hypercalcemia of malignancy	4 mg as a single dose infusion over no less than 15 mins; may repeat after a minimum of 7 days if serum calcium does not return to normal or remain normal after initial treatment (IV)
	Multiple myeloma - Bone metastasis	4 mg infusion for 15 mins every 3–4 weeks; the optimal duration of therapy is unknown (FDA dosage)
		Administration every 12 weeks was not inferior to every 4 weeks for 2 years (off-label dosage) (IV)
		Along with supplemental calcium and vitamin D can be added (oral)
	Osteopenia, secondary to ADT in prostate cancer patients	4 mg IV infused over 15 mins every 3 months (prophylactic dosage)
	Osteoporosis, male	5 mg IV infusion for 15 mins every 1 year (IV)
		Acetaminophen 1000 mg or ibuprofen 400 mg orally every 6 h for 3 days beginning 4 h after zoledronic acid infusion reduced the incidence of transient postdose influenza-like symptoms in a clinical trial
		Along with supplemental calcium and vitamin D can be added (oral)
	Osteoporosis, secondary prophylaxis in patients with recent low-trauma hip fracture	5 mg IV infusion for 15 mins every 1 year (IV)
		Acetaminophen 1000 mg or ibuprofen 400 mg orally every 6 h for 3 days beginning 4 h after zoledronic acid infusion reduced the incidence of transient postdose influenza-like symptoms in a clinical trial
		Along with supplemental calcium and vitamin D can be added (oral)
	Osteoporosis because of corticosteroid; treatment and prophylaxis	5 mg IV infusion for 15 mins every 1 year IV
		Acetaminophen 1000 mg or ibuprofen 400 mg orally every 6 h for 3 days beginning 4 h after zoledronic acid infusion reduced the incidence of transient postdose influenza-like symptoms in a clinical trial
		Along with supplemental calcium and vitamin D can be added (oral)
	Postmenopausal osteoporosis and prophylaxis	5 mg IV infusion for 15 mins every 1 year; optimal duration undetermined; periodically evaluate the need for continued therapy
		Acetaminophen 1000 mg or ibuprofen 400 mg orally every 6 h for 3 days beginning 4 h after zoledronic acid infusion reduced the incidence of transient postdose influenza-like symptoms in a clinical trial along with supplemental calcium

IV=Intravenous, BMD=Bone mineral density, IBD=Inflammatory bowel disease, FDA=Food and Drug Administration, ADT=Androgen deprivation therapy

Osteoporosis in immobilized patients

In immobilized patients or those using wheelchairs for long periods because of head injuries, spinal cord injuries, and limb fractures, rapid bone loss with an eventually higher risk of fracture, hypercalcemia, and, often, nephrolithiasis was evident.[17] Oral alendronate[43] and IV pamidronate are found to be useful and effective in reducing bone loss; however, their role in reducing the risk of fracture and nephrolithiasis is unclear.[44]

Paget's disease

The condition of disorganized bone remodeling where there is extreme bone resorption (osteoclastic activity) that is counteracted with improper bone deposition (osteoblastic activity) is known as Paget's disease or osteitis deformans. The commonly affected bones are the skull, pelvis, spine, lower limbs, and others. Paget's disease is confined more locally with few bones involved, whereas in osteoporosis, the bone-weakening/loss are generalized. The affected bone with Paget's disease eventually becomes leads to arthritis in the joints near the affected bone.[45,46] The elevated levels of serum alkaline phosphatase (ALP) are a primary indicator of Paget's disease along with bone pain.[47]

BPs are preferred to treat Paget's disease. They suppress the amplified bone resorption and aid in controlling the serum ALP levels. Owing to their greater antiosteoclastic activity, orally administered alendronate,[48] risedronate,[49] and tiludronate[50] and intravenously administered pamidronate[51] and zoledronate have gained immense attention in treating Paget's disease.[52]

Carcinomas

Most cancers that affect bones originate in other sites/organs and metastasize to the bone (secondary bone cancer). Subsequently, they cause hypocalcemia, intense pain, and eventually fracture. Thus, BPs are also widely used to treat malignant conditions, such as breast cancer, prostate cancer, multiple myeloma, renal carcinomas, and lung cancers, where there is bone metastasis in more than 80% of the cases because of the invasion of cancer cells into the bone and disruption of the bone homeostasis and remodeling process.[53]

The usage of BPs in patients with multiple myeloma, breast cancer, and prostate cancer is associated with decreased mortality.[54,55] Patients consuming oral BPs have an increased risk of esophageal cancer, which was recorded in Europe and North America.[56] In general, long-term BP therapy (>3–5 years) and age factor (>69 years) could contribute to esophageal cancer; however, data supporting this is unavailable.[55,57] The validated data related to BPs and esophageal cancer are extremely essential to understand this situation. In the malignant patients, BPs impede bone metastasis and also reduce bone pain. Recent research is exploring BPs for their anticarcinogenic activity and synergistic action, along with antimalignant drugs.[58,59]

Breast cancer

Women with breast carcinoma who were prescribed clodronate on a long-term basis witnessed a significant reduction of bone metastasis and reduced mortality in a 6-year follow-up study.[60] Premenopausal women with hormone-sensitive breast cancer receiving endocrine-based therapy who were administered IV zoledronic acid for approximately 6 months had reduced bone loss.[61] In postmenopausal women, receiving aromatase inhibitor medication to prevent estrogen-sensitive breast cancer, orally administration with risedronate showed an inhibitory effect on bone loss.[62]

Prostate cancer

Prostate carcinoma is concomitant with osteoblastic (not osteoclastic) activity, which is frequently known as sclerosis metastasis where osteoblastic stimulation occurs.[63] Despite the osteoblastic activity in sclerotic metastases, the osteolysis is a regular feature of prostate cancer bone disease. Certainly, bone destruction may be an obligatory part of cancer cell invasiveness in the bone.[64] Zoledronate was found to be effective for reduction in bone-related events like bone pain, skeletal destruction, and others in prostate cancer patients with bone metastases.[65,66] Etidronate has indicated a significant effect in lowering bone pain in prostate cancer patients with metastasis.[67]

Men with hormone-responsive prostate cancer (increased androgen levels) undergoing ADT may develop osteoporosis after the long-term usage of these androgen depriving drugs, which may, in turn, cause bone weakness and risk of fracture. These patients can benefit from the cautious administration of BPs. Administration of IV BPs like pamidronate[68] and zolendronate[69] was effective in inhibiting the skeletal destruction of hip and spine bones in patients with prostate cancer (nonmetastatic) undergoing androgen-depriving treatment. Orally administered risedronate is reported to prevent bone loss and maintain the skeletal integrity of hip and lumbar spine bones.[70]

Multiple myeloma

Multiple myeloma is the cancer of plasma cells, which plays a vital role in the immune system.[71] Initially, no symptoms are noticed; however, during the later stages, patients present with several symptoms such as bone pain, bleeding, frequent infections, and anemia. Several studies have reported that IV BPs, pamidronate, and zolendronate are very effective in impeding bone destruction and bone pain, and they are the preferred drugs in these cases because they improve survival.[72-74] However, in multiple myeloma, IV BPs (zolendronate and pamidronate) were documented with a higher incidence of developing adverse effects, that is, osteonecrosis of jaw (ONJ), which is an important reason for tailoring the drug regime in multiple myeloma cases.[75] In contrast, oral BPs therapy for multiple myeloma-associated bone disease was not documented in the literature.[17]

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a pediatric genetically inherited (autosomal gene mutation) skeletal disorder, which mainly occurs because of a defect in type-1 collagen synthesis, where the primary symptoms include brittleness of bone and secondary symptoms include loose joints, short height, and bluish sclera.[76,77] OI can exist in mild to severe forms with differing symptoms. A patient with OI may suffer from a few or multiple fractures in their lifetime. Diagnosis of this disease is difficult because there is no single test that could identify it. Eventually, DNA testing may be useful based on the symptoms.[78]

To date, complete remedial medication for this condition does not exist. Only supportive treatment procedures such as surgical implantation of long bones, physiotherapy, and medication for bone pain have been suggested.[79] In addition to such treatment procedures, BPs were first prescribed in 1987 as a supporting medication in children suffering from OI.[80] Thereafter, the usage of BPs in OI increased, but there exists uncertainty in selecting the type of suitable BPs and the supporting evidence is also inadequate.[81-83]

Safety profile of bisphosphonates

1. Cardiovascular effects

A follow-up communication issued by the US FDA revealed that the use of BPs did not contribute to an increased risk of serious or nonserious atrial fibrillation.[84] Heart rhythm disorders, including atrial fibrillation, are common among elderly individuals aged 65 years or older, the same age range of the study population reviewed here. Most of the reported cases of serious atrial fibrillation that the FDA reviewed to date occurred more than a month after the drug infusion, and no significant difference was observed in all events of atrial fibrillation between the treatments. Collectively, the FDA concluded that atrial fibrillation events observed in the initial review that may pertain to the entire class of BPs warrants further in-depth evaluation.[85]

1.a. Alendronate

Osteoporosis (oral route): One study found a significantly increased risk of heart failure with alendronate use (1.2% vs. 0.8% with controls); however, the risk dropped significantly with greater alendronate exposure (98% increased risk with defined daily dose of 0.25 mg or less vs. 69% increased risk with a defined daily dose of 0.26–0.8 mg).[86]

Although there is a theoretical increased risk of atrial fibrillation with high potency and parenteral administration of BPs, the association with respect to oral BPs remains unclear.[87]

1.b. Pamidronate

Hypertension: Patients with hypercalcemia of malignancy, and Paget's disease, developed hypertension during the clinical trials.

Hypotension: It was reported during postmarketing surveillance with high IV doses of pamidronate, and it was not reported with lower doses of pamidronate.[88]

Syncope and tachycardia: Six percent of patients who received pamidronate developed syncope and tachycardia.

Thrombophlebitis: Mild thrombophlebitis and soft-tissue symptoms including redness, swelling, and pain were reported during treatment with IV pamidronate.[89,90]

Residronate

Cardiac arrhythmia was observed in men during the long-term usage of risedronate for 2 years in a few cases. Moreover, in the clinical trials of risedronate, chest pain, hypertension, and peripheral edema were noticed in a few cases.[91]

Tiludronate

It was seen that 2.7% of patients receiving tiludronate sodium developed chest pain and peripheral edema.[50]

1.c. Zolendronate

Atrial fibrillation is one of the adverse effects that is more evident in postmenopausal osteoporotic women receiving zoledronate through the IV route; this was ruled out on the long-term administration of zolendronate in HORIZON Pivotal Fracture Trial.[92,93] The etiology for this condition, which is linked with electrophysiology of the heart, is unclear. However, the risk was less likely to happen with IV zolendronate in patients suffering from malignancy.[94]

2. Dermatological effects

2.a. Alendronate sodium

During postmarketing surveillance of alendronate, Stevens–Johnson syndrome and toxic epidermal necrolysis were documented.[95]

2.b. Clodronate

During clodronate administration, allergic skin rashes were rarely reported.[96] Patients over 70 years of age were reported with skin lesions like erythroderma[97,98] and necrobiotic palisading granuloma (NPG).[99]

2.c. Etidronate

It is known to cause angioedema, follicular eruption, macular rash, maculopapular rash, pruritus, Stevens–Johnson syndrome, and urticaria.[100]

2.d. Ibandronate

Erythema multiforme, Stevens–Johnson syndrome and Bullous dermatosis were observed during postmarketing surveillance.[101]

2.e. Risedronate

Postmarketing surveillance has reported skin reactions like rash, blisters, and hypersensitivity.[91,102]

2.f. Tiludronate and zolendronate

During the postmarketing surveillance, skin necrosis was noticed in addition to skin rashes and Steven–Johnson syndrome.[50]

3. Endocrine/metabolic effects

3.a. Alendronate

Hypocalcemia: It was noticed that patients having Paget's disease with high rates of osteoclast-mediated bone resorption who were treated with alendronate for a longer period suffered from hypocalcemia.[103] Very few patients were reported with hypophosphatemia.[104] Often, patients treated with IV BPs can present with hypocalcemia. It is more common in patients with osteoclast-mediated bone resorption (e.g., patients with Paget's disease). These hypocalcemic patients should be supplemented with calcium and vitamin D.[105] Patients suffering from myeloma treated with thalidomide and receiving zolendronic acid infusion can experience renal failure and hypocalcemia; hence, a certain level of caution is needed.[106]

3.b. Clodronate

Hyperkalemia: Hyperkalemia (elevated levels of serum potassium, 6.2–8.4 mEq/L) was reported in patients with parathyroid carcinoma and coexistent azotemia, and hyperchloremic acidosis was reported during IV clodronate treatment;[107] however, previous episodes of hyperkalemia had occurred in both patients, and the contributory role of clodronic acid is speculative.

Hypocalcemia: Hypocalcemia, occasionally symptomatic, were reported in a few patients during therapy with both oral and IV clodronic acids.[108]

3.c. Etidronate

Hyperphosphatemia: Can lead to increase in tubular reabsorption of phosphate.[109]

3.d. Ibandronate

Hypocalcemia: Similar to other BPs, ibandronate administration has resulted in a decrease in serum calcium. Hypocalcemia should be treated prior to initiating ibandronate therapy.[110]

3.e Pamidronate

Hypocalcemia: Serum calcium should be monitored in patients with Paget's disease undergoing pamidronate therapy at the time of initiation of treatment. Patients with hypoparathyroidism, possibly predisposing them to hypocalcemia.[88]

Hypokalemia, hypothyroidism, hypomagnesemia, and hypophosphatemia: Hypokalemia, hypothyroidism, hypomagnesemia, and hypophosphatemia were reported in patients with Paget's disease and hypercalcemia of malignancy in patients who received etidronate therapy.[88,111]

3.f. Residronate

Hyperparathyroidism: A daily dose of 5 mg risedronate and delayed-release risedronate 35 mg weekly dosage in postmenopausal osteoporotic patients were associated with increased levels of parathyroid hormone (PTH); however, negligible increased PTH levels were encountered in daily immediate-release risedronate-dosed patients.[112] Hypocalcemia and hypophosphatemia were also noticed in the treatment of postmenopausal osteoporotic women receiving delayed-release risedronate 150 mg/once a month and also among Paget's disease patients who received risedronate treatment.[91]

4. GIT effects

With oral alendronate, common adverse effects like diarrhea, abdominal distension, pain, constipation, and bleeding ulcers of the esophagus are noted.[95,113] The US FDA has reported esophageal cancer in patients using oral BPs for a longer period, in contrast to some other studies that revealed that there is no risk of esophageal cancer.[114] However, more reliable concrete data are essential to study the association between BPs and esophageal cancer.[53,115,116]

Esophagitis, esophageal ulcers, and esophageal erosions, were reported following oral BPs treatment, including alendronate.[95,117] Long-term usage of risedronate, ibandronate, and etidronate were also reported with esophageal cancer.[118]

5. Hepatic effects

Hepatotoxicity: Elevation in serum transaminase enzymes were reported in few hypercalcemic patients who received alendronate through the IV route.[119]

An increased concentration of hepatic enzymes and fatty changes were noticed in a case report of a 71-year-old woman and reversed to the normal range following the withdrawal of alendronate.[120,121] Increased liver transaminase levels in serum were noticed in a 61-year-old woman receiving IV ibandronate, the enzyme levels gradually reverted to normal within 1-year after stopping the drug.[121,122]

6. Immunologic effects

Lymphocytopenia, flu-like symptoms, urticaria, and, rarely, angioedema, were reported in postmarketing studies.[95,123]

Anaphylaxis was observed during postmarketing surveillance.

7. Musculoskeletal effects

Musculoskeletal pain is an apparent adverse effect of BPs. The US FDA emphasized the possibility of occurrence of severe musculoskeletal pain in patients undergoing BP therapy after first IV infusion, especially with amino BPs.[124] Cases of bone, joint, and/or muscle (musculoskeletal) pain were reported with the use of alendronate and risedronate.[125] Time of pain onset ranged from 1 day to 52 months (mean: 91 days, median: 14 days) after the initiation of therapy. While many patients experience relief after cessation of BPs, others have experienced a slower, partial response despite treatment with a variety of analgesics, including opioids.[126]

7.a. Atypical bone fractures

The risks of pelvic and femoral fractures were documented particularly in patients on long-term BPs. In long-term BP users, the persistent suppression of bone metabolism and impaired bone healing are the probable contributing factors predisposing to these fractures.[127] Risk of atypical femur fractures in BPs users was evaluated in various studies;[128] however, the resultant data revealed that the occurrence of atypical femur fractures is less likely.[129] Predominantly, these fractures were noticed in osteoporotic patients on BP therapy, and they are not observed in BP users of Paget's disease or hypercalcemia of malignancy.[130]

Apart from these fractures, some other features such as thickening of cortical bone, bilateral bone fractures, and delayed healing were also documented in the literature, and the occurrence of these features is unclear.[131]

7.b. Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a severe adverse effect of BPs. A high incidence of ONJ (94%) occurs in patients receiving IV BP therapy for a longer period. In 2003, Marx reported the first case of ONJ following IV administration of zolendronate[132] and pamidronate in patients with malignant conditions such as myeloma (7%–10%) and breast cancer (4%).[133,134] The incidence of this adverse effect increases with the administration of IV BPs.[135] A growing number of reports have attempted to describe the effect; however lowering dosage and increasing the dosage frequency has lessened the ONJ occurrence.[136] Moreover, orally administered BPs have slight incidence of ONJ.[137]

Presently, the BP-related osteonecrosis of the jaw (BRONJ) can be defined as the condition in which patients without a history of radiotherapy to the jawbone and with a history of BP usage or who are under BP medication develop necrotic lesions in the maxillofacial bones, particularly in the maxilla and mandible, after at least 8 weeks.[138,139] It is also known as "bis-phossy jaw" because it is similar with "phossy jaw," which is an occupational disease common in employees working in the phosphorous (matchstick) industry with inadequate protection.[140]

In a few recent studies, the usage of antiresorptive medications, such as denosumab (human monoclonal antibody), in cancer patients to prevent bone metastasis and antiangiogenesis medication, such as bevacizumab, for colorectal cancers were also associated with ONJ.[141] Therefore, the latest opinion is that the incidence of ONJ is not limited to BPs, and it can also flare up because of other antiresorptive medications. Hence, it is termed as medication-related osteonecrosis of the jaw (MRONJ).[142] Nevertheless, to date, the mechanism of ONJ in association with BPs and other antiresorptive agents remains unclear.

The possible mechanism may be that the antiosteoclastic effect of BPs cause osteoclastic inhibition by apoptosis[143] and suppress angiogenesis; therefore, the overall excessive obstruction of bone turnover occurs and eventually, an attempt to repair results in bone necrosis.[144,145] BPs have a tendency to deposit in these bones because they have an affinity to the bones, which undergoes excessive turnover; thus, BPs accumulate in the jawbones. Any surgical trauma to the jaw region (craniofacial bones) in the form of tooth extraction and the rupture of mucosa of jawbones because of artificial dentures, periodontal infections, and steroid therapy in severe immunocompromised cases leads to BRONJ.[146] BRONJ is a lethal lesion and is difficult to manage. In literature, to date, BP-associated osteonecrosis is not observed in any part or portion of human bones other than the jawbones (craniofacial bones).

Patient counseling points

The most common patient counseling points for the commonly prescribed BP areas are listed in Table 5.[12,27,147]

Use in special population

The use of BPs in special population is listed in Table 6.[12]

Monitoring parameters

The various monitoring parameters for patients prescribed with BPs are tabulated in Table 7.[12]

Table 5: Counseling points for patients prescribed bisphosphonates

Drug	Common indication	Administration	Dosing schedule	Possible adverse effects
Alendronate	Osteoporosis, Paget's disease, corticosteroid-induced osteoporosis	Tell patient to take a tablet with a full glass (6–8 ounces) of water while in an upright position	Once daily Once weekly Once in 6 months	Irritation of esophagus, abdominal pain, muscle pain
Pamidronate	Paget's disease, high blood calcium levels, some types of cancers	IV infusion over a period of time Drink more noncaffeinated liquids	Once in 1 month Once in 2 months Once in 3 months	Fatigue, breathing difficulties, UTIs
Risedronate	Paget's disease, osteoporosis	Fast-release tablets (oral) on an empty stomach 30 mins before breakfast Long-acting tablets after breakfast with plain water taken in an upright position and not to be taken lying down	Once daily Once weekly Once monthly	GI irritation, UTI, bone and muscle pain
Zolendonate	Paget's disease, high blood calcium levels, some types of cancers	IV infusion slow After infusion acetaminophen is given to reduce symptoms of acute-phase reactions	Once in 1 month Once in 3 months Once in year	Cancer patients: loss of sleep, hunger, and weight loss Other patients: Severe muscular bone pain, especially back pain
Etidronate	Paget's disease	Oral tablets: Should be taken on an empty stomach and 2 h before breakfast Long-acting tablets: Taken after breakfast with plain water and taken in an upright position and not to be taken lying down	Once per day not exceeding a maximum 6 months	Diarrhea, nausea, bone and muscle pain
Clodronate	Bone metastasis, high-blood calcium levels because of malignancies	Oral capsule on an empty stomach 30 mins before breakfast. To be taken in an upright position and not to be taken lying down IV infusion: 2–6 h slow infusion Drink more noncaffeinated liquids and plenty of water	Oral–daily IV–daily up to a week or 10 days	Esophageal irritation, abdominal pain Oral: Weight gain IV: Inflammation of veins
Ibandronate	Postmenopausal osteoporosis, postmenopausal osteoporosis, prophylaxis	Oral tablet: Taken on an empty stomach 60 mins before breakfast. To be taken in an upright position and not to be taken lying down IV injection: 15–30 seconds using the supplied needle	Oral: Once every month IV: Once every 3 months	Esophageal erosions, abdominal pain Bone and muscle pain Bronchitis (upper respiratory tract infection)
Tiludronate	Paget's disease	400 mg orally daily for 3 months	Oral: Daily for 3 months	Esophageal erosions, abdominal pain Bone and muscle pain Respiratory: Rhinitis and sinusitis

IV=Intravenous, UTIs=Urinary tract infections, GI=Gastrointestinal

Conclusions

BPs are commonly used drugs for treating osteoporosis and are considered effective. They are effective and safe, except for causing GI effects and rare effects such as osteonecrosis. Providing patient counseling can be helpful in early identification and prevention of the side effects associated with BPs.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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Table 6: Use of bisphosphonates in special population

BP	Children	Elderly	Renal Failure	Hepatic Failure	US FDA Pregnancy Category	Breastfeeding
Alendronate	Not indicated for use in pediatric patients	No dosage adjustments necessary	Renal impairment, (CrCl 35–60 mL/min): No dosage adjustment necessary	No dosage adjustments necessary	C	Infant risk cannot be ruled out
Clodronate	-	-	Renal insufficiency to avoid cumulative toxicity	-	-	
Etidronate	Safety and effectiveness not established in children	No dosage adjustments necessary	Renal impairment: Serum creatinine greater than 2.5–5 mg/dL given cautiously		C	Infant risk cannot be ruled out

BP=Bisphosphates, US FDA=United States Food and Drug Administration

Table 7: Monitoring parameters for patients undergoing bisphosphonate therapy

BP	Monitoring parameters
Alendronate	Biochemical markers of bone formation/resorption Radiologic evidence of fracture Serum calcium, electrolytes, and phosphate levels Periodic dental exams for signs of ONJ Renal function Paget's disease; ALP and/or urinary hydroxyproline
Clodronate	Biochemical markers of bone formation/resorption Radiologic evidence of fracture Serum calcium, electrolytes, and phosphate levels Periodic dental exams for signs of ONJ Renal function Paget's disease; ALP
Etidronate	In Paget's disease: A reduction in serum ALP, urinary hydroxyproline levels, osteoblast numbers, and osteoclast numbers indicates efficacy Improvements in pain, mobility, cardiac output, lamellar bone formation, or skin temperature may be indicative of efficacy Biochemical and radiographic response in patients with predominantly lytic lesions
Ibandronate	Increase in BMD Serum creatinine measurement Routine oral examination; prior to each dose
Pamidronate	Hypercalcemia: Serum calcium levels Paget's disease: ALP and urinary hydroxyproline Improvement in pain and bone lesions Serum creatinine; prior to each treatment CBC with differential and hematocrit/hemoglobin, especially for the first 2 weeks of treatment in patients with anemia, leukopenia, or thrombocytopenia Urine albumin; every 3–6 months in multiple myeloma Dental examination; before initiation of treatment
Risedronate	Paget's disease and normalization of serum ALP level Osteoporosis: BMD increase and reduction of evidence of vertebral fracture
Tiludronate	Biochemical markers of bone formation/resorption Radiologic evidence of fracture Serum calcium, electrolytes, and phosphate levels Periodic dental exams for signs of ONJ
Zoledronic acid	Hypercalcemia of malignancy: Normalization of serum calcium levels Paget's disease: Normalization or reduction of serum ALP Multiple myeloma or bone metastases from solid tumors: Lack of skeletal-related events suggests efficacy

BP=Bisphosphonate, ONJ=Osteonecrosis of the jaw, ALP=Alkaline phosphatase, BMD=Bone mineral density, CBC=Complete blood count

Conflicts of interest

There are no conflicts of interest.

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