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ZOLEDRONIC ACID: ONCE-YEARLY TREATMENT FOR OSTEOPOROSIS

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Osteoporosis is a skeletal disorder characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and an increased susceptibility to fractures, particularly of the hip, spine and wrist. It occurs in an estimated 44 million Americans, accounting for 55% of the people 50 years of age and older.[1] By the year 2020, 1 in 2 Americans is expected to either have or be at risk of developing osteoporosis.[2] Without appropriate therapy, annual hip fractures are estimated to increase from 300,000 to 6.2 million in the year 2050.[3]

A common evaluation marker in the diagnosis and evaluation of osteoporosis is the T-score measurement of the bone mineral density (BMD) derived from dual energy X-ray absorptiometry (DEXA) of the hip or spine.[3] T-score is a classification of BMD according to the standard deviation (SD) difference between a patient's BMD and that of a young-adult reference population established by the World Health Organization (WHO) in 1994. A normal T-score is -1.0 or higher, low bone mass (osteopenia) between -1.0 and -2.5, and osteoporosis as equal to or less than -2.5.[4,5] Additionally, excessive bone resorption by osteoclasts leads to decreased bone mass and bone strength. This resorption activity can be quantified by the presence of serum (alkaline phosphatase/ALP, C- and N-terminal propeptides of type 1 collagen) and urine (C- and N-telopeptides of type 1 collagen or CTx and NTx) biochemical markers. These markers reflect bone remodeling but do not indicate current BMD; therefore, do not replace DEXA for osteoporosis diagnosis.[3]

Bisphosphonates are the mainstay of therapy for osteoporosis.[6] Alendronate (Fosamax®), risendronate (Actonel®) and ibandronate (Boniva®) are the oral bisphosphonates indicated for prevention and treatment of osteopososis; whereas, ibandronate (Boniva®) and zoledronic acid (Reclast®) are the intravenous (IV) bisphosphonates for treatment of osteoporosis.[8] Oral bisphosphonates have poor intestinal absorption and can cause gastrointestinal intolerance, heartburn, esophageal irritation and esophagitis, which often reduce adherence.[9] At the end of one year of bisphosphonate therapy, approximately one-third of patients taking Qdaily dosing and less than one-half of those taking Qweekly dosing continued their therapy.[3,15] Zoledronic acid (Reclast®) is the first FDA-approved bisphosphonate for once-yearly IV treatment of postmenopausal osteoporosis. It is also approved for treatment of Paget's disease and recently, for treatment of osteoporosis in men.[14] Zometa® is another IV formulation of zoledronic acid indicated for treatment of hypercalcemia of malig-

INSIDE THIS ISSUE:

nancy, multiple myeloma and bone metastasis from solid tumors.[16] This article will review the safety, efficacy and tolerability of zoledronic acid (Reclast®) as an option in the management of osteoporosis.

PHARMACOLOGY AND PHARMACOKINETICS

Zoledronic acid is an inhibitor of osteoclast-mediated bone resorption. It has high binding affinity to bone mineral hence its long duration of action. Zoledronic acid rapidly partitions to bones and localizes preferentially at sites of high bone turnover. The enzyme farnesyl pyrophosphate synthase is its main molecular target in the osteoclast.[14]

No in vivo drug interaction studies have been performed for zoledronic acid. The drug has low affinity for blood components and has moderate protein binding capacity in human plasma. It is not metabolized and is excreted into the urine as the intact drug. Zoledronic acid clearance is independent of dose but dependent on creatinine clearance. No dosage adjustment is required in patients with creatinine clearance (CLcr) of ³ 35 mL/min but is not recommended for patients with severe renal impairment (CLcr <35 mL/min).[14]

CLINICAL TRIALS

Dose-Ranging Efficacy and Long-Term Safety

A multinational, one-year, phase 2 study by Reid et al randomized 351 postmenopausal women aged 45-80 years to receive either placebo (n=59) or intravenous zoledronic acid in doses of 0.25 mg (n=60), 0.5 mg (n=58), or 1 mg (n=53) at three-month intervals; a total annual dose of 4 mg as a single dose (n=60); or two doses of 2 mg administered six months apart (n=61).[17] The primary endpoint was the lumbar-spine BMD. At the end of the study, no significant differences among the zoledronic acid groups were observed. All zoledronic acid treatment groups had 4.3- 5.1% lumbar spine BMD higher than the placebo group ($p<0.001$) and 3.1-3.5% femoral neck BMD higher than placebo group ($p<0.001$). There was a significant decrease in serum CTx of 49-52% with zoledronic acid vs. 8% decrease with placebo ($p<0.01$).[14] Treatment-related dropout rates were similar to that in the placebo group although myalgia and pyrexia occurred more commonly in the zoledronic acid groups. Based on the active treatment groups' increase in BMD, decrease in serum bone turnover markers and low incidence of adverse events, the investigators concluded that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis.[14]

Devogelaer and colleagues investigated the efficacy and safety of zoledronic acid 4 mg over 5 years in postmenopausal osteoporosis.[18] This investigation was composed of the previous 1-year study by Reid et al[17] followed by two consecutive, 2-year, open-label extension studies. A total of 119 women completed the core study and were randomized to receive yearly doses of placebo (n=19), four 0.25-mg zoledronic acid doses (n=20), four 0.5-mg zoledronic acid doses (n=19), four 1-mg zoledronic acid doses (n=19), two 2-mg zoledronic acid doses (n=22), or one 4-mg zoledronic acid dose (n=20). Most study participants in the first extension study received annual zoledronic acid 1 mg every 3 months (n=105) while others received 0.5 mg every 3 months (n=14).[3,18] Patients who entered the second extension received either 4 mg per year of zoledronic acid (n=22) or calcium only (n=97) and were divided into three subgroups according to years of active treatment received (2 years, n=19; 3 years, n=78; or

Table 1: Zoledronic Acid vs. Placebo in the HORIZON Pivotal Fracture Trial[19,25]

OUTCOME MEASUREMENT	ZOLEDRONIC ACID	PLACEBO	RRR (95% CI)	NNT (95% CI)
Vertebral fracture (stratum I)	3.3%	11%	70% (62-76)	14 (13-15)
Hip fracture	1.4%	2.5%	41% (17-58)	98 (69-236)
Nonvertebral fracture	8.0%	11%	25% (13-36)	38 (26-72)
Any clinical fracture	8.4%	13%	33% (23-42)	24 (19-34)

RRR = relative risk reduction; NNT = number needed to treat

Table 2: Adverse Events of the HORIZON Pivotal Fracture Trial

EVENT	ZOLEDRONIC ACID (N=3862)	PLACEBO (N=3852)	P VALUE
Any adverse event, n (%)	3688 (95.5)	3616 (93.9)	0.002
Any serious adverse event	1126 (29.2)	1158 (30.1)	0.4
Death	130 (3.4)	112 (2.9)	0.27
Discontinuation of follow-up due to adverse event	80 (2.1)	70 (1.8)	0.41
Five most common post-dose symptoms (≤3 days after infusion)			
Pyrexia	621 (16.1)	79 (2.1)	<0.001
Myalgia	365 (9.5)	66 (1.7)	<0.001
Influenza-like symptoms	301 (7.8)	61 (1.6)	<0.001
Headache	273 (7.1)	90 (2.3)	<0.001
Arthralgia	245 (6.3)	76 (2.0)	<0.001
Any of the five most common post-dose symptoms			
After first infusion	1221 (31.6)	237 (6.2)	<0.001
After second infusion	253 (6.6)	79 (2.1)	<0.001
After third infusion	108 (2.8)	42 (1.1)	<0.001
Atrial fibrillation			
Any event	94 (2.4)	73 (1.9)	0.12
Serious adverse event	50 (1.3)	20 (0.5)	<0.001
Stroke			
Serious adverse event	87 (2.3)	88 (2.3)	0.94
Death from stroke	20 (0.5)	11 (0.3)	0.15

5 years, n=22). Changes in BMD measured by DEXA and bone turnover markers (bone ALP and CTx) were assessed. All subgroups showed substantial increases in BMD of lumbar spine (6.4-9%), proximal femur (4.9-5.5%), distal radius (2.2-3%), and total body (3.6-5%) by the end of the study. There was no sustained reduction in bone turnover in any of the treatment groups based on increases in ALP and CTx levels from month 24 in participants treated for 5 years. The most frequent adverse events were arthralgia, hypertension, back pain, nasopharyngitis, osteoarthritis, falls, bronchitis and pain in an extremity. A total of 8 patients (6.7%) experienced serious adverse events, with 7 of the 15 total events reported as cardiovascular-related. Six patients reported a fracture during the study. Devogelaer et al[18] concluded that zoledronic acid 4 mg once-yearly increased BMD and decreased bone resorption although this drug regimen may not be sufficient in reducing bone remodeling activity. Limitations of the study included small treatment groups, multiple treatment regimens, open-label design, and lack of randomization in both of the extension studies.

Fracture Risk Studies

The 3-year international, multicenter, randomized placebo-controlled Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial by Black et al was the first study to evaluate fracture risk with zoledronic acid use.[19] The trial included 7,736 women aged 65-89 (mean age = 73), who had BMD T-score of –2.5 or less at the femoral neck, with or without evidence of existing vertebral fracture; or a T-score of –1.5 or less, with at least two mild or one moderate existing vertebral fracture. Study participants were placed into one of two strata based on their use of osteoporosis medications at baseline. Stratum I included patients with no concomitant use of osteoporosis therapy (n=6,113); stratum II included those with baseline concomitant use of anti-osteoporosis therapy excluding bisphosphonates (n=1,652). The

investigators believed that permitting the use of non-bisphosphonate therapies would not have an important influence on the overall outcome as only alendronate and risedronate had nonvertebral fracture risk reduction data at the time of study.[20] Patients were randomly assigned to a single dose of 5 mg zoledronic acid infused over 15 minutes (n=3,889) or placebo (n=3,876) once a year for three consecutive years. Both groups received calcium and vitamin D supplementation. New vertebral fractures in stratum 1 and hip fracture in both strata were the primary endpoints of the trial.

During the 3-year period, the active treatment group had a 70% relative risk reduction of morphometric vertebral fracture as compared with placebo ($p<0.001$) and 41% relative risk reduction of hip fracture ($p=0.002$). The reduction for nonvertebral fractures, clinical fractures, and clinical vertebral fractures were 25%, 33%, and 77%, respectively (all comparisons, $p<0.001$). Results for fracture risk reduction are summarized in Table 1.

BMD scores at the total hip, lumbar spine and femoral neck were significantly increased by 6.02%, 6.71% and 5.06%, respectively. The effect of zoledronic acid on biochemical markers was similar to that reported for oral bisphosphanates. Bone remodeling levels after the infusions were also similar, supporting the view that the 3-year annual infusion of zoledronic acid improves bone strength without adversely affecting remodeling capacity. Adverse events were similar in two groups with pyrexia and myalgia being most commonly reported (Table 2). Serious atrial fibrillation, however, occurred more frequently in the zoledronic acid group (50 vs. 20 patients, $p <0.001$). The authors concluded that a once-yearly infusion of zoledronic acid significantly reduced the risks for vertebral, hip and other fractures.

Lyles and colleagues evaluated the safety and efficacy of zoledronic acid for the prevention of new clinical fracture in patients who had (<90 days of enrollment) undergone recent surgical repair of a hip fracture and were unable or unwilling to take an oral bisphosphonate.[21] The HORIZON Recurrent Fracture Trial was an international, multi-center, randomized, double-blind, placebo-controlled study involving men and women 50-95 years (mean age = 74.5), randomly assigned to receive either zoledronic acid (n=1,065) or placebo (n=1,062). Patients in the two groups received supplemental vitamin D and calcium. The median follow-up was 1.9 years. The study continued until at least 211 patients in the study population had confirmed clinical fractures. Zoledronic acid significantly reduced the incidence of any clinical fracture by 35%. The rates of any new clinical fracture were 8.6% in the active treatment group and 13.9% in the placebo group ($p=0.001$). In the safety analysis, 101 of 1,054 patients died in the zoledronic acid group (9.6%) vs. 141 of 1,057 patients in the placebo group (13.3%). This was a 28% reduction in deaths from any cause in the zoledronic acid group ($p=0.01$). Pyrexia, myalgia and bone and musculoskeletal pain were the most frequent adverse events reported. The rates for renal and cardiovascular adverse events, including atrial fibrillation and stroke, were comparable between study groups. The investigators concluded that once-yearly infusion of zoledronic acid within 90 days after low-trauma hip fracture repair was associated with new clinical fracture rate reduction and improved survival.[14,21]

Comparative Studies for Osteoporosis

Saag and colleagues evaluated the onset of action of single infusion zoledronic acid compared with weekly oral alendronate by comparing relative change from baseline in the bone resorption marker urine NTx at week 1.[22] The 24-week multicenter, randomized, double-blind, double-dummy trial, included postmenopausal women aged 45-70 years. Study participants were assigned to receive weekly alendronate 70 mg (n=59) or a single dose of zolendronic acid 5 mg (n=69). Both groups were supplemented with calcium and vitamin D. At week 1, zoledronic acid resulted in a significantly greater reduction in mean urine NTx from baseline than alendronate 70 mg ($p<0.0001$). The reported adverse events were comparable between study groups (zoledronic acid 91.3%, alendronate 86.4%). Transient, flu-like symptoms were the most common adverse events in the zoledronic acid group (18.8% vs. 5.1%). The majority of patients, including those who experienced flu-like symptoms, preferred the annual IV therapy (66.4%) compared to weekly oral therapy (19.7%).

A 12-month noninferiority trial involving zoledronic acid and alendronate was conducted by McClung et al.[23] The study involved postmenopausal women aged 45-79 years, with lumbar spine or femoral neck BMD T-score values of ≤ -2.0 who had previously taken alendronate for at least one year

Table 3: Summary of Zoledronic Acid Clinical Trials

STUDY	DESIGN	DOSE	RESULTS

Reid, et al. (2002)[17]	• 1-y randomized, double-blind, PCB-controlled trial
	• 45-80 y.o. postmenopausal women (n=351)
	• Primary endpoint: lumbar-spine BMD
		• PCB (n=59)
		• 5 ZA groups:
		  • 3 mo intervals: 0.25 mg (n=60), 0.5 mg (n=58), 1 mg (n=53)
		  • single 4 mg dose (n=60)
		  • 2 doses: 2 mg, 6 mo interval (n=61)
			• BMD increases similar in all the ZA groups:
			  • Spine values 4.3-5.1% higher than placebo group (p<0.001)
			  • Femoral neck values 3.1-3.5% higher than placebo group (p<0.001)

Devogelaer, et al. (2007)[18]	• 5-y study; 1-y core study;[17] 2 consecutive 2-y, open-label extension studies
	• 1st extension: majority receive 4 mg/yr
	• 2nd extension: 4 mg/yr or calcium only
	• Patients divided into three subgroups according to years of active treatment received (2, 3 or 5 years)
	• Primary endpoints: Changes in BMD and bone turnover markers
		• PCB (n=19)
		• ZA groups- annual dose:
		  • 4 doses 0.25 mg (n=20)
		  • 4 doses 0.5 mg (n=19)
		  • 4 doses 1 mg (n=19)
		  • 2 doses 2 mg (n=22)
		  • 1 dose 4 mg (n=20)
		• 1st extension study: ZA 1 mg q 3 months (n = 105), 0.5 mg q 3 months (n = 14)
		• 2nd extension study: 4 mg/yr of ZA (n=22) or calcium only (n = 97)
		  • 2 years (n=19)
		  • 3 years (n=78)
		  • 5 years (n=22)
			• BMD increases in all ZA subgroups:
			  • Lumbar spine (6.4-9%), Proximal femur (4.9-5.5%),
			  • Distal radius (2.2-3%), Total body (3.6-5%)
			• No evidence of progressive reduction of bone turnover markers; Increased marker levels after treatment discontinuation
			• Drug regimen causes insufficient reduction of remodeling activity in one third of patients

Black, et al. (2007)[19]	• 3-y, double-blind, placebo-controlled trial
	• 7,765 postmenopausal women
	• Primary end points: new vertebral fracture (pts not taking concomitant osteoporosis medications) and hip fracture (all pts)
		• PCB (n=3,876)
		• 5 mg ZA infused over 15 min (n=3,889)
			• Reduction of vertebral fracture:
			  • 3.3% (ZA) vs 10.9% (PCB)
			• Reduction of hip fracture:
			  • 1.4% (ZA) vs 2.5% (PCB)

Lyles, et al. (2007)[21]	• Randomized, double-blind, PCB-controlled trial • Median follow-up = 1.9 years • Primary end point: new clinical fracture	• PCB (n=1,062) • 5 mg ZA infused over 15 min (n=1,065) • Infusions administered <90 days after surgical repair of hip fracture	• New clinical fracture: • 8.6% (ZA) vs. 13.9% (PCB)
Saag, et al. (2007)[22]	• 24-week randomized, double-blind, double-dummy trial • Primary endpoints: reductions in urine NTx at week 1, patients' preference of weekly vs. yearly treatment	• 5 mg ZA infused over 15 min (n=69) • Alendronate 70 mg weekly (n=59)	• ZA had a significantly greater reduction in mean urine NTx from baseline (p<0.0001) • 66.4% preferred annual IV therapy vs. 19.7% weekly oral therapy

McClung, et al. (2007)[23]	• 1-y double-blind, double-dummy trial
	• Included postmenopausal women receiving oral alendronate for ≥ 1 year immediately prior to randomization
	• Primary endpoints: change in lumbar spine BMD, relative change in bone biomarkers
		• single infusion of PCB plus 52 weeks of oral alendronate 70 mg (n=112)
		• 5 mg ZA infused over 15 min plus 52 weeks of oral placebo (n=113)
			• Mean biomarker levels:
			  • Alendronate remained at or close to baseline levels
			  • ZA reduced from baseline after 3 months, returned to baseline after 6 months, and increased thereafter but remained within the premenopausal range
			• 78.7% preferred yearly infusion

Novartis Corporation Internal Study (2008)[14]	• 2-year randomized, doubleblind, active controlled study • 302 men aged 25-86 years (mean = 64)	• 5 mg ZA infused over 15 minutes (n=153) • Alendronate 70 mg weekly (n=148)	• Change in lumbar spine BMD relative to baseline: • 6.1% increase (ZA) vs. 6.2% increase (alendronate)

PCB = placebo

prior to randomization (mean = 4 years). Study patients were assigned to either single dose of zoledronic acid 5 mg IV infused over 15 minutes plus 52 weeks of oral placebo (n=113) or one placebo IV infusion plus 52 weeks of oral alendronate 70 mg (n=112). Both groups were given calcium and vitamin D supplementation. The primary endpoint of the study was the percent change in lumbar spine BMD from baseline to month 12. By the end of trial, zoledronic acid maintained BMD following the switch from alendronate. Mean biomarker levels after 3 months were reduced from baseline; after 6 months, returned to normal; and, increased thereafter but the levels remained within the premenopausal range. Over-all, reported adverse events were comparable between the groups (zoledronic acid 86.7%, alendronate 80.4%). Headache within the first 3 days post-infusion however, occurred more frequently with zoledronic acid (12.4%) vs. alendronate (6.3%). There was less frequency of flu-like symptoms in patients who switched from alendronate to zoledronic acid (0%) compared to previously reported by Saag et al[22] in bisphosphanate-naïve patients given zoledronic acid (18.8%). Once-yearly zoledronic acid was preferred by the majority of the study participants (78.7%). The investigators concluded that patients can be switched from once-daily oral alendronate to once-yearly IV zoledronic acid with maintenance of therapeutic effect for at least 12 months.[23]

Osteoporosis in Men

The efficacy and safety of zoledronic acid in men with osteoporosis or significant osteoporosis secondary to hypogonadism, were assessed in a 2-year randomized, multicenter, double-blind, active controlled trial involving 302 men aged 25-86 years (mean age of 64). Study patients were randomly assigned to receive an annual single dose of 5 mg zoledronic acid infused over 15 minutes (n=153) or a commercially available oral weekly bisphosphonate, alendronate (n=148). Both groups were supplemented with calcium plus vitamin D. Zoledronic acid was noninferior to alendronate based on the percentage change in lumbar spine BMD relative to baseline (zoledronic acid: 6.1% increase; active control: 6.2% increase). Adverse events reported were comparable between the two groups except for the higher incidence of post-dose symptoms in the zoledronic acid group, which occurred within three days after the infusion. The overall safety and tolerability of zoledronic acid was similar to oral weekly alendronate.[14]

DOSING, ADMINISTRATION AND COST

Zoledronic acid is available as Reclast® and Zometa®, approved for different indications. The recommended dose for Reclast® in the treatment of osteoporosis in postmenopausal women and men is 5 mg intravenously administered over no less than 15 minutes once a year. Patients must be supplemented with calcium and vitamin D if dietary intake is not sufficient to prevent hypocalcemia. Acetaminophen should be given at the time of IV infusion and at home for the next 72 hours as needed to minimize post-dose symptoms. Due to lack of clinical experience in patients with severe renal impairment, zoledronic acid is not recommended in patients with creatinine claearance of <35 mL/min. Patients, especially those receiving diuretic therapy, should be appropriately hydrated prior to administration of zoledronic acid to prevent impairment of kidneys. Zometa®, approved for treatment of malignancies, is administered as 4 mg infused over no less than 15 minutes as a one time dose or every 3-4 weeks. Dose adjustment is recommended in patients with baseline creatinine clearance of <60 mL/min.[14,16]

SAFETY ISSUES

Osteonecrosis of the jaw (ONJ) has been associated with the use of bisphosphonate. King and Umland[8] recently reviewed 44 published case reports and case series involving 481 patients with bisphosphonate-related ONJ. They found that ONJ occurred more frequently in patients receiving IV bisphosphonates (n=453, 94.2%) than those receiving oral bisphosphonates (n=28, 5.8%); patients who had cancer (n=451, 93.8%), most common diagnosis being multiple myeloma followed by breast, prostate and lung cancers; and history of glucocorticoid use (~75%). In the 449 patients who reported the inciting event preceding ONJ diagnosis, 68.8% (n=309) had tooth extraction or other surgical or invasive dental procedure while 20.7% (n=93) developed ONJ spontaneously.[8] Prescribers should perform a routine oral examination prior to initiation of bisphosphonate treatment. In patients with concomitant risk factors (e.g., cancer, chemotherapy, radiotherapy, corticos-

Table 4: Cost of Bisphosphonates for Treatment of Osteoporosis[9]

DRUG	DOSAGE	ANNUAL COST* (USD)
Alendronate		
Fosamax® (Merck)	10 mg/d	1127.85
	70 mg once/week	1093.04
Fosamax® Plus D	70 mg + 2800 IU D3 once/week	1097.72
	70 mg + 5600 IU D3 once/week	1084.20
Ibandronate		
Boniva® (Roche)	2.5 mg/d	1076.75
	150 mg once/month	1030.68
	3 mg IV every 3 months	1911.28
Risedronate		
Actonel® (Procter & Gamble)	5 mg/d	1076.75
	35 mg once/week	1072.24
	75 mg/day X 2 once/month	1078.08
Actonel with Calcium®	35 mg once/week + 500 mg Ca other days of the week	1073.80
Zoledronic acid		
Reclast® (Novartis)	5 mg IV once/year	1262.00

*Cost of one year's treatment for the drug alone, based on September 30, 2007 data from Wolters Kluwer Health.

teroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy), a dental examination with appropriate preventive dentistry should be considered prior to treatment and invasive dental procedures avoided while on treatment.[14]

The FDA did a one-year safety review to investigate the concerns raised regarding the increased risk of atrial fibrillation in bisphosphonate-treated patients. Placebo-controlled clinical trial data on 19,687 patients treated with bisphosphonate and 18,358 treated with placebo, followed for 6 months to 3 years, were submitted by sponsors of alendronate, ibandronate, risedronate, and zoledronic acid upon FDA request. No clear association between overall bisphosphonate exposure including increasing dose or duration of therapy, and rate of serious or non-serious atrial fibrillation was observed across all studies. The FDA is exploring the feasibility of conducting additional epidemiologic studies as they are aware of the conflicting results from the literature and other epidemiological studies. The FDA is also continuing to do post-market report monitoring on atrial fibrillation in bisphosphonate-treated patients. On November 12, 2008, the FDA concluded that healthcare professionals should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their bisphosphonate medication.[24]

SUMMARY

Bisphosphonates are the gold standard in the treatment of osteoporosis. Due to the complexity of oral bisphosphonate administration requirements and adverse effects, patients' adherence to therapy decreases and eventually their osteoporosis worsens. Available data on once-yearly IV infusion of zoledronic acid (Reclast®) demonstrates that it is safe, efficacious and well tolerated in both women and men with osteoporosis. This dosing regimen may increase adherence to therapy and ultimately improve clinical outcomes.

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