

Management of osteoporosis in the aging male: Focus on zoledronic acid

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Abstract: Osteoporosis in the aging male remains an important yet under-recognized and undertreated disease. Current US estimates indicate that over 14 million men have osteoporosis or low bone mass, and men suffer approximately 500,000 osteoporotic fractures each year. Men experience fewer osteoporotic fractures than women but have higher mortality after fracture. Bisphosphonates are potent antiresorptive agents that inhibit osteoclast activity, suppress *in vivo* markers of bone turnover, increase bone mineral density, decrease fractures, and improve survival in men with osteoporosis. Intravenous zoledronic acid may be a preferable alternative to oral bisphosphonate therapy in patients with cognitive dysfunction, the inability to sit upright, or significant gastrointestinal pathology. Zoledronic acid (Reclast) is approved in the US as an annual 5 mg intravenous infusion to treat osteoporosis in men. The zoledronic acid (Zometa) 4 mg intravenous dose has been studied in the prevention of bone loss associated with androgen deprivation therapy.

Keywords: male osteoporosis, bisphosphonates, zoledronic acid

Osteoporosis in the aging male

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.¹ The National Osteoporosis Foundation (NOF) estimates that over 14 million American men had osteoporosis or low bone mass in 2002.² One in four men older than 60 years of age will experience a fracture,³ yet age-related bone loss in men remains under-recognized and undertreated.

Sixteen percent of men older than 50 and 35% men older than 85 fall each year.⁴ Hip fractures in men increase mortality by fourfold in the first three months after fracture,⁵ and one-year mortality reaches 20%.⁶ Epidemiologic surveys consistently show higher mortality in men than women of similar ages after fracture.⁷ Among survivors of hip fracture, more than 1 in 4 becomes disabled in the following year,⁸ and nearly 1 in 5 will require long-term nursing home care.⁹ Care for patients after hip fracture is expensive to society. In the US, direct costs for patients with osteoporotic fractures is estimated at up to \$18 billion/year in 2002 dollars. White men account for 18% of these costs, or \$3.2 billion annually.¹⁰ Vertebral fractures also increase long-term mortality,^{3,7,11} cause persistent back pain, deformity, functional decline, and diminished quality of life.

Importantly, the prevalence of osteoporosis and osteoporotic fractures are expected to rise as men live longer. The NOF predicts that there will be 20.5 million American

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men with osteoporosis or low bone mass by 2020.² By 2025, annual costs for osteoporosis-related fractures is expected to be \$25.3 billion.²

Identifying men at high risk for osteoporotic fracture

Previous fracture is the strongest predictor of any future fracture. The Osteoporotic Fractures in Men (MrOS) Study¹² followed 5995 men aged 65 and older and showed that men with a history of fracture after 50 years had a twofold increased risk of nonvertebral fracture compared to men without prior fracture. A second important predictor of fracture is advancing age. The Dubbo Study showed that, compared to men aged 70–74 years, men older than 80 years had 28 times as many vertebral fractures, nine times as many hip fractures, and nearly five times as many overall fractures.¹³ Third, bone mineral density (BMD) predicts fracture risk. The use of BMD by dual energy X-ray absorptiometry (DEXA) to predict fracture risk is comparable to the use of blood pressure to predict stroke and is substantially better than using serum cholesterol to predict the risk of myocardial infarction. The MrOS investigators¹² also found that tricyclic antidepressant use (hazard ratio [HR] 2.36), the inability to complete a narrow walk trial (HR 1.70), falls in previous year (HR 1.59), and depressed mood (HR 1.72) all increased fracture risk independent of BMD.

Bone quality indicators such as cortical thickness, micro-architecture, turnover, porosity, damage accumulation, and the rate and quality of mineralization are other important predictors of fracture, yet they are difficult to incorporate into clinical practice.¹⁴ Compared to women, men have bones with larger cross-sectional areas, and as men age they tend to preserve trabecular number. Apart from bone density, both of these factors are thought to ameliorate fracture risk.

In addition to age-related bone loss, osteoporosis in men is frequently secondary to other comorbidities such as glucocorticoid use, hypogonadism, vitamin D deficiency, cigarette smoking, heavy alcohol intake, immobility, or inadequate dietary calcium intake. Studies among ambulatory men with osteoporosis indicate that 30%–64% have at least one identifiable risk factor.^{15,16} The World Health Organization (WHO) has developed the FRAX™ fracture risk assessment tool, a group of country- and ethnicity-specific risk calculators which allow an estimate of fracture risk based on historical and exam findings.¹⁷

Treatment strategies

Traditional nonpharmacologic therapies include treatments intended to increase bone mineral density, prevent falls,

and prevent fractures with falls. Several recent papers have reviewed the literature on fall prevention, hip protectors, and calcium and vitamin D supplementation in men.^{14,18,19} Weight bearing exercise can prevent falls²⁰ and increase BMD.²¹ Inadequate dietary calcium and vitamin D intake are risk factors for osteoporosis. The NOF recommends that individuals 50 years old and older consume 1200 mg calcium and 800–1000 IU vitamin D daily. Several studies of calcium and vitamin D supplementation have shown increased BMD, decreased fracture risk,^{22–24} and even decreased mortality²³ irrespective of baseline 25-hydroxyvitamin D levels. However, another large randomized controlled trial of calcium and vitamin D in secondary prevention of osteoporotic fractures showed no benefit.²⁵

The NOF recommends drug treatment for men aged 50 and older with prior hip or vertebral fracture, with osteoporosis (T-score ≤ -2.5 at the femoral neck or spine), or with osteopenia (T-score between -1.0 and -2.5 at the femoral neck or spine) and an absolute 10-year risk of hip fracture $\geq 3\%$ or 10-year risk of a major osteoporosis-related fracture $\geq 20\%$ based on the FRAX calculation.²⁶ Drugs for the treatment of osteoporosis can be classified into antiresorptive or anabolic agents. Antiresorptive agents, or drugs that inhibit osteoclast action, include most of the commonly used therapies in men such as calcitonin, testosterone, and bisphosphonates.

Calcitonin

Trovas and colleagues²⁷ randomized 28 osteoporotic men to receive daily intranasal calcitonin 200 IU or placebo. At 12 months, the treated group had significantly suppressed markers of bone turnover and greater BMD at the lumbar spine but not hip. Toth and colleagues²⁸ studied 71 men with idiopathic osteoporosis but no prior fracture. In these men, intranasal calcitonin daily during alternate months for 18 months significantly increased BMD at the spine and hip and decreased vertebral fractures.

Calcitonin is not approved in the US for the treatment of male osteoporosis.

Testosterone

Studies have consistently shown that testosterone replacement improves BMD in hypogonadal men.^{29–32} Snyder and colleagues³¹ randomized 108 men aged over 65 years without osteoporosis to daily testosterone patch or placebo. They found no treatment effect on BMD in the group as a whole or in men with baseline testosterone level >400 ng/dL. Anderson and colleagues³³ studied intramuscular testosterone injections every two weeks in men

with osteoporosis and prior vertebral fracture. In this population, the authors found that testosterone therapy suppressed markers of bone turnover and significantly increased lumbar spine BMD.

No studies have assessed the effect of testosterone replacement on fracture risk, and testosterone is not approved in the US for the treatment of osteoporosis.

Teriparatide

Teriparatide (1–34 PTH), stimulates bone formation. Teriparatide has been shown to raise BMD in men at the hip and spine more than alendronate alone,^{34,35} and it reduces vertebral fractures by 90%.³⁵

Teriparatide is approved by the US FDA for treatment of osteoporosis in men considered at high risk for fracture.

Bisphosphonates

Bisphosphonates are synthetic pyrophosphate analogues with a P-C-P backbone that is resistant to hydrolysis and two phosphate groups that bind hydroxyapatite with high affinity. The central carbon binds the R1 side chain, often a hydroxyl group, which binds calcium and allows for more stable interaction with the bone matrix.³⁶ The longer R2 side chain gives each bisphosphonate its characteristic properties and potency. Bisphosphonates can be classified based on the presence or absence of a nitrogen atom in the R2 side chain. The nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid) are more potent inhibitors of osteoclast action.³⁷

Mechanism of action

Bisphosphonates are poorly absorbed through the gut, with less than 1% bioavailability after oral administration.³⁸ The kidneys excrete approximately 50% of the drug unchanged.³⁹ The remaining bisphosphonates bind hydroxyapatite crystals on the bone surface with high affinity, where they are internalized by and accumulate in osteoclasts.

Within the osteoclast, the nonnitrogen containing bisphosphonates (etidronate, tiludronate) are incorporated into adenosine triphosphate (ATP). These nascent nonhydrolyzable ATP analogs are toxic to osteoclasts, leading to mitochondrial inhibition and osteoclast apoptosis.⁴⁰ The nitrogen-containing bisphosphonates inhibit the enzyme farnesyl pyrophosphate synthase (FPPS) in the HMG-CoA reductase pathway leading to cholesterol synthesis. In addition to cholesterol synthesis, this pathway produces the intermediate metabolites farnesol and geranylgeranol that are necessary for protein prenylation. Prenylation is

the posttranslational attachment of hydrophobic prenyl groups to cytoplasmic proteins to allow binding to the cell membrane.⁴⁰ Such modification allows the Ras superfamily of GTPases to exert changes in cytoskeletal function that produce the characteristic osteoclast ruffled border and allow osteoclast attachment to bone.⁴¹ Biopsies of alendronate-treated bone show greater numbers of osteoclasts and abnormal giant, hypernucleated osteoclasts detached from bone. The number of osteoclasts increased with cumulative dose of alendronate, suggesting that the drug may prolong osteoclast survival.⁴² Bisphosphonate potency, the ability to inhibit bone resorption *in vivo*, is directly related to drug ability to inhibit FPPS *in vitro*.³⁷ Nitrogen-containing bisphosphonates also inhibit osteoclast precursor differentiation and inhibit osteoblast-mediated osteoclast activation.³⁸

Evidence of benefit

Pamidronate

Several randomized controlled trials of pamidronate for the treatment of osteoporosis include men. Ryan and colleagues⁴³ randomized 122 subjects with prior vertebral fracture to oral pamidronate 300 mg/day (group A) for four weeks every 16 weeks, 150 mg/day (group B) for four weeks every eight weeks or placebo (group C). At 2 years, the authors reported significant reductions in serum osteocalcin (29% group A and 33% group B) and urinary deoxypyridinoline (16% group A, 21% group B, $p < 0.01$ for all comparisons to placebo). They found significant increases in BMD at the spine, hip, and total body (See Table 2).

Brumsen and colleagues⁴⁴ randomized 101 subjects with prior vertebral fracture to oral pamidronate 150 mg/day or placebo. At three years, the investigators found significant reductions in urinary hydroxyproline and serum alkaline phosphatase and significant increases in BMD at the lumbar spine (See Table 2). Men and women had similar increase in BMD in response to pamidronate. There were significantly fewer morphometric vertebral fractures (ARR 22%) in the pamidronate group, and the number needed to treat (NNT)

Table 1 Relative potency of bisphosphonates³⁷

Drug	Relative potency
Pamidronate (Aredia)	1
Alendronate (Fosamax)	4
Ibandronate (Boniva)	10
Risedronate (Actonel)	20
Zoledronic acid (Zometa, Reclast)	67

Table 2 Studies of bisphosphonates for the treatment of osteoporosis in men

Citation	Drug	Study design	N	Follow-up (mo)	Men	Avg age	Fracture RRR			Δ % increase BMD		
							Any	Vert	NV	H	FN	LS
Ryan et al ⁴³	pamidronate	RCT	122	24	9%	65.2						3.5%–5.0%
Brumsen et al ⁴⁴	pamidronate	RCT	101	36	23%	64.5	67%	67%			NS	5.3%
Boutsen et al ⁴⁵	pamidronate	RCT	27	12	44%	57				3.2%–4.8%	4.3%	6.3%–6.9%
Ho et al ⁴⁶	alendronate	PU	123	12	57%	64.2					NS	6.4%–7.0%
Orwoll et al ⁴⁷	alendronate	RCT	241	24	100%	63	86%	NS	2.6%		2.6%	5.3%
Ringe et al ⁴⁸	alendronate	RCT	134	36	100%	53	57%	NS			3.5%	8.0%
Ringe et al ⁵⁰	risedronate	RCT	316	12	100%	56.9	60%	NS	2.3%		1.6%	3.7%
Boonen et al ⁵¹	risedronate	RCT	284	24	100%	60.7	NS					4.6%
Reid et al ⁵²	risedronate	RCT	184	12	100%	57.7	82%					
Sato et al ⁵³	risedronate	RCT	280	18	100%	76.3		75%				
Kanaji et al ⁵⁶	risedronate	RCT	23	12	100%	63–87	56%					
Lamy et al ⁵⁵	ibandronate	PU	14	24	100%	57			0.9%		1.4%	6.7%
Ringe et al ⁶⁶	ibandronate	RCT	115	36	46%	64	62%	NS			3.3%	10.7%
HORIZON-RFT ⁶⁹	zoledronic acid	RCT	2127	36	24%	74.5	35%	46%	27%	6.4%	4.3%	
Poole et al ⁷²	zoledronic acid	RCT	27	12	78%	69.8				5.5%	NS	
Bolland et al ⁷⁵	zoledronic acid	RCT	43	24	100%	49.1				4.6%		6.3%
Brown et al ⁷⁹	zoledronic acid	PU	66	36	100%	42				4.3%		4.8%

Abbreviations: RCT, prospective, randomized controlled trial; PU, prospective, unrandomized trial; vert, vertebral; NV, nonvertebral; NS, not significant; H, total hip; FN, femoral neck; LS, lumbar spine. All comparisons are statistically significant with $p < 0.05$.

with pamidronate for three years to prevent one vertebral fracture was 5. Six subjects in the placebo group and three pamidronate-treated subjects experienced symptomatic vertebral fractures. Three subjects in the placebo group and one pamidronate-treated subject experienced nonvertebral fractures (ARR 4%). At the end of three years, 53 of the study subjects agreed to participate in an open-label two year extension of the trial. There were equal numbers from the pamidronate and placebo groups, and all subjects received oral pamidronate 150 mg/day. With pamidronate treatment, the differences in urinary hydroxyproline and serum alkaline phosphatase between the initial study groups disappeared. The BMD of the prior placebo group increased to greater extent compared to the prior treatment group such that, at the end of an additional two years there was no significant difference in femoral neck BMD between the groups. The subjects who received pamidronate for five years continued to have a small yet significant greater increase in lumbar spine BMD compared to those subjects who had initially received placebo.

Boutsen and colleagues⁴⁵ studied 27 subjects who required initiation of long-term glucocorticoid therapy at a dose of at least 10 mg/day prednisolone for polymyalgia rheumatica (16), inflammatory bowel disease (4), temporal arteritis (3),

and rheumatoid arthritis (2). The subjects were randomized to receive a single dose IV pamidronate 90 mg at the start of glucocorticoid therapy (group A); IV pamidronate 90 mg once followed by 30 mg IV pamidronate every three months (group B); and control (group C). Both treatment groups experienced significant decreases in bone-specific alkaline phosphatase, osteocalcin, and C-telopeptide at three months. At 12 months, however, all bone markers of the once-treated group had risen again and only group B observed a sustained decrease in bone resorption. At six and 12 months, there was significantly greater BMD at the lumbar spine, femoral neck, and total hip in both treatment groups compared to control (see Table 2). There were no fractures recorded during the 12 month study.

Pamidronate is not approved in the US for the treatment of osteoporosis in men or women.

Alendronate

Alendronate was the first bisphosphonate to be extensively studied in men. In a study by Ho and colleagues,⁴⁶ 80 subjects with either primary or secondary osteoporosis and prior vertebral fracture received alendronate 10 mg daily. The investigators also followed 43 matched controls. Over 12 months follow-up, the investigators found significantly

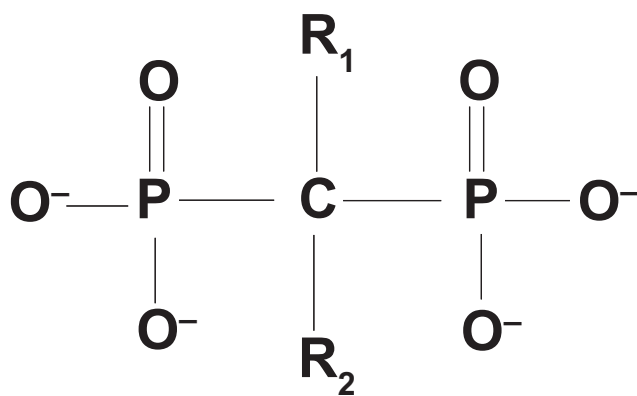


Figure 1 Generic bisphosphonate structure.

improved BMD at the lumbar spine and femoral trochanter but not femoral neck (See Table 2). Results were similar for women and men.

Orwoll and colleagues⁴⁷ randomized 241 men with osteoporosis to 10 mg daily alendronate or placebo. After two years of treatment, the authors observed a significant 59% decrease in urinary N-telopeptide of type I collagen and 38% decrease in bone-specific alkaline phosphatase in the alendronate group. In the alendronate-treated group, bone mineral density at 24 months increased significantly at the lumbar spine, total hip and femoral neck compared to placebo. Quantitative analysis of spine radiographs revealed significantly fewer vertebral fractures in the alendronate group (aldosterone–renin ratio [ARR] 6.3%) but no significant difference in nonvertebral fractures (See Table 2).

Agent	R ₁ side chain	R ₂ side chain
Etidronate	-OH	-CH ₃
Clodronate	-Cl	-Cl
Tiludronate	-H	-S- -Cl
Pamidronate	-OH	-CH ₂ -CH ₂ -NH ₂
Neridronate	-OH	-{CH ₂ } ₅ -NH ₂
Olpadronate	-OH	-{CH ₂ } ₂ N{CH ₃ } ₂
Alendronate	-OH	-{CH ₂ } ₃ -NH ₂
Ibandronate	-OH	-{CH ₂ -CH ₂ N -{CH ₂ } ₄ -CH ₃
Risedronate	-OH	
Zoledronate	-OH	

Figure 2 Comparison of structures of different bisphosphonates.

These findings were confirmed by Ringe and colleagues⁴⁸ in an open label study of 134 men with osteoporosis randomized to 10 mg daily alendronate or the vitamin D analog alfacalcidol 1 µg daily. With three years follow-up, they observed significantly greater increases in BMD at the lumbar spine and femoral neck in the alendronate-treated group. The alendronate group had significantly fewer vertebral fractures (ARR 13.9%, *p* = 0.04) and no difference in nonvertebral fractures (See Table 2).

A meta-analysis of the alendronate trials including 375 men⁴⁹ concluded that alendronate treatment significantly decreases the risk of vertebral fractures (odds ratio [OR] 0.36) in men with osteoporosis. There were not sufficient data to confirm a significant decrease in nonvertebral fractures.

Alendronate is approved in the US for the treatment of osteoporosis in men.

Risedronate

Ringe and colleagues⁵⁰ studied risedronate in 316 men with primary or secondary osteoporosis. Over half of those enrolled had a vertebral fracture prior to the start of the study. Subjects were randomized to risedronate 5 mg daily or control, and all received calcium and vitamin D supplementation. At 12 months, there was a significantly greater improvement in BMD at the lumbar spine, total hip, and femoral neck. At one year, the treated subjects experienced fewer vertebral fractures (ARR 7.6%, *p* = 0.028), a nonsignificant 42% decrease in nonvertebral fractures, and significantly less back pain than the control group (See Table 2).

Boonen and colleagues⁵¹ randomized 284 men with osteoporosis but without prior fracture to weekly risedronate 35 mg or placebo in 2:1 ratio. The risedronate-treated group had significant reductions in the bone turnover markers c-telopeptide, n-telopeptide, and bone-specific alkaline phosphatase at three months, and these effects persisted throughout the two-year study period. The treatment group also experienced significantly greater increases in BMD at the lumbar spine by three months and at the total hip and femoral neck by six months (see Table 2). These treatment differences increased throughout the study. The authors noted a nonsignificant trend toward overall fracture reduction, though the study was not powered to detect a difference.

Reid and colleagues⁵² studied 184 men enrolled in two RCT receiving daily risedronate 2.5 mg, risedronate 5 mg, or placebo for the prevention or treatment of glucocorticoid-induced osteoporosis (GIO). Prior to enrollment, the subjects had received either <3 months (prevention study) or >6 months (treatment study) chronic

oral glucocorticoid therapy of at least 7.5 mg/day prednisone or equivalent, most commonly for rheumatoid arthritis, lung disease, and polymyalgia rheumatica. At one year, the subjects treated with risedronate 5 mg/day experienced 61% decrease in urinary n-telopeptide and 20% reduction in bone-specific alkaline phosphatase. The GIO treatment study group treated with risedronate 5 mg experienced significant increases in BMD at the lumbar spine and femoral neck compared to baseline. In the GIO prevention study, risedronate 5 mg/day prevented the significant loss in BMD at the hip and lumbar spine seen in the placebo group. The authors reported that risedronate 2.5 mg/day produced similar yet smaller effects on BMD. When both risedronate treatment arms from both studies were combined, the authors found a 19% ARR in morphometric vertebral fractures at one year. However, fracture data were reported for only 96 of the 184 enrolled subjects.

Prior stroke is a risk factor for fracture, through immobility decreasing bone mineral density and by gait instability increasing risk for falls. Sato and colleagues⁵³ studied 280 men 65 years or older after hemiplegic stroke. The subjects were randomized to risedronate 2.5 mg daily or placebo and followed for 18 months. Urinary deoxyypyridinoline concentration decreased significantly compared to baseline and compared to placebo within the first six months of risedronate treatment and remained stable thereafter. The authors assessed BMD at the second metacarpal bones on both hemiplegic and unaffected sides. On the hemiplegic side, metacarpal BMD increased 2.5% in the risedronate-treated and decreased 3.5% in the untreated group. On the unaffected side, metacarpal BMD increased 3.3% in the treated and decreased 2.0% in the unaffected side. Differences between groups were highly significant ($p < 0.001$). During the study period, 87 men fell a total of 547 times. The risedronate group experienced fewer hip fractures (ARR 5.7%) and overall fractures (ARR 8.6%) though asymptomatic vertebral fractures were not assessed, and no vertebral fractures were reported (See Table 2). The NNT to prevent hip fracture was 16.

Hypogonadism affects approximately 50% men with leprosy due to gonadal atrophy from testicular *Mycobacterium leprae* infection.⁵⁴ As a result, osteoporosis is very common in men with leprosy. Among 197 men with leprosy residing at a national leprosarium, Ishikawa and colleagues⁵⁵ found the prevalence of osteoporosis to be 33% in men 50–59 aged years and 75% in men aged at least 80 years. Kanaji and colleagues⁵⁶ followed 23 elderly men with leprosy randomized to 2.5 mg daily oral risedronate or placebo and found

a significant reduction in urinary N-telopeptides and a significant increase in lumbar spine BMD at six and 12 months (See Table 2). Though there was a low incidence of vertebral fractures observed, the treatment group experienced fewer (ARR 1.06%).

Risedronate is approved in the US for the treatment of osteoporosis in men.

Limitations of oral therapy

Because of their relative ease of use and low cost of generic alendronate, oral bisphosphonates have become mainstays of osteoporosis pharmacotherapy. Yet oral dosing is poorly absorbed, may worsen gastrointestinal toxicities, and side effects can decrease patient compliance. Esophageal injury may occur in patients on oral bisphosphonates, though randomized trials have failed to show significant association. Even in patients who strictly adhere to recommended use directions, case reports have shown oral alendronate has the potential to cause erosive esophagitis, esophageal or gastric ulcers and esophageal strictures.⁵⁷ Recent reports of oral bisphosphonate-associated esophageal carcinoma have emerged.⁵⁸ A meta-analysis of 76 randomized controlled trials of osteoporosis drug trials found that esophageal ulcerations and complications such as perforation and hemorrhage were reported in trials of all bisphosphonates except zoledronic acid.⁵⁹ Other gastrointestinal symptoms related to oral bisphosphonates include pyrosis, dyspepsia, abdominal pain, nausea, and vomiting.

Long-term compliance with oral bisphosphonate therapy is low, and patients most commonly cite adverse drug effects as the reason for stopping therapy.^{60,61} One systematic review of seven observational studies of bisphosphonate compliance as measured by patient surveys indicates that the discontinuation rate at one year of daily dosing ranged 19%–29%. In the study that included men, the rate was 22%. However, when compliance is measured by administrative data, the discontinuation rate was 68% for daily dosing and 56% for weekly dosing. Moreover, 76% patients had at least some interruption in bisphosphonate therapy during the first year of therapy.⁶¹ The costs of bisphosphonate noncompliance are high. Patients who are less than 66% compliant with osteoporosis medications have significantly lower increases in BMD.⁶² In an analysis of insurance claims databases involving 35,537 women prescribed bisphosphonates, only 43% women filled at least 80% of their prescriptions. However, the medication-compliant women had 37% fewer hip fractures at 24 months.⁶³

Oral bisphosphonates are poorly absorbed, and dietary calcium, calcium supplements, and antacids further impede absorption. In order to optimize bioavailability, the patient should take the medication apart from food and all other medications for at least two hours before and 30 minutes after the dose. In order to minimize gastrointestinal side effects, the patient should take the medication with 6–8 ounces of water and remain upright for 30 minutes thereafter. In a review of three observational trials of adherence to dosing instructions, up to 52% patients did not comply with at least one instruction.⁶¹ In one of the studies, 26% patients were not taking risedronate correctly and among these patients 28% experienced adverse effects.⁶⁴

Factors associated with poorer bisphosphonate compliance include older age, male gender, nonwhite race, and greater number of comorbid conditions and nonosteoporosis medications. Compliance is improved with weekly vs daily dosing, and residence in a nursing home.^{61,65} Though not reported in these trials, compliance with the complex administration instructions is very likely also limited by cognitive dysfunction and physical debility.

Ibandronate

In an uncontrolled open label pilot, Lamy and colleagues⁶⁶ enrolled 14 men with primary osteoporosis and either a prior osteoporotic fracture or a BMD at least 1.5 standard deviations below the age-matched mean. Subjects received 2 mg IV ibandronate every three months. At two years, the authors noted significant reductions in osteocalcin and β -crosslaps assay for degradation products of type I collagen. During the two years of treatment, they showed significant increases in BMD at the lumbar spine, femoral neck, and total hip (See Table 2).

Another as yet unpublished trial of 168 men randomized to monthly oral ibandronate 150 mg or placebo has the primary outcome of change in lumbar spine BMD. One year follow-up has been completed, and data will soon be presented (personal communication).

Ringe and colleagues⁶⁷ studied 115 subjects with established glucocorticoid induced osteoporosis. The subjects required chronic prednisone use of at least 7.5 mg/day for other systemic illnesses, most commonly COPD, rheumatoid arthritis, or polymyalgia rheumatica. Subjects were randomized to 2 mg intravenous (IV) ibandronate every three months vs. daily oral alfacalcidol. Ibandronate-treated subjects experienced significantly greater increases in BMD at the spine and femoral neck, and improvements were progressive throughout the 36-month study period.

The ibandronate group had less lower back pain and less height loss. Though not powered to detect fracture difference, the study did show significantly fewer vertebral fractures in the ibandronate group (relative risk reduction [RRR] 62%) and a nonsignificant trend toward fewer nonvertebral fractures (See Table 2).

Ibandronate is not approved in the US for the treatment of osteoporosis in men.

Zoledronic acid

Currently available IV nitrogen-containing bisphosphonates include pamidronate, ibandronate, and zoledronic acid. Zoledronic acid is the only IV bisphosphonate FDA-approved for the treatment of osteoporosis in men. It has the highest binding affinity to hydroxyapatite and the highest skeletal uptake⁶⁸ and is the most potent osteoclast inhibitor. Zoledronic acid is the only bisphosphonate with an indication for annual use.

Evidence of benefit

The HORIZON investigators studied zoledronic acid in secondary prevention of osteoporotic fractures.⁶⁹ They randomized 2127 subjects (24% men) within 90 days of surgical repair of a hip fracture to receive 5 mg annual IV zoledronic acid or placebo with first dose given within 90 days of hip fracture repair. At 36 months, the treated group had significantly increased bone density at the total hip and femoral neck compared to the placebo group. Over 1.9 years median follow-up, they observed significant decreases in any new fracture (139 vs 92, ARR 5.3%), clinical vertebral fracture (39 vs 21, ARR 2.1%), nonvertebral fracture (107 vs 79, ARR 3.1%), and recurrent hip fracture (33 vs 23, ARR 1.5%; see Table 2). Further, in this population at high risk for deadly recurrent fractures, the zoledronic acid-treated group experienced a survival advantage (RRR 28%, ARR 3.7%).⁶⁹ Men enjoyed a greater survival benefit than women (overall mortality ARR 6.4%) and a marked reduction in cardiac-related deaths (RRR 62%, RRR 4.8%).⁷⁰

Zoledronic acid has been approved in the US for treatment of osteoporosis in men on the basis of an as yet unpublished trial.⁷¹ The study randomized 302 hypogonadal men to annual 5 mg IV zoledronic acid or weekly 70 mg oral alendronate. At two years, the zoledronic acid group had 6.1% increase in lumbar spine BMD compared to 6.2% increase in alendronate group. The all-cause mortality and serious adverse events were similar between treatment groups.

Poole and colleagues⁷² randomized 27 hemiplegic subjects within seven weeks after stroke zoledronic acid 4 mg

or placebo. The authors showed that treatment prevented significant bone loss at the hip. Without treatment, at one year the mean BMD of the total hip decreased 5.5% on the affected (hemiplegic) side and by 2.7% in the unaffected hip. With treatment, the mean BMD remained stable on the hemiplegic side and increased by 1% at the unaffected hip (see Table 2). 72% subjects fell, but there were no fractures during the study period.

Human immunodeficiency virus (HIV) infection and antiretroviral therapy are associated with low bone density and osteoporosis. Brown and colleagues⁷³ found that HIV-infected patients were 3.7 times as likely to have osteoporosis as uninfected individuals. Triant and colleagues⁷⁴ reported that HIV-infected men and women have a significantly higher prevalence of hip, vertebral, and wrist fractures. Bolland and colleagues⁷⁵ studied zoledronic acid in 43 HIV+ men with decreased bone mineral density receiving antiretroviral therapy. The men were randomized to 4 mg IV annual zoledronic acid or placebo. Urinary N-telopeptide decreased by 61%, and serum total alkaline phosphatase decreased by 21% from baseline by three months in the zoledronic acid-treated group. These values were significantly less than the untreated group, and the levels did not further decrease over the remaining two years in the study. In the zoledronic acid group, BMD increased significantly at the lumbar spine and total hip over the control group (see Table 2).

Studies confirm both clinical efficacy^{69,72,75} of annual zoledronic acid dosing and noninferiority compared to more frequent dosing,⁷⁶ but it is not yet known how long a single dose of zoledronic acid can suppress bone turnover. Borba and colleagues⁷⁷ showed persistent suppression of C-telopeptide and bone-specific alkaline phosphatase and persistent increase in bone mineral density at the lumbar spine and total hip at 18 months after a single dose of zoledronic acid. In an extension of a previous trial, Bolland and colleagues⁷⁸ showed persistence of drug effect in men at two years after a second annual dose of zoledronic acid in suppressing markers of bone turnover and increasing bone mineral density. Brown and colleagues⁷⁹ studied 66 subjects with osteopenia after curative cancer treatment. All subjects received a single dose 4 mg zoledronic acid and were followed for 36 months. Data were reported for men and women separately, and both showed durable decreases in urinary NTx/Cr and increases in BMD at the spine and hip after at 36 months after a single zoledronic acid dose. Less frequent dosing regimens offer potential advantages such as reduced toxicity, greater convenience, improved compliance, and reduced cost. Though markers of bone turnover remain

suppressed for more than one year, it is not known whether dosing zoledronic acid less than annually is as effective in terms of reduction in fracture risk.

Comparing therapies for osteoporosis

Few studies have made direct comparison of osteoporosis therapies in men. In theory, drugs such as teriparatide that stimulate bone formation may complement bisphosphonates (which inhibit osteoclast action) and provide even greater increases in BMD. Finkelstein and colleagues^{34,80} randomized 83 men with low bone mass to receive alendronate, teriparatide, or both daily. Subjects receiving alendronate started treatment at the beginning of the study, and subjects receiving teriparatide started at month 6. Sixty-three men completed the study. At 30 months, the authors found that teriparatide increased BMD at the lumbar spine and femoral neck significantly more than combination therapy, and combination therapy increased BMD at the lumbar spine and femoral neck significantly more than alendronate alone.³⁴ The authors went on to show that marker of bone turnover such as serum N-telopeptide (NTX), osteocalcin, and amino-terminal propeptide of type 1 procollagen increased markedly upon starting teriparatide monotherapy and then declined toward baseline. With alendronate monotherapy, the markers of bone turnover decreased and remained stable. Combination therapy led to an initial decline in bone markers on alendronate alone followed by a rebound with teriparatide so that levels returned to baseline or above. Alendronate pre-treatment blunted the treatment effect of teriparatide,⁸⁰ and the authors conclude that alendronate impairs the ability of teriparatide to increase bone turnover or increase the BMD at the lumbar spine and the femoral neck in men.

Welch and colleagues⁸¹ retrospectively studied 149 men treated with testosterone, alendronate, or both for at least one year. Men in the testosterone group were referred for treatment of hypogonadism, and men in the alendronate group were referred for treatment of osteoporosis. Yet at baseline, the groups were similar in terms of age, weight, body mass index, and BMD at the lumbar spine and total hip. Compared with the baseline values, lumbar spine BMD increased significantly by 2.1% in the testosterone group, 2.6% in the alendronate group, and 2.5% in the group receiving combination therapy. There were no significant differences in BMD at the lumbar spine or total hip between groups, suggesting that the combination of testosterone and alendronate does not appear to be superior to either drug used alone.

A recently conducted, unpublished trial at our institution directly compares alendronate and zoledronic acid in

the treatment of male osteoporosis. The investigators retrospectively reviewed the charts of 64 men: 26 received annual IV zoledronic acid 4 mg and 38 received weekly oral alendronate 70 mg. At one year, they found no differences in BMD at the lumbar spine or femoral neck between groups (personal communication).

Bisphosphonate use in bone loss due to androgen deprivation

Prostate cancer becomes increasingly common as men age, and androgen deprivation therapy (ADT) for prostate cancer places men at uniquely high risk for osteoporosis and fracture. ADT, which may include orchiectomy or GnRH agonist therapy, markedly reduces circulating testosterone to prepubertal levels. In one prospective cohort study of 152 men with nonmetastatic prostate cancer including 30 on acute ADT < 6 months and 50 on chronic ADT > 6 months, Greenspan and colleagues⁸² found that men starting ADT experienced significant reductions in bone mineral density (2.5% total hip, 4.0% spine) by 12 months follow-up. When compared to healthy age-matched controls and to patients with prostate cancer but not on ADT, the acute ADT had five- to tenfold increased bone density loss at multiple skeletal sites. When compared to men on chronic ADT, it appeared that the greatest bone loss occurred in the first 12 months of ADT. Shanahan and colleagues⁸³ measured fracture rates on 50,613 men with the diagnosis of prostate cancer. Among the men that survived five years after diagnosis, they found that 19.4% men on ADT experienced a fracture, as compared to 12.6% those not receiving ADT ($p < 0.001$). Furthermore, fractures at every site, fractures requiring hospitalization, and diagnosis of osteoporosis were all significantly increased in patients receiving ADT.

Smith and colleagues⁸⁴ studied 47 men with advanced or recurrent nonmetastatic prostate cancer. The authors randomized the subjects to receive pamidronate 60 mg

IV every 12 weeks plus leuprolide or leuprolide alone. All measured biomarkers of bone turnover; osteocalcin, bone-specific alkaline phosphatase, urinary deoxypyridinoline, and urinary N-telopeptide were significantly reduced in the pamidronate group. Treatment with pamidronate prevented the significant reductions in BMD experienced by the leuprolide-only group. They reported an absolute difference between groups in BMD at the lumbar spine and total hip, but there was no change in either group at the femoral neck (see Table 3).

Greenspan and colleagues⁸⁵ studied 112 men with non-metastatic prostate cancer receiving ADT in a partial-cross-over design. Subjects were randomly assigned to receive alendronate 70 mg weekly or placebo at enrollment. At 12 months, all subjects in the placebo group crossed over to the alendronate group, and subjects in the alendronate group were re-randomized to continue alendronate or placebo. At two years, the subjects randomized to alendronate treatment both times had the greatest decrease in N-telopeptide, C-telopeptide, type 1 procollagen, and bone-specific alkaline phosphatase. The alendronate-alendronate group also had the highest BMD at the lumbar spine, total hip, femoral neck, and distal 1/3 radius. Fractures were not studied. The investigators found that a second year of alendronate resulted in continued improvements in bone density and decreases in bone markers.

Delay in alendronate initiation (as in the placebo-alendronate group) resulted in lower bone density and decreased suppression of bone markers compared to early treatment.⁸⁵ Discontinuation of alendronate (in the alendronate-placebo group) resulted in increases in markers of bone turnover and significantly decreased BMD at all skeletal sites compared to the alendronate-alendronate arm. The authors also performed post-hoc analysis of changes in BMD depending on length of ADT prior to alendronate treatment. They found that men who received ADT for less than 36 months experienced significantly greater increases

Table 3 Trials in prostate cancer with ADT

Citation	Drug	Study design	N	Duration (mo)	Avg age	Δ% increase BMD		
						H	FN	LS
Smith et al ⁸⁴	pamidronate	RCT	47	48 wk	67	2.0%	NS	3.8%
Greenspan et al ⁸⁵	alendronate	RCT	112	12	71.4			
Ryan et al ⁸⁶	zoledronic acid	RCT	120	12	72	3.8%	3.6%	6.7%
Smith et al ⁸⁷	zoledronic acid	RCT	106	12	70.7	3.9%	3.3%	7.8%
Michaelson et al ⁸⁸	zoledronic acid	RCT	40	12	65.5	2.6%	2.1%	7.1%
Ryan et al ⁸⁹	zoledronic acid	RCT	42	12	65		4.2%	7.1%

Table 4 Incidence of side effects in zoledronic acid trials reporting safety analyses

	HORIZON-RFT ⁶⁹			Poole et al ⁷²			Bolland et al ⁷⁵			Brown et al ⁷⁹			Ryan et al ⁸⁶			Smith et al ⁸⁷			Michaelson et al ⁸⁸			Ryan et al ⁸⁹			Composite													
	ZA	P	n	ZA	P	n	ZA	P	n	ZA	P	n	ZA	P	n	ZA	P	n	ZA	P	n	ZA	P	n	ZA	P	n											
Any ADE	82%		1054	81%		1057		15		16		21		22		66		61		59		55		22		22		22		20		1316		1247				
any serious ADE	38%	41%									0%																											
death	10%	13%				7%		0%		0%		5%		0%		0%		0%		0%		2%		0%		0%		0%		14%		8%		11%				
stop study due to ADE	2%	2%				0%		6%		6%		10%		0%		0%		0%		0%		4%		0%		0%		0%		0%		0%		2%		2%		
ARF	6%	6%				7%								0%																								
CrCl <30 mL/min	7%	8%																																				
myalgias	3%	1%																5%		7%																		
flu-like symptoms	1%	0%														64%																						
headache	2%	1%																																				
arthralgia	3%	2%																13%		10%		22%		14%														
fever	7%	1%				20%				6%								11%		3%																		
atrial fibrillation	3%	3%																																				
CVA	4%	4%																																				
MI	1%	2%																																				
CV death	3%	5%																																				
bone, joint, or muscle pains	6%	3%																34%		27%		45%		27%		45%		27%		45%		30%						

Abbreviations: ZA, zoledronic acid; p, placebo; ADE, adverse drug effect; ARF, acute renal failure; CrCl, creatinine clearance; CVA, cerebrovascular accident; MI, myocardial infarction; CV, cardiovascular.

in BMD on alendronate than men who received ADT for 36 months or more.

Ryan and colleagues⁸⁶ studied 120 men with nonmetastatic prostate cancer on ADT for 12 months or less prior to enrollment. Subjects were randomized to zoledronic acid 4 mg IV every three months or placebo and stratified by duration of ADT (less than six months or 6–12 months). Treated subjects had significant reductions in urinary N-telopeptide and serum bone-specific alkaline phosphatase compared to the placebo group and significant improvements in BMD at one year at the femoral neck, total hip, and lumbar spine (see Table 3). The results were not differentiated based on duration of ADT. Taken together, these studies^{85,86} support initiation of bisphosphonates within one year of ADT and continued treatment for greater than one year in men on ADT.

Smith and colleagues⁸⁷ studied zoledronic acid in 106 men with nonmetastatic prostate cancer beginning ADT. Subjects were randomized to zoledronic acid 4 mg IV every three months or placebo. At one year, the placebo group lost 2%–3% BMD at the lumbar spine, femoral neck, and total hip. By comparison, treated group had gains in BMD and showed significantly greater BMD at each skeletal site (see Table 3).

Michaelson and colleagues⁸⁸ randomized 40 men with nonmetastatic prostate cancer on ADT and osteoporosis ($T < -2.5$), to receive a single dose 4 mg IV zoledronic acid or placebo. Subjects who received zoledronic acid had significant reductions in N-telopeptide and bone-specific alkaline phosphatase at 12 months as well as significantly greater BMD at the lumbar spine, total hip and femoral neck (see Table 3).

Ryan and colleagues⁸⁹ studied 42 men with hormone-sensitive prostate cancer with and without metastasis on ADT less than one year. The subjects were randomized to zoledronic acid 4 mg IV every three months or placebo. Skeletal sites with metastasis were excluded from DEXA measurement of BMD. At 12 months, subjects treated with zoledronic acid had significantly greater decreases in N-telopeptide and bone-specific alkaline phosphatase. Men with bone metastases had significantly higher baseline N-telopeptide and bone-specific alkaline phosphatase, but the improvements in suppression of these markers of bone turnover was independent of the presence of metastases. Treated subjects also had significantly greater BMD at the lumbar spine and femoral neck (see Table 3).

Raloxifene in ADT

Estrogen deficiency plays a significant role in bone loss in men. Doran and colleagues⁹⁰ randomized 50 elderly

men without osteoporosis to receive the selective estrogen receptor modulator (SERM) raloxifene 60 mg per day or placebo. At six months, the treated group overall showed no effect in decreasing urinary N-telopeptide (NTx) excretion. However, in the subset of men with baseline low estradiol levels (mean 22 pg/mL), raloxifene treatment decreased urinary NTx. Smith and colleagues⁹¹ found a similar treatment effect in 48 men with nonmetastatic prostate cancer on GnRH agonist therapy treated with raloxifene 60 mg daily. The average estradiol level was 5 pg/mL. At 12 months, the raloxifene-treated group had significantly decreased serum amino-terminal propeptide of type I collagen and significantly increased BMD in the total hip (+1.1% vs -2.6%, $p < 0.001$) and a nonsignificant trend to increased density in the lumbar spine (+1.0% vs -1.0%, $p = 0.07$).

Raloxifene is not approved in the US for the treatment of osteoporosis in men.

Indications

Zoledronic acid (Reclast) is approved in the US as an annual IV infusion of 5 mg to treat osteoporosis in men or women and to treat Paget's disease. Zoledronic acid is also marketed as a 4 mg dose (Zometa[®]) IV infusion every 3–4 weeks to treat hypercalcemia of malignancy, multiple myeloma, and bone metastases from all solid tumors including lung and prostate cancer.

Zoledronic acid is the only IV bisphosphonate approved in the US for the treatment of osteoporosis in men.

Adverse drug effects

Eight trials of zoledronic acid including men for nonmetastatic bone loss have been published,^{69,72,75,79,86–89} and all eight reported basic safety data such as number of subjects who died or withdrew because of adverse events. Six of these studies^{69,72,75,86,87,89} reported more extensive safety analyses. In the largest of these trials,⁶⁹ there was no association between zoledronic acid and early study withdrawal due to adverse event.

Prior studies⁹² have identified five typical infusion-related symptoms that occur in more than 30% subjects receiving a first dose zoledronic acid within three days of drug administration. These symptoms include myalgias, influenza-like symptoms, fever, arthralgias, and headache. The reported rates of these symptoms in the eight trials described are generally lower than in prior studies, though myalgias and fever were significantly more common in the zoledronic acid-treated subjects.⁶⁹ These symptoms are typically mild, resolve within 3–4 days, and occur less frequently with

successive infusions of the drug. Patients should be pretreated with acetaminophen.

Many symptoms were variably described among the studies. The frequency of a composite of reports of bone or back pain, myalgias, and arthralgias was 9% among zoledronic acid-treated subjects vs 5% among those receiving placebo. Currently the US FDA is investigating reports of “severe and sometimes incapacitating bone, joint, and/or muscle pains” in chronic use of bisphosphonates as a class.⁹³

Infusing zoledronic acid over at least 15 minutes reduces the risk of renal toxicity. In each of the studies cited, zoledronic acid was given over 15 minutes, and there was no significant difference in rates of rise of serum creatinine >0.5 mg/dL.^{69,72} Zoledronic acid 5 mg dose (Reclast[®]) is not recommended for patients with creatinine clearance <35 mL/min due to lack of experience in this patient population. Zoledronic acid 4 mg (Zometa[®]) is recommended at full dose for patients with estimated creatinine clearance >60 mL/min with dose reductions for creatinine clearances between 30–60 mL/min. Because of the lack of clinical data to date, it is not recommended for use in patients with creatinine clearance <30 mL/min. Asymptomatic and generally transient hypocalcemia and hypophosphatemia have been reported independent of baseline 25-OH vitamin D levels.⁷²

Osteonecrosis of the jaw (ONJ) is a serious complication of bisphosphonate use defined as an area of exposed bone in the maxillofacial region that does not heal within eight weeks after identification by a health care provider.⁹⁴ It appears that potency of the bisphosphonate and duration of exposure to the drug increase the risk of ONJ. Patient factors which increase the risk of ONJ include cancer diagnosis, chemotherapy, glucocorticoid use, tobacco use, and pre-existing dental and periodontal disease. Although the true incidence of ONJ is unknown, recent expert consensus⁹⁴ estimates 1/10,000 to less than 1/100,000 patient-years in patients receiving oral bisphosphonate treatment for osteoporosis.

In the above eight zoledronic acid trials including 2563 subjects studied over 6960 patient-years, not a single case of ONJ was reported. However, these numbers must be interpreted with caution in that cumulative exposure and duration of follow-up (average 1–2 years) may not be enough to detect ONJ. The incidence of ONJ in patients receiving IV zoledronic acid for treatment of malignancy is much higher, as high as 1%–10%.⁹⁴ Boonyapakorn and colleagues⁹⁵ prospectively studied 80 patients receiving monthly IV zoledronic acid or pamidronate for cancer diagnosis, most commonly multiple myeloma and breast cancer. Using dental radiographs and intraoral examinations, they

found that 22 (28%) patients developed ONJ after bisphosphonate exposure. The mean time from exposure to ONJ in the zoledronic acid-treated patients was 26 months. Initiation of bisphosphonate therapy need not be delayed for routine dental work, but patients should be counseled on the importance of dental hygiene and recommended to have regular dental visits for routine care.

Black and colleagues⁹² reported an increased incidence of serious atrial fibrillation in women treated with zoledronic acid infusion, and Heckbert and colleagues⁹⁶ found greater likelihood of prior alendronate use among 719 women with confirmed new onset atrial fibrillation. In contrast, Lyles and colleagues⁶⁹ found no association between zoledronic acid and atrial fibrillation, stroke, myocardial infarction, or death from cardiovascular causes. Sørensen and colleagues⁹⁷ retrospectively studied 13,586 Danish women with atrial fibrillation and atrial flutter and found that alendronate and etidronate use was not more common among affected patients than population controls (adjusted relative risk among women with current bisphosphonate use 0.95). US FDA review of 19,687 bisphosphonate-treated patients found no association with atrial fibrillation.⁹⁸ Whether bisphosphonate use predisposes a patient to atrial fibrillation remains an open question. However, this small potential risk must be considered in relation to potentially large benefits in terms of fracture reduction and survival.

Summary

Osteoporosis and low bone mass are under-recognized and undertreated in men. As the population ages, the rates of osteoporosis and osteoporotic fractures are expected to rise. Men with prior fragility fractures, older men, and men with lower BMD are at highest risk of fracture. Men with glucocorticoid use, hypogonadism, tobacco or heavy alcohol intake, vitamin D deficiency, or androgen deprivation therapy for prostate cancer are also at increased risk for osteoporosis. Laboratory evaluation for secondary causes of osteoporosis and radiographic screening for occult vertebral fractures in men with height loss are essential parts of the workup of men with osteoporosis. All men should receive adequate dietary calcium and vitamin D. Bisphosphonates are potent antiresorptive agents that inhibit osteoclast activity, suppress *in vivo* markers of bone turnover, and decrease fracture risk in patients at high risk of fracture. Intravenous zoledronic acid may be a preferable alternative to oral bisphosphonate therapy in patients with cognitive dysfunction, the inability to sit upright, or significant gastrointestinal pathology.

Disclosure

The authors report no conflicts of interest in this work.

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