Management Strategies for Osteoporosis in the Aging Male: Focus on Zoledronic Acid

Luigi Gennari, Daniela Merlotti and Ranuccio Nuti

Department of Internal Medicine, Endocrine-Metabolic Sciences and Biochemistry, University of Siena, Italy.
Corresponding author email: gennari@unisi.it

Abstract: Osteoporosis in men is an increasingly important clinical issue, that actually remains under-recognized and undertreated. Moreover there is no validated strategy for a systematic osteoporosis screening in men and decisions regarding treatment should be based on the absolute risk of fracture. Among the different treatment options, bisphosphonate therapy is becoming a mainstay in the treatment of male osteoporosis, even though evidence for the long-term efficacy and safety of therapies for osteoporosis in men remains limited. In this review, we report the current evidence on the use of zoledronic acid, a potent aminobisphosphonate that can be administered intravenously, for the prevention and treatment of osteoporosis in men.

Keywords: zoledronic acid, bisphosphonate, fractures, male osteoporosis, treatment of osteoporosis
Introduction
Osteoporosis is a skeletal disorder characterized by compromised bone strength and increased risk of fracture.1,2 It is one of the most common disorders in elderly subjects, estimated to be present in over 200 million individuals, with 75 million of these in Europe, Japan and the US.2–4

Over the past decade, most studies have focused on the pathogenesis, diagnosis, and treatment of osteoporosis in women. Nevertheless, recent epidemiological and observational studies have shown that osteoporosis in men is an increasing clinical issue. Importantly, partly because the world population is aging, it is estimated that the total number of hip fractures in men in 2025 will be similar to current estimates in women.5,6 To highlight this point, the 2004 Invest in Your Bones Campaign of the International Osteoporosis Foundation was fully dedicated to the problem of osteoporosis in men.

Osteoporosis occurs as the result of multiple mechanisms that together cause loss of bone mass and strength.7 Indeed, bone is a highly metabolically active tissue in which the processes of bone formation and bone resorption are continuous throughout life. The remodeling of the skeleton by coupling of osteoblast (the bone forming cell) and osteoclast (the bone resorbing cell) action ensures that a normal skeletal structure is maintained.8,9 In order to prevent the occurrence of damage bone remodeling adapts bone structure, and hence bone strength, to its loading circumstances.8 This action is mediated in most part by the osteocytes, cells that through cytoplasmic processes form a communicating network able to identify sites for remodeling when the prevailing physical loads are sensed.9 In this way, osteocytes might help to direct bone remodeling.

Failure to acquire optimal bone mass and strength during growth and or an unbalance in bone remodeling leading to bone loss throughout life may all contribute to the development of the disease. One of the major and easily measurable determinant bone strength and osteoporotic fracture risk is bone mineral density (BMD), as assessed by dual energy x-ray absorptiometry (DXA). According to W.H.O. criteria, osteoporosis is defined to exist when BMD values fall more than 2.5 standard deviations below the young adult reference mean.1 Many studies indicated that the risk of fragility fractures increases progressively as BMD declines.10,11 However, several other skeletal and extraskeletal characteristics contribute to bone strength and interact with BMD in determining the risk of fracture. These include bone macroarchitecture (shape and geometry), bone microarchitecture (at the trabecular and cortical level), matrix and mineral composition, as well as the rate of bone turnover and the degree of mineralization or microdamage accumulation, affecting the structural and material properties of bone.2,8,9

The recognition and measurement of these parameters is becoming more important, and their incorporation into algorithms of fracture detection remains the subject of active research. Moreover, age per se, weight, a positive family history, and a previous fracture are all major risk factors for osteoporosis in men as well as in women12,13 and the use of these factors along with BMD is considered to improve fracture prediction as compared with the use of BMD alone.

Epidemiology and Causes of Osteoporosis in Men
The lifetime risk of any clinical osteoporotic fracture of the hip, vertebrae or wrist in white men is 13% compared to 40% in women.4 Overall, about 30% of hip fractures, the most devastating consequences of osteoporosis, occur in men, and the number is expected to increase as the elderly population also expands. It has been estimated that the lifetime risk of a man suffering an osteoporotic fracture is actually greater than his likelihood of developing prostate cancer.14 Moreover, mortality rates following osteoporotic fractures are higher in men than in women, reaching 37.5% within a year after a hip fracture.13,15

The causes of bone loss in men may be different. Unlike women, men do not have a midlife fall in sex steroid hormone production due to menopause, leading to increase in bone remodeling rate, accelerated bone loss and higher fracture risk. Therefore, in the middle aged man bone loss proceeds very slowly, unless a disorder such as hypogonadism or other conditions (i.e. a therapeutic castration for prostate cancer) occurs.16 Moreover, bone loss in men during this period is characterized by trabecular thinning, due to reduced bone formation, rather than increased resorption, a characteristic of the postmenopausal woman.9,16,17 Loss of bone by trabecular thinning produces less loss of strength in the vertebral body than an equivalent loss of bone by trabecular...
perforation.9 Another important point that provides relative protection is the fact that men achieve larger body size than women by periosteal apposition, a mechanism that become operative at puberty and continues throughout life.9,18

As in females, osteoporosis in males could be due to specific, secondary etiologies requiring careful clinical evaluation. The three major causes of secondary osteoporosis in men (accounting for 40%–50% of all men with osteoporosis) are alcohol abuse, glucocorticoid excess (either endogenous Cushing’s syndrome or, more commonly, chronic glucocorticoid therapy), and hypogonadism.13,16,17,19 Other causes are also important to rule out, such as primary hyperparathyroidism, excessive thyroid hormone exposure (either hyperthyroidism or overtreatment with thyroid hormone), gastrointestinal disorders, chronic obstructive pulmonary disease, neuromuscular disorders, multiple myeloma or other malignancies, and use of other drugs (anticonvulsants, high-dose chemotherapeutics, selective serotonin reuptake inhibitors).13,16,17,20 Certainly, as in women, other factors, such as tobacco use, physical inactivity, leaness, low calcium intake, and reduced grip strength may contribute to accelerate bone remodeling also in men, therefore modifying the age-related pattern of bone loss or superimposing to the underlying secondary cause. Race and ethnicity are also strong predictors of osteoporosis, being low bone mass and fractures more prevalent in Caucasian and Asian men than in African or African-American men.16,17 Asian men generally have lower BMD than Caucasian men, but this difference is almost entirely explained by body weight. The remaining 50%–60% of cases without a recognized secondary cause includes senile and idiopathic osteoporosis. Most of the men in the latter category are less than 65–70 years of age. Of course, there are men over 70 whose cause is not known. The older the patient, however, the more we are likely to relate the osteoporosis to age and not to a specific or unknown cause. Clearly, the younger the patient the more likely it is that other explanations are needed to account for the syndrome. Importantly, most of the men with idiopathic osteoporosis present a rather typical clinical and histomorphometric phenotype that differs from age-related osteoporosis. In fact, they often show normal or slightly increased bone resorption but decreased bone formation,16,17 probably due to osteoblast dysfunction, as recently suggested by histomorphometry and in vitro studies.21–23 However the category is clearly a heterogeneous one with many different clinical phenotypes having been described. For example, osteoporotic men have been described with hypercalciuria with or without accelerated bone resorption.16 The mechanisms of bone loss in these men with hypercalciuria are still not clear, but is likely to differ from the idiopathic osteoporosis variant associated with osteoblast dysfunction, where alterations in IGF-1 and sex hormone levels have been often observed.16,17 Indeed, even though men do not undergo an equivalent of the menopause, both estrogen and androgen levels, and particularly their free bioavailable fractions, decline slowly but progressively after 50–60 years of age, apparently as a result of complex alterations in reproductive physiology, lifestyle factors, or increases in the levels of sex hormone binding globulin.16,17,24 Although androgen may directly affect periosteal cortical bone apposition and muscular strength, there is ample direct and indirect evidence indicating a major role for androgen aromatization into estrogens in the regulation of bone homeostasis in adult men.24 It has been also suggested that threshold concentrations of estradiol may be required to limit age-related bone loss and that up to 40%–50% of middle-aged or elderly men might fall below that threshold.24,25 Interestingly, a recent population-based cross-sectional study using high-resolution three-dimensional pQCT described age effects on bone microstructure in men as well as its relationship with hormonal variables.26 In young men, the conversion of thick trabeculae into more numerous, thinner trabeculae observed from young adult to mid-life was most closely associated with declining IGF-I levels. Conversely, sex steroids, and particularly bioavailable estradiol, appeared as the major hormonal determinant of trabecular microstructure in elderly men. Other hormonal factors, such as vitamin D insufficiency and age-related increases in serum PTH levels may also have a role in the pathogenesis of male osteoporosis, particularly in elderly individuals. Longitudinal evaluations are needed to verify these findings and to determine the relationships between sex steroids and other hormones to health outcomes in older men.

Overview of Osteoporosis

Management in Men

At present there is no validated strategy for a systematic osteoporosis screening in men. Decisions regarding
treatment should be based on the absolute risk of fracture. Even though the majority of fractures (up to 80%) occur in men whose BMD measurements are in the osteopenic rather than osteoporotic range, BMD actually remains a key factor in decision making. Based on current recommendation, bone densitometry is generally suggested in men 70 years of age or older, in younger subjects when major risk factors for osteoporosis are evident or in subjects with a previous fragility fracture. Moreover, specific risk-assessment tools such as FRAX (a new fracture assessment tool from the WHO) incorporating major clinical risk factors with age and BMD have been recently developed for the prediction of fracture risk in men 50 years of age or older.

Preventive interventions in males are similar to the approach used for women, and apply to all men. They include adequate calcium (1200–1500 mg/day) and vitamin D (400–800 IU/day) intake, avoidance of smoking or excessive alcohol consumption, weight-bearing exercise and use of fall-prevention programs. However, drug therapy should be initiated in all men at high risk for fracture.

Pharmacological agents have been less studied in men than in women with osteoporosis and only few treatments are currently approved for use in men. A list of treatment options approved in US by the FDA is given in Table 1. Many of the clinical trials, even those that have led to registration of the drug for men, have been conducted in limited samples, mainly addressing changes in BMD as primary endpoint, since they were not powered to assess fracture risk reduction. Moreover, osteoporosis in men is rarely recognized and treated, even after a fracture has occurred. A recent retrospective cohort study in 1,171 men aged 65 or older demonstrated that only 7.1% of osteoporotic subjects and 16% of those with a hip or vertebral fracture received medication for osteoporosis.

Bisphosphonate therapy is becoming a mainstay in the treatment of male osteoporosis. Initially, their use in men was based on several uncontrolled observational studies by assuming that therapeutic results were similar to favorable findings from previous trials in women. Then a first randomized, placebo-controlled trial reported an increase in BMD in men with low bone mass treated with alendronate, to an extent very similar to that seen previously in studies of postmenopausal women. The BMD increases were independent of baseline free testosterone, age (less or more than 65 yrs), BMD T-score (≤−2.5 or >−2.5) and presence or absence of prevalent vertebral fractures. Height loss was also reduced in the alendronate-treated group as well as the rate of incident vertebral fractures. The number of non-vertebral fractures was too low to evaluate the effect of alendronate treatment in their prevention. More recently, additional trials of alendronate became available, all showing similar positive effects on BMD and the prevention of vertebral fractures in the treatment of men with primary osteoporosis. A health economic study from Sweden indicated that treating osteoporotic men with alendronate was projected to be cost-effective, under the assumption of the same fracture-risk-reducing effect of alendronate for men as for women. Indeed, a meta-analysis evaluating cumulative anti-fracture efficacy of randomized controlled trials in men indicated that alendronate treatment efficiently decreases the risk of vertebral fractures in men with low bone mass or fractures, but there is currently insufficient evidence to prove a significant effect on non-vertebral fractures. Recent data from the first prospective, randomized, controlled study in men with primary osteoporosis demonstrated that risedronate has positive effects in increasing BMD and decreasing vertebral fractures at 1 year. A smaller study demonstrated a reduction in hip fracture incidence with risedronate treatment in men after stroke. Moreover, both alendronate and risedronate were also effective in men with secondary causes of osteoporosis including glucocorticoid excess, hypogonadism or transplantation, and have been approved for treatment of glucocorticoid-induced osteoporosis in men in a variety of countries.

<table>
<thead>
<tr>
<th>Antiresorptive agents</th>
<th>10 mg/day or 70 mg/week</th>
<th>5 mg/day or 35 mg/week</th>
<th>5 mg annual infusion</th>
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<td>Alendronate (oral)</td>
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<tr>
<td>Risedronate (oral)</td>
<td>10 mg/day or 70 mg/week</td>
<td>5 mg annual infusion</td>
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<tr>
<td>Zolendronate (iv.)</td>
<td>20 mg/day subcutaneous injection (in men considered at high risk for fracture)</td>
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**Table 1. FDA approved treatments for male osteoporosis.**
In addition to bisphosphonates, other compounds such as PTH or teriparatide (the recombinant 1–34 fragment of PTH) and calcitonin demonstrated a similar efficacy in men on BMD and bone turnover than in previous trials in women with postmenopausal osteoporosis. An open label study with nasal calcitonin also evidenced a decrease in vertebral fracture incidence. More consistent findings have been reported with PTH and particularly with teriparatide (as daily 20 mcg subcutaneous injection). In keeping with previous observations in females, a follow-up study of men with previous treatment teriparatide indicated a reduction in vertebral fracture incidence compared with placebo. Importantly, concurrent therapy with antiresorptive compounds such as bisphosphonates should be avoided during PTH treatment, although sequential therapy with alendronate have been recently shown to maintain or further enhance bone mass after PTH is discontinued. Moreover, in individuals who have been treated previously with an antiresorptive agent, the subsequent actions of PTH and teriparatide on bone density may be delayed transiently if bone turnover is markedly suppressed. Additional studies in men are currently ongoing with strontium ranelate (2 g/day) given orally, a compound that demonstrated vertebral and non-vertebral anti-fracture efficacy in women with postmenopausal osteoporosis through an uncoupling action on bone metabolism (with mild stimulation of bone formation combined with a mild antiresorptive effect).

Different treatment options may be reserved for selected patients, such as testosterone replacement in men with established primary hypogonadism, even though the effects on fracture risk remain unknown. However, bisphosphonates can be also used in this setting, as well as in cases of GnRH agonist-induced hypogonadism in prostate cancer patients. The latter represents a major cause of bone loss and increased fracture risk in men, generally requiring effective antiresorptive treatment. In men as in women, and particularly in elderly subjects, the efficacy of oral aminobisphosphonates such as alendronate or risedronate may be limited by their side effects and method of administration that often impair treatment adherence over long term use. Recently, annual infusions of more potent antiresorptive aminobisphosphonates such as zoledronic acid have been shown to be effective in primary and secondary osteoporosis in both genders, with consistent advantages with regard to patient adherence to treatment and possibly on anti-fracture efficacy.

**Zoledronic Acid Use in Male Osteoporosis**

**Mechanisms of action and preclinical evidences**

Zoledronic acid [1-hydroxy-2(1H-imidazol-1-yl) ethylidene bisphosphonate] is a third-generation imidazole ring containing aminobisphosphonate. This compound binds strongly to hydroxyapatite with the highest affinity among the other aminobisphosphonates so that it is more likely to be retained in bone during the remodeling cycle because of reattachment of bisphosphonate released during resorption. In addition, its increased potency over the other bisphosphonates in inhibiting osteoclastic bone resorption (through an action on the key enzyme farnesyl diphosphate synthase) allows the use of smaller doses. Studies with in vitro and in vivo test systems indicated that zoledronic acid is several times more potent than alendronate, risedronate and pamidronate (the latter also available as intravenous formulation) and can be administered intravenously for a brief period (15–30 minutes) in an ambulatory setting. Preclinical trials suggested that zoledronic acid is also safer than pamidronate in terms of renal toxicity, and confirmed its improved efficacy in suppressing bone resorption for a sustained period. Moreover, with the antiresorptive dose levels used in these studies there have been no detectable impairments of either bone formation or mineralization.

**Zoledronic acid efficacy in clinical trials**

As for other antiresorptive agents, the clinical efficacy of zoledronic acid was initially explored in postmenopausal osteoporosis or in mixed male and female populations with other conditions of high bone turnover (i.e. Paget’s disease of bone and multiple myeloma). The indication for postmenopausal osteoporosis was based on the HORIZON Pivotal Fracture Trial, which included 7765 elderly women who were randomly assigned to receive either a single 15-minute infusion of zoledronic acid (5 mg) or placebo at baseline, 12 and 24 months. During the 3-year period, treatment with zoledronic acid reduced the risk of morphometric vertebral fracture.
by 70% (Relative risk = 0.30, 95% CI = 0.24–0.38) and of hip fracture by 41% (Relative risk = 0.59, 95% CI = 0.42–0.83), compared to placebo. Women receiving zoledronic acid had also a significant improvement in BMD and bone turnover markers. Interestingly, in a smaller randomized, double-blind trial conducted in order to assess the safety and the efficacy of a single dose zoledronic acid 5 mg compared to oral alendronate 70 mg weekly in postmenopausal women (who had previously been treated with alendronate), better adherence and preference for once-yearly infusion was demonstrated. This was consistent with a similar comparative study, where zoledronic acid treatment was also associated with a more rapid and slightly increased effect on the suppression of bone turnover markers than alendronate. In that case, the majority of patients preferred the annual intravenous infusion to weekly alendronate, citing convenience as the primary reason.

Currently, the available evidence for efficacy of zoledronic acid in primary osteoporosis in men is from the HORIZON Recurrent Fracture Trial (HORIZON-RFT), performed in a population of patients treated after surgical repair of a hip fracture, which included about a quarter male subjects. The infusions were first administered within 90 days after surgical repair of the hip fracture. All patients were unable or unwilling to take an oral bisphosphonate and received supplemental vitamin D and calcium. At 36 months, the treated group (n = 1065) had significantly increased bone density at the total hip and femoral neck compared to the placebo group (n = 1062). Moreover, over a 1.9 years median follow-up, significant decreases in any new fracture (Relative risk = 0.65, 95% CI = 0.50–0.84), clinical vertebral fracture (Relative risk = 0.54, 95% CI = 0.32–0.92), nonvertebral fracture (Relative risk = 0.73, 95% CI = 0.55–0.98) were observed in zoledronic acid group compared with placebo (Fig. 1). In contrast, the incidence of new hip fractures was not significantly different (Relative risk = 0.70, 95% CI = 0.41–1.19). Importantly, in this population at high risk for deadly recurrent fractures, the zoledronic acid-treated group experienced a survival advantage compared with placebo (Relative risk = 0.72, 95% CI = 0.56–0.93), that in post hoc analysis appeared higher in men than in women (6.4% vs. 2.8% absolute risk reduction, respectively).

![Figure 1. Rates of new clinical fractures (vertebral, non vertebral, and any fractures) in zoledronic acid (n = 1065) vs. placebo (n = 1062) group in male and female subjects from the HORIZON Recurrent Fracture Trial (median follow-up 1.9 years). Treatments were first administered within 90 days after surgical repair of a hip fracture. All patients also received supplemental vitamin D and calcium. Data were obtained from published results of the trial (as described in reference 63).](image-url)
with a marked reduction in cardiac-related deaths (Fig. 2). Adding incident fractures to the model explained only part of the zoledronic acid effect on mortality, and compared to the placebo arm there was a similar incidence of, but decreased death from pneumonia, neoplasms, and cardiovascular disease in subjects treated with zoledronic acid, suggesting that the drug may influence physiologic reserve. Additional evidence for the use of zoledronic acid in men with osteoporosis has been recently provided by a study using annual 4 mg infusions off-label for patients intolerant to or non-adherent to oral bisphosphonate therapy for osteoporosis. Data about 41 men, with a number of infusions from 1 to 4 (average 2) and an average time between bone density measurements of 3.1 years were released in abstract form. The interval between infusions was usually more than one year. Annual changes in bone density were similar to what has been reported in men receiving oral bisphosphonates varying from 1.47% per year at the spine to 0.59% per year in the hip.

Zoledronic acid has been also investigated in conditions causing secondary osteoporosis in men. In an as yet unpublished trial on 302 hypogonadal men, BMD changes at the lumbar spine at 2 years were similar (about 6%) between annual zoledronic acid (5 mg IV) or weekly alendronate (70 mg, oral). A particular and serious condition of acquired hypogonadism is represented by androgen deprivation therapy (ADT) for prostate cancer which may include orchidectomy or GnRH agonist therapy. In both cases, testosterone and consequently estradiol levels are markedly reduced, and this places men at uniquely high risk for osteoporosis and fracture. Different bisphosphonates demonstrated to be effective in suppressing bone resorption and increasing BMD in men with ADT for prostate cancer, including zoledronic acid. Initial landmark studies in patients just initiating ADT (12 months or less prior to enrollment) showed that zoledronic acid 4 mg infusions every three months can significantly reduce bone turnover markers and increase BMD at multiple sites compared to placebo. A slightly different study with a similar zoledronic acid regimen in men with prostate cancer with and without metastasis (on ADT less than one year) demonstrated that the improvements in suppression of bone turnover were independent of the presence of metastases. All treated subjects also had significantly greater BMD at the lumbar spine and femoral neck compared with placebo. Moreover, a subsequent study in a smaller sample of 40 men on ADT with non-metastatic prostate cancer and osteoporosis suggested that a single 4 mg yearly dose of zoledronic acid may also be effective in this setting. 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, compared with placebo. More recently, a prospective, randomized, double-blind, placebo-controlled study was performed in 93 elderly patients from the Veterans Affair health care system, including 50 men on ADT for less than 1 year and 43 on ADT for greater than 1 year. Most of these patients had additional risk factors for osteoporosis such as sedentary lifestyle, smoking, lower calcium intake and preexisting vitamin D deficiency. They were randomized to 4 mg zoledronic acid intravenously every 3 months for 4 treatments or intravenous placebo. Consistent improvements in BMD over placebo were demonstrated for all patients including those on ADT for prolonged periods (Fig. 3). Additional small scale studies confirmed the efficacy of zoledronic acid (4 mg given every 3 months) on bone mass in osteoporotic men with ADT for prostate cancer. Of interest, follow-up analyses in one of these studies evidenced a decrease in BMD after 1 year from the last infusion, suggesting that annual administration of 4 mg zoledronic acid may be inadequate in this particular setting. Longer prospective studies with zoledronic acid are required to confirm decreased fracture rates.
in men on ADT, as well as to determine the optimal timing of treatment and dosing regimen.

Interestingly, zoledronic acid infusion was also effective in other conditions of secondary osteoporosis in men, such prolonged immobilization following a stroke, HIV infection or glucocorticoid-induced bone loss. In a small trial on 27 hemiplegic males seven weeks after stroke, zoledronic acid 4 mg prevented bone loss at the hip. While consistent BMD reductions were observed in the placebo group after 1 year (by 5.5% on the affected, hemiplegic side and by 2.7% in the unaffected hip), zoledronic acid treatment maintained or increased BMD (by 1%) on the hemiplegic side and the unaffected hip respectively.

HIV infection and antiretroviral therapy have been recently associated with osteoporosis and fractures. A small study in 43 HIV positive men receiving antiretroviral therapy demonstrated that an annual intravenous infusion of zoledronic acid 4 mg significantly reduced bone turnover markers and increased BMD at the lumbar spine and total hip over the control group. Interestingly, persistence of drug effect at two years after the second annual dose in suppressing markers of bone turnover and increasing BMD was demonstrated in 33 of these patients. This is consistent with results from a different study in 66 male and female subjects with low bone mass after curative cancer treatment, followed for 36 months after a single 4 mg zoledronic acid infusion. Data were reported for men and women separately, and both showed persistent and durable decreases in bone turnover and increases in BMD at the spine and hip after 36 months from zoledronic acid treatment. These results suggest that the antiresorptive effects of zoledronic acid last over 1 year and raise the possibility that in some settings the compound could be administered less frequently than annually. Randomized trials that address this issue should be performed in males as well as in females.

Glucocorticoids are used widely for treatment of many different medical conditions. Their negative influence on skeletal health is a major drawback such that the use of glucocorticoids constitutes the most common secondary cause of osteoporosis in both
Characteristics of glucocorticoid effects on bone include rapid bone loss, particularly at sites of cancellous bone (i.e., vertebrae) with accelerated bone resorption followed by profound suppression of bone formation. During the period of rapid bone loss, and sometimes within 3 months of initiation of therapy at daily doses as low as 2.5 mg of prednisone or the equivalent, fractures can occur and have been described in as many as 30%–50% of chronic glucocorticoid-treated patients. Even though oral bisphosphonates have been shown to be effective in the treatment of glucocorticoid-induced osteoporosis, intravenous bisphosphonates that can be used more intermittently with the same or greater antiresorptive potency present potential advantages, particularly in terms of compliance and adherence. In this respect, a recent study reported the results of a 1-year, multicenter, randomized, double-blind, double-dummy clinical trial designed to determine non-inferiority of a single intravenous infusion of zoledronic acid (5 mg) as compared to an approved oral dose of risedronate (5 mg/day) in the prevention and treatment of glucocorticoid-induced osteoporosis in a mixed male and female population. The primary end point of the study was percentage change from baseline in lumbar spine BMD. Secondary endpoints included BMD at other sites, changes in bone turnover marker levels and safety. The study results showed that zoledronic acid was not only not inferior to risedronate in increasing BMD of the lumbar spine, but that it was superior by demonstrating a significantly greater percentage change in BMD. Superiority was also demonstrated at the femoral neck, trochanter, and total hip BMD and in reducing bone turnover markers. These differences were evident within 6 months of treatment. Since study subjects were not selected on the basis of low bone mass, the results are likely to be applicable to a wide spectrum of individuals who are candidates for the prevention or treatment of glucocorticoid-induced osteoporosis. The magnitude of the effects of zoledronic acid on yearly BMD changes was similar to pivotal clinical trials that included a placebo group. However, the inference that the greater effects of zoledronic acid on BMD and bone markers could be extrapolated to actual differences in fracture efficacy requires a cautionary note. BMD and bone turnover account only incompletely for fracture efficacy. Moreover, even though BMD is a significant predictor of fracture risk in glucocorticoid-induced osteoporosis, fractures often occur in patients without a consistent reduction in BMD, likely due to the effects of glucocorticoids on other components of bone strength. Thus, additional studies are clearly needed to determine whether there are differences in the risk of fractures when zoledronic acid or oral bisphosphonates are used to prevent or to treat glucocorticoid-induced osteoporosis.

Additional indication about the efficacy of treatment with zoledronic acid for the prevention of bone loss in samples of male and female patients following kidney or allogeneic stem cell transplantation has been also provided.

Based on all these positive evidences and on preliminary unpublished data from a head-to-head trial in men (showing non inferiority of zoledronic acid over oral weekly bisphosphonates on BMD changes) zoledronic acid has been recently approved by the FDA to increase bone mass in men with osteoporosis as well as for the prevention and treatment of glucocorticoid induced osteoporosis (for patients expected to be on glucocorticoids for at least 12 months). The recommended regimen is an annual 5 mg infusion and patients must be adequately supplemented with calcium (1200 mg/day) and vitamin D (800–1000 IU/day) if dietary intake is not sufficient. Actually no clear indication about the duration of zoledronic acid treatment in male as well as in female osteoporosis has been released.

Safety and adverse events
In all published trials, zoledronic acid (either at 4 mg infusions every 3 months or at an annual 5 mg dose) was safe and generally well-tolerated. As observed with other nitrogen-containing bisphosphonates administered intravenously, zoledronic acid can induce an acute phase reaction with fever, musculoskeletal pain and other flu-like symptoms which occur after the first dose in approximately 33% of patients, with a decline to approximately 6% with a second dose and 3% with a third dose. These effects are transient, generally resolve within few days after administration and occur predominantly in patients who have not previously been exposed to a nitrogen-containing bisphosphonate. In fact, previous treatment with a bisphosphonate appears to provide some protection from acute phase reactions with zoledronic acid or...
other aminobisphosphonates. This adverse event seems to be related to the accumulation of isopentenyl diphosphate (IPP), the metabolite immediately upstream of farnesyl pyrophosphate (FPP) synthase in the mevalonate pathway by cells (most likely monocytes) in peripheral blood, due to the inhibition of FPP synthase by nitrogen bisphosphonates. IPP is known to be a ligand for the most common subset of γδ-T cells in humans, Vγ9Vδ2 T cells. Their activation perhaps via a selective receptor causes the release of TNF-α and thereby initiates the pro-inflammatory acute-phase response. Symptoms can be easily managed with the use of acetaminophen or a non-steroidal anti-inflammatory drug. Moreover, a recent observational study evidenced an increased prevalence of low vitamin D levels in patients experiencing an acute phase reaction after the first infusion of zoledronic acid.

Asymptomatic and generally transient hypocalcemia (with serum calcium in the range of 7.5 mg/dL) has been reported in a comparable number of patients in HORIZON-PFT and in HORIZON-RFT trials. However, it is possible that the continued administration of vitamin D and calcium in these studies may have masked the real incidence of hypocalcemia or reduced its severity. No clinically significant long-term effects of zoledronic acid on renal function have been observed so far with 5 mg annual infusions. A small and comparable number of patients (less than 2%) experienced elevation in serum creatinine of more than 44 µmol/L in HORIZON-PFT and HORIZON-RFT trials, without major differences with respect to placebo group. Moreover, at the end of 1 year the renal function recovered in most patients. Because of the lack of clinical data to date, zoledronic acid is not recommended for use in patients with creatinine clearance below 30–35 mL/min. Moreover, an increased nephrotoxicity has been described with zoledronic acid regimens for the treatment of hypercalcemia of malignancy or osteolytic bone disease, which may relate in great part to the higher annual doses and shorter dosing intervals employed for these indications.

Other minor adverse events associated with zoledronic acid may include local reactions at the infusion site (i.e. itching, redness and pain) or ocular manifestations (iritis, uveitis, episcleritis) which have been reported respectively in 0.7% and 0.2% of patients receiving zoledronic acid.

An increased incidence of atrial fibrillation with zoledronic acid was observed in HORIZON-PFT, but not in HORIZON-RFT. This association was also reported with the use of other aminobisphosphonates such as alendronate. However, different meta-analyses of randomized controlled trials and of observational studies and a recent FDA review of 19,687 bisphosphonate-treated patients revealed no evidence of a higher risk of atrial fibrillation associated with bisphosphonate use. Even in those studies in which an increase in risk of atrial fibrillation was identified, there was no evidence that this translated into increased mortality or increased risk of stroke.

Osteonecrosis of the jaw (ONJ) has been identified as a potential complication, particularly with long-term, high dose intravenous aminobisphosphonate therapy in malignant diseases. This is a rare disorder of the oral cavity that has been defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider. Actually, the etiology of ONJ is unknown and relevant prospective clinical trials to study pathogenic mechanisms are not available. Potential risk factors include long duration of exposure to bisphosphonate treatment, glucocorticoid use, recent dental extraction, invasive oral bone surgery, poorly fitting dental appliances and/or intraoral trauma, pre-existing dental or periodontal disease, cancer, anti-cancer therapy, and alcohol/tobacco abuse. To date, most cases of bisphosphonate-related ONJ (about 94%) have been reported in patients who received monthly intravenous bisphosphonates including zoledronic acid for the treatment of malignancies, particularly multiple myeloma and metastatic cancer. Conversely, the incidence of ONJ in patients treated for osteoporosis using bisphosphonates seems extremely rare (less than 1 in 100,000 patients). While ONJ has been described in up to 1%–10% of patients receiving intravenous zoledronic acid for treatment of malignancy, not a clinically confirmed single case was reported in trial using annual zoledronic acid infusions for osteoporosis. Thus healthy patients receiving zoledronic acid for osteoporosis do not require any special dental treatment beyond routine care and standard procedures. It is probably prudent for clinicians to do a routine oral examination before prescribing this or other aminobisphosphonates and to consider appropriate preventive dental
care prior to treatment in patients with a history of ONJ risk factors. Finally, there have been concerns about whether bone strength is impaired by the use of prolonged high doses of aminobisphosphonates. A recent study looking at comparable dosing of zoledronic acid vs. alendronate in a cohort of patients with osteoporosis did not evidence over-suppression of bone formation or impaired mineralization in biopsies from 23 patients. This was consistent with data obtained during zoledronic acid treatment for other conditions such as Paget’s disease of bone, showing no evidence of adynamic bone or qualitative abnormalities of bone formation. Despite the above evidences, different case series recently described “atypical” subtrochanteric and diaphyseal fractures of the femoral shaft and have suggested that the risk may be increased in long-term users of aminobisphosphonates. To this regard, a more recent revision of 3 major randomized controlled trials (including HORIZON-PFT, with more than 14,000 patients and more than 51,000 patient years of follow-up for up to 10 years) concluded that the risk of fracture of the subtrochanteric or diaphyseal femur associated with the use of bisphosphonates was extremely low, even among women who had been treated for as long as 10 years. Although estimates of the relative risk evidenced no significant association, confidence intervals were wide because of the small number of events, suggesting that the study was underpowered for definitive conclusions.

Overall, according to available data, the risk-benefit balance of zoledronic acid and other aminobisphosphonate therapy in male or female patients with osteoporosis and other forms of metabolic bone disease remains strongly positive.

Summary and Conclusions
Osteoporosis in men is an increasingly important clinical issue. About one in three osteoporotic fractures occur in men, and the consequences of these fractures are generally more severe than in women. Despite these evidences, osteoporosis remains under-recognized and under-treated in men. While the evidence base for the long-term efficacy and safety of therapies for osteoporosis in men remains limited, bisphosphonate therapy is becoming a mainstay in the treatment of male osteoporosis. Results from recent randomized controlled trials have indicated that oral agents such as alendronate or risedronate are effective in increasing BMD in men with low bone mass even though most of them were not powered to assess fracture risk reduction. Moreover, poor adherence to oral bisphosphonate therapy has been shown to compromise the efficacy of this treatment for fracture reduction and to increase medical costs, particularly in frail older adults. Within this context, intravenous zoledronic acid given as 5 mg once yearly may represent a convenient and effective treatment option that may have an advantage over oral agents, for which adherence to treatment regimens is a recognized problem. An additional potential advantage in favor of zoledronic acid is the recent evidence from the HORIZON-RFT trial showing that additionally to its effect in fracture risk reduction, male and female patients receiving zoledronic acid had lower mortality rates. This is a particularly important issue especially in the older and frail populations. To date, although the magnitude of effect on BMD and fracture prevention with zoledronic acid in mixed male and female populations appears to be at least similar to and possibly better than (in the case of vertebral fractures) that reported for other interventions, a direct comparison with other treatments cannot be made in the absence of head-to-head studies of fracture outcome. Moreover, we still lack information about the optimal dosing strategy for zoledronic acid in terms of cost-effectiveness and safety of long-term regimens, particularly in conditions of secondary osteoporosis such as during glucocorticoid treatment or ADT for prostate cancer. This information is especially important in view of the long duration of action of zoledronic acid and the concerns about possible deleterious effects from long-term over-suppression of bone turnover. In conclusion, additional comparative data on fracture efficacy and other indices of bone quality as well as on long term safety are awaited to definitively position zoledronic acid with respect to other agents for the prevention and treatment of primary and secondary osteoporosis in men.

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References