Clinical Medicine Insights: Therapeutics

REVIEW

Zoledronic Acid Once-yearly: What Role in the Prevention of Non-vertebral Osteoporotic Fractures?

Sheila Anne Doggrell

Discipline of Medical Sciences, Faculty of Science and Technology, Queensland University of Technology, Brisbane, QLD4001, Australia. Email: sheila.doggrell@qut.edu.au

Abstract: Osteoporosis is the most common bone disease. Low levels of oestrogens or testosterone are risk factors for primary osteoporosis. The most common cause of secondary osteoporosis is glucocorticoid treatment, but there are many other secondary causes of osteoporosis. Osteoporosis can be secondary to anti-oestrogen treatment for hormone-sensitive breast cancer and to androgen-deprivation therapy for prostate cancer. Zoledronic acid is the most potent bisphosphonate at inhibiting bone resorption. In osteoporosis, zoledronic acid increases bone mineral density for at least a year after a single intravenous administration. The efficacy and safety of extended release (once-yearly) zoledronic acid in the treatment of osteoporosis is reviewed.

Keywords: clinical trials, efficacy, fractures, osteoporosis, safety, zoledronic acid once-yearly

Clinical Medicine Insights: Therapeutics 2010:2 539–547

This article is available from http://www.la-press.com.

Introduction

Osteoporosis is the most common bone disease. Osteoporosis (porous bone, thinning of bone) affects >10 million people in the US, including 2 million men, at an annual cost of US$17 billion.[1] Osteoporosis is associated with low bone mass (low bone mineral density) giving rise to vertebral fractures and non-vertebral fractures. The vertebral fractures lead to stooped posture, loss of height, and back pain. An important site of non-vertebral is hip fractures, and nearly 2 million hip fractures occur each year in the US as a result of osteoporosis.[1] After hospital discharge, one in five people die within one year of hip fracture, and one in three require residential care placement.[1] The main defect in osteoporosis is incomplete refilling of resorption lacunae, which leads to gradual thinning or perforation of trabeculae, impaired trabecular connectivity and deterioration of bone microarchitecture.[2]

Low levels of oestrogens or testosterone are important risk factors for osteoporosis. Thus, postmenopausal women with low levels of oestrogens are at increased risk of osteoporosis. Older men have lower levels of testosterone, and reduced activity of the enzyme aromatase, which is responsible for transforming testosterone to oestrogens in men, and this leads to reduced levels of oestrogens.[3] Osteoporosis can also be secondary e.g. to glucocorticoid treatment for transplantation. Osteoporosis can be secondary to anti-oestrogen treatment for hormone-sensitive breast cancer and to androgen-deprivation therapy for prostate cancer. Bisphosphonates (e.g. zoledronic acid) are used in the treatment of primary and secondary osteoporosis.

Many of the bisphosphonates are administered orally at regular intervals (daily, weekly, monthly) with the subject having to fast beforehand and stand or sit in an upright position for 30 minutes afterwards to minimise alimentary tract side effects. This procedure is unpopular with subjects and many stop taking them. Thus, the adherence to oral bisphosphonates is low.[4] Zoledronic acid (1-hydroxy-2-imidazol-1-yl-phosphonoethyl bisphosphoric acid) is a bisphosphonate used intravenous predominantly on an annual basis in the treatment of primary osteoporosis.

There is evidence that serious adverse effects with zoledronic acid (e.g. osteonecrosis of the jaw) are mainly observed when zoledronic acid is used more than once-annually, which is usually in the prevention of bone loss associated with the treatment of cancer.[5] This review is predominantly of the efficacy and safety of once-yearly zoledronic acid in the treatment of primary osteoporosis or secondary osteoporosis due to glucocorticoid use, where osteonecrosis of the jaw is not an issue, but also considers the use of once-yearly zoledronic acid in the osteoporosis due to the treatment of cancer. When evidence for once-yearly zoledronic acid is not available, evidence with six-monthly zoledronic acid is considered. Trials with fracture endpoints are given priority over those with surrogate endpoints e.g. bone mineral density. Firstly, the effect of zoledronic acid in primary osteoporosis is considered, and then the effect of zoledronic acid in secondary osteoporosis such as the osteoporosis associated with glucocorticoid use. Thirdly, the effect of using once-annually zoledronic acid on the osteoporosis induced by the treatment for cancer is considered briefly. Finally, there is a commentary, which discusses the role and place of once-yearly zoledronic acid treatment in primary and secondary osteoporosis.

Primary Osteoporosis in Men and Women

Postmenopausal women with osteoporosis

Zoledronic acid has not been tested extensively in men with osteoporosis prior to fracture. Zoledronic acid was initially tested, in doses up to 4 mg annually, in postmenopausal women with osteoporosis prior to fracture. Thus, in 351 postmenopausal women with low bone mineral density (a T score lower than –2), several regimens of zoledronic acid infused over 5 minutes were shown to increase bone mineral density similarly.[6] These regimens included 0.25 mg, 0.5 mg or 1 mg zoledronic acid at 3 monthly intervals, 2 mg at sixth monthly intervals, and an annual intravenous dose of 4 mg.[6] After one year, all regimens of zoledronic acid increased bone mineral density in the spine by 4%–5% and the femoral neck by 3%–4%, compared to the placebo group.[6] No serious side effects were observed with zoledronic acid, but a few subjects experienced flu-like symptoms (e.g. myalgia, pyrexia), which were usually limited to the first administration of the zoledronic acid.[6] Thus, myalgia was observed in 10% of the zoledronic acid 4 mg group, compared to 2% of

the placebo group, pyrexia in 15% versus 3%, and nausea in 13% versus 5%.[6]

Some of postmenopausal women (119) were continued on 4 mg zoledronic acid (Zometa®) yearly, and were followed for another 4 years.[7] This extension showed continued benefit of zoledronic acid on bone turnover markers, with arthralgia as the most common adverse effect (18.2%), and no renal abnormalities.[7] However, the subjects lost height, and six had fractures (one vertebral, and 5 non-vertebral; three in the foot, one in the ankle, and one in the radius.[7] As, the initial part of this study had shown that maximal response to zoledronic acid was not obtained with 4 mg, this suggested, as had been shown with other bisphosphonates, that there was under dosing with zoledronic acid, and that better results (anti-fracture activity) may be obtained with a higher dose.[7] A dose of 5 mg has been used in some of the further studies with zoledronic acid. Subsequent to the initial study, it was shown that the incidence of adverse effects with zoledronic acid could be reduced by increasing the infusion time from 5 to 15 minutes.

This bone mineral density study was not powered, or long enough, to determine whether this increase in bone mineral density translated into decreased clinical outcomes. Thus, it remained of interest to know whether this decrease in bone mineral density translated into reduced fractures, and this was tested in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT), which was undertaken with postmenopausal women with osteoporosis, and used the higher 5 mg dose of zoledronic acid (Reclast®).[8] HORIZON-PFT enrolled postmenopausal women (65–89 years old) with a T score of −2.5 or less, with or without a vertebral fracture, or a T score of 1.5 or less with evidence of at least two mild or one moderate vertebral fracture.[8]

The 7765 enrolled women were placed in two strata—the first stratum was women not taking any osteoporosis medication, and the second stratum was women taking an allowed osteoporosis medication at randomisation.[8] Regardless of stratum, all women received oral daily calcium (1000–1500 mg) and vitamin D (400 to 1200 IU) and were randomised to placebo or a 15 minute intravenous injection of zoledronic acid 5 mg at baseline, 12, and 24 months.[8] The primary endpoints were new vertebral fractures in stratum 1 and hip fractures overall (strata 1 and 2). The incidence of new vertebral fractures in stratum 1 women after 3 years was 10.9% in the placebo group and this was significantly reduced in the zoledronic acid group (3.3%).[8] The incidence of hip fractures was 2.5% in the placebo group, and was reduced in the zoledronic acid group (1.4%).[8] Women in the zoledronic acid group lost less height (−4.2 mm) than in the placebo group (−7.0 mm).[8] The authors of this study suggest that the 70% reduction in vertebral-fracture rate observed with zoledronic acid is greater than that previously reported for oral bisphosphonates (40–50%),[8] and one factor that may contribute to this, is the poor adherence to oral bisphosphonates.

Around the infusion (≤3 days after infusion), there was a higher incidence of pyrexia (16.1% vs. 2.1%), myalgia (9.5% vs. 1.7%), influenza-like symptoms (7.8% vs. 1.6%), headache (7.1% vs. 2.3%) and arthralgia (6.3% vs. 2.0%) in the zoledronic acid than the placebo group.[8] Fortunately, these adverse effects were mainly mild to moderate, and mostly short term.[8]

One unexpected finding in HORIZON-PFT was that the incidence of cardiac arrhythmias was significantly higher in the zoledronic-acid group (6.9%) than the placebo group (5.3%), and this included a higher incidence of serious atrial fibrillations with zoledronic acid (1.3% vs. 0.5%).[8] For most of the subjects who developed atrial fibrillation, 47 of 50, the fibrillation occurred more than 30 days after the zoledronic acid infusion.[8] The cardiac arrhythmias were not associated with either an increased incidence of stroke or cardiovascular death.[8] The increased incidence of atrial fibrillation with zoledronic acid could not be explained, and the authors concluded that it "might be due to chance but should be further explored".[8] Further individual clinical trials have not found an increased incidence of atrial fibrillation with zoledronic acid (discussed below).

Subgroup analysis of HORIZON-PFT showed that the benefits of zoledronic acid on vertebral fractures were similar in most subgroups e.g. race, region, smoker vs. non-smoker, height, history of falls, walking distance, total hip bone mineral density.[9] Zoledronic acid was more effective at preventing vertebral fractures vertebral fractures in those aged under 70 years, normal creatinine clearance, and bone mass index ≥25 mg/m^2.[9] For non-vertebral and hip fractures, the benefits of zoledronic acid were similar in all subgroups.[9]

The results from HORIZON-PFT were used to compare zoledronic acid with the other agents available for treatment of postmenopausal osteoporosis.[10] This showed that zoledronic acid was more effective than the standard agents (risendronate, alendronate, ibandronate, strontium ranelate, raloxifene, or parathyroid hormone) at preventing vertebral, non-vertebral, and hip fractures.[10] Modelling showed that zoledronic acid also generates lesser total medical costs than the standard agents.[10] The total costs included the cost of treatment strategies, which included prescription costs, and follow-up costs for 3 years such as medical visits and laboratory tests, and the costs of managing vertebral, non-vertebral excluding hip, and hip fractures.[10]

A recent study shows that the benefits on zoledronic acid on bone mineral density in 581 postmenopausal women with low bone mass lasts up to two years.[11] After two years, the bone loss in the lumbar spine was 1.3% in the placebo group, compared to a gain of 5.5 and 4.3% with zoledronic acid administered once only or annually at the start of the two years, respectively.[11] This suggests that it may be possible to extend the dosing of zoledronic acid beyond annually in postmenopausal women with osteoporosis.

After hip fracture in men and women

After hip fracture, people are at an increased risk of a further fracture. Thus, there are 10.4 further fractures/100 person-years, which is 2.52 times the rate observed in those people who have not had a hip fracture.[12] Given this data, it would seem imperative that, after a hip fracture, subjects are treated with agents for osteoporosis, but this is not the case.[13] Surprisingly, there had been no major studies of agents for osteoporosis after hip fracture until zoledronic acid was studied. The HORIZON Recurrent Fracture Trial (HORIZON-RFT), tested whether the ability of zoledronic acid to increase bone mineral density translated into beneficial outcomes in women and men with a recent hip fracture.[14]

HORIZON-RFT enrolled subjects who were 50 years of age or older who had had a hip fracture that had undergone repair in the last 90 days.[14] The hip fracture had to involve minimal trauma; defined as a fall from standing height or lower. Subjects were allowed to continue their use of nasal calcitonin, selective estrogen-receptor modulators, hormone replacement, tibolone, and of external hip protectors.[14] A total of 2127 subjects were randomized, and they were predominantly white (~91%), female (~77%), with a mean age of 75 years.[14] At baseline, ~42% had a T score at the femoral neck of −2.5 or less, indicating osteoporosis, and a further ~34% had a T score >−2.5 to −1.5 indicating osteopenia.[14] All subjects received daily supplementation of oral calcium and vitamin D and received either zoledronic acid 5 mg or placebo by intravenous infusion within 90 days of surgical repair of the hip fracture and annually thereafter.[14]

The primary endpoint was a new clinical fracture, excluding facial and digital fractures, and fractures in abnormal bone (e.g. cancerous).[14] It was planned to monitor the subjects for up to 5 years, but after a median follow-up of 1.9 years, the Independent Data and Safety Monitoring Board recommended the trial be stopped as it had surpassed the pre-specified efficacy boundaries.[14] At that time, there were 139 fractures in the placebo group of 1062, and this was significant reduced to 92/1065 in the zoledronic acid group.[14]

Secondary endpoints included sites of fractures.[14] There were significantly less non-vertebral fractures in the zoledronic acid group (79) than in the placebo group (107), and less vertebral fractures in the zoledronic acid (21) than in the placebo group (39).[14] There were also less hip fractures in the zoledronic acid group (23) than in the placebo group (33), but this did not reach significance.[14] Secondary endpoints included death, and there were less deaths in the zoledronic acid group (101) than in the placebo group (141).[14] It is not known whether zoledronic acid has similar benefits in men and women, as no subgroup analysis of HORIZON-RFT has been published to date.

A similar number of adverse effects were reported in the zoledronic acid and placebo group. Myalgia occurred in significant more subjects in the zoledronic acid group (33, 3.1%) than the placebo group (9, 0.9%), as did pyrexia after the first infusion (72, 6.8% vs. 7, 0.9%).[14] In this study, there was no excess of influenza-like symptoms, headache, or arthralgia with zoledronic acid over the placebo group.[14] Also, there was no excess of cardiovascular events with zoledronic acid, including atrial fibrillation, which occurred in 29 subjects treated with zoledronic acid and 27 subjects treated with placebo.[14] This contrasts with the HORIZON PFT where an increase in atrial fibrillation was observed with zoledronic acid.[8]

Elderly postmenopausal women

A posthoc analysis of HORIZON-PFT and HORIZON-RFT pooled the data for postmenopausal women (aged ≥75 years) with osteoporosis (T-score ≤–2.5 at femoral neck or ≥1 prevalent vertebral or hip fracture) or a recent hip fracture.[15] In this group of 3888, the risk of any clinical fracture was reduced with zoledronic acid 5 mg from 5.7 to 4.1% after 1 year, and from 16.6 to 10.8% after 3 years.[15] The risk of clinical vertebral or non-vertebral fractures was also reduced by zoledronic acid after 3 years.[15] The risk of a hip fracture was lower with zoledronic acid (2.8%) than with placebo (3.6%), but this did not reach statistical significance in the aged ≥75 years, whereas the risk of hip fracture was significantly reduced in those less than 75 years.[15]

Major safety

The HORIZON Pivotal Fracture Trial in postmenopausal osteoporosis demonstrated an excess in atrial fibrillation with zoledronic acid,[8] whereas the HORIZON Recurrent Fracture Trial did not.[14] Both trials used 5 mg zoledronic acid intravenously annually, but the Pivotal Fracture Trial was evaluated after 3 years whereas the Recurrent Fracture Trial was followed-up after a 1.9 years. Thus, it is possible that atrial fibrillation is an effect of long term treatment with zoledronic acid, but there is no other evidence to support this to date.

Osteonecrosis of the jaw (necrotic bone in the oral cavity with local pain, soft-tissue swelling and/or loose teeth) is a rare complication with bisphosphonate treatment in osteoporosis. There was no evidence from HORIZON-PFT that zoledronic acid increased the incidence of osteonecrosis of the jaw in 3875 postmenopausal women with the once-yearly zoledronic acid regimen after 3 years,[8] and this was been confirmed by an independent, blinded adjudication committee.[16]

In subjects with cancer receiving bisphosphonates, the incidence of osteonecrosis of the jaw is dependent on the dose and duration of therapy, with an estimated incidence of 1%–12% after 36 months of exposure.[5] In osteoporosis, osteonecrosis of the jaw is rare with an estimated incidence of <1 case per 100,000 person-years of exposure, and it is not known whether this level is above that of the incidence in the general population.[5]

Glucocorticoid-induced Secondary Osteoporosis

Glucocorticoids are commonly used in the treatment of inflammation and immunodulatory disorders, and are a major cause of secondary osteoporosis, and the recent HORIZON trial has shown that zoledronic acid increases bone mineral density under these conditions.[17] The HORIZON trial compared intravenous zoledronic acid 5 mg to oral risendronate 5 mg for the prevention and treatment of glucocorticoid-induced osteoporosis in 833 subjects taking glucocorticoids for conditions such as rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus and asthma.[17] The prevention group had started glucocorticoids within the last 3 months, the treatment group had been taking glucocorticoids for longer than 3 months.[17] All groups were taking similar prednisolone-equivalent doses of glucocorticoids.[17] After 12 months, the bone mineral density at the lumbar spine and femoral neck was increased more in the zoledronic acid group than the risendronate group in both the prevention and treatment subjects.[17] There were 5 new vertebral fractures in the zoledronic acid combined group of 416 subjects and 3 new fractures in the risendronate group of 417 subjects.[17] These low fracture rates in glucocorticoid treated subjects may be due to the effectiveness of both the zoledronic acid and risendronate.[17] The authors considered that it was not ethical to undertake a placebo-controlled study of zoledronic acid in glucocorticoid-induced secondary osteoporosis,[17] presumably because risendronate had already been shown to reduce fractures in this secondary osteoporosis (reviewed in).[18]

Serious adverse effects were similar in both groups, but adverse effects were more common with zoledronic acid than risendronate.[17] There were no cases of atrial fibrillation or osteonecrosis of the jaw attributed to zoledronic acid.[17] Renal events occurred in 9 subjects with zoledronic acid and 6 subjects with risendronate, and all events were reversible.[17] Six subjects in each group had ocular events and these were conjunctivitis (5) and blepharitis with zoledronic acid, and blurred vision (2), episcleritis, conjunctivitis, diplopia, and increase in lacrimation with risendronate.[17] Pyrexia, myalgia and influenza-like illness were more common with zoledronic acid than with risendronate.[17] There was no difference in health-related quality-of-life data between groups, but most subjects preferred intravenous administration (~80%) to oral administration.[17]

During and after transplantation, immunosuppressants including glucocorticoids are used, and contribute to the bone loss. Fractures occur in 20%–40% of subjects in recipients of liver, kidney, heart and lung transplants, and occur most frequently in the first year after transplantation.[19] Zoledronic acid administered every 3 months (or more often) has been shown to be useful in preventing bone loss in liver and kidney transplantation, and in allogeneic stem cell transplantation (reviewed in),[20] and is not discussed further in this review, which is of zoledronic acid used once-yearly. It seems unlikely that zoledronic acid will be able to be used annually in liver transplantation, as the ability of zoledronic acid to prevent bone fractures after liver transplantation is lost within 12 months of treatment.[21] Thus, three 'late' asymptomatic fractures occurred in a group of 28 subjects who had had liver transplants, and been treated with zoledronic acid.[21]

Treatment for Cancer Induced Secondary Osteoporosis

The bone loss with anti-oestrogen treatment for hormone-sensitive breast cancer or androgen deprivation therapy for prostate cancer is major. Consequently, initially, zoledronic acid was given more often than once-yearly in cancer, as it is considered that zoledronic acid once-yearly would not be effective. The use of zoledronic acid more often than annually in the treatment of the osteoporosis associated with breast and prostate cancer has recently been reviewed.[22] In addition to preventing osteoporosis, zoledronic acid may have anti-cancer properties in its own right.[23] Unfortunately, with increasing dose and increasing frequency of zoledronic acid use in cancer, there is an increased incidence of osteonecrosis of the jaw.[5] Thus, recently, consideration has been given to improving the safety of zoledronic acid in the osteoporosis associated with the treatment of cancer to improve by using it once-yearly.

Zoledronic acid once-yearly has been shown to reduce bone loss in androgen deprivation therapy-induced bone loss in men with hormone-naïve prostate carcinoma.[24] In this study, 40 subjects with prostate cancer and bone metastases all received androgen deprivation therapy (i.e. gonadotropin-releasing hormone agonists) and at the same time either receive zoledronic acid 4 mg or placebo.[24] At baseline, there was no osteoporosis, but after 6 and 12 months, bone mineral density was decreasing in the placebo group.[24] In the zoledronic acid group, bone mineral density was increased at 6 months, and was at baseline levels after 12 months. This indicates that zoledronic acid once-yearly, administered at the same time as androgen deprivation therapy is started, may be suitable for preventing bone loss in subjects being treated with androgen deprivation therapy in prostate cancer.[24] However, if the zoledronic acid is given to the subjects who have already become osteoporotic due to the androgen deprivation therapy, bone mineral density is reducing after one year.[25] This shows that zoledronic acid once-yearly is not suitable for use after the androgen deprivation therapy has induced osteoporosis.[25]

Other Indications for the use of Zoledronic Acid Once-yearly

Small pilot clinical trials have suggested that zoledronic acid may be useful in the treatment of the osteoporosis associated with β-thalassemia, stroke, spinal cord injury, HIV-infected men, monoclonal gammopathy of underdetermined significance and rheumatoid arthritis.[20] Of these conditions, zoledronic acid annually has been assessed in stroke, spinal cord injury, and HIV-infected men, and shown to be suitable for use in stroke and HIV-infected men, but not in spinal cord injury. Thus, in a preliminary study, when 27 hemiplegic subjects were given calcium and vitamin D and randomised to placebo or zoledronic acid 4 mg, the placebo group lost 5.5% of bone mineral density at the hemiplegic hip whereas the zoledronic acid group had no change after a year.[26] On the unaffected hip, the placebo group lost bone mineral density (2.7%) whereas the zoledronic acid group had a small increase in bone mineral density (1%).[26] There were no fractures during the study, and the number of falls (72%) was the same in both groups.[26]

In HIV-infected men, who were also receiving calcium and Vitamin D supplements, zoledronic acid 4 mg annually over 2 years, the anti-resorptive effect of zoledronic acid was observed after 36 months.[27] The authors suggest that it may possible to use zoledronic acid less frequently than annually in this group.[27]

In subjects loosing bone mineral density after spinal cord injury, a preliminary study has shown that a single injection of zoledronic acid 4 or 5 mg prevented the bone loss at 6 months but not 12 months.[28] This suggests that zoledronic acid annually may be

useful in the treatment of the bone loss associated with stroke, but not spinal cord injury.

Commentary

Dose of zoledronic acid

Although zoledronic acid at 4 mg/annually was used in the first major study with zoledronic acid in osteoporosis,[6] subsequently studies have predominantly used 5 mg/annual. The reason for this change was that a maximal response to zoledronic acid on bone resorption markers was not obtained with 4 mg.[7] However, to date, there are no studies that have determined whether the maximum response to zoledronic acid is produced by the 5 mg dose, and this should be tested. There are also no head-to-head studies comparing the two doses of zoledronic acid and, consequently, it is not possible to determine whether the 5 mg dose has added benefits over the 4 mg dose.

Zoledronic acid in men

Elderly men develop osteoporosis and have hip fractures. The National Osteoporosis Foundation estimated that 17 million men in the US will have osteoporosis or low bone mass in 2010.[29] In men with osteoporosis, the oral bisphosphonates (alendronate and risendronate) have been shown to reduce vertebral fracture, and to cause a small non-significant decrease in non-vertebral fractures.[30] This suggests the more potent bisphosphonate zoledronic acid may be useful in treating men with osteoporosis. A trial has been undertaken to compare zoledronic acid with alendronate in men with osteoporosis,[31] and when the findings are published, we will know whether zoledronic acid is more efficacious and/or safer in men with osteoporosis than alendronate.

In HORIZON-RFT, where zoledronic acid was shown to reduce the number of fractures in subjects after hip fracture, ~23% of the subjects were male.[14] To date, no male subgroup analysis has been reported from this trial. Thus, this analysis should be reported, and/or a larger trial of zoledronic acid in men with osteoporosis after hip fracture should be undertaken.

Is zoledronic acid more beneficial than other agents in osteoporosis?

The HORIZON trials have clearly shown that zoledronic acid decreases fractures in postmenopausal women, and in men and women after hip fracture, but is zoledronic acid more effective than other bisphosphonates or other agents for preventing fractures? There are no head to head trials of zoledronic acid with other bisphosphonates in primary osteoporosis, and these are needed to give definite answers about effectiveness. However, as discussed by Black,[8] the 70% reduction in the vertebral fractures rate with zoledronic acid was greater than that observed previously for oral bisphosphonates (40%–50%) and for calcitonin or raloxifene. The recent HORIZON trial in glucocorticoid-induced osteoporosis showed that zoledronic acid had a greater effect on bone mineral density than risendronate,[17] but this trial was not powered to determine whether there were any differences in fracture rates between the groups. Thus, trials are needed to determine whether the increased bone mineral density with zoledronic acid compared with risendronate in secondary osteoporosis translates into reduced vertebral and non-vertebral fractures.

Parathyroid hormone preparations (teriparatide[32] or human parathyroid hormone, 1–84)[33] have a similar ability to zoledronic acid to decrease fractures. Both zoledronic acid and the parathyroid hormone compounds have reasonable good safety profiles in osteoporosis. Which is better? The results of the ongoing clinical trial in which zoledronic acid is being compared to teriparatide, and the combination of zoledronic acid and teriparatide, in women with osteoporosis,[34] may answer this question. It is also possible that, as zoledronic acid and teriparatide have different mechanisms of action, different subjects with osteoporosis may benefit from one or the other treatment.

Denosumab is a new treatment for bone loss. It is a human monoclonal antibody to the receptor activator of nuclear factor-κβ ligand (RANKL). RANKL is a cytokine that has an important role on the formation, function, and survival of osteoclasts. Denosumab prevents the interaction of RANKL with its receptor RANK on the osteoclasts, which leads the inhibition of osteoclasts-mediated bone resorption. In the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 months (FREEDOM) trial, after 36 months of treatment, denosumab was shown to reduce the incidence of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis.[35]

Thus, zoledronic acid and denosumab seem to have a similar ability to reduce fractures in postmenopausal women with osteoporosis. Consequently, the choice

between zoledronic acid and denosumab in these women may be on the basis of safety.

Both zoledronic acid and denosumab have been shown to be well tolerated in the treatment of postmenopausal osteoporosis. Zoledronic acid injection is associated with small excess of pyrexia, myalgia, influenza-like symptoms, headache, and arthralgia whereas denosumab caused a small excess in eczema, flatulence, and cellulitis.[35]

Only a direct comparator trial can provide a true comparison between zoledronic acid and denosumab in the treatment of postmenopausal osteoporosis. Such a trial should be undertaken. Also, as denosumab and zoledronic acid have different mechanisms, it is possible that they may have additive effects on bone mineral density and decreasing the incidence of fractures. Thus, the comparator study should also include a group combining zoledronic acid and denosumab.

Adherence to zoledronic acid

It is assumed that adherence to annually administered zoledronic acid will be higher than to oral bisphosphonates or other agents administered daily or weekly in osteoporosis, but this has not been tested. For the first year of treatment, a subject with osteoporosis will be covered by a single injection of zoledronic acid, and is likely to be more adherent than a subject taking daily or weekly medication for osteoporosis. Subjects with osteoporosis are usually recalled for zoledronic acid treatment on an annual basis, and this should give good adherence, but this needs to be monitored.

Zoledronic acid and glucocorticoid-induced secondary osteoporosis

The HORIZON study, of zoledronic acid once-yearly in subjects with glucocorticoid-induced osteoporosis, needs to be extended or repeated with larger numbers of subjects to determine whether zoledronic acid is equivalent, superior, or inferior to risendronate at reducing fractures. It seems unlikely that zoledronic acid will be able to be used once-yearly in the bone loss associated with liver transplantation, as the ability of zoledronic acid to prevent bone fractures after liver transplantation is lost within 12 months of treatment.[21]

Zoledronic acid once-yearly and cancer

The increased dose and increasing frequency of zoledronic acid use in cancer, is associated with an increased incidence of osteonecrosis of the jaw.[5] To avoid this, consideration is being given to using zoledronic acid once-yearly for the osteoporosis associated with the treatment of cancer. Zoledronic acid once-yearly has been shown to reduce bone loss in androgen deprivation therapy-induced bone loss in men with hormone-naïve prostate carcinoma provided it is given at the same time as the androgen deprivation therapy,[24] and not when osteoporosis has developed.[25] Further studies need to be undertaken to determine whether zoledronic acid once-yearly can be efficacious at preventing bone loss and safe in other bone loss associated with cancer treatment e.g. in breast cancer.

Conclusion: what role does zoledronic acid once-yearly have in the prevention of non-vertebral osteoporotic fractures?

In many clinical trials with zoledronic acid in osteoporosis, the primary outcome is change in bone mineral density. It is assumed that an increase in bone mineral density (surrogate endpoint) will lead to a decrease in fractures (clinical endpoint) and this has been confirmed for zoledronic acid once-yearly in postmenopausal women with osteoporosis, and men and women with osteoporosis after a hip fracture. Thus, zoledronic acid is an important medicine for the prevention of fractures in these cohorts. However, in glucocorticoid-induced secondary osteoporosis, the major trial with zoledronic acid once-yearly was too small or too short to detect any changes in clinical outcomes, and consequently we cannot be absolutely certain that the change in bone mineral density will be sufficient to improve clinical outcomes. Also, the role, if any, of zoledronic acid once-yearly in subjects with bone loss due to cancer treatment, needs to be determined.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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