ORIGINAL ARTICLE

Assess Utility of Once Yearly IV Injection of Zoledronic Acid 5 mg in Treatment of Osteoporosis

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ABSTRACT

Zoledronic acid is an approved FDA once yearly injection for the treatment of osteoporosis. Although it is widely prescribed in our institution (Hamad Medical Corporation) in Qatar, yet there is no available data covering the efficacy and safety profile in Qatar. This study aimed to determine the usefulness of Zoledronic acid 5 mg in the treatment of Osteoporosis regarding the change in BMD (primary end point) and B-CTX (secondary end pint) from baseline and evaluate the safety and tolerability of this medication by assessing the reported ADRs. This is a retrospective observational study, a total of 108 patients with confirmed diagnosis of Osteoporosis were identified, and received at least one dose of Zoledronic Acid 5 mg annual infusion for treatment of Osteoporosis, through Hamad Medical Corporation (HMC) during the study period between January 2009 and May 2011. Patient's medical profile was reviewed for Bone Mineral Density (BMD), and for the bone turnover marker (B-CTX). Additionally, to identify the adverse drug reactions, the nurse's records of IV admixture room, patients profile and drug information center were reviewed. Patients who received Zoledronic acid 5 mg annual infusion showed significant increase in BMD values for the lumbar spine at (L2-L4) after the first dose and the second dose as well by (6.63 and 20% and P values of 0.039 and 0.024 respectively), the values of lumbar spine at (L2) trend to be increased over the two years (% P>0.05). After the second dose, femoral neck and total hip BMD values tend to be decreased without reaching significant values. The biochemical markers were improved post-Zoledronic acid 5 mg annual dose by 17.9% and 10.9% (p values 0.161 and 0.14 respectively). A headache, flue-like symptoms, and fever were the most common adverse drug reaction associated with Zoledronic acid 5 mg IV administration. The once-yearly injection of Zoledronic acid 5 mg improves BMD at the lumbar spine, shows good tolerability and favorable safety profile. No evidence was found that the IV administration of Zoledronic acid 5 mg showed improvement in the BMD of femurs and bone turnover marker (B-CTX), or proves its association with severe ADR.

Key words: Zoledronic acid, treatment, osteoporosis

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INTRODUCTION

According to IDF fact sheet 2012, one-third of women and one-fifth of men over 50 years will suffer from an osteoporotic fracture during their lifetime.[1] Osteoporosis is one of the leading causes of morbidity and decreased the quality of life all over the world, particularly in the Middle East where the Mediterranean population was found to have lower bone mass when compared with the western population.[2] WHO has defined osteoporosis as "increase fracture risk as result of decreased bone mass, collagen and mineral content of the bone".[3] Bone strength is determined by several non-invasive and precise methods. Bone densitometry, Dual-energy x-ray absorptiometry (DXA), which measures the bone mineral content (BMC) of an expressed region as grams of bone mineral, or bone mineral density (BMD) expressed as grams of mineral per unit projected area of the bone.[4] In addition to the bone turnover biomarker; beta-carboxy-terminal collagen crosslinks (B-CTX), it is a blood test that is highly related to the bone turnover.[5]

Osteoporosis is becoming a major concern in Qatar due to its high prevalence and evidence of an early expected decline in BMD of the spine and femoral sites and Qataris showing lower BMD values at the spinal site than other females from Western and Arab countries.[2] Despite the importance of this health problem, there are not enough studies in the Middle East to assess the efficacy of antiosteoporotic medications, especially Zoledronic acid in the Middle East. Etiology of Osteoporosis varies to include; hormonal loss like the postmenopausal stage and androgen-deprivation cases, secondary to glucocorticoid use or other drugs, physical inactivity, and genetic predisposition.[6]

The overall goal of this pilot study is to investigate the utility of annual intravenous infusion of Zoledronic acid 5 mg in postmenopausal women, in addition to other affected population such as Senile Osteoporosis and Glucocorticoids-induced Osteoporosis. The efficacy will be assessed by determining the change from baseline in BMD (lumbar spine, femoral neck, and total hip) and in bone turnover marker C-telopeptide of type I collagen (B-CTX), after the first and second doses. Additionally, to evaluate the ADRs reported by patients, doctors or nurses submitted to drug information center, added to the patient medical profile or documented in IV room records. There is lack of data regarding the efficacy and safety of Zoledronic acid among our diverse population, this knowledge gap, adversely affect our practice in management of osteoporosis in Qatar, which might render the expert recommending Zoledronic acid, resulting in under treatment of patients.

PATIENTS AND METHODS

The Medical Research Center (MRC) at Hamad Medical Corporation (HMC) approved the study protocol. A Waiver of Authorization was granted to allow access to patient's medical records without explicit written permission from each patient. Each patient's name and other personally identifiable information were not entered into the database and cases were identified only by unique numeric identifier code to assure confidentiality. However, a table connecting patient's identifiers and digital study code is kept with the principal investigator in a locked cabinet, to allow any audit or investigation.

This retrospective observational study was carried out during the period from January 2009 until May 2011. Patients included in the study were those with osteoporosis (Postmenopausal Senile or Glucocorticoids-induced Osteoporosis), the diagnosis was confirmed by:

- History of hip or vertebral fracture
- Patients without fracture history but a BMD value -2.5 SD or lower

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- Bone mineral density (BMD value between -2.5 SD and -1 SD) with major osteoporotic fracture probability ≥20% or hip fracture probability ≥ 3%.

However, patients were excluded from the study in case of:

- The Zoledronic acid 5 mg was prescribed for indications other than Osteoporosis like:
- Treatment of hypokalemia
- Metastatic bone disease
- Paget disease
- Heritable skeletal disorder, like osteogenesis imperfect

Young patients with juvenile osteoporosis

- Patients who received the Zoledronic acid infusion but died before commencing the study because of difficulty in securing their files
- Patients do not have a BMD baseline because many doctors confirm their diagnosis on criterion other than BMD
- Patients do not have enough follow up data (BMD) due to :
- Patient's incompliance; DXA scan date is scheduled and they did not attend
- Patient's death
- Patient left the country for good.

The primary endpoint was to assess the change in hip and spine BMD after the first and second doses of Zoledronic acid 5 mg intravenous infusion in patients with confirmed Osteoporosis. The secondary endpoint was to determine the change in B-CTX after administration of once-yearly injection of Zoledronic acid. In addition to verifying the safety and tolerability of Zoledronic acid 5 mg on the patients who received the Zoledronic, within the study period. Descriptive statistics (such as mean, median and standard deviation) will be used to summarize and interpret all adverse drug reactions, demographic and clinical characteristics of the patients without drawing inferences about the population in general. Bone mineral density (BMD), and bone turnover marker (B-CTX) obtained before and after intervention were compared using paired t-test that is a test used when the same subject is used to collect data for both groups. The pre-test and the post-test scores were paired for statistical purposes. P-Values smaller than 0.05 were considered as statistically significant and results were presented with a 95% confidence interval. All statistical analysis was completed using the Statistical Packages of Social Science (SPSS) program version 18.0.

RESULTS

In this study, the net sample size was 108 that consisted of 16 male and 92 female patients with mean age of (63.53 years, SD ± 11.3911) [Figure 1]. The patients are from different nationalities including 59% Qatari men/women and 41% non-Qatari men/women with the initial diagnosis of 50% Postmenopausal Osteoporosis, 25% Glucocorticoid-induced Osteoporosis and 25% senile Osteoporosis, as illustrated in Table 1.

One year following administration of the first dose of Zoledronic acid 5 mg infusion, the lumbar spine BMD at L2 increased by 2.5% (P=0.592), at L2-L4 increased by 6.63% (P=0.039). The left femoral neck BMD increased by 3.95% (P=0.131), the left total hip BMD decreased by 3.74% (P=0.458). The right femoral neck BMD decreased by 5% while the right total hip increased by 4.4% (P>0.05) [Table 2].

After the second dose of Zoledronic acid 5 mg infusion, the lumbar

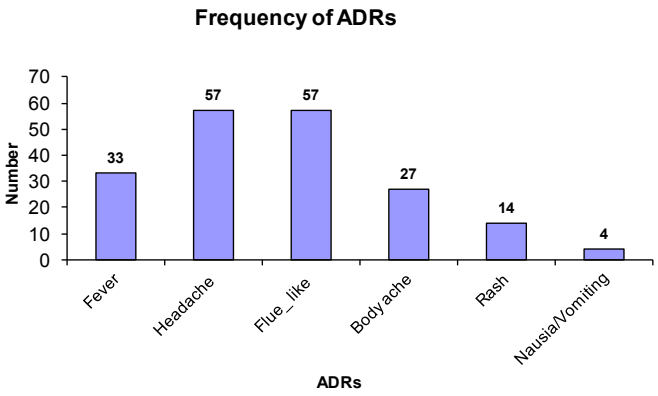

Figure 1: Reported adverse drug reaction during the study period

spine BMD at L2 increased by 8.6% (P=0.505) and at lumbar spine at L2-L4 rose 20% (P=0.024). The BMD of left femoral neck decreased by 8.27% (P=0.350) and of the left total hip was reduced by 25.8% (P=0.193). A 4.9% reduction in the mean BMD value of right femoral neck was observed (P=0.421), and a 5.73% decrease in the mean BMD value of right total hip was observed (P=0.547) [Table 2].

During the study period, there was a decrease in the mean value of B-CTX by 17.9% (P=0.161) after the first dose of Zoledronic acid 5 mg. And declined by 10.9% (P=0.460) is observed after the second dose [Table 3].

Regarding the ADRs, the number of patients who suffered from a headache and flu-like symptoms within three days of the infusion was high within the post-treatment symptom among our subjects, with lower rates of fever, body ache, rash, nausea, and vomiting. On the other hand, there were no reports of severe adverse drug reaction like AF and jaw osteonecrosis, atypical fracture, renal impairment or hypocalcaemia.

DISCUSSION

Each patient had baseline BMD using DXA scan before starting therapy and one year after each Zoledronic acid 5 mg annual infusion according to National Osteoporosis Foundation expert consensus (2003) recommendations. Any change in BMD value from baseline was considered as a treatment effectiveness indicator. The resulted of our study revealed an improvement in lumbar spine BMD by 6.63% after the first dose and by 20% (P=0.039 and 0.024 respectively) after the second dose. In line with our results multicenter, randomized, double-blind, placebo-controlled trial, affirmed the increase of the lumbar spine BDM by 6.7% (P<0.001) after the third dose in postmenopausal women.[7] Additionally, one more study asserted the benefit of Zoledronic acid injection in postmenopausal women with low bone mineral density, in term of increment of BMD at lumbar spine by 4.3-5.1% higher than those observed in the placebo group (P<0.001).[8]

However, the left total hip and right femoral neck BMD showed a non-significant decrease by 1.8%, and 2.24% respectively were observed in our study post the first dose. This indicates the failure to respond to therapy with Zoledronic acid 5 mg. However, these results might be due to chance and further studies are required in this aspect. However, the current literature showed opposite results to our study. The HORIZON-Pivotal Fracture Trial, a 6% increment of the total hip BMD and 5.1% rise of the femoral neck BM (P<0.001 for all comparators).[7] Moreover, one more study compared the effect Zoledronic acid versus placebo in postmenopausal women, on femoral neck BMD, the study revealed an increase of the BMD by 3.1-3.5% (P<0.001).[8]

The bone turnover marker, serum C-telopeptide of type I collagen

Table 1: Baseline characteristic of the study population

Characteristics Mean (SD) age (years)	Number 63.53 +/- SD (11.3911)
Gender	
Female	85.2%
Male	14.8%
Nationality	
Qatari	59%
Non-Qatari	41%
Number of doses	
Patients received 1 dose	100%
Patients received 2 doses	15.7%
Baseline lumbar spine BMD g/cm2	
L2	-1.987 +/- SD (1.3460)
L2-L4	-1.814 +/- SD (1.2675)
Base line left femur BMD g/cm2	
Neck	-1.519 +/-SD (0.9950)
Total	-1.074 +/-SD (1.0766)
Base line right femur BMD g/cm2	
Neck	-1.386 +/- SD (1.0683)
Total	-1.142 +/- SD (1.0720)
Baseline B-CTX	209.33+/- SD (145.444)

Table 2: BMD change from baseline after the first and second doses

	Difference	% Difference	Significance
L2 base – L2 post 1st dose	+ 0.05	+ 2.5%	0.592
L2-L4 base -L2-L4 post 1st dose	+ 0.12	+ 6.63%	0.039
Lt N base – Lt N post 1st dose	+ 0.06	+ 3.95%	0.131
Lt T base – Lt T post 1st dose	- 0.04	- 3.74%	0.458
Rt N base – Rt N post 1st dose	- 0.07	- 5%	0.255
Rt T base – Rt T post 1st dose	+ 0.05	+ 4.4%	0.410
L2 base – L2 post 2nd dose	+ 0.18	+ 8.6%	0.505
L2-L4 base –L2-L4 post 2nd dose	+ 0.36	+ 20%	0.024
Lt N base – Lt N post 2nd dose	- 0.12	- 8.27%	0.350
Lt T base – Lt T post 2nd dose	- 0.23	- 25.8%	0.193
Rt N base – Rt N post 2nd dose	- 0.07	- 4.9%	0.421
Rt T base – Rt T post 2nd dose	- 0.07	- 5.73%	0.547

Table 3: The B-CTX change from baseline after the first and the second doses

	Difference	% Difference	Significance
B-CTX base – B-CTX post 2nddose	- 37.4	+ 17.9%	0.161
B-CTX base – B-CTX post 2nd dose	-18	10.9%	0.460

(B-CTX) along with BMD or instead of it, is a monitoring parameter of treatment efficacy and improvement or change in osteoporotic status. Although the results of B-CTX change during Zoledronic acid 5 mg treatment were non-significant, they tend to be decreased by 9.7% after the first dose and by 5.77% after the second dose. Despite non-significance; these results are comparable with results obtained from previous studies. The data obtained from a randomized, double-blind placebo-controlled trial showed a significant reduction in bone turnover marker serum C-telopeptide of type I collagen by 59%. This was documented during treatment with Zoledronic acid 5 mg when compared with placebo group (P<0.001).[7] Also, the data added by biochemical markers of bone turnover, particularly serum C-telopeptide of type I collagen, was significantly suppressed with a median decrease of 65 to 83% in a study of 351 post-menopausal women with Osteoporosis that was designed to evaluate the effect of Zoledronic acid 5 mg annual infusion.[8]

Furthermore, a study assessed 833 men and females, ages between 18-85 years, who received>7.5 mg per day or equivalent oral prednisolone for less than three months (as prevention) or more than three months (as treatment). Zoledronic acid 5 mg annual infusion showed faster and consistent reduction in bone turnover markers when compared to Residronate oral daily dose.[9] A one-year double-blind, double-dummy trial to investigate the efficacy of IV Zoledronic acid 5 mg versus oral alendronate 70 mg, resulted in decreased bone turnover markers in Zoledronic acid 5 mg group after three months returned to baseline after six months. Further increment over the baseline occur but still within the premenopausal range.[10]

Acute phase reactions are the most common ADR associated with nitrogen-containing bisphosphonates (NBPs) use. They occur maximally within 24 to 36 hours after IV administration of bisphosphonates and are self-limiting symptoms that resolve within 2 to 3 days.[11] A study reported that acute phase reactions were presented as, pyrexia in 16.1% of patients, myalgia 9.5%, flu-like symptoms 7.8% and arthralgia 6.3%.[12] It usually appears in 30% of patients post the first dose in a decreasing manner with following doses to be 6.6% post the second dose and to reach 2.8% post the third dose.[11] The anticipated mechanism of the acute phase reaction is; mevalonate pathway inhibition caused by NBPs, leading to rapid and copious stimulation of Tumor Necrosis Factor alpha (TNFα) and Interleukin 6 (IL6) by peripheral blood cells γ δ T-cells, in addition to intracellular accumulation of isopentenyl pyrophosphate (IPP) as a result of FPP synthetase inhibition.[13-16] The acute phase reaction can be abrogated by pre-administration of statins (HMG-CoA reductase inhibitor), which in turn inhibits NBP-induced production of these pro-inflammatory cytokines by γ δ T cells through blockage of the mevalonate pathway, in addition to inhibition of FPP and prevent IPP intracellular accumulation.[17-19] Another approach is the administration of paracetamol or ibuprofen shortly after administering the dose.[20] Moreover, there is a suggested association between post-dose symptoms and Vitamin D deficiency, which emphasizes the importance of vitamin D supplementation before the dose, to reduce the incidence of these symptoms.[21]

ADRs reported in this study are post-dose symptoms that resolved within three days, like a headache and flow-like symptoms which are associated with Zoledronic acid 5 mg administration, observed in 53% of patients. A slightly lower percentage was observed with fever, body ache, rash and nausea and vomiting. There were no reports of severe or serious ADRs like AF, atypical fracture, ONJ, hypocalcaemia or renal impairment.

The main difficulty of this study was the small sample size that was not enough to significantly detect the changes in most of the monitoring parameters (BMD and B-CTX) pre and post Zoledronic acid 5 mg dose. The main reason behind that was patient's non-compliance, the only possible way to overcome this problem is sending reminder messages or calling the patients to remind them about their doctor's appointment, DXA scan date or B-CTX test before the scheduled date.

No reports of serious adverse drug reactions were detected. The expected reason for this is a lack of connection between the administered medication and the developed ADR because of a lack of knowledge about possible ADR of each medication. Also, the lack of awareness of the importance of reporting each adverse event and submitting the reports to the drug information center according to HMC policy. To

overcome this problem, the clinical pharmacist should be involved in ADR detection, monitoring, and reporting.

CONCLUSION

The results of this small-scale study illustrate a significant increase in lumbar spine BMD at L2-L4 after each dose of Zoledronic acid 5 mg annual infusion. None of the other studied variables were able to show a significant change from baseline. Acute phase reactions are the only reported ADRs, where a headache and flu-like symptoms had the highest rate of the reported acute phase reactions.

Small sample size, non-compliance and suboptimal ADRs reporting emphasize the importance of pharmacist role in overcoming these limitations, highlighting the importance of further studies to be done to evaluate the utility of Zoledronic acid 5 mg, with implementing the clinical pharmacist in the pharmaceutical care plan to overcome the previously mentioned limitations.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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