Original Article

Observational Study on Efficacy of Ibandronate Sodium 3 mg IV Injection in Treatment of Postmenopausal Osteoporosis

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Objective: To evaluate the efficacy of Ibandronate sodium 3 mg IV injection in routine clinical practice for treatment of postmenopausal osteoporosis.

Materials and Methods: With approval of the Ethical Committee, 21 bisphosphonate naïve patients were recruited to receive Ibandronate sodium 3 mg IV injection every three months for 12 months. After the last injection, the patients were followed up at months 12 and 18. The serum level of bone resorption marker, the carboxy-terminal collagen crosslinks (sCTX) were measured at baseline, one week, and every three months before the next injection. Bone mass density (BMD) were evaluated at baseline and month 12. Adverse events were evaluated. Serum creatinine were evaluated at baseline, end of treatment, and end of follow up.

Results: Median sCTX reduction was 86.9% within one week after injection from 614.5 pg/mL to 84.0 pg/mL. Median sCTX declined to 329.0, 289.0, 305.0, 285.0 pg/mL at month 3, 6, 9, and 12, respectively. Six months after the last treatment, median sCTX was elevated to 433.0 pg/mL or 75.1% of the baseline. Two non-responders, or 9.5%, with low sCTX at the baseline were found. At month 12, lumbar spine and hip BMD were significantly increased by 4.29% (p=0.003), and 2.20% (p=0.05), respectively. For safety perspective, there was no change in median estimated glomerular filtration rate (eGFR) level from baseline to month 12. Mild to moderate adverse effects had occurred in 33.3% of the patients, myalgia and flu-like symptoms were the most common findings.

Conclusion: Ibandronate injection is effective for postmenopausal osteoporosis treatment. It rapidly reduced sCTX to lower than the average level of premenopausal reference range, which could relate to fracture risk reduction. It has significantly increased lumbar spine and hip BMD. Safety profile was promising with a quick off-response and an unchanged renal function. Ibandronate injection has better compliance and advantage for patients having difficulty in complying with oral treatment.

Keywords: IV bisphosphonate; Postmenopausal osteoporosis; Bone turnover marker; Quick off-response

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Osteoporosis is the disease of reducing bone strength and increasing fracture risk. In 2001, it was reported that 28.8% of Thai women aged over 70 years old had osteoporosis[1]. Approximately one-third to one-half of women will sustain at least one osteoporosis fracture during their lifetime[2]. Hence, this debilitating condition with its significant morbidity and mortality, has important implications for public health[3].

Vertebral fracture is the most common fracture that is found in postmenopausal osteoporosis with age more than 50 years old[4]. Risk of vertebral fracture is increasing by advanced age and previous fracture. Morbidity and mortality rate significantly increase compared to the one without fracture.

Bisphosphonate group is a potent bone resorption and is a drug of choice to treat postmenopausal osteoporosis. Nowadays, due to their efficacy in reducing bone resorption and preventing osteoporotic fractures, it has been listed in Thailand national list of essential medicine (NLEM) 2018 for treating patients with osteoporosis.

Despite proven efficacy, oral bisphosphonates have low intestinal absorption at around 0.7%[5-7] and their absorption is potentially further reduced by concomitant food or beverages. Gastrointestinal (GI) irritation is the most common adverse effects

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of oral bisphosphonates. To ensure GI tolerability and maximum bioavailability, patients taking oral bisphosphonates must adhere to stringent dosing guideline. Since osteoporosis is a silent disease, approximately 50% of patients discontinue oral bisphosphonate within the first year[8]. The previous study of weekly oral bisphosphonate in Thailand showed that non-adherence rate was 26.2% at 24 weeks[9].

Poor adherence of oral bisphosphonates leads to sub-optimal fracture protection. Adherence rate of 50% has led to almost no fracture protection while 80% adherence rate has led to less than 50% of optimal fracture protection[10]. Intravenous (IV) bisphosphonates have lower GI adverse effects and higher adherence than oral form. Bisphosphonates in both oral and IV dosage forms are available in Thailand. Ibandronate is one of the drugs in this group with many dosage forms.

Bone turnover markers or biochemical markers of bone turnover (BMT) have the ability to detect changes in bone turnover rate since the early weeks of treatment[11]. They are cheap and non-invasive, which can be measured from the fasting blood sampling in the early morning. Bone resorption marker, especially carboxy-terminal telopeptide cross-linked type 1 collagen, is highly sensitive in monitoring the efficacy of antiresorptive drugs such as bisphosphonate treatment. Both biochemical marker of bone turnover and bone mineral density (BMD) are surrogate marker for efficacy of antiresorptive treatment. American association of endocrinologist recommends that stable or increasing BMD with no evidence of new fractures or BMT at or below the median value of premenopausal women are indicated successful osteoporosis treatment[12].

Ibandronate efficacy and safety have been demonstrated in previous studies. To the best of the authors knowledge, IV Ibandronate has never been studied before in Thailand. The present study aimed to evaluate the efficacy of IV Ibandronate on its efficacy and tolerability in term of the increase in BMD and the reduction of bone resorption marker carboxy-terminal collagen crosslink (CTX) as primary outcomes. In addition, the adherence to the treatment and the adverse events will be studied as the secondary outcomes.

Materials and Methods

"The open-labeled prospective study was approved by the ethical review board of this institution (MURA2016/656) and followed the Declaration of Helsinki." The present study was conducted to investigate efficacy of IV Ibandronate in postmenopausal women with osteoporosis in routine practice. Study population was postmenopausal women attending the orthopedic out-patient clinic at Ramathibodi Hospital. The inclusion criteria were patient with the BMD T-score of lumbar spine or femoral neck or total hip lower than –2.5, normal complete blood count, normal kidney function, and willing to participate the study after completing informed consent. The participants who had previous treatment with bisphosphonates were excluded.

Sample size was calculated, based on sample size for one sample continuous outcome as following formula[13].

$N = (Z\sigma/E)^2$

Z is the values from standard normal distribution (Z=1.96 for 95%), σ is the standard deviation of outcome variable, which is % mean CTX reduction from previous study (σ=21.8)(9). E is the desired margin of error (E=10%). Sample size calculation was 20. An additional 20% was included for the loss to follow-up. Therefore, the sample was 22 patients.

Fifty post-menopausal women eligible and willing to complete the informed consent were recruited. Twenty-three patients fulfilled the criteria and agreed to attend the protocol. All patients were treated with IV Ibandronate 3 mg at month 0, month 3, 6, and 9, in the observation room, orthopedic out-patient clinic of Ramathibodi Hospital. They were given concomitantly with daily 1,000 mg of calcium carbonate, equivalent to 400 mg elemental calcium and monthly 20,000 IU of vitamin D2 during the study. Then they were asked to be followed at week 1 then every three months for one year and additional follow-up at six months after the end of the protocol. All baseline characteristics were recorded, including age, age at menopause, underlying diseases, BMD of lumbar spine, neck and total hip, and renal function test.

The serum CTX (sCTX) was measured by electro-chemiluminescence immunoassay (ECLIA, Roche Diagnostics GmbH, Mannheim, Germany) at week 1, month 3, 6, 9, 12, and 18. Moreover, BMD was measured by DXA (Hologic; Massachusetts, United States) at baseline and at month 12 while serum creatinine was measured at baseline, month 12 and 18. The total analytical coefficient of variation (CV) of ECLIA for CTX was less than 5% and intra-individual CV was 9.6%, so the least significant change (LSC) that can be considered statistically different was calculated as 27%. Because of its low

CV and large change with antiresorptive therapy, sCTX has greater utility for assessing efficacy of bisphosphonate treatment than other markers.

CV of Hologic DXA at that moment were 0.69% for total spine (L1-L4), 1.0% for femoral neck, and 0.80% for total hip. The calculations of LSC that was considered statistical difference for BMD at each site were 2%, 3%, and 2.2% for lumbar spine, neck, and total hip, respectively.

Well-trained clinical research associates recorded the experiences of possible adverse events such as flu-like symptom, myalgia, local injection site reactions, nausea, and vomiting.

Statistical analysis

The results were analyzed based on intention to treat for efficacy and safety profiles. Continuous variables were reported using median and range. Categorical variables were reported by the percentage. Normal distribution of data was determined by Shapiro-Wilk test. Wilcoxon signed rank test was employed to compare paired continuous variables while one-sample Wilcoxon signed rank test was employed to compare continuous variables to the standard value.

The significant level was defined at p-value less than 0.05. All statistical analysis was performed by SPSS Statistics, version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient baseline characteristics.

From the 50 consecutive postmenopausal women who fulfilled the criteria, 23 patients were eligible for the study and 21 patients completed the protocol. Overall baseline characteristics of the patients were recorded including the median age of 66 with a range of 55 to 70 years and the median menopausal age of 51 with a range of 45 to 57 years. Median T score of BMD at lumbar spine, femoral neck, and total hip were –2.60 with a range of –4.20 to –1.10, –2.60 with a range of –3.60 to –1.90, and –1.80 with a range of –2.90 to –0.60, respectively (Table 1).

Table 1. Baseline characteristics of the treatment group

Variables	Ibandronate injection; median (range)
Age (years)	66 (55 to 70)
Menopausal age (years)	51 (45 to 57)
Serum CTX (pg/mL)	614 (234 to 1070)
Serum creatinine (mg/dL)	0.68 (0.36 to 0.96)
BMD	
Lumbar spine BMD(g/cm^2)	0.72 (0.53 to 0.88)
Lumbar spine T-score	–2.60 (–4.20 to –1.10)
Femoral neck BMD (g/cm^2)	0.53 (0.41 to 0.60)
Femoral neck T-score	–2.60 (–3.60 to –1.90)
Total hip BMD (g/cm^2)	0.65 (0.52 to 0.79)
Total hip BMD T-score	–1.80 (–2.90 to –0.60)

CTX=carboxy-terminal collagen crosslink; BMD=bone mass density

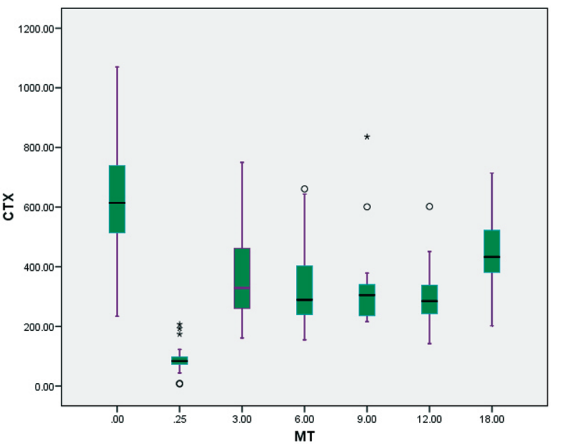

Figure 1. Median of bone resorption marker (serum CTX) from the baseline until the end of treatment. The means of sCTX were clinically significant reduction.

Efficacy analysis

Baseline serum CTX was 614.5 with a range of 234.0 to 1070.0 pg/mL and reduced rapidly to 84.0 with a range of 7.0 to 207.0 pg/mL at one week after initial injection. Median sCTX were maintained below the average level of premenopausal range at every interval. At months 3, 6, 9, and 12 median sCTX were 329.0 with a range of 161.0 to 750.0, 289.0 with a range of 155.0 to 661.0, 305.0 with a range of 216.0 to 836.0, and 285.0 with a range of 142.0 to 602.0 pg/mL, respectively (Figure 1). The percentages of median sCTX reduction were at the level proven to have fracture risk reduction. It was a reduction of 53.66% at month 12 after the initial injection (Figure 2).

There were two non-responders, defined by resorption BMT showing the average sCTX reduction as –5.7% and –11.4%.

At month 12 or after one year of treatment, DXA was repeated and BMD of the lumbar spine and total hip were significantly increased by 4.29% and 2.20%, respectively, from the baseline (p=0.003 and 0.05). Median BMD of femoral necks were also increased by 1.70%, without statistical significance (p=0.085) (Figure 3).

Table 2. The serum CTX levels during treatment

Variables	CTX (pg/mL); median (range)	p-value[1]	% median CTX change	p-value[2]
Pre-treatment	614.50 (234.00 to 1070.00)			
1 week	84.00 (7.00 to 207.00)	<0.001	–86.90	<0.001
3 months	329.00 (161.00 to 750.00)	<0.001	–38.40	0.003
6 months	289.00 (155.00 to 661.00)	<0.001	–48.29	0.013
9 months	305.00 (216.00 to 836.00)	<0.001	–50.27	0.004
12 months	285.00 (142.00 to 602.00)	<0.001	–53.66	<0.001
18 months	433.00 (202.00 to 714.00)	<0.003	–24.90	0.658

CTX=carboxy-terminal collagen crosslink

Significant improvement of sCTX reduction has to be lower than least significant change

[1] Median sCTX different to baseline, [2] Compared to the least significant change

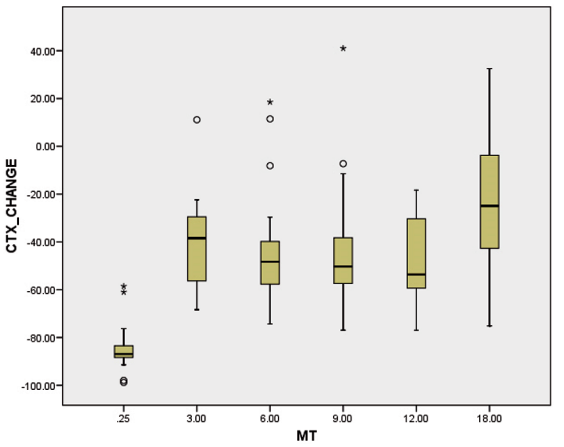

Figure 2. Percentage of serum CTX reduction according to time.

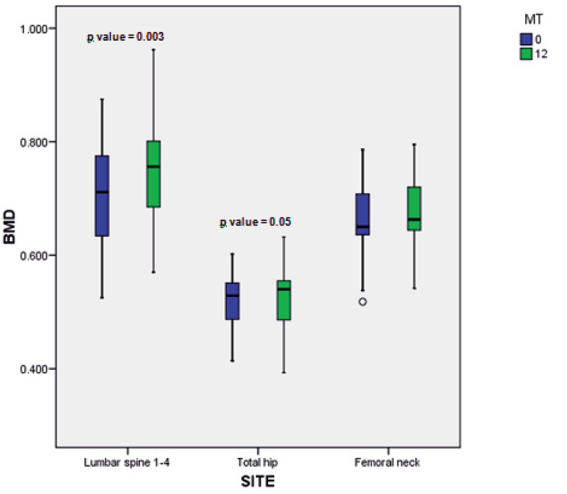

Figure 3. Median BMD at the baseline and month 12 showed increase in each site.

At the last follow up, month 18 median sCTX increased to 433.0 with a range of 202.0 to 714.0 pg/mL, which was almost the same level as baseline. It should be noted that CTX change was less than LSC (Table 2).

Safety assessment

There was no change in eGFR from baseline to the end of treatment (Figure 4). Median eGFR were 86.2 mL/minute/1.73 m² at baseline and 85.2 mL/minute/1.73 m² at the end of treatment (p=0.058). Seven patients or 33.3%, revealed adverse events, and myalgia was the most common adverse event with mild to moderate symptoms. Five patients had myalgia and four of them needed rescued medication. Most adverse events occurred after the initial injection and resolved within one week, except that one patient still had symptom after the second injection. One patient had cerebrovascular thrombosis at nine months after the last injection identified as non-investigated drug related. Non-responders were revealed in two patients (9.5%) by biochemical marker of bone turnover. All of them had low baseline BMT and their sCTX were lower than 340 pg/mL.

Severe suppression of bone remodeling cycle leads to serious adverse events including atypical femoral fracture (AFF) and avascular necrosis of the jaw (ONJ). The over suppression of CTX lower than 150 to 200 pg/mL is vulnerable to ONJ[14].

From the present study result, almost all patients had sCTX between the lower half and –1SD of pre-menopause level. Three patients had sCTX reduction to the level of over suppression but not less than 200 pg/mL at month 12. However, the sCTX was return to premenopausal level at the end of study. There was no patient having sCTX level less than 150 pg/mL at month 3, 6, 9, and 12.

Two patients were lost follow-up after initial injection and classified as non-compliance. Therefore, there was 8.7% (2 of 23) patients of non-compliance

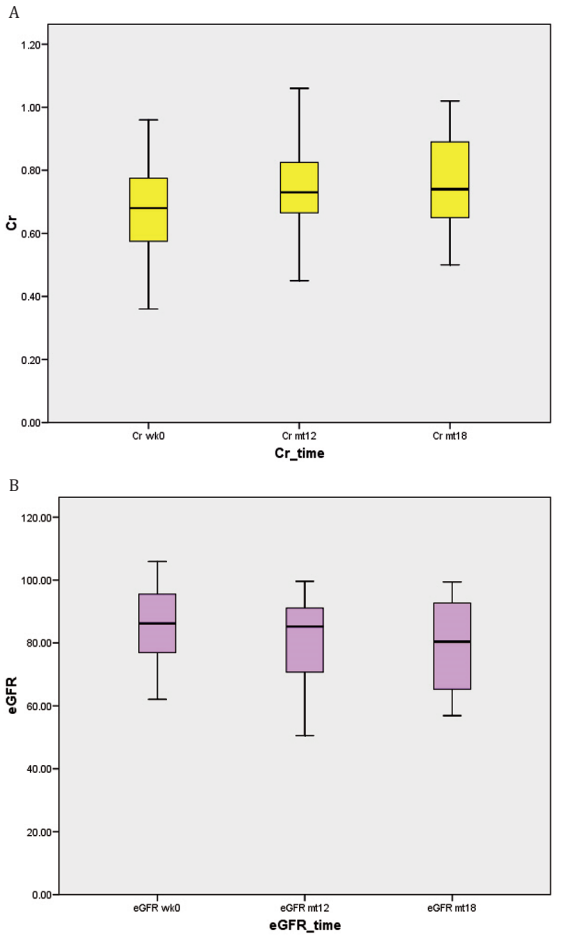

Figure 4. Serum creatinine level (A) and eGFR (B) at the baseline and follow-ups.

in the present study (Table 3).

One patient aged 67 had a car accident and suffered hip fracture at month 6. Thus, this incidence was not considered as severe adverse event of the present trial because it was not a fragility fracture. She had continued the protocol with regular follow-up after the surgery.

Discussion

The IV Ibandronate has showed the rapid onset by sharply declining the resorptive bone marker, which was an 86.9% reduction at the first week after the injection. Afterwards, it maintained within the lower half of reference range of premenopausal level or CTX range 100 to 650 pg/mL and a mean of 300 pg/mL[15], and had a 53.7% median reduction from the baseline, which is the optimum or the ideal level for osteoporosis treatment[16]. It also had a quick off-response after treatment discontinuation,

Table 3. Adverse effects and non-compliance rate of the treatment group

Variables	Treatment; n (%)
Adverse effects	7 (33.3)
Myalgia	5 (23.8)
Flu-like symptom	4 (19.0)
Pain	4 (19.0)
Non-compliance	2 (8.7)
CTX <200 pg/mL	
• 3 months	2 (9.5)
• 6 months	2 (9.5)
• 9 months	0 (0.0)
• 12 months	3 (14.3)
CTX <100 pg/mL	
• 3 months	0 (0.0)
• 6 months	0 (0.0)
• 9 months	0 (0.0)
• 12 months	0 (0.0)

CTX=carboxy-terminal collagen crosslink

consequently the resorptive BMT had gradually increased and nearly reached the baseline (75%) at month 18. This is supported by the pharmacological structure of Ibandronate showing a low binding affinity to hydroxyapatite. It will distribute more widely in bone tissue and have the quicker offset of action after treatment discontinuation. The higher affinity bisphosphonates will bind more abundantly to the bone surface and will have less penetration into the bone surface[17]. These results confirm that IV Ibandronate has high efficacy in bone remodeling inhibition with a widely distribution along the bone and has a quick offset of bone remodeling suppression.

In the present study, there were two non-responders defined by resorption BMT with a mean CTX reduction of –5.7% and –11.4%. Their serum CTXs at baseline were 234 and 340 pg/mL, and the BMD at month 12 revealed no improvement. The non-responders in the present study seem like post-menopausal women with lower level of BMT or low-turnover osteoporosis, which are not suitable candidate for treatment with anti-resorptive drugs, especially bisphosphonates[18]. An interesting point from the present study was that all the patients including non-responders had markedly reduced BMT at first week after IV Ibandronate. It is theoretically that after BP administration, and during molecules of BP are circulating in extracellular fluid, they affect to surrounding osteoclasts and lead to apoptosis. Afterwards, the rest of BP molecules have to attach and penetrate to the new bone formation. In case of

low-turnover osteoporosis, which has a very slow rate of bone resorption and new bone formation, only few BP molecules could attach to the new bone formation. Subsequently, most of the BP molecules remained in extracellular fluid and later, eliminated through kidney excretion[19].

One patient aged of 67 had a car accident and suffered hip fracture at month 6. She had continued the study protocol with regular follow-up after the surgery for internal fixation. This incidence was not regarded as severe adverse event of the present trial because it was a traffic accident and not a fragility fracture. Her serum CTX had much highly increased to 836 pg/mL after the injury and returned to 24% reduction to 451 pg/mL from the baseline of 593 pg/mL at month 12. However, her BMD at month 12 had increased 9% at lumbar spine and 5.8% at total hip but decreased –5% at femoral neck. Thus, she responded to IV Ibandronate.

If these two non-responders and the patient with hip fracture, which might have an effect to the higher median sCTX after treatment in total, were excluded, then percentage of sCTX reduction would be 55.24%. The substantial reduction of the sCTX delineates the anti-fracture efficacy of the drug[20].

Regarding the severe suppression of potent anti-resorptive bisphosphonates, the present study has revealed that none of the patients had sCTX less than 150 pg/mL during the treatment with IV Ibandronate. This elucidates that IV Ibandronate is one of the potent anti-resorptive drugs that has optimal efficacy and has no over suppression of bone remodeling. Therefore, the serious adverse effects including ONJ and AFF are avoidable.

Two patients were lost follow-up after the initial injection and were categorized as non-compliance. There are 8.7% of non-compliance to IV Ibandronate in the present study, which is much lower than oral bisphosphonates[8].

BMD gain after one year of IV Ibandronate therapy has showed 4.29% increase in bone density at lumbar spine and total hip 2.20%, with statistical significance (p=0.003, p=0.05). It also increases in BMD at femoral neck without statistical significance by 1.70% (p=0.085). Although the present study is a short term follow up, nevertheless, it has showed a significant increase in lumbar spine and hip BMD within one year of IV Ibandronate treatment. This result is similar to the previous study at 4.29% versus 4.8%[21].

One patient in the present study had no improvement of BMD, although she had good response to treatment by more than 50% reduction of sCTX. The authors tried to find out the cause or any risk factor, and one of the causes is low serum 25(OH)D level. The recommended level by IOF for osteoporosis treatment group is 30 ng/mL. Her serum 25(OH)D was 22 ng/mL at month 6 and 19.9 ng/mL at month 18. Nevertheless, she had to continue the protocol without vitamin D supplement until the end of the protocol.

Regarding safety profile, no new eventful adverse event was revealed in the present study. Adverse events in the present study were frequently reported among patients treated by Ibandronate injection[21], which were myalgia and flu-like symptom. However, these acute phase reactions usually subsided within days and did not occur in the next injection, except one patient still had the reaction on the second dose but with less severity. Renal function is a highly concerned issue, especially for IV bisphosphonates and in the present study, no participant had abnormal change in serum creatinine. Due to the advanced age in these osteoporosis patients, the eGFR that is a mathematically derived entity based on individual serum creatinine level, gender, and age, was also calculated, and compared. Again, there was also no statistically significant change in median eGFR from the baseline.

Conclusion

Ibandronate injection has an optimal efficacy to reduce serum CTX, increase lumbar spine and hip BMD. Its potency to inhibit bone resorption marker to a lower half of pre-menopause level. Moreover, the product has good renal safety profile with low adverse effects and quick off-response.

An injectable form of Ibandronate has better compliance than the poor absorption oral bisphosphonate. With the benefits of good compliance, optimal efficacy, and safety profile, IV Ibandronate injection every three months is likely to be advantageous for patients who cannot tolerate oral bisphosphonates or having difficulty in complying with oral treatment. Therefore, it may be considered as an alternative option to accomplish the efficacious treatment for post-menopausal osteoporosis.

What is already known on this topic

Bisphosphonate group is a drug of choice for postmenopausal osteoporosis treatment. The anti-fracture efficacy was proven to satisfactory for reduction of vertebral, non-vertebral, and hip fractures. Oral bisphosphonates have low absorption

and need to be taken after overnight fasting with plain water. On the contrary to IV bisphosphonates, which directly infuse into the circulation, is another choice to avoid the problems of drug absorption and GI irritation.

In literature review, studies indicate that patients who take oral bisphosphonates only 80% of the recommended dose will benefit only 50% of anti-fracture efficacy. In chronic silent disease of osteoporosis, the adherence to the treatment is an important factor to achieve a good outcome. Long-acting bisphosphonates have better compliance and are usually prescribed to the osteoporotic patients, nowadays.

Major concern of the adverse reaction of bisphosphonates is their potent inhibition of osteoclast function and causes an over-suppression of bone turnover. Long-term treatment of these potent anti-resorptive drugs have serious side effects, including AFF and osteonecrosis of the jaw.

What this study adds

The authors have revealed that IV bisphosphonate, especially IV Ibandronate, has a rapid onset and can reduce resorption BMT within the first week after the initial injection. Ibandronate IV injection of 3 mg every quarterly has optimal efficacy for Thai post-menopausal osteoporosis, which includes a significant increase in lumbar and hip BMD at one year after treatment and remarkable safety profile. It suppresses bone turnover rate to the optimal level, which is around 54% reduction of resorption BMT (sCTX) and maintains the level within the lower half of the premenopausal range throughout the period of treatment.

Ibandronate has a quick off-response, which was demonstrated by the recovery of bone turnover suppression as soon as six months after cessation of the treatment. The resorption BMT has gradually increased to approach the baseline at the interval follow-ups. Therefore, the serious adverse events of over-suppression of bone remodeling are not inevitable and is convenient for the health care providers to stop or temporarily suspend the treatment whenever they require.

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Conflicts of interest

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