Assessing the effectiveness of Aclasta for osteoporosis in patients with femoral head fractures

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Abstract. Assessing the effectiveness of Aclasta for osteoporosis in patients with femoral head fractures at Thong Nhat Hospital in Ho Chi Minh City. A number of 156 patients with femoral head fractures and osteoporosis in orthopaedic department at Thong Nhat in Ho Chi Minh City were assigned to a randomized controlled trial from 01 Jan 2013 to 01 Jan 2014, divided into 2 groups.75 case were treated with Aclasta, 81 patients were received Placebo. Most of them had been followed for at least 1 year about new bone fractures and T-score index before and 1 year after treatment. New fractures were found about 8% in the Aclasta group, and 13.6% in the Placebo group, statistical significance ($p < 0.001$). Vertebral fractures different from Aclasta 1.3%; Placebo groups 3.7% and the incident femoral head fracture in turn is 2.6% and 3.7%. T-Score improved significantly after 1 year in Aclasta group, the proportion of patients with T-score in this group change from the lack to normal bone is 33.3% and 8% compared to the placebo group was 7.4% and 0%, difference was statistically significant ($p < 0.001$). Using Aclasta for treatment of osteoporosis after femoral head fracture surgery reduce the incidence of new fractures and T-score improvement in patients with femoral head fractures accompany with osteoporosis, especially in elderly patients.

Key words: osteoporosis, postmenopausal osteopenia, bone density, fractures, zoledronic acid.

INTRODUCTION

Osteoporosis is a metabolic bone disease caused by progressive bone loss. It is characterized by low bone mineral density (BMD) and structural deterioration of bone tissue leading to bone fragility and increased the risk of fractures. This is common in women after menopause,when a woman's ovaries stop producing the female hormone,oestrogen, which keeps bones healthy. It also occurs in men and women with increasing age.

The symptoms of osteoporosis, generally speaking, are from the fractures they cause. New fractures after surgery on femoral head fractures in osteoporotic patients lead to a failure of treatment. Treatment with Aclasta (zoledronic acid) - an intravenous bisphosphonate - for osteoporosis once a year can improve this situation (Black et al., 2006, 2010; Lyles et al., 2007; Siris et al., 2006; Nguyen et al., 2006). Aclasta is given as an infusion lasting at least 15 minutes. Aclasta works by slowing down bone resorption, which allows the boneforming cells time to rebuild normal bone. This allows bone remodeling to go back to normal and protects the bones from being weakened.

Aclasta is also used to treat Paget's disease of the bone in adults. This is a disease where the normal process of bone growth is changed. For Paget's disease, each dose of Aclasta may work for longer than one year.

Each vial of Aclasta contains 5mg of zoledronic acid. Each vial also contains: mannitol, sodium citrate, water for injections.

The majority of side effects with Aclasta are mild to moderate and occur within the first three days of administration. Patients should be advised about the post-dose symptoms which are commonly seen following administration of an intravenous bisphosphonate. These include flu-like symptoms such as fever, myalgia, flu-like illness, headache, and arthralgia (Hayer et al. 2017; Miller et al. 2017; Reid et al. 2018; European Med. Agency, 2015; Aclasta (zoledronic acid), 1 Oct. 2020; Aclasta, 28 Sep. 2020).

We premised the study at Thong Nhat Hospital in Ho Chi Minh City on the large number of elderly patients with osteoporosis, the high rate of femoral head fractures and the high incidence of fractures after surgical interventions. All the patients did agree to participate in the experiment and do not deny the results of the experiment to be provided in the research paper.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

This study aims to assess the effectiveness of Aclasta for osteoporosis in patients with femoral head fractures at Thong Nhat Hospital in Ho Chi Minh City.

MATERIALS AND METHODS

Subjects

We had enrolled 156 osteoporotic patients with femoral head fractures from the Department of Orthopedic Trauma Hospital in Ho Chi Minh City between January 1, 2013 and January 1, 2014. The recommended dose is 5 mg given as an intravenous (into a vein) infusion once a year. Infusions are given by a doctor or nurse over at least 15 minutes.

Patients with bisphosphonate sensitivity, creatinine clearance <30mm / min, cancer, metabolic disease and a predicted survival time of < 6 months were excluded from the study.

Study design

This study was a randomized, placebo-controlled trial with at least 1-year follow- up. Patients with femoral head fractures and osteoporosis were randomly assigned to receive either an infusion of Aclasta or Placebo after surgery.

Fractures in people with osteoporosis usually occur at the hip, spine or wrist. These can lead not only to pain, but also to considerable deformity and disability, such as stooped posture from curvature of the spine, and loss of mobility (Ji and Yu, 2015).

The femoral head fractures must have been due to small impact force (such as falling while standing or from a low elevation) and the patients must have been able to walk prior to their fractures. There are factors associated with an increased risk of osteoporosis-related fractures. These include general factors that relate to aging and sex steroid deficiency, as well as specific risk factors such as use of glucocorticoids (which cause decreased bone formation and bone loss), reduced bone quality, and disruption of microarchitectural integrity. Bone loss can occur without any symptoms, until the fracture actually occurs.

We calculated T-score by measuring the bone mineral density of the patients' femoral neck that was not fractured to diagnose osteoporosis.

Patients received adequate Calcium and Vitamin D supplements 14 days before the infusion.

All patients in Aclasta group must not take any concomitant osteoporosis medications after the infusion.

We followed the patients at the department's clinic once a month for the minimum of one year after they were discharged and assessed the following variables:

- Baseline characteristics of patients: Gender, age, T-score before the treatment.
- New fracture events are monitored at least one year after osteoporosis treatment, except for face and toe fractures.
- T-score after 1 - year follow-up treatment.

RESULTS

Baseline Characteristics of the Patients

Table 1. Description of the characteristics of the study participants

	Gender		Age				T-score before treatment
	Men	Women	<60	60-69	70-79	≥80	≤ -2.5
Placebo (n=81)	20 (24.7%)	61 (75.3%)	14 (17.3%)	19 (25.3%)	34 (41.9%)	14 (17.3%)	81 (100%)
Aclasta (n=75)	17 (22.7%)	58 (77.3%)	12 (16%)	21 (28%)	31 (41.3%)	11 (14.7%)	75 (100%)
P	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

The basic characteristics in the two groups namely Gender, Age, T-score before the treatment were similar (P > 0.05 for all comparisons) (Table 3.1). The vast majority of patients are females, because osteoporosis mostly affect older women. All patients had T-score before the treatment of -2.5 or less, which indicates the diagnosis of osteoporosis.The greater the negative number, the more severe the osteoporosis.

New fractures

Table 2. The one-year incidence of new fractures in the two study groups

Type of Fracture	Placebo (n=81) *No. of patients*	Aclasta (n=75)	p Value
Any clinical fracture	11 (13.6%)	6 (8%)	<0.001
Femoral head fracture	3 (3.7%)	2 (2.6%)	<0.05
Vertebral fracture	3 (3.7%)	1 (1.3%)	<0.05

A total of 17 of 156 patients (10.9%) had any new clinical fracture during the study, of whom 11 of 81 (13.6%) were in the placebo group and 6 of 75 (8%) were in the zoledronic-acid group (significant difference, $P < 0.001$) (Table 3.2). It can be seen that fractures in Placebo group occurred approximately twice as much as in Aclasta group. The rates of a new femoral head fracture were 3.7% (3 patients) in the placebo group and 2.6% (2 patients) in the zoledronic acid group ($P < 0.05$); the rates of a new vertebral fracture were 3.7% (3 patients) and 1.3% (one patient), respectively ($P < 0.05$). The difference in the last two types of fractures is not that enormous, but the effectiveness of Aclasta is clearly obvious. Also, patients with reduced bone mineral density and fractures have significantly increased risk for future fractures.

Our outcomes are consistent with the studies by Black et al. (2007) and Lyle et al. (2007).

T-score

Table 3. T-score after one year in case group (Aclasta) and control group (placebo) (N = 156)

T-score	Placebo (n = 81) *No. of patients*	Aclasta (n = 75)
Osteoporosis (Less than -2.5)	75 (92.6%)	44 (58.7%)
Osteopenia (-2.5 to -1)	6 (7.4%)	25 (33.3%)
Normal (More than -1)	0 (0%)	6 (8%)
p Value	< 0.001	

There is a significant change in T-score after 1 year of follow-up in 2 groups. The rate of patients (92.6%) whose T-score remained at the osteoporosis level in placebo group was greater than in the Aclasta group (58.7%). The rate of patients with osteoporosis at baseline to have a transition to osteopenia in Aclasta group (33.3%) was more tremendous than in placebo group (7.4%) (Table 3.3). In this case, differences in changing of T-scores are truly impressive. While none of patients in placebo group made the transition to normal T-scores, there were 6 (8%) in the zoledronic-acid group. These results illustrate the effectiveness of Aclasta. We found the similar results in the some reports by Black et al. (2010), Siris et al. (2006) and Nguyen et al. (2006).

DISCUSSION

The study showed efficacy of Aclasta in patients with osteoporosis, but its efficacy in women with osteopenia has not been studied much. The decrease in estrogen levels after the start of menopause causes a sustained drop in bone density in most women. About 25% of postmenopausal women can be classified as fast bone losers, and they could be discovered by the measurement of bone loss and bone resorption markers. Most fractures in postmenopausal women take place in those with osteopenia, so therapies that are effective in women with osteopenia are also needed. These types of fractures can be extremely debilitating and lead to many complications. A new 6-year, double-blind trial was conducted in 2018, which illustrated Aclasta's role in fracture prevention. It involved 2000 women with osteopenia (defined by a T score of −1.0 to −2.5 at either the total hip or the femoral neck on either side) who were 65 years of age or older (Gass and Dawson-Hughes, 2006; Sözen et al. 2017; Patient education, 29 Sept. 2020) . Participants were randomly assigned to receive four infusions of either zoledronate at a dose of 5 mg (zoledronate group) or normal saline (placebo group) at 18-month intervals. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not provided to patients. Participants who were not already taking vitamin D supplements received cholecalciferol before the trial began (a single dose of 2.5 mg) and during the trial (1.25 mg per month). The primary end point was the time to first occurrence of a nonvertebral or vertebral fragility fracture (Rothman et al. 2017; Dhillon, 2016; Dalle Carbonare et al. 2010).

The results of this study showed that women who received zoledronate had significantly lower risk of fractures (Liu et al. 2015; Mortiz et al. 2019). A fragility fracture occurred in 190 women in the placebo group and in 122 women in the zoledronate group (hazard ratio with zoledronate, 0.63; 95% confidence interval, 0.50 to 0.79; $P<0.001$). The number of women that would need to be treated to prevent the occurrence of a fracture in 1 woman was 15 (Pouresmaeile et al. 2017). As compared with the placebo group, women who received zoledronate had a lower risk of nonvertebral fragility fractures (hazard ratio, 0.66; $P=0.001$), symptomatic fractures (hazard ratio, 0.73; $P=0.003$), vertebral fractures (odds ratio, 0.45; $P=0.002$), and height loss ($P<0.001$).

The current trial showed that treatment with zoledronate every 18 months, with minimal use of calcium supplements, reduced the risk of fragility fractures (vertebral and nonvertebral) over the course of 6 years in older women with hip bone mineral density characterized as osteopenia (Lems and Raterman, 2017; Qaseem et al. 2017; Akkawi and Zmerly, 2018).

Both trials illustrated that treatment with zoledronic acid reduces the risk of fractures by approximately two times.

CONCLUSIONS

Being a systemic skeletal disease, osteoporosis becomes an important public health and financial issue that is associated with increased mortality and morbidity. It is a common and silent disease until it is complicated by fractures that become common.

The intravenuous administration of Aclasta reduced the incidence of new fractures and improved the T-score in patients with osteoporosis that underwent surgery on the femoral head fractures, especially in elderly patients.

The drug has been associated with a significant reduction of the risk of vertebral, hip, and nonvertebral fractures in women with postmenopausal osteoporosis.

It also produces an increase in bone mineral density and reductions in the markers for bone turnover, and is generally well tolerated. All this makes zoledronic acid a drug of first choice in the treatment of osteoporosis.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Aclasta (zoledronic acid). About this medication. Retrieved from https://chealth.canoe.com/drug/getdrug/aclasta (accessed October 1 2020)

Aclasta. Zoledronic acid. Consumer Medicine Information. Retrieved from https://www.medsafe.govt.nz/Consumers/CMI/a/aclasta.pdf (accessed 28 September 2020)

Akkawi I. and Zmerly H. (2018). Osteoporosis: current concepts. *Joints*, 6(2):122-127.

Black D.M., Delmas P.D., Eastell R., Reid I.R., et al. (2007). Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N. Eng. J. Med.*, 356(18):1809-1822.

Black D.M., Kelly M.P., Genant H.K., Palermo L., et al. (2010). Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N. Eng. J. Med.*, 362(19):1761-1771.

Dalle Carbonare L., Zanatta M., Gasparetto A., and Valenti M.T. (2010). Safety and tolerability of zoledronic acid and other bisphosphonates in osteoporosis management. *Drug, Healthcare Pat. Safety*, 2:121-137.

Dhillon S. (2016). Zoledronic acid (Reclast®, Aclasta®): a review in osteoporosis. *Drugs*, 76(17):1683-1697.

European Medicines Agency. (2015). Aclasta (zoledronic acid). Retrieved from: https://www.ema.europa.eu/en/documents/overview/aclasta-epar-summary-public_en.pdf

Gass M. and Dawson-Hughes B. (2006). Preventing osteoporosis-related fractures: an overview. *Am. J. Med.*, 119(4):3-11.

Hayer P.S., Deane A.K.S., Agrawal A., Maheshwari R., et al. (2017). Effect of zoledronic acid on fracture healing in osteoporotic patients with intertrochanteric fractures. *Int. J. Appl. Basic Med. Res.*, 7(1):48.

Ji, M. X. and Yu, Q. (2015). Primary osteoporosis in postmenopausal women. *Chron. Dis. Transl. Med.*, 1(1):9.

Lems W.F. and Raterman H.G. (2017). Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. *Therapeut. Adv. Musculoskel. Dis.*, 9(12):299-316.

Liu M., Guo L., Pei Y., Li N., et al. (2015). Efficacy of zoledronic acid in treatment of osteoporosis in men and women-a meta-analysis. *Int. J. Clin. Experiment. Med.*, 8(3):3855-3861.

Lyles K.W., Colón-Emeric C.S., Magaziner J.S., Adachi J.D., et al. (2007). Zoledronic acid and clinical fractures and mortality after hip fracture. New *England J. Med.*, 357(18):1799-1809.

Miller P.D., Pannacciulli N., Brown J.P., Czerwinski E., et al. (2016). Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. *J. Clin. Endocrin. Metabol.*, 101(8):3163-3170.

Moritz M., Knezevich E., and Spangler M. (2019). Updates in the treatment of postmenopausal osteoporosis. *U.S. Pharmacist*, 44(9):32-35.

Nguyen N.D., Eisman J.A., and Nguyen T.V. (2006). Anti‐hip fracture efficacy of bisphosphonates: a Bayesian analysis of clinical trials. *J. Bone Min. Res.*, 21(2):340-349.

Patient education: Bone density testing (Beyond the Basics). Retrieved from https://www.uptodate.com/contents/bone-density-testing-beyond-the-basics (accessed 29 September 2020)

Pouresmaeili F., Kamalidehghan B., Kamarehei M., and Goh Y.M. (2018). A comprehensive overview on osteoporosis and its risk factors. *Therapeut. Clin. Risk Manag.*, 14:2029-2049.

Qaseem A., Forciea M.A., McLean R.M., and Denberg T.D. (2017). Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann. Internal Med.*, 166(11):818-839.

Reid I.R., Horne A.M., Mihov B., Stewart A., et al. (2018). Fracture prevention with zoledronate in older women with osteopenia. *N. Eng. J. Med.*, 379(25):2407-2416.

Rothman M.S., Lewiecki E.M., and Miller P D. (2017). Bone Density Testing Is the Best Way to Monitor Osteoporosis Treatment. T *Am. J. Med.*, 130(10):1133-1134.

Siris E.S., Harris S.T., Rosen C.J., et al. (2006). Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clinic Proceedings* , 81(8):1013-1022.

Sözen T., Özışık L., and Başaran N. Ç. (2017). An overview and management of osteoporosis. *Eur. J. Rheumatol.*, 4(1):46.

Sosa Henríquez M., Groba Marco M., and Díaz González J.M. (2010). Zoledronic acid in the treatment of osteoporosis. *Rev Osteoporos. Metab. Miner.*, 2(4):21-30.