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## Safety of Zolindronic Acid in Osteoporosis: A Descriptive Cross Sectional Study

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### 1. Abstract

All bisphosphonates including zolindronic acid improve BMD in osteoporosis and decrease risk of spine, hip and other non-vertebral fractures significantly. The purpose of this study was to assess safety of zolindronic acid in osteoporosis in Kashmiri population. This was a descriptive cross sectional study conducted in tertiary care hospital of Kashmir valley. 77 pts were enrolled in the study with documented osteoporosis who received 5 mg zolindronic acid infusion with adequate prior hydration. All pts were followed for immediate adverse effects following infusion. Mild symptoms did occur in the form of fever, arthralgias, myalgias, muscle cramps and nausea. Majority of the symptoms subsided within two to three days of infusion. Our observations conclude that zolindronic acid is very much safe and fairly tolerated drug in osteoporosis.

### 2. Introduction

Bisphosphonates define a class of drugs widely indicated since 1990s to treat osteoporosis in men and women. Their effectiveness in treating osteoporosis and other conditions is related to their ability to inhibit bone resorption [1,2,3].

FDA approved indications of bisphosphonates are:

Post-Menopausal Osteoporosis

Osteoporosis in Men

Glucocorticoid Induced Osteoporosis

Hypercalcemia of Malignancy

Paget Disease of Bone

Malignancies with Metastasis to Bone

Non Fda Approved Indications Are

Osteogenesis Imperfecta in Children and Adults

Prevention of Glucocorticoid Induced Osteoporosis

Bisphosphonates are structurally similar to native pyrophosphates and are divided into 2 groups

Nitrogen containing and Non-nitrogen containing bisphosphonates: Nitrogen containing are Zolindronic acid, alendronate, risedronate, ibandronate and pamidronate, Non nitrogen containing are etidronate, clodronate and tiludronate. All bisphosphonates inhibit bone resorption by attaching to hydroxyapatite binding sites on the bone particularly in area of active resorption. As osteoclasts resorb bone the bisphosphonate embedded in the bone is released and impairs the osteoclasts ability to continue bone resorption [2,4,5]. Nitrogen containing bisphosphonates are much more potent antiresorptive than Non-nitrogen containing bisphosphonates. Also Non nitrogen containing bisphosphonates are found to have high potential to inhibit bone mineralization and can cause osteomalacia. For this reason, they are no longer in broad based use. Alendronate reduces vertebral fracture risk by about 50%, hip fractures, and other non-vertebral fractures by about 30% [6,7]. Risedronate reduces vertebral and non-vertebral fractures by about 40% [8]. Zolindronic acid reduces vertebral fracture risk by 70% and other non-vertebral risk by 35% [9-11]. It is administered as 4 mg/5mg IV infusion over 15 to 30 minutes' yearly. Bisphosphonates are usually well tolerated. Common adverse effects include GI intolerance and acute phase reactions. Acute phase reaction generally described as fever, myalgias, fatigue chills and arthralgias. Symptoms are typically transitory resolving within 3 to 7 days of infusion and can be reduced by common antipyretics and antihistaminics.

### 3. Materials and Methods

**3.1. Study design:** Descriptive cross sectional study.

**3.2. Results:** 77 patients were included in our study. 73 females and 4 males. Predominant age group was between 51-60 years (n=34) followed by 61-70 years(n=22),41-50(n=17),71-80(n=2) and >80 years(n=2). The co morbidities in our patients were in order as postmenopausal (n=58), hypertension(n=41), Hypothyroidism (n=24), Diabetes mellitus 15(n=15), corticosteroid intake (n=5),COPD(n=4),smokers(n=4),hyperparathyroidism(n=4),Rheumatoid arthritis(n=1) The adverse effects reported in our patients in order of decreasing frequency were Fever (n=64) 83%,dry mouth(n=61) 79%,arthralgias (n=47) 61%, nausea (n=39)51%,myalgias (n=30) 39%, insomnia (n=18 )23%,anorexia (n=14) 18%,bone pains (n=12) 15% hyperaesthesias (n=10) 13%,fatigue(n=9) 12%,taste

disturbances (n=7) 9%,sweating(n=6) 7% and diarrhea(n=4) 5%.

**3.3. Discussion:** Seventy-seven subjects were enrolled in our study with documented osteoporosis. Youngest patient in our study was 41-year-old and oldest being 85 years of age. Most of our subjects were in 61-70-year age group (28%). Comorbidities in our study patients included postmenopausal (75%), hypertension (53%), hypothyroidism (31%), diabetes mellitus (19%), corticosteroid intake (6%), COPD (5%), smokers (5%), hyperparathyroidism (5%) and rheumatoid arthritis (1.2%).

All subjects in our study received zolindronic acid 5 mg intravenous infusion over 15 to 30 minutes with adequate prior hydration. All patients enrolled in the study were followed closely for appearance of adverse reactions to document safety of zolindronic acid. The commonest adverse reaction observed was fever seen in 83% of the patients. Most of the patients became febrile within 12 hours of infusion and it subsided in 2 to 3 days with paracetamol. Fever has been reported in 21% of patients receiving zolindronic acid for metastatic prostatic cancer [12]. 55% females with breast cancer and bone metastasis who received zolindronic acid experienced fever compared to 33% in the placebo arm [13]. In a phase III study of patients with breast cancer or myeloma, the incidences of fever and myalgia from zoledronic acid were equivalent to those from pamidronate-over 30% of patients [14, 15]. Typically occurring within 48 h of infusion, fever is usually low-grade, though occasionally associated with rigors [16-19]. Accompanying bone pain has also been reported in over half of the patients [14, 15]. In our reference study 15% of patients experienced bone pains 12 to 24 hours after infusion. The pain, however, may occur without fever and usually starts about 12 h after infusion, commonly felt in spines, ribs, and lower limbs, not necessarily near the site of metastases. Severe pain limiting daily activity and lasting several days has been described uniquely among patients with cystic fibrosis receiving pamidronate [20]. Arthralgias and myalgias were reported in 61% and 39% respectively in our study. For the elderly, these musculoskeletal symptoms may cause an unsteady gait; therefore, fall precautions should be exercised [21]. Nausea and anorexia was observed 51% and 18% of our study patients respectively. clinical trials on zolindronic acid suggest that almost 1 in 3 patients experience such adverse effects with the first infusion and incidence decreases significantly with subsequent infusions [22]. other less common events reported were insomnia 23%, hyperaesthesias 13%, fatigue 12%, taste disturbances 9% and diarrhea in 5% of the patients. These inflammatory reactions appear to be the result of an increase in cytokine release from macrophages and monocytes. The reactions typically are self-limited and resolve completely within 24 to 48 h. Supportive and symptomatic management with NSAIDs, acetaminophen and antihistaminics is sufficient. Dose reduction for the first treatment or a test dose does

not appear to help reduce the incidence or severity of reactions during the treatment, but pre-medication with acetaminophen or ibuprofen may help [15].

#### 4. Conclusion

Zolindronic acid and other bisphosphonates are of paradigm importance in the management of osteoporosis. Minor adverse reactions are expected with majority of formulations especially those with intravenous route of administration. These acute phase reactions are usually self-limiting and fairly tolerated by the patients with some requiring antipyretics and antihistaminics for symptomatic relief.

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#### 6. Conflict of Interest

NIL

#### 7. Acknowledgement

NIL

#### References

- Otto S, Pautke C, Wyngaert TVD, Niepel D, Schiodt M. Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases. *Cancer Treat Rev.* 2018; 69: 177-187.
- Farrell KB, Karpeisky A, Thamm DH, Zinnen S. Bisphosphonate conjugation for bone specific drug targeting. *Bone Rep.* 2018; 9: 47-60.
- Miller K, Steger GG, Niepel D, Lüftner D. Harnessing the potential of therapeutic agents to safeguard bone health in prostate cancer. *Prostate Cancer Prostatic Dis.* 2018; 21(4): 461-472.
- Frediani B, Giusti A, Bianchi G, Dalle Carbonare L, Malavolta N, Cantarini L, et al. Clodronate in the management of different musculoskeletal conditions. *Minerva Med.* 2018; 109(4): 300-325. .
- Bernardi S, Di Girolamo M, Necozone S, Continenza MA, Cutilli T. Antiresorptive drug-related osteonecrosis of the jaws, literature review and 5 years of experience. *Musculoskelet Surg.* 2019; 103(1): 47-53.
- Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA.* 1998; 280(24): 2077-82.
- Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Fracture Intervention Trial Research Group. Lancet.* 1996; 348(9041): 1535-1541.
- Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA.* 1999; 282(14): 1344-1352.
- Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007; 356(18):1809-1822.
- Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med.* 2007; 357(18): 1799-1809.
- Black DM, Delmos PD, Eastel R. once yearly zolindronic acid for treatment of postmenopausal osteoporosis. *N Eng J Med.* 2007; 3356: 1809-1822.
- Saad F, Gleason DM, Murray R. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* 2002; 94(19): 1458-1468.
- Kohno N, Aogi K, Minami H. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol.* 2005; 23(15): 3314-3321.
- Rosen LS, Gordon D, Kaminski M. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer.* 2003; 98(8): 1735-1744.
- Rosen LS, Gordon DH, Dugan W Jr. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer.* 2004; 100(1): 36-43.
- Carbonare LD, Zanatta M, Gasparetto A. Safety and tolerability of zolindronic acid and other bisphosphonates in osteoporosis management. *Drug health care and patient safety.* 2010; 2: 121-137.
- Wysowski DK, chang JT. Alendronate and risedronate; reports of severe chills and bone pain. *Arch int medicine.*2016; 27(11): 3383-3385.
- Gallacher SJ, Ralston SH, Patel U, Boyle IT. Side-effects of pamidronate. *Lancet.* 1989; 2: 42-43.
- Adami S, Bhalla AK, Dorizzi R. The acute-phase response after bisphosphonate administration. *Calcif Tissue Int.* 1987; 41(6): 326-331.
- Haworth CS, Selby PL, Webb AK. Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis. *Lancet.* 1998; 352(9142): 1753-1754.
- Karapetis CS, Kotasek D, Norman JE, Sage RE. Acute gait disturbance associated with pamidronate infusion. *Aust N Z J Med.* 1997; 27(6): 719-720.
- Black DM, Delmos PD, Eastel R. Horizon pivotal fracture trial. Once yearly zolindronic acid for treatment of postmenopausal osteoporosis. *N Eng J Med.* 2007; 3356: 1809-1822.