

Zoledronic Acid (ZOL) Markedly Improves Bone Mineral Density (BMD) for Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) and Bone Loss

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Introduction

MGUS occurs in 5% of individuals over 70 years of age and these patients have been found to have increased rates of bone resorption. MGUS patients have higher bone resorption and prevalence of osteopenia/osteoporosis compared to sex and aged-matched patients without evidence of MGUS. Not only do patients with MGUS have a higher prevalence of osteopenia/osteoporosis than the normal population but they also have an increased risk of fractures. ZOL has been shown to increase bone density in the treatment of gonadotropin agonist-induced osteoporosis in men with prostate cancer without metastatic bone disease when administered every 3 months at 4 mg. The rationale for the use of ZOL for patients with osteopenia/osteoporosis in the setting of MGUS is based on these studies coupled with the knowledge that patients with MGUS have a higher prevalence of bone loss and fracture risk. To date, no agents have been formally studied in the treatment of osteopenia/osteoporosis associated with MGUS. A schedule of 4 mg every 6 mos has been shown to be safe and effective in increasing bone density for other cancer patients without metastatic bone disease but with significant bone loss.

Objectives

The primary objective of this study is to:

- Determine the effect of ZOL on BMD of lumbar spine, utilizing Dual energy X-ray absorptiometry (DEXA) scan, among patients with MGUS with associated osteopenia/osteoporosis

World Health Organization established the definition of osteopenia and osteoporosis based on a comparison of BMD with the young adult reference mean. A BMD value of 1.0 to 2.5 standard deviations below the young adult reference mean is osteopenia. A BMD value of 2.5 standard deviations or more below the young adult mean confirms the diagnosis of osteoporosis.

The secondary objectives of this study are to:

- Determine the effect of ZOL on BMD of total hip
- Determine the effect of ZOL on skeletal fractures in MGUS patients with osteopenia/osteoporosis
- Determine the effect of ZOL on serum M-protein levels
- Determine the proportion of patients treated with ZOL that develop multiple myeloma or other related malignancies
- Determine the safety of the use of ZOL in the treatment of MGUS patients with osteopenia/osteoporosis

Study Design

This open-label study was designed to evaluate the efficacy and safety of this dose and schedule of ZOL for MGUS patients with significant loss of bone.

Major Inclusion Criteria:

- ≥ 18 years of age
- Diagnosis of MGUS
- Osteopenia/Osteoporosis (T-score worse than -1) as verified by a DEXA scan

Major Exclusion Criteria:

- Prior use of oral bisphosphonates or fluorides for more than three months total within the last two years
- Prior use of intravenous bisphosphonates within the last two years
- Known secondary causes of osteopenia/osteoporosis other than MGUS (patients with concomitant postmenopausal osteopenia/osteoporosis were not be excluded)
- Current systemic corticosteroid therapy of an equivalent of ≥ 10 mg of prednisone/d
- Disorders of the parathyroid or thyroid glands
- Known history of currently active malignancy
- Treatment with other agents known to affect osteoclastic activity
- Use of Selective Estrogen Receptor Modulators in the preceding three months
- Prior or current use of recombinant parathyroid hormone
- KPS < 60 and/or Life-expectancy < 3 months

Treatment Schema:

- ZOL at 4 mg was administered IV at 0, 6, and 12 months.
- To assess the efficacy of ZOL therapy, DEXA scans and skeletal surveys were conducted at screening and one month after the final ZOL infusion (13 months)

Results

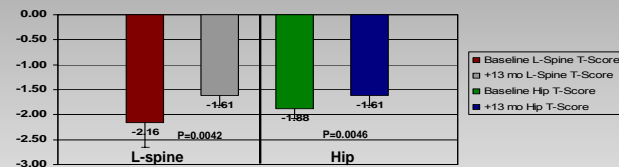
Table 1 - Patient Demographics (n=54)

Median Age (Range), Years	67 (50-91)
Male:Female	26:28
Mean Baseline L-spine T-score (Range)	-2.16 (-3.97 to -1.10)
Mean Baseline Hip T-score (Range)	-1.88 (-3.50 to -1.00)
Mean Baseline Serum M-Protein (Range), g/dl	0.9 (0.0 - 2.7)

Table 2 - Patient Responses

Mean Δ L-Spine T-Score (Range), n=27	0.55 (-0.40 to 3.90)
Percent L-Spine Improvement (Range), P-value	25.5% (-19.0% to +134%), P=0.0042
Mean Δ Hip T-Score (Range), n=28	0.27 (-0.60 to 2.00)
Percent Hip Improvement (Range), P-value	14.4% (-54.5% to +163%), P=0.0046
Patients with New Fractures	0
Patients Progressing to Multiple Myeloma	0

Mean T-Scores Before and After 13 mo ZOL Treatment



Adverse Events:

- No development of osteonecrosis of the jaw (ONJ)
- No significant adverse renal events

Summary

- One patient developed chronic lymphocytic leukemia while on study whereas no other patient showed progression to myeloma or a related B-cell disorder
- No patient developed osteonecrosis of the jaw or a significant adverse renal event
- During the study, no patient developed a new fracture
- ZOL administered at 4 mg every 6 months
- significantly improves BMD for MGUS patients with bone loss (osteopenia/osteoporosis)
- safe and well-tolerated
- effective treatment to prevent the development of new fractures in this high risk population