Evaluation and Management of Bone Health in MGUS, Multiple Myeloma and Cancer

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Disclosures

Relevant Financial Relationships:

None

Off Label Usage:

Skeletal anabolic agents in MGUS/Myeloma

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Learning Objectives

The learner will be able to:

- Recognize that cancers are associated with bone loss and increased fracture risk
- Identify alterations in bone mass and fracture risk that occur in monoclonal gammopathies
- Describe both pharmacologic and non-pharmacologic approaches to reduce bone loss and fracture risk in cancer patients

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Cancer is a Major Risk for Bone Loss

- Bone mineral density (BMD) measured in 1,041 adult cancer patients in Germany
  - Mean age 57.1 years
  - Mean 22.5 months since diagnosis
  - 16% had osteoporosis
  - 44% had osteopenia
- Low BMD was independent of sex or cancer type
- This rate is substantially higher than in the general population

Reuss-Borst et al. (2012) *Osteoporos. Int.* 23:1437.

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Risk for Bone Loss in Cancer

- Bone loss in cancer results from multiple causes
  - Direct cancer cell effects
  - Effects of cancer therapies
    - Chemotherapy
    - Corticosteroids
    - Aromatase inhibitors (AI's)
    - Androgen deprivation therapy (ADT)
- Therapies have led to improved patient survival and longevity
  - Treatment can have significant skeletal effects

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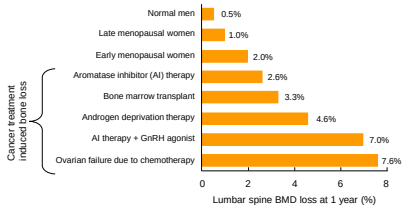
BMD Loss with Cancer Therapies



Uluckan et al. (2009) Primer Metab. Bone Disease Disord. Miner. Metab. 386.

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Cancer Cell Growth in Bone

- Cancer cells grow within bone
  - Induce osteoblasts and osteoclasts to produce factors which stimulate further cancer cell growth
- Skeleton is the most common site of metastasis
  - Post-mortem incidence rates
    - Breast 73%; prostate 68%; thyroid 42%; lung 36%;
    - Renal 35%; melanoma 35%; head/neck 12%; GI 5%

Suva et al. (2011) *Nature Rev. Endocrinol.* 7:208.

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Monoclonal Gammopathies

- Result from the clonal proliferation of plasma (antibody producing) cells within the bone marrow cavity
- Represent a spectrum of disease
  - Monoclonal gammopathy of undetermined significance (MGUS) - asymptomatic
  - Smoldering multiple myeloma
  - Multiple myeloma - symptomatic

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Updated IMWG Criteria For Diagnosis[7,8]

MGUS	Smoldering Myeloma	Multiple Myeloma
• M protein <3 g/dL • Clonal plasma cells in BM <10% • No myeloma defing events	• M protein ≥3 g/dL (serum) OR ≥500 mg/24 hrs (urine) AND/OR • Clonal plasma cells in BM ≥10% - 60% AND • No myeloma defining events	• Underlying plasma cell proliferative disorder AND 1 or more myeloma defining events • ≥1 CRAB* feature • Clonal plasma cells in BM ≥60% • Serum free light chain ration ≥100 • >1 MRI focal lesion ≥5mm

*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatine clearance < 40 mL/min or serum creatine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

Abbreviations: BM, bone marrow; CT, computed tomography; MRI, magnetic resonance imaging; IMWG, International Myeloma Working Group; PET, positron emission tomography; ULN, upper limit of normal.

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Multiple Myeloma

- Approximately 20,000 new cases/year in the US
- Represents 15% of hematologic malignancies
- Risk increases with increasing age

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MAYO CLINIC

Skeletal Lesions in Myeloma

- 80-90% of patients with myeloma have bone involvement
  - Spine, ribs, pelvis, skull, femur, humerus
- Severe Features
  - Intractable pain
  - Increased fracture risk
  - Hypercalcemia (high blood calcium)
  - Risk for nerve compression
- Also generalized bone loss (osteoporosis)

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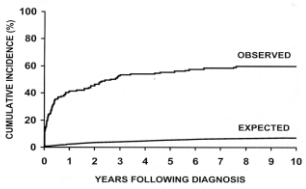
Fracture Incidence in Myeloma



Melton et al J Bone Miner Res. (2005) 20:487-93.

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Site Specific Fracture Risk in Myeloma

Site	Relative Risk
Thoracic/lumbar vertebrae	33
Ribs	15
Clavicle/scapula/sternum	13
Cervical vertebrae	7.4
Arm (other than humerus)	6.9
Pelvis	6.1
Humerus	1.8

Melton et al J Bone Miner Res. (2005) 20:487-93.

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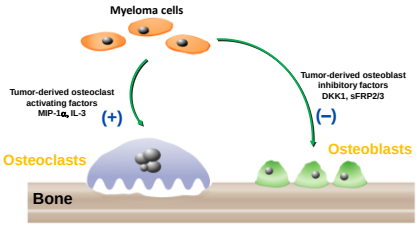
Myeloma Bone Disease



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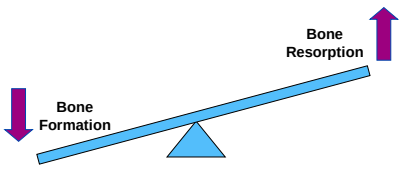
Myeloma Cells Disrupt Bone Remodeling



Net Result = Bone Loss

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Pharmacologic Management of Myeloma Bone Disease

- Current recommendations
  - Pamidronate 90 mg/monthly (or less often)
  - Zoledronate 4 mg/monthly (or less often)
  - Denosumab 120 mg/monthly
- Anti-resorptives improve skeletal outcomes
  - Bone pain
  - Hypercalcemia
  - Fractures

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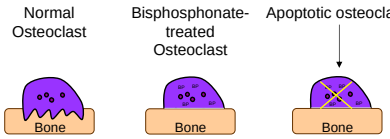
Bisphosphonates Target Mature Osteoclasts



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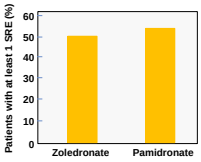
Skeletal Related Event Risk – Zoledronate vs. Pamidronate



Lipton et al. (2003) Cancer J. 98:1735.

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Reduced Bisphosphonate Dosing May Benefit Myeloma Patients

- In MM patients who had completed ~ 1 year of initial bisphosphonate therapy, continued monthly treatment did not reduce skeletal-related-events vs placebo
- Continued monthly bisphosphonate therapy significantly ↑ ONJ risk vs monthly therapy for one year followed by ↓ to an every 3 month schedule

Attal et al. (2006) Blood 108:3289; Corso et al. (2007) Leukemia :1545; Himelstein et al. (2017) JAMA 317:48.

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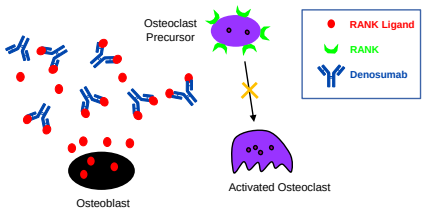
Denosumab Inhibits Osteoclast Formation



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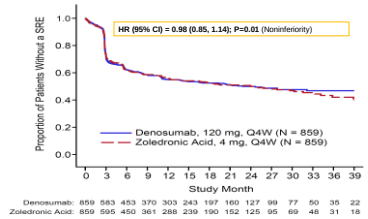
Primary Endpoint: Non-inferiority for Time to First On-Study Skeletal-Related Event



Raje et al (2018) Lancet Oncol. 19:370

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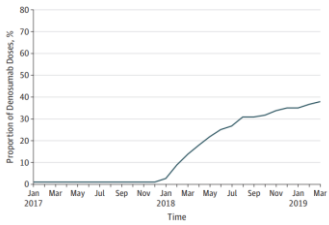
Figure. Proportion of Denosumab Doses Administered to Medicare Beneficiaries With Multiple Myeloma



Gupta et al. (2019) JAMA Oncol. 6:296

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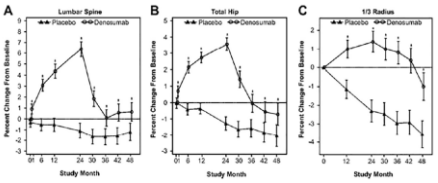
Bone Loss With Denosumab Discontinuation



Tsourdi et al. (2017) Bone 105:11

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Bone. 2017 Dec;105:11-17. doi: 10.1016/j.bone.2017.06.003. Epub 2017 Aug 5.

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS.

Tsourdi E[1], Langdahl B[2], Cohen-Solal M[3], Aubry-Rozier B[4], Eriksen EF[5], Guañabens N[6], Obermayer-Pietsch B[7], Ralston SH[8], Eastell R[9], Zillikens MC[10]
Author information

Abstract

INTRODUCTION: The optimal duration of osteoporosis treatment is controversial. As opposed to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation. Recent reports imply that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.

METHODS: The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the effects of stopping denosumab and provide advice on management.

RESULTS: Data from phase 2 and 3 clinical trials underscore a rapid decrease of bone mineral density (BMD) and a steep increase in bone turnover markers (BTMs) after discontinuation of denosumab. Clinical case series report multiple vertebral fractures after discontinuation of denosumab and a renewed analysis of FREEDOM and FREEDOM Extension Trial suggests, albeit does not prove, that the risk of multiple vertebral fractures may be increased when denosumab is stopped due to a rebound increase in bone resorption.

Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement by ECTS

Elena Tsourdi,[1,2] M. Carola Zillikens,[3] Christian Meier,[4] Jean-Jacques Body,[5] Elena Gonzalez Rodriguez,[6] Athanasios D. Anastasilakis,[7] Bo Abrahamsen,[8,9] Eugene McCloskey,[10] Lorenz C. Hofbauer,[1,2,11] Nuria Guañabens,[12] Barbara Obermayer-Pietsch,[13,14] Stuart H. Ralston,[15] Richard Eastell,[10] Jessica Pepe,[16] Andrea Palermo,[17] and Bente Langdahl[18]

(2021) JCEM 106:264-281

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Denosumab Therapy Considerations

- Denosumab does not cause osteoclast apoptosis like bisphosphonates; rather it prevents pre-osteoclasts from becoming active osteoclasts.
- Therefore, any treatment with denosumab must be followed by a bisphosphonate (such as a dose of zoledronic acid) to limit rebound bone resorption. The timing of bisphosphonate treatment relative to the last dose of denosumab is not clear.
- May be a good option for patients with renal dysfunction or limited life expectancy

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The Monoclonal Gammopathy Spectrum

- MGUS always precedes multiple myeloma
- Present on average ~ 15 years prior to diagnosis
- Progression to MM occurs at ~ 1% per year
- MGUS incidence increases with age
  - 3.2% age > 50 and 7.5% age > 85
  - US census data -> ~ 3.4 million US individuals

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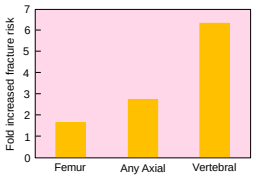
Bone Disease Also Occurs in MGUS



Melton et al. (2004) J Bone Miner Res 19:25; Kristinsson et al. (2010) Blood 116:2651.

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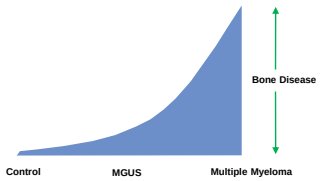
Bone Disease in Monoclonal Gammopathies



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Bone Disease in MGUS

- Whether bone loss occurs in MGUS is unclear
  - Bone turnover markers are reported as unchanged/increased in different studies
  - Some (but not other) studies with DXA have shown decreased BMD
- The pathophysiologic basis for the increase in fracture rates is unknown

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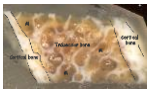
Gold Standard: Bone Biopsy



- Invasive
- Requires sedation
- Typically obtained from iliac crest only
- May not be very useful for accurate longitudinal assessments, as biopsy site will be different

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Limitations of DXA

- Does not differentiate cortical from trabecular bone
- Projectional image – 2D measure of a 3D structure
- Underestimates BMD of smaller bones, and overestimates BMD of larger bones

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High Resolution pQCT (HRpQCT)

- Ability to obtain a "non-invasive bone biopsy"
- In vivo assessment of bone geometry, density and microarchitecture at extremely high resolution (61µm)
- Ability to construct microfinite element models of bone strength to derive estimates of fracture risk

XtremeCT

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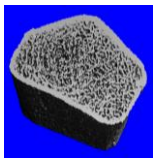
HRpQCT

- Cortical parameters
  - Cortical thickness (CTh)
  - Cortical vBMD (CvBMD)
  - Cortical area
  - Periosteal circumference
  - Endosteal circumference



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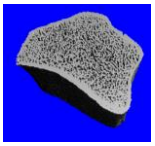
HRpQCT

- Trabecular parameters:
  - Bone fraction (BV/TV)
  - Trabecular number (TbN)
  - Trabecular thickness (TbTh)
  - Trabecular separation (TbSp)
  - Trabecular area
  - Trabecular vBMD (TbvBMD)



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Comparison of HRpQCT with Gold Standard µCT

HRpQCT	µCT				
	BV/TV	TbN	TbTh	TbSp	CTh
BV/TV	0.99				
TbN		0.96			
TbTh			0.97		
TbSp				0.98	
CTh					0.98

Laib et al. 1999 P-values for all correlations < 0.0001

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Study to Assess for Skeletal Changes in MGUS
Methods

- Study subjects matched for age-, sex-, and body mass index
  - 50 MGUS subjects (20 female/30 male; mean age 70.5 years)
  - 100 control subjects (40 female/60 male; mean age 70.2 years)
- Areal BMD (2D) at the radius, spine and hip using standard DXA imaging
- Ultradistal radius vBMD (3D) and structure using HRpQCT

Ng et al. Blood (2011) 118:6529

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Study Subject Characteristics

	MGUS	Controls	P-value
Total, N	50	100	
Age, yr	70.5±1.4	70.3±1.0	0.927
Sex, N			
Male	30	60	
Female	20	40	
Height, m			
Male	177±1.4	176±0.8	0.424
Female	161±1.4	162±1.0	0.602
Weight, kg			
Male	89.0±2.4	89.3±1.9	0.931
Female	72.1±3.6	74.0±1.9	0.616
BMI, kg/m²			
Male	28.4±0.7	28.8±0.5	0.647
Female	27.8±1.4	28.2±0.7	0.768

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MGUS Patients have Decreased Volumetric Bone Mineral Density and Microstructure

	Controls (Mean±SEM)	MGUS (Mean±SEM)	Difference (%)	P-value
Trabecular vBMD (mg/cm³)	335±7	300±10	-10.4%	0.005
Trabecular BMD (mg/cm³)	161±4	150±6	-6.8%	0.080
Cortical vBMD (mg/cm³)	862±7	822±12	-4.7%	0.001
Cortical Thickness (mm)	0.88±0.03	0.80±0.03	-9.5%	0.029
Trabecular Thickness (mm)	0.074±0.001	0.068±0.001	-8.1%	0.004

Ng et al. (2011) Blood 118:6529

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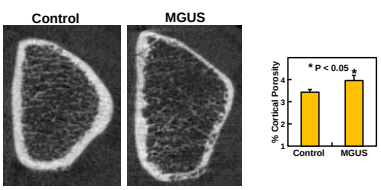
MGUS is Associated with Increased Cortical Porosity



Farr et al. (2014) Blood 123:647.

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Bone Loss in Multiple Myeloma

- Factors associated with myeloma bone disease include:
  - Osteoblast inhibition
    - Dickkopf 1 (DKK1) [Wnt pathway inhibitor]
  - Osteoclast activation
    - Macrophage inflammatory protein-1α (MIP-1α)

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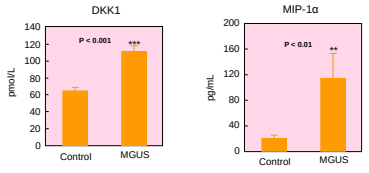
The Osteoblast Inhibitor DKK1 and Osteoclast Activator MIP-1α are Increased in MGUS



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The Skeletal Significance of MGUS
Bone Changes Revealed by HRpQCT

- Although MGUS is associated with increased rates of vertebral, axial, and hip fractures (Melton et al. JBMR 19:25, 2004), in our study DXA imaging was relatively insensitive for bone loss in MGUS
- HRpQCT of the radius in MGUS showed decreases in cortical thickness, cortical vBMD, trabecular thickness, and BV/TV
- MGUS subjects had markedly elevated serum levels of the Wnt pathway inhibitor, DKK1, and the osteoclast activation factor, MIP-1α

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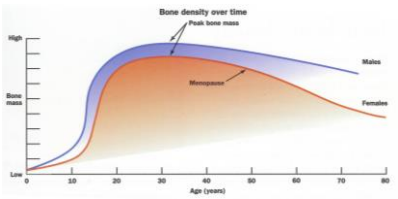
Bone Density Throughout the Lifespan



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Working Hypothesis

The increased fracture risk seen in MGUS results from both the normal aging process and the effects of cytokines common to monoclonal gammopathies on bone cell (osteoblast and osteoclast) function

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Bisphosphonate Use in MGUS

- Alendronate (70 mg/weekly) ↑ bone density at the spine and hip in osteoporotic MGUS patients
- Zoledronic acid (4 mg/every 6 months) ↑ bone density at the spine and hip in MGUS patients with osteopenia/osteoporosis[2]
- Neither study was large enough to evaluate fracture as an endpoint

Pepe et al. (2008) Calcif. Tissue Int. 82:418; Berenson et al. (2008) Clin. Cancer Res. 14:6289

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Treatment of the MGUS Patient

- Patients with MGUS (and likely SMM) are at increased fracture risk
- Given this increased risk, a proactive approach is warranted
  - May include DXA, counseling on fall risks, lifting recommendations, ensuring adequate calcium and vitamin D intake
- In patients with documented osteoporosis (by DXA, history of a fragility fracture, height loss, or kyphosis), medical intervention with anti-resorptive therapy (such as a bisphosphonate) is warranted
- In patients with osteopenia, medical therapy to limit bone loss and fracture risk may be appropriate and must be considered carefully

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PERSPECTIVE

JBMR

Unveiling Skeletal Fragility in Patients Diagnosed With MGUS: No Longer a Condition of Undetermined Significance?

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ABSTRACT

Monoclonal gammopathy of undetermined significance (MGUS) is a common finding in clinical practice, affecting greater than 3% of adults aged 50 years and older. As originally described, the term MGUS reflected the inherent clinical uncertainty of distinguishing patients with a benign stable monoclonal plasma cell disorder from subjects destined to progress to malignancy. There is now clear epidemiologic evidence, however, that patients with MGUS suffer from a significantly increased fracture risk and that the prevalence of MGUS is increased in patients with osteoporosis. Despite this relationship, no clinical care guidelines exist for the routine evaluation or treatment of the skeletal health of patients with MGUS. Recent work has demonstrated that circulating levels of at least two cytokines (CCL3/MIP-1α and DKK1) with well-recognized roles in bone disease in the related monoclonal gammopathy multiple myeloma are also increased in patients with MGUS. Further, recent imaging studies using high-resolution peripheral quantitative CT have documented that patients with MGUS have substantial skeletal microarchitectural deterioration and deficits in biomechanical bone strength that likely underlie the increased skeletal fragility in these patients. Accordingly, this Perspective provides evidence that the "undetermined significance" portion of the MGUS acronym may be best replaced in favor of the term "monoclonal gammopathy of skeletal significance" (MGSS) in order to more accurately reflect the enhanced skeletal risks inherent in this condition.

KEY WORDS: MGUS; OSTEOPOROSIS; FRACTURE; DXA; HRPQCT

Drake (2014) J Bone Min Res. 29:2529

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Patient #1: 66 y/o Male with MGUS

- Resident of Michigan
- MGUS identified during evaluation for osteopenia
- Referral to Mayo Hematology MGUS Clinic
- IgG lambda; M-spike 0.7 with normal free light chains and FLC ratio
- DXA BMD lowest at L femur neck: T-score -2.2
- Biochemical evaluation for secondary causes completely normal
- Recommended initiation of alendronate 70 mg weekly x 5 years prior to consideration of a BP holiday

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Patient #2: 71 y/o Female with MGUS

- Lives in NYC and divides her care between HSS and Mayo
- Diagnosed with osteoporosis in 2014 at Mayo following T12 VCF which occurred while lifting
- BP recommended but patient did not initiate
- Noted to have low level IgG kappa MGUS (M protein 'small') in 2017
- Referral to Mayo Hematology MGUS Clinic
- LS DXA showed T-score -3.6
- Due to planned spinal fusion, now willing to initiate therapy

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Patient #2: 71 y/o Female with MGUS

- After full discussion, initiated abaloparatide + calcium/vitamin D
- Repeat DXA at 18 months showed LS BMD increase of +8.2%
- Since fusion had not yet occurred, patient was interested in additional improvement of LS BMD
- Initiated romosozumab monthly (within 1 month of FDA approval)
- Repeat DXA at 12 months showed LS BMD increase of +16%
- Total LS BMD increase 24% over 30 months
- Spinal fusion surgery at HSS; spine surgeon described bone as 'good'
- Provided zoledronate, with plans for yearly x 3 and re-evaluation

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Patient #3: 69 y/o Female with Myeloma

- Resident of Colorado
- Diagnosed in 2017 with anemia and acute renal failure
- IgG kappa; M-spike 5.6; 95% bone marrow plasma cells
- Lytic lesions of the posterior left 5th rib and along the axial and proximal appendicular skeleton
- Initiated on chemotherapy
- BMD by DXA showed lowest R total hip T-score -2.9; compared to BMD performed 24 months previously, -19.5% LS and -25.4% R TH decreases
- Optimized vitamin D and calcium intake when hypercalcemia was resolved
- Initiated romosozumab – results pending

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NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases

MAYO CCaTS

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THANK YOU

Questions

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