

Monoclonal gammopathy of undetermined significance: a consensus statement

James R. Berenson,^{1,2} Kenneth C. Anderson,³ Robert A. Audell,⁴ Ralph V. Boccia,⁵ Morton Coleman,⁶ Meletios A. Dimopoulos,⁷ Matthew T. Drake,⁸ Rafael Fonseca,⁹ Jean-Luc Harousseau,¹⁰ Douglas Joshua,¹¹ Sagar Lonial,¹² Ruben Niesvizky,⁶ Antonio Palumbo,¹³ G. David Roodman,¹⁴ Jesus F. San-Miguel,¹⁵ Seema Singhal,¹⁶ Donna M. Weber,¹⁷ Maurizio Zangari,¹⁸ Eric Wirtschafter,¹ Ori Yellin² and Robert A. Kyle¹⁹

¹Institute for Myeloma & Bone Cancer Research, ²Oncotherapeutics, West Hollywood, CA, ³Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, ⁴Cedars-Sinai Medical Center, Los Angeles, CA, ⁵Center for Cancer and Blood Disorders, Bethesda, MD, ⁶Center for Lymphoma and Myeloma, Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA, ⁷Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra Hospital, Athens, Greece, ⁸Division of Endocrinology and Metabolism, College of Medicine, Mayo Clinic, Rochester, MN, ⁹Mayo Clinic Arizona, Scottsdale, AZ, USA, ¹⁰Department of Haematology, University Hospital Hotel-Dieu, Nantes, France, ¹¹Institute of Haematology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia, ¹²Winship Cancer Institute, Emory University, Atlanta, GA, USA, ¹³Divisione di Ematologia dell'Università di Torino, Torino, Italy, ¹⁴Veterans Affairs Pittsburgh Healthcare System, Department of Medicine/Hematology-Oncology, Pittsburgh, PA, USA, ¹⁵Hospital Universitario Salamanca, CIC, IBMCC (USAL-CSIC), Salamanca, Spain, ¹⁶The Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, ¹⁷Department of Lymphoma and Myeloma, MD Anderson Cancer Center, Houston, TX, ¹⁸University of Utah, Division of Hematology, Blood/Marrow Transplant and Myeloma Program, Salt Lake City, UT, and ¹⁹Division of Hematology, Mayo Clinic, Rochester, MN, USA

Summary

On February 25, 2009, a panel of international experts on plasma cell dyscrasia and skeletal disease met to discuss monoclonal gammopathy of undetermined significance (MGUS). This non-malignant B-cell disorder is the most common plasma cell dyscrasia and is associated with an increased risk of developing serious B-cell disorders. Individuals with MGUS also have an increased risk of osteoporosis and osteopenia associated with an increased likelihood of developing fractures especially in the vertebral column, peripheral neuropathy and thromboembolic events. The goal of the meeting was to develop a consensus statement regarding the appropriate tests to screen, evaluate and follow-up patients with MGUS. The panel also addressed the identification and treatment of MGUS-related skeletal problems, thromboembolic events and neurological complications. The following consensus statement outlines the conclusions and marks the first time that a consensus statement for the screening and treatment of MGUS has been clearly stated.

Keywords: monoclonal gammopathy of undetermined significance, fractures, peripheral neuropathy, osteoporosis.

Introduction

Definition of monoclonal gammopathy of undetermined significance (MGUS)

MGUS is a plasma cell proliferative disorder that consistently precedes multiple myeloma (MM) (Landgren *et al*, 2009a; Weiss *et al*, 2009). MGUS is characterized by a plasma cell content of <10% in the bone marrow (BM), a monoclonal (M) protein spike of ≤30 g/l and no end organ damage (CRAB – hypercalcaemia, renal insufficiency, anaemia and bone lesions) (International Myeloma Working Group, 2003).

Frequency of MGUS

A population-based study from the Mayo Clinic involving 21 463 residents in Olmsted County, MN, showed that 3.2% of persons older than 50 years of age had MGUS, and for persons older than 70 years, the prevalence was more than 5%. Nearly 9% of males aged 85 years and older were diagnosed with this condition (Kyle *et al*, 2006). Despite the common occurrence of this condition, especially in the elderly, MGUS is markedly underdiagnosed in the general population because of the lack of specific M-protein-related symptoms or signs in these individuals. MGUS patients show none of the classic symptoms or signs associated with malignant B-cell disease, which typically include hypercalcemia, renal failure, anemia, loss of energy, fatigue, bone pain and lytic bone lesions (Kyle, 1978, International Myeloma Working Group, 2003).

Correspondence: James R. Berenson, MD, Institute for Myeloma & Bone Cancer Research, 9201 W. Sunset Blvd., Suite 300, West Hollywood, CA 90069 USA. E-mail: jberenson@imbcr.org

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Risk factors for MGUS

A recently published study suggests that the risk of developing MGUS is higher among individuals who have first-degree relatives with either MM or MGUS (Vachon *et al*, 2009). Similar to MM, the incidence of MGUS is higher among African American and African individuals although IgM MGUS occurs less commonly in this racial group (Singh *et al*, 1990; Cohen, 2006; Landgren *et al*, 2006). Interestingly, unlike Caucasians with MGUS who show an age-related increase in risk, African Americans have similar prevalence rates between the ages of 50 and 79 years (Landgren & Weiss, 2009). Consistent with the lower incidence of MM in the Japanese population, preliminary findings suggest that the prevalence of MGUS is also lower in this racial group (Iwanaga *et al*, 2007a). Recent findings show that Nagasaki atomic bomb survivors who were less than 20 years of age at the time of exposure to the bomb and closer to the hypocenter are at higher risk to develop MGUS (Iwanaga *et al*, 2007b). In addition, pesticide applicators were shown to be at increased risk to develop MGUS in a large prospective cohort study (Landgren *et al*, 2009b) consistent with the higher risk of MM previously reported among farm workers (Cantor & Blair, 1984).

Relationship to multiple myeloma

Landgren *et al* (2009a) examined serum samples from 71 MGUS patients who were diagnosed with MM from 2 to 9.8 years from the initial identification of the monoclonal gammopathy. Using assays for M-proteins (electrophoresis/immunofixation) and kappa-lambda free light chains (FLCs), they found that 2 years prior to the diagnosis of MM, an M-protein was present in all cases (95% confidence interval [CI]: 87.2–100.0%). Four years prior to the diagnosis of MM, a monoclonal protein was found in 98.3% of serum samples (90.8–100.0%). At 5, 6, 7 and 8 years prior to the diagnosis of MM, MGUS was present in 94.6% (95% CI: 81.8–99.3%), 100.0% (86.3–100.0%), 93.3% (68.1–99.8%) and 82.4% (56.6–96.2%) of available serum samples, respectively. Weiss *et al* (2009) conducted a similar study by testing sera from US military service members who, 2–15 years after sera collection, were diagnosed with MM. They detected a monoclonal gammopathy in 27 of the 30 samples tested (90%). These two recent studies suggest that, in nearly all cases, MM is preceded by the presence of a monoclonal gammopathy without evidence of myeloma or another serious B-cell disorder.

Risk of serious B-cell disorders

MGUS was initially referred to as 'benign monoclonal gammopathy' (Kyle, 1984) until a 1978 Mayo clinic study of 241 MGUS patients showed that these individuals were at increased risk for developing serious B-cell disorders, such as MM and Waldenström macroglobulinemia (Kyle, 1978). In a

larger cohort of MGUS patients ($n = 1384$) who were diagnosed with this disorder at the Mayo Clinic between 1960 and 1994, MM and related serious B-cell disorders developed at a rate of approximately 1% per year (Kyle *et al*, 2002). The relative risk (RR) for development of a serious B cell disorder was 25.0 for MM, 2.4 for IgM lymphoma, 8.4 for primary amyloidosis and 46.0 for Waldenström macroglobulinemia. The cumulative probability for progression to one of these diseases was 10%, 21% and 26% after 10, 20 and 25 years of follow-up, respectively. In the most recent update to their original study of 241 patients, Kyle *et al* (2004) reported that the actuarial rate of malignant disease progression was 17%, 34% and 39% at 10, 20 and 25 years of follow-up, respectively.

Risk factors for progression of MGUS to a serious B-cell disorder

The Mayo Clinic study found that the initial level of serum M-protein was the most important predictive factor for progression to a serious B-cell disorder (Kyle *et al*, 2002). Ten years following the diagnosis of MGUS, the relative risk of progression was 6%, 7%, 11%, 20%, 24% and 34% among individuals with an initial M-spike of ≤ 5 , 10, 15, 20, 25 and 30 g/l, respectively. The type of serum M-protein was also predictive of progression to more serious disease states; patients with IgM or IgA types were at increased risk for progression compared to patients with an IgG protein.

Additional risk factors have been identified for the transformation of MGUS to a more serious B-cell disorder. Rajkumar *et al* (2005) found that MGUS patients with an abnormal serum ratio of free kappa to lambda immunoglobulin light chains in the serum were more likely to progress to malignant disease. An abnormal FLC ratio, defined as <0.26 or >1.65 , was determined by the highly sensitive FLC assay. Performed by an automated analyzer, the assay has proven to be reproducible based on extensive testing of healthy volunteers and patients with myeloma, amyloidosis and renal dysfunction (Bradwell *et al*, 2003). Rajkumar *et al* (2005) reported that patients with an abnormal FLC ratio had a RR of progression of 3.5 compared to patients with a normal ratio (95% CI: 2.3–5.5; $P < 0.001$); the results were independent of the size and type of serum M-protein. Patients with three risk-specific factors, including an abnormal serum FLC ratio, non-IgG MGUS and serum M-protein levels ≥ 15 g/l, had a risk of progression of 58% after 20 years of follow-up. This group was labeled as 'high risk MGUS.' For any patients in whom only two of the risk factors were found, the so-called 'high-intermediate risk' group, 37% of the patients progressed to more serious B-cell disorders. Individuals with only one risk factor comprised the 'low intermediate' risk group and had a 21% risk of progression. In the 'low risk' group, for whom none of the risk factors were present, the risk of progression was only 5%. Thus, these investigators established the first risk stratification model for MGUS. In a study of 407 MGUS

patients, Pérez-Persona *et al* (2007) showed that when >95% of the plasma cells within the plasma cell BM compartment were phenotypically aberrant (clonal PC), there was a significantly higher risk of progression to a serious B-cell disorder. This pattern was present in 18% of MGUS patients and these patients had a cumulative probability of progression at 5 years of 25% as compared to only 5% for patients without this feature.

Malignant cancer development among MGUS patients has also been independently tied to the presence of circulating plasma cells. Kumar *et al* (2005) found that circulating plasma cells predicted shorter median progression-free survival. Furthermore, they found circulating plasma cells to be a predictor of shorter median overall survival.

Other medical problems associated with MGUS

MGUS has been associated with a higher risk of other medical problems. These include osteoporosis/osteopenia and associated skeletal complications, especially vertebral compression fractures (VCFs) (Melton *et al*, 2004; Pepe *et al*, 2006; Bida *et al*, 2009). In an Olmsted County-based study, 488 MGUS patients were followed for 3901 person-years in order to monitor fracture status. Relative risk of fracture was calculated by standard incidence ratios (SIRs); MGUS patients were at increased risk for vertebral fractures (SIR, 6.3; 95% CI, 5.2–7.5) and hip fractures (SIR, 1.6; 95% CI, 1.2–2.2) when compared to expected rates in the community. For all axial fractures combined, MGUS patients had a relative risk (SIR) of 2.7 (95% CI, 2.3–3.1) (Melton *et al*, 2004). Studies have also shown that MGUS patients have increased osteoclastogenesis and abnormally high bone resorption (Jakob *et al*, 2002; Politou *et al*, 2004). A recent population-based study in Olmsted County confirmed that MGUS is associated with vertebral and hip fractures and osteoporosis (Bida *et al*, 2009).

For persons with a peripheral neuropathy (PN), a monoclonal gammopathy is discovered in the serum about 10% of the time, a significantly higher prevalence than observed in the general population (Kelly *et al*, 1981). In addition, a recent large population-based study showed that MGUS patients have a higher risk of PN (Bida *et al*, 2009). However, a recent large population-based cohort study did not demonstrate that MGUS patients show a higher risk of developing PN, and the authors suggested that most cases of PN among MGUS patients are not likely to be related to this disorder (Bida *et al*, 2009). Roughly one-third of the patients with monoclonal gammopathies and PN have MM, lymphoma, osteosclerotic myeloma, POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes), AL amyloidosis, or another plasma cell disorder, while the remainder have MGUS (Kyle & Dyck, 1993; Kelly, 1985; Kissel & Mendell, 1995). PN is most commonly associated with IgM MGUS (60% of cases), followed by IgG (30%), and IgA (10%) (Gosselin *et al*, 1991; Yeung *et al*, 1991). While the exact nature of the association

between PN and MGUS has not been fully elucidated, it has been shown that patients with IgM-related neuropathy often have anti-myelin associated glycoprotein antibodies in the serum (Melmed *et al*, 1983; Steck *et al*, 1983). By contrast, antibodies with this activity are usually absent in IgG- and IgA-associated neuropathies; these neuropathies tend to be more varied in their clinical phenotype (Drappatz & Batchelor, 2004).

Some studies have shown that MGUS patients are also more likely to experience thromboembolic events, such as deep vein thrombosis (DVT). Kristinsson *et al* (2008) examined the records of 2374 MGUS patients who had been admitted at least once to a US Veterans Affairs hospital. They found that the RR of DVT for MGUS patients was 3.3 (95% CI: 2.3–4.7) and that patients were at the greatest risk for developing DVT during the first year after diagnosis of MGUS (RR = 8.4; 95% CI: 5.7–12.2) (Kristinsson *et al*, 2008). Two small hospital-based studies also found that MGUS patients are at increased risk for DVT (Sallah *et al*, 2004; Srkalovic *et al*, 2004). However, a recent large population-based study does not show a higher risk of thromboembolic events among MGUS patients (Bida *et al*, 2009).

Consensus statements

Given these associated complications as well as the high risk of transformation to serious B-cell disorders, it is clear that MGUS patients should continue to be monitored indefinitely. Yet there has been no consensus within the medical community regarding whom to screen and how to proceed post-diagnosis. In fact, most MGUS is diagnosed during an evaluation for another medical problem, such as a peripheral neuropathy or unexplained bone loss (Bladé, 2006). Herein, we provide guidelines that will enable more efficient screening for MGUS and evaluation for related problems as well as more effective treatment once the condition and associated conditions have been discovered. These consensus statements were developed from a comprehensive discussion of each of the topics listed below among attendees at the day-long workshop. Each topic was discussed based on a review of the published literature and discussed among all members of the workshop. The specific recommendations that are outlined below were developed from input from all of the attendees at the workshop. When consensus was not reached among all attendees, the various views of the members are outlined in detail.

Whom to screen

Given the common occurrence of this disorder, screening would ideally encompass anyone older than 50 years; we do not, however, advocate universal screening in this population. It is unnecessary to impose the excessive emotional burden of a positive diagnosis among individuals who in general have a low risk of progressing to a malignant disorder. Moreover, universal screening in the elderly would result in higher costs for patients and insurers.

Given that MGUS is associated with a higher risk of osteoporosis/osteopenia and associated skeletal complications [especially fractures, as indicated above (Jakob *et al*, 2002; Melton *et al*, 2004; Politou *et al*, 2004; Pepe *et al*, 2006; Bida *et al*, 2009)], we recommend that anyone with age-inappropriate bone loss who does not have another known risk factor for this condition undergo screening for the presence of a monoclonal gammopathy. We define 'age-inappropriate' to include pre-menopausal females and males younger than 65 years who have clinical findings that are of concern for decreased bone mass [such as those with height loss or fragility (non-traumatic) fractures] or who have undergone dual energy X-ray absorptiometry (that showed osteoporosis or osteopenia. [Osteopenia is traditionally defined as a T-score between -1 and -2.4 and osteoporosis as a T-score less than or equal to -2.5 , where the T-score defines the number of standard deviations below mean bone density for a healthy young adult (mid-to late-20's) of the same sex as the patient.]

African Americans with age-inappropriate bone loss (osteopenia or osteoporosis) are also likely to be at increased risk for MGUS. A retrospective study of hospital records from African American and Caucasian veterans in the United States found that the age-adjusted prevalence of MGUS was three times higher for the African American cohort (Landgren *et al*, 2006). In addition, the age-adjusted incidence of MM was twice as high for African Americans in the study. However, osteoporosis and fractures are less common in this population than it is among Caucasians. For example, while a Caucasian male over 50 years of age has a 5–6% chance of fracture in his lifetime, an African American male in the same age range has only a 3% chance (American Medical Association, 2001). Similar findings have been reported in women (Barrett-Connor *et al*, 2005). Thus, we recommend that African Americans at any age with low bone mineral density (BMD) or who have sustained a low-energy fragility fracture, be considered for evaluation to determine whether they have a monoclonal gammopathy.

Persons with unexplained proteinuria or elevated total protein in the blood should also be screened because elevated protein levels often result from the presence of a monoclonal gammopathy.

Finally, PN without a defined etiology warrants evaluation for MGUS. Patients with PN frequently (10% incidence) are found to have a monoclonal gammopathy (Kelly *et al*, 1981). While the nature of the association between these two conditions is not well understood, unexplained PN should be an indication to perform tests to determine whether the patient shows the presence of a monoclonal gammopathy.

Which laboratory tests to perform

Individuals undergoing screening for MGUS should undergo serum and urine protein electrophoresis (SPEP and UPEP) and immunofixation, both of which are relatively simple and inexpensive tests.

How to proceed with evaluation after a monoclonal gammopathy has been identified

A. Additional laboratory tests

1. At the time of initial diagnosis

It is important to rule out a more serious B-cell disorder among patients in whom a monoclonal gammopathy is identified. The size of the M-protein should be quantified both in the serum and urine by electrophoresis in order to assess a patient's risk for development of a more serious disease. Among individuals demonstrating an M-protein in the urine on initial screening, a 24-h urine specimen must be collected in order to measure total and M-protein levels. Quantitative immunoglobulins (Igs) (serum) should be determined in order to assess the size of the M-protein and whether or not the patient has depressed levels of uninvolved Igs. Moreover, the physician should order a complete blood count (CBC) and routine blood chemistry tests in order to determine renal function. Serum electrolytes including calcium should also be determined. Finally, serum FLC testing should be performed as a screening procedure to help assess the risk for development of MM.

2. Follow-up tests

The frequency of follow up laboratory testing for patients with MGUS has not been clearly defined. Initially, the M-protein level should be determined every 4–6 months for approximately the first 1–2 years following identification of the monoclonal gammopathy. Some panel members believe that all individuals should undergo periodic testing every 6 months indefinitely, whereas other panel members believe that tests can be done less frequently (every 1–2 years) depending upon the risk factors. Patients should have tests performed that are similar to those done at the time of initial diagnosis.

B. Bone marrow biopsy and aspirate

1. At the time of initial diagnosis

There was no consensus regarding the requirement for BM aspirate and biopsy for patients who have been diagnosed with a monoclonal gammopathy. Half of the panel argued that only MGUS patients with higher levels of M-proteins (>15 g/l) and abnormal FLC ratios should undergo these procedures, as they are more likely to have MM or another serious B-cell disorder (Kyle *et al*, 2002). The other panel members advocated that all patients with a monoclonal gammopathy, regardless of the size of the initial M-spike, should undergo these invasive tests. These members believe that any patient with a monoclonal gammopathy is at a relatively high risk for having a serious B-cell disorder requiring treatment; and, thus, the early identification of these more serious conditions will be important. Age can also be a factor for consideration upon deciding whether to perform a BM aspirate; thus among patients <65 years it is

more reasonable to perform this test due to their longer life expectancy. In addition, if there is any doubt regarding the diagnosis of a B-cell disorder, then the BM examination is absolutely necessary. The panel does not recommend fluorescence *in situ* hybridization (FISH) testing of BM for patients with monoclonal gammopathies in which the clinician believes that there is a low likelihood to find evidence of MM. There is no data to suggest that findings by FISH would impact the management of MGUS.

2. Follow-up testing

Once the patient has been determined to have MGUS and not a more serious B-cell disorder, patients should undergo another BM aspirate and biopsy only if there are signs or symptoms suggesting progression to a more serious B-cell disorder or if there is another reason (e.g. unexplained cytopenia) to perform such tests.

C. Assessment of bone disease

1. At the time of initial diagnosis

Most members of the panel believe that all patients diagnosed with a monoclonal gammopathy should undergo a bone survey in order to identify possible lytic lesions as well as the presence of fractures which may indicate a more serious B-cell disorder or clinically significant skeletal-related problems. A minority of the members suggested that the performance of bone X-rays should be restricted to patients with bone pain, larger M-proteins and other additional risk factors for the development of myeloma. Among patients with specific sites of pain, further evaluation with magnetic resonance imaging (MRI) and/or computerized tomography scans may be indicated.

Although plain X-rays may suggest the presence of generalized bone loss (osteopenia or osteoporosis), this is not an accurate way to determine BMD. Thus, once MM has been excluded, the vast majority of the panel members believe that individuals with a monoclonal gammopathy should be further evaluated by DXA in order to accurately assess BMD because of their higher risk of significant bone loss. At present, the only test for bone health in which a T-score is used as the outcome measure is the DXA scan. This will preferably be performed at central sites (lumbar spine and hip). The site (hip or spine) with the lowest single score should be used to place the patient into a general category (i.e. if the hip T-score is in the osteopenic range but the spine T-score is in the osteoporotic range, the patient should be considered to have osteoporosis). If neither the results from the hip or spine can be interpreted (as for example among individuals >136 kg or patients with scoliosis or degenerative changes to the spine and hip replacements), then the 1/3 radius may be used. This will determine whether the MGUS patient has reduced bone mass and may be an appropriate candidate for treatment with skeletal anti-resorptive therapies to limit their future fracture risk. However, a small minority of members of the panel do

not believe that this test should be performed on all patients with MGUS.

2. Follow-up tests

Follow up radiological evaluation should only be performed if there are symptoms and signs of bone disease progression (new pain, fracture, loss of mobility, etc.) or progression of the monoclonal gammopathy to a more serious B-cell disorder.

The panel recommends that patients with MGUS and osteoporosis or osteopenia have follow-up DXA imaging approximately every 2 years to evaluate their response to skeletal anti-resorptive therapy. Among patients without evidence of osteoporosis or osteopenia at baseline, the panel members recommend reevaluation with DXA every 5 years. These assessments should be performed at the hip and spine (if available as per above), but the 1/3 radius can be used if necessary.

Treatment

A. Prevention of serious B-cell disorders

Although patients with MGUS are at increased risk to develop more serious B-cell disorders, no treatment to prevent this outcome has been established as effective. The low rate of development of serious B-cell disorders (1%/year) among patients with MGUS means that any studies to determine the efficacy of interventions to prevent this must involve very large numbers of patients with long follow-up (>10 years). However, recent advances in identification of individuals at higher risk for transformation may allow the design of trials that can be completed in a reasonable time frame with much smaller numbers of MGUS patients.

B. Bone-related problems

1. Medical management

a. Vitamin D and calcium

Because MGUS individuals show a much higher degree of bone loss and fractures than age- and sex-matched controls (Jakob *et al*, 2002; Melton *et al*, 2004; Politou *et al*, 2004; Pepe *et al*, 2006; Bida *et al*, 2009), prevention and treatment of bone-related problems is important in these patients. The frequent occurrence of Vitamin D deficiency in the elderly (Omdahl *et al*, 1982; Gloth *et al*, 1995) – a population at high risk for MGUS (International Myeloma Working Group, 2003) – makes it important to assess serum levels of this vitamin at baseline. Regardless, MGUS patients with T-scores ≤ -1 should maintain an oral intake of 800–1000 iu/d vitamin D, and be instructed to maintain a calcium intake (dietary, plus supplemental if necessary) of between 1200 and 1500 mg/d. For those patients who are found to be vitamin D-deficient, vitamin D supplementation should be increased accordingly, and periodic testing of 25-hydroxyvitamin D levels should be performed.

b. Anti-bone resorptive therapy

We recommend that MGUS patients who have evidence of VCFs or who are osteoporotic be initiated on anti-bone resorptive therapy, and that MGUS patients with osteopenia be strongly considered for this type of treatment. Recent results showed the ability of bisphosphonates to improve bone density in this clinical setting (Berenson *et al*, 2008; Pepe *et al*, 2008). A recent open-label study of 54 patients with MGUS and either osteoporosis or osteopenia demonstrated that zoledronic acid 4 mg significantly improved bone density when administered at 0, 6 and 12 months (Berenson *et al*, 2008). After 13 months of treatment, BMD of the posteroanterior lumbar spine and nondominant proximal femur increased by 22% and 8%, respectively. A second study that included MGUS patients with evidence of either osteoporosis or VCFs showed that 18 months of treatment with oral alendronate 70 mg/week increased BMD 6.1% in the lumbar spine and 1.5% in the hip (Pepe *et al*, 2008). Importantly, neither study was powered to assess fracture outcomes as a primary endpoint. No randomized studies comparing these two bisphosphonates to placebo or each other in MGUS patients have been completed to date. However, since the MGUS patients in these trials, unlike cancer patients, were not on other treatments that may have improved their bone density, these two studies suggest the benefits of bisphosphonates for treatment of MGUS-associated osteopenia/osteoporosis. Certainly, other classes of drugs have proven effective in the setting of osteoporosis without cancer including calcitonin, raloxifene, teriparatide, other orally administered bisphosphonates and, most recently, the receptor for activation of nuclear factor- κ B ligand inhibitor, denosumab (Overgaard *et al*, 1992; Lieberman *et al*, 1995; Ettinger *et al*, 1999; Harrington *et al*, 2004; McClung *et al*, 2006; Saag *et al*, 2007), but whether these drugs would be effective for patients with MGUS is unknown. Moreover, denosumab has received favorable support from regulatory advisory committees in both Europe and the United States but it has not yet been approved. Although teriparatide, raloxifene and calcitonin are approved for the treatment of osteoporosis in the benign setting and may be considered alternative therapies for MGUS subjects with osteoporosis, the panel favors the use of bisphosphonates for their superior anti-fracture efficacy among patients with osteoporosis and their demonstrated ability to improve bone density in the setting of MGUS with bone loss. At present, the data are insufficient to recommend only zoledronic acid for the management of MGUS patients with osteoporosis or osteopenia at a dosing schedule (every 6 months) as shown to be effective in a single-arm clinical trial (Berenson *et al*, 2008) but is more frequent than that which is currently Food and Drug Administration (FDA)-approved for the standard therapy of osteoporosis from benign causes (annually). Other bisphosphonates licensed for the treatment of osteoporosis, including alendronate or risedronate administered orally once weekly, may also be administered in the setting of MGUS, as we described from the positive results of the alendronate trial

(Pepe *et al*, 2008). In terms of duration of therapy, data from the Fracture Intervention Trial Long-term Extension study suggests that 10 years of alendronate therapy did not significantly reduce the incidence of all fractures but did reduce clinically recognized VCFs compared to 5 years of treatment in the setting of osteoporosis from benign causes (Black *et al*, 2006). However, whether these results apply to patients with a higher risk of fractures, especially in the vertebral bodies, in the setting of MGUS is unknown. Thus, we would recommend 5 years of initial therapy and then a discussion between the patient and health care provider regarding whether to continue the treatment based on updated results from clinical trials and the relative perceived benefits compared to risk of continued treatment with bisphosphonates.

While side effects associated with bisphosphonate treatment may occur, zoledronic acid 4 mg every 6 months when administered to MGUS or other cancer patients has not been associated with an increased incidence of the most serious complications including osteonecrosis of the jaw (ONJ) or renal impairment (Brufsky *et al*, 2007; Berenson *et al*, 2008). Nonetheless, MGUS patients receiving bisphosphonates should be monitored for these potential harmful side effects. Patients receiving bisphosphonate therapy should visit their dentist before treatment begins and at least once a year during treatment. This will facilitate early detection and treatment of potential dental problems that may increase the risk of ONJ (Bagan *et al*, 2007).

2. Skeletal evaluation and consideration for surgical management

As mentioned previously, persons with MGUS are at increased risk for fractures, especially involving the vertebral bodies (Melton *et al*, 2004; Gregersen *et al*, 2006). Patients in whom fractures are identified should be further evaluated by a bone specialist. Other reasons to visit a bone specialist include prolonged or increased back pain for more than 4–6 weeks, new onset of soft tissue swelling, deep bone pain, or an increase in the requirement for pain medication. Patients who are clinically considered at high risk based upon physical examination for a VCF (e.g. those with significant back pain) should undergo an MRI with sagittal short tau inversion recovery sequences to image osseous oedema. These individuals may also be more likely to have MM, and it is important to rule out this diagnosis in this high-risk group.

For patients with painful VCFs regardless of whether these fractures are from malignant or non-malignant causes, balloon kyphoplasty has proven to be a safe and efficient minimally invasive surgical technique with a quick recovery time that markedly reduces bone pain and improves quality of life (Lieberman *et al*, 2001; Berenson *et al*, 2009; Wardlaw *et al*, 2009); and, thus, this procedure should be considered for MGUS patients with symptomatic VCFs. In a randomized trial of cancer patients (median age of 64 years, range 40–88 years; 37% with MM) with VCFs, kyphoplasty markedly improved Roland-Morris Disability and pain scores compared to patients who received non-surgical interventions (Berenson *et al*,

2009). The number of adverse events was not different between the two groups. In a recent randomized trial involving 300 patients with VCFs without malignancy except in four cases (median age of 73 years), kyphoplasty significantly improved short-form (SF)-36 physical component summary scores compared to controls (Wardlaw *et al*, 2009). In addition, kyphoplasty, unlike vertebroplasty (see below), also confers the added benefit of potential height restoration, which can help to correct altered biomechanics (Shen & Kim, 2006). As this procedure has been shown to be effective and without significant morbidity for both cancer and non-cancer patients with VCFs, it is likely to offer similar benefits for MGUS patients with VCFs although no specific studies have been done in this patient population.

Vertebroplasty is another minimally invasive procedure which has been used to reduce pain for patients with VCFs. However, two recent double-blind, randomized studies showed that patients treated with vertebroplasty had no benefits compared to those undergoing a sham procedure as assessed with Roland Morris Disability and pain scores

(Buchbinder *et al*, 2009; Kallmes *et al*, 2009). Vertebroplasty has also been associated with rare but serious local neurological and cardiopulmonary complications resulting from cement extravasation, leakage and embolization (Orsini *et al*, 1987; Pinto, 1993; Padovani *et al*, 1999; Ratliff *et al*, 2001). The incidence of cement extravasation ranges from 30% to 70% after vertebroplasty compared with less than 10% after kyphoplasty (Chiras *et al*, 1997; Hulme *et al*, 2006; Taylor *et al*, 2006), and more serious complications are observed less frequently with kyphoplasty (Atalay *et al*, 2005).

C. Peripheral neuropathy

Patients with MGUS are more likely to experience PN in some (Kelly *et al*, 1981) but not all studies (Bida *et al*, 2009), and effective treatments for this complication have involved corticosteroids (Roglio *et al*, 2008), plasmapheresis (Cornblath *et al*, 1987; Dyck *et al*, 1991) and rituximab (Zaja *et al*, 2003). The panel suggested that, in the majority of patients, the risks and side effects of these treatments outweigh the potential benefits. In patients with more significant symptoms and

Question	Recommendation
Who do you screen for MGUS?	Testing for the following populations 1. Age-inappropriate osteoporosis/osteopenia 2. All African Americans with osteoporosis 3. Unexplained proteinuria or elevated total protein levels in the blood 4. An unexplained peripheral neuropathy
What tests should screening involve?	Screening should involve 1. Quantification of the M-spike in the serum and/or urine by electrophoresis 2. Determination of the type of monoclonal protein 3. Blood counts and routine chemistries 4. Serum free light assay may have prognostic value 5. Bone marrow aspirate and biopsy may be performed for individuals with high-risk features
Should follow-up testing be done and how often?	1. Every 3–6 months initially 2. Frequency over time may vary depending upon the size of the M-protein and other risk factors for progression to a more serious B-cell disorder
Should bone surveys be done during follow-up?	If not on all patients, then at least among patients with 1. Bone pain 2. Larger M-proteins 3. Additional risk factors for the development of a more serious B-cell disorder
What to consider when MM has been excluded and MGUS ruled in?	1. Bone mineral density determination by dual energy X-ray absorptiometry 2. Vitamin D and calcium doses optimized 3. MGUS patients with either osteoporosis or osteopenia should also be considered for anti-bone resorptive therapy especially with bisphosphonates
What do you do for MGUS patients who have developed fractures?	1. Should be seen by a bone specialist 2. Kyphoplasty for treating symptomatic vertebral compression fractures

Table I. Recommendations for Evaluation and Management of MGUS.

morbidity, these treatments may be necessary. Alternative treatments, such as α -lipoic acid (Ziegler *et al*, 1995, 1999; Reljanovic *et al*, 1999), acetyl-L-carnitine (Bianchi *et al*, 2005; Maestri *et al*, 2005), benfotiamine (Simeonov *et al*, 1997; Haupt *et al*, 2005), methylcobalamin (Ide *et al*, 1987; Yaqub *et al*, 1992), and topical capsaicin (Scheffler *et al*, 1991; Capsaicin Study Group, 1992), have been extensively used and may offer benefit without the adverse event and addiction profiles that may occur with other PN treatments. More recently, gabapentin and pregabalin have been used to palliate these symptoms in some patients (Tsavaris *et al*, 2008; Vondracek *et al*, 2009). Importantly, these therapeutic options have been studied most extensively in diabetic neuropathy but these treatments have also been used in the oncological setting.

D. Thromboembolic events

Although individuals with MGUS have been shown to be at higher risk to develop DVTs in most (Sallah *et al*, 2004; Srkalovic *et al*, 2004; Kristinsson *et al*, 2008) but not all studies (Bida *et al*, 2009), routine anticoagulation was not recommended by the panel. However, physicians should be aware of this heightened risk in MGUS compared to non-MGUS individuals. This is likely to lead to diagnosis and treatment of DVTs that may have otherwise gone undetected.

Conclusions

MGUS is a common disorder in the elderly, and recent studies suggest not only that these individuals have a higher risk of developing MM and serious B-cell disorders but also are at increased risk for bone loss with associated skeletal fractures and possibly peripheral neuropathy and thromboembolic events. Table I summarizes the recommendations of our consensus panel for evaluation, follow up and treatment of patients with this disorder.

Overall, this consensus statement should help guide the management of patients with this common yet not well-understood or often recognized disorder. MGUS should continue to receive close scrutiny from the medical community, due to its increased risk for progression to malignant diseases, and its close association with other significant health problems especially with bone loss and resulting frequent development of fractures.

Disclaimer

This consensus statement was conducted according to the World Medical Association Declaration of Helsinki and Good Clinical Practice for clinical trials.

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