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# Optimizing the monitoring of patients with plasma cell dyscrasias

## El seguimiento óptimo de los pacientes con enfermedades de las células plasmáticas

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## INTRODUCTION

In the United States, multiple myeloma is the 14th most common cancer with an estimated 24,050 patients diagnosed in 2014. Myeloma represents 1.4% of all new cancer in the United States with a median age at diagnosis of 69 and a median age at death of 75. The five-year survival for the years 2004 through 2010 is 44.9%. With the introduction of novel agents, deep responses ≥nCR are now approaching 60%. The assessment of patients with multiple myeloma has utilized measurement of either the M-spike or the quantitative heavy chain by nephelometry. These techniques, based on 1960s technology, have major drawbacks. The half-life of IgG is 25.8 days.[1] As a consequence, confirmation of a >90% reduction in M protein (VGPR) can take 10 weeks, even when marked cytoreduction of the myeloma population has occurred. This delay is not consistent with an individualized management strategy for myeloma patients. The normal level for IgG in human serum is 15,000 mg/L and for IgM 500 mg/L. The visual detection of a monoclonal peak on a serum protein electrophoresis can occur with levels as low as 2,000 mg/L. However, particularly for IgA monoclonal proteins that migrate in the beta region, transferrin, C3, and beta lipoprotein interfere with the estimates of the M-spike.[2] At low levels, immunoglobulin levels cannot distinguish polyclonal from the myeloma immunoglobulin.

Immunofixation is ten times more sensitive than serum protein electrophoresis, allowing the recognition of a monoclonal band at 200 mg/L. Unfortunately, this technique is qualitative and not quantitative and can only determine the presence or absence of

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a band. The reproducibility of a 24-hour urine requires accurate collection, is dependent on the level of renal function, and is a sample that most laboratories find undesirable for processing. Over the past decade, the introduction of the immunoglobulin free light chain nephelometric assay allows reproducible measurements of the immunoglobulin free light chain down to 10 mg/L, making it 200 times more sensitive than serum protein electrophoresis and 20-fold more sensitive than immunofixation. The coefficient of variation of the test is <3%.

The total kappa/lambda light chain quantification in the monitoring of patients with multiple myeloma found that the assay was not more sensitive than immunofixation.[3] The immunoglobulin free light chain assay uses an antibody that only recognizes the epitopes present on the internally facing light chain that is not exposed in an intact immunoglobulin molecule. This led to the recognition of light chain monoclonal gammopathy of undetermined significance. It is found in 3.3% of patients who are routinely screened, with a prevalence of 0.8% and a risk of progression to multiple myeloma of 0.3%/100 person years. Light chain MGUS is a particular risk factor for the development of AL amyloidosis as it was found in 11 of 20 patients who ultimately developed AL.

## Use in MGUS/SMM

An abnormal free light chain ratio, when combined with the size of the M-spike, by serum protein electrophoresis (>1.5 g/dL) and immunofixation (IgG or non-IgG) will classify MGUS patients into three distinct categories with an annual risk of transformation of approximately 0.5% per year, 1% per year, and 2% per year.

In smoldering multiple myeloma, the light chain ratio also predicts the risk of progression. An iFLC/uFLC ratio >8 with >10% plasma cells and a serum M protein of >3 g/dL is considered high risk. The International Myeloma Working Group has adopted iFLC/uFLC >100 as a defining feature for active myeloma and an indication for immediate chemotherapy in the absence of CRAB symptoms (hypercalcemia, cast nephropathy, anemia, and bone disease).

## Light chain assay as a leading indicator of response and relapse

The short half-life of the free light chain assay allows rapid assessment of response such that within two weeks of therapy initiation, it is possible to estimate progression-free survival based on the iFLC.[4] Other groups have demonstrated the predictive value of free light chains measured after two cycles of chemotherapy. Overall survival could be estimated at the end of eight weeks.[5] In one trial, 54 of 520 patients presented with an intact immunoglobulin, myeloma progression was heralded by a rise in the free light chains.[6]

The sensitivity of the free light chain assay has eliminated the need for regular monitoring of the 24-hour urine in patients with light chain myeloma and has reduced the need for using bone marrow biopsies for assessing patients with multiple myeloma.[7] In one trial of 428 patients with a monoclonal gammopathy, discontinuation of urine studies and reliance on an algorithm using serum studies alone failed to detect 0.5% of patients with urinary monoclonal proteins.[8] A review of eligibility criteria in clinicaltrials.gov demonstrates that the immunoglobulin free light chain has been incorporated into the eligibility criteria for clinical trials. The frequency of non-secretory myeloma, previously quoted as high as 5% of myeloma patients,[9] has now fallen to 0.5%.

## Use in solitary plasmacytoma

An abnormal involved serum free light chain value in the presence of solitary plasma-

cytoma is an important risk factor for the development of multiple myeloma with 64% of patients having an abnormal serum free light chain ratio at diagnosis.[10] In a cohort of 116 patients, the risk of progression at five years was 44% in patients with an abnormal free light compared to 26% in those with a normal free light ratio.[11]

### Amyloidosis

The light chain has revolutionized the diagnosis, staging, and monitoring of patients with immunoglobulin light chain amyloidosis. Unlike multiple myeloma, only 40% of patients with amyloidosis have a detectable immunoglobulin heavy chain in the serum. The quantity of heavy chain is small, rarely >3 g/dL, with a median <1 g/dL. Prior to the light chain assay, it was difficult to assess hematologic response. An immunoglobulin free light chain abnormality is found in 98% of patients with amyloidosis, and changes in the light chain have become integrated into the hematologic response criteria. Light chain measurements are also part of the staging system of AL. A dFLC of >180 mg/L, when combined with the cardiac biomarkers NT-proBNP and troponin, create a reliable separation of patients into four groups with markedly different median survivals. The light chain levels are also prognostic for survival, reflecting the size of the plasma cell clone responsible for amyloid protein synthesis.

### Cast nephropathy

Immunoglobulin free light chains in the serum are predictive for the risk of development of myeloma cast nephropathy. It would be uncommon to see cast nephropathy develop if the involved free light chain is <500 mg/L, and patients who have a normal free light chain level have no risk of cast nephropathy.[12]

### Other plasma cell disorders

The serum immunoglobulin free light chain was measured in 83 patients with newly diagnosed POEMS syndrome. Sixty-seven percent showed an elevated serum free lambda light chain level. Patients with POEMS frequently have a component of polyclonal hyperglobulinemia, making the measurement of the involved serum free light chain a useful adjunct in assessment.[13] The free light chain assay has been used in Waldenström macroglobulinemia, to predict response and progression earlier than changes in the IgM or the M-spike.[14] The serum free light chain correlates with tumor burden markers and is capable of differentiating IgM MGUS from Waldenström macroglobulinemia.[15]

### Cost effective use

Although a valuable test, it is relatively expensive compared to traditional measures. Although, in large statistical models the ratio has been promoted as the ideal method of monitoring, I actually find the ratio to be confusing. Small changes in the uninvolved immunoglobulin light chain can cause large swings in the ratio, which can be misleading. Renal failure impacts the level of the immunoglobulin light chain. However, when measured serially over time, the involved free light chain level can be utilized to monitor the disease process. When resources are an issue, I believe it is justified to serially measure only the involved free light chain and ignore the uninvolved free light chain. This decreases the cost of the assay by 50%.

## CONCLUSION

The introduction of the immunoglobulin free light chain test has eliminated the need for 24-hour urine protein electrophoresis.[16] It is important in assessing prognosis and risk of transformation in

MGUS and smoldering myeloma. The free light chain assay is now standard for clinical trials in multiple myeloma and has redefined patients who are asymptomatic but for whom immediate therapeutic intervention is indicated.[17] The use of the light chain assay will identify patients at risk for the development of light chain amyloidosis; and in AL, it is part of the staging and response criteria. Nonsecretory and oligosecretory disease is now rare. The assay is an important indicator of early response and relapse. It should be routine in all patients with a plasma cell disorder.

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