

Serum Free Light-chain Assay for the Diagnosis, Management, and Prognosis of Multiple Myeloma

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ABSTRACT

In recent decades, new serum biomarkers have been developed for routine laboratory practice, such as assaying serum free light chains and more recently, assaying immunoglobulin heavy and light chain isotypes (Hevylite).

In this work, we highlight the interest of new biomarkers (Hevylite Test) in the management of monoclonal gammopathies because of the technical advantages it confers and the sensitive and unique clinical information that can be drawn from them.

Data from the latest studies show changes in the practice and use of Freelite and Hevylite tests in particular situations in the diagnosis and monitoring of MM, in situations where the monitoring of the tumor mass by conventional techniques is difficult. Freelite and Hevylite tests are proving to be of great benefit. The sFLC assay has already been recommended by international myeloma experts since 2009. There is no doubt that an integration of the Hevylite test for the diagnosis and monitoring of IgA MM will be done in the near future.

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Introduction

In 2015, the International Myeloma Working Group (IMWG) revised the diagnostic criteria for multiple myeloma (MM). The update was initiated following the identification of reliable biomarkers to accurately distinguish patients with smoldering multiple myeloma (SMM) with a high probability of progression to MM and an imminent risk of stroke terminal organs. This update was also motivated by the therapeutic trials conducted over the last ten years, which showed evidence suggesting that early intervention at the SMM stage in high-risk patients could improve overall survival (1). The update shows that the criteria CRAB (calcium, renal insufficiency, and anemia or bone lesions) are not sufficient to make a diagnosis of MM candidate treatment. Patients can now benefit from early treatment to prevent the onset of

advanced multi-organ dysfunction and minimize the accumulation of cytogenetic abnormalities.

The new diagnostic criteria for MM recommend the use of specific biomarkers to define the disease, as well as the use of modern imaging tools to diagnose bone damage to MM. This update of the definition criteria for MM has also led to the revision of the definition of MMS and other disorders related to monoclonal dysglobulinemias.

The serum free light-chain assay (sFLC) is widely recognized and has found its place in the diagnostic, prognostic and therapeutic approach of monoclonal gammopathies.

Currently, there are two reagents for assaying sFLCs: Freelite reagent from The Binding Site, marketed since 2001 (2) and N-Latex FLC reagent from Siemens Healthcare Diagnostics, available

since 2011 (3). The Freelite test composed of monospecific anti-FLC kappa (k) and anti-FLC lambda (l) polyclonal antibodies (Ac) can be performed either by nephelometric technique or by turbidimetric technique.

The N latex FLC assay using anti-LC monoclonal mAbs respectively type k or l is intended only for nephelometry. The antibodies of both reagents recognize masked epitopes when the Ig is intact, and which are only accessible if the Ig light chains are free. It has been shown that the results of sFLC assays obtained with the reagents of two companies and different instruments are globally consistent but non-transposable (4, 5).

In the absence of available international standards, it is recommended to monitor patients by the same technique and in the same laboratory. Currently, the recommendations of the IMWG are based exclusively on the results obtained with the Freelite test of The Binding Site. The sFLC assay provides four indicators for the management of patients with monoclonal Ig:

- The FLC k / l ratio: monoclonality indicator;
- The involved FLC (iFLC): FLC involved corresponding to the production of the monoclonal light chain;
- The uninvolved FLC (uFLC): non-involved FLC corresponding to the production of polyclonal light chains;
- The dFLC (difference (iFLC - uFLC) which is informative for the response to the treatment. The FLC report is often disturbed in the MM, associated with the SPE and the IF, it makes it possible to diagnose all the patients with gammopathies monoclonal (6).

In the SMM, an abnormal FLC ratio is associated with a higher risk of progression to MM [7]. At present, the existence of a very abnormal FLC ratio (iFLC / uFLC \geq 100) when abnormal medullary plasmocytosis exceeds 10% confirms the diagnosis of MM.

In order to increase the sensitivity of this criterion, a minimum level of iFLC is required (at least 100 mg / L). The choice of the IMWG to include this parameter among the events defining the MM (myeloma defining events: MDE) is justified by the results of various independent studies. In 2012, Larsen et al. found a significantly

abnormal FLC (iFLC / uFLC \geq 100) in 90 of 586 MMS patients (15%) (8).

The risk of progression to MM in the first 2 years with an iFLC / uFLC ratio \geq 100 was 72% (with a median progression at 15 months); the cumulative risk of progression to MM or AL amyloidosis at 2 years was 79%. Kastritis et al. worked on a cohort of 96 MMS patients and found that 7% had an iFLC / uFLC ratio \geq 100.

Within 18 months, almost all of these patients (98%) progressed to symptomatic MM (with an iFLC / uFLC ratio \geq 100 the median progression to MM was 13 months) (9). In a third study, patients with SMM with an iFLC / uFLC ratio \geq 100 had a risk of progression of 64% at 2 years (10). These three studies allowed the integration of this parameter among the new events defining the MM.

Definition criteria of the MM:

At present, the diagnosis of MM requires the presence of one or more events defining the MM, in addition to the existence of at least 10% of abnormal plasma cells or an extra-medullary solitary plasmocytoma. MDEs include characteristic CRAB signs, as well as three biomarkers reaching the predetermined threshold: - at least 60% of abnormal plasma cells in the bone marrow; And / or the existence of at least two focal osteolytic lesions on magnetic resonance imaging (MRI); And / or the ratio iFLC / uFLC \geq 100, with an iFLC greater than 100 mg / L. These three biomarkers are associated with an increase of more than 80% in the risk of progression to symptomatic MM (proven by at least 2 independent studies). Thus, patients with MMS and having at least one of these markers have a high probability of developing multi-organ disorders. Delay therapy until documentation of the findings does not appear to be in the patient's best interest (11), this update of the MM criteria allows for early access to treatment for patients at imminent risk of transformation.

Serum free light-chain assay Vs immunochemical analysis of 24-hour Urine

In MM patients, evaluation of the response to treatment is prognostically important. In fact, obtaining a complete response after treatment with high doses of chemotherapy is correlated with long-term survival and progression-free survival (12, 13).

According to the IMWG criteria for monitoring patients with MM, the response to treatment should be assessed by electrophoresis quantification of the monoclonal component in the serum and in the 24-hour urine (14, 15). For patients with light chain multiple myeloma (LCMM), the measurement of the monoclonal component cannot be evaluated in the serum, it must be done by immunochemical analysis of 24-hour urine; the disease is measurable as soon as the excretion of the isolated monoclonal light chain exceeds a minimum of 200 mg per day.

In practice, this recommendation contains several pitfalls. In fact, the monitoring of the isolated monoclonal light chain in the urine is complicated to perform because of pre-analytical constraints, both for the patients (collection of all the rarely complete urine, especially in the elderly) and for the laboratory in charge of this determination (pre-analytical constraints).

In addition, at the analytical level, the quantification of the monoclonal component is difficult and in some situations may not reliably reflect the tumor response, because of the renal metabolism of light Ig chains and renal function-related changes. It has been shown for many years that the monitoring of the tumor mass could also be carried out by the assay of sFLC using polyclonal antibodies, which proved to be a reliable marker especially for the evaluation of the residual disease (16, 17).

It has been suggested that the Freelite test could replace urine protein electrophoresis (UPE) for monitoring of LCMMs because of better analytical sensitivity (1.5 mg / L vs. 30-50 mg / L) and better accuracy (5% vs. > 15%). However, in 2009, additional studies were still needed and IMWG [18] experts did not recommend this test for monitoring MM patients, except in the case of non-secretory or pauci-secretory MM.

More than fifteen years after the introduction of the sFLC assay in the management of monoclonal gammopathies, what is the place of this assay compared to the immunochemical analysis of the urine in the follow-up of the myeloma?

In an attempt to answer this question, Dr. Jill Corre from the Genomic Unit of Myeloma (Professor Hervé Avet-Loiseau, University Hospital of Toulouse), during his address at the American

Society of Hematology (ASH) conference in 2014 and at the Euromedlab congress in 2015, presented the results of the Francophone Intergroup of Myeloma (IFM) on the response to the treatment of patients included in the 2009 MFI trial from November 2010 to December 2012, following the recent diagnosis of Messrs. The exclusion criteria for this study were serum creatinine > 25 mg / L or creatinine clearance < 60 mL / min. Of the 700 patients (< 66 years) included in the 2009 IFM / DFCI protocol, 115 patients had an LCMM (16.4%) and 585 patients had intact Ig myeloma (intact immunoglobulin multiple myeloma: IIMM). Of these 585 patients with intact Ig, 331 patients had a measurable FLC (≥ 100 mg / L with the Freelite test) at the time of diagnosis (patient population selected for the purpose of comparison for treatment follow-up in this study). After a course of VRD (velcade-revlimid-dexamethasone), all patients were evaluated locally by serum protein electrophoresis (SPE) and UPE. After 3 courses of VRD, all patients were evaluated centrally by SPE and UPE but also by the sFLC assay. At the end of the first course, the response assigned by the evaluation of the monoclonal component according to the IMWG recommendations in the LCMM seems aberrant. Indeed, in the population of patients with a LCMM, based on the evaluation of the monoclonal component by the UPE, 52/84 or 62% of the patients had a very good partial response (VGPR) (with normal UPE, monoclonal component detectable only by IF).

In comparison, in patients with an IIMM, SPE was abnormal in 100% of cases, which corresponds to the expected result: no IIMM patient reached VGPR after a single course of treatment. After 3 courses, 88/112 or 79% of the LCMM patients were in VGPR compared to only 70/331, ie 21% of the IIMM patients. In contrast, levels of response to LCMM treatment (achieved by standardization of the sFLC ratio) after 3 courses of treatment are statistically comparable with the levels achieved in the IIMM (peak assessment with PSA): 58% of the LCMMs and 52% of the MMI responded.

The findings of this study show that the evaluation by sFLC assay of treatment response in patients with LCMM is more reliable than by measuring the urinary excretion of the isolated

monoclonal light chain, dependent on renal function. of the patient and subject to individual variations. The evaluation of this response by sFLC assay is statistically comparable in patients with LCMM and in patients with an MIMI.

Dr. Corre therefore suggests that the sFLC assay may be a better marker for monitoring the LCMM than the standard urinary isolated monoclonal light chain techniques currently recommended and that this test could replace urine analysis to evaluate the answer in the LCMM. In another French study, published in *Haematologica* in 2015, Thomas Dejoie et al. compared the sFLC assay with conventional techniques (urinary and urinary PE / IF after 24h urine collection) in a cohort of 182 patients: 25 patients with LCMM and 157 with IIMM, all included in the IFM protocol 2007-02. The objective of this study was to evaluate the monoclonal component during treatment follow-up, after 2 and 4 cycles of chemotherapy and after autologous stem cell transplantation (19).

At the time of diagnosis, each of the 25 patients with a LCMM had a light chain measurable by both methods, the sFLC assay with an abnormal ratio in 100% of the cases and the UPE. In patients with MIM, the ratio of sFLC was abnormal in 154/157 (98%) patients, while only 85/157 (54%) were positive for urinary IF and 67/157 (43%) for UPE.

In addition, 98/157 (62%) of the IIMM had a patient measurable by sFLC and only 55/157 (35%) by UPE. With regard to the evaluation of the treatment response, in all patients, the comparison between the standard methods recommended by the IMWG criteria (SPE and UPE) and those tested (SPE and sFLC) showed excellent agreement between methods for 155/192 (81%) patients (weighted kappa = 0.85 (0.68-0.98)).

Among the discordant responses (37/192), the most significant differences were in a patient with a progressing LCMM, informative in sFLC but not UPE (negative) and two patients with an LCMM, informative in UPE that indicated progression but with stable sFLCs.

In addition, of three MIMI patients who had relapsed with monoclonal free light chains, 2/3 were informative with both methods (FLC and UPE) and the last, informative only in FLC. A comparison of the sFLC and UPE assays during follow-up (Figure

20) showed that: 1) after 2 cycles of chemotherapy the urinary IF had become negative in 9/19 (47%) of patients with LCMM and in 19/44 (43%) of patients with MIM, whereas the sFLC assay had normalized in only 2/19 (11%) of patients with LCMM and in 27% of patients with MIM. In patients with IIMM, normalization of SPE was observed in 4/44 (9%); 2) after 4 courses of chemotherapy and after autograft, 14/21 (67%) of patients with LCMM had normalized their urinary IF, while the ratio of sFLC returned to normal in only 3/21 (14%) and 8/21 (38%) of patients with LCMM respectively.

In patients with MIM, 54% and 71%, respectively, had normalized their urinary IF, while 23% and 29% had standardized the sFLC ratio. The authors conclude that the different methods are valid but that the sFLC assay is a more sensitive marker than the 24 hour urine PE for tumor mass monitoring, a better concordance with the serum monoclonal component over the course of the study. follow-up having been observed. Replacing the urine analysis with the sFLC assay would not significantly affect the assessment of treatment response in these two populations.

An interrogation nevertheless remains: at the cytological and histological level, there is a lack of data concerning the analysis of the bone marrow, which can make it possible to decide on the complete or non-response of the patients according to the criteria of the IMWG. In addition, it would be important to know whether the examinations were performed on concentrated urine or not, since this may affect the sensitivity of urine tests.

In conclusion, it still seems premature to systematically replace the immunochemical analysis of 24-hour urine with the sFLC assay, when this technique is feasible and informative. Especially since the analysis of urine is essential for the evaluation of renal function and type of kidney damage (analysis of proteinuria and albuminuria).

Regarding the monitoring of hematologic disease, the use of the sFLC assay appears to be better correlated with tumor mass and response after treatment.

The Hevylite test in the management of multiple myeloma:

Since 2009, a new Hevylite assay developed and marketed by The Binding Site is available for the management of patients with monoclonal gammopathy (20). Anti-heavy and light chain specific polyclonal antibodies are used against epitopes of the heavy chain and light chain constant contact region.

Using these specific antisera it is possible to quantify Ig heavy and light chain isotypes. The Ig can thus be analyzed in pairs (IgGk / IgG1, IgAk / IgA1, IgMk / IgM1) to calculate the ratio of the concentration of the monoclonal Ig involved to the concentration of the non-involved Ig, in the same way as k / l ratios are established when using the sFLC assay. Numerous studies have evaluated the performance of the Hevylite test as a biological marker in various clinical circumstances during plasma cell pathologies.

In 2015, at the Euromedlab congress, Professor Katzmann discussed the contribution of the Hevylite assay in the biological analysis of monoclonal gammopathies. He recalled that the first-line biological assessment performed in the presence of a suspicion of monoclonal gammopathy includes an SPE followed by an IF.

Currently, the IMWG recommends screening based on the combination of SPE, IF and sFLC assay, to diagnose virtually all monoclonal gammopathies. These exams appear as having the best report sensitivity and simplicity of realization. Professor Katzmann cited several publications about HLC assay in the diagnostic (20, 21), prognostic (22-24) and in the follow-up of plasma cell pathology (25, 26).

Professor Katzmann recalled the case of a patient with MM IgA published in 2011, for which the use of the Hevylite test provided early information on the evolutionary recovery of MM, while conventional tests did not yet allow conclude (21). The Hevylite test can thus enhance biological monitoring of MM and supplement information on the polyclonal and monoclonal response during MM.

In this presentation, the Hevylite ratio is earlier in predicting the relapse of MM than conventional tests. Professor Katzmann recalled that in MIOs, the

level of monoclonal Ig evaluated by SPE is highly variable at concentrations below 10 g / L (27) and remains inaccurate for concentrations greater than 20 g / L in because of the saturation of the color (28). The estimation of the monoclonal peak is also difficult for SPE in case of electrophoretic migration outside the gamma globulin zone. This is particularly the case for monoclonal IgA isotype IgA which preferentially migrate in the beta-globulin zone. Therefore, monoclonal IgA can be masked or confused with other serum proteins such as transferrin or complement moieties. In addition, the electrophoretic migration may be in the form of a broad band or in the form of two or three bands corresponding to a mixture of mono- and multimeric molecules making the quantization of the peak less reliable. In this case, the only quantitative alternative remained until then the weighting of total IgA.

The nephelometric weighting of Ig allows the analysis of low Ig concentrations but measures the totality of Ig and does not allow the distinction between polyclonal Ig and monoclonal Ig. As for the IF, although very sensitive, this technique remains qualitative; it allows the typing of monoclonal Ig but does not provide precise information on the amount of the monoclonal component. Professor Katzmann presented the results of a retrospective Mayo Clinic study on a cohort of 365 patients with IgG MM.

The HLC ratio was abnormal in 354 (97%) patients. The 11 patients with a normal HLC ratio had monoclonal Ig in very low concentration and below the SPE limit of detection. In a cohort of 153 MM IgA, the HLC ratio was also abnormal in 97% (148) patients (data presented at the Euromedlab congress).

Hevylite assays were also evaluated on a population of MGUS. Of 726 MGUS IgG, 117 IgA and 156 IgM, the HLC ratio was abnormal in 330 (45%), 104 (89%) and 137 (90%) cases respectively [22]. The interest of the HLC test was also evaluated in 30 patients with IgA MM. The HLC test gives correlated results with the SPE and the IF.

The equal or even increased sensitivity of the HLC test with respect to SPE has been emphasized for monoclonal IgA (26). Professor Katzmann presented the results of a retrospective study of

Boyle et al. performed on a cohort of 157 patients (68 patients followed at Lille University Hospital and 89 patients included in the IFM protocol 2005-01) with MM (25).

The concentration of the monoclonal Ig measured by the Hevylite test correlated with that estimated by the SPE. The HLC ratio was abnormal in all patients. In 157 patients, 12 patients (8%) had a monoclonal Ig level $<10 \text{ g/L}$, including 4 patients for whom monoclonal Ig was not quantifiable on SPE.

The results indicate that Hevylite assays are:

1) more sensitive than SPE and allow accurate quantification of monoclonal Ig low concentrations and migrating as a wide band;

2) At least as sensitive as serum IF and have the benefit of being quantitative

3) could replace SPE, IF and total IgA assay in follow-up of IgA MM patients.

During his speech at the Euromedlab congress, Professor Leleu described the clinical benefits of the Hevylite assay in the management of monoclonal gammopathies. One of the advantages of this test is that it makes it possible to evaluate the existence of a selective immunosuppression (decrease of IgA in case of IgA monoclonal gammopathy, for example).

This selective immunosuppression, which affects matched Ig and can not be assessed by PSA or weighted Ig, seems important, especially in the follow-up of MM [23] and in the evaluation of the risk of progression of MGUS (22).

Professor Leleu highlighted the performance of the test as a biomarker in MM follow-up recalling the findings of Ludwig's team in a retrospective study of a cohort of 156 patients (100 MM IgG and 56 MM IgA). The results were compared with conventional tests used in the MM follow-up report (SPE, IF, total Ig assay and sFLC assay). The Hevylite ratio was abnormal in all patients (100%).

Monoclonal Ig was unquantifiable on SPE in 46% IgA MM and 4% IgG MM. The Hevylite ratio has been shown to be more sensitive than IF and may be able to detect relapses earlier than usual biomarkers of multiple myeloma (23).

The Boyle study also demonstrated the higher sensitivity of the Hevylite test compared with SPE for the detection of low-level monoclonal Ig and when these are masked by other serum proteins

migrating to the same level (25). The results of the study by Donato et al. suggest that the Hevylite ratio is a more sensitive marker of residual disease than the IF and that it could detect relapses earlier than conventional MM biomarkers (21).

This test could enhance biological monitoring of MM and complement information on the polyclonal (selective immunosuppression) and monoclonal (specific monoclonal component) response. Professor Leleu recalled the results of Bradwell et al. in which it was demonstrated that the abnormal Hevylite ratio is predictive of a shorter survival and this in relation to the suppression of the non-monoclonal isotype.

The extreme values of the ratio (<0.01 and >200), in combination with the beta 2-microglobulin assay, may have a higher prognostic value than the current ISS (International staging system) score (24). The two speakers on the subject have thus shown that this new dosage has today its place in the management of monoclonal gammopathies because of the technical advantages it confers and the sensitive and unique clinical information that can be obtained from it.

Conclusion

The data presented on these latest studies announce changes in the practices and use of Freelite and Hevylite tests in specific diagnostic situations and in MM follow-up. In situations where the monitoring of the tumor mass by conventional techniques is difficult, the tests Freelite and Hevylite prove to be of great contribution. The sFLC assay has already been recommended by international myeloma experts since 2009. There is no doubt that an integration of the Hevylite test for the diagnosis and monitoring of IgA MM will be done in the near future.

Conflict of Interest

Authors declared no conflict of interest.

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