IgMκ and IgMλ Measurements for the Assessment of Patients with Waldenström’s Macroglobulinaemia

Eileen Boyle¹, Salomon Manier¹, Julie Lejeune², Guillemette Fouquet¹, Stephanie Guidez⁸,⁹, Sarah Bonnet¹, Houria Debarri¹, Helene Demarquette¹, Remy Dulery¹, Julie Gay¹, Bernadette Hennache⁶, Brigitte Onraed⁵, Jean-Luc Fauchecompré³, Suzanna Schraen³, Thierry Faco³, Hervé Avet-Loiseau⁴, Sylvie Chevret², Veronique Leblond⁵, Stephen Harding⁶,⁷, and Xavier Leleu⁸,⁹

Abstract

Purpose: Accurate quantification of monoclonal IgM immunoglobulins is essential for response assessment in patients with Waldenström’s macroglobulinaemia (WM). The propensity of IgM to form multimers in serum makes sample evaluation by current laboratory methods particularly challenging.

Experimental Design: We assessed the precision and linearity of IgMκ and IgMλ heavy/light chain (HLC, Hevylite) assays, and established reference intervals using 120 normal donor sera. We compared the quantitative performance of HLC assays with serum protein electrophoresis (SPE) and total IgM nephelometry for 78 diagnostic samples and follow-up samples from 25 patients with WM. Comparisons were made between the three methods for diagnostic sensitivity and response assessment.

Results: IgMκ and IgMλ HLC assays showed low imprecision and good linearity. There was good agreement between summed HLC (IgMκ + IgMλ) and total IgM (measured nephelometrically; $R^2 = 0.90$), but only moderate agreement between involved IgM HLC and SPE densitometry ($R^2 = 0.49$). Analysis of 120 normal donor sera produced the following normal ranges: IgMκ: 0.29–1.82 g/L; IgMλ: 0.17–0.94 g/L; IgMκ/IgMλ ratio: 0.96–2.30. Using these ranges, IgM HLC ratios were abnormal in all WM presentation sera tested, including 15 with non-quantifiable SPE. Despite discordance in quantitation, responses assigned with HLC assays showed excellent agreement to those based on international guidelines using SPE or total IgM; although abnormal HLC ratios indicated residual disease in some patients with negative electrophoresis results.

Conclusions: Nephelometric assessment of IgMκ and IgMλ HLC pairs offers a quantitative alternative to traditional laboratory techniques for the measurement of monoclonal IgM and may aid in the management of WM.

Introduction

Waldenström's Macroglobulinaemia (WM) is a lymphoplasmacytic lymphoma characterized by the production of monoclonal IgM immunoglobulins. Infiltration of bone marrow and extramedullary sites by malignant B cells, and elevated IgM concentrations are responsible for the majority of symptoms (1), which vary considerably amongst patients. Clinical features directly attributable to the IgM monoclonal protein include hyperviscosity, amyloidosis, peripheral neuropathy, acquired von Willebrand disease, and cold hemagglutinin disease (2).

Quantification of monoclonal IgM at presentation correlates to disease burden and is an important tool for assessing treatment response and progression in patients with WM. However, no single method for the measurement of monoclonal IgM has been endorsed, due in part to the inter-patient heterogeneity of monoclonal proteins. International guidelines (3) recommend measurement of the monoclonal IgM by serum protein electrophoresis (SPE) or total IgM quantitation by nephelometry/turbidimetry, when SPE is unreliable. A number of studies have identified discordance between the two methods, reporting an over-read by nephelometry/turbidimetry compared with SPE quantification, which inhibits a direct comparison of results (4–6). The nephelometric over-read is thought to be caused by accelerated immune complex formation due to the size and multimeric nature of IgM. Furthermore, the quantitation of monoclonal IgM by SPE can frequently pose problems, specifically: (i) failure of the monoclonal protein to migrate from the point of application on the SPE gel, due to the bulk and iso-electric point of the protein (7), (ii) poor analytical sensitivity of SPE at low IgM concentrations, as the
monoclonal immunoglobulin becomes obscured by the poly-
clonal background, and (iii) samples that contain cryoglobulins
(which may affect up to 20% of WM patients) need to be analyzed
at high temperatures to prevent precipitation of the monoclonal
IgM.

Serum IgM molecules are pentameric repeats of the same mono-
mer. The monomer, similar to all other immunoglobulins, is made
up of mirror-imaged identical heavy and light chains. The close
proximity of the heavy chain Cα1 constant domain and light chain
Cκ constant domain forms the structural basis of the heavy/light
chain (Hevylite, HLC) immunoassays. Hevylite antisera are specific
for junctional epitopes that span the heavy and light chain constant
domains. These turbidimetric/nephelometric assays separately
quantify the light chain types of each immunoglobulin class (IgG,
IgA, IgM, Igκ, and Igλ). Studies have demonstrated that
HLC measurements and the corresponding HLC ratios are able to
identify clonal disease in patients with multiple myeloma and AL
amyloidosis and can be more sensitive than SPE in many instances
(8–10). The purpose of this study was to assess the analytical performance of IgMk and IgMλ HLC assays and to compare the performance of these assays with SPE and total IgM nephelometric assays for the diagnosis and monitoring of WM patients.

Materials and Methods

IgMk and IgMλ assay validation

Total IgM (Siemens Healthcare Ltd.), IgMk and IgMλ (Hevylite,
The Binding Site) were measured on a Siemens BNII nephelo-
meter (Siemens Healthcare Ltd.). SPE was performed using Sebia
Hydrasys II (France).

Precision studies were performed following the CLSI Evalua-
tion of Precision Performance of Clinical Chemistry Approved
Guideline EP5-A. Intra-assay precision was determined with 84
replicates on 3 different serum samples for each of the IgM HLC
assays. The 3 sera represented low, healthy, and high concentra-
tions. Interassay precision for each HLC assay was determined
using 3 different reagent lots on one analyzer. The study was
carried out over 21 working days, with two runs per day.

Linearity was determined for 3 batches of IgMk and IgMλ HLC
assays using a 10-fold dilution series of 3 monoclonal IgMk and 3
monoclonal IgMλ serum samples. Values reported at neat were
extrapolated to produce expected values for each dilution. These
were compared with observed values for both assays, and correla-
tions between observed an expected (R²) were recorded.

Adult reference intervals were derived by measuring IgMk HLC
concentrations, IgMλ HLC concentrations, and IgMk/IgMλ HLC
ratios for 120 serum samples from healthy adult blood donors.
Ninety-five percentile reference intervals (and 90% confidence
intervals) were established.

Clinical assessment

Comparisons between summed HLC (IgMk + IgMλ) and
nephelometric total IgM were made for 110 normal adult sera and
diagnostic samples from 78 WM patients validating the clinical sensitivity of IgM HLC assays at diagnosis in WM
disease. In a subset analysis, IgM involved HLC (IHLC) and
total IgM measurements were compared with SPE measure-
ments in diagnostic samples from 66 WM patients with quanti-
tifiable SPE bands.

Clinical sensitivity of IgM HLC assays at diagnosis was evalu-
ated using presentation sera from 78 patients with WM. For the
evaluation of IgM HLC assays in response assessment, 25 WM
patients were monitored with SPE, total IgM, and IgM HLC during
therapy. Hematologic responses were assigned using recommenda-
tions from the third International Workshop on WM (11).
Comparisons were made between responses assigned using HLC
assays and those assigned using SPE and total IgM.

The study was approved by "Comite de la tumorothèque/IRB" of
Lille, France and the CHRU of Lille review board in accordance
with national regulations in France, and conducted according to the
Declaration of Helsinki.

Statistical analysis

Quantitative method comparisons were made using Passing-
Bablok regression, linear regression and Bland-Altman analysis.
Qualitative method comparisons were made using Weighted
Kappa analysis; values >0.81 correspond to almost perfect agree-
ment (12). Analyze-It for Microsoft Excel (Version 2.25, Analyze-
It software Ltd.) statistical software was used for data analyses.

Results

Assay validation

For IgMk HLC assays, intra-assay imprecision was between
2.8% and 5.6%, and inter-assay imprecision was between 2.7%
and 3.3%. For IgMλ HLC assays, intra-assay imprecision was
between 2.7% and 4.2%, and inter-assay imprecision was
between 1.1% and 2.8% (Supplementary Table S1). There was
good linearity for 3 batches of IgMk and 3 batches of IgMλ assays

| Table 1. Reference intervals for IgMk and IgMλ HLC concentrations and IgMk/IgMλ HLC ratios. |
|-----------------|-----------------|-----------------|-----------------|
|                | IgMk (g/L)      | IgMλ (g/L)      | IgMk/IgMλ ratio |
| Median          | 0.63            | 0.36            | 1.71            |
| 95th Percentile range | (0.36–1.26)     | (0.20–0.78)     | 1.09–2.22       |
| 90% Confidence intervals | (0.31–0.57) to (1.15–1.45) | (0.19–0.22) to (0.71–0.85) | (1.00–1.14) to (2.19–2.26) |

NOTE: Median values and 95th reference ranges (with 90% confidence intervals) were derived from 120 blood donor sera.
when tested against pooled serially diluted serum samples ($R^2 = 0.99$ for all batches; Supplementary Table S2). Reference intervals for IgM$_k$ and IgM$_l$ HLC concentrations and the IgM$_k$/IgM$_l$ HLC ratio are presented in Table 1.

**Method comparisons**

Quantitative comparisons between summated (IgM$_k$ + IgM$_l$) HLC values and total IgM levels are shown in Fig. 1A and B. Sera from 110 normal donors and 78 WM patients were analyzed together. There was good agreement between the assays with a Passing-Bablok regression equation of $y = -0.32 + 1.17x$ (95% CI proportional bias: 1.1–1.2; Fig. 1A) and a linear regressions $R^2$ of 0.90. Bland-Altman analysis identified a systemic bias of 1.8 g/L (95% CI systemic bias, 0.9–2.7 g/L) with 95% limits of agreement of −10.7 to 14.3 (Fig. 1B).

**Figure 1.**

Comparison of electrophoretic and nephelometric methods for measuring monoclonal IgM ($M$-IgM). Passing Bablok linear regression and Bland-Altman correlation and agreement for $M$-IgM vs. total IgM measurements (A and B), involved HLC (iHLC) versus SPE densitometry (E and F), and total IgM versus SPE densitometry (C and D). Line of equality (gray line), Passing Bablok fit (red line), bias (blue line), and 95% limits of agreement (broken blue line) are shown.
Monoclonal IgM concentrations measured using the involved IgM HLC (iHLC) were compared with those quantified using SPE densitometry using presentation sera from 66 WM patients with quantifiable SPE (Fig. 1C and D). There was poor agreement between concentrations reported by iHLC and SPE, with a Passing-Bablok analysis regression equation of $y = -0.69 + 1.44x$ (95% CI proportional bias, 1.3–1.6; Fig. 2C) and a linear regression $R^2$ of 0.85. Bland-Altman analysis identified a systemic bias of 5.4 g/L (95% CI systemic bias, 4.0–6.9 g/L) with 95% limits of agreement of −6.0 to 16.9 (Fig. 2D).

Clinical sensitivity

IgMk and IgMl HLC values at clinical presentation for 78 patients with WM are shown in Fig. 2. IgM HLC ratios were abnormal in 78 of 78 (100%) patients, including 12 of 78 (15%) patients with SPE bands that were not accurately quantifiable (hollow circles; Fig. 2).

Serial serum samples were available for 25 of 78 patients. Four of 25 patients (all IgMx) presented with oligosecretory disease (<10 g/L monoclonal IgM; median: 5.8 g/L; range: 2.6–9.2) and, therefore, could not be monitoring using either SPE or total IgM. By comparison, all 4 presented with abnormal HLC ratios (median 27.4; range: 6.1–337.8), and for each oligosecretory patient, the HLC ratio remained abnormal throughout follow-up. An additional 4 patients presented with non-quantifiable SPE bands, but could be monitored using total IgM (median, 19.9 g/L; range, 19.0–20.0). Although 21 of 25 could be monitored using standard techniques (17/25 using SPE; 21/25 by total IgM), all 25 patients had abnormal HLC ratios at presentation and could subsequently be monitored using HLC assays.

A quantitative comparison between SPE densitometry and total IgM levels was performed using the same presentation sera from 66 WM patients with quantifiable SPE (Fig. 1E and F). There was moderate agreement between the assays with a Passing-Bablok regression equation of $y = 0.69 + 1.44x$ (95% CI proportional bias, 1.3–1.6; Fig. 2C) and a linear regression $R^2$ of 0.85. Bland-Altman analysis identified a systemic bias of 5.4 g/L (95% CI systemic bias, 4.0–6.9 g/L) with 95% limits of agreement of −0.0 to 16.9 (Fig. 2D).

Table 2. Method comparison for response assessment.

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<th>VGPR</th>
<th>CR</th>
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NOTE: Responses were assigned using iHLC changes and compared against those obtained by monoclonal IgM measurements by SPE densitometry (A) and nephelometric total IgM measurements (B).
21 patients (2 IgMκ and 4 IgMλ) achieved a complete response (CR) during follow up; in each case the HLC ratio remained abnormal. In addition, 10 of 21 (40%) patients (8 IgMκ and 2 IgMλ) progressed; in each case changes in IgM HLC ratio identified the progression, and in 2 of 10 patients changes in IgM HLC ratio offered an earlier indication of progression (48 and 189 days earlier, respectively).

Figure 3 shows monitoring information for one IgMκ WM patient who progressed from a CR. The patient achieved a CR at day 196 (total IgM: 1.4 g/L; SPE/IFE negative); monoclonal IgM was detected at day 1091 (total IgM: 5.0 g/L; IgMκ: 3.1 g/L) and progression from CR was assigned at day 1,259 (total IgM: 8.8 g/L; IgM HLC ratio: 0.96 to 2.3). By comparison, IgM HLC ratios were abnormal throughout monitoring, including 895 days when SPE and IFE were negative (Fig. 3B).

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<th>Time (days)</th>
<th>Total IgM (g/L)</th>
<th>IgMκ (g/L)</th>
<th>IgMλ (g/L)</th>
<th>IgM HLC ratio</th>
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Discussion
Quantification of serum IgM plays an important role in the monitoring of WM patients (13). However, assessment by SPE can be challenging (14) and evaluation with nephelometric assays is seldom concordant, the latter routinely reporting greater serum monoclonal IgM concentrations than the former (5). The complexities of monitoring monoclonal IgM may contribute to the
dissociation between IgM responses and clinical status observed in some patients. By recommendation, patient responses are measured either by SPE or total IgM, with IFE being used to determine equivocal responses. In practice it is likely that both SPE and total IgM are requested simultaneously. Helyvite assays offer an alternative method for identifying and quantifying monoclonal immunoglobulins. An abnormal HLC ratio indicates monoclonality, although an MHL value (or difference between involved and uninvolved HLC, dHLC) provides the monoclonal protein concentration. The utility of IgA HLC for monitoring monoclonal IgA, which is often difficult to quantify by SPE, has been acknowledged by a number of groups (15–17). Here, 15% of patients presented with a monoclonal IgM that could not be accurately quantified by SPE. By comparison, all patients had an appropriately abnormal IgM HLC ratio, that is, IgM/k and IgM/l patients had IgM HLC ratios above and below the 95% reference interval, respectively. Similar diagnostic sensitivity of IgM HLC ratios for WM patients has reported by others (97%–100%; refs. 18, 19).

The HLC assays demonstrated acceptable precision and linearity. Moreover, our IgM HLC normal ranges correlated well with previously published ranges (20). Quantitative comparisons between SPE, total IgM and HLC analysis showed that monoclonal IgM concentrations measured by SPE were considerably lower than values reported by iHLC, with a systemic under read of 11.8 g/L (Fig. 1C and D). In comparison, total IgM and summed HLC displayed much better agreement, with a systemic bias of 1.7 g/L (Fig. 1A and B). Similar discordance between electrophoretic techniques and automated immunoassays has been reported previously (4, 5, 21) and was also demonstrated in our study by comparison of SPE densitometry with total IgM nephelometry (Fig. 1E and F). Murray and colleagues (4) suggest that nephelometric analysis over estimates monoclonal IgM levels at high concentrations due to the polymeric nature of IgM. However, there is no conclusive proof that SPE densitometry, when accurately quantifiable, offers a better reflection of monoclonal IgM concentrations than total IgM or IgM iHLC.

It is important to note that, although there is poor numerical agreement between monoclonal IgM values measured by SPE and iHLC, there is an extremely good correlation between the two methods for assigning response (WK 0.84). Furthermore, in 2 of 25 patients the IgM/k/IgM/l HLC ratio remained abnormal when SPE and IFE indicated a CR; this is in keeping with a number of previous studies reporting that HLC ratios have a higher sensitivity than electrophoresis during response assessment in some patients with IgG and IgM MM (10, 15, 17).

Although electrophoretic techniques can monitor gross quantities of intact immunoglobulins accurately, at low concentrations this can be difficult (17) and the properties of the immunoglobulin can lead to misinterpretation (16). Although total IgM assays may provide some clarity, they are unable to differentiate monoclonal IgM levels from polyclonal IgM background. By comparison, the combined assessment of monoclonal immunoglobulin production and polyclonal isotype matched pair suppression by IgM HLC offers a substantial improvement in clinical sensitivity. Here, HLC analysis was particularly useful for monitoring low level monoclonal IgM in four oligosecretory WM patients.

In summary, our results indicate that IgM HLC assays may obviate the need for a battery of tests to monitor WM patients effectively. Further prospective evaluation of the use of HLC assays to assess response in WM is warranted.

Disclosure of Potential Conflicts of Interest
S.J. Harding is an R&D director in The Binding Site Group. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Conception and design: E. Boyle, S. Manier, V. Leblond, X. Leleu
Development of methodology: B. Onraed, J.-L. Faucompré, V. Leblond, X. Leleu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Boyle, S. Manier, G. Fouquet, S. Guidera, B. Bonnet, H. Debarri, R. Dulery, J. Cay, B. Onraed, J.-L. Faucompré, S. Schraen, T. Facon, H. Avert-Loiseau, V. Leblond, X. Leleu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Manier, J. Lejeune, B. Hennache, T. Facon, S. Chevret, V. Leblond, X. Leleu
Writing, review, and/or revision of the manuscript: S. Manier, G. Fouquet, H. Debarri, R. Dulery, T. Facon, H. Avert-Loiseau, V. Leblond, S. Harding, X. Leleu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Dulery, B. Onraed, J.-L. Faucompré, S. Schraen, T. Facon, S. Chevret, X. Leleu
Study supervision: S. Harding, X. Leleu
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