Heavy / light chain immunoassays measuring IgMκ and IgMλ provide an alternative method for quantifying monoclonal IgM immunoglobulins

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Background: International guidelines recommend either monoclonal IgM (M-IgM) quantification by densitometry or total serum IgM quantification by nephelometry/turbidimetry for monitoring patients with Waldenström's macroglobulinaemia (WM). Novel nephelometric/turbidimetric immunoassays have become available that quantify IgMkappa and IgMlambda (heavy/light chain, HLC) and from which HLC IgMkappa/IgMlambda ratios are calculated providing an indication of clonality. Here we report the utility of HLC assays in the quantification of M-IgM proteins in patients with IgM paraproteinemias. Patients and methods: Analyses were carried out in 122 serum samples from 54 patients (16 WM, 25 IgM monoclonal gammopathy of undetermined significance (MGUS), 6 lymphoplasmacytic lymphoma, 3 non-Hodgkin's lymphoma, 3 chronic lymphocytic leukaemia and 1 IgM multiple myeloma) assessed at Wexham Park Hospital NHS Trust, UK. Median age was 73 (44-91) years and M/F ratio 31/23. HLC IgMκ and IgMλ concentrations were measured with Hevylite (The Binding Site Ltd., Birmingham, UK) on the SPAPLUS turbidimetric analyser (The Binding Site, UK). Total IgM concentrations were measured by immunoturbidimetry on the Roche Modular p800 series. CZE was performed on the Sebia Capillarys 2 system. Responses were assigned following international guidelines (Owen et al., British Journal of Haematology, 2013, 160:171) using percentage (%) change in M-IgM by CZE, total IgM and difference HLC (i.e. involved–uninvolved HLC, dHLC) concentrations in follow up samples relative to baseline. Correlations were assessed using Passing-Bablok regression, coefficient of determination (R2) and weighted kappa (WK) analysis. Normal ranges: HLC: IgMkappa: 0.29-1.82 g/L; IgMlambda: 0.17-0.94 g/L; IgMkappa/IgMlambda ratio: 0.96-2.30; total IgM: 0.5-2 g/L. Results: At baseline, all 54 patients had a quantifiable band by CZE (median (range): 8.5 (2-44) g/L), elevated total serum IgM (13.2 (2.2-79.7) g/L) and abnormal HLC IgM ratio (42κ: 77.84 (2.65-1449.00); 12λ: 0.04 (0.005-0.78); involved HLC (iHLC): 11.27 (1.71-106.60) g/L; dHLC: 10.99 (0.46-106.20) g/L). There was good correlation between total IgM measurements and HLC IgMκ+IgMλ concentrations (y=1.17x-0.29; R2=0.85). When compared to CZE, both dHLC (2.24x–5.59, R2=0.75) and total IgM (y=1.81x-2.52, R2=0.93) measurements showed a linear but systemic higher result. In patients with at least 2 follow up samples (n=12 by CZE and total IgM (number of samples: 3 (2-15), follow up: 416 (65-729) days; n=8 patients by HLC (number of samples: 2 (2-6), follow up: 416 (129-551) days), there was good correlation between the % changes during follow up in M-IgM by CZE and dHLC (y=0.85x-0.16; R2=0.80; n=23 samples) and total IgM (y=0.94x-0.06, R2=0.94; n=55 samples). Weighted kappa (WK) analysis showed substantial agreement between the responses assigned by CZE and dHLC (WK=0.86, n=8

patients) and total IgM (WK=0.89, n=12 patients). Furthermore, there was perfect agreement in the responses assigned by dHLC and total IgM (WK=1, n=8 patients).
Conclusion: HLC immunoassays provide an alternative method of quantifying M-Ig for monitoring patients with IgM paraproteinemias. Larger clinical studies are required to confirm these results.