Multiple myeloma (MM) is a malignant disorder in which plasma cells of a single clone proliferate and accumulate in the bone marrow, leading to bone destruction and bone marrow failure. These abnormal plasma cells secrete monoclonal Ig. It is estimated that 24,050 new MM cases will occur in the US in 2014 (1.4% of all new cancer cases), with a median age at diagnosis of 69 years (1).

The diagnosis of MM is based on the presence of monoclonal plasma cells, monoclonal Ig, and myeloma-related organ and tissue impairment including bone lesions. Aside from the standard laboratory testing, identification of monoclonal Ig (paraprotein) by serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) are the current gold standards supported by the International Myeloma Working Group (IMWG) for diagnosis and monitoring therapy (2). SPEP is a simple laboratory technique established in the 1950s, in which serum is applied to a support medium and exposed to an electric current, and the different serum fractions separate into 5 bands: albumin, α1, α2, β, and γ globulin fractions (3). Special attention is given to the γ region, which is mainly composed of IgG. IFE testing, introduced in the 1980s, uses the same protein separation principle as SPEP but also identifies the abnormal Ig present with isotype- and light chain–specific antibodies (4).

Following the criteria established by the IMWG, monitoring patients with IgG or IgM MM is generally not problematic since close to 90% of the IgG and IgM paraproteins will migrate in the γ globulin region of the SPEP, allowing easy identification and quantification (5, 6). On the other hand, IgA paraprotein evaluation, as well as a minority of IgG and IgM paraproteins, can be a challenge owing to their frequent migration in the β region of the SPEP, where they can be concealed or blurred by other β region proteins such as transferrin, β-lipoprotein, and complement component 3. IgA paraprotein identification and quantification, therefore, can be quite difficult and complicate the monitoring of treatment in these patients (5–7). In these cases, the recommended approach by the IMWG is the use of nephelometry for IgA quantification (2). However, if the IgA concentration by nephelometry is within the reference interval, the presence or monitoring of an IgA paraprotein cannot be assessed.

Because of these potential problems of monitoring IgA paraproteins in MM patients during therapy, a new approach for the assessment of IgAκ and IgAλ heavy/light chain (HLC) analysis has been introduced (8–11). The potential benefit of the HLC quantification method is to provide an accurate quantification for IgA clonal expansion by measuring total IgAκ, total IgAλ, and IgAκ/IgAλ ratios (9). Immunoglobulins contain unique conformational epitopes at the junctions of the heavy and light chain constant regions that are recognized by specific antibodies that bind to the junction sites of the isotype heavy chain (IgG, IgM, IgA) and light chain (κ or λ). This allows HLC pairing determination and quantification (IgGκ, IgGλ, IgAκ, IgAλ, IgMκ, and IgMλ) by nephelometry (9).

In this issue of Clinical Chemistry, Katzmann et al. (11) present noteworthy data on the clinical validation for the HLC approach, emphasizing its utility for monitoring IgA paraprotein. Katzmann et al. developed a workflow by first performing the analytical validations for the distinctive HLC assays (IgGκ, IgGλ, IgAκ, IgAλ, IgMκ, and IgMλ) in the clinical laboratory and establishing their own central 99% reference intervals to define clonality. Second, they evaluated the percentages of abnormal HLC ratios and HLC quantification in 518 known IgG and IgA MM patient samples and correlated them to the observed paraprotein concentrations as determined by SPEP. They then assessed the utility of HLC assays for monitoring IgG and IgA paraproteins in post-treatment samples.

Their studies of monitoring paraproteins by HLC assays provide a clear distinction of when these methods can be useful or simply redundant to the SPEP. In the case of IgG paraprotein, SPEP and HLC assays per-
formed equivalently when measuring percentage change of paraprotein during treatment. The comparable performance was related to the fact that all monitored IgG paraproteins in this study were in the γ region. For these paraproteins, the equal sensitivities of SPEP and HLC assays indicated no additional advantage for HLC. The data presented by Katzmann et al. highlight that SPEP monitoring for IgG paraproteins that are located in the γ region continues to be an accurate and easy method to perform in the clinical laboratory (11). This study did not evaluate the performance of HLC testing for monitoring the rare IgG paraproteins migrating in the β region, which is an important point to consider for the use of HLC assays in the future, since it may have value for the cases in which IgG paraproteins migrate in the β region.

The use of HLC clearly showed an advantage over SPEP to quantify monoclonal IgA paraproteins in the β region. In the Katzmann et al. study, all 30 IgA MM patients examined had IgA paraproteins migrating in the β region as documented by IFE; 7 of those patients did not show paraproteins by SPEP (11). In this scenario, IgA HLC assay evaluation was useful for monitoring outcome posttreatment and performed equally to IFE, indicating that the IgA HLC assay can provide an accurate alternative method to assess paraproteins migrating in the β region.

Thus, HLC assessment of clonality is clearly useful for both diagnosis and monitoring of MM patients whose paraproteins are difficult to identify because of β region migration. However, IgA HLC assays should not be routinely used for all MM. I believe that for proper use of HLC assays, they should be ordered only for the paraprotein identified by IFE when migrating in the β region and not for γ region paraproteins, for which SPEP performs quite well.

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