Response to

Interference of daratumumab on the serum protein electrophoresis

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Letter to the Editor

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To the Editor,

Jialal and Pahwa note the importance of daratumumab interference with monoclonal protein quantitation in multiple myeloma [1]. We agree that daratumumab may interfere with monoclonal protein quantitation. While the focus of our manuscript was to describe a method to reduce the risk of inaccurate response classification [i.e. very good partial response (VGPR) vs. complete response (CR)] [2], inaccurate quantitation due to positive interference by daratumumab could give the impression of resistance to therapy.

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One point of clarification is that the clinical consequences of the described bias are difficult to estimate. Statistical significance aside, the effect size of the bias appears to be largely below the reference change value (RCV) as determined from biological variation and imprecision data for monoclonal proteins [3, 4]. The estimated RCV for monoclonal proteins ranges from 27% to 56%. The reported median bias of 10% and the maximum observed bias of approximately 32% are thus largely within the combined biological variation and noise of monoclonal protein quantitation by serum protein electrophoresis (SPE; scanning densitometry). In the same line, imprecision of the SPE method may explain the reported interference of M-protein concentration in patients in which the M-protein does not co-migrate with daratumumab. Daratumumab consistently migrates as a sharp band at the same electrophoretic location, and interference on quantification with nonoverlapping M-proteins is therefore not expected. Further, it is unlikely that the daratumumab treatment course would change as a result of a ≤1 g/L positive bias; the maximum mean (±standard deviation) reported maximum concentration for daratumumab at the end of the initial weekly dosing schedule at a dose of 16 mg/kg is 915 (410) μg/mL [5]. We agree that further studies aimed at determining if there is a clinical impact are warranted.

With respect to the daratumumab immunofixation reflex assay (DIRA), this method is not intended to address the issue of quantitation, but rather to determine if the patient has achieved immunofixation-negative serologic CR or not. We only recommend selective use to differentiate response classification for several reasons: (1) there is a lack of available antisera available to most laboratories; (2) as Jialal and Pahwa state, there is an added expense and complexity in immunofixation interpretation; and (3) laboratories running SPE typically do not know if daratumumab is present in most routinely obtained SPE samples. Thus, DIRA is recommended in selected cases using experienced interpreters, where it is essential to accurately differentiate VGPR versus CR, for example, as part of a

clinical trial. In the future, use of a DIRA-like assay during routine patient management may become more widespread if a commercial version becomes available.

Overall, the issue of quantitative interference may be ameliorated by avoiding collection of samples immediately after treatment with daratumumab or any other monoclonal therapy [6]. The utility of serum free light chains as an unaffected metric of treatment response is well justified [7]. The authors can confirm that serum free light-chain assays are also unaffected by rituximab, trastuzumab, bevacizumab, infliximab, cetuximab, adalimumab, natalizumab, and siltuximab (McCudden, C, et al; unpublished data). As such, serum free light-chain (sFLC) analysis seems indeed a good alternative for patients with light-chain multiple myeloma; however, serum immunofixation electrophoresis monitoring is more sensitive than sFLC analysis in patients with an intact M-protein [8]. Moreover, one parameter cannot replace the other to assess therapy response. For a patient with an intact M-protein to be classified as having a stringent complete remission, as defined by the International Myeloma Working Group, the serum must be negative as determined by IFE, along with a normal sFLC ratio [9].

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References

1. Jialal I, Pahwa R. Quantification of daratumumab in the serum protein electrophoresis. Clin Chem Lab Med 2017;55:e27–8.
2. McCudden C, Axel AE, Slaets D, Dejoie T, Clemens PL, Frans S, et al. Monitoring multiple myeloma patients treated with daratumumab: teasing out monoclonal antibody interference. Clin Chem Lab Med 2016;54:1095–104.
3. Booth R, McCudden CR. Reference change value (RCV) for monoclonal immunoglobulins measurement by agarose gel based serum protein electrophoresis. Abstract presented at: the Annual Conference of the Canadian Society of Clinical Chemists. Edmonton, Alberta, Canada, 2016.
4. Katzmann JA, Snyder MR, Rajkumar SV, Kyle RA, Therneau TM, Benson JT, et al. Long-term biological variation of serum protein electrophoresis M-spike, urine M-spike, and monoclonal serum free light chain quantification: implications for monitoring monoclonal gammopathies. Clin Chem 2011;57:1687–92.
5. Clemens PL, Yan X, Lokhorst HM, Lonial S, Losic N, Khan I, et al. Pharmacokinetics of daratumumab following intravenous infusion in relapsed or refractory multiple myeloma after prior proteasome inhibitor and immunomodulatory drug treatment. Clin Pharmacokinet 2015;15(Suppl 3):e269–70.
6. McCudden CR, Voorhees PM, Hainsworth SA, Whinna HC, Chapman JF, Hammett-Stabler CA, et al. Interference of monoclonal antibody therapies with serum protein electrophoresis tests. Clin Chem 2010;56:1897–9.
7. Rosenberg AS, Bainbridge S, Pahwa R, Jialal I. Investigation into the interference of the monoclonal antibody daratumumab on the free light chain assay. Clin Biochem 2016;49:1202–4.
8. Singhal S, Vickrey E, Krishnamurthy J, Singh V, Allen S, Mehta J. The relationship between the serum free light chain assay and serum immunofixation electrophoresis, and the definition of concordant and discordant free light chain ratios. Blood 2009;114:38–9.
9. Durie BGM, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.