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What's liver got to do with it? Hepatic response and survival in AL amyloidosis

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In this issue of Haematologica, Muchtar and colleagues report the largest multicenter validation study of hepatic response criteria in systemic light chain (AL) amyloidosis, demonstrating that achievement of hepatic response (as defined by International Society of Amyloidosis (ISA) criteria) is associated with superior overall survival (1,2). The study addresses an important gap in the field. While cardiac and renal response criteria have undergone validation and extensive refinement (specifically, the development of graded organ response criteria), hepatic response has remained comparatively understudied, despite the substantial morbidity associated with liver involvement (3-6).

The central question raised by this study is not whether hepatic response matters (it does), but rather *why* it matters. Does hepatic recovery directly influence survival, or is hepatic response a secondhand indicator of broader systemic improvement?

The findings are consistent with a great deal of previous work demonstrating an association between deep suppression of amyloidogenic light-chain production and subsequent organ recovery. Patients achieving hematologic complete response (hCR) or very good partial response (hVGPR) consistently experience higher rates of organ improvement and superior survival than those achieving lesser responses (5,7).

The current study builds upon prior work from the Mayo Clinic by Rees and colleagues, who analyzed 130 patients with hepatic AL amyloidosis and identified deep hematologic response, marked baseline alkaline phosphatase elevation, and kappa light-chain isotype as predictors of hepatic response (8). Some (but not all) of these observations were reproduced in the present multicenter analysis, validating the prognostic significance of hepatic response across a broad international population and reconfirming the association between hepatic response and overall survival.

The study highlights long-recognized issues related to verifying organ involvement and assessing organ response in patients with AL amyloidosis. Hepatic involvement in this study was defined largely by alkaline phosphatase (AP) elevation attributed to liver amyloid deposition (1). Consistent with standard clinical practice, histologic confirmation was not required, nor was systematic imaging used to quantify hepatic amyloid burden. As a result, the actual degree of hepatic involvement in individual patients remains uncertain. There are also other reasons AP is an imperfect biomarker of hepatic amyloid burden. The authors themselves acknowledge that concomitant cardiac involvement may produce passive hepatic congestion and cholestatic abnormalities that contribute to AP elevation independently of liver amyloid infiltration (1). Improvement in AP may therefore reflect recovery of hepatic amyloid disease, improvement in cardiac function, or both.

An additional observation of note is the prognostic significance of baseline total bilirubin levels. While baseline AP levels in this study were not associated with survival, even modest elevations in bilirubin were highly prognostic, with a threshold of only 0.4 mg/dL identifying patients with markedly inferior outcomes (1). This finding differs from the earlier Mayo Clinic analysis, in

which baseline bilirubin was not associated with survival (8). Whether this discrepancy reflects differences in cohort composition (specifically, concomitant cardiac involvement by AL), other aspects of patient selection, or statistical power remains uncertain. Regardless, the current findings suggest that bilirubin may warrant further study as an additional marker of clinically meaningful hepatic involvement.

In the multivariable analyses performed as part of this analysis, baseline cardiac stage was incorporated into the survival models but graded cardiac response was not (1). Baseline stage reflects disease severity at diagnosis, whereas cardiac response reflects subsequent organ recovery. Both are known to have prognostic significance. In a previous multicenter study, Muchtar and colleagues demonstrated that progressively deeper cardiac responses are associated with markedly superior survival (6). Inclusion of graded cardiac response in the current model might therefore have attenuated some of the prognostic impact attributed to hepatic response. Consistent with this, in the subgroup analyses presented in Figure 4, hepatic response was associated with a pronounced survival advantage in patients with concurrent cardiac involvement, whereas the separation between survival curves appeared less striking among patients without cardiac involvement (1). While the study was not powered to formally test this interaction, the findings are compatible with the possibility that part of the prognostic significance attributed to hepatic response reflects parallel cardiac recovery, rather than as evidence that hepatic response is a wholly independent determinant of survival.

In the earlier Mayo Clinic study, hepatic response was associated with improved survival at the 6-month landmark but not at later landmark analyses, whereas the present multicenter study demonstrated a more consistent association between hepatic response at later time points and survival (8). This discrepancy may reflect differences in patient selection. There are differences in key reported baseline clinical factors such as frequency of cardiac involvement and use of proteasome inhibitor-based induction, whereas other characteristics included in the report by Rees, et al. (such as rates of non-cardiac, non-renal organ involvement) are not reported in the current study.

Finally, the therapeutic context of the study must be considered. Most patients were treated before incorporation of daratumumab into frontline therapy. Since publication of the ANDROMEDA trial, daratumumab-CyBorD has become standard treatment and has substantially increased rates of deep hematologic responses while accelerating organ recovery (7). Further, amyloid-depleting therapies with the capacity to positively impact organ responses in subsets of AL-amyloidosis patients are under development (9). It is thus plausible that a more modern patient cohort could be expected to realize higher rates of hepatic response than reported here in the non-transplanted patients, while avoiding the (presumably toxicity-related) delay in time to hepatic response seen with transplant.

This study by Muchtar and colleagues represents an important advance in the field. It validates hepatic response as a clinically meaningful endpoint while highlighting the challenges of measuring true hepatic recovery in AL amyloidosis. Future studies incorporating contemporary therapies, advanced imaging modalities, and dynamic assessment of concomitant cardiac

responses will further clarify whether biochemical hepatic response reflects recovery of the liver itself or, more broadly, recovery of the patient as a whole – and which is truly key to patient survival.

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