

# **Regression of cardiac AL amyloid following chemotherapy demonstrated by cardiovascular magnetic resonance**

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Systemic light-chain (AL) amyloidosis is characterized by deposition in the interstitial space of aggregated misfolded monoclonal immunoglobulin light chains in the form of amyloid fibrils. The presence and severity of cardiac involvement in AL amyloidosis is the main driver of prognosis (1). Serum concentration of brain natriuretic peptides and echocardiographic parameters are currently the reference standard for assessing cardiac responses, but neither directly quantifies the amyloid burden. Cardiovascular magnetic resonance (CMR) with tissue characterization is a sensitive tool for characterizing myocardial amyloid deposits: late gadolinium enhancement (LGE) tracks increasing cardiac infiltration, from subendocardial LGE to transmural as the disease progresses (2). Native myocardial T1 and extracellular volume (ECV) offer a continuous rather dichotomous measurement of amyloid burden and have been shown to track clinical disease in cardiac amyloidosis, and improve diagnostic accuracy and patient stratification (3).

The aim of this study was to evaluate cardiac AL amyloid serially using CMR including measurements of the myocardial ECV. The study group comprised 31 consecutive patients diagnosed with cardiac AL amyloidosis (21 (68%) male, age  $61 \pm 9$  years) who underwent serial CMR evaluation with T1 mapping as well as comprehensive clinical assessment (ECG, echocardiogram, CMR, serum amyloid-P [SAP] scintigraphy and NT-proBNP measurements) before and after chemotherapy in our center between 2011 and 2015. The clonal hematologic response was evaluated according to international consensus criteria (4). All subjects underwent CMR performed at 1.5-T (Avanto or Aera, Siemens Healthcare, Erlangen, Germany). T1 mapping was acquired using Modified look-locker inversion recovery or the shortened modified look-locker inversion recovery. Conventional 2-dimensional LGE was acquired with magnitude inversion recovery or phase-sensitive inversion recovery (PSIR). After a bolus of gadoterate meglumine (0.1 mmol/kg, gadolinium-DOTA, Dotarem, Guerbet S.A. France) and LGE imaging, ECV was measured as previously described (2). Regression in the cardiac amyloid burden was defined as a decrease in ECV by 2SD. Changes in the visceral amyloid burden were assessed using serial SAP scintigraphy (5).

At baseline, the overall prevalence of LGE was 27 of 31 (87%) patients with an average ECV of  $54 \pm 11\%$ . The pattern of LGE was transmural in 9 subjects (29%) and subendocardial in 18 (58%); four patients (13%) had no LGE. The overall hematologic response rate was 61% (19 patients) comprising: complete response (CR) in 36% (10 patients); very good partial response (VGPR) in 29% (9 patients); and partial response (PR) or no response (NR) in 39% (12 patients) (4). Reduction in ECV attaining the CMR criteria for regression of amyloid occurred in 13 patients. The prevalence of regression was significantly higher in patients with CR/VGPR versus patients in PR/NR ( $p < 0.01$ ). No patients without a hematological response showed evidence of amyloid regression (Figure 1). The mass changed concordantly in 7 of the 13 patients (54%) whose amyloid regressed and the LGE pattern changed in 5 (38%). More than 30% reduction in NT-proBNP levels was present in 9 (69%) of patients with amyloid regression. Overall, regression of amyloid was associated with improvements in NT-proBNP, LV mass, left atrial area and diastolic function parameters. Regression of cardiac amyloid by CMR correlated with regression of extra-cardiac amyloid measured by SAP scintigraphy. By contrast, among patients whose ECV did not diminish, there were deteriorations in parameters of left ventricular and right ventricular systolic function and maximal wall thickness.

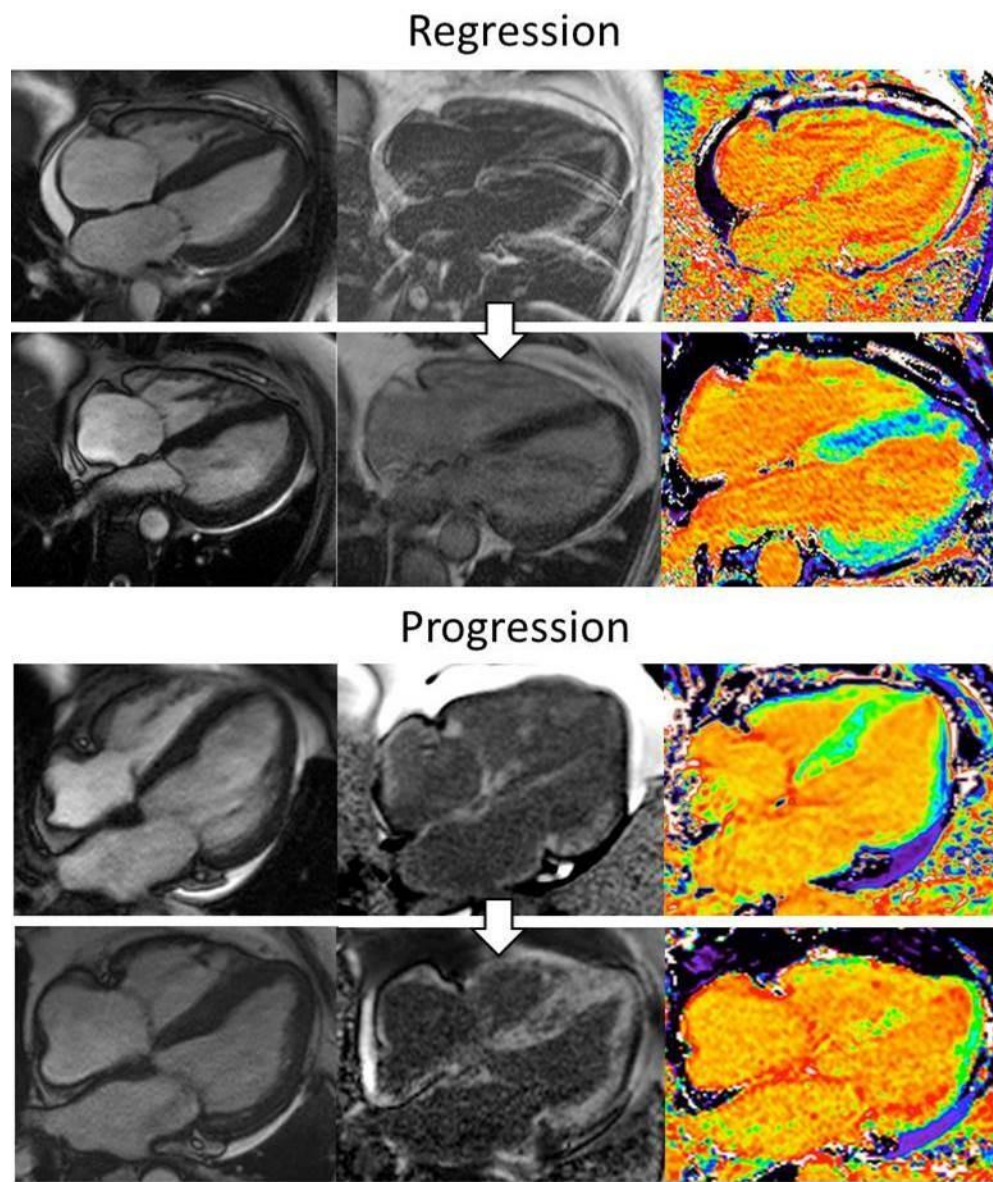
Cardiac organ response has historically been sought using echocardiography, but improvements are seldom evident, engendering the belief that cardiac amyloid may only stabilize following successful chemotherapy. The serial CMR studies we report here demonstrate that regression of cardiac amyloid following a substantial response to chemotherapy is a relatively common phenomenon, occurring in 42% of patients in our cohort. Whilst reduction in native T1 and ECV could in part be related to reduction in myocardial edema, the magnitude of reduction in native T1, ECV, reversal of LGE pattern as well as correlation with regression in other organs as measured by SAP scintigraphy, provide compelling evidence of cardiac amyloid regression. Tracking changes in the cardiac amyloid burden has the potential to redefine cardiac response to treatment, enabling the stratification of patients with lower risk of progression and better prognosis and in whom the need to

intensify chemotherapy may not be required. Furthermore, the development of immunotherapies to promote regression of amyloid is well advanced and the ability to measure amyloid regression could be of great value as an endpoint.

Limitations of this study include retrospective analysis of a small patient cohort with different time intervals between the scans. There is a survival bias in that we quote only subjects with paired scans. Finally, two different T1 mapping techniques were used during the period in which these patients were recruited.

### **References:**

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**Figure 1.** Four-chamber cine image in diastole (left); corresponding late gadolinium enhancement image (middle) and ECV mapping before and after chemotherapy in two patients, one regressor by CMR (top) and one that progressed by CMR (bottom).