Assessment of treatment response in cardiac AL amyloidosis using CMR mapping – results at 3 months, 6 moths and 1 year post-chemotherapy

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ABSTRACT

Introduction: Cardiac involvement in immunoglobulin light chain (AL) amyloidosis is the major determinant of survival. Cardiac response to chemotherapy is conventionally assessed by serum brain natriuretic peptide (NT-proBNP) and echocardiography, but neither quantify amyloid burden.

Hypothesis: We assessed the hypothesis that CMR with T1 mapping and extracellular volume measurements can evaluate amyloid burden in cardiac AL amyloidosis tracking changes over time at 3 months, 6 months and 1 year after chemotherapy.

Methods: 94 patients with cardiac AL amyloidosis were studied serially using CMR with T1 mapping and extracellular volume at baseline and 3 months, 6 months and 12 months post-chemotherapy.

Results: At 6 months, 62% of patients achieved a complete or very good partial haematological response, and 38% a partial response or no response. Amyloid regression was detectable in only one patient, however, amyloid progression was detectable in 34% of patients at 6 months. Although this occurred in the PR group, it also occurred in the CR and VGPR groups (63%). At one year, 64% patients achieved a CR or VGPR. Regression of amyloid was seen in 30% patients, all with CR or VGPR and 0 patients in PR or NR ($p<0.05$). However, not every patient with good haematological response had amyloid regression by CMR, having 4 of these patients amyloid progression. Importantly, these 4 patients achieved the good haematological response late (after the first 6 months of chemotherapy). 46% patients with changes in ECV consistent with regression of amyloid had visual changes in LGE. Amyloid regression was associated with significant reduction in LV mass and reduction in NT-pro BNP ($p<0.05$) and in native T1 ($p<0.01$).

Conclusion: In newly diagnosed and treated AL amyloidosis, CMR demonstrates the dynamic biology of infiltration: increasing rapidly, particularly if chemotherapy fails to switch off light chain production promptly; regressing more slowly (by 1 year) if effective. Serial monitoring of myocardial infiltration has the potential for new AL amyloidosis therapeutic regimes based on myocardial organ response.

Keywords: Amyloidosis, CMR, T1 mapping, ECV

INTRODUCTION

Systemic light-chain (AL) amyloidosis is a complication of clonal B-cell disorders, which is characterized by deposition in the interstitial space of aggregated misfolded monoclonal immunoglobulin light chains (LC) in the form of amyloid fibrils. The presence and severity of cardiac involvement in AL amyloidosis is the main driver of prognosis [1]. Patients with cardiac AL amyloidosis and symptomatic heart failure frequently die in less than 6 months[1], but median survival has nearly doubled over the past decade, mainly due to the remarkable progress in chemotherapy. The direct effect of chemotherapy, i.e. the hematologic response, is predominantly evaluated by serial measurements of serum free light chains [2].

Serum concentration of brain natriuretic peptides and echocardiographic parameters are currently the reference standard for assessing cardiac responses [3], but neither directly quantifies the amyloid burden [4]. Both brain natriuretic peptide and myocardial strain are a marker of prognosis in cardiac AL amyloidosis [3, 5], but represent processes downstream of amyloid deposition with brain natriuretic peptide confounded by renal impairment [5] and strain not well standardized and affected by changes in preload and afterload.

Cardiovascular magnetic resonance (CMR) with tissue characterization is a sensitive tool for characterizing myocardial amyloid deposits: late gadolinium enhancement (LGE) shows a continuum of cardiac infiltration, from subendocardial LGE to increasing transmurality as the disease progresses [6]. T1 mapping can distinguish and measure the myocyte and extracellular amyloid compartments separately [7-10]. Native myocardial T1 and extracellular volume (ECV) measurements have been shown to track clinical disease in cardiac amyloidosis, and improve diagnostic accuracy and patient stratification [4, 7, 11-15]. SAP scintigraphy can specifically quantify amyloid in non-cardiac organs. Several studies have shown turnover and regression of amyloid deposits from the liver, kidneys and elsewhere with corresponding clinical benefit in terms of organ function and survival as well as the relation of this process to production of the amyloid fibril precursor protein [16-22].
However the usual lack of significant structural and functional changes on conventional echocardiography after successful chemotherapy has led to the common belief that regression

of myocardial amyloid takes place either extremely slowly or not at all [23]. We have demonstrated that cardiac amyloidosis can regress in a small retrospective CMR cohort[24]. The aim of this study was to evaluate cardiac AL amyloid serially in a large prospective cohort, using state of the art cardiovascular MR (CMR) including measurements of the myocardial extracellular volume (ECV), which is the site of the amyloid deposits [25].

METHODS

Setting and study design

A prospective study of patients with biopsy proven AL amyloidosis undergoing chemotherapy. The study group comprised all consecutive patients diagnosed with cardiac AL amyloidosis who underwent serial CMR evaluation with T1 mapping as well as comprehensive clinical assessment (ECG, echocardiogram, CMR, SAP scintigraphy and NT-proBNP measurements) at the National Amyloidosis Centre, Royal Free Hospital, London, UK from 2016 to May 2018. The clonal hematologic response was evaluated using repeated serum and urine electrophoresis and immunofixation and serum free light chain (FLC) measurements, according to international consensus criteria. Normal FLC levels with normal kappa/lambda ratio and negative serum and urine immunofixation was considered a complete response (CR), a reduction in the dFLC to <40 mg/L a very good partial response (VGPR), >50% reduction in dFLC was a partial response (PR) and no response (NR) was less than PR [26, 27].

Echocardiography acquisition and analysis

Echocardiographic assessments were performed using a Vivid E9 ultrasound machine (GE, Healthcare, Milwaukee, Wisconsin, USA). Image quality was optimised by adjusting probe frequency (range 1.7-2.0MHz), high frame rates (60-120 s-1) and acquisition during quiet respiration. LV structure, systolic and diastolic assessment was performed according to published recommendations [28-30]. Pulse wave Tissue Doppler velocity was measured in the septal and lateral mitral annulus region in the 4-chamber view to obtain peak systolic (S'), peak early diastolic (e') and peak late diastolic (a') tissue velocities; septal and lateral velocities were averaged to obtain a mean value. Myocardial strain assessment was performed with appropriate image optimisation. 2-3 cardiac cycles of all views were digitally stored for offline analysis using standard software (EchoPac PC dimension software version 112, GE Healthcare).

All the echocardiogram analysis was performed blinded to CMR results. Myocardial deformation was assessed using speckle tracking. The LV was divided into 6 segments in each of the long axis (LAX) views. The endocardium was manually traced in each segment and a

region of interest (ROI) automatically generated to cover the myocardium. The ROIs were adjusted to optimise the tracking quality if needed.

CMR Image Acquisition and analysis

All subjects underwent CMR on a 1.5-T clinical scanner (Avanto or Aera, Siemens Healthcare, Erlangen, Germany). Within a conventional clinical scan (pilots, transverse white and black-blood images, SSFP-cines images to assess volumes and mass) LGE imaging was acquired with both magnitude inversion recovery (MAG-IR) and phase-sensitive inversion recovery (PSIR) sequence reconstructions with SSFP read-outs. T1 measurement was performed with the use of the modified look-locker inversion (MOLLI) recovery sequence. For T1 mapping, 3 short axis T1 maps (base, middle and apex) were manually contoured at the endocardial and epicardial border, segmented into an American Heart Association 16-segment model using the right ventricular insertion points. After a bolus of gadoterate meglumine (0.1 mmol/kg, gadolinium-DOTA, Dotarem, Guerbet S.A. France) and LGE imaging, ECV was calculated as: ECV = (1 − hematocrit) × [ΔR1myocardium] / [ΔR1bloodpool]), where ΔR1 is the difference in relaxation rates (1/T1) pre-contrast and post-contrast. Total amyloid volume was measured with the formula total amyloid volume = ECV x LV myocardial volume (where LV myocardial volume was calculated as LV mass x 1.05). The LGE pattern was classified by 2 different observers (A.M.N. and M.F.) blinded to the other data into 3 groups according to PSIR LGE transmurality: group 1, no LGE; group 2, subendocardial LGE only; and group 3, transmural LGE (Figure 1).

Regression in the cardiac amyloid burden was considered when there was a significant decrease in ECV (a fall of 2SD – 0.05) and progression in the cardiac amyloid burden when there was a significant increase in ECV (2SD + 0.05).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 22 (IBM, Somers, New York). All continuous variables were normally distributed (Shapiro-Wilk), other than NT-proBNP, which was ln transformed for bivariate testing. These are presented as mean ± standard deviation (SD) with non-transformed NT-proBNP presented as median and interquartile range.

Comparisons between groups were performed by paired T test; the χ^2 test or Fisher exact test was used to compare discrete data, as appropriate. Statistical significance was defined as $p < 0.05$. To assess the agreement of the assignment of the LGE pattern by 2 different observers, the intraclass correlation coefficient was calculated. Statistical significance was defined as $p<0.001$.

RESULTS

Study Population and baseline characteristics

Demographic and clinical features of the patient cohort are summarized in Table 1.

Ninety-four patients with biopsy proven systemic AL amyloid were included (55 male, 59%; age 65±9 years). The mean interval between the serial assessments was 14±6months.

At baseline, the overall prevalence of LGE was 88 of 94 (88 %) patients with an average ECV of 46±8%. Three patterns of LGE are observed: no LGE; subendocardial LGE and transmural LGE, (figure 1). The pattern of LGE was transmural in 33 subjects (35 %) and subendocardial in 50 (53 %); eleven patients (12 %) had no LGE. There was right ventricular LGE in 75%. There was good agreement in the assignment of these patterns between two observers (ICC 0.92, 95% CI 0.87-0.95).

CMR findings at 3 months post-chemotherapy

20 patients had a CMR assessment 3 months after starting chemotherapy. 65% of patients achieved good haematological response (45% complete response and 20% very good partial response). 25% of patients had partial response and 10% had no response to chemotherapy. Amyloid regression was not detectable at 3 months after chemotherapy, however there was amyloid progression by CMR (classified by increased in ECV) in 6 patients (30%). 14 patients (70%) had stable ECV and LGE pattern.

Of the 6 patients with amyloid progression, 1 achieved a complete response, 3 patients attained very good partial response and 2 patients achieved a partial clonal response.

CMR findings at 6 months post-chemotherapy

67 patients had a CMR assessment 6 months after starting chemotherapy. 62% of patients achieved good haematological response (41% complete response and 21% very good partial response). 24% of patients had partial response and 14% had no response to chemotherapy. Amyloid regression was only detectable in 1 patient at 6 months after chemotherapy, however there was amyloid progression by CMR in 22 patients (34%) (Figure 2). 42 patients (65%) had stable ECV and LGE pattern.

The haematological response at 6 months post-chemotherapy correlated only partially with the CMR response. Of the 22 patients with amyloid progression, 8 achieved a complete response (37%), 6 patients (27%) attained very good partial response, 6 patients achieved a partial response and 2 patients (9%) had no response to chemotherapy.

Changes in the ECV consistent with regression of amyloid correlated with reduction in LV ejection fraction ($p<0.01$) and increased native T1 values ($p<0.001$).

CMR findings at 1 year post-chemotherapy

50 patients had a CMR assessment 1 year after chemotherapy. 64% of patients achieved good haematological response (42% complete response and 22% very good partial response). 26% of patients had partial response and 10% had no response to chemotherapy.

Amyloid regression by CMR (classified by reduction in ECV) was detectable in 15 patients (30%) at 1 year after chemotherapy (Figure 3). Amyloid progression by CMR occurred in 11 patients (24%) and 22 patients (46%) had stable ECV values and stable LGE pattern.

All the patients with amyloid regression (30%) by CMR achieved a good haematological response (CR or VGPR) and 0 patients in partial response or no response ($p<0.05$). However, not every patient with good haematological response had amyloid regression by CMR. 4 patients with good haematological response at 1 year post-chemotherapy had amyloid progression. Importantly, these 4 patients achieved the good haematological response late (after the first 6 months of chemotherapy).

46% patients with changes in ECV consistent with regression of amyloid had visual changes in the pattern of LGE.

In one patient the LGE pattern went from transmural to subendocardial and in 5 from subendocardial to no LGE.

Overall regression of amyloid was associated with improvements in NT-proBNP ($p<0.05$), reduction in LV mass ($p<0.01$) and in NT-proBNP ($p<0.05$). By contrast, among patients whose ECV did not diminish (“non-regressors”), there was reduction in LV ejection fraction ($p<0.01$).

DISCUSSION

The remarkable progress in drug therapies developed for multiple myeloma has translated into improved outcomes in AL amyloidosis [31]. Median survival in patients with AL amyloidosis has nearly doubled over the past decade [32] but mortality in the first year after diagnosis remains unchanged at approximately 45%, reflecting the high incidence of advanced cardiac involvement. There are two interrelated measures of response to treatment in AL amyloidosis: the hematologic and organ responses, i.e. suppression of the underlying clonal B-cell disorder (and hence reduced production of amyloid-forming immunoglobulin light chain protein), and the consequent benefit of reduced amyloid formation in terms of amyloidotic organ function. The measurement of serum free light chains has proven to be a robust marker of clonal disease response and a very good partial response, currently defined as dFLC (the difference in concentration between the aberrant versus uninvolved class of light chain) less than 40 mg/L, or better is associated with much improved survival [33, 34]. Cardiac organ response has historically been sought using echocardiography, but improvements are seldom evident, even after prolonged periods. Cardiac organ response is mostly now sought by reduction in serum NT-proBNP concentration, which surprisingly often falls within just weeks to months after a substantial haematologic response has been achieved. The early rapid decrease in NT-proBNP is thought to more greatly reflect diminished cardiotoxicity resulting from reduced abundance of harmful pre-fibrillar light chain aggregates than a reduction in myocardial amyloid burden. Whatever the mechanism, falls in NT-proBNP concentration of 30% or 300 ng/L from baseline following a clonal response to chemotherapy are associated with favourable clinical outcomes [35, 36]. Whilst SAP scintigraphy is unable to image amyloid in the moving heart, this and other clinical measurements have confirmed that extra-cardiac amyloid deposits, for example in the liver, spleen and kidneys, are often gradually cleared when the supply of the respective amyloid precursor protein is substantially reduced. The characteristic absence of echocardiographic

improvements under these circumstances has engendered the belief that cardiac amyloid, in contrast, may only stabilize following successful chemotherapy [36].

The emergence of advanced myocardial tissue characterization by magnetic-resonance, specifically T1 mapping with native T1 and ECV measurements has made it possible to estimate cardiac amyloid load *in vivo*. The serial CMR studies we report here compellingly demonstrate that substantial regression of cardiac amyloid following an adequate response to chemotherapy is a relatively common phenomenon, happening in 27% of our patient's population at one year after chemotherapy with no regression at 3 months and in only 1 patient at 6 months post-chemotherapy. Our results confirm the importance of achieving a good haematological response promptly, as the prevalence of amyloid regression was significantly higher in patients attaining a CR/VGPR compared to patients attaining only a PR or NR but also show the great potential of CMR to shed light on the cardiac response to treatment. Very interestingly, the only four patients who achieved a good haematological response and had amyloid progression by CMR at 1 year post-chemotherapy achieved the good response late, having only partial clonal response at 6 months. We also demonstrated substantial reduction in cardiac amyloid burden combined with improvement in NT-proBNP and LV mass.

Whilst reduction in native T1 and ECV could in part be related to reduction in myocardial oedema, which has been postulated to contribute to remarkably high native T1 values during phases of rapid amyloid accumulation [10], the magnitude of reduction in native T1, ECV and reversal of LGE pattern provide compelling evidence of cardiac amyloid regression.

These results could have immediate clinical implications for the management of patients with AL amyloidosis. Chemotherapy improves survival in patients with systemic AL amyloidosis, but chemotherapy is associated with substantial toxicity; mortality is highest during the first 3 months of treatment in keeping with our findings of amyloid progression. Tracking changes in cardiac amyloid burden could redefine cardiac response to treatment, acknowledging that long term studies remain required to correlate changes in cardiac amyloid load with overall survival.

The development of immunotherapies to promote regression of amyloid is well advanced [37-39]. At least three antibody therapies are currently in clinical trial, one of which that targets the SAP present in all types of amyloid has already been confirmed to trigger rapid clearance of amyloid in the liver and kidney [35]. The ability to measure changes in cardiac amyloid load over time could be of great value as an endpoint in early stage drug development and dose ranging.

This study has several limitations. Not all our patients had all the follow up studies and there is a survival bias in that we quote only subjects with paired scans – it may be that the extent of differences are underestimated if, for example, PR or NR subjects who amyloid accumulate die before follow-up scanning.

The findings of this study shed new light on the pathophysiology and natural turnover of cardiac amyloid, demonstrating the dynamic biology of infiltration: increasing rapidly, particularly if chemotherapy fails to switch off light chain production promptly; regressing more slowly (by 1 year) if effective. Serial monitoring of myocardial infiltration has the potential for new AL amyloidosis therapeutic regimes based on myocardial organ response.

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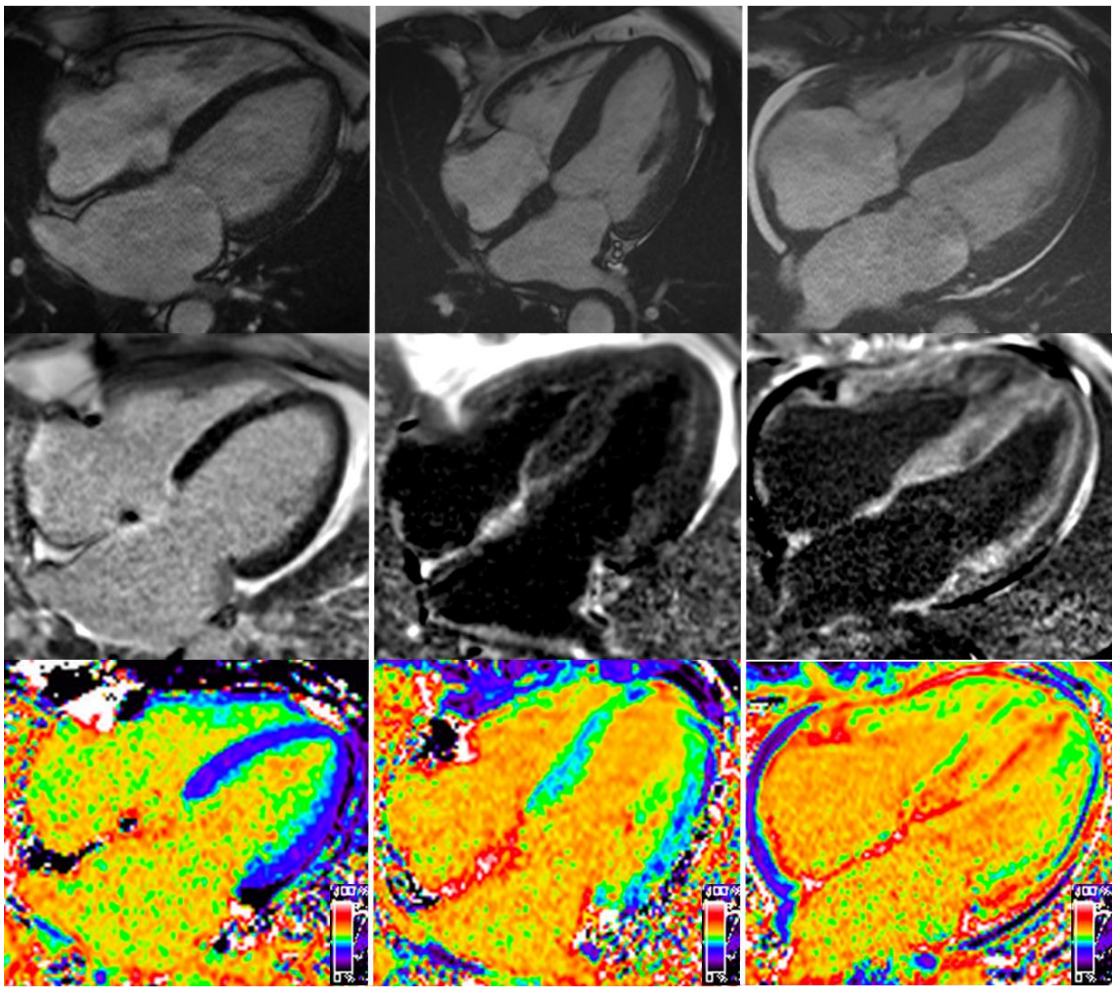

Figure 1. Four-chamber SSFP cine image in diastole of three patients (top); corresponding late gadolinium enhancement image (middle) showing no LGE (middle left), subendocardial LGE (centre) and transmural LGE (middle right); and corresponding ECV maps (bottom).

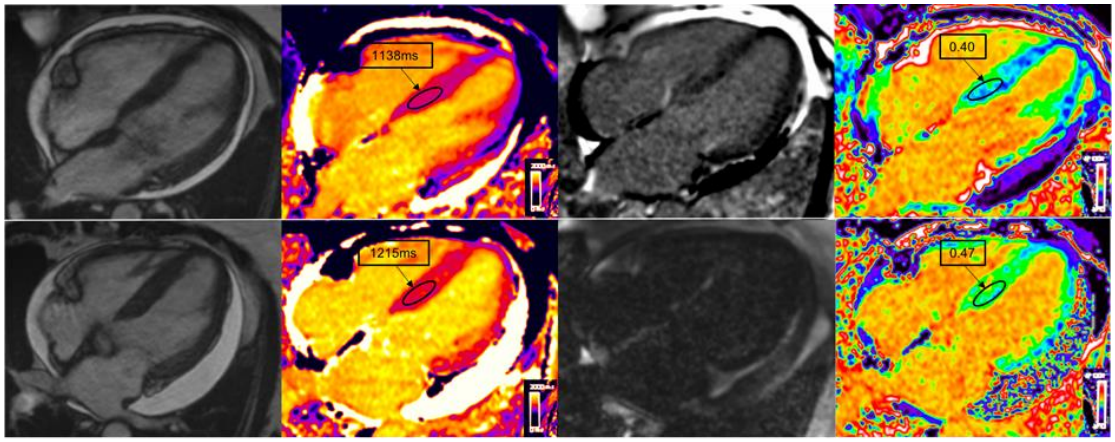

Figure 2. Baseline (top panel) and 6 months after chemotherapy (bottom panel) showing progression of AL amyloidosis by CMR. Top panel; 4 chamber view SSFP cine, corresponding 4Ch view native T1 map, late gadolinium enhancement (LGE) image and extracellular volume fraction (ECV) map showing mildly elevated native T1 values, no clear LGE and mildly elevated ECV values. Bottom panel; 4 chamber view SSFP cine, corresponding 4Ch view native T1 map, LGE and ECV map showing very high native T1 values, subendocardial LGE and moderately elevated ECV values.

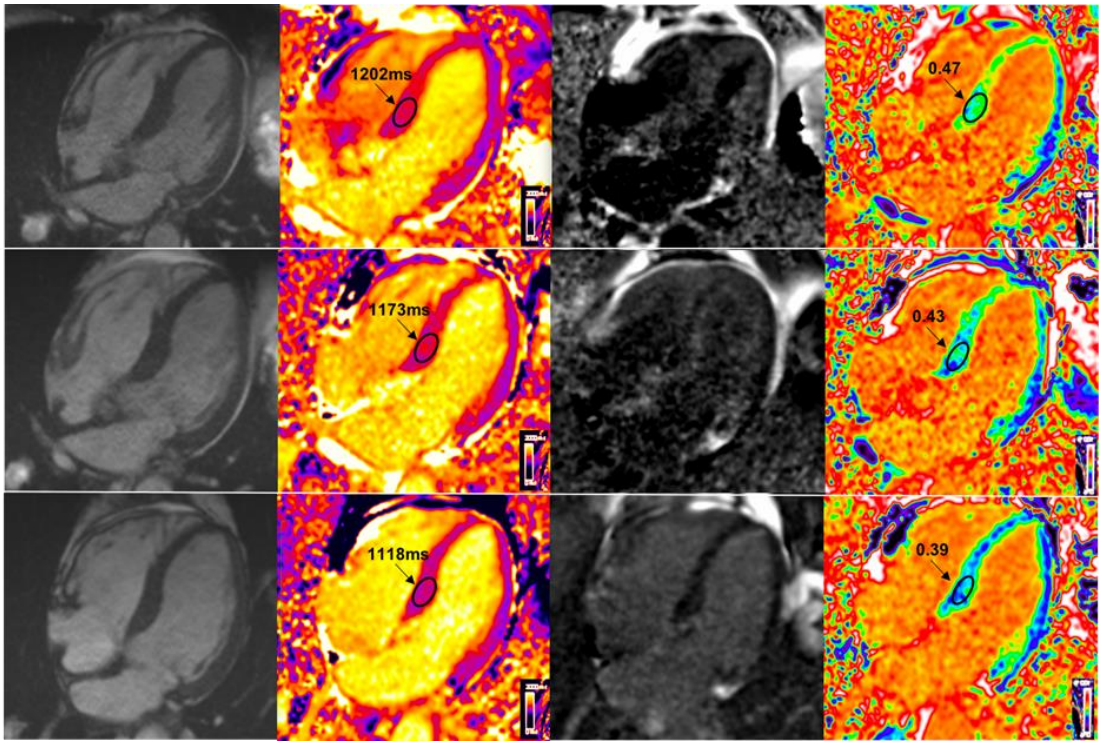

Figure 3. Baseline (top panel), 6 months after chemotherapy (mid panel) and 12 months after chemotherapy (bottom panel) showing regression of AL amyloidosis by CMR. Top panel; 4 chamber view SSFP cine, corresponding 4Ch view native T1 map, late gadolinium enhancement (LGE) image and extracellular volume fraction (ECV) map showing elevated native T1 values, subendocardial LGE and moderately elevated ECV values. Mid panel; 4 chamber view SSFP cine, corresponding 4Ch

view native T1 map, LGE and ECV map showing mildly elevated native T1 values, still subendocardial LGE and mildly elevated ECV values. Bottom panel; 4 chamber view SSFP cine, corresponding 4Ch view native T1 map, LGE and ECV map showing borderline native T1 values, no LGE and borderline ECV values.

Table 1. Baseline characteristics, biomarkers, echocardiographic and CMR parameters in patients with AL amyloidosis.

Characteristics	TOTAL (N=94)
Sex	
Men	55
Women	39
Age (y)	65± 9
Biomarkers	
NT-proBNP (ng/L)	2114 (766-5440)
CMR parameters	
LVEDV (mL)	123 ± 32
LVESV (mL)	43 ± 18
Maximal IVS (mm)	15 ± 4
LV mass (g)	178 ± 69
SV (mL/m^2)	79 ± 21
LVEF (%)	65 ± 9
LA area (cm^2)	26 ± 8
RA area (cm^2)	23 ± 7
MAPSE (mm)	9 ± 3
TAPSE (mm)	16 ± 5
Native T1 (msec)	1147 ± 57
ECV (%)	46 ± 8

AL, light-chain amyloidosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; IVS, interventricular septum; LV, left ventricular; SV, stroke volume; LVEF, left ventricular ejection fraction; LA left atrium; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; ECV, extracellular volume.
All continuous variables are presented as mean and standard deviation with non-transformed NT-proBNP presented as median and interquartile range.