Role of implantable intracardiac defibrillators in patients with cardiac immunoglobulin light chain amyloidosis

Tamer Rezk[1,2], Carol J Whelan[1] , Helen J Lachmann[1], Marianna Fontana[1], Sajitha Sachchithanantham[1], Shameem Mahmood[1], Fakhar Khan[3], Raj Khiani[3], Joseph Tomson[3], Taryn Youngstein[1], Julian D Gillmore[1], Philip N Hawkins[1] and Ashutosh D Wechalekar[1]

[1]National Amyloidosis Centre, University College London, London, U.K

[2]UCL Centre for Nephrology, Division of Medicine, University College London U.K

[3]Royal Free Hospital, Cardiology Department, London, U.K

Correspondence:

Dr Ashutosh Wechalekar
National Amyloidosis Centre,
University College London (Royal Free Campus)
Rowland Hill Street, London NW3 2PF, UK
Tel: +44 (0)20 7433 2758
E-mail: a.wechalekar@ucl.ac.uk

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Systemic light chain (AL) amyloidosis is a rare disorder characterized by the tissue deposition of misfolded immunoglobulin light chains (Pepys, 2006). One third of patients with cardiac AL amyloidosis present with a significant elevation of both N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T (TnT) concentration (Mayo Stage III disease) which is associated with poor outcomes (Kyle and Gertz, 1995) (median survival of 9-12 months) and a high early mortality within the first few months of diagnosis (30-40%)(Wechalekar et al., 2016). The main cause of this significant and early mortality is sudden cardiac death (SCD) – both ventricular tachyarrhythmias (Lin et al., 2010) and bradycardia (Sayed et al., 2015) have been observed as terminal events but the trigger remains unclear. ICD implantation is a logical therapeutic intervention but efficacy, criteria for patient selection and long term survival benefit have yet to be determined.

We report the UK experience with ICD implantation in a cohort of 15 patients with cardiac AL amyloidosis managed by a uniform supportive care, treatment and comprehensive assessment pathway from June 2010 to November 2015. Organ involvement and hematological responses were defined as per the international amyloidosis consensus criteria. Chemotherapy treatment was undertaken as per the UK amyloidosis treatment guidelines (Wechalekar et al., 2015) with cardiac patients admitted for 48-72 hours of continuous ECG monitoring at the start of chemotherapy. Patients with serious recurrent ventricular arrhythmias (defined as non-sustained ventricular tachycardia (more than 4 beats of VT and lasting less than 30 seconds) on more than one occasion in the presence of syncope/presyncope or sustained VT) were considered for ICD implantation. All patients were treated in accordance with the Declaration of Helsinki and provided informed consent.

The baseline characterics were: median age 51 years (range 37-80), median serum high-sensitivity TnT 60ng/L (range 22-326 ng/L), median NT-proBNP 5178 ng/L (range 2220 – 34,153); Mayo Staging II, IIIa and IIIb were 4/15, 8/15 and 3/15 respectively. All patients had cardiac involvement with renal, liver and nerve involvement in 7/15 (47%%), 5/15 (33%) and 1/15 (7%) patients respectively. 4 (27%) patients gave a history of recurrent syncope. At presentation, five patients were receiving β-blocker therapy. All patients received chemotherapy with front line Bortezomib or Thalidomide based regime.

13 (87%) patients were in sinus rhythm. 2 (13%) had atrial fibrillation. One patient had evidence of 1st degree atrio-ventricular conduction block. Diastolic dysfunction was mild, moderate and severe in 2 (13%), 6 (40%) and 7 (47%), respectively. Median global left ventricular strain was −9.5% (range −0.08 to −18.2%) and median left ventricular ejection fraction (LVEF) was 53% (range 40-65 %).

Median time to ICD implantation was 13 days from first presentation, median follow-up was 4.9 months (range 1.35 – 66.12). Fourteen patients (93%) underwent ICD implantation for primary prevention - 12 had non sustained VT and 2 sustained VT with spontaneous reversion. Only one patient underwent implantation for secondary prevention after ventricular fibrillation. 13/15 (87%) of the patients were started on oral amiodarone after ICD implantation. The remaining 2 patients received beta blocker therapy (one of whom was intolerant of amiodarone, the other was thyrotoxic). After ICD implantation, NSVT was detected in 6 (40%) patients (five on amiodarone and one on beta blockers).

Four patients had therapy from their ICD, three for ventricular arrhythmias and one patient had pacing for bradyarrhythmia. Two out of these four patients have since died. Overall, 13 out of 15

patients are alive with overall survival at 3, 6 and 12 months of 93%, 82% and 82% respectively. Of the patients who died, one had VF after 8 days of commencing treatment, successfully reverted to sinus rhythm after ICD shock but died ten day later for further intractable VF despite appropriate shocks. The second patient had Mayo stage 3b disease, developed VF during her 2nd cycle of chemotherapy, was appropriately shocked and remained in sinus rhythm but had refractory clonal disease and died over 3 months later with end stage heart failure.

Although survival in systemic AL amyloidosis has substantially improved, early mortality has essentially remained unchanged with no clear consensus on either the immediate or long term options for prevention of SCD. ICD implantation is a potentially attractive option. A quarter of the patients in the current cohort received appropriate therapy from the ICD, an additional third of patients had NSVT which did not need ICD intervention and a good overall survival of 82% at 12 months. In the immediate short term, ICD was life-saving in all cases who received appropriate therapy but only two out of the four patients achieved longer term survival. (Venner et al., 2012). The German amyloidosis group failed to demonstrate any benefit from ICD with a high mortality of 47% - including appropriate shock therapy in only 2 patients (11%) and only one patient surviving post therapy (Kristen et al., 2008). Contrarily, two other studies from the US, reported appropriate shock therapy in just over a third the patients (Varr et al., 2014, Lin et al., 2013) - data similar to our current results. Limitations of our study include patient selection, small sample size and the majority of our patients were on routine amiodarone after ICD implantation.

Table 1 summarises the data available (counting our cohort) in 82 patients reported to date. The majority of ICD implantation was for primary prevention and 28% of patients actually required device therapy. Importantly, nearly three quarters of all patients who had therapy from their ICD survived immediately following therapy – potentially allowing time for delivery of chemotherapy

to reduce the light chain burden. Longer term survival (determined in AL by amyloid burden, organ involvement, haematolgic response and treatment toxicity) was only 50% and was probably not impacted directly by ICD. We propose an algorithm for consideration of ICD implantation in patients with AL amyloidosis (Figure 1) – to consider ICD implantation for patients with moderate cardiac involvement (Stage II and IIIa) and focus arrhytmima prevention in patients with the most advanced disease (Mayo stage IIIb) .

In conclusion, ICD implantation, in selected patients with AL amylodiosis, deliver appropriate therapy and are life saving in the short term but long term survival benefit remain unclear. Formal prospective studies of device therapy in AL amyloidosis are urgently needed.

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Author Contributions:

TR, CW and ADW conceived the manuscript. CW, HJL, MF, SS, SM, FK, RK, JT, TY, JDG and ADW were responsible for care and follow up of patients during the study. All authors reviewed the final manuscript.

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Figure Legends

Figure 1

Approach to ICD implantation in cardiac AL amyloidosis.

Table 1. Analysis of studies to date on ICD implantation in patients with cardiac amyloidosis.

Study/Date	**Device**	**Patients with AL**	**Primary/ secondary prevention**	**Appropriate therapy from device (%)**	**Survival post therapy (%)**	**Survival during follow up of patients who received appropriate therapy (%)**	**Overall survival for cohort**
Varr et al (2014)	ICD	15	11 Primary prevention 4 Secondary prevention	5/15 (33%)	4/5 (80%)	1/4 (25%)	
Lin G et al (2013)	ICD	33	25 Primary prevention 8 Secondary prevention	12/33 (36%)			10/33 (30%)
Kristen et al (2008)	ICD	19	19 Primary prevention	2/19 (11%)	1/2 (50%)	1/2 (50%)	10/19 (53%)
Current series	ICD	15	14 Primary prevention 1 Secondary prevention	4/15 (27%)	3/4 (75%)	2/4 (50%)	13/15 (87%)
ALL Studies	ICD	82	69 Primary prevention 13 Secondary prevention	23/82 (28%)	8/11 (73%)	4/10 (40%)	33/67 (49%)