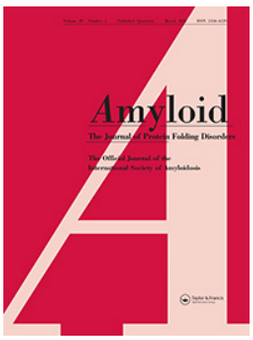

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RESEARCH ARTICLE

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# The experience of hereditary apolipoprotein A-I amyloidosis at the UK National Amyloidosis Centre

Oliver C. Cohen[a], Iona J. Blakeney[a], Steven Law[a], Sriram Ravichandran[a], Janet Gilbertson[a], Dorota Rowczenio[a], Shameem Mahmood[a,b], Sajitha Sachchithanantham[a,b], Brendan Wisniowski[a], Helen J. Lachmann[a], Carol J. Whelan[a], Ana Martinez-Naharro[a], Marianna Fontana[a], Philip N. Hawkins[a], Julian D. Gillmore[a]* and Ashutosh D. Wechalekar[a,b]*

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**ABSTRACT**

**Introduction:** Hereditary apolipoprotein A-I (AApoAI) amyloidosis is a rare heterogeneous disease with variable age of onset and organ involvement. There are few series detailing the natural history and outcomes of solid organ transplantation across a range of causative APOA1 gene mutations.

**Methods:** We identified all patients with AApoAI amyloidosis who presented to the National Amyloidosis Centre (NAC) between 1986 and 2019.

**Results:** In total, 57 patients with 14 different APOA1 mutations were identified including 18 patients who underwent renal transplantation (5 combined liver-kidney (LKT) and 2 combined heart-kidney (HKT) transplants). Median age of presentation was 43 years and median time from presentation to referral was 3 (0–31 years). Involvement of the kidneys, liver and heart by amyloid was detected in 81%, 67% and 28% of patients, respectively. Renal amyloidosis was universal in association with the most commonly identified variant (Gly26Arg, $n = 28$). Across all variants, patients with renal amyloidosis had a median creatinine of 159 μmol/L and median urinary protein of 0.3 g/24 h at the time of diagnosis of AApoAI amyloidosis and median time from diagnosis to end-stage renal disease was 15.0 (95% CI: 10.0–20.0) years. Post-renal transplantation, median allograft survival was 22.0 (13.0–31.0) years. There was one early death following transplantation (infection-related at 2 months post-renal transplant) and no episodes of early rejection leading to graft failure. Liver transplantation led to regression of amyloid in all four cases in whom serial $^{123}$I-SAP scintigraphy was performed.

**Conclusions:** AApoAI amyloidosis is a slowly progressive disease that is challenging to diagnose. The outcomes of transplantation are encouraging and graft survival is excellent.

**Abbreviations:** AFib: Aα-chain fibrinogen; ALECT2: leucocyte chemotactic factor 2 amyloid; ALP: alkaline phosphatase; ATTR: amyloid transthyretin; CMV: cytomegalovirus; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HDL: high-density lipoprotein; HKT: combined heart-kidney transplantation; KD: kidney transplantation; Kda: kilo Dalton; LKT: combined liver-kidney transplantation; NAC: National Amyloidosis Center; OS: overall survival; SAP: serum amyloid-P component

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Apolipoprotein AI; amyloidosis; transplantation; APOA1; survival

## Introduction

Systemic amyloidosis refers to a group of heterogeneous disorders characterised by the misfolding of a normally soluble protein into insoluble fibrils, which deposit within organs leading to dysfunction [1]. AL amyloidosis remains the most common type, resulting from production of light-chain immunoglobulin by a clonal cell population in the marrow, and accounts for approximately half of all cases of amyloidosis [2]. Hereditary forms of amyloidosis are autosomal dominant (albeit with variable penetrance) with specific clinical manifestations dependent upon the mutated gene in question. Apolipoprotein A-I (AApoAI) amyloidosis is the third most commonly diagnosed form of hereditary amyloidosis in the UK after hereditary transthyretin (ATTR) and fibrinogen α-chain (AFib) amyloidosis. Causative mutations in the APOA1 gene can lead to deposition of amyloid within the heart, liver, kidneys, testis, nerves, larynx and skin with a mean age of onset of 58 years [3].

Apolipoprotein A-I is 28-Kda, non-glycosylated and the main apolipoprotein of HDL [4]. Eighteen different amyloidogenic AApoAI variants with resultant slowly progressive organ dysfunction have thus far been reported. A study of 253 carriers of the Leu75Pro variant found that 62% developed amyloidosis whilst 38% remained asymptomatic [3]. Renal [5–12], cardiac [8,13–17] and hepatic [5,7,8,12,18] involvement occurs in association with 11, 6 and 5 such

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variants, respectively. AApoAI amyloidosis can present with amyloid deposition in unusual sites such as localised deposits in the aortic intima (with associated angina) [19], testes and palate [6] without co-existent critical amyloidotic organ dysfunction.

We present here the long-term outcomes of a cohort of patients diagnosed with AApoAI amyloidosis to document the natural history of the disease and the outcomes of patients who underwent single and combined solid organ transplantation.

## Methods

### Patients

All patients diagnosed with AApoAI amyloidosis at the UK National Amyloidosis Centre (NAC), who presented between 1986 and 2017, were included within the study. Diagnosis was based on histological proof of amyloid by Congo red staining, the finding of an underlying established or novel genetic mutation associated with AApoAI amyloidosis and confirmation of the amyloid fibril type by immunohistochemistry or mass spectrometry. Patients underwent a comprehensive annual assessment at the NAC including clinical assessment, blood monitoring of organ function, urinary protein measurement, echocardiography and $^{123}$I-serum amyloid-P component (SAP) scintigraphy as previously described [20]. Organ involvement was defined by the characteristic appearance of amyloid deposits on $^{123}$I-SAP scintigraphy, echocardiography (in the case of cardiac involvement) or histology. $^{123}$I-SAP scintigraphy visualises amyloid deposits in the visceral organs including liver, spleen, kidneys and adrenal glands but does not detect amyloid in other organs such as the heart, larynx, testis, skin or nerves. Data from patients 1, 2, 3, 7, 8, 13, 17 and 18 (Table 1) had been included within a prior publication from our centre 30 but the current study included an updated analysis.

Overall survival (OS) was calculated from date of presentation to death from any cause whilst renal allograft survival was calculated as time from transplantation to recurrence of end-stage renal disease (ESRD); patient deaths without renal allograft failure were censored. In cases whereby patients received a 2nd renal transplant, the time to recurrence of ESRD after the 1st transplant was used in the analysis.

### Statistical analysis

Statistical analysis was performed using SPSS version 25. Approval for analysis and publication was obtained from the National Health Service institutional review board; written consent was obtained from all patients in accordance with the Declaration of Helsinki. Patients were censored at their last NAC visit. The Kaplan–Meier method was used to analyse survival outcomes using the log-rank test to compare differences between stratified Kaplan–Meier analyses.

## Results

Fifty-seven patients with AApoAI amyloidosis were included within the study. Thirty-three (58%) patients were male and twenty-four (42%) were female. Median age at presentation was 43 (17–75) years. There was no difference in age of presentation between males and females ($p = .30$). Full baseline characteristics by APOA1 mutation are detailed in Table 2. Overall, renal, hepatic and cardiac involvement was detected in 81%, 67% and 28% of patients, respectively. Furthermore, 11% presented with neuropathy, 11% with laryngeal involvement and 4% with testicular involvement. At diagnosis, the median serum creatinine was 149 µmol/L (range 51–718 µmol/L) with an estimated glomerular filtration rate (eGFR) of 41 ml/min (<15->90 ml/min). The median alkaline phosphatase (ALP) was 145.5 IU/L (44–554 IU/L). In terms of cardiac biomarkers, median NT-proBNP was 355 ng/L (21–14,478 ng/L) and median

**Table 1.** Characteristics of patients with hereditary apolipoprotein A-I amyloidosis undergoing solid organ transplantation.

| Patient No. | APOAI variant | Organ(s) transplanted | Time to ESRF (years) | Amyloid load at Tx | Other organ involvement | Patient Status | Time from Tx to death/ censor (years) | Cause of death | Graft with recurrent amyloid/time to recur | Amyloid load* at death/censor |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Del 70-72 | Kidney | 6.0 | Large | Retinal | Alive | 27.3 | n/a | Yes | Unknown |
| 2 | Gly26Arg | Liver-Kidney | 19.0 | Large | Nil | Dead | 18.0 | Unknown | Yes | Small |
| 3 | Gly26Arg | Kidney | 6.0 | Moderate | Liver, PN | Dead | 19.7 | Unknown | Yes | Moderate |
| 4 | Gly26Arg | Kidney | 8.0 | Large | Liver | Dead | 21.8 | Unknown | Yes | Large |
| 5 | Leu60Arg | Kidney | 13.0 | Large | Liver | Dead | 13.1 | Liver failure | Yes | Unknown |
| 6 | Gly26Arg | Kidney | 9.0 | Large | Liver | Alive | 10.8 | n/a | No | Moderate |
| 7 | Leu60Arg | Heart-Kidney | 1.0 | Small | Liver | Dead | 23.1 | Unknown | Yes | Large |
| 8 | Arg173Pro | Heart-Kidney | 10.0 | None | Testis, Choroid | Dead | 14.9 | Progressive amyloidosis | Yes | None |
| 9 | Gly26Arg | Kidney | 0 | Moderate | Heart, Liver | Alive | 9.0 | n/a | No | Moderate |
| 10 | Gly26Arg | Liver-Kidney | 9.2 | Not done | Nil | Alive | 10.1 | n/a | No | Small |
| 11 | Trp50Arg | Liver-Kidney | 8.0 | Large | Nil | Alive | 4.6 | n/a | No | Not done |
| 12 | Gly26Arg | Kidney | 4.1 | Moderate | Nil | Alive | 15.0 | n/a | No | Small |
| 13 | Leu64Pro | Kidney | 1.3 | Large | Nil | Dead | 13.2 | Progressive amyloidosis | Yes | Not done |
| 14 | Gly26Arg | Kidney | 1.1 | Moderate | Cardiac | Alive | 11.8 | n/a | Yes | Large |
| 15 | Leu60Arg | Liver-Kidney | Pre-emptive | Large | Nil | Alive | 1.0 | n/a | No | Small |
| 16 | Trp50Arg | Kidney | 1.0 | Moderate | Liver | Alive | 4.0 | n/a | Yes | Large |
| 17 | Leu60Arg | Liver-Kidney | 20.0 | Large | Nil | Alive | 17.6 | n/a | No | Small |
| 18 | Trp50Arg | Kidney | 10.0 | Large | Liver | Dead | 0.2 | CMV | No | Unknown |

*Amyloid load is defined based upon visual assessment of SAP scintigraphy during a multi-disciplinary team meeting.

**Table 2.** Patient baseline characteristics by APOAI variant.

| APOAI variant | *N* (%) | Ethnicity | Age at presentation | Presenting features | Organ involvement | Amyloid load* |
|---|---|---|---|---|---|---|
| Gly26Arg | 28 (49.1%) | Irish: 19<br>British: 9 | 42.5 (17–59) | CKD, Proteinuria, HTN (26),<br>PN (1),Hepatic dysfunction (1) | Renal: 28 (100.0%)<br>Hepatic: 22 (78.6%)<br>Cardiac: 5 (17.9%)<br>Peripheral nerve: 5 (17.9%) | Large: 6 (21.4%)<br>Moderate: 9 (32.1%)<br>Small/Equivocal: 5 (17.9%)<br>None: 5 (17.9%)<br>Not done: 3 (10.7%) |
| Leu60Arg | 7 (12.3%) | British | 34 (23–67) | CKD, Proteinuria, HTN | Renal: 7 (100.0%)<br>Hepatic: 7 (100.0%)<br>Cardiac: 3 (42.9%)<br>Gastric: 1 (14.3%) | Large: 4 (57.1%)<br>Moderate: 2 (28.6%)<br>Not done: 1 (14.3%) |
| Arg173Pro | 6 (10.5%) | British | 44.5 (32–66) | Hoarse voice (2), CHF (2),<br>Asymptomatic screening (2) | Cardiac: 6 (100.0%)<br>Laryngeal: 5 (83.3%)<br>Renal: 1 (16.7%)<br>Hepatic: 1 (16.7%)<br>Choroidal: 1 (16.7%)<br>Testicular: 1 (16.7%)<br>Cutaneous: 1 (16.7%) | Small/Equivocal: 2 (33.3%)<br>None: 4 (66.7%) |
| Trp50Arg | 5 (8.8%) | British: 3<br>Polish Jewish: 2 | 42 (19–57) | CKD, Proteinuria, HTN | Renal: 5 (100.0%)<br>Hepatic: 3 (60.0%) | Large: 2 (40.0%)<br>Moderate: 1 (20.0%)<br>Small: 2 (40.0%) |
| His155Metfs*46,delCc.535 | 2 (3.5%) | British | 73 (71–75) | CKD, Proteinuria, HTN | Renal: 2 (100.0%)<br>Peripheral nerve: 1 (50.0%) | Small: 2 (100.0%) |
| Leu64Pro | 1 (1.8%) | Italian | 56 | Proteinuria, Oedema | Renal, Hepatic | Large |
| Leu90Pro | 1 (1.8%) | British | 75 | CHF | Cardiac | None |
| Ala175Pro | 1 (1.8%) | British | 38 | Dysphonia, Infertility | Larynx, Testis | None |
| Del 70-72 | 1 (1.8%) | British | 21 | Proteinuria, HTN | Renal, Retinal | Large |
| E70-W72 | 1 (1.8%) | British | 33 | Hepatic dysfunction | Renal, Hepatic | Large |
| F71Y | 1 (1.8%) | Turkish | 65 | Proteinuria, HTN | Palate, Liver | Small |
| Gln172Pro | 1 (1.8%) | Tanzanian | 65 | CHF | Cardiac | None |
| Glu34Lys | 1 (1.8%) | Polish | 27 | Proteinuria, oedema | Renal, Hepatic | Large |
| Phe71Tyr | 1 (1.8%) | British | 47 | Palatal lump | Palatal, Hepatic | Moderate |

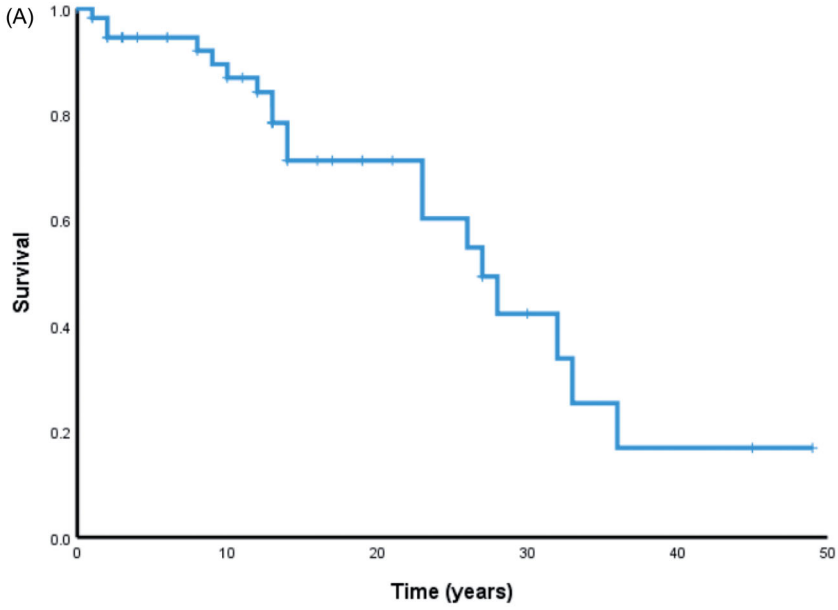
Abbreviations: CKD: chronic kidney disease; HTN: hypertension; PN: peripheral neuropathy; CHF: congestive heart failure.
*Amyloid load is defined based upon visual assessment of SAP scintigraphy during a multi-disciplinary team meeting.

Troponin T, 10 pg/ml (6–137 pg/ml). The visceral amyloid load on $^{123}$I-SAP scintigraphy was graded as none in 12 (23%), small in 12 (23%), moderate in 13 (25%) and large in 16 (30%) cases ($^{123}$I-SAP scintigraphy was not performed in 4 patients). Median overall survival from diagnosis was 27.0 (21.3–32.7) years (Figure 1).

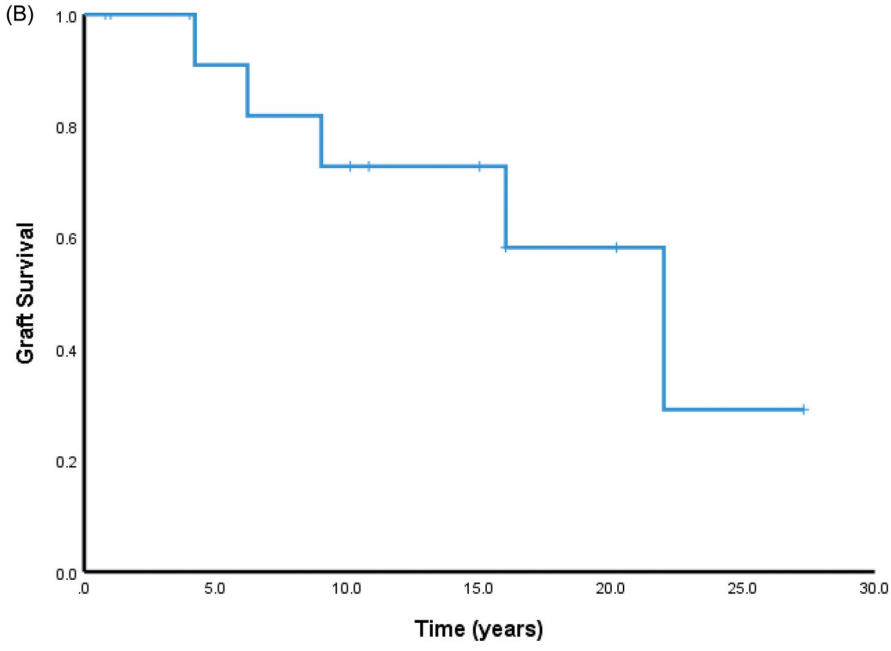
Patients with renal amyloidosis had significantly worse renal function at diagnosis (serum creatinine: 159 µmol/L vs. 103 µmol/L, $p = .0004$; eGFR: 37 ml/min vs. 67 ml/min, $p = .0001$) but median proteinuria was not significantly higher (0.3 g/24 h vs. 0.15 g/24 h, $p = .06$) than those without renal involvement. Patients with hepatic amyloid had a significantly higher ALP (244 IU/L vs. 77 IU/L, $p < .0001$) and patients with cardiac amyloidosis had higher NT-proBNP (1461 ng/L vs. 271 ng/L, $p = .006$) values at the time of diagnosis although Troponin T concentration was not significantly different between those with and without cardiac amyloidosis (14 pg/ml vs. 11 pg/ml, $p = .52$).

The most commonly identified amyloidogenic AApoAI variant was Gly26Arg ($n = 28$) and 68% of patients with this variant were of Irish ancestry. At presentation, all patients with this variant had either impaired renal excretory function, proteinuria or hypertension alone or in combination. At the time of diagnosis, median eGFR was 34 ml/min (<15–75 ml/min), median urinary protein loss was of 0.2 g/24 h (0.1–4.0) and 10 patients were receiving therapy for hypertension. Median serum creatinine ($p = .11$) and median eGFR ($p = .10$) were comparable at the time of diagnosis between those with the Gly26Arg variant and those with renal involvement associated with other pathogenic AApoAI variants, although proteinuria was significantly lower among those with Gly26Arg (0.15 g/24 h vs. 1.7 g/24 h, $p = .01$) and serum albumin was significantly higher (45 g/L vs. 40 g/L, $p = .003$). Whilst the only Gly26Arg patient with nephrotic range proteinuria was already dialysis-dependent at diagnosis, none of the 6 other patients with nephrotic syndrome (Leu60Arg [$n = 2$], Trp50Arg [$n = 2$], His155Metfs*46 [$n = 2$]) had ESRD at the time of diagnosis. One patient with Gly26Arg presented with a debilitating amyloidotic peripheral neuropathy and subtle renal dysfunction. This patient had four affected brothers; one with predominant neuropathy and three with predominant nephropathy. All patients with Leu60Arg and Trp50Arg-associated AApoAI amyloidosis had nephropathy. All patients with Arg173Pro-associated AApoAI amyloidosis had cardiac involvement, although only 2 of 6 (33%) such patients had symptomatic heart failure from amyloid cardiomyopathy.

Forty-six patients presented with renal involvement and 21/46 patients reached ESRD. Excluding one patient with ESRD at presentation, median time to ESRD from date of presentation and date of diagnosis by Kaplan–Meier analysis was 19.0 (95% CI: 7.5–30.6) years and 15.0 (95% CI: 10.0–20.0) years respectively. At Censor, 11 patients had undergone kidney alone transplantation (KT) after reaching ESRD and 7 patients had undergone a combined solid organ transplant (5 LKT and 2 HKT). Three patients with ESRD died without receiving transplants and one was listed for kidney transplantation but lost to follow up.




| Time (years) | 0 | 10 | 20 | 30 | 40 |
|---|---|---|---|---|---|
| n | 57 | 37 | 18 | 6 | 2 |




| Time (years) | 0 | 5 | 10 | 15 | 20 | 25 |
|---|---|---|---|---|---|---|
| n | 18 | 14 | 13 | 9 | 7 | 5 |

**Figure 1.** Survival. (A) Overall survival of all patients from diagnosis of apolipoprotein A-I amyloidosis. (B) Renal graft survival in patients who received a renal allograft with apolipoprotein A-I amyloidosis.

Of 11 patients who received KT (3 live, 8 cadaveric), 5 died (Table 1). Median survival from diagnosis was 32 (20.9–43.1) years and from KT was 19.7 (15.2–24.1) years. There was one early death due a cytomegalovirus (CMV) infection within 2 months of KT. Two patients died with documented amyloid recurrence within the renal allografts both 13 years after KT but both renal allografts were functioning at the time of death and neither death was attributed to ESRD. Two patients had renal allograft failure in the context of recurrent amyloid and proceeded to a second KT, 6 and 16 years after their first KT; both had functioning second renal allografts at the time of death. In the 6 living patients, 4 had functioning grafts (Table 1 Patient No/years post-KT: 16/4.0, 6/10.8, 12/15.0 and 1/

**Table 3.** Published apolipoprotein A-I amyloidosis series of ≥10 patients.

| Study | *n* | APOAI variants | Ethnicity | Median age at presentation | Organ involvement by variant | Time from presentation to end-stage renal failure (ESRF) (years) | Organ transplantation |
|---|---|---|---|---|---|---|---|
| Gregorini et al. [3] | 135 | Leu75Pro | Italian | 58.1 | Renal (107/135)<br>Hepatic (65/135)<br>Testis (62/135) | Median age at ESRF 71.8 years | – |
| Pinney et al. [28] | 16 | Not documented | Not documented | – | Renal (16/16) | 5.9 | 1 combined liver-kidney transplant and 13 kidney transplants |
| Traynor et al. [32] | 16 | Gly26Arg | Irish | 48 | Renal (15/16)<br>PN (6/16) | 9* | 1 combined liver-kidney and 4 kidney transplants |
| Gillmore et al. [31] | 10 | Leu60Arg (3)<br>Gly26Arg (2)<br>Del70–72 (2)<br>Trp50Arg (1)<br>Leu64Pro (1)<br>Arg173Pro (1) | English<br>Irish<br>Welsh<br>Polish-Jewish<br>Italian<br>English | 30.5 | Renal (10/10)<br>Cardiac (Leu60Arg, Arg173Pro)<br>Hepatic (Leu64Pro, Trp50Arg, Gly26Arg) | 8 | 2 combined liver-kidney, 2 combined heart-kidney and 6 kidney transplants |
| Scalvini et al. [23] | 10 | Leu75Pro | Not stated | 35.7 | Testis (10/10) | n/a | – |
| Gregorini et al. [22] | 13 | Leu75Pro | Italian | 55 | Renal (13/13)<br>Hepatic (10/13)<br>Cardiac (1/13) | – | – |
| Obici et al. [21] | 13 | Leu75Pro | Italian | 56 | Hepatic (12/13)<br>Renal (9/13)<br>Testis (2/13) | – | – |

*Based on available data for nine patients.

27.3) whilst 2 KTs had failed at 4.2 (Patient 14) and 9.0 (Patient 9) years post-KT, respectively. None of the patients who underwent KT had clinically significant cardiac amyloidosis although two such patients had evidence of possible early cardiac amyloid infiltration on imaging only. Within the cohort of patients who received a KT and including the two patients who received two KTs, median renal allograft survival (with censoring of deaths with a functioning allograft) was 16.0 (3.1–28.9) years.

Two patients received HKTs. Time from HKT to death in patients 7 and 8 was 23.1 and 14.9 years, respectively. Patient 7's renal allograft failed after 22.1 years with multifactorial aetiology including recurrent amyloid. This patient received a second live donor KT but died suddenly (cause unknown) 9 months later with a functioning renal allograft. Patient 8 died with functioning allografts but had evidence of amyloid recurrence in both organs and declining function; 1 month prior to death, the patient had chronic kidney diseases (CKD) stage 4 (eGFR 24 ml/min) and a characteristic amyloid echocardiogram with progressively increasing left ventricular wall thickness (to 14 mm) and worsening 2-D longitudinal strain (to −10.7%) on annual imaging over the 5-year period prior to death.

Five patients received LKTs (including one patient who was due for LKT but actually had the KT performed 3 years after the liver transplant as a result of tumour detected in the donor kidney at the time of the LKT procedure); the other LKTs were simultaneous. There was one death in this group at 18 years post-LKT (cause of death unclear – both grafts were functioning well and death not due to amyloidosis). One patient required a second liver transplant (LT) due to hepatic allograft failure from biliary strictures and recurrent infection. This patient's grafts are functioning well 3.9 years post-second LT. At censor, the remaining three patients were alive with functioning grafts and no evidence of amyloid recurrence in either allograft at 10.1, 1.0 and 17.6 years post-LKT, respectively. Serial $^{123}$I-SAP scintigraphy, performed in four of the five LKT patients, all showed marked splenic amyloid regression following the LKT procedure.

## Discussion

This study reports the natural history and long-term outcomes of patients with hereditary AApoAI amyloidosis associated with 14 different amyloidogenic APOA1 mutations and represents the largest series of patients with the Gly26Arg variant reported to date. To our knowledge, this is also the largest series reporting long term outcomes in transplanted patients with hereditary AApoAI amyloidosis, including seven patients who underwent combined solid organ transplants. Our findings illustrate an excellent overall median renal allograft survival within this patient population of 22 years from transplantation.

The natural history of AApoAI amyloidosis remains poorly documented due to a lack of large case series (Table 3). One series of 135 Italian patients exclusively examined the natural history of the Leu75Pro variant [3]. This study

documented an increasing penetrance with age finding that 98.7% of mutation carriers aged >80 years old had evidence of amyloidotic organ involvement. This study also found a mean age of onset of 58.1 years, consistent with other studies of the same variant [21,22]. In contrast, we found a younger age of onset in our patient cohort with multiple AApoAI variants of 43 years. An Irish study of 16 patients with AApoAI amyloidosis also documented a younger age of onset of 48 years likely reflecting variation in age of symptom onset between genetic variants. Finally, the Italian study [3] found that age of onset was significantly lower in males than females (54.8 vs. 63.6 years) due to the earlier onset of testicular disease. A study of 10 patients with isolated testicular AApoAI amyloid confirmed this finding, documenting an average age of onset of just 35.7 years [23]. Our study found no difference in age of presentation based on sex possibly reflecting the small proportion of patients (4%) with documented testicular involvement.

In AApoAI amyloidosis, organ involvement and clinical phenotype is partly dependent upon the specific disease-causing mutation. In certain previously published series, renal involvement has been documented in a majority of patients (Table 3) and, as such, is commonly viewed as the primary target organ in AApoAI amyloidosis. In our series, renal involvement was universal in patients with the Gly26Arg variant who progressed slowly to ESRD (over median 19 years from presentation) such that early detection to optimise management of factors contributing to ESRD such as hypertension are of critical potential importance. Hepatic involvement was typically associated with hepatomegaly due to infiltration by amyloid but liver failure was relatively unusual; however it has been reported in a Spanish family with a Leu60Phe71 deletion/insertion of Val60Thr6 within the APOA1 gene [18]. Cardiac AApoAI amyloidosis was universal among patients with the Arg173Pro, Leu90Pro and Gln172Pro variants, some of whom has Grade 1 positivity on Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-DPD) scintigraphy, and led to a gradually progressive restrictive cardiomyopathy manifesting as congestive cardiac failure [14]. It is critical therefore, to consider AApoAI amyloidosis in patients with cardiac amyloidosis and similarly, not to discount the possibility of AApoAI amyloidosis in patients with amyloidosis without renal involvement. Other clinical manifestations which were observed in our cohort and which have previously been reported include infertility [6,15], hoarse voice/dysphonia [6,14,16,17] polyneuropathy [5,6,11,15] and cutaneous lesions [13,14].

Silent organ dysfunction and resultant diagnostic delays pose a challenge in documenting the natural history of this rare disease, particularly in patients without a clear family history. Furthermore, once patients present, symptoms are often non-specific leading to further diagnostic delay. In this series, patients waited a median of 3 years from presentation to diagnosis of AApoAI amyloidosis. AApoAI amyloidosis should be considered in patients in whom amyloidosis is suspected on clinical or histological grounds especially in the context of a family history of amyloidosis, or in the absence of a clonal dyscrasia or inflammatory disease. In such patients who have renal involvement by amyloid, AFib and leukocyte chemotactic factor 2 (ALECT2) amyloidosis must also be considered. In renal AL, AA and AFib amyloidosis, patients typically present with proteinuria which is often in the nephrotic range [24–26]. However, patients with renal AApoAI amyloidosis in this series generally had low-level proteinuria (median 0.3 g/24 h), although there were exceptions. In keeping with our findings, the Italian study of patients with Leu75Pro reported >0.5 g/day of proteinuria in just 12% of affected patients [3]. Consequently, the presence of CKD without significant proteinuria may still be consistent with AApoAI amyloidosis. Furthermore, evidence of a plasma (or B cell) dyscrasia should prompt both a bone marrow aspirate/trephine and definitive biopsy to exclude AL amyloidosis.

Amyloid recurrence within an allograft together with continued amyloid accumulation in non-transplanted organs historically caused controversy with respect to organ transplantation in amyloidosis. However, recent studies reporting transplant outcomes in patients with AL and AA amyloidosis have demonstrated comparable death-censored graft survival to matched controls with other causes of ESRD; 10-year graft survivals in AL and AA amyloidosis in one recent study were 93% and 78%, respectively [27]. Allograft survival in patients with AApoAI amyloidosis has been shown to be significantly longer than in those with AL, AA or AFib amyloidosis [28]. In this study of renal transplant outcomes specifically in patients with AApoAI amyloidosis, we demonstrate a median renal allograft survival of 22 years, which is superior to the 13.1 years that we previously reported [28]. The exceptionally slow rate of amyloid re-accumulation justifies the use of renal transplantation in patients with AApoAI amyloidosis. Notably, no patient who received a renal allograft (with the exception of the two patients who received LKTs) had cardiac involvement by amyloidosis at the time of transplantation. In AL amyloidosis, the presence of cardiac involvement has been shown to increase the risk of death in patients undergoing KT [29] and although in AApoAI amyloidosis presence of cardiac amyloidosis should not be considered an absolute contra-indication to KT or LKT, careful assessment of cardiac function and reserve prior to surgery is essential. Both patients in this series who received HKT had excellent long term allograft function again highlighting the benefits of combined solid organ transplantation in AApoAI amyloidosis.

Approximately 50% of circulating AApoAI protein is synthesised in the liver such that liver transplantation (LT) substantially reduces production of the amyloidogenic variant precursor protein [30]. Accordingly, we found that all four patients who underwent pre- and post-transplantation $^{123}$I-SAP scintigraphy had amyloid regression following LT which was evident within 6 months in one case. Our group had previously demonstrated marked regression in patient 17 [31] following LT (prior to the renal transplant whilst the patient remained on dialysis). At present, there are no drugs that can directly remove existing AApoAI amyloid deposits such that LT represents the only way to achieve

amyloid regression in this disease. Improvement in AApoAI amyloid-associated peripheral neuropathy has previously been reported following LKT [31]. Given the excellent outcomes in AApoAI amyloidosis patients with kidney and heart transplants in the absence of LT however, routine use of LT in AApoAI amyloidosis cannot be justified unless there is either a failing liver (which may be due to extensive hepatic amyloidosis) or progressive amyloidotic dysfunction of another organ which is life threatening or causing significant functional impairment.

In summary, we report here the outcomes of 57 patients with hereditary AApoAI amyloidosis including 18 patients who underwent organ transplantation. AApoAI amyloidosis is a slowly progressive disease with amyloidotic organ tropism which depends, in part, on the specific AApoAI variant in question. Early recognition of this rare disease remains challenging. Outcomes of organ transplantation in patients whose amyloidotic organs are failing are excellent with median renal allograft survival of 22 years among patients receiving a KT, LKT or HKT.

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Our centre previously published the outcomes of organ transplantation in patients with hereditary AApoAI amyloidosis in 2006 [31]. This study includes some patients previously published there with extension of follow up where applicable and includes further unpublished data of the NAC experience of organ transplantation in AApoAI amyloidosis since 2006 as well as data from non-transplanted patients.

## Disclosure statement

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