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## Kidney Transplantation in Patients With AA Amyloidosis: Outcomes in a French Multicenter Cohort



Chloë Schwarz, Sophie Georgan-Lavialle, Yannis Lombardi, Olivier Marion, Frédéric Jambon, Christophe Legendre, David Marx, Charlene Levi, Fatouma Toure, Moglie Le Quintrec, Mickael Bobot, Marie Matignon, Amaury Dujardin, Mehdi Maanaoui, Sébastien Cuozzo, Arwa Jalal-Eddine, Kevin Louis, Inna Mohamadou, François Brazier, Tristan De Nattes, Claire Geneste, Eric Thervet, Didier Ducloux, Valentin Mayet, Raphaël Kormann, Antoine Lanot, Agnès Duveau, Mohamad Zaidan, Laurent Mesnard, Nacera Ouali, Eric Rondeau, Camille Petit-Hoang, Vincent Audard, Aurélie Deshayes, Anissa Moktefi, Marion Rabant, David Buob, Hélène François, and Yosu Luque

**Rationale & Objective:** Outcomes of kidney transplantation for patients with renal AA amyloidosis are uncertain, with reports of poor survival and high rates of disease recurrence. However, the data are inconclusive and mostly based on studies from the early 2000s and earlier.

**Study Design:** Retrospective multicenter cohort study.

**Setting & Participants:** We searched the French national transplant database to identify all patients with renal AA amyloidosis who underwent kidney transplantation between 2008 and 2018.

**Exposures:** Age, cause of amyloidosis, use of biotherapies, and C-reactive protein levels.

**Outcomes:** Outcomes were all-cause mortality and allograft loss. We also reported amyloidosis allograft recurrence, occurrence of acute rejection episodes, as well as infectious, cardiovascular, and neoplastic disease events.

**Analytical Approach:** Kaplan-Meier estimator for mortality and cumulative incidence function method for allograft loss. Factors associated with patient and allograft survival were investigated using a Cox proportional hazards model and a cause-specific hazards model, respectively.

**Results:** 86 patients who received kidney transplants for AA amyloidosis at 26 French centers

were included. The median age was 49.4 years (IQR, 39.7-61.1). The main cause of amyloidosis was familial Mediterranean fever (37 cases; 43%). 16 (18.6%) patients received biotherapy after transplantation. Patient survival rates were 94.0% (95% CI, 89.1-99.2) at 1 year and 85.5% (77.8-94.0) at 5 years after transplantation. Cumulative incidences of allograft loss were 10.5% (4.0-17.0) at 1 year and 13.0% (5.8-20.1) at 5 years after transplantation. Histologically proven AA amyloidosis recurrence occurred in 5 transplants (5.8%). An infection requiring hospitalization developed in 55.8% of cases, and there was a 27.9% incidence of acute allograft rejection. Multivariable analysis showed that C-reactive protein concentration at the time of transplantation was associated with patient survival (HR, 1.01; 95% CI, 1.00-1.02;  $P = 0.01$ ) and allograft survival (HR, 1.68; 95% CI, 1.10-2.57;  $P = 0.02$ ).

**Limitations:** The study lacked a control group, and the effect of biotherapies on transplantation outcomes could not be explored.

**Conclusions:** This relatively contemporary cohort of patients who received a kidney transplant for AA amyloidosis experienced favorable rates of survival and lower recurrence rates than previously reported. These data support the practice of treating these patients with kidney transplantation for end-stage kidney disease.

Complete author and article information provided before references.

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Amyloidosis is characterized by extracellular deposition of amyloid, an insoluble fibril formed by the accumulation of misfolded proteins in a particular  $\beta$ -sheet conformation. Deposition can occur in all tissues and leads to progressive organ dysfunction. Amyloidosis is a heterogeneous group of diseases encompassing more than 30 different types, depending on the precursor protein.<sup>1</sup> After wild-type transthyretin cardiac amyloidosis and immunoglobulin light-chain amyloidosis, AA amyloidosis is the most frequent systemic amyloidosis in epidemiologic studies.<sup>2-4</sup> It results from the accumulation of serum amyloid A (SAA), the production of which is mediated by inflammatory cytokines. SAA may accumulate in all

chronic inflammatory states, which can be secondary to infections, inflammatory rheumatological or intestinal diseases, and monogenic autoinflammatory diseases such as familial Mediterranean fever (FMF). Kidney involvement is frequent in AA amyloidosis, and, in the largest series to date of 374 patients with AA amyloidosis, it led to kidney failure in 44% of cases and was the major prognostic factor.<sup>5</sup>

Survival of patients with AA amyloidosis undergoing long-term dialysis is poor.<sup>6,7</sup> Kidney transplantation may be considered in these patients, but concerns remain regarding increased mortality and the possibility of amyloidosis recurrence in the graft. In a retrospective

**PLAIN-LANGUAGE SUMMARY**

AA amyloidosis is a severe and rare disease. Kidney involvement is frequent and leads to end-stage kidney disease. Because of the involvement of other organs, these patients are often frail, which has raised concerns about their suitability for kidney transplantation. We reviewed all patients with AA amyloidosis nephropathy who underwent kidney transplantation in France in the recent era (2008-2018) and found that the outcomes after kidney transplantation were favorable, with 85.5% of patients still alive 5 years after transplantation, a survival rate that is comparable to the outcomes of patients receiving a transplant for other forms of kidney diseases. Recurrence of amyloidosis in the transplanted kidney was infrequent (5.8%). These data support the practice of kidney transplantation for patients with AA amyloidosis who experience kidney failure.

French multicenter study, Kofman et al reported outcomes of 59 patients with AA amyloidosis who underwent kidney transplantation between 1981 and 2009 and found a less favorable overall survival, with frequent infections. Disease recurrence occurred in 14% of cases and was associated with poorer outcomes.<sup>8</sup> Other studies are consistent with these findings and report poor survival and recurrence rates between 8% and 26%.<sup>9-15</sup> In a recent series by Law et al, survival of AA amyloidosis kidney transplant recipients (N = 48) was comparable to that in controls with diabetic nephropathy.<sup>15</sup> Overall, series regarding kidney transplantation in patients with AA amyloidosis are rather small and heterogenous. There is also a lack of recent data, and all the cited studies had very long inclusion periods.

To date, treatment of AA amyloidosis relies on treating the underlying inflammatory process to prevent further amyloid deposition. In patients with FMF, colchicine has historic efficacy in preventing amyloidosis,<sup>16</sup> including in the setting of kidney transplantation.<sup>17</sup> In the recent era (since 2010), new anti-inflammatory treatments known as biotherapies have been more widely used in systemic autoinflammatory diseases, namely anti-interleukin (IL) 1 and anti-IL-6 therapies: they proved effective in the control of symptoms and systemic inflammation.<sup>18</sup> Similarly, in chronic inflammatory rheumatic and inflammatory bowel diseases, anti-tumor necrosis factor (TNF)- $\alpha$  therapies drastically changed disease prognosis and may reduce amyloidosis occurrence.<sup>19,20</sup>

Considering these observations, we hypothesized that kidney transplantation for patients with AA amyloidosis may have better outcomes in the era of such biotherapies. We thus conducted a retrospective multicenter cohort study focusing on the recent period of 2008-2018: all patients with AA amyloidosis who underwent kidney transplantation in France during this time were included. The objectives of the present study are to describe the

cohort (cause of AA amyloidosis, treatments received), report transplantation outcomes, and try to identify factors associated with patient and graft survival.

**Methods****Patients**

To identify all patients with AA amyloidosis who underwent kidney transplantation during the period of interest, we searched the French national transplant database CRISTAL (Agence de la Biomédecine) using the criteria “nephropathy = amyloidosis” and “transplantation period = 07/01/2008-06/30/2018”. We then contacted each transplant center, and medical records of identified cases were reviewed. Inclusion criteria were age of at least 18 years at the time of transplantation, a diagnosis of AA amyloidosis nephropathy, and a kidney transplantation during the period of interest. Renal AA amyloidosis diagnosis was confirmed histologically by a kidney biopsy or by the presence of AA amyloid deposition in another tissue and the coexistence of nephropathy. Exceptions were made for cases of proven FMF with a history of progressive proteinuric kidney disease without another plausible cause. If a patient received more than one transplant during the period of interest, each transplant was included as a separate case.

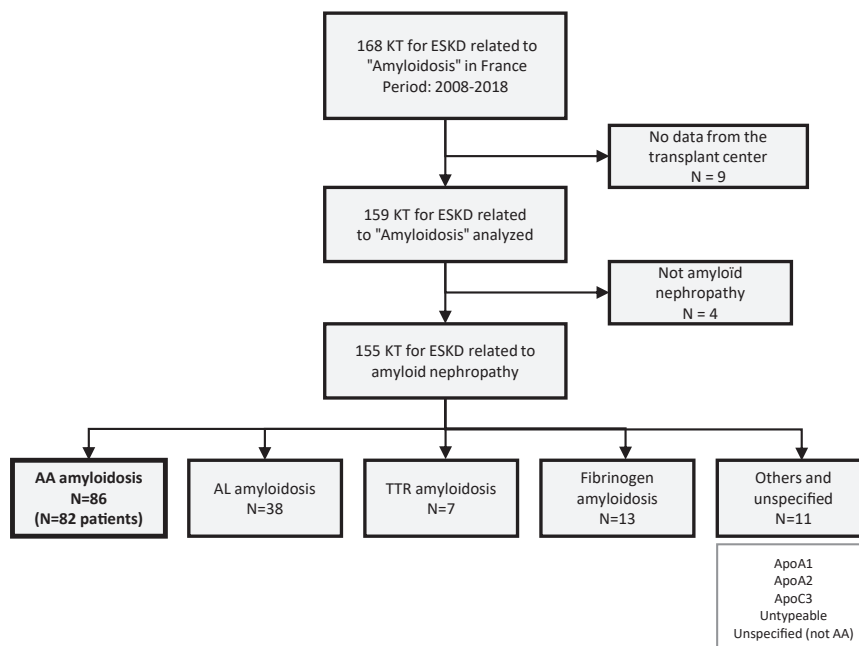
**Data**

Patients' medical files were examined retrospectively, and data were recorded anonymously regarding initial characteristics, characteristics of transplantation, and outcomes after transplantation.

Initial characteristics such as demographic data, C-reactive protein (CRP) level at the time of transplantation, cardiovascular disease and diabetes, cause of AA amyloidosis, etiologic treatments before transplantation, duration of dialysis, and number of prior transplantations were recorded.

Characteristics of transplantation included combined transplant, type and age of the donor, cold ischemia time, immunologic characteristics (presence of anti-human leukocyte antigen antibodies and anti-human leukocyte antigen donor-specific antibodies), and immunosuppressive regimen.

Outcomes after transplantation included all-cause mortality and graft failure at 1 and 5 years; occurrence of a biopsy-proven acute graft rejection, an infection requiring hospitalization, an opportunistic infection (according to the definition by Fishman et al in 2007<sup>21,22</sup>), cancer, or a cardiovascular event (myocardial infarction, acute congestive heart failure, pulmonary embolism, ischemic stroke) during follow-up and the time of occurrence for each event; urinary protein-creatinine ratio (UPCR) and glomerular filtration rate estimated by the MDRD (Modification of Diet in Renal Disease) Study formula at different times (3 months, 1 year, and 5 years after transplantation and at last follow-up); and CRP levels annually during follow-up. Of note, SAA levels were not available for most patients, and CRP was therefore chosen



**Figure 1.** Flow chart presenting the inclusion process of transplants in the study. Data are presented as number of transplants unless otherwise specified. Abbreviations: AL, immunoglobulin light chain; ESKD, end-stage kidney disease; KT, kidney transplant; TTR, transthyretin.

as a surrogate marker because its reliability in the scope of amyloidosis has been established.<sup>23,24</sup> Administration of a biotherapy was also recorded.

Immunoprophylaxis varied according to each center's practice. In regard to pneumocystosis prevention, the general strategy was to prescribe cotrimoxazole for a minimum of 12 months in the absence of adverse effects; the drug was then continued or stopped depending on the physician's preference. There was no uniform protocol among the different centers in regard to cytomegalovirus prophylaxis.

During follow-up, kidney graft biopsies were performed according to each local center's practice. There was no systematic biopsy during follow-up at some centers, whereas others performed protocol biopsies at 3 months after transplantation, at 12 months after transplantation, or both. All biopsy specimens were analyzed locally, and evidence of Congo red stain analysis was recorded. When possible, biopsies were reanalyzed and additional Congo red stain was performed if missing. Recurrence of AA amyloidosis in the graft was defined by positive Congo red staining with apple-green birefringence under polarized light and anti-SAA immunohistochemical staining of amyloid deposits. The duration of follow-up was recorded, and follow-up was continued until July 1, 2020.

### Statistical Analysis

Quantitative data are presented as medians and IQRs. Categorical data are presented as counts and percentages. Survival functions of time-to-event outcomes were estimated using the Kaplan-Meier estimator (for mortality) or the cumulative incidence function method (for graft loss)

and compared using the log-rank test or Gray's test, respectively. Missing data were not imputed, and the proportions of missing data are shown in the tables. Factors associated with patient survival and death-censored graft survival were investigated using a Cox proportional hazards model and a cause-specific hazards model, respectively. Studied factors were selected among initial characteristics for their clinical relevance.

A  $P$  value  $<0.05$  was considered statistically significant. All statistical tests were performed using R software (version 2020; R Foundation for Statistical Computing).

### Ethical Statement

Kidney donation followed the 2008 Declaration of Istanbul principles and the French Agence de la Biomédecine regulations. All patients signed informed written consent for the use of part of the biopsy specimen for scientific purposes. All procedures and the use of tissues were performed in accordance with the principles of the Declaration of Helsinki. According to French regulations (Jardé law), observational studies involving no intervention do not require institutional ethical approval, so none was sought for the present study (General Data Protection Regulation number 2216254; Commission nationale de l'informatique et des libertés).

### Results

A total of 168 kidney transplants in 31 centers met the aforementioned search criteria. After contacting each center, 159 transplants were analyzed, and 86 were identified as cases of AA amyloidosis, accounting for 82

**Table 1.** Patient Characteristics

Characteristic	AA Amyloidosis Transplants (n = 86)	Missing Data
Age at KT, y	49.4 (39.7-61.1)	0
Female sex	32 (37.2%)	0
BMI, kg/m <sup>2</sup>	22.2 (20.0-24.3)	8 (9.3%)
Preexisting diabetes	3 (3.5%)	0
Preexisting hypertension	45 (52.3%)	4 (4.7%)
Geographic origin		4 (4.7%)
Western Europe	25 (29.1%)	
Turkey, Georgia, Armenia	27 (31.4%)	
Northern Africa	30 (34.9%)	
Cause of amyloidosis		0
FMF	37 (43.0%)	
Other genetic autoinflammatory syndrome	6 (7.0%)	
Chronic inflammatory disease	19 (22.1%)	
Chronic infection	11 (12.8%)	
Unknown	13 (15.1%)	
CRP at KT, mg/L	4.4 (2.8-15.2)	18 (20.9%)
Duration of dialysis before KT, mo	39.5 (19.0-63.8)	0
Second or third KT	9 (10.5%)	0
Age of donor, y	53 (39-65)	5 (5.8%)
Living donor	4 (4.7%)	0
Cold ischemia, min	901 (700-1,200)	4 (4.7%)
Anti-HLA antibodies at KT	38 (44.2%)	10 (11.6%)
DSA at KT	10 (11.6%)	4 (4.7%)
Anti-thymocyte induction	41 (47.7%)	3 (3.5%)
Length of follow-up, mo	55.8 (28.3-86.8)	0

Quantitative data are presented as median (IQR) and categorical data as n (%). Abbreviations: BMI, body mass index; CRP, C-reactive protein; DSA, donor-specific antibody; FMF, familial Mediterranean fever; HLA, human leukocyte antigen; KT, kidney transplantation.

patients in 26 centers. Details of all amyloidosis types are shown in a flow chart in [Fig 1](#).

### Patients' Characteristics

Initial characteristics of patients are shown in [Table 1](#). Median age at the time of transplantation was 49.4 (39.7-61.1) years, and median body mass index was 22.2 (20.0-24.3) kg/m<sup>2</sup>. Three patients (3.5%) had preexisting diabetes, and 45 (52.3%) had preexisting hypertension. Histological diagnosis of AA amyloidosis was made by a kidney biopsy in 47 cases (54.7%) and by another tissue biopsy in 31 cases (36.0%); in the remaining 8 cases (9.3%), histological evidence of AA amyloidosis was not found (these were exclusively patients with FMF with no other plausible cause of nephropathy). Causes of amyloidosis were FMF (37 transplants [43.0%]), another autoinflammatory syndrome (6 transplants [7.0%],

including TNF receptor-associated periodic syndrome, hyper-immunoglobulin D syndrome, Schnitzler's syndrome, and cryopyrin-associated periodic syndrome), chronic inflammatory disease (19 transplants [22.1%], including Crohn's disease [n = 9], ankylosing spondylitis [n = 4], rheumatoid arthritis [n = 2], Castleman's disease [n = 2], Rosai-Dorfman disease [n = 1]), and the association of Crohn's disease with ankylosing spondylitis [n = 1]), and chronic infection (11 transplants [12.8%], including mycobacterium tuberculosis infection [n = 5], bronchiectasis [n = 3], cystic fibrosis [n = 1], Hirschsprung's disease with chronic perineal abscesses [n = 1] and chronic sacral pressure ulcer [n = 1]); the cause of AA amyloidosis was unknown for the remaining 13 cases (15.3%).

Before transplantation, 44 patients (51.2%) received colchicine, 13 (15.1%) anti-IL-1 therapy, 3 (3.5%) anti-IL-6 therapy, and 4 (4.7%) anti-TNF- $\alpha$  therapy. After transplantation, 33 patients (38.4%) received colchicine, 12 (14.0%) anti-IL-1 therapy, 1 (1.2%) anti-IL-6 therapy, and 3 (3.5%) anti-TNF- $\alpha$  therapy. A total of 16 patients (18.6%) received biotherapy after transplantation. Median CRP level on the day of transplantation was 4.4 (2.8-15.2) mg/L, and 29 patients (33.7%) had a CRP level >5 mg/L.

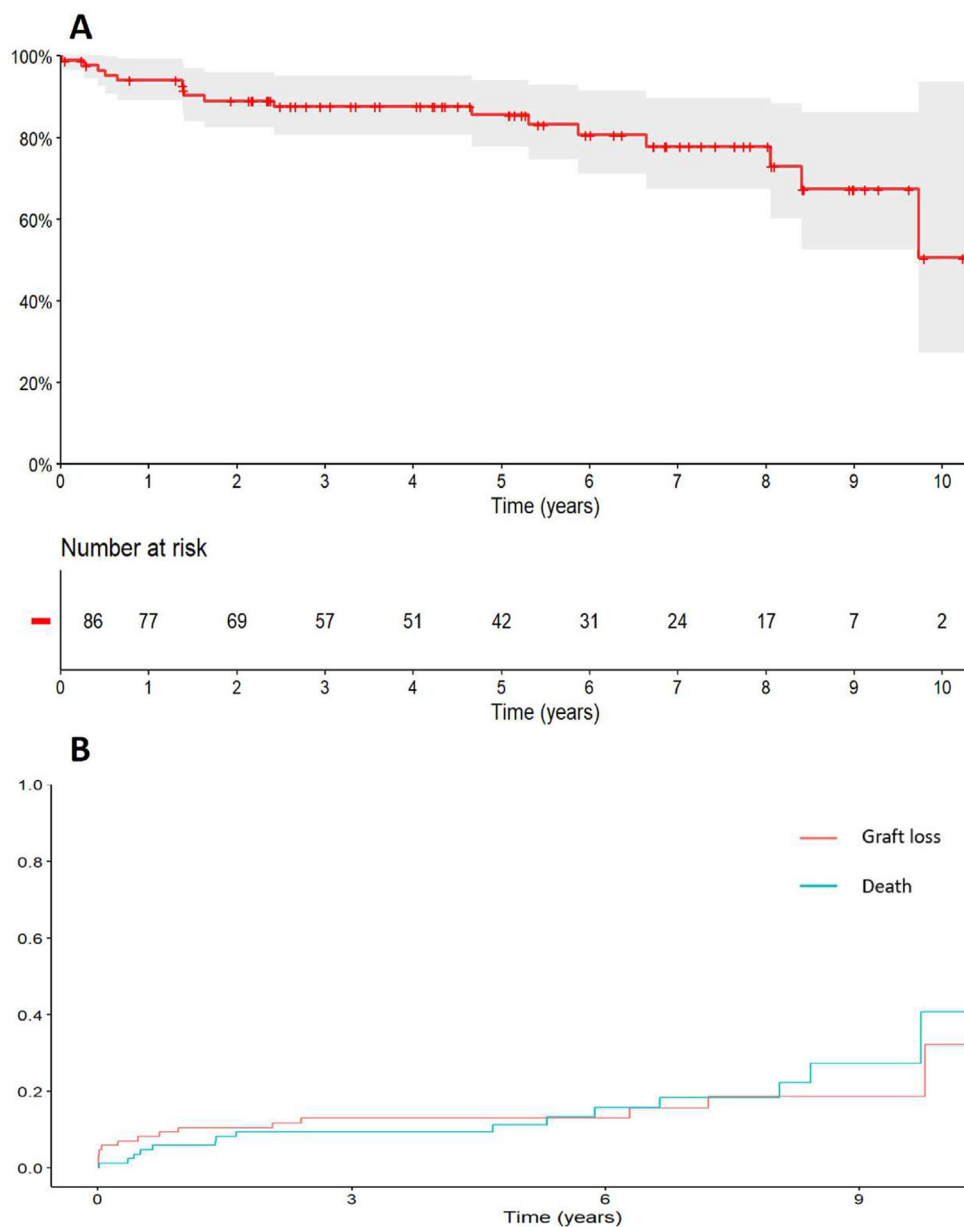
Characteristics of donors and transplants are given in [Table 1](#). Of note, there were 3 combined transplants (liver, heart, and lung, respectively). The presence of anti-human leukocyte antigen antibodies at the time of transplantation was noted in 44.2% of cases, and the presence of donor-specific antibodies was noted in 11.6%. Nine patients (10.5%) had received immunosuppression previously because of a previous transplant. The immunosuppressive regimen consisted of induction by anti-thymocyte globulin in 41 cases (47.7%) and basiliximab in the remaining 45 cases (53.3%); maintenance therapy included at some point during follow-up corticosteroids (all cases), calcineurin inhibitors (all cases; tacrolimus for 74 patients [91.9%] and cyclosporine for 19 [22.1%]), mycophenolate mofetil (83 cases; 96.5%), azathioprine (11 cases; 12.8%), mammalian target of rapamycin inhibitors (9 cases; 10.5%), and belatacept (5 cases; 5.8%). In addition, 8 patients (9.3%) received rituximab as part of induction therapy or as treatment of an acute rejection episode.

Median duration of follow-up was 55.8 (28.3-86.8) months, for a total of 413.1 person-years.

### Overall and Graft Survival

[Figure 2A](#) illustrates patient survival. A total of 17 patients died during follow-up, for survival rates of 94.0% (95% confidence interval [CI], 89.1%-99.2%) at 1 year and 85.5% (95% CI, 77.8%-94.0%) at 5 years after transplantation. Causes of death were infection (9 cases; 52.9%), cardiovascular disease (3 cases; 17.6%), cancer (1 case; 5.9%), and unknown (4 cases; 23.5%).

[Figure 2B](#) shows the cumulative incidence of graft loss and death (analyzed as competing risks) during follow-up. At 1 year, the cumulative incidence of graft loss was 10.5%



**Figure 2.** Kaplan-Meier estimate of patient survival (A) and cumulative incidence of mortality and graft loss (B) in patients with AA amyloidosis. Tables represent patients at risk.

(95% CI, 4.0%-17.0%), and at 5 years, it was 13.0% (95% CI, 5.8%-20.1%). All-cause graft failure rates were 16.3% (95% CI, 4.9%-27.8%) at 1 year and 24.2% (95% CI, 9.9%-38.3%) at 5 years after transplantation.

Among functioning grafts, the median estimated glomerular filtration rates were 55 (41-68) mL/min/1.73 m<sup>2</sup> at 1 year and 45 (33-65) mL/min/1.73 m<sup>2</sup> at 5 years after transplantation.

### Amyloidosis Recurrence

During follow-up, a total of 5 histologically confirmed amyloid disease recurrences occurred in allografts (5.8% of the cohort) after a median time of 23.5 (23.1-33.3)

months. The main features of these recurrences are presented in Table 2. At recurrence, the median glomerular filtration rate was 28 (26-35) mL/min/1.73 m<sup>2</sup> and the median UPCr was 0.6 (0.2-1.6) g/g. The diagnosis was made on a protocol 3-month biopsy for 1 patient and on an indicated biopsy for the other 4 patients. Among these patients, mean CRP level during follow-up was 7.8 (5.2-16.3) mg/L.

In comparison, in the whole AA amyloidosis cohort, the median UPCrs were 0.2 (0.1-0.3) g/g at 1 year and 0.1 (0.0-0.2) g/g at 5 years; 2 patients had proteinuria >1 g/g at 1 year, as did 1 patient at 5 years. During follow-up, in the 62 cases with available data, mean CRP level was 6.8

**Table 2.** Description of AA Amyloidosis Allograft Recurrence Cases

Pt. No./Age at KT, y	Cause of Amyloidosis	Specific Therapy <sup>a</sup>	Mean CRP, mg/L <sup>b</sup>	UPCR, g/g					eGFR at Recurrence, mL/min/1.73 m <sup>2</sup>	Location of Deposits	Outcome
				3 mo	1 y	5 y	At Recurrence	Time Until Recurrence, mo			
1/65	Schnitzler syndrome	Anakinra	2	0.2	0.1	0.1	0.2	41	Capsular	Died with functioning graft after 116 mo <sup>c</sup>	
2/46	Unidentified genetic syndrome	None	7	NA	0.1	0.0	1.6	24	Glomerular and vascular	Lost graft after 86 mo; alive at last follow-up (89 mo)	
3/60	FMF	Colchicine	171	0.8	0.3	NA	2.3	26	Glomerular and vascular	Lost graft after 28 mo; died after 33 mo (multivisceral amyloidosis)	
4/38	Ankylosing spondylitis	Etanercept	6	0.1	0.1	0.1	0.2	35	Interstitial	Alive with functioning graft at last follow-up (101 mo)	
5/60	Unknown	None	21	0.6	0.2	NA	0.6	28	Vascular	Alive with functioning graft at last follow-up (32 mo)	

Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FMF, familial Mediterranean fever; KT, kidney transplantation; NA, not available; UPCR, urine protein-creatinine ratio.  
<sup>a</sup>Any anti-inflammatory treatment relative to the cause of amyloidosis that was received after KT.  
<sup>b</sup>Mean CRP measurement including all annual values until recurrence.  
<sup>c</sup>Ultior graft biopsy did not show amyloid deposits.

(3.0-16.0) mg/L; mean CRP level during follow-up was >5 mg/L in 38 cases.

Of note, a total of 102 kidney graft biopsies were performed in 67 patients during follow-up (37 indicated and 65 per protocol, including 43 performed at 3 months and 22 at 1 year after transplantation). For 57 of these biopsies (55.9%), analysis included Congo red stain. In total, 44 patients had at least one kidney graft biopsy that included Congo red stain analysis during follow-up (51.2% of the whole AA amyloidosis cohort) after a median time of 12.0 (3.0-23.4) months.

**Acute Rejection Episodes and Infectious, Cardiovascular, and Neoplastic Disease Events**

Table 3 summarizes the occurrences of immunologic, infectious, cancer, and cardiovascular events during follow-up. Twenty-four patients (27.9%) had at least one episode of acute graft rejection (12 cellular, 7 antibody-mediated, and 5 mixed) after a median of 4.0 (IQR, 0.9-8.1) months. An infectious episode requiring hospitalization was recorded for 48 patients (55.8%) after a median of 4.8 (IQR, 0.7-20.0) months; the most frequent infections were pyelonephritis (23 cases), pneumonia (14 cases), and intestinal infection (5 cases). Thirteen patients (15.1%) presented with an opportunistic infection: fungal infection, pneumocystis pneumonia, cytomegalovirus disease, varicella, and tuberculosis (n = 7, 2, 2, 1, and 1, respectively). Twenty-two patients (25.8%) experienced an acute cardiovascular event, and 6 (7.0%) were diagnosed with cancer.

The use of biotherapy after transplantation was not associated with the occurrence of an acute rejection episode (4 acute rejection episodes in the 16 patients treated with biotherapy vs 20 in the other 70 patients; P = 0.9, log-rank test) or the occurrence of infection requiring hospitalization (9 occurrences in the 16 patients treated with biotherapy vs 39 in the other 70 patients; P = 0.8, log-rank test).

**Factors Associated With Patient Survival**

As shown in Fig 3A, there was no significant difference in patient survival according to cause of AA amyloidosis (FMF, other genetic autoinflammatory syndrome, chronic autoinflammatory disease, chronic infection, unknown cause; P = 0.08, log-rank test). Similarly, patient survival was comparable between patients with AA amyloidosis secondary to autoinflammatory diseases (FMF, other autoinflammatory syndromes, and inflammatory diseases) and patients with AA amyloidosis secondary to other causes (infection and unknown origin; P = 0.6, log-rank test; Fig 3B).

Univariable and multivariable analyses using a Cox proportional hazards model were performed to test the associations of different variables with patient survival (Table 4). In the univariable analysis, age at transplantation (hazard ratio [HR], 1.06; 95% CI, 1.02-1.11; P = 0.002), preexisting diabetes (HR, 5.09; 95% CI, 1.44-18.00;

**Table 3.** Immunologic, Infectious, and Neoplastic Disease and Cardiovascular Events During Follow-up in the AA Amyloidosis Group

Event	n (%) <sup>a</sup>	Time, mo (IQR) <sup>b</sup>
Cellular acute graft rejection	17 (19.8%)	4.7 (1.0-6.3)
Antibody-mediated acute graft rejection	12 (14.0%)	6.6 (2.1-24.5)
Acute graft rejection (cellular or antibody-mediated)	24 (27.9%)	4.0 (0.9-8.1)
Infection requiring hospitalization	48 (55.8%)	4.8 (0.7-20.0)
Opportunistic infection	13 (15.1%)	22.3 (5.2-27.5)
Cardiovascular event	22 (25.8%)	36.2 (15.6-59.8)
Cancer	6 (7.0%)	36.1 (26.4-53.9)

<sup>a</sup>Number of transplants that presented at least one episode.

<sup>b</sup>Median time to onset of the first episode.

$P = 0.01$ ), and CRP level at transplantation (HR, 1.01; 95% CI, 1.00-1.02;  $P = 0.02$ ) were associated with patient survival. In the multivariable model, age at transplantation (HR, 1.10; 95% CI, 1.03-1.18;  $P = 0.007$ ), preexisting diabetes (HR, 10.62; 95% CI, 1.94-58.05;  $P = 0.006$ ), and CRP level at transplantation (HR, 1.01; 95% CI, 1.00-1.02;  $P = 0.01$ ) remained statistically associated with patient survival.

### Factors Associated With Graft Survival

Cause of AA amyloidosis (FMF, other autoinflammatory syndrome, chronic autoinflammatory disease, chronic infection, unknown cause) was not associated with graft survival ( $P = 0.9$ , Gray's test). Graft survival was similar between patients with AA amyloidosis secondary to autoinflammatory diseases (FMF, other genetic syndromes, and inflammatory diseases) and those with AA amyloidosis secondary to other causes (infection and unknown origin;  $P = 0.6$ , Gray's test).

Univariate and multivariate analysis using a cause-specific hazard model were performed to test the associations of different variables with graft survival (Table 5). In the univariate analysis, only the presence of donor-specific antibodies at the time of transplantation was statistically associated with graft survival (HR, 4.57; 95% CI, 1.13-18.40;  $P = 0.03$ ). In the multivariate model, donor-specific antibodies at the time of transplantation (HR, 9.59; 95% CI, 2.28-40.35;  $P = 0.002$ ), CRP level at the time of transplantation (HR, 1.68; 95% CI, 1.10-2.57;  $P = 0.02$ ), and cold ischemia time (HR, 0.99; 95% CI, 0.99-1.00;  $P = 0.04$ ) were statistically associated with graft survival.

### Discussion

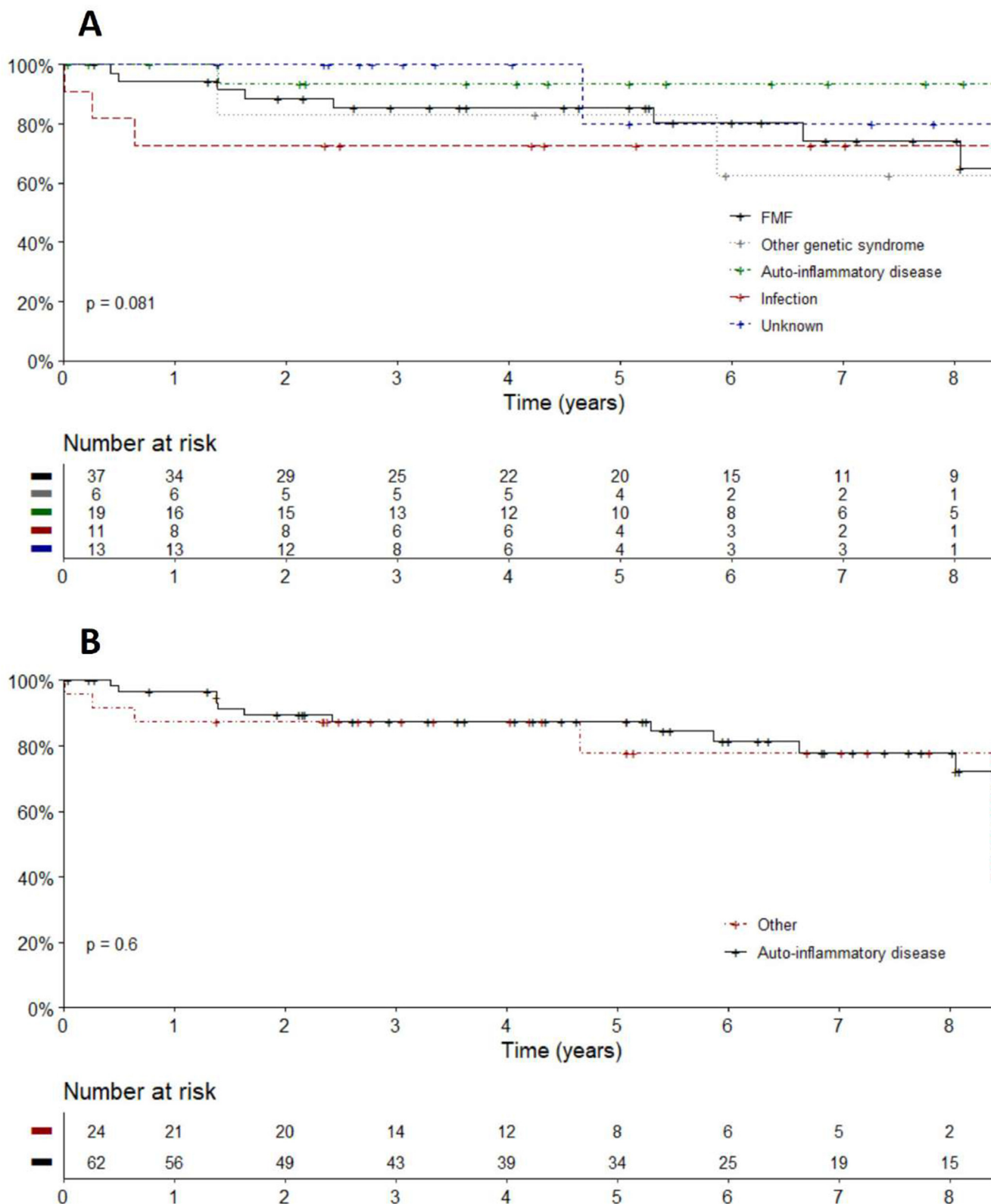
To our knowledge, the present study is the largest cohort to report outcomes of kidney transplantation in patients with renal AA amyloidosis. Our main findings are high overall and graft survival rates and a low amyloidosis

recurrence rate, suggesting that patients with AA amyloidosis can benefit from kidney transplantation with favorable outcomes.

As a mean of comparison in the absence of a control group for our cohort, data for 34,776 patients from the French transplantation database (Agence de la Bio-médecine, rapport Rein 2018<sup>25</sup>) between 2007 and 2017 demonstrate a patient survival rate of 88.4% at 5 years (95% CI, 88.0-89.0) and an all-cause graft survival rate of 78.6% (95% CI, 78.1-79.1). During almost the same time period, in our cohort, the patient survival rate was slightly lower but comparable (85.5% [95% CI, 77.8%-94.0%] at 5 years). The overall graft survival rate in our cohort was 75.8% (95% CI, 61.8%-90.1%) at 5 years, which is also similar to national data. Interestingly, Kofman et al previously reported a 5-year patient survival rate of 82.5%<sup>8</sup> for patients who received transplants between 1981 and 2009 that is similar to the findings in our study, which is somewhat surprising given the improvements in post-transplantation global care. This probably reflects that the overall survival of kidney transplant recipients did not improve during this time period in France (the 5-year survival rate of patients who received transplants between 1996 and 2000 was 92.4%, vs 87.8% between 2012 and 2014), an outcome we attribute to kidney recipients being older and having more comorbidities in recent years than in earlier eras. Indeed, in the study by Kofman et al, the mean age at transplantation was 44.1 years, compared with a median of 49.4 years in the present study.

In contrast, most previously published series of kidney transplant recipients with AA amyloidosis reported poorer patient survival compared with controls: the historic series of Pasternack et al reported a patient survival rate of approximately 50% at 3 years (vs 79% in controls with glomerulonephritis,  $n = 45$ ).<sup>9</sup> Similarly, Kofman et al reported a 5-year survival rate of 82.5%, versus 94.2% for the matched control group ( $P = 0.028$ ).<sup>8</sup> A Turkish study focusing exclusively on AA amyloidosis secondary to FMF that included 81 kidney transplant recipients also found lower survival rates compared with controls without amyloidosis (92.5% vs 100% at 5 years;  $P = 0.02$ ).<sup>14</sup> Finally, Law et al recently reported a survival rate of AA amyloidosis kidney transplant recipients ( $N = 48$ ) of 84% at 5 years, which was comparable to that in controls with diabetic nephropathy but lower than that in controls with autosomal-dominant polycystic kidney disease.<sup>15</sup> The 5-year patient survival rate of 85.5% in our cohort is comparable to, or even a bit better than, outcomes in most of the series cited here. However, it should be noted that the data from these earlier studies are heterogenous, and, in particular, transplant periods span a very long time, with all studies including transplants from before 1990. Our hypothesis that better pre- and posttransplant control of the disease that causes AA amyloidosis in the more recent era would lead to a higher survival could not be verified, even though there might be a trend toward better results. In terms of potential consequences of the hypotension that





**Figure 3.** Kaplan-Meier estimates of patient survival in patients with AA amyloidosis according to the cause of amyloidosis. (A) Patients are separated into 5 main causes of AA amyloidosis. (B) The autoinflammatory disease group includes genetic autoinflammatory syndromes and chronic inflammatory diseases. Tables represent patients at risk in each group. Statistical difference was assessed with the log-rank test. Abbreviation: FMF, familial Mediterranean fever.

**Table 4.** Association of Different Factors With Patient Survival in AA Amyloidosis KT Recipients

Factor	Alive (n = 69)	Dead (n = 17)	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P	HR (95% CI)	P
Age at KT, y	47.2 (37.9-58.8)	61.3 (56.2-65.6)	1.06 (1.02-1.11)	0.002	1.10 (1.03-1.18)	0.007
Duration of dialysis before KT, mo	39 (20-62)	40 (18-77)	1.01 (0.99-1.02)	0.2	1.01 (0.99-1.02)	0.3
Preexisting diabetes	0	3 (17.6%)	5.09 (1.44-18.00)	0.01	10.62 (1.94-58.05)	0.006
CRP at KT, mg/L	4.5 (2.7-13.3)	4.3 (3.1-21.5)	1.01 (1.00-1.02)	0.02	1.01 (1.00-1.02)	0.01

Each factor was analyzed individually (univariate analysis) before performing a multivariate analysis (Cox model). Abbreviations: CRP, C-reactive protein; KT, kidney transplantation.

is classically associated with amyloidosis, 5.8% of the present cohort experienced primary nonfunction and 27.9% had delayed graft function. Even if these rates are higher than usually observed, the association with AA amyloidosis is uncertain because we do not have a record of measured blood pressure during follow-up.

Another important finding of our study is the low rate of AA amyloidosis recurrence in the graft compared with other studies: we found an incidence of 5.8%, whereas most other studies reported rates ranging from 8%<sup>9,26</sup> to 26%.<sup>14</sup> In the largest series, the rates were 14%,<sup>8</sup> 19%,<sup>13,15</sup> and 26%.<sup>14</sup> Again, we hypothesize that our low recurrence rate is a result of a more recent transplantation period, in the era of biotherapies, enabling better control of the underlying inflammatory disease. However, these different recurrence rates may be explained by differing attitudes toward histological monitoring during follow-up. Unfortunately, none of the cited studies detail the number of biopsies performed during follow-up. In the present study, a high number of biopsies was performed (65 protocol biopsies), but the diagnosis of subclinical amyloidosis recurrence may have been underestimated, as only 44 patients (51.2%) underwent at least one kidney biopsy with Congo red stain analysis. However, very few patients had proteinuria during follow-up (only 2 patients had a UPCR >1 g/g at 1 year after transplantation, along with 1 at 5 years), which suggests that clinically significant recurrences were not underdiagnosed. Because of this low recurrence rate, the present study lacked the statistical power to explore an association between amyloidosis recurrence and patient or graft survival and to identify factors associated with disease recurrence.

In contrast, we observed a high occurrence of acute graft rejection episodes in the cohort: 27.9% of patients with AA amyloidosis experienced at least one cellular or

antibody-mediated acute rejection episode during follow-up. Our hypothesis is that the concern for infection in these potentially susceptible patients led to lower dosing of immunosuppressive agents.

Another important finding of the present study was the association of CRP concentration with survival outcomes. Indeed, a high CRP concentration at the time of transplantation was linked to poorer patient and graft survival rates on multivariate analysis. To our knowledge, ours is the first study to report such an association. Indeed, Pinney et al showed an association between median SAA concentration during follow-up and the recurrence of amyloid on the graft.<sup>13</sup> Similarly, Sarihan et al showed higher CRP levels during follow-up in patients with amyloid recurrence.<sup>14</sup> However, none of the large series reported a significant association of SAA or CRP levels with patient or graft survival.<sup>8,13-15</sup> This association with patient and graft survival again highlights the importance of controlling the underlying inflammatory disease before transplantation. In general, we believe careful selection before transplantation is particularly important for patients with AA amyloidosis; it should include a screening of other organs' involvement and consider the underlying disease activity.

Biotherapies are a focus of interest for this purpose. In the present study, only 18.6% of the amyloidosis cohort received biotherapy after transplantation (anti-IL-1, anti-IL-6, or anti-TNF- $\alpha$ ). The recent series by Law et al is the only other study of AA amyloidosis kidney transplant recipients to include patients receiving biotherapies: 33.3% of their cohort (n = 16) received such treatments after transplantation.<sup>15</sup> Other small series have illustrated that anti-IL-1 therapies can be used safely in the transplantation setting.<sup>27-31</sup> A recent review of cases reported 37 kidney transplant recipients undergoing anti-IL-1

**Table 5.** Association of Different Factors With Graft Survival in AA Amyloidosis KT Recipients

Factor	Functioning Graft (n = 71)	Graft Loss (n = 15)	Univariate Analysis		Multivariate Analysis	
			HR (95% CI)	P	HR (95% CI)	P
Age of donor, y	53 (38-65)	52 (44-63)	1 (0.97-1.04)	0.9	1.02 (0.98-1.05)	0.4
Cold ischemia, min	911 (735-1,263)	810 (579-995)	0.99 (0.99-1.00)	0.1	0.99 (0.99-1.00)	0.04
DSA at KT	7 (9.9%)	3 (20.0%)	4.57 (1.13-18.40)	0.03	9.59 (2.28-40.35)	0.002
CRP at KT, mg/L	4.2 (2.6-12.2)	12.8 (3.0-45.5)	1.47 (0.98-2.18)	0.06	1.68 (1.10-2.57)	0.02

Each factor was analyzed individually before performing a multivariate analysis (cause-specific hazards model). Data are presented as n (%) or median (IQR) in each group. The HR is presented with its 95% CI and corresponding P value. Abbreviations: CI, confidence interval; CRP, C-reactive protein; DSA, donor-specific antibodies; HR, hazard ratio; KT, kidney transplantation.

therapy and 22 undergoing anti-TNF- $\alpha$  therapy, with low infection and rejection rates<sup>32</sup> suggesting that biotherapies are safe to use in this setting. The retrospective nature of our study and relatively infrequent use of biotherapies limits the ability to analyze the effect of these treatments on kidney transplant outcomes. More studies are needed to investigate these aspects.

In conclusion, the present study found that AA amyloidosis kidney transplant recipients experienced favorable survival outcomes and lower recurrence rates than previously reported. These data support the practice of treating these patients with kidney transplantation for end-stage kidney disease.

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