3e CONGRÈS FRANCOPHONE MULTIDISCIPLINAIRE DE L'AMYLOSE

Progrès réalisés et à venir !

Jeudi 13 juin 2024

Fondation Biermans-Lapôtre ■PARIS

Quoi de neuf sur le rein à l'ISA ?

Dr Camille COHEN

MD-PhD Service de Néphrologie - Hôpital Bichat - Paris

Centre de recherche sur l'inflammation (CRI) - INSERM U1149

Team leader "maladie rénale et immunoglobulines monoclonales"

Hôpital Bichat Claude-Bernard AP-HP

Inserm

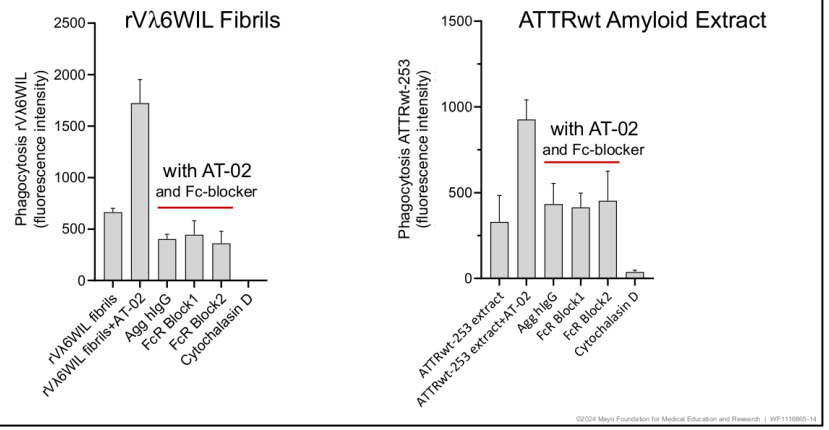
Institut national de la santé et de la recherche médica

CRI CENTRE de RECHERCHE sur l'INFLAMMATION

IKMG

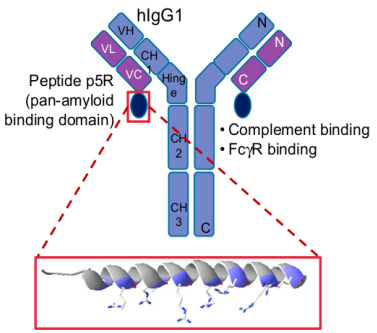
BASIC SCIENCE

AT-02-INDUCED PHAGOCYTOSIS OF pHrodoRED-AMYLOID IS FcR-DEPENDENT



CHARACTERIZATION OF THE PEPTIDE-ANTIBODY FUSION AT-02

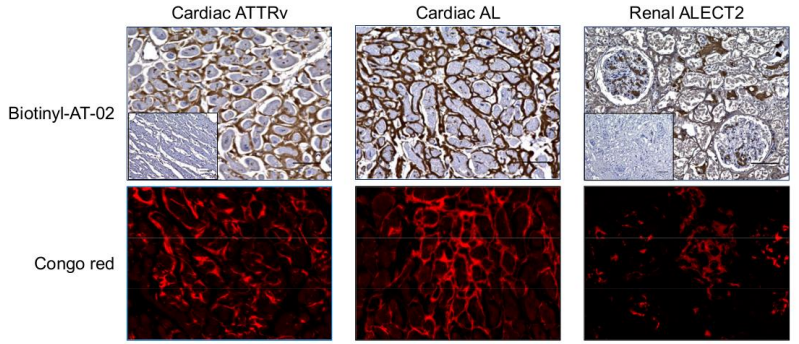
STUDIES TO SUPPORT ITS USE AS AN IMMUNOTHERAPY IN PATIENTS WITH AMYLOIDOSIS



- AT-02 is a humanized IgG1-peptide fusion reagent.
- The pan-amyloid reactive peptide p5R is fused to the C-terminal of the light chain.
- Peptide p5R binds fibrils and hypersulfated glycosaminoglycans via electrostatic interactions.
  - Same peptide technology as the ^{124}I-AT-01 and ^{99m}Tc-AT-05 imaging agents which has shown to bind in key organs in patients with many types of amyloid.
- AT-02 was designed to be capable of:
  1. Targeting amyloid deposits *in vivo*.
  2. Binding to many types of amyloid.
  3. Opsonizing the deposits and promoting macrophage-mediated phagocytosis.

Johnathan Wall

AT-02 SPECIFICALLY BINDS AMYLOID IN TISSUE SECTIONS



SINGLE-CELL, SPATIAL ANALYSIS OF THE RENAL AL IMMUNOME SUPPORTS A T CELL-MEDIATED TISSUE TOXICITY MECHANISM

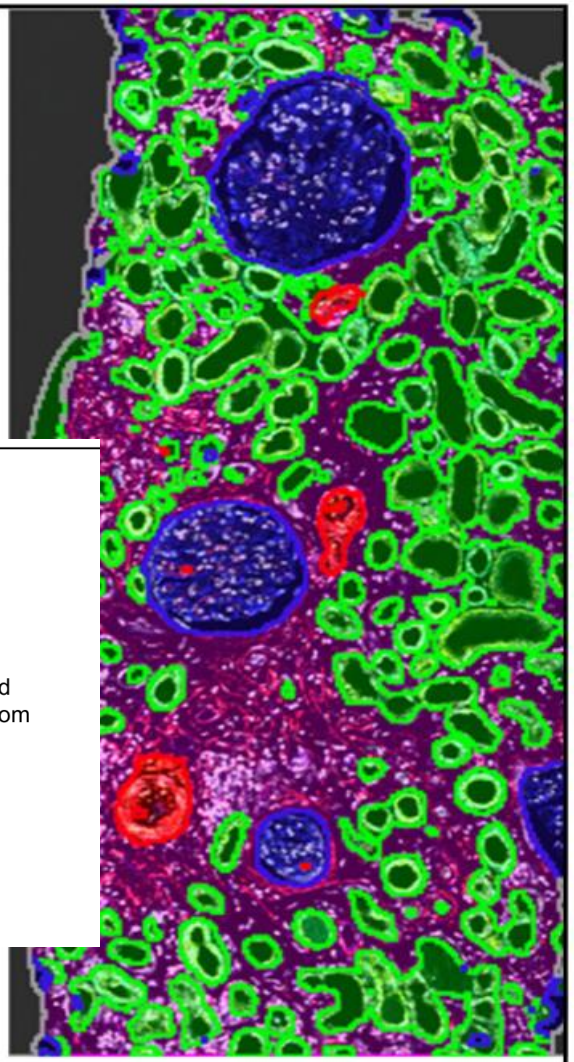
CHARIS CHARALAMPOUS

Resident physician, Internal Medicine,

Georgetown University Hospital

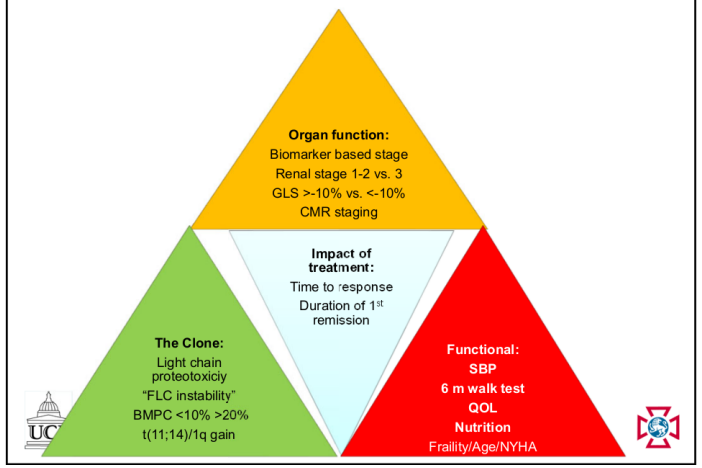
KEY POINTS

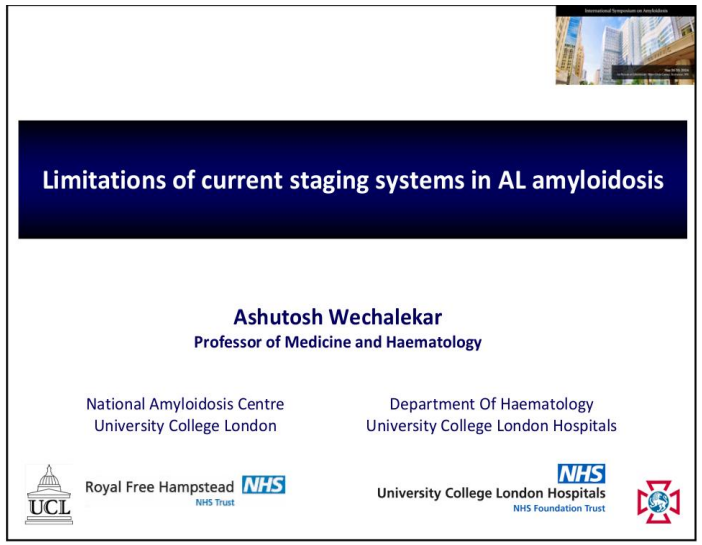
- T-cells were increased in AL vs. controls and in higher renal stages
- B-cells were lower in amyloid cases, which could be a surrogate of immunoparesis noted in plasma cell dyscrasias or a reflection of the increase in T cell percentage
- In AL, T cells were closer to glomeruli compared to (normal) controls and further away from blood vessels, which suggests active extravasation from blood vessels and chemotaxis to glomeruli
- Limitations: not whole-slide approach, small dataset



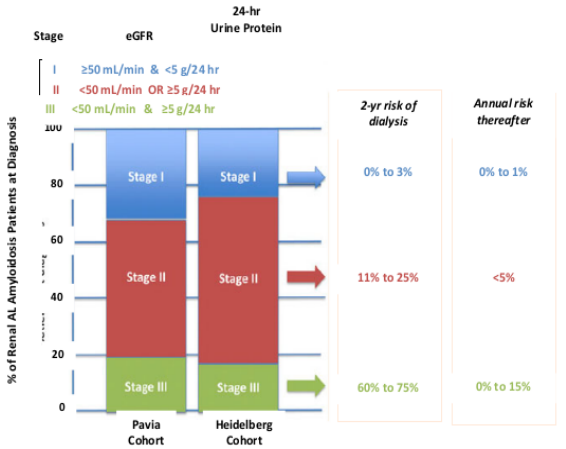
Diagnostic
Traitement de l'AL

The wider view of factors impacting outcomes





Renal stage : important but often forgotten/ignored



Variable		HR (95% CI)	P
CKD stage	2	1	<.001
	3	2.06 (1.22-3.49)	
	4	7.07 (4.01-12.47)	
24 hr urine protein (g/24h)	<3	1.34 (0.23-1.14)	.05
	3-10	1	
	>10	1.48 (0.92-2.38)	
Serum albumin (g/L)	<20	3.04 (1.57-5.88)	.003
	>30	1	

Dispenzieri. Blood. 2014;124:2315.
Palladini et al Blood. 2014 Oct 9;124(15):2325-32.
Pinney et al J Clin Oncol 2011;29:674.

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A PHASE II STUDY OF DARATUMUMAB AND POMALIDOMIDE IN PREVIOUSLY TREATED PATIENTS WITH AL AMYLOIDOSIS

Paolo Milani[1,2], Ombretta Annibali[3], Marco Basset, Martina Ciardo, Martina Nanci, Mario Nuvolone[1,2], Roberta Mussinelli[1], Claudia Bellofiore[2], Valeria Tomarchio[3], Pietro Benvenuti[1], Giuseppe Sanna[2], Andrea Foli[2], Giampaolo Merlini[1,2], Giovanni Palladini[1,2]

1. Department of Molecular Medicine, University of Pavia, Pavia, Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

2. Fondazione Policlinico Campus Biomedico di Roma, Roma

METHODS

This study will be a multicenter (University of Pavia, Pavia – Campus Biomedico, Roma), open label, single-arm, phase II study on previously treated patients with AL amyloidosis.

Key inclusion criteria:

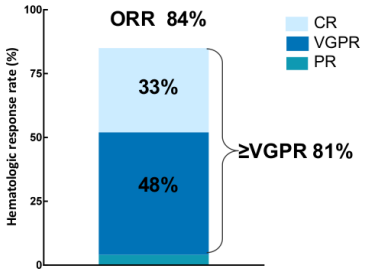
- Histologic diagnosis of AL amyloidosis;
- **At least one line (and no more than 3 lines)** with an alkylating agent and/or a PIn and dexamethasone and not be in VGPR or CR at the time of inclusion (patients who did not reach VGPR or patients in VGPR or better but with an hematological relapse can be included);
- **dFLC > 20 mg/L with an abnormal κ/λ ratio;**
- Symptomatic organ involvement (heart, kidney, liver/GI tract, PNS);

Key exclusion criteria:

- Bone marrow plasma cells >30% and clinically symptomatic multiple myeloma with lytic bone lesions;
- **NT-proBNP > 8500 ng/L and hs-troponin I >100 ng/L (cardiac stage IIIb patients);**
- Repetitive ventricular arrhythmias on 24h Holter ECG despite anti-arrhythmic treatment, except if a pacemaker has been implanted;
- Chronic atrial fibrillation with uncontrolled heart rate

RESULTS

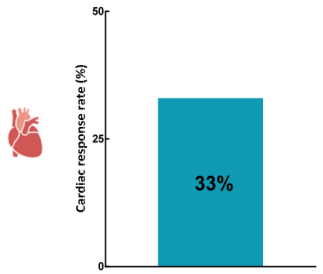
Hematologic response was reached at day 8 in 20/27 (74%) cases.

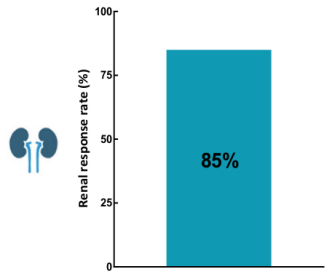


Minimal residual disease by next generation flow cytometry (sensitivity **10^{-6}**) was negative in 3/9 evaluated patients in CR.

RESULTS

Cardiac and renal responses evaluated at cycle 6





MAYO CLINIC

UNMET NEEDS IN THE TREATMENT OF AL AMYLOIDOSIS

EFSTATHIOS KASTRITIS

AMYLOIDOSIS REFERRAL CENTER, PLASMA CELL DYSCRASIA UNIT, DEPARTMENT OF CLINICAL THERAPEUTICS, NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS GREECE

END-STAGE RENAL DISEASE IN PATIENTS WITH AL

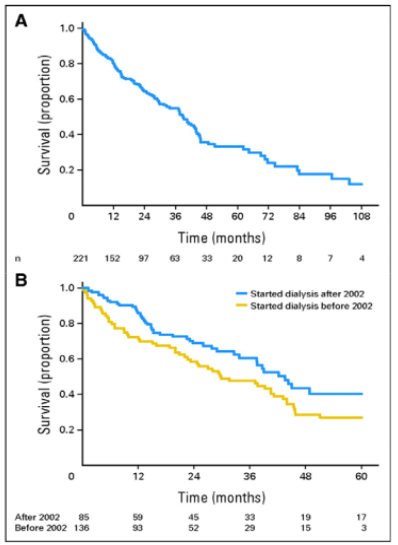
Progression to ESRD requiring dialysis has devastating effects on patients quality of life but…

- What is the course of the disease after starting dialysis?
- How are these patients treated after starting dialysis?
- How are they followed and how are they respondig tio treatment ?
- What tools do we have to follow and evaluate the disease?
- Have the new therapies helped patients with ESRD?

OA16 (#501) Outcomes of Patients with AL Amyloidosis and End-stage Renal Disease After Initiation of Therapy
F. Theodorakakou

WHAT IS THE COURSE OF THE DISEASE AFTER ESRD?

- UK study included patients with renal AL between 1987 and 2008 (NAC)
- 221 patients started dialysis but 127 only after their first visit to NAC
- Median survival time from start of dialysis was 39 months
- Patients who started dialysis after 2002 survived longer than did patients starting dialysis before 2002 (43.6 v 29.8 months, P = 0.05)



Pinney J et al J Clin Oncol 2010

MAYO CLINIC

OUTCOMES OF PATIENTS WITH AL AMYLOIDOSIS AND END-STAGE RENAL DISEASE AFTER INITIATION OF TREATMENT

FOTEINI THEODORAKAKOU[1], LILLI S. SESTER[2], UTE HEGENBART[2], PAOLO MILANI[3], CLAUDIA BELLOFIORE[3], ERASMIA PSIMENOU[1], CHARIKLEIA GAKIOPOULOU[4], MELETIOS A. DIMOPOULOS[1], GIOVANNI PALLADINI[3], STEFAN O. SCHÖNLAND[2], EFSTATHIOS KASTRITIS[1]

[1]DEPARTMENT OF CLINICAL THERAPEUTICS, NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, ATHENS, GREECE; [2]DEPARTMENT OF INTERNAL MEDICINE V-HEMATOLOGY, ONCOLOGY AND RHEUMATOLOGY, UNIVERSITY OF HEIDELBERG, HEIDELBERG, GERMANY; [3]AMYLOIDOSIS RESEARCH AND TREATMENT CENTER, DEPARTMENT OF MOLECULAR MEDICINE, UNIVERSITY OF PAVIA, AND FONDAZIONE IRCCS POLICLINICO SAN MATTEO, PAVIA, ITALY; [4]FIRST DEPARTMENT OF PATHOLOGY, NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, ATHENS, GREECE.

PATIENTS AND METHODS

- The analysis included ***355 patients*** with AL amyloidosis and with renal involvement or patients without confirmed renal involvement during diagnosis, which *started dialysis after at least one month from primary treatment initiation*.
- The patients were treated in three European centers, Athens (n=76), Heidelberg (n=184) and Pavia (n=95).
- Median follow up of the whole cohort was 62 months.

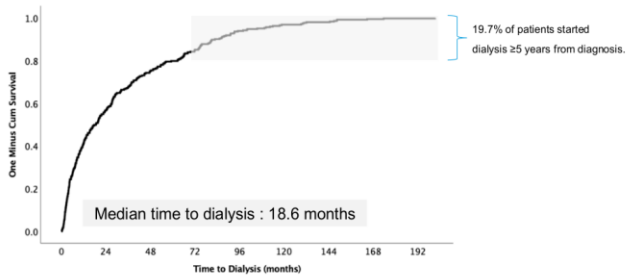
BASELINE CHARACTERISTICS *AT THE TIME OF INITIAL DIAGNOSIS*

Characteristics	N=355
Age, years (median)	63
Male / female	58% / 42%
Diagnosed after 2018	43.7%
Organ involvement	
Cardiac	57%
Renal	92%
Liver	18%
Soft tissue	16%
PNS	19%
Only renal involvement	25% (n=88)
Mayo stage 1 / 2 / 3A / 3B	25% / 48% / 12% / 15%
Renal stage 1 / 2 / 3	9% / 51% / 40%

Characteristics	N=355
eGFR, ml/min/1.73 m^2 (median/range)	39 (1.02-149.8)
Proteinuria, mg/24h (median/range)	7490 (140-36120)
Serum albumin, g/dl (median/range)	3 (0.5-5.5)
Bone marrow infiltration,%	10 (10-90)
κ / λ light chain type	24% / 76%
iFLC, mg/L (median/range)	134.6 (5.9-6224.4)
dFLC, mg/L (median/range)	111.9 (1.0-6213.7)

RESULTS: *AT THE TIME OF DIALYSIS INITIATION*

- Median time to dialysis was 18.6 months.
- 70 (19.7%) patients started dialysis ≥5 years from diagnosis.



RESULTS: HEMATOLOGIC RESPONSE STATUS *AT THE TIME OF DIALYSIS INITIATION*

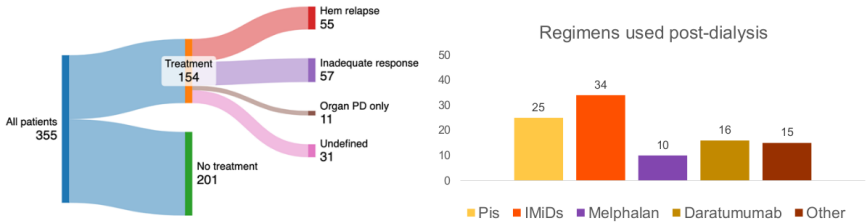
		N=355
Hematologic response status		
	hemCR/VGPR	27%
	hemPR	17%
	No hem response	28%
	Hem relapse	27%
iFLC, mg/L (median)		102.5
dFLC, mg/L (median)		55.7
Normal FLC ratio (0.26-1.65)		22.3%
Normal FLC ratio adjusted for ESRD (0.37-3.1)		23.4%

RESULTS: DIALYSIS

- 300/355 (84.5%) patients underwent hemodialysis.
- 55/355 (15.5%) patients underwent peritoneal dialysis.
- ***Only 9 (2.5%) patients underwent renal transplantation.***
- ***In 33 (9.3%) patients dialysis was discontinued.***

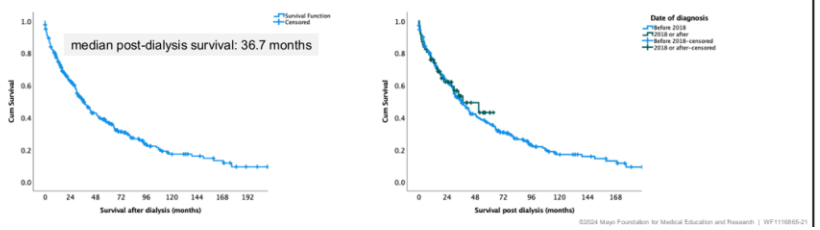
RESULTS: TREATMENT *AFTER DIALYSIS INITIATION*

- After starting dialysis, 154 (43%) patients received further therapy, due to: hematologic relapse in 55 (36%), inadequate response in 57(37%), organ progression only in 11 (7%).
- Regimens used post-dialysis were PI-based in 25%, IMiDs-based in 34%, melphalan-based in 10%, daratumumab-based in 16% and other regimens in 15%.



RESULTS: OUTCOMES *AFTER DIALYSIS INITIATION*

- Median overall survival from the start of primary therapy was 81.1 months and median post-dialysis survival was 36.7 months.
- Post-dialysis survival has not significantly improved in the more recent era.



RESULTS: MULTIVARIATE ANALYSIS (OS)

	p-value	HR ratio	95% CI
Heart involvement	**0.003**	2.375	1.335-4.051
BMPC at diagnosis	**0.005**	1.950	1.220-3.119
Light chain type	0.053	1.719	0.993-2.974
dFLC≥50mg/L at dialysis	**0.001**	2.201	1.354-3.579

RESULTS: CAUSES OF DEATH

- 240 (67.6%) patients have died
- Causes of death included
  - disease progression in 90 (37.5%) patients,
  - sepsis in 19 (8%),
  - cardiac-related in 26(11%),
  - renal failure in 4(2%) and
  - other/unknown in 104 (43%).

Il n'y a pas que l'AL dans la vie

BEYOND AL AND ATTR: CLINICAL FEATURES OF "OTHER" TYPES OF SYSTEMIC AMYLOIDOSIS

LAURA OBICI, MD

Consultant, Amyloidosis Research and Treatment Centre

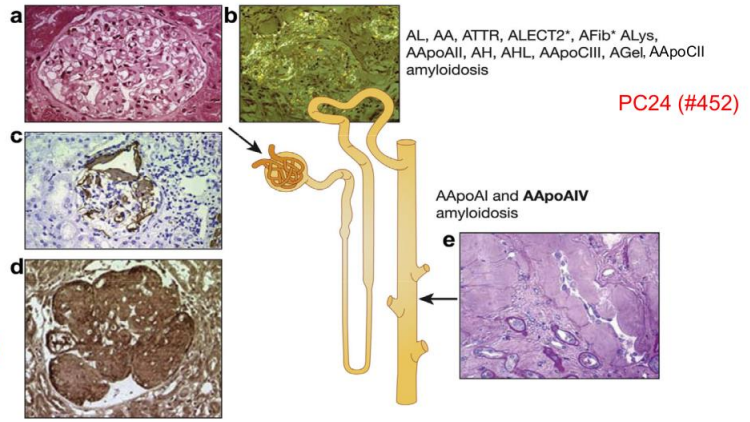
Leader, Rare Diseases Unit

IRCCS Fondazione Policlinico San Matteo

Pavia, Italy

Fondazione IRCCS Policlinico San Matteo

THE KIDNEY IS THE MAJOR TARGET ORGAN IN SEVERAL RARE FORMS OF SYSTEMIC AMYLOIDOSIS



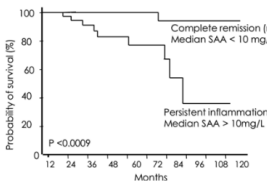
PC24 (#452)

PC14 (#153)

Obici et al. Kidney Int 2016

AA AMYLOIDOSIS

REDUCTION OF THE SAA PRECURSOR RESULTS IN IMPROVEMENT OF ORGAN DYSFUNCTION AND EXTENDED SURVIVAL



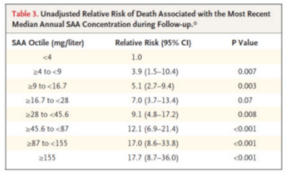
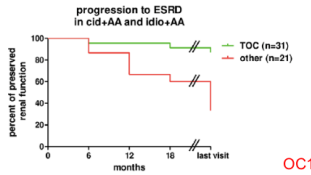


Table 3. Unadjusted Relative Risk of Death Associated with the Most Recent Median Annual SAA Concentration during Follow-up.*

SAA Octile (mg/liter)	Relative Risk (95% CI)	P Value
<4	1.0	
≥4 to <9	3.9 (1.5–10.4)	0.007
≥9 to <16.7	5.1 (2.7–9.4)	0.003
≥16.7 to <28	7.0 (3.7–13.4)	0.07
≥28 to <45.6	9.1 (4.8–17.2)	0.008
≥45.6 to <87	12.1 (6.9–21.4)	<0.001
≥87 to <155	17.0 (8.6–33.8)	<0.001
≥155	17.7 (8.7–36.0)	<0.001

OC14 Biomarker-based renal response and progression criteria in AA amyloidosis



p = 0.0006 log-rank test

Original Investigation AJKD

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

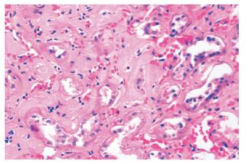
85.5% survival at 5 years
87% graft survival at 5 years
5.8% recurrence rate

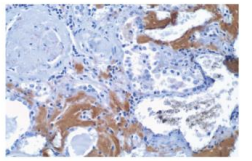
OC12 Antisense oligonucleotide therapy for familial AA amyloidosis. A N of 1 trial

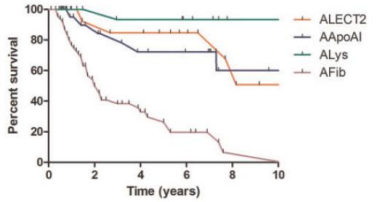
Gillmore et al. Lancet 2001; Lachmann et al. NEJM 2007 Kyvaskay et al. Annn Rheum Dis 2024; Schwarz et al. AJKD 2024

LEUKOCYTE CHEMOTACTIC FACTOR 2 AMYLOIDOSIS (ALECT2)

- Third most common type of renal amyloidosis
- Highly prevalent in ethnically based non-Caucasian populations
- Non hereditary, individual homozygous for the common I40V allele
- Kidney cortex interstitium and peritubular capillaries
- Liver, adrenal, spleen deposition
- Low-level proteinuria
- Reduced eGFR
- Frequently asymptomatic







PC86 (#320) and PC87 (#386)

Benson et al. Kidney Int 2008; Said et al. Kidney Int 2014; Larsen et al. Amyloid 2016; de la Cruz Jasso Am J Clin Pathol 2023; Rezk et al. Nephrol Dial Transplant 2018; Ha et al. JBC 2024.

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ISA
INTERNATIONAL SOCIETY OF AMYLOIDOSIS

ANTISENSE OLIGONUCLEOTIDE THERAPY FOR FAMILIAL AA AMYLOIDOSIS, A N OF 1 TRIAL

NELSON LEUNG[1,2], TEREZA KMOCHOVÁ[3,*], ELLEN D MCPHAIL[4], SURENDRA DASARI[5], LENKA NOSKOVÁ[3], ALEŠ HNÍZDA[3], KATEŘINA HODAŇOVÁ[3] , MARTINA ŽIVNÁ[3,8], SAMIH H NASR[4], JAKUB SIKORA[3,6], JASON D. THEIS[4], JULIE A. VRANA[4], STANLEY T CROOKE[7], ANTHONY BLEYER[3,8], STANISLAV KMOCH[3,8]

[1]DIVISION OF NEPHROLOGY AND HYPERTENSION, MAYO CLINIC, ROCHESTER, MINNESOTA, USA, [2]DIVISION OF HEMATOLOGY, MAYO CLINIC, ROCHESTER, MINNESOTA, USA, [3]RESEARCH UNIT FOR RARE DISEASES, DEPARTMENT OF PEDIATRICS AND INHERITED METABOLIC DISORDERS, FIRST FACULTY OF MEDICINE, CHARLES UNIVERSITY, PRAGUE, CZECH REPUBLIC, [4]DEPARTMENT OF LABORATORY MEDICINE AND PATHOLOGY, MAYO CLINIC, ROCHESTER, MINNESOTA, USA, [5]DEPARTMENT OF QUANTITATIVE HEALTH SCIENCES, MAYO CLINIC, ROCHESTER, MINNESOTA, USA, [6]INSTITUTE OF PATHOLOGY, FIRST FACULTY OF MEDICINE, CHARLES UNIVERSITY IN PRAGUE AND GENERAL TEACHING HOSPITAL IN PRAGUE, PRAGUE, CZECH REPUBLIC [7]NLOREM, CARLSBAD, CALIFORNIA, USA, [8]SECTION ON NEPHROLOGY, WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE, WINSTON-SALEM, NC, USA
INSTITUTE OF PATHOLOGY, FIRST FACULTY OF MEDICINE, CHARLES UNIVERSITY, PRAGUE, CZECH REPUBLIC

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BIOMARKER-BASED RENAL RESPONSE AND PROGRESSION CRITERIA IN AA AMYLOIDOSIS: RESULTS FROM THE PAVIA-HEIDELBERG STUDY

Marco Basset[1], Ute Hegenbart[2], Laura Obici[1], Eloisa Riva[3], Paolo Milani[1], Ettore Pasquinucci[4], Andrea Foli[1], Martina Nanci[1], Martina Ciardo[1], Chiara Corpina[1], Claudia Bellofiore[1], Francesca Benigna[1], Pietro Benvenuti[1], Giuseppe Sanna[1], Roberta Mussinelli[1], Mario Nuvolone[1], Riccardo Albertini[5], Giampaolo Merlini[1], Stefan Schönland[2], Norbert Blank[2], Giovanni Palladini[1]

[1]Amyloidosis Research and Treatment Center, IRCCS Policlinico San Matteo and Department of Molecular Medicine, University of Pavia; [2]Division of Hematology, Oncology and Rheumatology, Department of Internal Medicine V, Amyloidosis Center, Heidelberg University Hospital; [3]Hematology Department, Hospital de Clinicas, Facultad de Medicina, Montevideo; [4]Nephrology and Dialysis Unit, A. Manzoni Hospital, Lecco; [5]Laboratory of Clinical Chemistry, Fondazione IRCCS Policlinico San Matteo

BACKGROUND

AL amyloidosis

Validated organ response criteria:
- Cardiac response
- Renal response (24-proteinuria)
- Renal response (UACR)

Validated organ progression criteria:
- Cardiac progression
- Renal progression

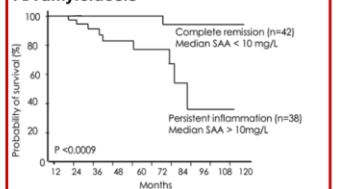
Palladini G, et al. JCO 2012
Palladini G, et al. Blood 2015
Basset M, et al. CCLM 2022

ATTR amyloidosis

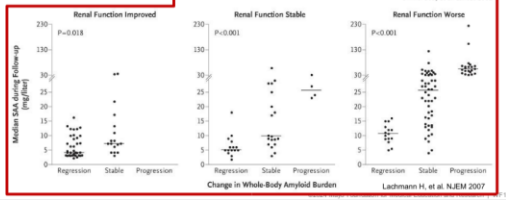
Validated organ progression criteria:
- Cardiac progression

Iannou A, et al. JACC 2024

AA amyloidosis



Gillmore JD, et al. Lancet 2001



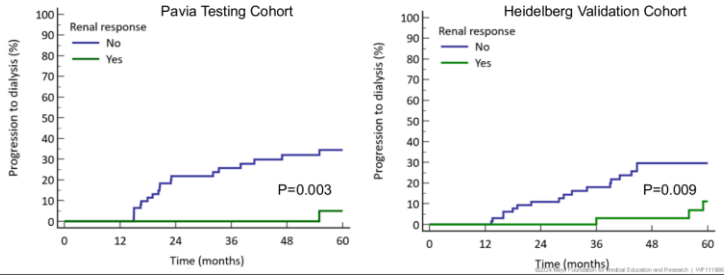
Lachmann H, et al. NJEM 2007

RESULTS – PATIENT POPULATION

Variables	Pavia 147 patients N (%) – median (IQR)	Heidelberg 156 patients N (%) – median (IQR)
Age, years	55 (46-66)	55 (43-64)
Sex, male	62 (42)	68 (44)
Organ involvement: Kidney / Heart	140 (95) / 19 (13)	150 (96) / 21 (13)
SAA, mg/L	26.0 (10.5-70.7)	47.7 (19.7-114.2)
C reactive protein, mg/L	18.3 (5.6-39.9)	20.1 (9.4-47.5)
Survival stage: I / II / III	75 (61) / 29 (24) / 18 (15)	73 (52) / 47 (34) / 19 (14)
Renal stage: I / II / III	30 (23) / 61 (48) / 37 (29)	35 (27) / 59 (46) / 35 (27)
Underlying inflammatory condition: Rheumatologic diseases / Idiopathic AA IBD / AID / Recurrent infections	 53 (36) / 43 (31) 21 (14) / 16 (10) / 14 (9)	 57 (37) / 38 (24) 8 (5) / 48 (31) / 5 (3)
Treatment with biologics	33 (22)	68 (44)
Dialysis before diagnosis	17 (12)	20 (13)
Time to second evaluation, months	12.5 (10.1-20.2)	11.0 (9.5-17.3)

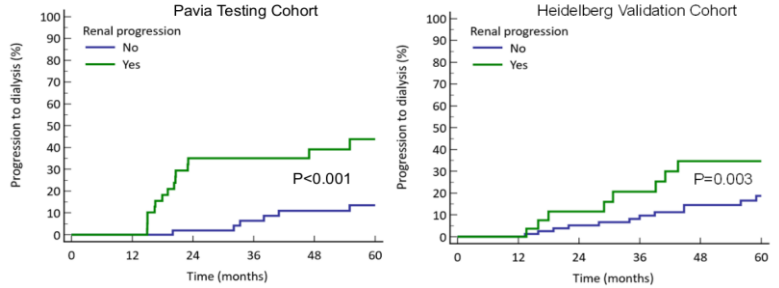
RESULTS – RENAL RESPONSE

Proposed criterion	Definition
Renal response	Reduction in 24h-proteinuria >40%, without a worsening of eGFR >20%



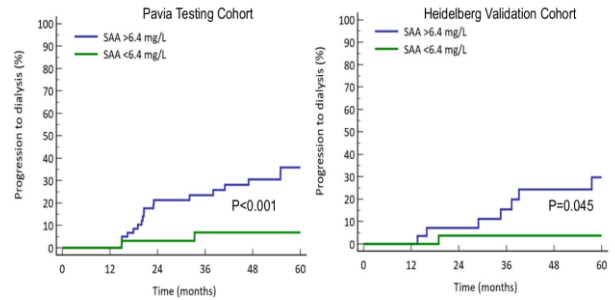
RESULTS – RENAL PROGRESSION

Proposed criterion	Definition
Renal progression	Reduction in eGFR >20%



RESULTS – SAA NORMALIZATION

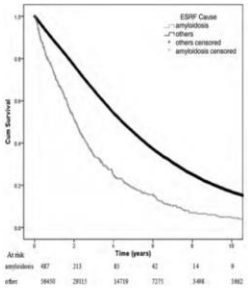
Criterion	Definition
SAA normalization	SAA <6.4 mg/L



Et la greffe (de rein) ?

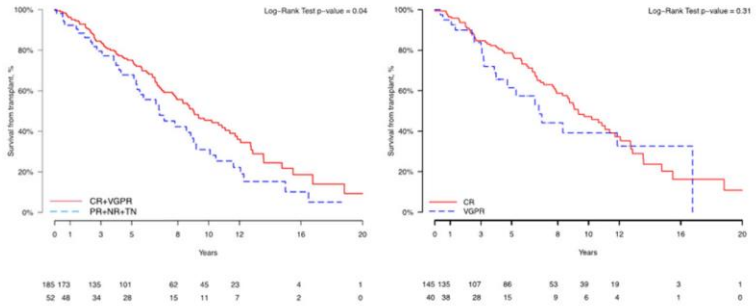
- Review the role of kidney transplantation in AL amyloidosis
- Explore the questions of who can be transplanted, when should the transplant be performed, is a stem cell transplant required and the immunosuppressive regimen used in transplantation.

Amyloidosis Patients Have A Poorer Survival On Dialysis vs Others



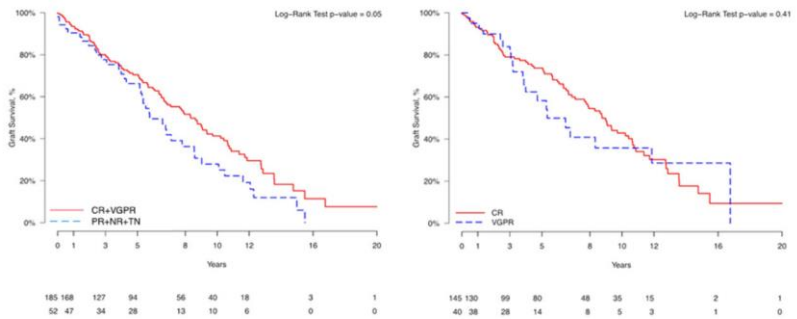
Tang et al. NDT 2013

IKMG Study of Kidney Transplantation in 237 AL Amyloidosis



Havasi et al. Blood Cancer J 2022

Graft Survival in the IKMG Study



Havasi et al. Blood Cancer J 2022

Outcomes After Kidney Transplant Based On the Pretransplant Hematologic Response

Outcomes	CR (n = 37)	VGPR (n = 6)	PR (n = 5)	NR (n = 3)	Treatment-naive (n = 9)
Patient survival					
1 yr	100	100	100	33.3	77.8
3 yrs	95.7	100	75.0	33.3	77.8
5 yrs	90.3	100	37.5	33.3	77.8
Graft survival (death-censored)					
1 yr	100.0	100	100	50.0	100.0
5 yrs	95.7	100	100	50.0	100.0
Graft survival (death-noncensored)					
1 yr	100.0	100.0	100.0	33.3	88.9
5 yr	95.7	100.0	37.5	33.3	77.8
Recurrence-free survival					
3 yrs	96.3	80.0	66.7	100.0	100.0
5 yrs	96.3	53.3	0.0	0.0	85.7

Heybeli et al. Kidney Int. 2021

MERCI DE VOTRE ATTENTION !