

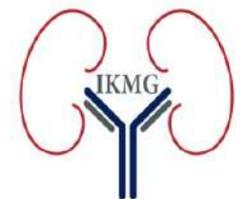
Quoi de neuf sur le rein à l'ISA ?

Dr Camille COHEN

MD-PhD Service de Néphrologie - Hôpital Bichat - Paris

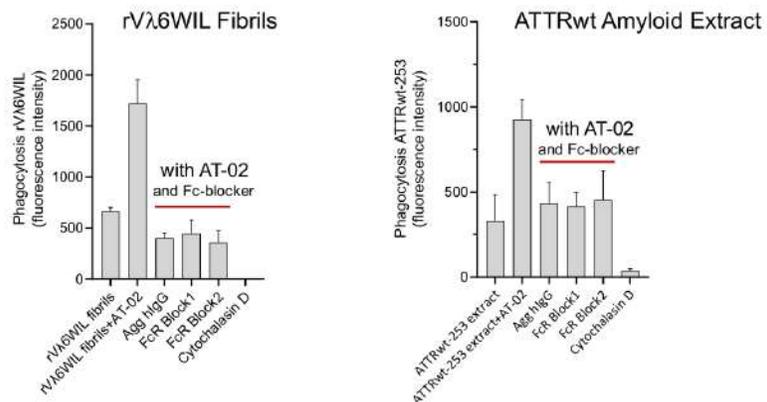
Centre de recherche sur l'inflammation (CRI) - INSERM U1149

Team leader "maladie rénale et immunoglobulines monoclonales"



BASIC SCIENCE

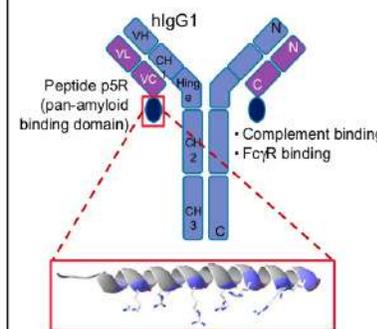
AT-02-INDUCED PHAGOCYTOSIS OF pHrodoRED-AMYLOID IS FcR-DEPENDENT



©2024 Mapi Foundation for Medical Education and Research | MF110865.14

CHARACTERIZATION OF THE PEPTIDE-ANTIBODY FUSION AT-02

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

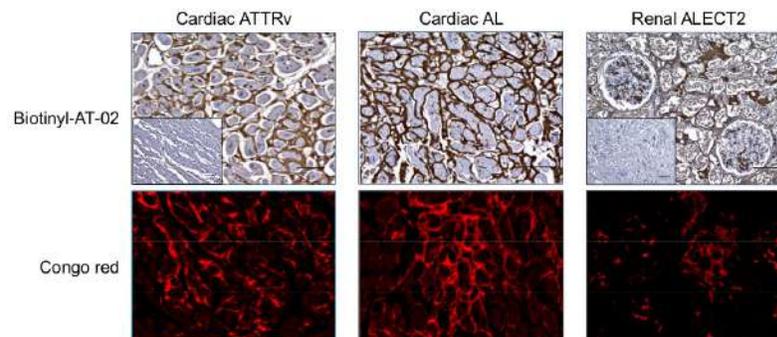


- AT-02 is a humanized IgG1-peptide fusion reagent.
- The pan-amyloid reactive peptide p5R is fused to the C-terminal of the light chain.
- Peptide p5R binds fibrils and hypersulfated glycosaminoglycans via electrostatic interactions.
- Same peptide technology as the ¹²⁴I-AT-01 and ^{99m}Tc-AT-05 imaging 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.

©2024 Mapi Foundation for Medical Education and Research | MF110865.14

Johnathan Wall

AT-02 SPECIFICALLY BINDS AMYLOID IN TISSUE SECTIONS



©2024 Mapi Foundation for Medical Education and Research | MF110865.17

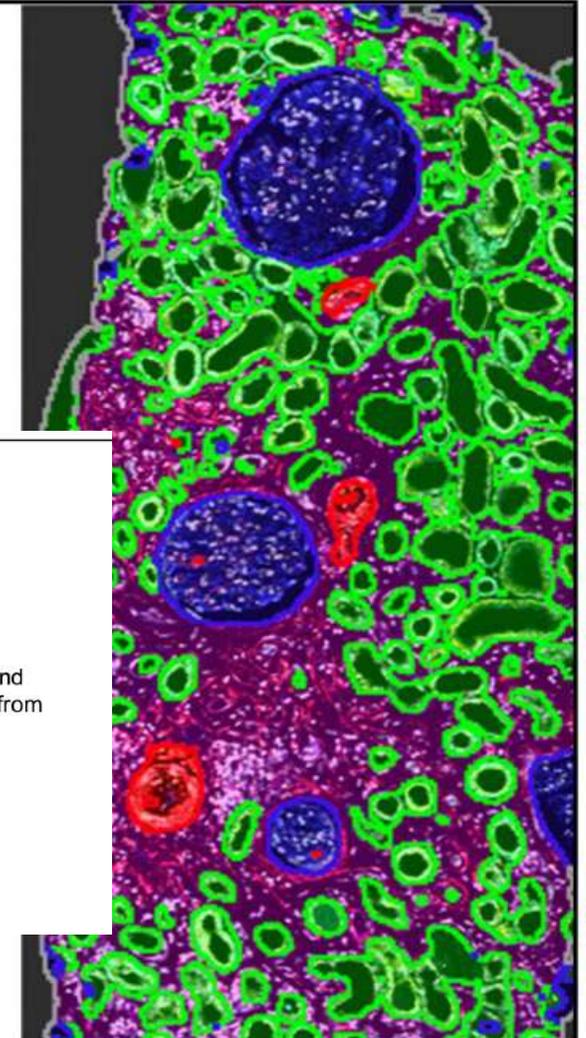
SINGLE-CELL, SPATIAL ANALYSIS OF THE RENAL AL IMMUNOME SUPPORTS A T CELL-MEDIATED TISSUE TOXICITY MECHANISM

CHARIS CHARALAMPOUS

Resident physician, Internal Medicine,
Georgetown University Hospital

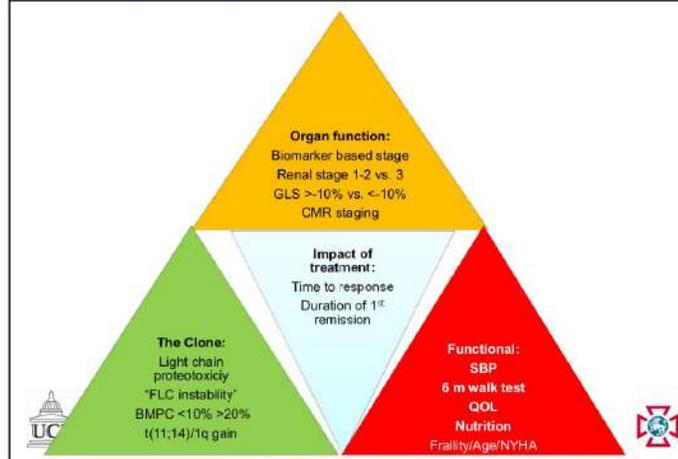
KEY POINTS

- 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

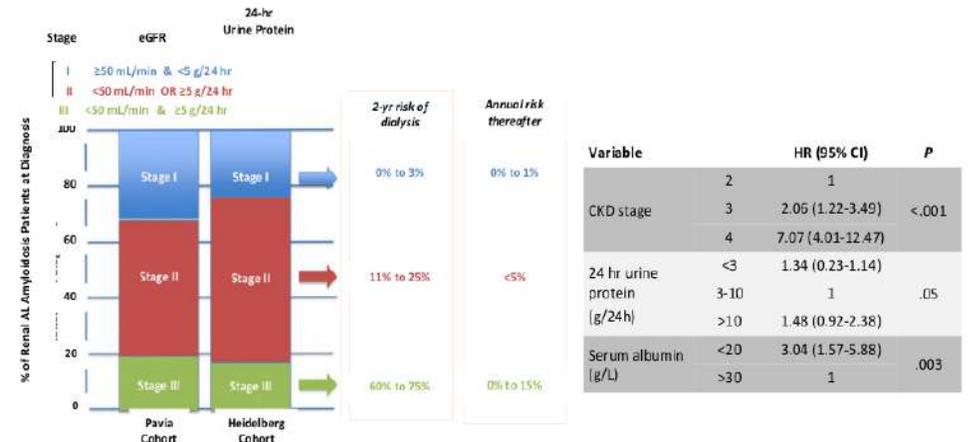


Diagnostic Traitement de l'AL

The wider view of factors impacting outcomes



Renal stage : important but often forgotten/ignored



Limitations of current staging systems in AL amyloidosis

Ashutosh Wechalekar
Professor of Medicine and Haematology

National Amyloidosis Centre
University College London

Department Of Haematology
University College London Hospitals



Royal Free Hampstead
NHS Trust

University College London Hospitals
NHS Foundation Trust



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.



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

Paolo Milani^{1,2}, Ombretta Annibaldi³, Marco Basset, Martina Ciardo, Martina Nanci, Mario Nuvolone^{1,2}, Roberta Mussinelli¹, Claudia Bellofiore², Valeria Tomarchio³, Pietro Benvenuti¹, Giuseppe Sanna², Andrea Foli², Giampaolo Merlini^{1,2}, Giovanni Palladini^{1,2}

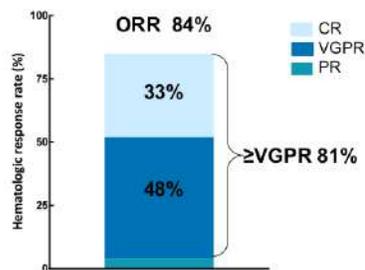
1. Department of Molecular Medicine, University of Pavia, Pavia, Amyloidosis Research and Treatment Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

2. Fondazione Policlinico Campus Biomedico di Roma, Roma

©2024 Novus Foundation for Medical Education and Research. 1-WF11-0282.2

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.

©2024 Novus Foundation for Medical Education and Research. 1-WF11-0282.2

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:

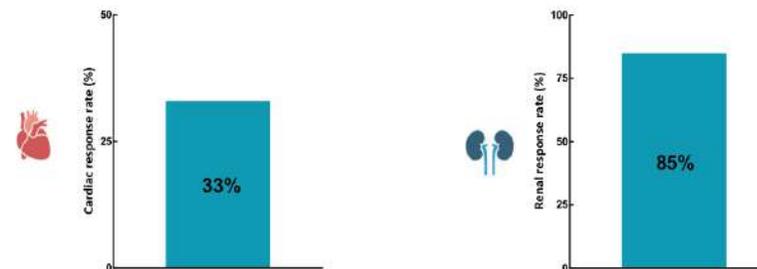
- Histologic diagnosis of AL amyloidosis;
- **At least one line (and no more than 3 lines)** with an alkylating agent and/or a PI and dexamethasone and not be in VGPR or CR at the time of inclusion (patients who did not reach VGPR or patients in VGPR or better but with a hematological relapse can be 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

Cardiac and renal responses evaluated at cycle 6



©2024 Novus Foundation for Medical Education and Research. 1-WF11-0282.2



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

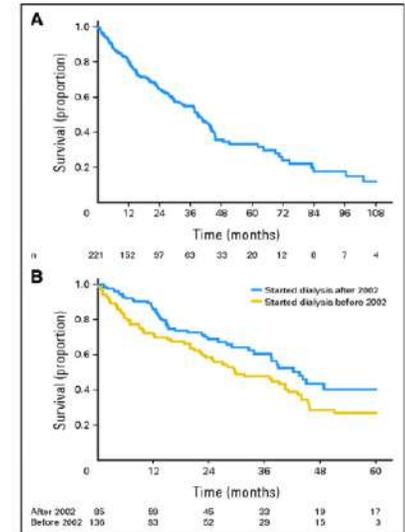
Progression to ESRD requiring dialysis has devastating effects on patients quality of life but...

- 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 responding to 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



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

FOTEINI THEODORAKAKOU¹, LILLI S. SESTER², UTE HEGENBART², PAOLO MILANI³, CLAUDIA BELLOFIORE³, ERASMIA PSIMENOU⁴, CHARIKLEIA GAKIOPOULOU⁴, MELETIOS A. DIMOPOULOS¹, GIOVANNI PALLADINI⁵, STEFAN O. SCHÖNLAND², EFSATHIOS KASTRITIS¹

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

©2024 Mayo Foundation for Medical Education and Research. 1. 001110001-04

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.

©2024 Mayo Foundation for Medical Education and Research. 1. 001110001-04

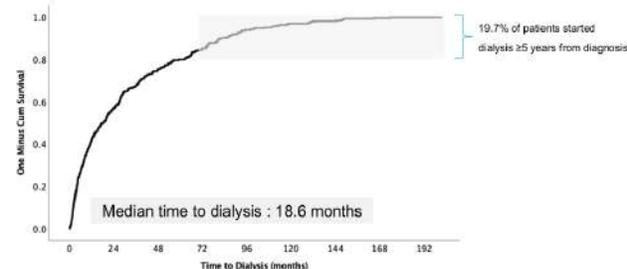
BASELINE CHARACTERISTICS AT THE TIME OF INITIAL DIAGNOSIS

| 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

| Hematologic response status | | N=355 |
|---|--|-------|
| 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% |

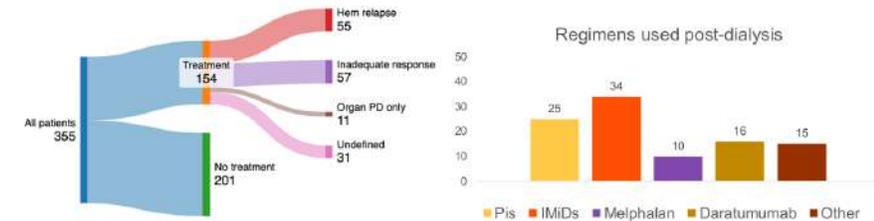
©2024 Mayo Foundation for Medical Education and Research. 1. 001110001-04

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.**

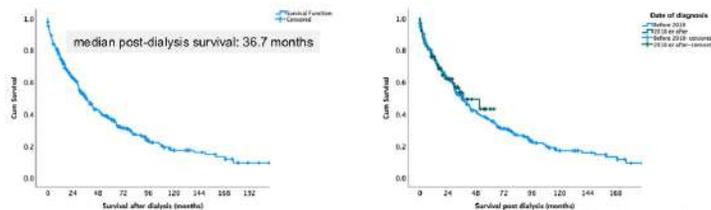
RESULTS: TREATMENT AFTER DIALYSIS INITIATION

- 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

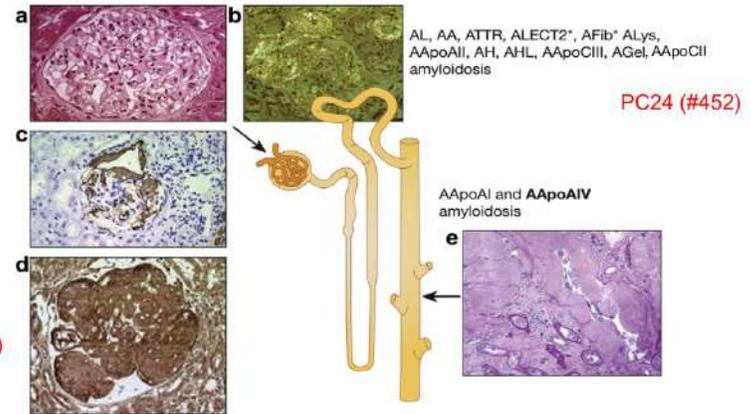
IRCCS Fondazione Policlinico San Matteo

Pavia, Italy



Fondazione IRCCS Policlinico San Matteo

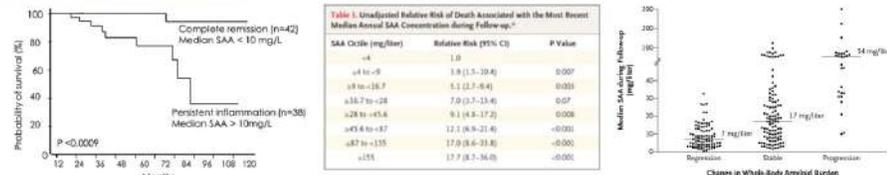
THE KIDNEY IS THE MAJOR TARGET ORGAN IN SEVERAL RARE FORMS OF SYSTEMIC AMYLOIDOSIS



Journal of Internal Medicine 2018

AA AMYLOIDOSIS

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



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

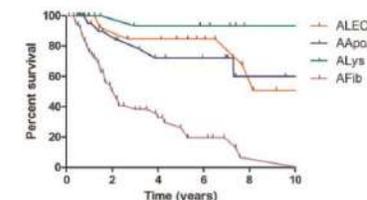
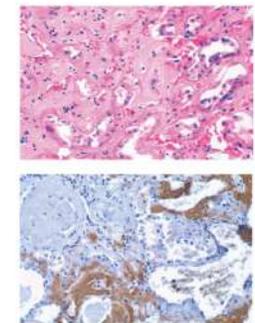


OC12 Antisense oligonucleotide therapy for familial AA amyloidosis. A N of 1 trial

* n = 8,000; Kaplan-Meier test. Obici et al. J Am Soc Nephrol 2019; 30:1111-1120. Obici et al. Nephrol Dial Transplant 2020; 35:1111-1120. Obici et al. Nephrol Dial Transplant 2020; 35:1111-1120.

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.

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

NELSON LEUNG^{1,2}, TEREZA KMOČHOVÁ^{3,*}, ELLEN D MCPHAIL⁴, SURENDRA DASARI⁵, LENKA NOSKOVÁ³, ALEŠ HNÍZDA³, KATEŘINA HODAŇOVÁ³, MARTINA ŽIVNÁ^{3,8}, SAMIH H NASR⁴, JAKUB SIKORA^{3,6}, JASON D. THEIS⁴, JULIE A. VRANA⁴, STANLEY T CROOKE⁷, ANTHONY BLEYER^{3,8}, STANISLAV KMOCH^{3,8}

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

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

Marco Basset¹, Ute Hegenbart², Laura Obici¹, Eloisa Riva³, Paolo Milani¹, Ettore Pasquinucci⁴, Andrea Foli¹, Martina Nanci², Martina Ciardo¹, Chiara Corpina¹, Claudia Bellofiore¹, Francesca Benigna¹, Pietro Benvenuti¹, Giuseppe Sanna¹, Roberta Mussinelli¹, Mario Nuvolone¹, Riccardo Albertini⁵, Giampaolo Merlini¹, Stefan Schönland², Norbert Blank², Giovanni Palladini¹

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

© 2024 Mass Foundation for Medical Education and Research. | SPT1198512

BACKGROUND

AL amyloidosis

Validated organ response criteria:

- Cardiac response
- Renal response (24-proteinuria)
- Renal response (UACR)

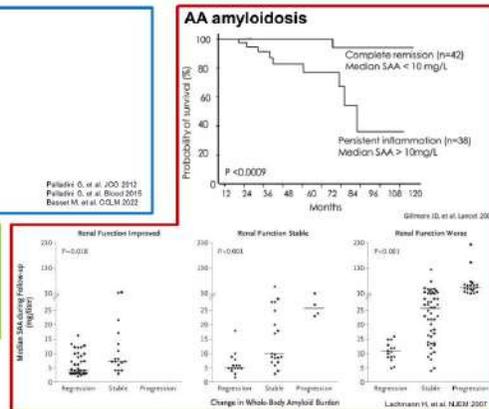
Validated organ progression criteria:

- Cardiac progression
- Renal progression

ATTR amyloidosis

Validated organ progression criteria:

- Cardiac progression

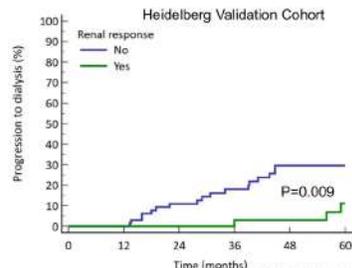
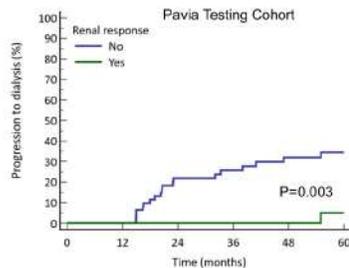


RESULTS – PATIENT POPULATION

| 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) |

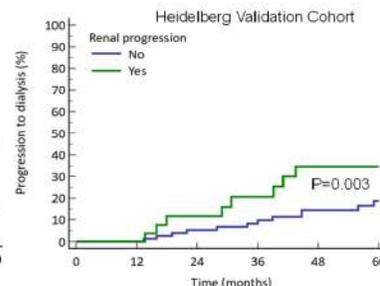
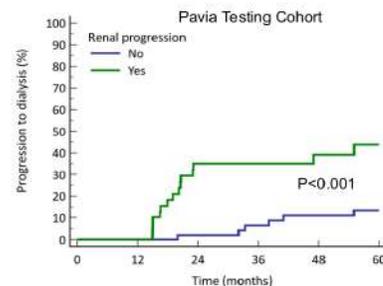
RESULTS – RENAL RESPONSE

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



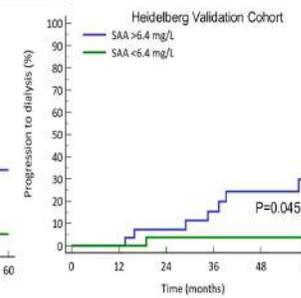
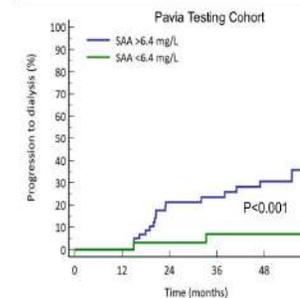
RESULTS – RENAL PROGRESSION

| Proposed criterion | Definition |
|--------------------|------------------------|
| Renal progression | Reduction in eGFR >20% |



RESULTS – SAA NORMALIZATION

| Criterion | Definition |
|-------------------|---------------|
| SAA normalization | SAA <6.4 mg/L |

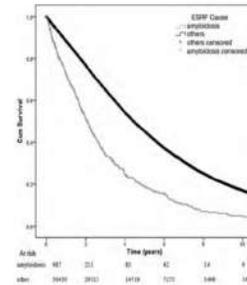


Et la greffe (de rein) ?



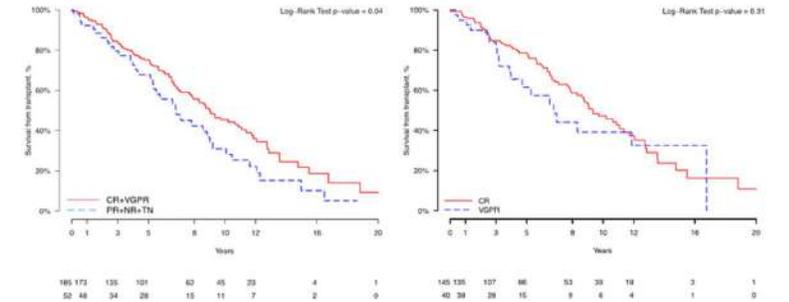
- Review the role of kidney transplantation in AL amyloidosis
- Explore the questions of who can be transplanted, when should the transplant be performed, is a stem cell transplant required and the immunosuppressive regimen used in transplantation.

Amyloidosis Patients Have A Poorer Survival On Dialysis vs Others



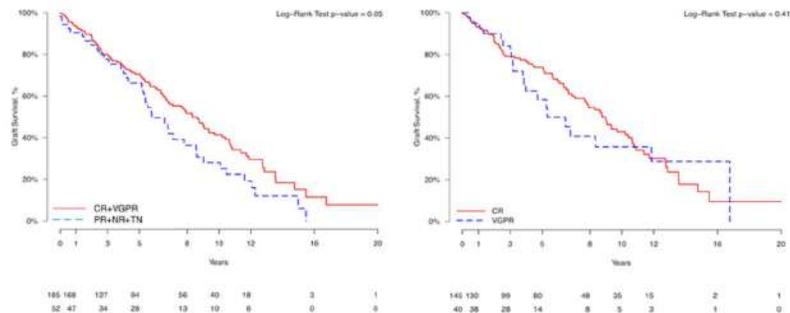
Tanaka et al. NDT 2015

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-naïve (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 !