EDEMA IN A PATIENT WITH RECURRENT RESPIRATORY INFECTIONS - Case Report

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CASE REPORT (1)
56 year-old white woman

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- **Intermittent lower limbs oedema for 1 year**
  - **November 2010:**
    - respiratory infection (« bronchitis »)
    - legs oedema
    - proteinuria
    - treatment with antibiotics → resolution of oedema
  - **March 2011:**
    - pneumococcal infection (pneumonia)
    - recurrence of peripheral oedema
    - proteinuria in nephrotic range (3 – 4 g/24 hours)

CASE REPORT (2)

- **Medical history:**
  - asthma since 19 year-old (atopic: pollens, house dust)
  - sinusitis (multiple)
  - nasal polyposis (x surgical cures)
  - multiple respiratory infections each year
  - no allergy to Aspirin

- **Physical examination:**
  - blood pressure: 120/80 mmHg
  - nasal speech
  - prolonged aspiration or wheezing
  - legs edema – no neuropathy

CASE REPORT (3)
Laboratory data

C-reactive protein	5 mg/dl
WBC	7200
Serum creatinine	1.06 mg/dl
Polyclonal hypergammaglobulinemia	
ANA	neg
ANCA	neg
IgE	456 UI/ml (N < 114)
IgG subclasses	N
α1-antitrypsin	N
Mutations cystic fibrosis	neg
Proteinuria	3.4 g/24 hr without nephrotic syndrome

CASE REPORT (4)
Complementary investigations

- Kidney ultrasound: N
- Renal veins doppler ultrasound: N
- Renal isotopic scan (DMSA): N
- Sinuses CT scan:
  - sinusitis (maxillary, ethmoid, frontal) and polyposis
  - examination: nasal and sinuses polyposis
- Chest CT scan: bronchiectasis bilateral

CASE REPORT (5)

- **Proteinuria (nephrotic range) and peripheral edema + chronic sinus infections, nasal polyps and bronchiectasis**

  Δ ?
  - **AMYLOIDOSIS (secondary to chronic infection)**
  - **Membranous glomerulonephritis**
  - **Focal glomerular sclerosis**
  - **Membrano-proliferative glomerulopathy**
  - **Minimal change**

- **Renal biopsy: Amyloidosis AA**

  Associated to chronic infection (bronchiectasis)

AMYLOIDOSIS (1)
What are amyloidosis?

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- Group of diseases with extracellular deposition of proteins in characteristic amyloid fibriles
- Insoluble fibrillar proteins > localized or broadly distributed in vital organs (kidney most commonly involved)
- During fibril formation, glycosaminoglycans interact with amyloid protein promoting its aggregation (abnormal folding) and deposition in tissues
- More than 25 precursor proteins of amyloid have been identified

AMYLOIDOSIS (2)

Classification (nature of the fibrils deposits)

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Amyloid Protein	Protein Precursor	Systemic/ Localized	Related Disease or Involved tissues
AA	Serum Amyloid A	S	Chronic inflammation or infection
AL	Ig-derived λ or κ light chains	S, L	Plasma cell clone associated
Other forms of amyloidosis affecting kidney derived from: Fragment of Heavy Chains + Light (AHL) ; Heavy Chain (AH) ; Transthyretin (ATTR) - familial, related to TTR mutations ; Fibrinogene A α chain (AFib) ; Apo (AApo AI, II, IV) ; Lysozyme (ALys) ; Gelsolin (AGcl) ; Leucocyte Chemotactic Factor$_2$ (ALECT$_2$)			
Aβ	Aβ protein precursor	L	Alzheimer's disease Cerebral amyloid angiopathy
Aβ2M	Beta2-microglobulin	S	Chronic hemodialysis

AMYLOIDOSIS AA (3)
Secondary

- Progressive and fatal condition
- Patients with chronic inflammatory diseases (RA, chronic infections, Crohn, FMF,…)
- Insidious and progressive:
  - symptoms present in later stages of the disease
  - significant damage at that time in vital organs
- Median survival 4 – 8 years after diagnosis
- No specific therapy

AMYLOIDOSIS AA (4)

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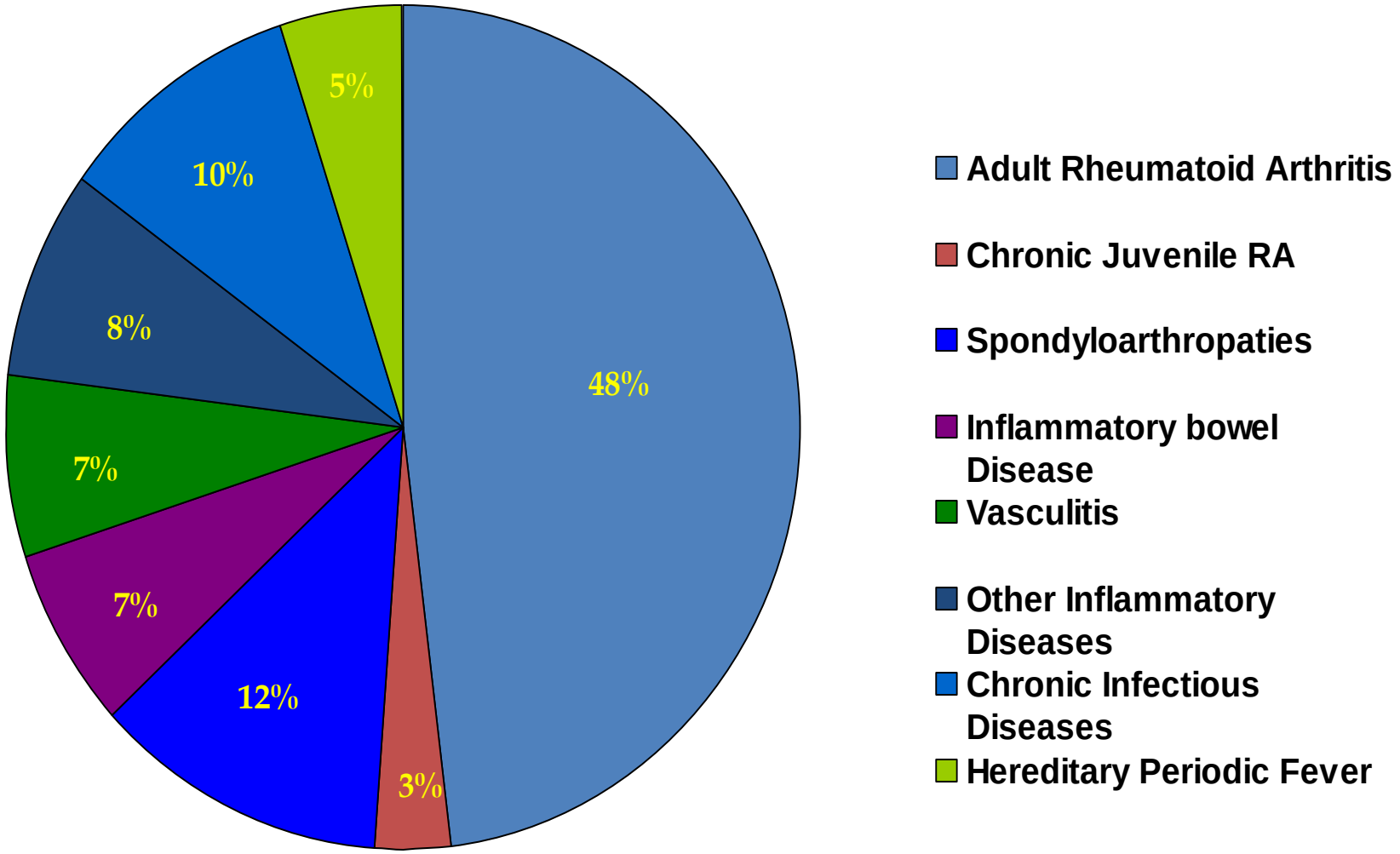
Who is at risk of AA amyloidosis?

Prerequisite: chronic inflammatory and infectious conditions

	Lifetime incidence of AA Amyloidosis
Rheumatoid arthritis	3 – 10%
Psoriatic Arthritis	3 – 13%
Chronic Juvenile Arthritis	0.14 – 17%
Ankylosing Spondylitis in children	4.5%
Inflammatory bowel Disease	0.4 – 2%
Familia Mediterranean Fever	8 – 37% Majority of untreated patients
Chronic Infectious Diseases (tuberculosis, leprosy, bronchiectasis, chronic osteomyelitis, chronic pyelonephritis)	Up to 10%

AMYLOIDOSIS AA (5)
Prevalence

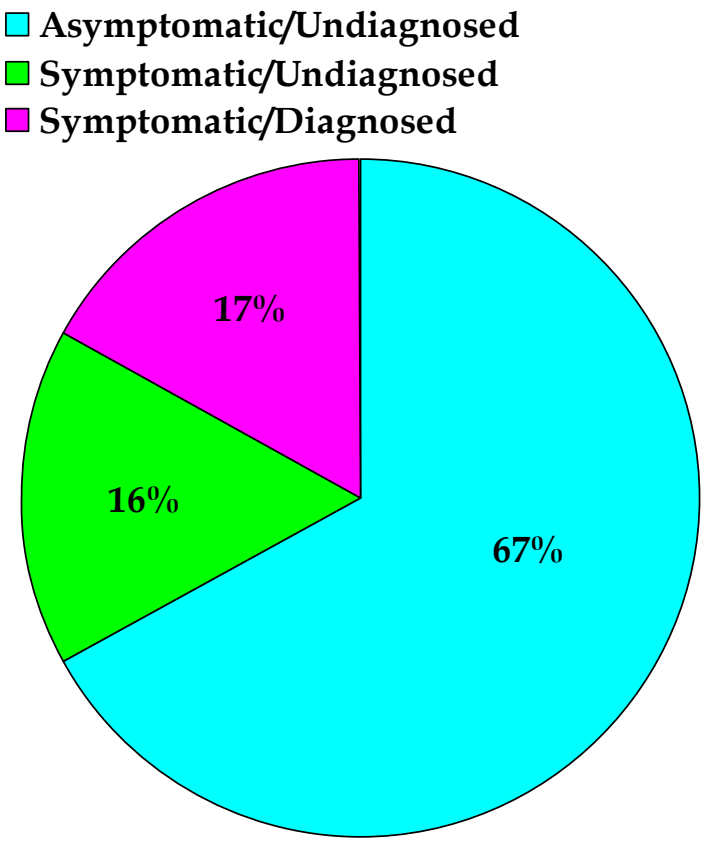


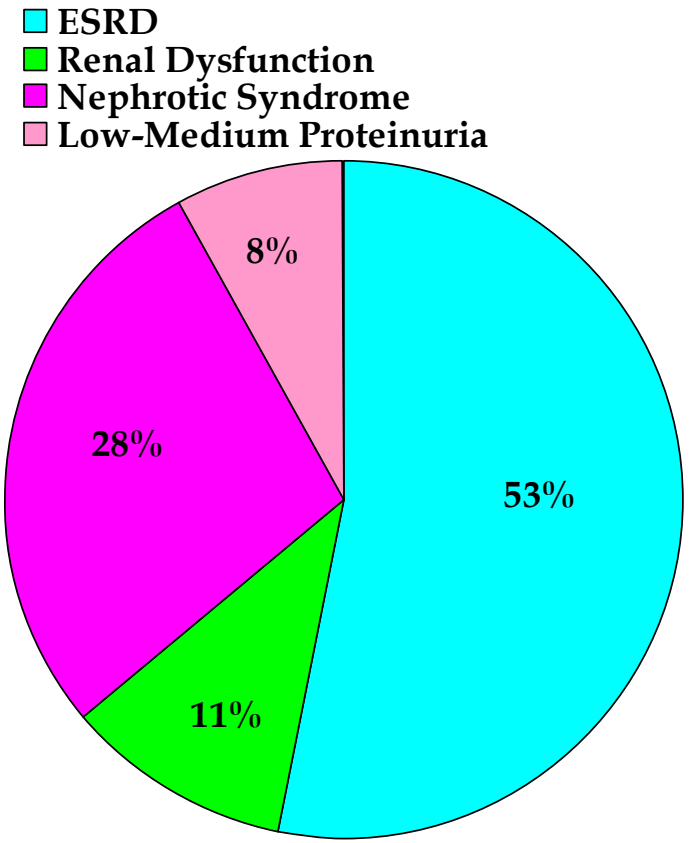
AMYLOIDOSIS AA (6)

- AA asymptomatic over extended time and largely undiagnosed

- Many patients with AA amyloidosis have end-stage renal disease (ESRD) at time of diagnosis

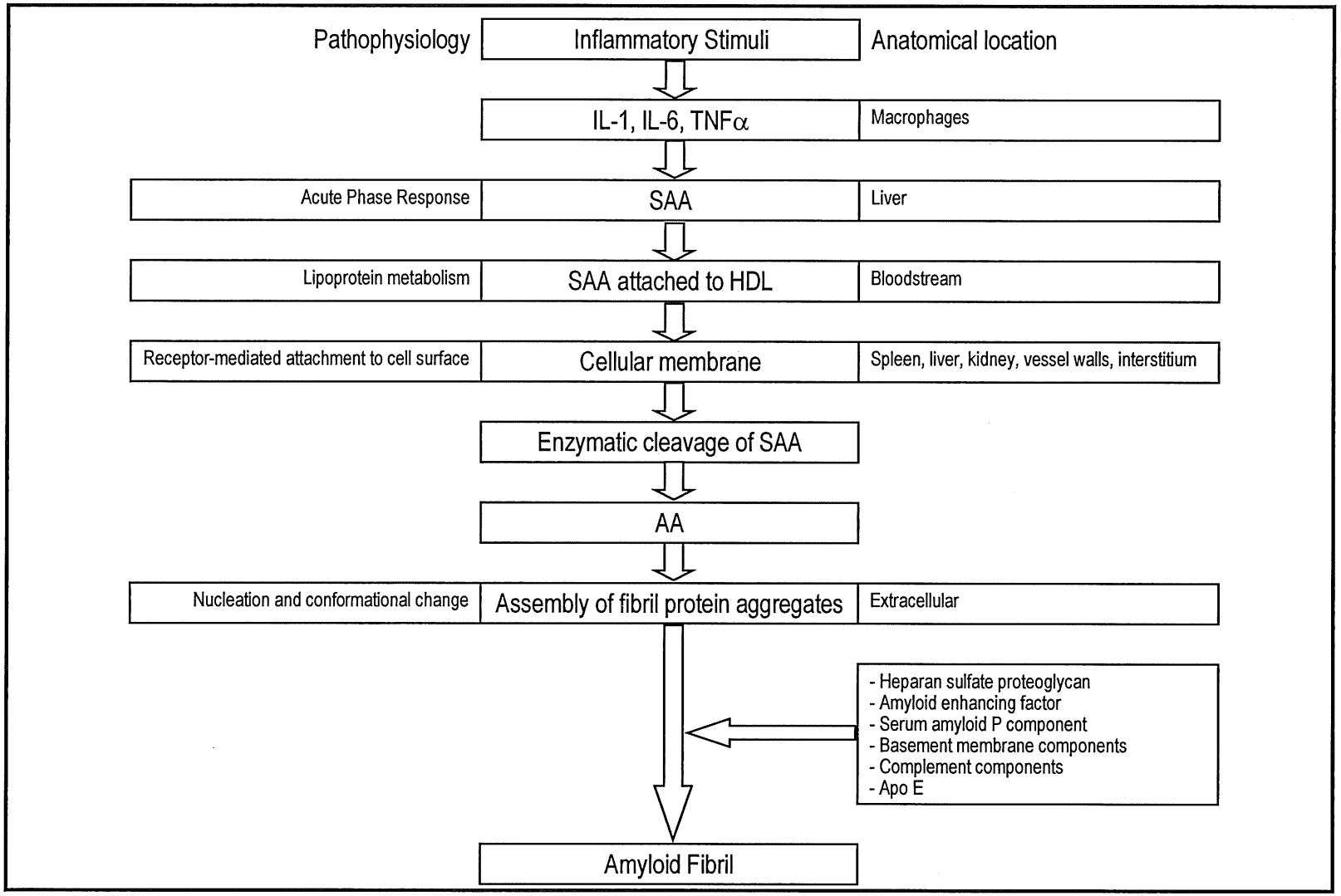
AMYLOIDOSIS AA (7)





AMYLOIDOSIS AA (8)
Pathogenesis

- **Overproduction of serum amyloid A (SAA) by the liver under transcriptional regulation by inflammatory cytokines**
  (N. Engl. J. Med. 349; 583: 2003; FEBS Lett 583; 2685: 2009)


Pathophysiology
Inflammatory Stimuli
Anatomical location
IL-1, IL-6, TNFα
Macrophages
Acute Phase Response
SAA
Liver
Lipoprotein metabolism
SAA attached to HDL
Bloodstream
Receptor-mediated attachment to cell surface
Cellular membrane
Spleen, liver, kidney, vessel walls, interstitium
Enzymatic cleavage of SAA
AA
Nucleation and conformational change
Assembly of fibril protein aggregates
Extracellular
- Heparan sulfate proteoglycan
- Amyloid enhancing factor
- Serum amyloid P component
- Basement membrane components
- Complement components
- Apo E
Amyloid Fibril

AMYLOIDOSIS AA (9)
Diagnosis

- **History: high level of suspicion**
  - long-standing inflammatory disease, uncontrolled for more than 5 years
- **Physical examination and symptoms:**
  - signs of renal disease (hypertension, peripheral edema)
  - GI complaints
  - hepatomegaly/splenomegaly
  - deforming arthritis
- **Laboratory studies:**
  - non-specific tests: proteinuria, elevated CRP, elevated ESR, elevated SAA, decreased albumin
  - polyclonal hypergammaglobulinemia
  - renal function tests
- **Biopsy:**
  - subcutaneous fat aspiration
  - rectal biopsy
  - kidney biopsy
- **Scintigraphy:**
  - radiolabelled SAP scanning (+ follow-up)
- **Histologic staining:**
  - Congo red staining and immunostaining with specific antibodies directed against AA fibril proteins

AMYLOIDOSIS AA (10)
Methods used for identification

Target Organ or Tissue	Kidney	Gastrointestinal	Rectum	Abdominal Fat Aspiration
Sensitivity	92 – 100%	90 – 94%	69 – 97%	35 – 84%
Specificity	100%	100%	100%	100%
Advantages	High sensitivity	Well tolerated Low risk of complications	Less hazardous than kidney or liver biopsy	Easy to perform in outpatient clinic Minimal patient preparation Low risk of complications
Disadvantages	Risk of bleeding	Need expensive endoscopic equipment	Occasionally uncomfortable for the patient Risk of bleeding	An adequate technique is necessary for good results Low sensitivity
Staining Methods	H & E for histological patterns Congo red: Polarized light for Congo red green birefringence Immunohistochemistry: Antibodies against AA			

Natural history and outcome in systemic AA amyloidosis (1)

- Prospective study (n = 374)
- AA amyloidisos follow-up: 86 months
- Etiologies:
  - chronic inflammatory arthritis 60%
  - chronic sepsis (bronchiectasis, osteomyelitis,…) 15%
  - periodic fever syndromes 9%
  - Crohn disease 5%
  - miscellaneous and unknown (lymphoma, vasculitis,…) 11%

Lachman et al, N engl J Med 356: 2381 (2007)

Natural history and outcome in systemic AA amyloidosis (2)

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Characteristics of the patients

- Duration of inflammatory disease and diagnosis (median): 17 years (0 – 68)
- End stage renal failure present at baseline: 41%
- Serum amyloid A protein (SAA) concentration mean value: 28 mg/l (0.7 – 1610)
- C-reactive protein value: 20 mg/l (0.7 – 206)
- Proteinuria: 3.9 g/day (0 – 26)
- Creatinine clearance: 41 ml/min

Natural history and outcome in systemic AA amyloidosis (3)

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Outcome

- 44% of patients died
- Median survival: 133 months
- Factors associated with risks of death and progression to end-stage renal failure:
  - older age
  - end stage renal failure at baseline
  - reduced serum albumin concentration
  - SAA levels: non powerful risk factor
  - if > 155 mg/l → risk of death 17 times higher than if SAA < 4 mg/l

Natural history and outcome in systemic AA amyloidosis (4)

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Aim of the treatment

- **To reduce SAA (serum amyloid A protein) by anti-inflammatory therapy:**
  - **amyloid deposits regressed in 60% of patients with median SAA levels < 10 mg/l**
  - **improvement of renal function by modifying disease control takes months or years**
  - **relapse after removed inflammatory disease could be very rapid**
- **To reduce amyloid deposits**

  → new therapeutic approach

CASE REPORT (6)

- Patient treated with surgery (sinusitis), prevention and treatment of respiratory infections
- Low levels of CRP for 2 years
- Episode of viral gastroenteritis
  - ARF → no recovery
  - Dialysis

Eprodisate for the treatment of renal AA amyloidosis (1)

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Eprodisate (Neurochem – Canada)

- **Negatively charged sulfonated molecule low molecular weight**
- **Structural similarities to heparan sulfate (glycosaminoglycans)**

⇒ **Inhibition of development of amyloid deposits in tissues**

⇒ **Interfere with the interactions between amyloidogenic proteins and glycosaminoglycans**

Eprodisate (2)

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Effect of Eprodisate in patients with AA amyloidosis and kidney involvement

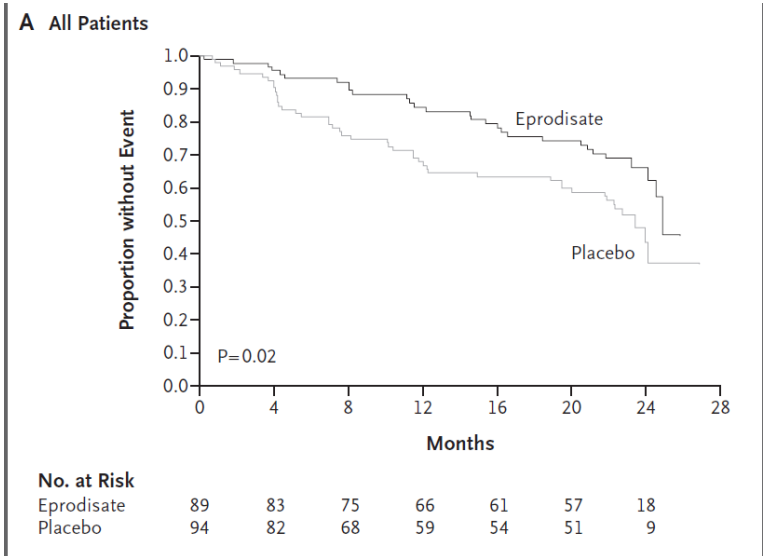
- Prospective (randomized double-blind) study (n = 183)
- Renal function:
  - creatinine clearance (median): 65 ml/min
  - clearance < 60 ml/min: 46%
  - nephrotic syndrome: 40%
- SAA concentration: 16 mg/l (6 – 41)
- C-reactive protein: 9.2 mg/l
- Eprodisate: 800 – 2400 mg/day

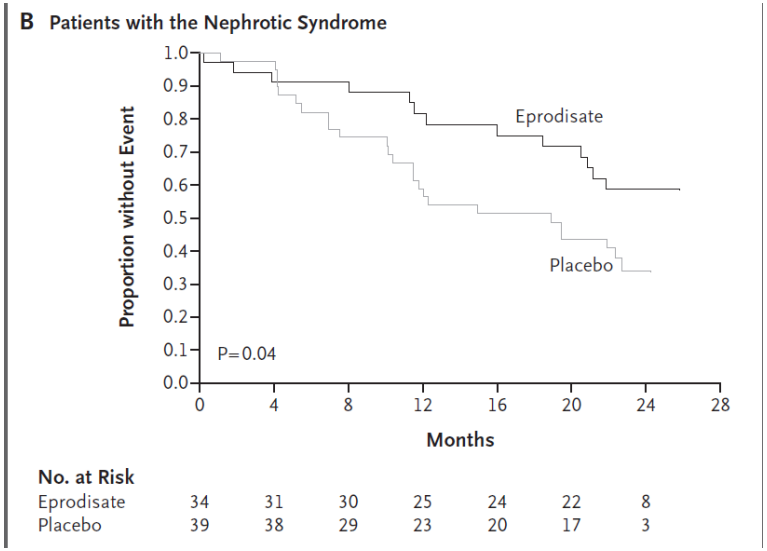
⇒Assessment of renal function progression and death

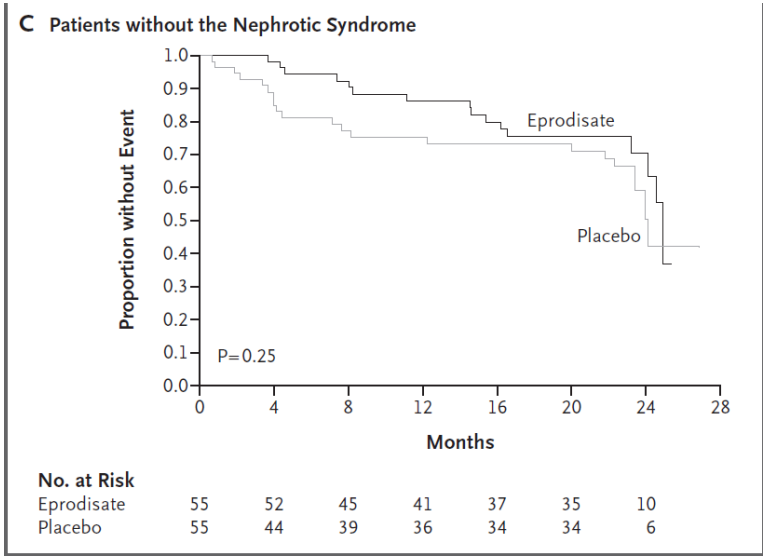
Dember L, N Engl J Med 356: 2349 (2007)

Eprodisate (3)

- **Eprodisate reduces the risk of renal function decline (- 42%):**
  - **worsening of renal function:**
    - **eprodisate: in 27% of patients (-10 ml/min/year)**
    - **placebo: in 40% of patients (-15 ml/min/year)**
- **No effect on proteinuria:**
  - **eprodisate prevents new amyloid formation and deposits**
  - **no effect on SAA concentration (toxic for glomerules → proteinuria)**
- **Effect of eprodisate more apparent among patients with nephrotic syndrome**
- **No difference in the risk of death**


A All Patients
Proportion without Event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Eprodisate
Placebo
P=0.02
0
4
8
12
16
20
24
28
Months
No. at Risk
Eprodisate 89 83 75 66 61 57 18
Placebo 94 82 68 59 54 51 9


B Patients with the Nephrotic Syndrome
Proportion without Event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Eprodisate
Placebo
P=0.04
0
4
8
12
16
20
24
28
Months
No. at Risk
Eprodisate 34 31 30 25 24 22 8
Placebo 39 38 29 23 20 17 3


C Patients without the Nephrotic Syndrome
Proportion without Event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Eprodisate
Placebo
P=0.25
0
4
8
12
16
20
24
28
Months
No. at Risk
Eprodisate 55 52 45 41 37 35 10
Placebo 55 44 39 36 34 34 6

Other potential therapeutic options

- **Favorable effect of biological drugs on renal function during treatment of inflammatory diseases associated with AA amyloidosis (case reports, case series)**
- **Anti-IL6: Tocilizumab (RoActemra®)**
  - **Rheumatic diseases (RA, Behcet, polyarteritis nodosa, …)**
  - **Inflammatory bowel disease (Crohn)**
  - **Tuberculosis**
- **Anti-TNFα: Infliximab, Etanercept**
  - **RA, SpA, TRAPS, …**

Anti-IL6 more effective than anti-TNF on renal function (rate remission 72% vs 40%, GFR improved 72% vs 34%)
(Retrospective study (n=42); Mod. Rheumatol. Jan 24; 134: 2014)