Eprodisate for the Treatment of Renal Disease in AA Amyloidosis

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ABSTRACT

BACKGROUND

Amyloid A (AA) amyloidosis is a complication of chronic inflammatory conditions that develops when proteolytic fragments of serum amyloid A protein (SAA) are deposited in tissues as amyloid fibrils. Amyloid deposition in the kidney causes progressive deterioration in renal function. Eprodisate is a member of a new class of compounds designed to interfere with interactions between amyloidogenic proteins and glycosaminoglycans and thereby inhibit polymerization of amyloid fibrils and deposition of the fibrils in tissues.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of eprodisate in patients with AA amyloidosis and kidney involvement. We randomly assigned 183 patients from 27 centers to receive eprodisate or placebo for 24 months. The primary composite end point was an assessment of renal function or death. Disease was classified as worsened if any one of the following occurred: doubling of the serum creatinine level, reduction in creatinine clearance by 50% or more, progression to end-stage renal disease, or death.

RESULTS

At 24 months, disease was worsened in 24 of 89 patients who received eprodisate (27%) and 38 of 94 patients given placebo (40%, P=0.06); the hazard ratio for worsening disease with eprodisate treatment was 0.58 (95% confidence interval, 0.37 to 0.93; P=0.02). The mean rates of decline in creatinine clearance were 10.9 and 15.6 ml per minute per 1.73 m² of body-surface area per year in the eprodisate and the placebo groups, respectively (P=0.02). The drug had no significant effect on progression to end-stage renal disease (hazard ratio, 0.54; P=0.20) or risk of death (hazard ratio, 0.95; P=0.94). The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Eprodisate slows the decline of renal function in AA amyloidosis. (ClinicalTrials.gov number, NCT00035334.)

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THE AMYLOIDOSES CONSTITUTE A GROUP of diseases in which proteins are deposited extracellularly in the tissues as insoluble fibrils, causing progressive organ dysfunction and death.[1] Amyloid A (AA) amyloidosis, also referred to as secondary amyloidosis, is a rare but serious complication of chronic inflammatory diseases and chronic infections. The amyloidogenic protein in AA amyloidosis is a proteolytic fragment of serum amyloid A protein (SAA), an acute-phase reactant produced by the liver. The kidney is the organ most frequently affected in AA amyloidosis.[2] Ongoing deposition of amyloid in the kidney results in proteinuria and progressive loss of renal function. The gastrointestinal tract, the liver, the autonomic nervous system, and, less frequently, the heart, are other sites of AA amyloid deposition.

Treatments that reduce production of the amyloidogenic protein can improve organ function and survival in immunoglobulin-light-chain–related (AL) amyloidosis and hereditary transthyretin-associated (ATTR) amyloidosis.[3-8] In AA amyloidosis, production of SAA can sometimes be decreased by treatment of the underlying inflammatory condition.[9] In many patients, however, production of SAA cannot be sufficiently suppressed, and formation of AA amyloid fibrils and their deposition in the tissues persist. No treatment directly targets AA amyloid formation.[1]

Several lines of investigation suggest that glycosaminoglycans, such as heparan sulfate, are critical in the pathogenesis of amyloidosis. Interactions between amyloidogenic proteins and glycosaminoglycans promote fibril assembly and stabilize amyloid deposits in tissues.[10-14] Eprodisate (Kiacta, Neurochem) is a negatively charged, sulfonated molecule of low molecular weight that has structural similarities to heparan sulfate.[14,15] The compound, a member of a new class of agents that interfere with interactions between amyloidogenic proteins and glycosaminoglycans,[14-16] inhibits the development of amyloid deposits in the tissues in mouse models of AA amyloidosis.[14,15] To determine whether eprodisate prevents the progression of AA amyloidosis in humans, we conducted a multicenter, randomized, double-blind, placebo-controlled trial in patients with AA amyloidosis–associated nephropathy.

METHODS

PARTICIPANTS

Patients with AA amyloidosis and kidney involvement were enrolled from 27 centers in 13 countries. The diagnosis of AA amyloidosis required histologic demonstration of Congo red staining and birefringence with the use of polarized microscopy and reactivity with anti-AA antibodies by immunohistochemical analysis, immunofluorescence, or immunoelectron microscopy. Kidney involvement was defined as 24-hour urinary excretion of more than 1 g of protein in two 24-hour urine collections obtained at least 1 week apart within 3 months before study entry, or creatinine clearance of less than 60 ml per minute according to two measurements performed at least 1 week apart within 3 months before study entry. The exclusion criteria were kidney disease other than AA amyloidosis, creatinine clearance less than 20 ml per minute, serum creatinine concentration more than 3 mg per deciliter (265 μmol per liter), diabetes mellitus, elevated liver enzymes (alanine transaminase, aspartate transaminase, or alkaline phosphatase more than 5 times the upper limit of normal), or bilirubin more than 1.5 times the upper limit of normal. The study was approved by the institutional review boards at each center. All patients provided written informed consent.

STUDY PROCEDURES

Patients were randomly assigned in equal proportions to receive eprodisate or placebo. The placebo, provided by Neurochem, consisted of capsules that were identical in appearance to active drug. The identity of the study medication was indicated on a card inside an individual sealed envelope. Patients were stratified according to nephrotic status (nephrotic versus non-nephrotic) and treatment center. Classification as nephrotic required a 24-hour urinary excretion of more than 3 g of protein, a serum albumin concentration of less than 3.4 g per deciliter, and either the presence of peripheral edema or the use of diuretics to treat peripheral edema.

The study drug was administered orally twice daily at least 1 hour before or 2 hours after a meal. Because eprodisate is excreted by the kidney, the initial dose was based on creatinine clearance. Patients with creatinine clearance rates of less than

30 ml per minute received a total of 800 mg of eprodisate per day in two divided doses, those with rates of 30 to 80 ml per minute received a total of 1600 mg of eprodisate per day in two divided doses, and those with rates of more than 80 ml per minute received a total of 2400 mg of eprodisate per day in two divided doses. Doses were decreased during the study if creatinine clearance decreased. Treatment of the underlying inflammatory disease was determined by the patient's physician. For those patients who were being treated with angiotensin-converting–enzyme inhibitors, cytotoxic agents, tumor necrosis factor (TNF) antagonists, or colchicine, stability of the dose was required for 3 months before enrollment.

Patients underwent randomization and the study drug was initiated at a baseline visit within 1 month after the screening evaluation. Follow-up visits occurred at 1, 4, 8, 12, 16, 20, and 24 months after randomization, and patients were contacted by telephone at 2, 6, 10, 14, 18, and 22 months after randomization. At each visit, creatinine clearance and urinary protein excretion were measured by 24-hour urine collection. Compliance with study medication was assessed by pill counts at each visit and expressed as the percentage of the number of pills prescribed that had been taken.

At baseline and at the 12- and 24-month visits, abdominal fat was collected by aspiration for Congo red staining and quantification of amyloid content by an enzyme-linked immunosorbent assay with murine monoclonal antibodies to SAA.[17] Staining of abdominal fat and quantification of amyloid were performed in the laboratory of one of the investigators by persons who were unaware of treatment assignment.

Study medication was continued for 24 months unless the patient had progression to end-stage renal disease, had an adverse event that precluded further use of study medication, withdrew from the study, or required a rescue medication. Rescue medications included cytotoxic agents, colchicine, and anti-TNF agents initiated because of manifestations of AA amyloidosis.

SAA concentration was determined by latex nephelometry with a Dade Behring BNII autoanalyzer in the laboratory of one of the investigators.[18] Erythrocyte sedimentation rates were measured at the study sites. All other laboratory measurements were performed at central laboratories (Covance Central Laboratory Services).

OUTCOME MEASURES

The primary end point was a composite assessment of renal function or death. Disease was classified as worsened if the serum creatinine concentration was twice the baseline value, creatinine clearance decreased by 50% or more from baseline, progression to end-stage renal disease occurred, or the patient died. End-stage renal disease was defined as the need for initiation of maintenance dialysis. Disease was classified as improved if creatinine clearance increased by at least 50% from baseline and none of the indicators of worsened disease were present. Disease was classified as stable if none of the indicators of either worsened or improved disease were present. Each patient's disease status was determined by an endpoint adjudication committee composed of a subgroup of investigators who were unaware of the patient's treatment status.

Among the major secondary outcomes were slope of creatinine clearance, change in proteinuria, resolution or development of chronic diarrhea, and change in the amyloid content of abdominal fat. In all analyses that included creatinine clearance, the measured value was normalized for body-surface area.

STATISTICAL ANALYSIS

Two analyses of the primary composite end point were performed. The proportions of patients in the two treatment groups who had worsened, improved, or stable disease at the 24-month visit were compared by the Cochran–Mantel–Haenszel row mean-scores test, with the last observation carried forward for those who discontinued participation before 24 months. The times to first event of worsened disease in the two treatment groups were compared by Cox proportional-hazards analysis. Patients with no follow-up data after the baseline visit were classified as having worsened status. The P value for the Cox proportional-hazards analysis was calculated by the Wald chi-square test. For both the Cochran–Mantel–Haenszel test and the Cox proportional-hazards model, the patients were stratified according to baseline nephrotic status. The analyses were performed according to the intention-to-treat principle.

Additional Cox proportional-hazards analyses were performed with adjustment for potentially important baseline variables and time-dependent variables. Event-free survival was estimated with the use of the Kaplan–Meier method, and comparisons between survival curves were made with the use of the log-rank test. The slopes of creatinine clearance for the two treatment groups were compared by the Iman–Conover test. All statistical analyses were two-sided, and P values less than 0.05 were considered to indicate statistical significance.

With a sample size of 180 patients, the study had 85% power at a two-sided alpha level of 0.05 to detect an absolute difference of 20% in the proportion of patients in the treatment groups who had worsened disease. This calculation assumes a rate of worsening disease of 40% in the placebo group.

Interim safety analyses of data were performed by an independent data and safety monitoring board unaware of treatment assignment. The safety analyses were performed after 30 patients had been followed for at least 4 months and every 8 months thereafter until completion of the study. Interim analyses of efficacy were not performed.

The study was designed by a group of the investigators in collaboration with the sponsor, Neurochem. Data were collected by the study teams at each site and transmitted to the sponsor. The complete data set was maintained at Quintiles Canada. Statistical analyses and data interpretation were conducted by the investigators, by Neurochem, and by consultants from Quintiles Canada and Syreon with the use of SAS software, version 8.2. The investigators made the decision to publish the findings, were responsible for writing the article, had unrestricted access to the data, and were not limited by the sponsor with regard to statements made in the article. Drs. Dember, Balshaw, and Hauck vouch for the integrity and completeness of the data.

RESULTS

PATIENTS

Between July 11, 2001, and February 14, 2003, a total of 261 patients were screened and 183 were randomly assigned to treatment with eprodisate (89 patients) or placebo (94 patients). The final study visit occurred on December 2, 2004. A total of 124 patients (63 in the eprodisate group and 61 in the placebo group) completed 2 years of the study (Fig. 1). Approximately half the patients who discontinued participation early did so because of progression to end-stage renal disease or death.

Table 1 lists the baseline characteristics of the patients. Rheumatoid arthritis (49% of patients) and familial Mediterranean fever (19%) were the most common underlying inflammatory diseases. Underlying chronic infection was more frequent in the eprodisate group than in the placebo group, and several of the patients in the eprodisate group with chronic infection also had a chronic inflammatory disease. The median serum creatinine concentration at baseline was slightly higher in the placebo group than in the eprodisate group (1.3 mg per deciliter vs. 1.1 mg per deciliter [115 μmol per liter vs. 97 μmol per liter], P=0.05). The mean diastolic blood pressure in the supine position was slightly lower in the eprodisate group than in the placebo group (78 mm Hg vs. 82 mm Hg, P=0.01), but no significant differences between groups in either systolic or diastolic blood pressure were found at any of the follow-up visits. The mean compliance with drug administration was 95.3±8.7% in the eprodisate group and 94.6±12.8% in the placebo group. Blinding of treatment assignment was maintained for all patients for the duration of the study.

PRIMARY COMPOSITE END POINT

Because improvement of renal disease was so infrequent in both groups (improvement occurred in only one patient in the eprodisate group and two patients in the placebo group), patients with improved or stable disease were grouped together, as prespecified, for the analysis of disease status. At the end of follow-up, disease was worsened in 24 of 89 patients assigned to eprodisate (27%) and 38 of 94 assigned to placebo (40%, P=0.06). When the original three-category classification of patient outcomes (improved, stable, or worsened disease) was maintained, the P value for the difference between the two treatment groups was 0.08.

According to Cox proportional-hazards analysis, treatment with eprodisate was associated with a 42% reduction in the risk of worsening renal disease or death (hazard ratio, 0.58; 95% confidence interval [CI], 0.37 to 0.93%; P=0.02) (Ta-

Figure 1. Enrollment and Outcome of Patients.
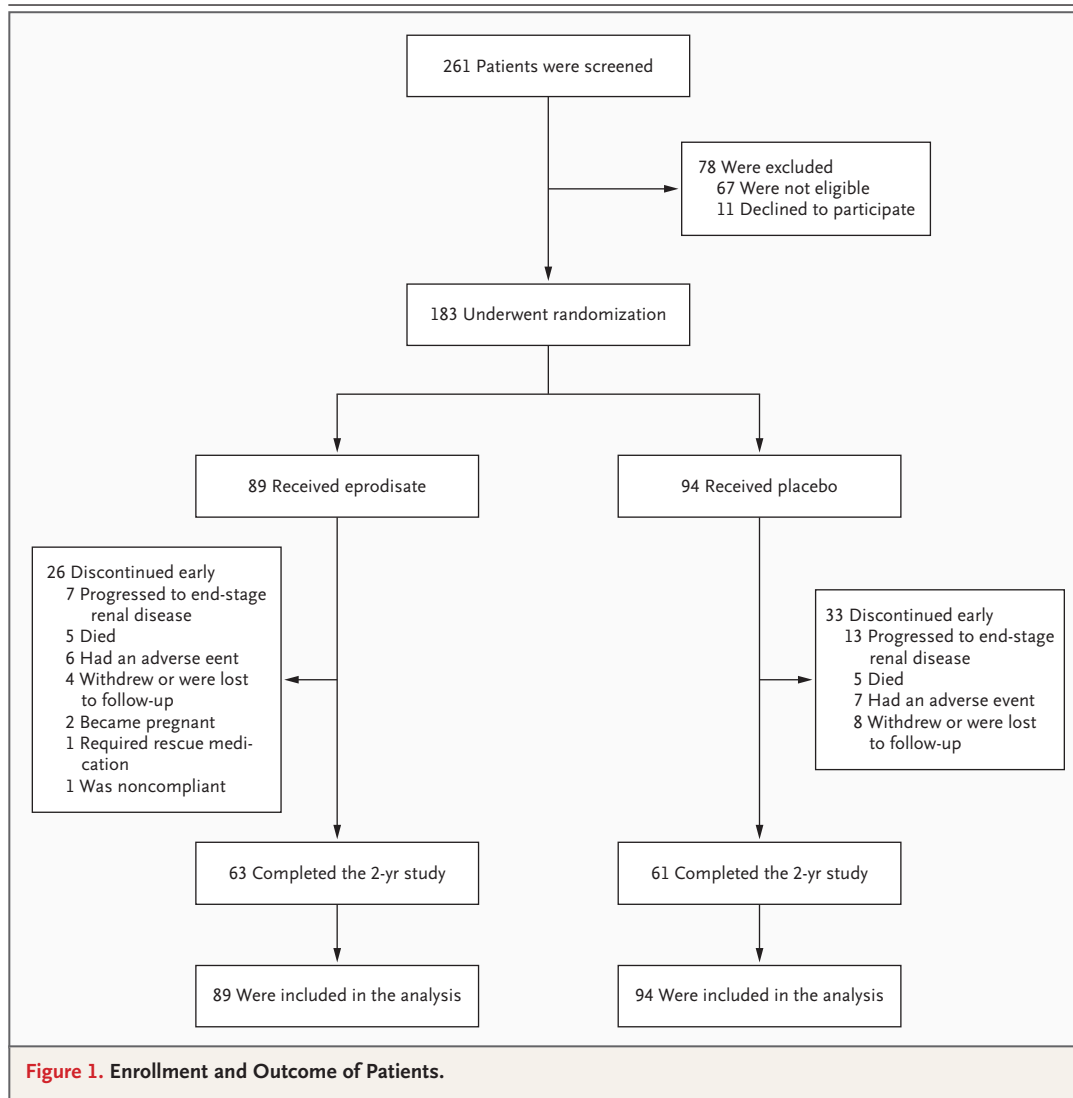
ble 2 and Fig. 2A). The risk reduction with epro-disate was maintained after adjustment of the analysis for potentially important baseline variables and for SAA concentration as a time-dependent variable (Table 2). The benefit of eprodisate on the primary composite end point of renal function or death was due to its effect on the progression of renal disease (Table 2). There was no significant difference between the two groups in the risk of death.

SECONDARY OUTCOMES

The mean (±SE) slope of creatinine clearance was −10.9±5.1 ml per minute per 1.73 m² of body-surface area per year in the eprodisate group, as compared with −15.6±4.0 ml per minute per 1.73 m² per year in the placebo group (P=0.02). The change in the urinary protein excretion between baseline and study completion varied substantially within both treatment groups, but overall there was no significant difference in either group between the mean (±SD) baseline and final values (−0.03±3.5 g per 24 hours in the eprodisate group and −0.22±3.1 g per 24 hours in the placebo group, P=0.92). Similarly, there was no significant difference between treatment groups in the proportion of patients with chronic diarrhea at study completion (4% in the eprodisate

Table 1. Baseline Demographic and Clinical Characteristics of Patients.*

Characteristic	Eprodisate (N = 89)	Placebo (N = 94)	P Value†
Female sex (% of patients)	55	61	0.45
Age (yr)	50±14	52±13	0.40
Weight (kg)	67.1±17.6	64.9±13.1	0.63
Systolic blood pressure (mm Hg)	130±23	132±19	0.22
Diastolic blood pressure (mm Hg)	78±12	82±11	0.01
Underlying disease (% of patients)‡			
Inflammatory arthritis	70	64	0.40
Hereditary fever syndromes	17	22	0.35
Chronic infection	21	9	0.01
Inflammatory bowel disease	3	7	0.22
Duration of biopsy-proven amyloidosis (mo)			0.65
Median	22.4	24.8	
Interquartile range	0.2–387.0	0.4–230.7	
Inflammatory markers			
SAA§			0.14
Median (mg/liter)	16.0	24.0	
Interquartile range (mg/liter)	6.5–41.2	7.6–51.7	
<10 mg/liter (% of patients)	35	27	
10–50 mg/liter (% of patients)	47	47	
51–100 mg/liter (% of patients)	10	12	
>100 mg/liter (% of patients)	8	14	
C-reactive protein (mg/liter)¶			0.14
Median	9.2	15.3	
Interquartile range	3.8–22.7	5.1–26.5	
Erythrocyte sedimentation rate (mm/hr)‖			0.31
Median	58.5	77.0	
Interquartile range	37.0–96.0	40.0–104.0	
Renal function			
Serum creatinine (mg/dl)**			0.05
Median	1.1	1.3	
Interquartile range	0.8–1.7	0.9–1.8	
Creatinine clearance (ml/min/1.73 m² of body-surface area)			0.16
Median	65.9	51.9	
Interquartile range	39.9–101.1	36.8–79.7	
Creatinine clearance <60 ml/min/1.73 m² (% of patients)	46	57	0.11
Proteinuria (g of protein/24 hr)			0.98
Median	3.1	3.2	
Interquartile range	1.2–5.4	1.2–6.0	
Nephrotic syndrome (% of patients)††	38	42	0.65

Table 1. (Continued.)

Characteristic	Eprodisate (N = 89)	Placebo (N = 94)	P Value†
Extrarenal disease (% of patients)			
Orthostatic hypotension	5	12	0.11
Hepatomegaly	6	6	1.00
Chronic diarrhea	11	11	1.00
Medications (% of patients)			
ACE inhibitor or ARB	49	52	0.72
TNF antagonist	10	12	0.57

* Plus–minus values are means ±SD. SAA denotes serum amyloid A protein, ACE angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, and TNF tumor necrosis factor.

† The chi-square or Fisher's exact test was used for categorical data; Wilcoxon's rank-sum test was used for continuous data. For variables that are not normally distributed, the Iman and Conover approach of a model based on the treatment group and adjusted for nephrotic status at baseline was used.

‡ Inflammatory arthritis includes rheumatoid arthritis, psoriatic arthritis, and reactive arthritis. Hereditary fever syndromes include familial Mediterranean fever and the Muckle–Wells syndrome. Chronic infection includes osteomyelitis, tuberculosis, and bronchiectasis. Because several patients had more than one underlying disease, the sum of the proportions in each category is more than 100%.

§ The normal value for SAA is less than 10 mg per liter.

¶ The normal value for C-reactive protein is 0.287 mg per deciliter or less.

‖ Normal values for erythrocyte sedimentation rate are 0 to 15 mm per hour for men 50 years of age or younger, 0 to 20 mm per hour for men over 50 years of age, 0 to 20 mm per hour for women 50 years of age or younger, and 0 to 30 mm per hour for women over 50 years of age.

** To convert the values for creatinine to micromoles per liter, multiply by 88.4.

†† A diagnosis of nephrotic syndrome requires all of the following: proteinuria more than 3 g of protein per 24 hours, serum albumin less than 3.4 g per deciliter, and edema or use of diuretics to treat edema.

group vs. 1% in the placebo group, P=0.34) or in the change in the amyloid content of abdominal fat between baseline and study completion (41±1664 ng per milligram of fat in the eprodisate group vs. −132±824 ng per milligram of fat in the placebo group, P=0.45). SAA concentrations fluctuated substantially within both groups throughout the study but did not differ significantly between the groups at any time point.

THE NEPHROTIC SYNDROME

Within both treatment groups, disease worsening occurred more frequently among patients with than among those without the nephrotic syndrome, and the effect of eprodisate on the primary composite end point was more apparent among patients with the nephrotic syndrome (Fig. 2B). However, there was no significant interaction between baseline nephrotic status and treatment effect (P=0.23).

ADVERSE EVENTS

The frequency and types of adverse events were similar in the two treatment groups (Table 3).

Five patients in each group died during or within 15 days after completion of administration of the study drug. The causes of death in the eprodisate group were ischemic stroke in two patients, the nephrotic syndrome in one patient, gastrointestinal hemorrhage in one, and pneumonia in one. The deaths in the placebo group were due to ischemic stroke, amyloid cardiomyopathy, bowel perforation, sepsis, and pancytopenia in one patient each. None of the deaths were considered by the investigators to be related to the study drug. Two patients in the eprodisate group became pregnant. In both cases, the study medication was discontinued as soon as the pregnancy was known. Both patients elected to terminate the pregnancy.

DISCUSSION

We found that eprodisate reduced the progression of AA amyloidosis–associated renal disease. Eprodisate decreased the risk of the primary end point, a composite of worsening renal function or death, by 42%, and the reduction in risk was largely independent of baseline renal function or

Table 2. Cox Proportional-Hazards Models for the Primary End Point.*		
Variable	Hazard Ratio (95% CI)	P Value
Covariates of adjusted models		
None	0.58 (0.37–0.93)	0.02
Underlying disease†	0.56 (0.35–0.90)	0.02
Baseline serum creatinine concentration	0.61 (0.38–0.98)	0.04
Baseline creatinine clearance	0.57 (0.37–0.94)	0.03
Baseline urinary protein excretion	0.56 (0.35–0.90)	0.02
Baseline use of ACE inhibitor or ARB	0.60 (0.37–0.95)	0.03
Baseline blood pressure‡	0.57 (0.36–0.92)	0.02
Baseline SAA concentration	0.61 (0.38–0.99)	0.04
SAA concentration throughout study	0.59 (0.37–0.95)	0.03
Components of primary composite outcome		
Doubling of serum creatinine concentration	0.41 (0.19–0.86)	0.02
≥50% Reduction in creatinine clearance	0.48 (0.28–0.82)	0.01
End-stage renal disease	0.54 (0.22–1.37)	0.20
Death	0.95 (0.27–3.29)	0.94

* All models were adjusted for the stratification variable of nephrotic status. ACE denotes angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, and SAA serum amyloid A protein.
† Underlying disease was categorized as rheumatoid arthritis, familial Mediterranean fever, or other.
‡ Mean arterial blood pressure values were calculated from systolic and diastolic blood pressure measurements.

SAA concentration throughout the study. As compared with placebo, eprodisate significantly reduced the risk of a doubling of serum creatinine, the risk of a 50% reduction in creatinine clearance, and the slope of decline in creatinine clearance. These benefits are clinically meaningful and were evident early in the course of treatment. The adverse-event profiles of the drug and the placebo were not significantly different.

The risk reductions associated with eprodisate for the dichotomous renal end points (doubling of serum creatinine or a 50% or greater decrease in creatinine clearance) are substantial, as is the effect of the drug on the slope of creatinine clearance. The decline in creatinine clearance was 4.7 ml per minute per 1.73 m² per year greater in the placebo group than in the eprodisate group, a relative difference of 30%. The effect of the drug on progression to end-stage renal disease was not significant (hazard ratio, 0.54; P=0.20). Many of the patients had substantial renal impairment at baseline. Creatinine clearance was less than 60 ml per minute for more than half the patients and between 20 ml per minute and 30 ml

per minute for 13% of the patients. It is possible that the drug would have a greater benefit if initiated at earlier stages of disease.

Although eprodisate decreased the rate of deterioration in renal function, it did not affect proteinuria. In AA amyloidosis, proteinuria probably results from damage caused by the amyloid deposits as well as from glomerular toxicity of the SAA oligomers or protofibrils, which are the precursors to mature fibrils. Rapid resolution of proteinuria has been reported in AA amyloidosis when the underlying inflammatory disease is in remission and SAA concentrations have returned to normal, despite the persistence of glomerular amyloid deposits.[19,20] According to its putative mechanism of action, eprodisate should prevent new amyloid formation but have no effect on the concentration of SAA and might not reduce the formation of SAA oligomers or protofibrils. The benefit of the drug for renal deterioration may result from a reduction in the rate of amyloid formation, whereas the persistence of fibril precursors may explain its lack of effect on proteinuria. The benefit of eprodisate was more appar-

Figure 2. Kaplan–Meier Estimates of Event-free Survival.

Panel A shows survival for all patients. Survival for patients with (Panel B) and for those without (Panel C) the nephrotic syndrome are also shown. An event is any component of the composite end point of worsened disease. The number of patients at risk for the end point drops markedly between 20 and 24 months because many patients completed their final study visit just before 24 months. Only patients who completed their final study visit at 24 months or later are included in the at-risk population at 24 months.

A All Patients

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

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

No. at Risk						
Eprodisate	55	52	45	41	37	35	10
Placebo	55	44	39	36	34	34	6

ent in the subgroup of patients with the nephrotic syndrome. High-grade proteinuria is probably an indicator of activity of the underlying inflammatory disease and identifies patients at greatest risk for progression of amyloid-associated organ dysfunction.

As expected, treatment with eprodisate did not affect SAA levels. Eprodisate had no detectable effect on the amyloid content of abdominal fat, a finding consistent with the observation that the amyloid content of abdominal fat persists or decreases very slowly after 2 or more years in patients with AL or ATTR amyloidosis after interventions that eliminate new amyloid production (Skinner M et al. and Hazenberg B et al.: unpublished data).

Our trial has some limitations. Although the study was randomized, serum creatinine concentrations were slightly higher in the placebo group than in the eprodisate group. A difference in baseline renal function could explain the better outcomes in the eprodisate group, but the risk reduction associated with eprodisate persisted when the analyses were adjusted for baseline creatinine concentration or creatinine clearance. In addition, treatments for the underlying inflammatory diseases were not standardized. However, the treating physicians were unaware of treatment assignment, inflammatory markers did not differ between groups throughout the duration of the study, and the effect of eprodisate on the primary outcome was maintained after time-dependent adjustment for SAA levels. Thus, it is unlikely that differences in the status of the underlying inflammatory disease were responsible for the observed benefit of the drug. The numbers of adverse events in the eprodisate and placebo groups were similar, but additional experience will be needed to further evaluate the safety of the drug.
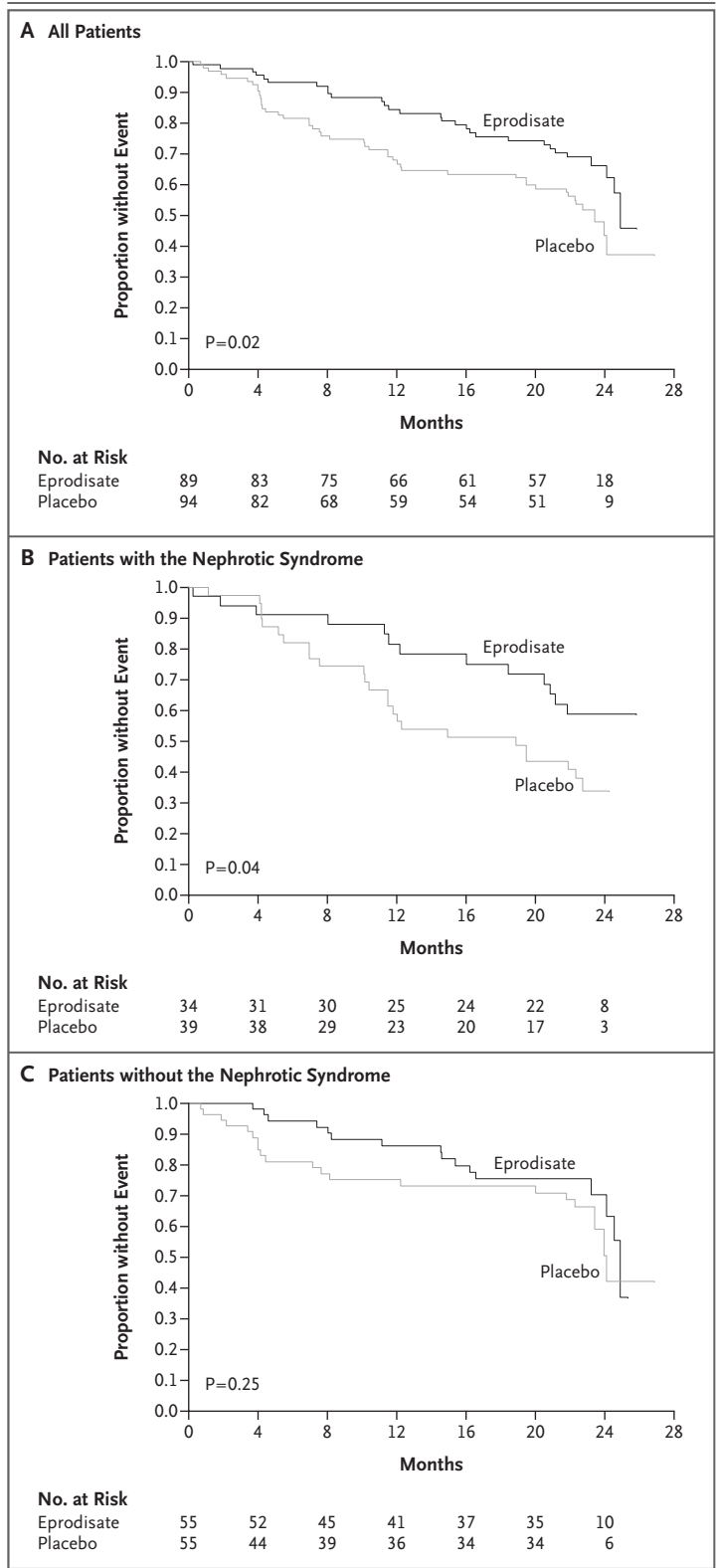
Table 3. Adverse Events.*

Event	Eprodisate (N = 89)	Placebo (N = 94)
	no. of patients (%)	
Patients with at least one adverse event	87 (98)	87 (93)
Most common nonserious adverse events†		
Musculoskeletal disorder	37 (42)	32 (34)
Diarrhea	34 (38)	26 (28)
Upper respiratory symptoms	29 (33)	29 (31)
Headache	26 (29)	28 (30)
Nausea or vomiting	24 (27)	25 (27)
Abdominal pain or dyspepsia	23 (26)	30 (32)
Cough or bronchitis	23 (26)	20 (21)
Edema	16 (18)	17 (18)
Dizziness	10 (11)	5 (5)
Hypertension	9 (10)	10 (11)
Pruritus	9 (10)	7 (7)
Tachycardia, palpitations, or atrial fibrillation	8 (9)	7 (7)
Toothache	8 (9)	5 (5)
Anemia	7 (8)	10 (11)
Renal insufficiency	6 (7)	6 (6)
Fatigue	6 (7)	7 (7)
Pneumonia	6 (7)	2 (2)
Urinary tract infection	5 (6)	5 (5)
Chest pain	5 (6)	3 (3)
Insomnia	5 (6)	3 (3)
Patients with at least one serious adverse event‡	32 (36)	39 (42)
Most common serious adverse events§		
Myocardial infarction	2 (2)	0
Diarrhea	3 (3)	2 (2)
Vomiting	2 (2)	1 (1)
Gastrointestinal hemorrhage	0	2 (2)
Pneumonia	3 (3)	2 (2)
Gastroenteritis	0	2 (2)
Infection	2 (2)	0
Hyperkalemia	0	2 (2)
Renal impairment	7 (8)	11 (12)
Nephrotic syndrome	2 (2)	0
Dyspnea	2 (2)	2 (2)
Death	5 (6)	5 (5)

* P>0.05 for all comparisons between treatment groups.
† The most common nonserious adverse events are defined as those experienced by at least 5% of the patients in the eprodisate group.
‡ A serious adverse event is defined as any event that was fatal, life-threatening, or disabling; resulted in hospitalization or prolongation of a hospitalization; was associated with a congenital abnormality or cancer; or was regarded by the investigator as serious.
§ The most common serious adverse events are defined as those experienced by at least 2% of all patients or by at least two patients in either group.

The trial has several strengths. The sample size of 183 patients is substantial for this rare disease. The patients were heterogeneous with respect to underlying disease, race or ethnic group, and duration of disease, making it likely that we can generalize the findings to patients with AA amyloidosis due to a variety of inflammatory conditions. Compliance in the study was high, and the end points were rigorous and clinically meaningful.

In conclusion, eprodisate delays the progression of AA amyloidosis–associated renal disease. The drug directly targets formation of AA amyloid rather than the underlying inflammatory condition and is a member of a new class of compounds designed to interfere with amyloid–glycosaminoglycan interactions. This treatment approach has potential applicability to other types of amyloidosis, including AL amyloidosis, familial amyloidosis, and Alzheimer's disease.[15,21]

APPENDIX

The composition of the EFAAT Group committees is as follows: Protocol Steering Committee — L.M. Dember, P.N. Hawkins, B.P.C. Hazenberg, M. Skinner; Data and Safety Monitoring Committee — A. Bhargava, A. Faragasso, K. Levy; End-Points Adjudication Committee — L.M. Dember, B.P.C. Hazenberg, P. Keown, H. Lachmann, P.N. Hawkins, M. Skinner; Investigators: *Finland* — K. Kaarela, Rheumatism Foundation Hospital, Heinola; *France* — G. Grateau, Hôpital Tenon, Paris; E. Hachulla, Hôpital Claude Huriez, Lille; X. Puéchal, Centre Hospitalier du Mans, Le Mans; *Israel* — A. Livneh, Sheba Medical Center, Tel-Hashomer; I. Rosner, Bnai Zion Medical Center, Technion Faculty of Medicine, Haifa; *Italy* — G. Merlini, L. Obici, Amyloidosis Center, Foundation IRCCS Policlinico San Matteo, Pavia; *Lithuania* — I. Butrimiene, G. Kirdaite, D. Povilenaite, A. Venalis, Vilnius University Institute of Experimental and Clinical Medicine, Vilnius; *the Netherlands* — J. Bijzet, B.P.C. Hazenberg, University Medical Center Groningen, University of Groningen, Groningen; *Poland* — A. Filipowicz-Sosnowska, Institute of Rheumatology, Warsaw; P. Wiland, A. Chlebicki, Medical University, Wroclaw; *Russia* — O. Lesnyak, N. Koryakova, A. Sibiryakova, Regional Hospital No. 1, Yekaterinburg; E.L. Nasonov, M. Stanislav, Russian Academy of Medical Sciences Institute of Rheumatology, Moscow; *Spain* — J.A. Jover, Hospital Clinico Universitario San Carlos, Madrid; J. Muñoz Gómez, Hospital Clinic, Barcelona; X. Tena Marsà, Hospital Universitari Germans Trias i Pujol, Badalona; J. Valverde Garcia, Hospital Universitari de Bellvitge, Barcelona; *Tunisia* — H. Ben Maïz, F. Ben Moussa, R. Goucha, H. Kaaroud, Hôpital Charles Nicolle, Tunis; *Turkey* — H. Direskeneli, M. Temel, Marmara University Faculty of Medicine, Istanbul; A. Gul, S. Kamali, University of Istanbul (Capa), Istanbul; G. Hatemi, H. Ozdogan, University of Istanbul, Cerrahpasa Faculty of Medicine, Istanbul; *United Kingdom* — P.N. Hawkins, H.J. Lachmann, National Amyloidosis Center, Royal Free Hospital, London; J.A. Hunter, Gartnavel General Hospital, Glasgow; *United States* — L.M. Dember, M. Skinner, Boston University School of Medicine, Boston; M.D. Benson, Indiana University School of Medicine, Indianapolis; A. Dispenzieri, Mayo Clinic, Rochester, MN; P.D. Gorevic, Mt. Sinai Medical Center, New York.

REFERENCES

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med 2003; 349:583-96.
2. Gertz MA, Kyle RA. Secondary systemic amyloidosis: response and survival in 64 patients. Medicine (Baltimore) 1991;70:246-56.
3. Dember LM, Sanchorawala V, Seldin DC, et al. Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. Ann Intern Med 2001;134:746-53.
4. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004;140:85-93.
5. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. Blood 2004;103:3960-3.

6. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004;103:2936-8.
7. Holmgren G, Ericzon BG, Groth CG, et al. Clinical improvement and amyloid regression after liver transplantation in hereditary transthyretin amyloidosis. Lancet 1993;341:1113-6.
8. Herlenius G, Wilczek HE, Larsson M, Ericzon BG. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation 2004;77:64-71.
9. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. Lancet 2001;358:24-9.
10. Snow AD, Willmer J, Kisilevsky R. Sulfated glycosaminoglycans: a common constituent of all amyloids? Lab Invest 1987;56:120-3.
11. Lyon AW, Narindrasorasak S, Young ID, et al. Co-deposition of basement membrane components during the induction of murine splenic AA amyloid. Lab Invest 1991;64:785-90.
12. Stenstad T, Magnus JH, Husby G. Characterization of proteoglycans associated with mouse splenic AA amyloidosis. Biochem J 1994;303:663-70.
13. Kisilevsky R. The relation of proteoglycans, serum amyloid P and apo E to amyloidosis current status, 2000. Amyloid 2000;7:23-5.
14. Gervais F, Morissette C, Kong X. Proteoglycans and amyloidogenic proteins in peripheral amyloidosis. Curr Med Chem Immun Endocr Metab Agents 2003;3:361-70.

15. Kisilevsky R, Lemieux LJ, Fraser PE, Kong X, Hultin PG, Szarek WA. Arresting amyloidosis in vivo using small-molecule anionic sulphonates or sulphates: implications for Alzheimer's disease. Nat Med 1995;1:143-8.

16. Gervais F, Chalifour R, Garceau D, et al. Glycosaminoglycan mimetics: a therapeutic approach to cerebral amyloid angiopathy. Amyloid 2001;8:Suppl 1:28-35.

17. Hazenberg BP, Limburg PC, Bijzet J, van Rijswijk MH. A quantitative method for detecting deposits of amyloid A protein in aspirated fat tissue of patients with arthritis. Ann Rheum Dis 1999;58:96-102.

18. Wilkins J, Gallimore JR, Tennent GA, et al. Rapid automated enzyme immunoassay of serum amyloid A. Clin Chem 1994;40:1284-90.

19. Crowley S, Feinfeld DA, Janis R. Resolution of nephrotic syndrome and lack of progression of heroin-associated renal amyloidosis. Am J Kidney Dis 1989;13:333-5.

20. Verschueren P, Lensen F, Lerut E, et al. Benefit of anti-TNFalpha treatment for nephrotic syndrome in a patient with juvenile inflammatory bowel disease associated spondyloarthropathy complicated with amyloidosis and glomerulonephritis. Ann Rheum Dis 2003;62:368-9.

21. Gervais F, Paquette J, Morissette C, et al. Targeting soluble Abeta peptide with tramiprosate for the treatment of brain amyloidosis. Neurobiol Aging 2007;28: 537-47.

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