No Improvement in Survival of Patients with Amyloidosis Associated with Inflammatory Rheumatic Diseases — Data from the Finnish National Registry for Kidney Diseases

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ABSTRACT. ***Objective.*** To assess the incidence and outcome of renal replacement therapy (RRT) among patients with amyloidosis associated with inflammatory rheumatic diseases.

Methods. Patients with amyloidosis entering RRT from 1987 to 2002 were identified from the Finnish Registry for Kidney Diseases. Five hundred two patients were identified, 80% of whom had amyloidosis associated with an underlying rheumatic disease. They were followed from the time of entering RRT until death or until the end of 2003 using the Finnish national mortality files.

Results. During the study period, there was no decline in the number of patients with amyloidosis entering RRT. Mean age of patients with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) increased significantly from 1987 to 2002 ($p < 0.001$). Male sex and a diagnosis of JIA indicated an increased risk of mortality. The median survival time after entering RRT was 2.11 years for RA (95% CI 1.93 to 2.69), 2.37 years for ankylosing spondylitis (95% CI 1.11 to 4.31), and 3.05 years for JIA (95% CI 2.19 to 4.23). The 5-year survival rates among patients with the corresponding diagnoses were 18% (95% CI 14% to 23%), 30% (95% CI 14% to 48%), and 27% (95% CI 14% to 41%), respectively.

Conclusion. No decline was seen in the number of patients with amyloidosis associated with inflammatory rheumatic diseases accepted for RRT, but over the years, the age of patients with RA or JIA entering RRT was seen to increase. The outcome of patients with amyloidosis and endstage renal disease associated with rheumatic diseases remains poor. (First Release April 15 2008; J Rheumatol 2008;35:1334–8)

Key Indexing Terms:
RENAL REPLACEMENT THERAPY AMYLOIDOSIS ANKYLOSING SPONDYLITIS
RHEUMATOID ARTHRITIS RENAL DISORDER JUVENILE IDIOPATHIC ARTHRITIS

Due to the decline in the prevalence of tuberculosis and other chronic infections, inflammatory rheumatic diseases have become the most common cause of secondary amyloidosis or AA amyloidosis. Especially in Europe, amyloidosis has been the most feared complication of inflammatory rheumatic diseases. Uremia caused by renal amyloidosis has appeared as a cause of death in Finnish patients with rheumatoid arthritis (RA) at an exceptionally high rate, with similar trends for patients with ankylosing spondylitis (AS) and juvenile idiopathic arthritis (JIA)[1-4].

In a population-based mortality series of patients with RA from Finland, 15% of surplus deaths were due to renal amyloidosis[1]. Lehtinen examined the mortality and causes of death in a cohort of 398 patients with AS admitted to hospital for the first time between 1961 and 1969[5]. After a mean followup of 25 years an overall mortality rate 1.5 times higher than expected was observed, with a high incidence of deaths mainly due to amyloidosis. In a nationwide analysis on causes of mortality in patients ≤ 24 years with JIA, amyloidosis accounted for 42% and 17% of deaths in the periods 1969-79 and 1980-90, respectively[4].

The data from recent decades are controversial concerning a possible change in the incidence of overt clinical amyloidosis associated with inflammatory rheumatic diseases. A Japanese series in which the occurrence of this form of amyloidosis was studied using renal biopsy material from 1979 to 1996 did not show any decline[6]. However, there is a report from a single center in Finland with a sharp decline of new cases admitted to dialysis due to amyloidosis among patients

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Accepted for publication February 27, 2008.

with inflammatory joint diseases in the 1990s[7]. This was explained by a marked shift from the use of only symptomatic treatment or a single disease modifying antirheumatic drug (DMARD) to the more common use of immunosuppressive drugs and/or combinations of at least 2 DMARD[7]. With respect to JIA there are reports of a decreased incidence of amyloidosis and a better prognosis[4,8-11], which also has been attributed to a more active treatment strategy and mainly to the use of cytotoxic drugs. In addition, there is a Finnish report from the Rheumatism Foundation Hospital, which acts as secondary center, of a sharp decline in the annual number of subcutaneous abdominal fat tissue aspiration biopsies for detecting amyloidosis due to inflammatory rheumatic diseases that can be attributed to a change in the number of patients with clinical suspicion of amyloidosis[12].

Overall, amyloidosis associated with rheumatic diseases carries a poor outcome. In their recent study of a population-based Finnish RA series, Sihvonen and colleagues reported that renal amyloidosis is associated with a mortality rate over 2-fold compared to population controls[13]. Similarly, Kuroda, *et al* reported a survival rate of 75% at 28 months of an amyloidosis series from a university hospital in Japan[14].

In our study, the data of the National Finnish Registry for Kidney Diseases were analyzed to assess the incidence and outcome of renal replacement therapy (RRT; dialysis or kidney transplant) in patients with amyloidosis associated with inflammatory rheumatic diseases. To our knowledge this is the first nationwide report to focus on the outcome of amyloidosis associated with rheumatic diseases.

MATERIALS AND METHODS

We scrutinized the files of the National Finnish Registry for Kidney Diseases for patients with amyloidosis associated with RA, AS, or JIA over the period 1987-2002. Patients enter the registry the same day as the first dialysis treatment for chronic uremia is provided. Altogether, 502 patients were identified, 401 (80%) of whom had amyloidosis associated with an underlying rheumatic disease: 332 (66%) had RA, 26 (5%) AS, and 43 (9%) JIA. From 1965 on, this registry has an estimated 97% to 99% coverage of all patients accepted for RRT[15]. Information on deaths was obtained by database linkage with the Population Register Centre in Finland. The database linkage was possible because of the Finnish system of unique personal identification numbers for all citizens. The study was approved in the ethical committee of the North-Karelia Central Hospital.

We were able to assess the mortality of patients with amyloidosis in the register only from 1987 onwards, because the international disease classification did not differentiate primary and secondary amyloidosis from one another before then. We divided the series into 4-year periods (1987-90, 1991-94, 1995-98, 1999-2002) to evaluate the possible differences in the incidence and prognosis of amyloidosis and renal insufficiency necessitating RRT. The patients were followed from the time of entering RRT until death or until the end of 2003, whichever occurred first, using the national mortality files of Statistics Finland. The mean duration of followup for patients with RA, AS, and JIA was 2.8, 3.6, and 3.9 years, respectively.

The demographic data of the patients are shown in Table 1. The female-to-male ratio did not differ from the sex distribution generally reported in these diseases. Hemodialysis dominated as the first treatment schedule of RRT in all 3 diagnosis groups. Thirty (9%) out of the 332 patients with RA, 6 (23%) of 26 patients with AS, and 13 (30%) of 43 patients with JIA had undergone renal transplantation. The mean (SD) delay from entering the register to renal transplantation varied from 17.4 (8.9) months for RA to 12.9 (6.2) months for JIA.

Table 1. Demographic and clinical data of 401 patients with amyloidosis associated with inflammatory rheumatic diseases according to the Finnish Registry for Kidney Diseases.

Variables	RA, n = 332	AS, n = 26	JIA, n = 43
Female/male, n	233/99	7/19	32/11
Age at the time of entering RRT, mean (SD), yrs	61 (10)	56 (9)	40 (15)
First treatment			
Hemodialysis, n (%)	269 (81)	20 (77)	30 (70)
Peritoneal dialysis, n (%)	63 (19)	6 (23)	13 (30)
Renal transplant, n (%)	30 (9)	6 (23)	13 (30)
Time to transplant, mo median (range)	17 (4–41)	14 (7–40)	15 (3–41)

RA: rheumatoid arthritis; AS: ankylosing spondylitis; JIA: juvenile idiopathic arthritis; RRT: renal replacement therapy.

Statistical analyses. The results were expressed as mean or median, standard deviation (SD) or interquartile range (IQR), and 95% confidence intervals (95% CI). Groups were compared using t-test and analysis of variance (ANOVA). Survival probabilities were estimated by Kaplan-Meier method. The 95% CI for the median survival time was obtained by bias-corrected bootstrapping (5000 replications). The prognostic factors predicting the duration of the survival time were analysed using proportional hazard regression models, called Cox's regression models.

RESULTS

There was no decline in the number of patients entering RRT in each diagnosis of inflammatory rheumatic diseases during 4 consecutive 4-year periods from 1987 to 2002. Mean age of patients with RA and JIA entering RRT increased significantly from 1987 to 2002 ($p < 0.001$; p for linearity < 0.001; Figure 1). We divided the patients within each disease group (RA, AS, JIA) into 3 different age categories (< 45 yrs, 45–65 yrs, and > 65 yrs) according to the followup period (1987-90, 91-94, 95-98, 99-2002). There were 12 patients (14.5%) with RA under the age of 45 in the first period, but only 2 patients (2.2%) in the last. During the corresponding time periods, the number of patients with RA over 65 years of age was 13 (15.7%) and 46 (51.1%), respectively. The corresponding figures for JIA under age of 45 were 8 patients (88.9%) versus 4 patients (40%), and for the age group of 45-65, 1 (11.1%) patient and 6 (60%) patients, respectively. In the AS group, no such trend was discernible.

The median survival times (95% CI) on RRT were 2.11 years (1.93–2.69) for RA, 2.37 years (1.11–4.31) for AS, and 3.05 years (2.19–4.23) for JIA (Figure 2). The mean followup times in the same groups were 2.8, 3.6, and 3.9 years. The 5-year (95% CI) survival rates among patients with these diagnoses were 18% (14–23%), 30% (14–48%), and 27% (14–41%), respectively.

Male sex and a diagnosis of JIA were independent risk factors of mortality with hazard ratios (95% CI) of 1.48

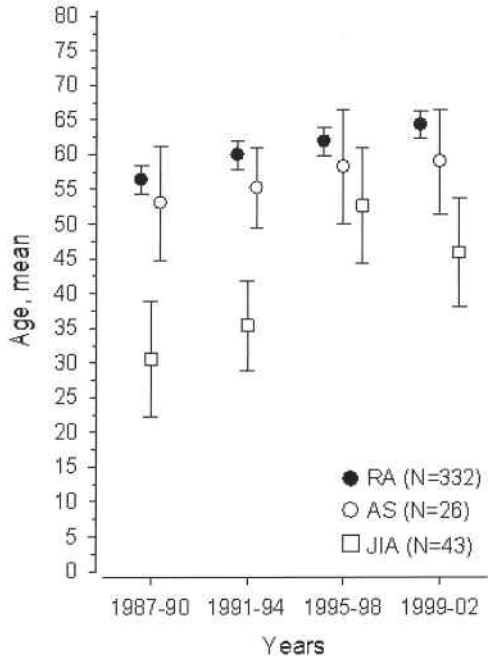

Figure 1. Mean age (95% CI) at acceptance for renal replacement therapy by diagnosis group from 1987 to 2002.

(1.20–1.84) and 1.55 (1.08–2.23), respectively (Table 2). However, the treatment modality (hemodialysis or peritoneal dialysis) showed no effect on the prognosis. There was no statistically significant change in the prognoses of patients with-

in any disease group over the whole followup period of 1987 to 2002.

Table 3 shows that the inflammatory rheumatic disease itself dominated as the cause of death, varying from 63% in AS to 79% in JIA.

DISCUSSION

In our study, a rheumatic disease as a cause of amyloidosis with renal failure necessitating RRT occurred in as much as 80% of the overall number of cases with amyloidosis. The prognoses of the patients were extremely poor, i.e., the median survival time ranged from slightly more than 2 years for RA to 3 years for JIA. In addition, a chronic inflammatory rheumatic disease was the main cause of death in 83% of all the patients studied. There are scant data on the outcome of AA amyloidosis differentiating its cause[16]. Instead the data reported hitherto are mainly based on amyloidosis regardless of its type[17-19]. To our knowledge, our series is the first nationwide report to focus on the outcome of amyloidosis associated with rheumatic diseases, *per se*.

In our patients, the diagnosis of amyloidosis was based on observation of green birefringence in polarized light after Congo red staining of tissue specimens, and on a clinical picture compatible with amyloidosis associated with chronic inflammatory diseases (AA amyloidosis). The verification of AA amyloidosis requires immunohistochemical typing with serum amyloid A protein (SAA) antiserum and exclusion of other amyloidoses. In this retrospective biopsy material,

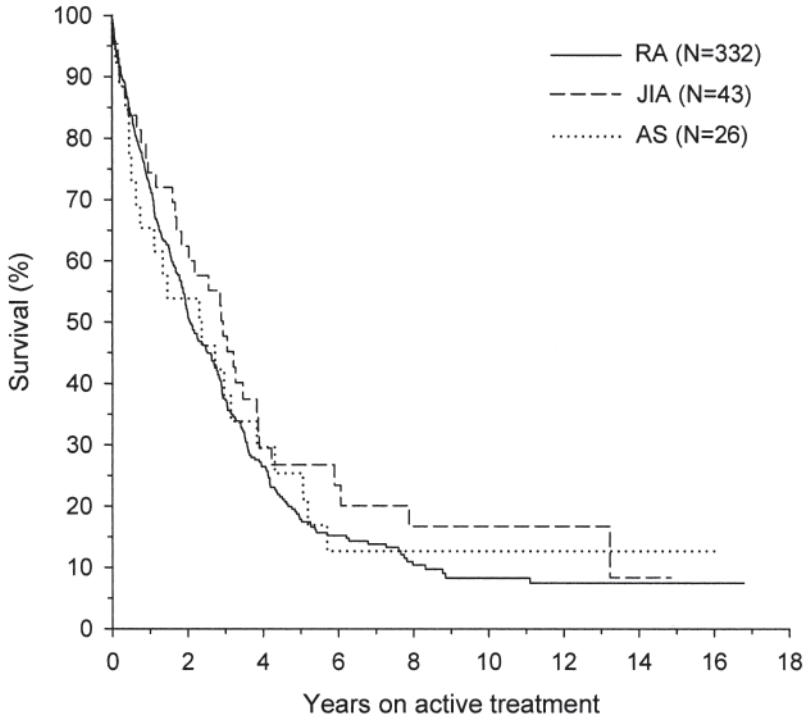

Figure 2. Product-limit survival for patients with amyloidosis associated with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis (AS) after acceptance to renal replacement therapy.

Table 2. Predictive factors for survival of patients entering renal replacement therapy (RRT) (Cox regression models).

Risk Factor	Hazard Ratio (95% CI)	p
Sex (male)	1.48 (1.20 to 1.84)	< 0.001
Disease type		
Rheumatoid arthritis	1.0 (reference)	
Ankylosing spondylitis	0.85 (0.55 to 1.32)	0.46
Juvenile idiopathic arthritis	1.55 (1.08 to 2.23)	0.019
Age at time of entering RRT	1.04 (1.03 to 1.05)	< 0.001
Dialysis type		
Hemodialysis	1.0 (reference)	
Peritoneal dialysis	1.10 (0.82 to 1.48)	0.51
Time periods of entering RRT		
1987–90	1.0 (reference)	
1991–94	0.99 (0.76 to 1.31)	0.97
1995–98	0.83 (0.60 to 1.15)	0.26
1999–2002	0.93 (0.66 to 1.30)	0.66

Table 3. Main causes of death in 333 deceased patients out of 401 subjects with endstage renal disease due to amyloidosis associated with inflammatory rheumatic diseases.

Main Cause of Death	RA (n = 277) n (%)	AS (n = 22) n (%)	JIA (n = 34) n (%)
Infections	6 (2.2)	0	1 (3)
Malignant neoplasms	5 (1.8)	1 (5)	1 (3)
Endocrinological diseases	1 (0.4)	0	0
Cardiovascular diseases	45 (16.2)	6 (27)	3 (9)
Gastrointestinal diseases	10 (3.6)	1 (5)	2 (6)
Musculoskeletal disorders	208 (75.1)	14 (63)	27 (79)
Accidents and violence	2 (0.7)	0	0

obtained from several different hospitals around the country over the study period, typing had not been performed systematically. However, the occurrence of other amyloidoses than AA amyloidosis in patients with chronic inflammatory rheumatic diseases would be rare and unexpected, but cannot be completely excluded. There are no reports on the incidence or prevalence of AL amyloidosis in Finland, but the incidence rate can be estimated to be similar to the 8–10 per million reported from the United States[20]. All hereditary amyloidoses except AGel amyloidosis are extremely rare in Finland. AGel amyloidosis has a characteristic clinical picture with corneal lattice dystrophy and cranial neuropathy as the main clinical manifestations, and the Finnish families with this type of amyloidosis are well characterized. It is further to be noted that in a hospital series of 73 Finnish patients with RA and amyloidosis, immunohistochemical typing showed that the amyloid deposits were of the AA type in all but one case (R. Koivuniemi, personal communication).

When we looked for predictive factors for mortality as adjusted by age and time period, we found that male sex and a diagnosis of JIA implied an increased risk of mortality. The time from entering RRT to renal transplant was shorter for patients with JIA than for those with RA or AS. This may be due to a more active treatment strategy and lack of contraindications for renal transplant in younger subjects. However, this approach did not improve the prognoses of patients with JIA. While the overall rate of renal transplant in patients with endstage renal failure is reported to be over 50% in Northern Europe[21] and 60% in Finland[22], it is surprisingly low in patients with inflammatory rheumatic diseases according to our data.

If we compare the incidence of RRT per 1 million inhabitants between the different disease groups according to the Finnish Registry for Kidney Diseases, the number of patients on dialysis due to primary and secondary amyloidosis increased from 3 in 1980 to 7 in 2000, but compared to other causes, especially Type 2 diabetes, the increase was moderate[22]. There seems to be a decline in the overall incidence of amyloidosis from 2000 onwards[22]. However, in our study covering cases up to the end of 2002, no such decline in the incidence of amyloidosis due to rheumatic diseases was detected, although an active DMARD policy of the last decade can be demonstrated by a marked increase in the annual number of users of DMARD, especially methotrexate, from 1995 onwards in Finland[23]. It appears that the increased use of combination DMARD and biologic agents, which effectively suppress the acute-phase reaction, subsequently preventing the formation of amyloidosis and slowing down its progression, was not yet reflected in the results obtained in our study.

In our series, the peak incidence of overt amyloidosis, especially in patients with RA and JIA, shifted towards older age. It is to be noted that we now accept older patients to RRT. Thus, the proportion of older patients entering RRT has grown significantly during the past 15 years. On the other hand, the peak incidence of onset of RA has shifted towards older age[24]. However, there are some data to show that the onset of amyloidosis can be retarded. According to a Dutch amyloid registry the median time between the onset of arthritis and the detection of clinical amyloidosis increased modestly — by 3 years — from 16 years in the 1960s to 19 years in the 1990s[25]. Similarly, no cases of amyloidosis associated with JIA at the juvenile age were documented over the past 15 years at the Rheumatism Foundation Hospital, which cares for two-thirds of the Finnish patients with JIA[11].

We must realize that patients with inflammatory rheumatic disorders are still at increased risk for the development of amyloidosis. In addition, patients with positive abdominal subcutaneous fat aspiration biopsy for amyloid although without overt clinical signs of amyloidosis may also develop endstage renal disease[26]. However, as shown in the study of natural history and outcome in systemic AA amyloidosis with 374 patients including 224 subjects with chronic inflammatory arthritis, decreased SAA concentration is associated with favorable renal outcome, stabilization, or regression of amyloid deposits, and prolonged survival[16]. Thus in cases with

confirmed diagnosis, aggressive immunosuppressive treatment including biological drugs should be instituted.

We conclude that there was no decline in the number of patients with amyloidosis accepted for RRT from the late 1980s to the first years of the 2000s. This finding contrasts with the clinical experience of a reduced incidence of subcutaneous fat aspiration biopsies staining positively for amyloid. We assume that the group of patients with inflammatory rheumatic diseases at risk for development of amyloidosis has not changed. Due to better control of inflammation, it takes more time — and patients become older — before amyloidosis becomes clinically manifest. Our data show that despite RRT the prognoses of patients with amyloidosis still remain poor. However, the increased use of combination DMARD and biologic agents can be expected to gradually lead to a lower number of patients with an overt clinical amyloidosis necessitating RRT.

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