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Amyloidosis Associated with Inflammatory Rheumatic Diseases in Finland

Declining Incidence and Better Outcome

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UNIVERSITY OF TAMPERE

To my family

LIST OF ORIGINAL CONTESTS

1. ABSTRACT

The aim of this study, which is based on registries, is to look for both the incidence and the outcome of amyloidosis associated with rheumatic diseases. The analysis of amyloid in this study is based on Congo red staining.

The subcutaneous abdominal fat tissue aspiration biopsy (ASFA) files of the Heinola Rheumatism Foundation Hospital (RFH) with over 3300 biopsies from 2600 patients from 1987 to 2002 were re-evaluated. From 1993 onwards, ASFA and/or rectal biopsy was performed on all patients with a clinical suspicion of amyloidosis at the Kainuu Central Hospital. The Finnish Registry for Kidney Diseases was scrutinized to find cases with amyloidosis associated with rheumatic diseases. Data on the use of antirheumatic drugs was collected from two sources: the Social Insurance Institution's Drug Reimbursement Register, and the Sales Register of the National Agency for Medicines.

Over the past 15 years, no new cases of amyloidosis associated with juvenile idiopathic arthritis (JIA) have been documented for juveniles in Finland. Before that period but later than 1975, 24 JIA patients under the age of 19 were found. As a sign of renal disease at the time of the diagnosis of amyloidosis, 16 patients (67%) presented with proteinuria, but none of the 24 patients had renal insufficiency. The 5-year survival rate of the series was 87.5 % (95% CI 75 to 100%) and the 10-year-survival 75% (57 to 92%). Ten patients (42%) of the 24 died during a mean follow-up of 15.2 (range 1.5-27.6) years. The main cause of death was related to JIA in all but one. The patients treated with prednisolone alone from the diagnosis of amyloidosis onwards had a mortality rate significantly higher than those on disease modifying anti-rheumatic drugs (DMARDs) and/or cytotoxic drugs (p=0.002). At the end of the follow-up, 14 patients (58%) were alive, 12 with normal renal function (3 of them had undergone renal transplantation), one had renal insufficiency, and one proteinuria. Proteinuria disappeared definitely in 3 patients who were proteinuric (two of them with nephrotic syndrome) at baseline, and their renal function remained normal.

New diagnoses of amyloidosis in the consecutive five-year periods from 1993 to 2007 onwards in the Kainuu district were 11, 3 and 5, respectively. During the study period, there was a mean annual incidence of amyloidosis of 1.8 (95% CI 1.1-2.8)/100 000 inhabitants. At the end of 2007, there were eight subjects with amyloidosis giving a point prevalence of 12.0 / 100 000 (95% CI 5.2-23.6). Five patients of the 19 underwent hemodialysis because of terminal uraemia and three of them also had renal transplantation.

Overall, 12 (63%) patients died after a median survival time of 6 (95%CI 4-8) years. One third of them died from amyloidosis. The five-year survival rate of the series was 67% (95% CI 41-86).

According to the data of the Finnish Registry for Kidney Diseases, there was no decline in the number of patients with amyloidosis entering renal replacement therapy (RRT) from 1987 to 2002. The mean age of patients with rheumatoid arthritis (RA) and JIA increased significantly ($p<0.001$). Male sex and a diagnosis of JIA indicated an increased risk of mortality. The median survival time (95% confidence interval) after entering RRT was 2.11 (1.93 to 2.69) years for patients with RA, 2.37 (1.11 to 4.31) years for those with ankylosing spondylitis (AS) and 3.05 (2.19 to 4.23) years for those with JIA. The 5-year (95% CI) survival rates among patients with the corresponding diagnoses were 18 (14 to 23) %, 30 (14 to 48) % and 27 (14 to 41) %, respectively.

The incidence of RRT was looked for from the Finnish Registry for Kidney Diseases covering the years 1995-2008. Altogether 264 cases were identified. 229 of them had RA, 15 AS and 20 JIA. When the total annual number of new admissions to RRT varied between 20 and 37 at the end of 1990´s, it was under half of that from 2002 onwards. Over this period, the number of users of low-dose methotrexate (MTX) increased 3.6-fold, the drug being the most frequently used DMARD in Finland. The present nationwide series is the first to show that the incidence of end-stage renal disease due to amyloidosis associated with rheumatic diseases is decreasing. An obvious reason for this is intensive anti-rheumatic drug therapy.

Among 150 AS patients within the ASFA files of RFH there were 12 patients with positive amyloid staining. Five of them were without signs of clinical amyloidosis at the time of biopsy. After more than ten years´ follow-up, two of these patients were alive and free of clinical symptoms of amyloidosis. The three other patients developed proteinuria and renal insufficiency which necessitated hemodialysis in two, and both of them died from AS within 15 years from the diagnosis of subclinical amyloidosis. The third patient died from gastrointestinal bleeding after 8 years.

The RFH biopsy files revealed 70 patients with a clinical diagnosis of psoriatic arthritis (PsA). Forty-one (59%) of the patients met the Caspar criteria for PsA including three cases with a positive biopsy for amyloid, of whom two were treated with biologicals and are reported here in more detail. Both patients had subclinical amyloidosis at the time of positive ASFA biopsy. Despite of use of MTX and low-dose prednisolone in one case, the patient's renal function deteriorated, and she was first treated with etanercept.

However, her renal function did not stabilize until the treatment was changed to tocilizumab. The other patient's active psoriatic spondyloarthropathy was also resistant to MTX and low-dose prednisolone. Biological therapy with adalimumab was started when she had a moderate renal failure. Later, she developed proteinuria but her renal function stabilized. According to the review of literature including the two cases above, biological drugs seem to be beneficial in amyloidosis associated with DMARD-resistant rheumatic diseases in the vast majority of the cases.

During the study period, the incidence and prognosis of amyloidosis have gradually improved from the 1980´s onwards. Today, amyloidosis is no more encountered in JIA patients in their juvenile age, and the incidence of amyloidosis is also decreasing in patients with adult RA. From the early 2000's the number of new admissions to RRT has been reduced by half. At the same time, the use of MTX has increased almost 4-fold. In DMARD-resistant cases, the use of biologicals seems promising.

2. LIST OF ORIGINAL PUBLICATIONS

I Immonen K, Savolainen HA, Hakala M. Why can we no longer find juvenile idiopathic arthritis-associated amyloidosis in childhood or in adolescence in Finland? Scand J Rheumatol 2007; 36:402-9

II Vasala M, Kautiainen H, Immonen K, Hakala M. More evidence of declining incidence of amyloidosis associated with inflammatory rheumatic diseases. Scand J Rheumatol 2010; 39:461-5.

III Immonen K, Finne P, Grönhagen-Riska C, Pettersson T, Klaukka T, Kautiainen H, Hakala M. A marked decline in the incidence of renal replacement therapy for amyloidosis associated with inflammatory rheumatic diseases – Data from nationwide registries in Finland. Amyloid 2011; 18:25-8.

IV Immonen K, Savolainen A, Kautiainen H, Hakala M. Longterm outcome of amyloidosis associated with juvenile idiopathic arthritis. J Rheumatol 2008; 35:5:907-12

V Immonen K, Finne P, Hakala M, Kautiainen H, Pettersson T, Grönhagen-Riska C. No improvement in survival of patients with amyloidosis associated with inflammatory rheumatic diseases - Data from the Finnish National Registry for Kidney Diseases. J Rheumatol 2008; 35:1334-8

VI Immonen K, Helin H, Lehtinen K, Hakala M. The usefulness of subcutaneous fat tissue aspiration biopsy for early confirmation of amyloidosis in patients with active ankylosing spondylitis: comment on the article by van Gameren et al. Arthritis and Rheumatism 2007; 56:2467-8

VII Immonen K, Kauppi M, Hakala M. Experiences on the use of biological drugs in psoriatic arthritis associated amyloidosis. Scand J Rheumatol 2011; 40:236-8

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3. ABBREVIATIONS

AA	Amyloid A
ACR	American College of Rheumatology
ADA	adalimumab
AGel	Amyloid Gelsolin
AL	Light-chain amyloid
Anti-TNF	anti-tumor necrosis factor
ARA	American Rheumatism Association
AS	ankylosing spondylitis
ASFA	abdominal subcutaneous fat aspiration
AZA	azathioprine
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
DDD	defined daily dose
DMARD	disease-modifying antirheumatic drug
GFR	glomerular filtration rate
GSTM	gold sodium aurothiomalate
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ETA	etanercept
EULAR	European League Against Rheumatism
GI	gastrointestinal
HCQ	hydroxychloroquine
HLA	human leukocyte antigen
HR	hazard ratio
ILAR	International League of Associations for Rheumatology
IL-1	interleukin 1
INF	infliximab
IQR	interquartile range

JIA	juvenile idiopathic arthritis
MBL	mannose-binding lectin
MMPs	matrix metalloproteins
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PsA	psoriatic arthritis
PU	proteinuria
RA	rheumatoid arthritis
RF	rheumatoid factor
RFH	Rheumatism Foundation Hospital
RI	renal insufficiency
RRT	renal replacement therapy
RTP	renal transplantation
SAA	serum amyloid A
SAP	serum amyloid P
SASP	salazosulfapyridine
SE	shared epitope
SII	social insurance institution
SSZ	sulphasalazine

4. INTRODUCTION

The word amyloid is derived from the Greek *amylon* and the Latin *amylum*. The word used to refer to a plant starch that stains in a manner similar to cellulose when exposed to iodine. In 1854, the German pathologist Rudolph Virchow (Sipe & Cohen 2000) was the first to use the term *amyloid* to describe extracellular accumulation in tissues and organs as insoluble low molecular weight protein fibrils in β-pleated sheet configurations with characteristic staining patterns.

Amyloidosis is a heterogeneous group of diseases characterized by extracellular deposition of normally soluble plasma proteins into congophilic amyloid fibrils affecting virtually any organ system leading to organ dysfunction and failure. Amyloidosis has been the most feared complication in inflammatory rheumatic diseases, being one of the main causes of decreased life span among these patients (Myllykangas-Luosujärvi et al. 1995). The most common immediate cause of death in patients with rheumatic diseases associated amyloidosis has been renal failure.

In the clinical context, amyloidosis associates with longstanding inflammatory activity reflected by high C-reactive protein (CRP) concentrations in serum. The normalization of CRP has been shown to prevent the progression of amyloidosis (Lachmann et al. 2007), thus becoming the main target of therapy.

Although the treatment of rheumatic diseases has much developed during the recent decades, there is scant evidence of a possible decline in the incidence of amyloidosis or its better prognosis in these diseases. These questions form the main topics of this study.

5. REVIEW OF THE LITERATURE

5.1. Classification of amyloidosis

Earlier, amyloidosis was classified into reactive or secondary amyloidosis, primary amyloidosis and hereditary amyloidosis. Today, all amyloid types are preferably named after their major fibril protein (Table 1). This gives us a simple and rational nomenclature for the increasing number of amyloid disorders, systemic and localized, known in humans and animals (Westermark et al. 2007). The modern nomenclature of amyloidosis now includes 27 human (Westermark, et al. 2007) fibril proteins: each of which is a major fibril protein in extracellular deposits, and has the characteristics of amyloid, including affinity for Congo red with resulting green birefringence (Bennhold 1923, Westermark & Stenkvist 1973).

Table 1. Classification of systemic amyloidosis.

Nomenclature	Precursor of Fibril	Organ Involvement	Treatment
AA	Serum amyloid A protein	Kidney, GI-tract, liver, spleen	Treatment of underlying inflammatory process
AL	Monoclonal immunoglubulin light chains	Heart, kidney, liver, peripheral and autonomic nervous system, GI-tract	Chemotherapy of underlying plasma cell dyscrasia, kidney and heart transplantation
Aβ2M	β2-microglobulin	Musculoskeletal system	High-flux dialysis membranes, kidney transplantation
ATTR	Normal plasma transthyretin	Senile heart, vessels	Symptomatic
ATTR	Genetically variant transthyretin	Peripheral and autonomic nerves, heart, GI-tract	Liver transplantation
ACys	Genetically variant cystatin C	Cerebral hemorrhage	Symptomatic
AGel	Genetically variant gelsolin	Corneal lattice dystrophy, cranial neuropathy	Symptomatic corneal transplantation
AApoAI	Genetically variant apolipoprotein AI	Liver, kidney, heart	Symptomatic transplantation
AApoAII	Genetically variant apolipoprotein AII	Kidney, heart	Symptomatic transplantation
AFib	Genetically variant fibrinogen A α chain	Kidney	Symptomatic transplantation
ALys	Genetically variant lysozyme	Kidney, liver, spleen	Symptomatic transplantation
Aβ	β-protein precursor (and rare genetic variants)	Cerebrovascular and intracerebral plaque amyloid in Alzheimer´s disease, occasional familial cases	

Biochemical methods are sometimes required in order to confirm or identify the

amyloid type in unfixed or in formalin-fixed tissue samples (Kaplan et al. 2004, Linke et al. 2006).

The most common systemic types of amyloidosis are AA amyloidosis (formerly called secondary amyloidosis), which is related to chronic inflammation, and AL amyloidosis (formerly primary amyloidosis), which is related to monoclonal immunoglobulin light chain production seen in multiple myeloma or lymphoproliferative disorders. The rarely encountered amyloid Gelsolin (AGel) -type amyloidosis has the highest prevalence worldwide in Finland. It relates to hereditary mutations of the gelsolin gene leading to substitution of aspartic acid by tyrosine in the gelsolin molecule (Maury et al. 1990, Ghiso et al. 1990). Each type of amyloid has different clinical symptoms, signs and treatment options.

5.2. Incidence and prevalence of amyloidosis

Light chain (AL) amyloidosis is the most frequently diagnosed form of systemic amyloid in the western world (Wechalekar et al. 2008). In the state of Minnesota in the US, Kyle et al. (1992) reported an annual incidence of 0.6-1/100 000. AL amyloidosis complicates about 15 % of myeloma patients. Eighty per cent of AL amyloidosis patients have benign monoclonal gammopathy (Pettersson & Konttinen 2010). While there is no data on the prevalence of AL amyloidosis in Finland, it is thought to be more unusual than AA amyloidosis.

AGel amyloidosis affects about six hundred people in the world of whom five hundred reside in Finland (Kiuru S 1998). This mutation has been previously found, besides Finland (Maury et al. 1990), also in Denmark, in the Czech Republic and in France (Kiuru S 1998). It is a familial polyneuropathy characterized by an association of corneal lattice dystrophy, cutis laxa and cranial neuropathy. Two mutations are known. Life expectancy is not affected, but quality of life is altered (Meretoja 1969, Kiuru 1998, Contégal F et al. 2006).

5.2.1. Incidence and prevalence of amyloidosis in inflammatory rheumatic diseases

The prevalence of amyloidosis associated with the rheumatic diseases varies greatly

depending on the study population and methods used for its evaluation (Table 2).

Table 2. Prevalence of amyloidosis in certain inflammatory rheumatic diseases according to different studies.

Disease/ study indication for amyloid	Study	Country	Number of patients/ Number with amyloid (%)	Mean disease duration (years)	Biopsy	Comments and study period
RA/clinical symptoms	Laine 1955	Finland	289/83 (28.7)	NA	Different sites	Hospitalized patients
	Lender 1972	Israel	54/6 (11)	9	Rectal	3 patients with nephrotic syndrome
	Wiland 2004	Poland	121/35 (28.9)	16	ASFA	Severe hospitalized cases, 1996-2001
	Arapakis 1963	UK	115/6 (5.2)	All with ≥10	Rectal	Randomized hospitalized patients
	Calguneri 2006	Turkey	526/6 (1.1)	5	NA	Retrospective evaluation of med. records of all patients, 1988-2003
RA/screening	Tiitinen 1993	Finland	102/11(10.8)	All with ~15	ASFA	Inception cohort (1973-75) with a15-year FU
	Päi 1993	Estonia	47/11 (23)	NA	ASFA	Consecutive patients
	Kobayashi 1996	Japan	407/54 (13.3)	16	GI	Consecutive patients, 1989-91
	Fonseca 2001	Portu-gal	964/33 (3.4)	14	ASFA, rectal, renal	Consecutive patients, 1977-97
	Gomez-Casanovas 2001	Spain	313/61 (19.5)	7	ASFA	RA ≥ 5 years, 1983-98
	El Mansoury 2002	Egypt	112/8 (7.1)	17	ASFA	RA ≥ 5 years, 1999
	Kuroda 2002	Japan	1006/71 (7.1)	17	GI	1988-95
	Ishii 2003	Japan	217/17(7.8)	16	ASFA	2002-3
	Wakhlu 2003	India	113/30 (26.5)	10	ASFA	RA ≥ 5 years, 2000-1
	Younes 2009	Tunisia	107/23(21.5)	12	ASFA, MSGB	Consecutive patients, 2005-6

RA/autopsy	Mutru 1976	Finland	41/7 (17)	NA	Autopsy, 100%	1959-74
	Boers 1987	NL	132/14 (10.6)	15	Autopsy (100%) study focused to renal findings	1958-84
	Suzuki 1994	Japan	81/17 (21)	NA	Autopsy, 100%	1960-90
	Myllykangas-Luosujärvi 1999	Finland	1666/ 97 (5.8)	19	Autopsy, 27%	Population-based mortality study
	Koivuniemi 2008	Finland	369/35 (9.5%)	17 (data available from 1973 onwards)	Autopsy, 100%	1952-91
AS/clinical symptoms	Ben Taarit 2005	Tunisia	210/8 (3.8%) with renal amyloidosis	NA	Screening of med. records, ,renal biopsy	Retrospective study, AS seen during a 27-year period
AS/screening	Gratacos 1997	Spain	137/11 (8.0)	24	ASFA	AS ≥5 years, 1983-94
	Singh 2007	India	72/5 (6.9)	15	ASFA	AS≥5 years, 2004-6
AS/autopsy	Lehtinen 1993	Finland	398/19 (4.8)	NA	Autopsy, 55%	All AS patients admitted to hospital, 1961-69
JIA/clinical symptoms	Schnitzer 1977	Canada	243/18 (7.4)	10	Rectal, renal	1961-1976
	Rostopowicz-Denisiewicz 1977	Poland	407/75 (11)	NA		1962-75
	Stoeber 1981	Germany	2062/65 (3.1)	NA	NA	1952-79

RA= rheumatoid arthritis; AS=ankylosing spondylitis; JIA=juvenile idiopathic arthritis; ASFA= abdominal subcutaneous fat aspiration; GI = gastrointestinal; MSGB = minor salivary gland biopsy; FU = follow up; NA = not available

In historical hospital-based RA series, in which clues for amyloidosis based on overt clinical signs such as proteinuria or renal insufficiency, prevalence figures as high as 29% have been reported (Vainio et al. 1955). In the 1970´s, only 4% of RA patients with amyloidosis lacked demonstrable clinical signs of renal involvement (Wegelius et al. 1980), and all JIA patients who developed amyloidosis had proteinuria (Schnitzer & Ansell 1977). According to autopsy studies, the prevalence of amyloidosis in RA has

varied between 17% (Mutru et al. 1976) and 6% (Myllykangas-Luosujärvi et al. 1999). In a Finnish autopsy series from the 1980´s, the prevalence of amyloidosis in AS was as low as 4% (Myllykangas-Luosujärvi et al. 1998). The prevalence of JIA associated overt clinical amyloidosis varies between 1-10% (Filipowicz-Sosnowska et al. 1978, Özdogan et al. 1991, David et al. 1993). The European prevalence figures are higher (up to 10.8%) than those reported from American centres (1.8%) (Filipowicz-Sosnowska et al. 1978).

In the recent years, there have been some screening studies using abdominal subcutaneous fat tissue aspiration (ASFA) biopsies taken from consecutive patients to document the prevalence of amyloidosis. A high number of patients with such an approach represents subclinical cases. A Spanish study showed positive ASFA biopsies in 16% of consecutive RA patients; in 73% of the patients amyloidosis remained subclinical during a mean follow-up time of 7 years (Gómez-Casanovas et al. 2001). Gratacos et al. (1997) reported a positive ASFA test in 7% of 137 patients with AS. In this series, the disease remained subclinical in half of the patients over 5 consecutive years.

5.3. Pathogenesis of AA amyloidosis

Chronic inflammation with a longstanding cytokine-driven acute-phase reaction including increased concentrations of the circulating acute phase reactant serum amyloid A (SAA) is a prerequisite for the development of AA amyloidosis (Maury & Teppo 1982). SAA, normally a soluble plasma protein, is deposited in the extracellular space of the tissues as abnormal insoluble AA amyloid fibrils. The mechanism and physiological factors promoting amyloidosis are largely unknown. The process implies that natively folded disease-causative proteins undergo a β-sheet conformational transition through an energetically unfavourable process, and further polymerize into amyloid fibrils. (Naiki & Nagai 2009). All amyloid deposits contain the serum amyloid P component (SAP), which has a specific binding motif for the common conformation of amyloid fibrils. SAP is highly protected against proteolysis and when bound to amyloid fibrils makes them resistant to degradation (Tennent et al. 1995). Proteoglycans are also common in amyloid deposits and contribute extensively to the carbohydrate composition of amyloid (Kisilevsky 2000). Heparan sulfate can influence and promote misfolding of polypeptides into proamyloidogenic intermediates rich in β-sheet and may also function as a structural template organizing self-assembly steps (Elimova et al. 2009). The increased amyloid fibril production and decreased clearance of amyloid protein result in disruption of overall

organ function leading to overt clinical disease, such as renal failure. Several toxic mechanisms at the tissue levels have been proposed. Firstly, amyloid invades the extracellular space of organs destroying their normal architecture and function. In addition, oligomers could exhibit toxic effects by destabilizing cellular membranes (Lashuel et al. 2002).

5.3.1. Role of genes and proteins for susceptibility to amyloidosis associated with rheumatic diseases

5.3.1.1. Major histocompatibility complex

The study of the genetics of amyloidosis in rheumatic diseases was first focused on the major histocompatibility antigens. Pasternack and Tiilikainen (1977) noticed a high frequency of HLA-B27 in patients with amyloidosis associated with RA. The association was strongest in a group of male patients with amyloidosis whose RA had begun at an early age and who lacked demonstrable rheumatoid factor in serum. Tiitinen et al. (1992) found no significant differences between Finnish and Polish patients with RA and secondary amyloidosis in the frequency of HLA-A, -B, -C and –DR antigens compared with control RA patients and blood donors. Migita et al. (2006) suggested that in Japanese patients with RA, the presence of a double set of the *04 shared epitope (SE) is associated with a higher risk of developing amyloidosis.

5.3.1.2. SAA genotype

SAA is encoded by a family of 4 SAA genes, SAA1, SAA2, SAA3 and SAA4, all clustered in the short arm of chromosome 11 (Mavragani et al. 2007). Polymorphisms in the gene coding for SAA1 have been identified as a risk factor for the development of amyloidosis (Obici et al. 2009). However, SAA 1 gene polymorphism varies greatly among different districts and races. The frequency of the SAA1.3 allele is about 40% among the Japanese, whereas it is much lower among Caucasians (Nakamura et al. 2006, Yamada & Wada 2003). The frequency of SAA1.1 is 76% among Caucasians and that of SAA1.3, only 5% (Booth et al. 1998). The first data on the association of the SAA1 genotype and AA amyloidosis came from Japanese studies; showing that the SAA1.3 allele is a definite risk factor for amyloidosis, whereas the SAA1.1 allele is protective

(Baba et al. 1995, Moriguchi et al. 1999). Instead, in Caucasian populations, the presence of SAA1.1 allele has been shown to be an amyloidogenic risk factor (Booth et al. 1998). However, this genetic association could not be confirmed in a series of Finnish patients with RA (Terai et al. 2005).

5.3.2. Cellular and extracellular tissue factors

Human AA amyloid deposits are mostly formed by N-terminal fragments of SAA, pointing to proteolytic cleavage of the precursor as a key event in the pathogenesis of this form of amyloidosis (Merlini & Bellotti 2003, Obici et al. 2009). The role of metalloproteinases (MMPs) in the pathogenesis of amyloidosis was suggested by Müller et al. (2000). The MMPs modulate the extracellular matrix and are present in AA amyloid deposits (Müller et al. 2000). SAA1 induces the production of MMPs by mononuclear phagocytes (Lee et al. 2005, Migita et al. 1998). In a recent study, van der Hilst et al. (2008) showed that SAA 1.1 is more susceptible to degradation by MMP-1 compared with SAA 1.5, and they suggested this phenomenon to be a potential explanation for the higher risk of amyloidosis for the patients with the former phenotype.

Proinflammatory cytokines appear to hamper the proteolysis of SAA by monocytes, leading to the generation of SAA fragments (Phipps-Yonas et al. 2004, Migita et al. 2001). Proinflammatory cytokines thus both induce the production of the amyloid precursor and impair its degradation which results in an accumulation of the amyloidogenic metabolites in the phagocytes. An experimental study showed that IL-18 induces SAA synthesis (Tanaka et al. 2004). Maury et al. (2004) reported that RA patients with amyloidosis have higher levels of IL-18 in their sera compared with RA patients without amyloidosis.

Monocytes mediate SAA degradation and have been proven to initiate the development of AA amyloidosis in human cell models (Obici et al. 2009). In the case of depressed phagocytic capacity of monocytes, as in for instance in an individual carrying a mannose binding lectin (MBL) 2 O allele, the likelihood of developing clinical amyloidosis would increase (Maury et al. 2007). In a recent paper, Maury et al. (2007) showed that variant MBL2 structural genotype constitutes a significant risk factor for amyloidosis in RA and that the increased risk is probably related to MBL-mediated impairment of mononuclear phagocyte function. This observation points to the possibility that the genetic background may affect the ability of mononuclear phagocytes to effectively process and degrade SAA proteins (Obici et al. 2009).

5.4. AA amyloidosis in rheumatic diseases

5.4.1. Risk factors for amyloidosis

After a 15-year follow-up examination of a RA inception cohort, Tiitinen et al. (1993) analysed risk factors for the development of amyloidosis which was detected by ASFA biopsy in 11(10.9 %)/102 patients. The baseline variables did not show any prognostic value, while after three years, morning stiffness lasted longer and both erythrocyte sedimentation rate (ESR) and CRP were significantly higher in patients who later developed amyloidosis. Men with RA are at a higher risk of amyloidosis than are similarly affected women (Gertz et al. 1991, Koivuniemi et al. 2008). In AS, high disease activity and peripheral arthritis of the large joints carry an increased risk for the development of amyloidosis (Husby 1980, Lehtinen 1984). Quantification of the amount of amyloid in subcutaneous fat tissue by a semiquantitative scoring system reflects disease severity, as measured by the number of organs involved, and even predicts decreased survival independently of other well-known factors (van Gameren et al. 2010). The determination of either HLA-antigens or the SAA1-genotype can not be considered to have any prognostic value on an individual level.

5.4.2. Diagnosis of amyloidosis in patients with rheumatic diseases

The diagnosis of amyloidosis is based on the documentation of amyloid in tissue specimens. In clinical settings, amyloid is usually detected by the ASFA technique (Westermark & Stenkvist 1973), and sometimes from rectal or renal biopsy specimens using Congo red staining. Congo red with resulting green birefringence in polarized light is still the golden standard for verification of amyloid. There is some evidence that rectal biopsy is more sensitive than ASFA in detecting amyloid (Klemi et al. 1987, Marsik et al. 2008). However, van Gameren et al. (2006) stressed the conveniency of ASFA, its low risk and low cost. They commented that false negative results in ASFA biopsies are commonly due to insufficient tissue material, inadequate staining technique, improper use of polarizing instruments and insufficient light intensity of microscopy. The biopsies of kidney, liver and heart have a high sensitivity (87-98%) (van Gameren et al. 2006).

The determination of the type of amyloid can be made by immunohistochemistry from

tissue specimens. However, because other types of amyloidosis than AA are extremely rare in rheumatic diseases (Koivuniemi 2009), typing is not routinely made in clinical practice in Finland today. SAP scintigraphy may help show organ involvement and therapy response (Hawkins et al. 1990a). The availability of the method is very limited at clinics.

5.4.3. Clinical manifestations of AA amyloidosis

Although AA amyloidosis can develop rapidly, the median latency of clinically significant amyloidosis from the onset of an inflammatory disease is almost two decades (Hazenberg & van Rijswijk 2000, Lachmann et al. 2007). Renal dysfunction, such as proteinuria, nephrotic syndrome or renal failure, is the main clinical feature of AA amyloidosis associated with inflammatory rheumatic diseases. Hepatic involvement and autonomic neuropathy usually occur late in the disease but in contrast to AL amyloidosis, cardiac involvement is rare (Lachmann & Hawkins 2006). Gastrointestinal (GI) motility disturbances are more unusual than in AL amyloidosis, and peripheral neuropathy is very rare. Sometimes GI bleeding, malabsorption, hepatomegaly, splenomegaly or goitre can be a clue for the diagnosis (Petre et al. 2008). According to Hawkins et al. (1990b) adrenal amyloid deposits were evident in 41% of patients in SAP scintigraphy, but only < 2% needed long-term adrenocorticoid replacement therapy.

5.4.4. Treatment

The aim of the treatment of amyloidosis in rheumatic diseases is to suppress the activity of inflammation by DMARDs, cytostatics and glucocorticoids, i.e. to normalize serum CRP and SAA. There are no randomized controlled trials of the effect of cytotoxic drugs or DMARDs. Ahlmen et al (1987) reported a small randomized series of RA amyloidosis comparing cytostatic (chlorambucil) and symptomatic treatment with a mean follow-up of approximately 4 years. The cumulative proportion of survivors at 60 months was 89% and 27%, respectively. Thereafter, few case reports have documented a positive effect of the use of azathioprine (Shapiro et al. 1995) or methotrexate (Komatsuda et al. 1998) in nephrotic syndrome caused by amyloidosis in patients with RA. Savolainen (1999) reported a follow-up of 79 consecutive patients with juvenile idiopathic arthritis (JIA)

refractory to any previous therapy, whose chlorambucil treatments were initiated during the period 1982 - 1995. Seven out of 11 patients with amyloidosis had proteinuria, which cleared completely in 4 and almost completely in one. After a mean follow-up of 8.5 years, 14 patients (18%) of the 79 were in complete remission without drugs.

There are promising treatment results of the use of biological drugs for this condition from the recent years. Today, an increasing number of patients with RA associated amyloidosis are treated with anti-TNF-α therapy. Gottenberg et al. (2003) reported anti-TNF-α therapy to be well-tolerated and safe in 15 patients with inflammatory rheumatic diseases associated amyloidosis and renal involvement: sustained proteinuria decreased in 3 patients, and renal function stabilized in 5 other patients. Based on an analysis of 25 patients with different rheumatic diseases treated with anti-TNF-α therapy, Fernández-Nebro et al. (2005) concluded that these drugs may be useful for the treatment of amyloidosis: they can significantly reduce acute-phase proteins and proteinuria and can stabilize renal function in patients with renal amyloidosis.

The effect of anti-TNF-α therapy on amyloidosis can be postulated to be due to the rapid lowering effect on SAA levels. Actually, Perry et al. (2008) reported that 5 out of 9 RA patients treated with etanercept had an immediate decrease of SAA to less than 11 mg/L. The suppression of SAA below 10 mg/L halts the progression of the disease and is strongly associated with a prolonged survival (Lachmann et al. 2007). Furthermore, some case reports (such as Okuda et al. 2006, Sato et al. 2009, Nishida et al. 2009) show that tocilizumab has an excellent ability to suppress serum amyloid A levels and could therefore be an important therapeutic strategy in amyloidosis secondary to rheumatic diseases. There is preliminary data on a positive effect of the IL-1 receptor antagonist (anakinra) in AA amyloidosis associated nephrotic syndrome (Leslie et al. 2006).

A recent advance in the treatment of amyloidosis is eprodisate which has been shown to slow down the progression of renal failure in AA amyloidosis (Dember et al. 2007). The compound is a negatively charged, sulphonated molecule of low molecular weight having structural similarities with heparan sulfate. It interferes with the interactions between amyloidogenic protein and glycosaminoglycans, and inhibits deposition of amyloid on a tissue level (Dember et al. 2007). There are some reports of a positive effect of oral administration of dimethyl sulfoxide on GI and renal involvement of amyloidosis (Amemori et al. 2006), but the drug is not in clinical use. Accoding to a preliminary report, CPHPC ((R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexa-noyl]pyrrolidine-2

carboxylic acid), a novel bis(D-proline) drug which specifically targets SAP, produced a sustained >95% depletion of circulating SAP and a circa 90% reduction in the SAP content in tissue level (Gillmore et al. 2010).

Renal replacement therapy is needed in severe cases of end-stage renal disease (ESRD). The outcome of patients with AA amyloidosis in RRT is poor with a median survival of less than one and half years according to a recent report (Bergesio et al. 2008).

5.4.5. Monitoring of the effect of therapy

SAA is sensitive to change and accurately reflects alterations in disease activity, being the most sensitive marker available for the assessment of treatment responses in RA (Perry et al. 2008). Because SAA measurement is usually not routinely available, the effect of therapy is monitored through the changes in the level of CRP. It is known that the concentrations of these acute phase proteins correlate closely (Gertz et al. 1985). Renal function should be regularly assessed by using tests that estimate glomerular filtration rate (GFR) calculated on the basis of serum creatinine, adjusted by age, sex and race (Marsik et al. 2008). SAP scintigraphy has been reported to be useful in the follow up of a treatment response (Hawkins et al. 1990a). Amyloid A protein quantification in fat tissue, which has been shown to be a sensitive and specific method for the detection of clinically overt AA amyloidosis, is also suggested as a potential method for monitoring the treatment response over time (Hazenberg et al. 2007).

5.4.6 Outcome

Overall, amyloidosis associated with rheumatic diseases carries a poor outcome. Until now, uraemia caused by renal amyloidosis has been a major cause of death in Finnish patients with RA, AS and JIA (Myllykangas-Luosujärvi et al. 1995 & 1998, Savolainen&Isomäki 1993, Lehtinen 1993). Laakso et al. (1986) carried out a 10-year prospective study to assess the mortality and causes of death within in a cohort of 1000 RA patients – treated for the 1st time at hospital during the years 1959-68 – and 1000 non RA subjects. The proportion of deaths from amyloidosis was 5.8% among male and 12.8% among female RA patients. The average duration of RA before death was 16.1 years

(range 8-33 years) for male and 21.8 years (range 15-40 years) for female RA patients. In the series of RA patients before the 1990´s, the disease shortened the median life span by 8 (Myllykangas-Luosujärvi et al. 1995) and 10 (Lehtinen 1993) years in RA and AS, respectively. The first of these studies comprised 1666 RA subjects who died in Finland in 1989. About 15% of excess mortality was due to amyloidosis. It was regarded as an immediate cause or an intervening antecedent cause of death in 64 cases (3.8%) and as a contributory cause of death in 33 cases (2%). Amyloidosis was diagnosed during life in 89 patients and was detected at autopsy in eight.

Lehtinen (1993) investigated the mortality and causes of death among 398 hospitalized patients with AS admitted for the first time during the years 1961-1969. After a mean follow-up time of 26 years, 152 (38%) patients had died, the cause of death being secondary amyloidosis in 19, contributing to 13% of all causes of death. It was approximated that patients with AS have a mortality rate 1.5 times higher than expected, which was mostly explained by amyloidosis (Lehtinen 1993).

The Heinola inception cohort which started in 1973-75, included a total of 117 patients with recent seropositive RA. At the 20-year check-up, 14 of the initial 103 patients had developed secondary amyloidosis (13.6%), and 9 (64.3%) of the 14 had died (Jäntti et al. 2002).

In the JIA study based mainly on the Finnish nationwide drug reimbursement register, Savolainen and Isomäki (1993) found 24 deaths during 1969-79 and 23 during 1980-90. The direct cause of death was amyloidosis in 11 patients in the earlier period and in 4 patients in the later period. Amyloidosis accounted for 42% of all causes of death during the earlier period and for 17% during the later period.

Ylinen at al. (1992) reported a 3-year survival of 37% in 37 patients with secondary amyloidosis who entered dialysis treatment between the years 1974 and 1987. Sihvonen and her co-workers (2004) reported renal amyloidosis to be associated with a mortality rate over twofold compared to population controls. In a Japanese AA amyloidosis series from an university hospital (Kuroda et al. 2005), a survival rate of 75% at 28 months was reported.

All the above mentioned studies deal with patients treated with monotherapy before the widespread use of MTX and combination therapy.

6. AIMS OF THE STUDY

The aims of the present study were to analyse possible changes in the epidemiology, clinical picture and treatment and outcome of AA amyloidosis in different rheumatic diseases over recent decades. The specific focuses were:

1. changes in its incidence and prevalence
   - in all of Finland (I) and in the Kainuu district specifically (II)
   - among patients admitted to RRT (III)
2. changes in its outcome
   - in all of Finland (IV) and in the Kainuu district specifically (II)
   - among patients admitted to RRT (V)
3. the impact of subclinical amyloidosis (VI, VII)
4. the effect of treatment on AA amyloidosis (II, IV-VII).

7. SUBJECTS AND METHODS

7.1. Methods

The patient selection of the present study was based on a number of registers, i.e. the amyloid register of the Rheumatism Foundation Hospital (RFH) (substudies I, IV and VI-VII – Figure 1.), the Finnish Registry for Kidney Diseases (III and V) and the clinical register of Kainuu Central Hospital (II).

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                    ┌─────────────────────────────────────────┐
                    │ File of abdominal subcutaneous fat       │
                    │ aspiration                               │
                    │ biopsies (N=3376) with 2604 patients     │
                    │ from 1987 to 2000                        │
                    └─────────────────────────────────────────┘
                          │        │        │        │
Number of patients with a  ┌────┐  ┌────┐  ┌─────┐  ┌────┐
diagnosis of rheumatic     │ RA │  │ AS │  │ JIA │  │PsA │
disease                    │N=2136│ │N=150│ │N=248*│ │N=70│
                          └────┘  └────┘  └─────┘  └────┘
                             │       │       │        │
Number of patients        ┌────┐  ┌────┐  ┌────┐  ┌────┐
with positive amyloid     │ NA │  │13# │  │ 24 │  │ 3  │
staining                  └────┘  └────┘  └────┘  └────┘
```
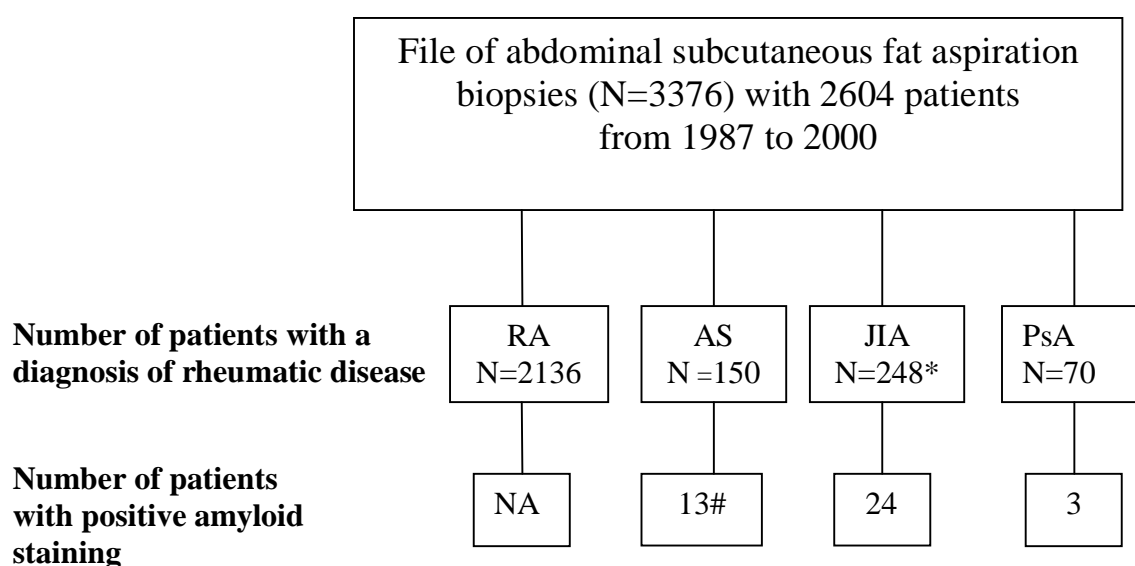
*The number includes cases gathered through reviewing the medical records of RFH from 1975 to 2005.
\# 5 patients with a subclinical amyloidosis at the time of positive biopsy.

Figure 1. Distribution of patients according to positive abdominal subcutaneous fat aspiration biopsies and diagnosis of rheumatic disease in the amyloid register of the Rheumatism Foundation Hospital.

In addition, the data were supplemented by other registers, such as the hospital discharge register (I and IV), the Social Insurance Institution´s Drug Reimbursement Register and the Sales Register of the National Agency for Medicines (III), and the cause of death register of the Population Register Centre (V). The database linkage of data in different registers is possible through the Finnish system of unique personal identification numbers for all citizens.

The National Agency for Medicines publishes drug consumption statistics on the basis of sales from wholesalers to pharmacies. The unit of measurement is the defined daily dose (DDD), calculated per 1,000 inhabitants per day.

The verification of amyloid was based mainly on ASFA biopsy by the demonstration

of green birefringence in polarized light after Congo red staining (Westermark & Stenkvist 1973). Almost all of the specimens forming the amyloid register of RFH (I, IV, VI-VII) were assessed by the same pathologist at the Department of Pathology in Tampere University Hospital. In addition, a few cases with gastrointestinal and kidney biopsies were included in the study (II, IV) which allowed the comparison of the accuracy of these methods (II). Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula which employs serum creatinine, age, sex, body weight and race in calculation (Cockcroft & Gault 1976).

7.1.1. Statistical analysis

Substudy II. The results were expressed as mean or median, standard deviation (SD) or interquartile range (IQR) and 95 per cent confidence intervals (95% CI). Kaplan-Meier curves were used to illustrate the cumulative proportions of survival. Incidence rates with 95% CI were calculated per 100 000 assuming a Poisson distribution. Incidences between the five-year periods were analysed using exact Poisson regression analysis.

Substudy IV. The results were expressed as mean or median, range or interquartile range (IQR). The Kaplan-Meier curve was used to illustrate information on the cumulative proportions of survival, and the difference between the groups was tested by using the permutation type Log-rank test. 95 per cent confidence intervals of survival rate were obtained by bias-corrected bootstrapping (1000 replications).

Substudy V. The results were expressed as mean or median, standard deviation (SD) or interquartile range (IQR) and 95 per cent confidence intervals (95% CI). The groups were compared using the t-test and analysis of variance (ANOVA). Survival probabilities were estimated by using the Kaplan-Meier method. The 95% confidence interval 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.

7.2. Ethical aspects

Substudies I, IV, VI-VII were approved by the ethical committee of the Päijät-Häme Central Hospital and substudies III and V by that of the North-Karelia Central Hospital.

The review of the patient register of the rheumatological division of Kainuu Central Hospital was approved by the chief medical officer of the hospital (II).

7.3. Subjects

7.3.1. Incidence of amyloidosis in juvenile idiopathic arthritis (JIA) (I)

The study was focused on subjects in the care of the Department of pediatrics of RFH, i.e. on patients under the age of 19. Altogether 24 subjects were found (Figure 1) who fulfilled the International League Against Rheumatism 2001 criteria (Petty at al. 2004). After interviewing the doctors who treat JIA patients in the five university hospitals in Finland it was concluded that no other pediatric and adolescent patients were found suffering from JIA associated amyloidosis in the study period.

7.3.2. Outcome of amyloidosis in JIA (IV)

Study IV comprises the same JIA patients as substudy I. All subjects alive were interviewed by telephone regarding their marital status, fertility, number of children, type of residence, schooling, employment, other diseases and joint prostheses. The patients were followed up until death or until the end of 2003. The data was collected in 2004.

The demographic and clinical characteristics of the 24 patients are shown in Table 3.

Table 3. Characteristics of 24 children with juvenile idiopathic arthritis and amyloidosis (I and IV).

Characteristic	
Number of girls, (%)	19 (79)
Age at first symptoms of JIA, mean (range), years	4.7 (1 – 11)
Age at diagnosis of JIA, mean (range), years	5.1 (1 – 12)
Time from onset of JIA to diagnosis of SA, median (IQR), years	8 (4,12)
Disease course type, n (%)	
Extended oligoarthritis	2 (8)
Juvenile spondylarthropathy	1 (4)
Polyarthritis	10 (42)
Systemic	11 (46)
HLA-B27 present, n (%)	13/22* (59)
Rheumatoid factor present, n (%)	1 (4)
Anti-nuclear antibodies present, n (%)	10 (42)

SA = secondary amyloidosis; IOR = interquartile range;* HLA typing was not performed in two of the 24 cases

.
The indications for searching for amyloidosis in the 24 patients were proteinuria (N=15), goitre (N=2), or continuously high disease activity as assessed by clinical assessment and CRP (N=7).

At the diagnosis of amyloidosis, 17 patients were on one DMARD with prednisolone, two on a combination of DMARDs with prednisolone and five on prednisolone alone. Fourteen patients had undergone arthroplasties (2-9 operations per patient) by the end of 2003.

7.3.3. Occurrence and outcome of amyloidosis in a community-based series (II)

The Kainuu Central Hospital is the only secondary health care centre in the Kainuu district and covers an adult population ($\geq$ 16 years of age) of approximately 67000. The treatment team was active as of 1993 searching for cases with amyloid in tissue specimens of ASFA biopsy and/or rectal biopsy among patients with rheumatic diseases. The following criteria for the performance of biopsy were in use: ESR over 40 mm/h at two consecutive visits at 3-6 month intervals, proteinuria (> 0.5 g/day) or serum creatinine over 150 μmol/l. In addition, renal biopsy was performed on patients with proteinuria and with a high suspicion of amyloidosis in whom staining for amyloid in specimens taken by ASFA or rectal biopsy were negative. Furthermore, the Department of Pathology had been asked to screen for amyloidosis the histopathological specimens taken at gastroscopy or colonoscopy when performed on patients with inflammatory rheumatic diseases. The patients were followed to the end of 2007 or until death. Causes of death were confirmed from death certificates.

7.3.4. Incidence of amyloidosis in patients with rheumatic diseases admitted to renal replacement therapy (RRT) (III)

The files of the Finnish Registry for Kidney Diseases were assessed to search for patients who had undergone RRT due to amyloidosis associated with RA, AS or JIA over the period 1995-2008. Patients are entered into the registry on the day of their first dialysis treatment for chronic uraemia.

7.3.5. Outcome of amyloidosis in patients with rheumatic diseases admitted to RRT (V)

As in substudy III, the files of the Finnish Registry for Kidney Diseases were reviewed to assess the prognosis of amyloidosis in patients with rheumatic diseases admitted to RRT over the period 1987-2002. Altogether 502 patients were identified, 401 (80%) of whom had some rheumatic disease: 332 (66%) had RA, 26 (5%) AS and 43 (9%) JIA.

The series was divided into four-year periods (1987-90, 1991-94, 1995-98, 1999-02) to evaluate the possible differences in the incidence and prognosis of amyloidosis and renal insufficiency necessitating RRT. The patients were followed up from the time of entering RRT until death or till the end of 2003, whichever occurred first, using the national mortality files of Statistics Finland. The mean duration of follow-up for patients with RA, AS and JIA was 2.8, 3.6 and 3.9 years, respectively.

The demographic data of the patients is shown in Table 4.

Table 4. Demographic and clinical data of 401 patients with amyloidosis associated with inflammatory rheumatic diseases according to the Finnish Registry for Kidney Diseases (V).

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)	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 transplantation, n (%)	30 (9)	6 (23)	13 (30)
Time to transplantation, months, median (range)	17 (4 – 41)	14 (7 – 40)	15 (3 – 41)

RRT = renal replacement therapy

The female-to-male ratio did not differ from the sex distribution generally reported in these diseases. Hemodialysis (HD) dominated as the first treatment schedule of RRT in all three diagnosis groups. Thirty (9%) of the 332 RA patients, 6 (23%) of the 26 AS patients

and 13 (30%) of the 43 JIA patients 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.

7.3.6. Outcome of patients with anylosing spondylitis (AS) associated amyloidosis (VI)

In the amyloid files of RFH from 1987 to 2000, there were 13 patients with positive ASFA among the 150 patients with AS who had undergone biopsy (Figure 1). The patients were followed up until death or till the end of December 2003, whichever occurred first. Their demographic and clinical data is shown in Table 5.

Table 5. Clinical features and follow-up data of 13 ASFA+ AS patients (VI)

Sex/Pre-ASFA disease duration	Clinical features at the time of biopsy PU/RI (+/-)	CRP ↑*/↑↑*	Treatment after biopsy	Last FU-data PU/RI	Last CRP ↑*/↑↑*	Outcome/causes of death/ FU (years)
F/24	-/-	↑↑	Combination and single DMARDs; cyclophosphamide. 3 years; long-term predn	-/-	N	Alive/10
M/28	-/+	↑	Single DMARD; short-term predn	-/+	↑↑	Died/Renal cancer/6.5
F/23	-/-	↑↑	Single DMARD	+/+	↑↑	Died/GI bleeding/7.5
M/18	-/-	↑↑	Single DMARD; chlorambucil 6.5 years; long-term predn	+/+	N	Died/Hemodialysis/ AS/ Cervical spine fracture/15
M/13	-/-	↑↑	NSAIDs	NA	N	Alive/13.5
M/26	-/+	↑↑	Combination DMARDs; Cycloph. 0.75 years; long-term predn	+/+	N	Alive/14
M/22	+§/-	↑↑	Single DMARD; chlorambucil 2.5 years; long-term predn	+/-	↑	Alive/14
M/10	+/-	↑↑	Combination DMARDs; long-term predn	-/-	↑↑	Alive/2
M/23	+§/+	↑↑	Single DMARD; long-term predn	+§/+	N	Alive/2
M/24	+/+	↑↑	Single DMARD; long-term predn	-/-	N	Alive/3.5
M/26	-/-	↑↑	Single DMARD	+/+	↑↑	Died/Hemodialysis/

							AS/ Pneumonia/14.5
M/32	+/+	↑	Single DMARD; chlorambucil 2.5 years; long-term predn	-/+	N		Alive/5
M/21	+/+	↑↑	Predn	+/+**	N		Alive/10

*↑ = C-reactive protein (CRP) ≤ 50, ↑↑ CRP > 50 mg/L. PU = proteinuria; RI = renal insufficiency by serum creatinine and/or by creatinine clearance deviating from normal limits; § = nephrotic syndrome; Predn = prednisolone; FU = follow-up ** clear progression of renal insufficiency which may be partly due to chronic glomerulonephritis

Among these 13 patients 5 subclinical cases were found. The focus of the substudy was the outcome of subclinical amyloidosis associated with AS.

The median (range) disease duration of AS among the 5 patients at the time of documentation of amyloid was 23 (13-26) years. In the post-biopsy period, four patients used DMARDs; they were used as combination therapy in one patient and as single therapy in three. In addition, two of the patients used long-term cytostatic therapy (chlorambucil or cyclophosphamide) combined with low-dose prednisolone. All five patients also had peripheral arthritis which , for four of them, necessitated one or more total joint replacement operations of the large joints.

7.3.7. Outcome of patients with psoriatic arthritis (PsA) associated amyloidosis (VII)

The biopsy files revealed 70 patients with clinical diagnoses of PsA analysed by Congo red staining of ASFA specimens to show amyloid (Figure 1). The medical records of the patients were reviewed. Forty-one (59%) of the 70 patients met the Caspar criteria for PsA (Taylor et al. 2006) including three cases with positive biopsies for amyloid. The patients treated with biologicals were included in this substudy.

8. RESULTS

8.1. Incidence of amyloidosis in JIA (I)

No new childhood or adolescent cases of SA could be detected over the past 15 years (Figure 2). At the time of positive biopsy specimens for amyloid, 18 patients (75%) of the 24 patients had clinical manifestations of amyloidosis, i.e. renal disorder (N=16) and goitre. (N=2).
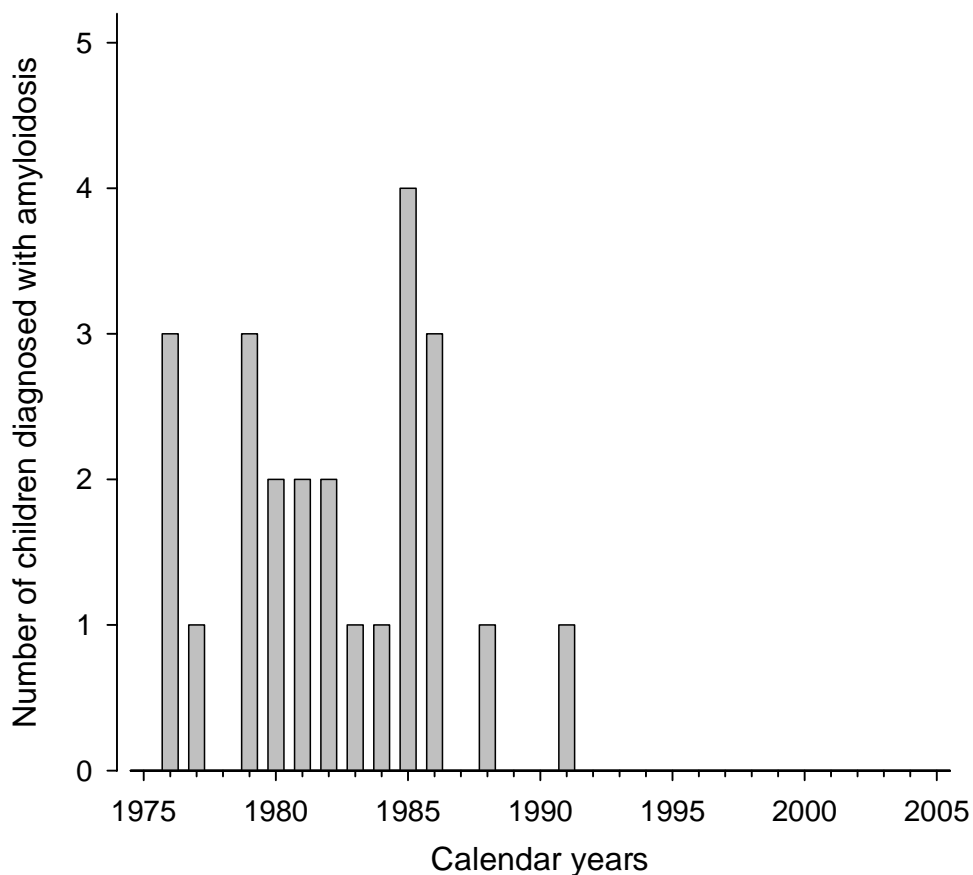

Figure 2. Number of new cases with secondary amyloidosis in juvenile idiopathic arthritis documented in childhood and adolescence in Finland from 1975 to 2005.

8.2. Outcome of amyloidosis in JIA (IV)

At the time of verification of amyloidosis, none of the 24 patients had renal insufficiency. There were 16 proteinuric patients. Proteinuria cleared completely in four (2

with nephrotic syndrome at baseline) and almost completely in one with nephrotic syndrome. Four of these 5 patients were on chlorambucil and one on methotrexate after the documentation of amyloidosis. Three of the 5 were completely free of proteinuria. Eight patients of the 24 showed no signs of renal disorder at the beginning, but 2 developed renal insufficiency.

Amyloid material was still present in renal tissue in all three patients in whom the renal biopsy was repeated. However, their initially positive rectal and/or subcutaneous tissue samples turned negative for amyloid and their proteinuria cleared.

Renal transplantation. Seven patients altogether underwent renal transplantation (RTP) after a mean (range) of 12 (4 to 21) years from the diagnosis of amyloidosis. Four of them died, one during an operation, and the 3 others after a mean survival time of 6.3 years. The mean (range) follow-up of the three patients alive was 9.3 (8.7-9.8) years.

At the end of the follow-up, 14 patients were alive, 12 with normal renal function (3 of them with RTP), one with renal insufficiency and one with proteinuria (the initial amount of 10 g/day decreased to 1.5-2 g/day). 42% of the patients alive were on antihypertensive medication.

Comorbidities. Half of the patients had hypertension. Three had chronic uveitis leading to blindness in one. One patient died of leuchaemia probably associated with the chlorambucil treatment.

*Survival***.** During a mean (range) follow-up of 15.2 (1.5-27.6) years, 10 patients (42%) of the 24 died, including 4 out of the 7 with RTP. The 5-year survival rate of the series was 87.5% (95% CI 74 to 100%), and 10-year survival 75% (95% CI 56 to 92%) (Figure 3).
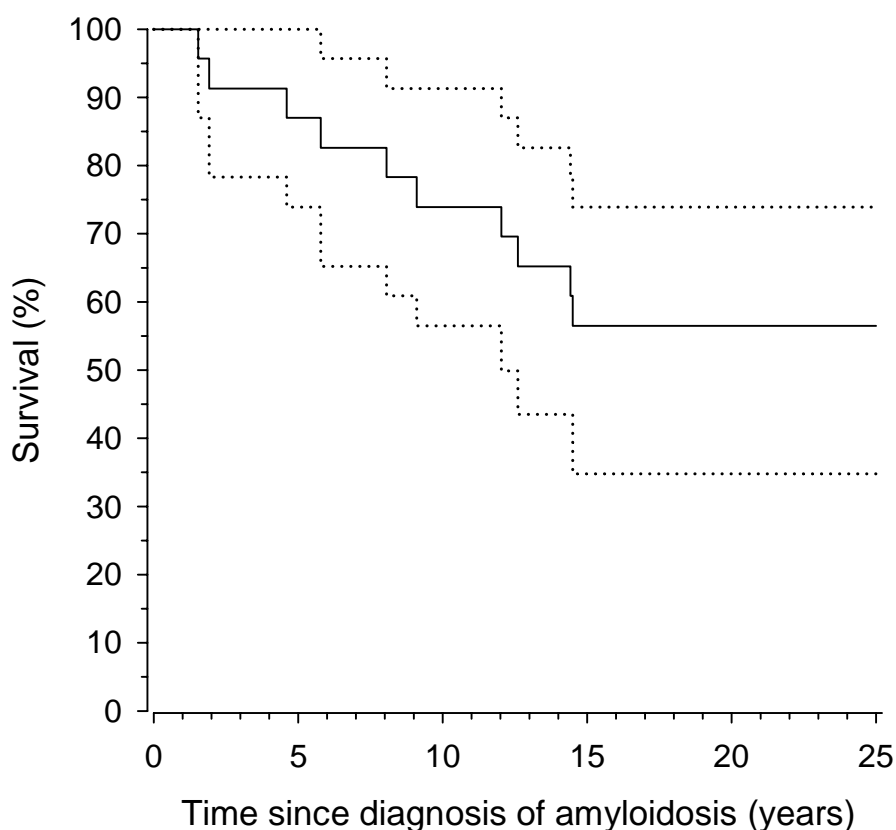
Figure 3. Product-limit survival curves for juvenile idiopathic arthritis patients after diagnosis of secondary amyloidosis (IV).

Gender did not affect the number of deceases: two (40%) of five males and eight (42%) of 19 females died.

JIA was the main cause of death in 9 out of 10 deceased patients. The immediate causes of death were amyloidosis in 6 patients and infection in 4. In addition, one patient died from leukaemia with a 19-month history of chlorambucil treatment (cumulative dose 930 mg).

The median (IQR) lifespan from the diagnosis of amyloidosis of the 14 patients alive was 20 (18, 23) years.

DMARD therapy vs. outcome. Altogether 14 patients had some cytostatic therapy during the immediate post-biopsy period. All the 4 patients who continued on prednisolone monotherapy from the first documentation of amyloidosis onwards died, compared to 6 of the 20 patients [survival 69% (95%CI 45-86%)] on whom a DMARD was continued or changed for another compound (p = 0.002). Two of the patients treated with chlorambucil died, one of amyloidosis and the other of leukaemia, compared to 8 of the 16 not treated with chlorambucil (p=NS).

Social data of the patients alive at the end of follow-up.

Working status: At the end of 2003, 9 patients were on a disability annuity due to JIA, 4 worked full time, and one was working towards a university degree.

Fertility: One female patient had delivered one child and another one had 2 children. Fertility was examined in 2 patients, and found to be normal in one female, whereas one male was found to be infertile. The remaining 9 patients were not planning to have children.

8.3. Occurrence and outcome of amyloidosis in a community-based series (II)

From 1993 onwards, ASFA and/or rectal biopsies were performed on 94 patients with a decreasing number of cases during the consecutive 5-year periods (Table 5). The total numbers of the corresponding biopsies were 86 and 70, yielding amyloid positive findings in 9% and 17%, respectively. Simultaneous ASFA and rectal biopsy was performed in 62 cases with a total number of 12 (19%) amyloid positive cases; all of them were positive by rectal biopsy and 7 (11%) by ASFA. New diagnoses of amyloidosis in the consecutive five-year periods from 1993 onwards were 11, 3 and 5, respectively (Table 6).

Table 6. Number of tissue specimens taken/positive for amyloid classified according to target tissue in 5-year periods from 1993 to 2007 (II).

Target tissue	Number of tissue specimens taken/positive for amyloid per period			
	1993-97	1998-2002	2003-2007	Total
ASFA	66/7	11/0	9/1	86/8
Rectal mucosa	57/9	9/2	4/1	70/12
Colonic mucosa	NA/0	NA/1	NA/1	NA/2
Gastric mucosa	NA/1	NA/0	NA/1	NA/2
Renal tissue	0/0	1/0	2/2	3/2
Total number of amyloid positive patients	11	3	5	19

In 13 of them (10, 2 and 1) the diagnosis was confirmed by ASFA and/ or rectal biopsy made on the basis of the criteria for clinical suspicion of amyloidosis. In two patients the diagnosis of amyloidosis was based on renal biopsy which was performed due to renal insufficiency without proteinuria in one and due to progressive proteinuria in the other. In

four additional cases, tissue amyloid was documented in the screening of mucosal specimens taken at either gastroscopy or colonoscopy from patients without any signs of amyloidosis. The last case of amyloidosis in our data was verified in 2006.

At the end of 2007, there were eight subjects [seven (6 with RA and one with spondylarthropathy) from the study period 1993-2007, and one (with JIA) diagnosed before 1993] with rheumatic diseases associated amyloidosis at the age of ≥16 giving a point prevalence of 12.0 / 100 000 inhabitants (95% CI 5.2-23.6). In 1993-2007, the mean number of inhabitants at the age of ≥16 in the Kainuu district was 69 600. This gives a mean annual incidence of amyloidosis of 1.8 (95% CI 1.1-2.8)/100 000. The corresponding annual incidence figures for the consecutive 5-year periods from 1993 onwards were 3.2 (1.6-5.7), 0.9 (0.2-2.5) and 1.4 (0.5-3.4), respectively (p=0.29).

Seventeen (89%) of the 19 patients with amyloidosis had seropositive RA, one had undifferentiated spondylarthropathy (SpA) and one had AS. The median (range) age of the patients at the onset of their rheumatoid disease was 35 (22-70) years and the median age of these patients at the time of verification of amyloidosis was 62 (52-80) years. None of the patients were under the age of 50 at the time of the diagnosis of amyloidosis. Methotrexate was the commonest individual DMARD, used by seven (37%) of the 19 patients. Four (21%) patients never used immunosuppressive drugs.

At the time of verification of amyloidosis, four (21%) of the 19 patients had normal renal function (eGFR ≥ 90 ml/min/1.73m^2), one of them with proteinuria (Table 6). None of the 19 patients had organomegaly or symptomatic gastrointestinal involvement at the time of verification of amyloidosis.

Eighteen of the 19 patients (95%) had major joint deformities, and at least one total joint replacement surgery had been necessary in 14 patients (74%). Seven (37%) patients had major extra-articular manifestations. RA associated changes in the cervical spine (atlantoaxial subluxation or atlantoaxial impaction) were documented in nine patients (47%) and three of them were operated because of progressive damage of the cervical spine.

Follow-up and outcome data. An overall treatment strategy was activated after the diagnosis of amyloidosis. Cyclophosphamide treatment was started for three patients and combination DMARD therapy for three patients who had had DMARD monotherapy. DMARD therapy was also instituted for the two patients with NSAID alone. Biological therapy was initiated for only one patient.

During the follow-up, 5 patients underwent hemodialysis because of terminal uraemia

and three of them underwent renal transplantation (Table 7)

Table 7. Long-term outcome of 19 patients with rheumatic diseases associated amyloidosis classified according to renal function at the time of verification of amyloidosis (II).

Variable	eGFR (ml/min/1.73 m^2)			
	≥ 90	60-89	15-59	<15
N total/N with PU	4/1	7/4	6/2	2/2
Dialysis/RTP (N)	0/0	1/0	2/1	2/2
Deceased (N)/Survival, years, mean (range)	1/3.5	5/5.4 (2.1-8.9)	4/ 5.1 (2.4-7.9)	2/9.3 (7.7-8.2)
Cause of death (N)	Lymphoma (1)	CVD (2) RA/amyloidosis (1) RA/infection (1) Sudden death/ amyloid cardiomyopathy? (1)	CVD (1) RA/lung fibrosis (1) RA/amyloidosis (2)	CVD (1) AS/amyloidosis (1)
Outcome of patients alive (N)/FU, years, mean (range)	Normal RF (2)/ 6.5 (1.3-11.7) Slightly ↓ GFR (1)/1.8	Normal RF (1)/9.5 Slightly ↓ GFR (1)/1.3	Slightly ↓ GFR after RTP (1)/8.9 ↓ GFR (1)/2.5	0

N = number; CVD = cardiovascular disease; PU = proteinuria > 0.5 g/day; RTP = renal transplantation; eGFR = estimated glomerular filtration rate; RF = renal function: normal RF = eGFR > 90 ml/min/1.73 m^2, Sligthly ↓ GFR = eGFR 60-89 ml/min/1.73 m^2; ↓ GFR = 30-59 ml/min/1.73 m^2

Four of the 5 patients – two with a renal transplant – deceased with a mean (SD) time of 5.9 (4.5) years from the beginning of hemodialysis to death. The mechanisms of death in the two deceased patients with renal transplants were infection associated with chronic rejection seven years after transplantation in one and cardiac failure associated with renal insufficiency after a five-year period with a well functioning renal transplant in the other. Overall, 12 (63%) of the 19 patients died after a median survival time of 6 (95% CI 4-8) years. The five-year survival rate of the series was 67% (95% CI 41-86%) (Figure 4).
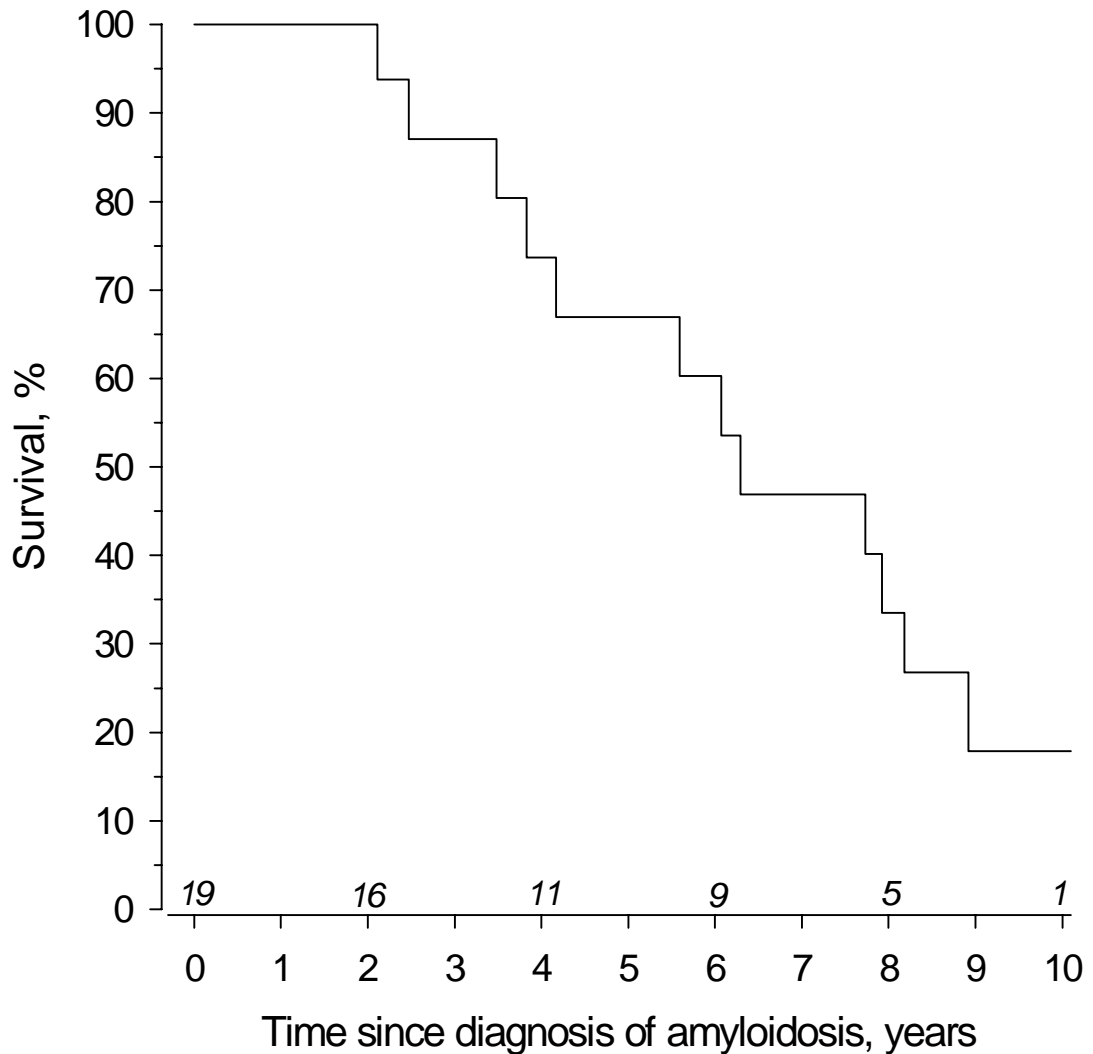
Figure 4. Product-limit survival curve for rheumatic diseases associated amyloidosis after verification of amyloid at biopsy. The number of patients at each time point on whom the estimates were based (II).

The main causes of death in the study were RA or AS in seven cases (N=6/1). Four of the six patients with RA as the main cause of death were considered to have died from amyloidosis (two patients had an associated infection, one renal insufficiency, one rejection of the transplanted kidney). Four patients died of a cardiovascular disease which was cardiac in two (acute myocardial infarction and cardiac insufficiency of unknown cause one each), cerebral infarction in one and pulmonary embolism in one. Except for one case, all the other deaths (N=11) occurred among the patients with impaired renal function (eGFR $\leq$ 89 ml/min/1.73 m^2) at the time of verification of amyloid.

Data on patients alive. At the end of the follow-up, seven patients were alive, six of them had RA and one had undifferentiated SpA. Their mean (SD) follow-up time was 5.3 (4.5) years. Data on their eGFR is shown in Table 7. Two patients had constant

proteinuria.

8.4. Incidence of amyloidosis in patients with rheumatic diseases admitted to RRT (III)

Altogether 378 patients were identified, 264 (69.8%) of whom had amyloidosis associated with an underlying rheumatic disease. 229 of them had RA, 15 AS and 20 JIA. There has been a progressive decline in the number of new admissions to RRT since the early 2000's. While the total annual number of new cases varied between 20 and 37 until 2000, it has been approximately 10 from 2002 onwards (Figure 5).
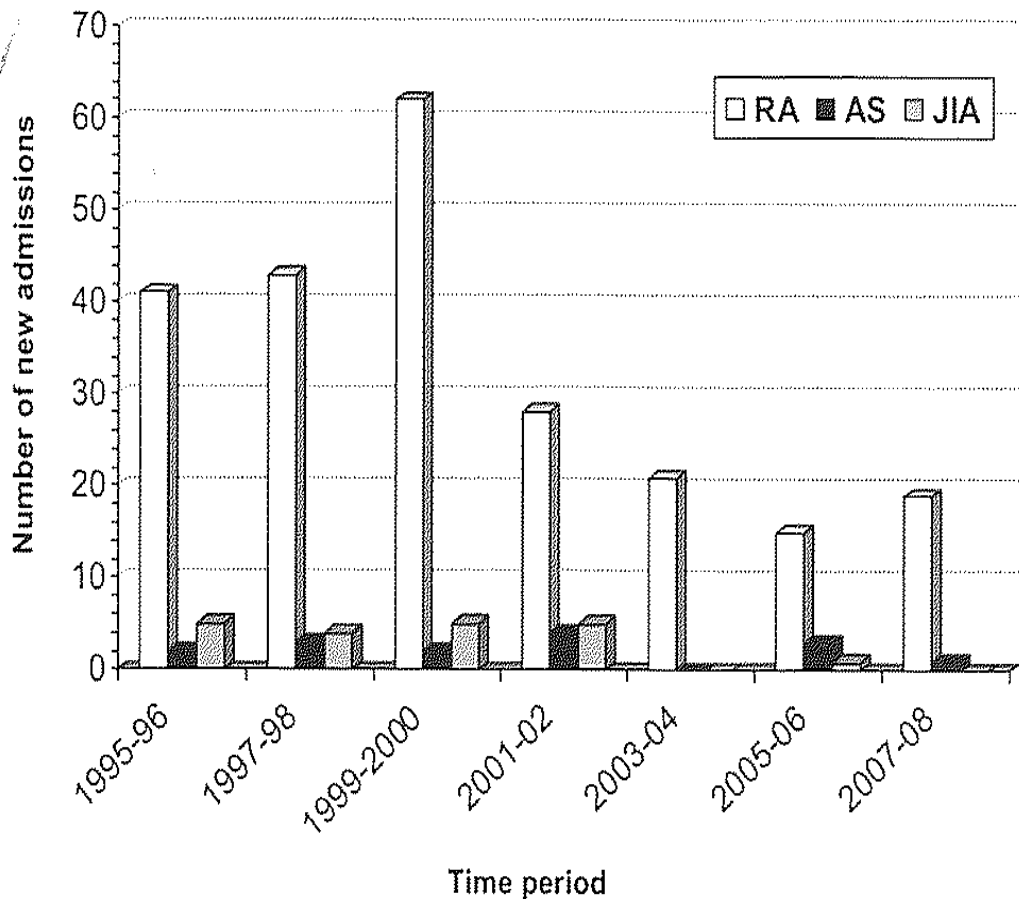

Figure 5. Number of new patients admitted to renal replacement therapy (Finnish Registry for Kidney Diseases) because of amyloidosis associated with rheumatoid arthritis (RA), ankylosing spondylitis (AS) or juvenile idiopathic arthritis (JIA) per 2-year period over the years 1995-2008.

The number of users of DMARDs has increased steadily since the mid-1990's (Figure

40

6). Low-dose MTX was the most frequently used DMARD in 2008 with 24 324 recipients of special reimbursement. The corresponding figure was 6800 in 1995, i.e. the growth has, in relative terms, been 3.6-fold. In 2008, there were 19 082 users of salazosulfapyridine (SASP) (1.7-fold increase), and the respective figure for hydroxychloroquine (HCQ) was 16 737 (2.9-fold increase).

The use of three TNF-α inhibitors (infliximab, etanercept and adalimumab) has also increased since their introduction in the early 2000's. In 2003, the DDDs for infliximab and etanercept were 0.21 and 0.05, respectively. The corresponding figures in 2008 for the same agents and adalimumab were 0.42, and 0.33, respectively. These substances can be used for other indications than rheumatic diseases, too, but the sales register does not reveal the purpose of use (Figure 6).
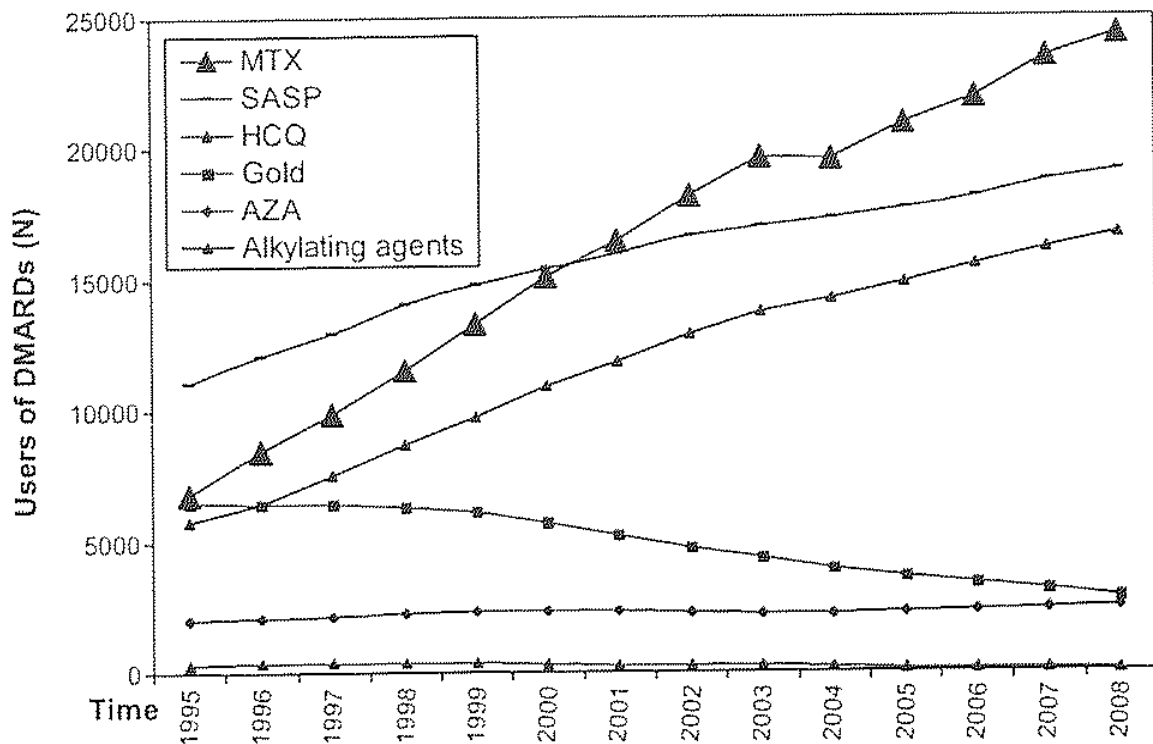

Figure 6. Number of users of disease modifying anti-rheumatic drugs (DMARDs) in Finland from 1995 to 2008. The most used DMARDs and alkylating agents (cyclophosphamide and chlorambucil) are included. MTX = methotrexate; SASP = salazosulfapyridine; HCQ = hydroxychloroquine; AZA= azathioprine; Gold = sodium aurothiomalate.

8.5. Outcome of amyloidosis in patients with rheumatic diseases admitted to RRT (V)

The 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 7).
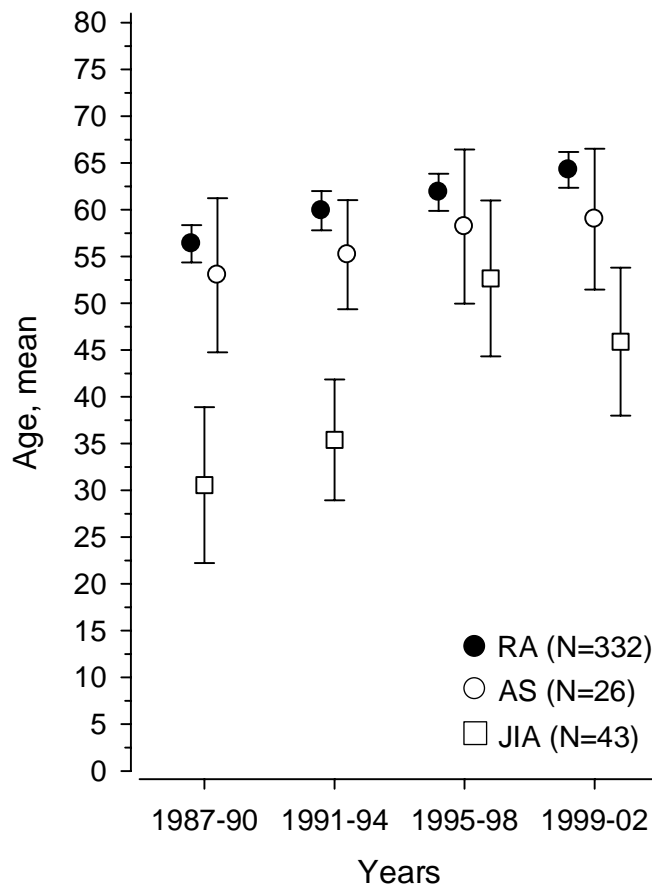

Figure 7. Mean age (95% CI) at acceptance for renal replacement therapy by diagnosis group from 1987 to 2002 (V). RA = rheumatoid arthritis, AS = ankylosing spondylitis, JIA = juvenile idiopathic arthritis

Looking at the periods 1987-90, 91-94, 95-98 and 99-02, 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 RA patients over 65 years of age was 13 (15.7%) and 46 (51.1%), respectively. The corresponding figures for JIA under the age of 45 were 8 patients (88.9%) vs. 4 patients (40%) and for the age group of 45-65, one (11.1%) patient and 6 (60%) patients, respectively. In the AS group, no such trend was discernible.

The median survival times (95% confidence interval) on RRT were 2.11 years (1.93 to 2.69) for RA, 2.37 years (1.11 to 4.31) for AS and 3.05 years (2.19 to 4.23) for JIA (Figure 8).
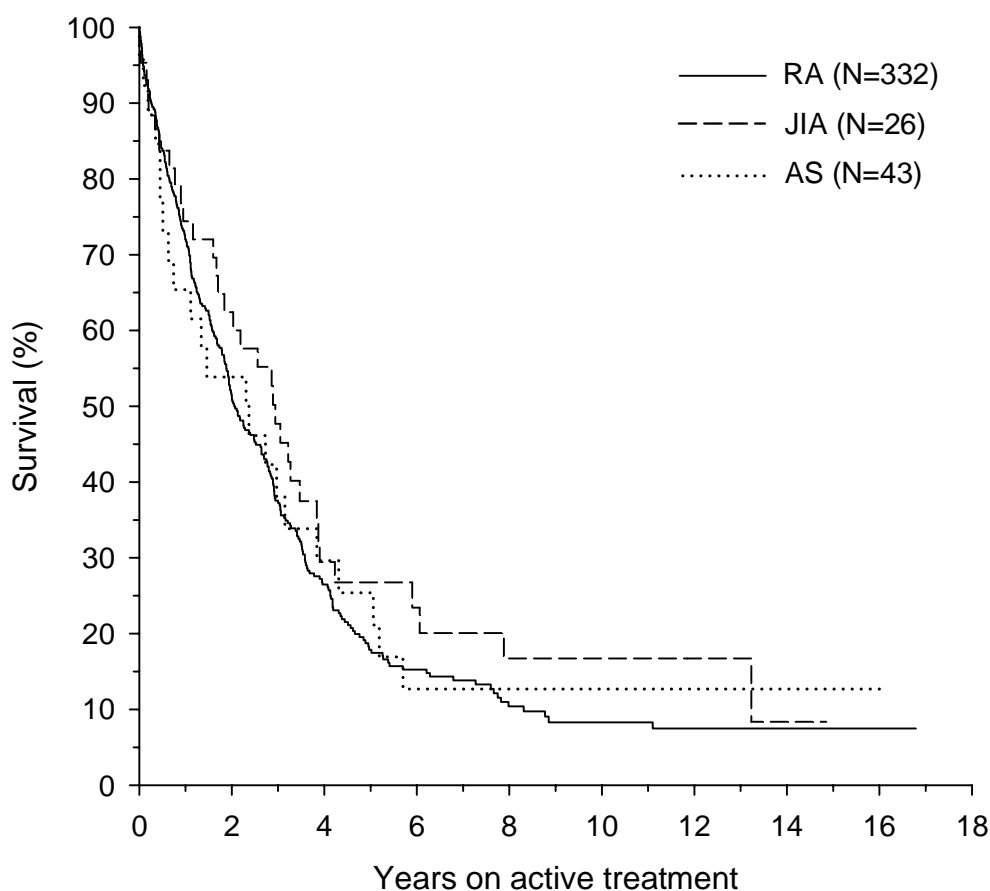
Figure 8. Product-limit survival for patients with amyloidosis associated with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and ankylosing spondylitis (AS) after acceptance to renal replacement therapy (V).

The mean follow-up 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 to 23) %, 30 (14 to 48) % and 27 (14 to 41) %, respectively. The survival on RRT did not improve from 1987 to 2002.

Male sex and a diagnosis of JIA were independent risk factors of mortality with hazard ratios (HRs) (95% CI) of 1.48 (1.20 to 1.84) and 1.55 (1.08 to 2.23), respectively. 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 within any disease group over the whole follow-up period of 1987 to 2002.

Inflammatory rheumatic disease itself dominated as the cause of death, varying from 63% in AS to 79% in JIA.

8.6. Outcome of patients with AS associated amyloidosis (VI)

The outcome of the 13 patients with positive ASFA biopsies out of the 150 biopsied patients is shown in Table 5. After over ten years´ follow-up, two patients out of the five with subclinical amyloidosis at the time of biopsy were alive. They were still free of clinical symptoms of amyloidosis. The three other patients had developed proteinuria and renal insufficiency which had necessitated hemodialysis in two; both of them died from AS 15 years after the diagnosis of amyloidosis. The third patient died from gastrointestinal bleeding 8 years after the diagosis. Seven patients of the 8 who had clinical amyloidosis at diagnosis were alive after a mean follow up time of seven years. One of the patients died from renal cancer after 6.5 years of follow-up.

8.7. Outcome of patients with PsA associated amyloidosis (VII)

Two patients with amyloidosis associated with PsA treated with biological drugs are reported. Despite of the use of MTX and low-dose prednisolone, renal function in one of the patients deteriorated, and she was first treated with etanercept. However, her renal function did not stabilize until the treatment was changed to tocilizumab. The other patient with active psoriatic spondyloarthropathy had subclinical amyloidosis. Her disease did not respond to MTX and low-dose prednisolone. Biological therapy with adalimumab was started when she had a moderate renal failure. She developed proteinuria later but her renal function stabilized.

9. DISCUSSION

9.1. General discussion

Many epidemiological studies in Finland rely on accurate national registries. The hospital discharge register covers all hospitals, including both the outpatient and inpatient visits. The Social Insurance Institution (SII) is responsible for the administration of the national sickness insurance scheme, including drug reimbursements for the entire population. Patients with rheumatic diseases are entitled to this special reimbursement on the basis of a doctor's certificate. The entitlement concerns DMARDs but not non-steroidal anti-inflammatory drugs.

The Finnish Registry for Kidney Diseases was established in 1965. It has an estimated 97 to 99% coverage of all patients accepted for RRT in the country (Finne et al. 2005). From the end of the 1980´s, the clinical practice of RFH was that of active search for amyloidosis by ASFA biopsy in RA patients with active disease and/or signs of a renal disorder (Tiitinen et al. 1988, Tiitinen 2005). All the amyloid biopsy result sheets of RFH from 1987 onwards were stored as an uniform file at the Department of Pathology of Tampere University Hospital. During the years of this study, RFH acted mainly as a secondary centre for the Päijät-Häme and Kymenlaakso districts, and to a lesser degree, as the tertiary centre for the whole country.

It is evident that reports of the manifestations of rheumatic diseases, such as amyloidosis, are often based on patient populations treated in secondary or tertiary clinics which may skew the results. The data of the hospital-based registries of the present series was comprehensive, i.e. the Kainuu Central Hospital is the only specialized centre in the area, and the juvenile patient population of RFH has been estimated to represent around 60% of all children treated for JIA at that time in Finland (Haapasaari 2006).

The retrospective nature of the series limited the possibilities of assessing different prognostic factors for amyloidosis.

9.2. Incidence and prevalence of amyloidosis associated with rheumatic diseases (I-III)

The most striking result of the present series was that JIA associated amyloidosis is disappearing. No new cases of amyloidosis have been encountered during the past 15 years in Finland. For comparison, Ylijoki (1998) reported an incidence of amyloidosis of

3.3% among a JIA patient series with 25 years´ follow-up at a Finnish university clinic. However, in Ylijoki's study, the diagnosis was based on the clinical picture without a thorough screening by biopsies.

The same trend has appeared regarding amyloidosis associated with other rheumatic diseases. Laiho et al. (1999) reported that during the preceding 10 years, the use of ASFA decreased by 43%. There are no comparable studies with similar protocols to assess the incidence of amyloidosis as the protocol that was used in the Kainuu substudy, i.e. active inflammation and/or signs of renal disorder. This approach gave a mean annual incidence of amyloidosis of 1.8 (95% CI 1.1-2.8)/100 000 inhabitants during the years 1993-2007 with a decreasing trend towards the end of the period.

Compared with the historical series (Table2), the Kainuu study showed an extremely low prevalence of amyloidosis in RA of 1.1 %. There are some studies searching for amyloid in consecutive patients which have shown positive ASFA biopsy results in 16% in RA (Gómez-Casanovas et al. 2001) and 7% in AS (Gratacos et al. 1997). In both studies, the vast majority of the patients had subclinical amyloidosis.

Also renal insufficiency due to amyloidosis is decreasing in frequency. Kaipiainen-Seppänen et al. (2000) reported that the number of new cases of amyloidosis associated with RA requiring dialysis has declined at Kuopio University Hospital since the late 1990´s. According to the data of the Finnish Registry for Kidney Diseases, the annual number of new admissions to RRT due to amyloidosis associated with rheumatic diseases was stable from 1987 to 2002. However, after that period, the annual number of cases has been reduced by at least half. From 1995 onwards, the number of users of low-dose methotrexate (MTX) has increased 3.6-fold, the drug being the most frequently used disease modifying anti-rheumatic drug in Finland. A recent study by Rantalaiho et al. (2011), also based on the nationwide drug reimbursement register, reported that combination therapy including methotrexate is the most commonly prescribed treatment strategy for early RA in Finland today.

9.3. Diagnostic methods (I-II, IV, VI-VII)

Our results support the view that rectal biopsy is a more sensitive method than ASFA in the verification of amyloid (Klemi et al. 1987, Dillon et al. 1989). However, ASFA biopsy is preferred, because it is easy to perform and has a low complication risk

(Westermark & Stenkvist 1973, van Gameren et al. 2006). ASFA biopsy shows good sensitivity: 82% by routine assessment (Klemi et al. 1987). By using a more thorough examination (three smears), van Gameren et al. (2006) reported a sensitivity as high as 93% and a specificity of 100%. A negative result does not exclude amyloidosis, however. Although rare, also false positive results may occur, e.g. due to overinterpretation of occasional long, slender, green strands representing collagen (Blumenfeld & Hildebrandt 1993).

If clinically indicated, a biopsy from another affected organ should be performed, such as the kidney or the gastrointestinal (GI) tract. A GI biopsy for screening of amyloid should be remembered in a patient with a rheumatic disease admitted to gastroscopy or colonoscopy for any reason.

9.4. Impact of subclinical amyloidosis (VI-VII)

It has been recommended that ASFA biopsies should be regularly performed on patients with active inflammation (Tiitinen et al. 1988, Tiitinen 2005). By this approach, a relatively high number of patients with subclinical amyloidosis are found. There is a discrepancy in opinions about the impact of this finding (Calin 2004, Gómez-Casanovas et al. 2001, Gratacos et al. 1997). During follow-ups of 5-7 years, the subclinical amyloidosis was reported to progress to clinical amyloidosis in 12-25% of patients, mostly with signs of renal involvement (Gómez-Casanovas et al. 2001, Gratacos et al. 1997). Accordingly, three of the five AS patients with subclinical amyloidosis in substudy VI developed a clinical renal disorder which necessitated hemodialysis in two. All of them had a fatal outcome which was related to amyloidosis. The fact that there can be a lag in the onset of clinical amyloidosis of $\geq$ 10 years − as was shown also in the PsA patients in substudy VII − may obscure the importance of the finding.

9.5. Treatment of rheumatic diseases associated amyloidosis with disease modifying anti-rheumatic drugs (from primary to tertiary prevention) (I-VII)

Primary prevention (I). The time period of the present study covers the past 25 years. During this period, the treatment strategy of rheumatic diseases changed from monotherapy to combination DMARDs (Möttönen et al. 1999, Rantalaiho et al. 2010) and

gradually to the combination of DMARDs with biological drugs. This allows a constantly better control of inflammation. At the best, this means primary prevention of amyloidosis. Accordingly, no new cases of JIA associated amyloidosis in childhood or adolescence could be detected during the past 15 years.

Secondary prevention (II, IV, VI-VII). Most studies (Gracatos et al. 1997, Cómes-Casanovas et al. 2001, Calin 2004) have concluded that subclinical amyloidosis has little significance, and the finding does not necessarily indicate intensification of treatment. However, the results of the present series suggests that an amyloid-staining positive ASFA biopsy carries a remarkable risk for the development of clinically overt amyloidosis. Hence, finding amyloid always alerts to the re-evaluation of the treatment. It is to be noted that the disease in many of these patients seems to be resistant to DMARDs. Therefore, biological therapy is preferred.

Tertiary prevention (treatment of amyloidosis) (II, IV-V, VII). Data from a recent large series of patients with AA amyloidosis showed that the progression of manifest amyloidosis can be retarded by controlling inflammation (Lachmann et al. 2007). The results of the present study indirectly support this view. Firstly, compared with historical studies (Husby 1980, Hazenberg et al. 1994, Myllykangas-Luosujärvi et al. 1995) and according to the data of the Kainuu series, the time from the onset of arthritis to the diagnosis of amyloidosis has increased. Accordingly, the time from the onset of a rheumatic disease to the onset of an end-stage renal disease, i.e. admittance to RRT, has markedly increased. Secondly, in the JIA substudy, DMARDs and/or cytostatics for amyloidosis were associated with a decrease in mortality compared to treatment with prednisolone as a single drug. It is to be noted that during the follow-up of the Kainuu substudy only one of the 15 patients with eGFR ≥ 30 ml/min/1.73 m^2 needed hemodialysis which can be indirectly attributed to active policy of anti-rheumatic drug therapy.

9.6. Treatment of rheumatic diseases associated amyloidosis with biological drugs (VII)

Including the cases in this study, there are 7 documented patients with PsA associated amyloidosis treated with anti-TNF-α: four with infliximab (INF) (Fernández-Nebro et al. 2005, Fiehn &Andrassy 2004), three with ETA (Fernández-Nebro et al. 2005, and the present cases) and one with ADA (the present case). Fernández-Nebro et al. described 4 patients – 3 on INF and one on ETA. The patients who were treated with INF had ≥2 years of follow-up. All had impaired renal function which stabilized during the therapy and their

proteinuria also decreased. One patient who had concomitant chlorambucil therapy died of a pulmonary infection. The reported follow-up of the patient with ETA in their series is too short (8 weeks) (Fernández-Nebro et al. 2005) to draw any firm conclusions of the efficacy of the drug. Fiehn and Andrassy reported a good primary result in a patient treated with INF (Fiehn &Andrassy 2004). However, the follow-up time was less than one year.

On the basis of three case reports hitherto, the efficacy of tocilizumab on RA and JIA associated amyloidosis seems promising (Okuda et al. 2006, Sato et al. 2009, Inoue et al. 2010). Two reports documented rapid normalization of serum amyloid A levels (Okuda et al. 2006, Inoue et al. 2010). The present case is the first to report the efficacy of tocilizumab in PsA associated amyloidosis. However, experiences from larger series of patients are required in order to draw firm conclusions.

9.7. Outcome of amyloidosis associated with rheumatic diseases

The patient selection, e.g. screening of consecutive patients without a clinical suspicion of disease *versus* cases with overt clinical signs of amyloidosis such as renal dysfunction, is an essential factor influencing the interpretation of the results. This must be taken into account when comparing the data of the present study with those of the previous studies.

9.7.1. Outcome of amyloidosis in JIA (III-IV)

Substudy IV (RFH study). Ten JIA patients (42%) of the 24 died during a mean follow-up of 15 years, including 4 out of 7patients with RTP. The 5-year survival was 88% while the 10-year-survival was 75%. David et al. (1993) reported a 10-year survival of 80% in 57 chlorambucil treated patients, but only 24% of 19 patients were never treated with cytostatics.

In the present series, the main cause of death was related to JIA in all but one. The immediate causes of death were amyloidosis in 6 patients and infection in 4. According to David and Woo (1992), 84% of 79 JIA patients with amyloidosis died from renal failure. Infection was the second most common cause of death. In the present study, 14 patients (58%) with a median follow-up time of 20 years were alive, and 86% of them had normal renal function.

Substudy III (Registry for Kidney Diseases). The median survival time in JIA patients who had undergone RRT was 3.1 years (Figure 1). The 5-year survival rate was 27%. In the whole series – considering all rheumatic diseases – male sex and a diagnosis of JIA implied independent risk factors of mortality with hazard ratio (HR) of about 1.5.

9.7.2. Outcome of amyloidosis in rheumatoid arthritis (II-III)

Substudy II (Kainuu study). Five patients out of 19 with rheumatic diseases associated amyloidosis underwent hemodialysis because of terminal uraemia and three of them also had RTP. Overall, 12 (63%) patients died after a median survival time of 6 years. One third of them died from amyloidosis. The five-year survival rate was 67%. In their recent study of a population-based Finnish RA series, Sihvonen and her co-workers reported that renal amyloidosis in RA is associated with a mortality rate over twice that of population controls (2004). Half of the patients of the present series died from their basic rheumatic disease, amyloidosis being a cause of death in four (33%) of the total number of 12 deaths. That is why cardiovascular diseases, a well known cause of excess death in patients with inflammatory rheumatic diseases (Solomon et al. 2003, Peters et al. 2004), were underrepresented in this series. Infection was the immediate cause of death in two cases and the main cause of death in one patient.

Although rheumatic diseases associated amyloidosis carries a poor prognosis, according to the data of the present series, the survival of patients with amyloidosis is improving. In the 1980's, the median survival time of RA patients with clinical amyloidosis was 3 years (Myllykangas-Luosujärvi et al. 1995, Gertz 1991). In contrast, in the present series the median survival was 6 years.

Substudy III (Registry for Kidney Diseases). Three-hundred thirty-two (66%) of the 401 patients with rheumatic diseases reported to the Registry for Kidney Diseases due to amyloidosis associated end-stage renal disease had RA. Among them, the median survival time on RRT was 2.1 years. The 5-year survival rate was 18%.

10. CONCLUSIONS

- The incidence of amyloidosis associated with rheumatic diseases has declined considering the whole spectrum of the disease, i.e. from subclinical stage to end-stage renal disease.

- This has been most dramatic for JIA patients: Among them, amyloidosis is not encountered anymore in childhood or adolescence.
- Since the beginning of the 2000's, the number of patients admitted to RRT due to end-stage renal disease associated with amyloidosis has been reduced by half.

- There may be more than a ten-year lag in the development of clinical amyloidosis after a positive ASFA biopsy. The finding of subclinical amyloidosis has possibly been overlooked in the earlier studies due to the short duration of the follow-up periods.

- There was faint evidence on that DMARD therapy retards the progression of amyloidosis. In the refractory cases of PsA, the use of biologicals seemed promising.

- Compared to historical cases, the outcome among patients with amyloidosis has improved. However, if the disease has progressed to end-stage renal disease the outcome is extremely poor. From 1987 to 2002, there was no change in the survival of patients admitted to RRT.

- There may be several reasons for the declining incidence and improved outcome:

- Treatment modalities – methotrexate, combination of DMARDs and biologicals – have improved during the last two decades, making remission a realistic goal of therapy (primary prevention).
- The use of ASFA biopsy helps diagnose amyloidosis in its subclinical phase and enables the intensification of therapy thereafter (secondary prevention).
- Better control of inflammation, i.e. decline of CRP by effective anti-rheumatic drug therapy (tertiary prevention).

11. ACKNOWLEDGEMENTS

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13. ORIGINAL PUBLICATIONS

LETTERS

Why can we no longer find juvenile idiopathic arthritis-associated amyloidosis in childhood or in adolescence in Finland?

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The prevalence of secondary amyloidosis (SA) in juvenile idiopathic arthritis (JIA) varies between 1% and 10% (1–3). The European prevalence figures (up to 10.8%) (1–3) are higher than those reported from centres in the USA (1.8%) (2). Ylijoki in 1998 (4) reported an incidence of SA of 3.3% among a patient series with 25 years' follow-up at a Finnish university clinic.

For the present series we scrutinized the patient registers of the Department of Paediatrics in the Rheumatism Foundation Hospital (RFH) from 1975 to the end of 2005 to look for cumulative incidence of SA in patients with JIA. In addition, we assessed amyloidosis biopsy files of RFH of over 2600 biopsies, with 248 from patients with JIA from 1986 onwards. The study focused on subjects in the care of the Department of Paediatrics that is on those under the age of 19.

Twenty-four patients with JIA-associated SA were identified, the latest case dating back to 1991 (Figure 1). The demographic data and disease characteristics of the patients are shown in Table 1. At the time of amyloid biopsy, 17 patients had clinical manifestations of SA, that is proteinuria without renal insufficiency (n=15), and goitre (n=2). In addition, seven patients had undergone biopsy due to unrelenting disease activity judged by the clinical picture and levels of C-reactive protein. Thirty-seven biopsies were performed in total. The biopsies were performed on: subcutaneous fat (eight biopsies), buccal cavity (simultaneous biopsy on tongue and buccal mucosa counted as one) (10), gastrointestinal tract (eight), kidney (nine), and thyroid gland (two). Two or three biopsies at different locations had to be performed for nine patients before yielding a positive sample.

The Department of Paediatrics of the RFH, acting as the only tertiary centre for inflammatory joint disorders for children in Finland, has traditionally taken care of 60–75% of the JIA patients in the country; that is, almost all the patients with severe disease have been treated there. In the present series, we looked for trends in JIA-associated SA over the past 30 years. The most important finding was that

no new childhood or adolescent cases of SA appeared over the past 15 years. We also interviewed all the paediatric rheumatologists of the five university hospitals in Finland, which act as secondary centres, to find all possible paediatric and adolescent patients suffering from JIA-associated SA in that period. No new cases came up. Thus it seems that JIA-associated SA before adult age has disappeared or is at least extremely rare in Finland. At a minimum, the present data show that JIA-associated SA can be slowed down sufficiently to be no longer present in childhood or in adolescence.

Our treatment strategy to maximally control the inflammation with disease-modifying anti-rheumatic drugs (DMARDs) and local and systemic cortico-steroids must be seen as the most important explanation for the finding. Reports, including our earlier ones (1, 5, 6), suggest that cytostatics both diminish the incidence of SA and improve its prognosis when used as a secondary prevention. In Finland during two consecutive 11-year periods (1969–79 and 1980–90) the percentage of amyloidosis as a direct cause of death decreased from 42% (10 patients) to 17%
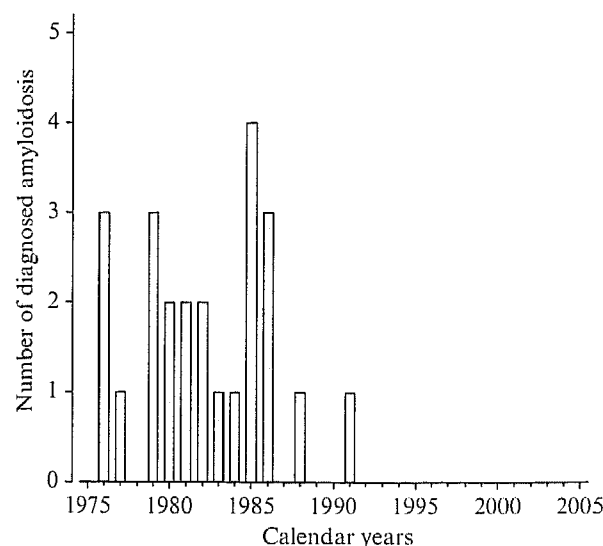

Figure 1. Number of new cases with secondary amyloidosis in juvenile idiopathic arthritis documented in childhood and adolescence from 1975 to 2005 in Finland.

Table 1. Characteristics of 24 children with juvenile idiopathic arthritis (JIA) and amyloidosis.

Characteristic	
No. of girls, n (%)	19 (79)
Age at symptoms of JIA (years), mean (range)	4.7 (1–11)
Age at diagnosis of JIA (years), mean (range)	5.1 (1–12)
Time from onset of JIA to diagnosis of SA (years), median (IQR)	8 (4–12)
Disease course type, n (%)	
Extended oligoarthritis	2 (8)
Juvenile spondylarthropathy	1 (4)
Polyarthritis	10 (42)
Systemic	11 (46)
HLA B27 present, n (%)	13/22* (59)
Rheumatoid factor present, n (%)	1 (4)
Antinuclear antibodies present, n (%)	10 (42)

SA, secondary amyloidosis; IQR, interquartile range. * HLA typing was not performed in two out of the 24 cases.

(four patients), which could be indirectly attributed to a more active DMARD treatment policy (5). The standard practice to treat JIA in Finland has switched from the dominance of intramuscular gold and chloroquine preparations in the 1970s to azathioprine in the early 1980s, and to an increasing use of methotrexate since the mid-1980s to its present use as the gold standard of the treatment of JIA (7, 8).

The data hitherto from different series of JIA-associated SA show that the disease type most commonly represented is systemic disease (1). This shows a slight difference compared to our series, where the systemic and polyarticular type have an equal frequency.

In conclusion, over the past 15 years, no new cases of JIA-associated SA have been documented in childhood or adolescence in Finland. We look forward to seeing whether a similar trend will be reported from other countries.

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More evidence of declining incidence of amyloidosis associated with inflammatory rheumatic diseases

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Objective: To assess the incidence, prevalence, and outcome of amyloidosis associated with inflammatory rheumatic diseases.

Methods: An observational study was performed in the outpatient department of Kainuu Central Hospital from 1993 to 2007. The following criteria were used for the performance of abdominal subcutaneous fat aspiration (ASFA) and/or rectal biopsies: erythrocyte sedimentation rate (ESR) > 40 mm/h at two consecutive visits; and proteinuria (> 0.5 g/day) or serum creatinine > 150 µmol/L. Renal biopsy was performed when there was a high suspicion of amyloidosis in cases with negative findings in the above-mentioned biopsies. In addition, amyloid staining was used routinely for mucosal specimens taken in gastroscopy and colonoscopy. The patients were followed until death or to the end of 2007.

Results: New diagnoses of amyloidosis in the consecutive 5-year periods from 1993 onwards numbered 11, 3, and 5, respectively. During the study period, there was a mean annual incidence of amyloidosis of 1.8 [95% confidence interval (CI) 1.1–2.8)/100 000]. At the end of 2007 there were eight subjects with amyloidosis, giving a point prevalence of 12.0/100 000 (95% CI 5.2–23.6). Five patients out of the 19 underwent haemodialysis because of terminal uraemia and three of them also had renal transplantation. Overall, 12 (63%) patients died after a median survival time of 6 (95% CI 4–8) years, one-third from amyloidosis. The 5-year survival rate of the series was 67% (95% CI 41–86).

Conclusion: Amyloidosis is rarely encountered today. ASFA or rectal biopsy facilitates its early diagnosis.

The decrease in the prevalence of chronic infectious diseases, such as tuberculosis and osteomyelitis, has meant that the main cause of amyloid A (AA) amyloidosis nowadays is inflammatory rheumatic diseases. Amyloidosis associated with rheumatic diseases is more common in Europe and Japan than in the USA (1–4). To date, uraemia caused by renal amyloidosis has appeared as a cause of death in Finnish patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and juvenile idiopathic arthritis (JIA) at an exceptionally high rate (5–8). The methods of controlling inflammation in rheumatic diseases and thereby lowering the risk of amyloidosis have improved considerably in recent years. However, there are still patients whose arthritis is resistant to conventional disease-modifying anti-rheumatic drugs (DMARDs) and biological agents, and who are thus at an increased risk of developing amyloidosis (9).

In this paper, we report the annual incidence and prevalence of amyloidosis associated with inflammatory rheumatic diseases in the Kainuu district in northern Finland from 1993 to 2007, focusing on the outcome of the disease.

Patients and methods

Kainuu Central Hospital is the only secondary health-care centre in the Kainuu province and covers an adult population (≥ 16 years of age) of approximately 67 000. According to the regional treatment protocol, the rheumatological unit of the Central Hospital is responsible for the diagnosis and institution of therapy in all cases with RA and other chronic inflammatory rheumatic diseases and also the follow-up of the active and progressive disease types.

We have been active since 1993 in searching for cases with amyloid in tissue specimens of abdominal subcutaneous fat aspiration (ASFA) biopsy and/or rectal biopsy among patients with rheumatic diseases. The following criteria for the performance of biopsy have been in use:

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erythrocyte sedimentation rate (ESR) > 40 mm/h at two consecutive visits at 3–6-month intervals, proteinuria (> 0.5 g/day) or serum creatinine > 150 μmol/L. In addition, a renal biopsy was performed on patients with proteinuria and with a high suspicion of amyloidosis in whom amyloid specimens taken by ASFA or rectal biopsy were negative. Furthermore, since 1993 our Department of Pathology has been routinely screening the histopathological specimens for amyloid taken from patients with inflammatory rheumatic diseases in connection with gastroscopy or colonoscopy. In our study, the diagnosis of AA amyloidosis was based on the demonstration 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. Estimated glomerular filtration rate (eGFR) was calculated by serum creatinine, age, sex, and race (10). The patients were followed to the end of 2007 or until death. Causes of death were obtained from death certificates.

Statistical analysis

The results are expressed as mean or median, standard deviation (SD) or interquartile range (IQR) and 95% confidence intervals (CIs). Kaplan–Meier curves were used to illustrate the cumulative proportions of survival. Incidence rates with 95% CI were calculated per 100 000 assuming a Poisson distribution. Incidences between the 5-year periods were analysed using exact Poisson regression analysis.

Results

From 1993 onwards, ASFA and/or rectal biopsies were performed on 94 patients, with a decreasing number of cases during the consecutive 5-year periods (Table 1). The total number of corresponding biopsies were 86 and 70, yielding amyloid-positive findings in 9% and 17%, respectively. ASFA and rectal biopsy were performed simultaneously in 62 cases, with a total number of 12 (19%) amyloid-positive cases; all of them were positive by rectal biopsy and seven (11%) by ASFA. New diagnoses of amyloidosis in the consecutive 5-year periods from 1993 onwards numbered 11, 3, and 5, respectively (Table 1). In 13 of these (10, 2, and 1), the diagnosis was confirmed by ASFA and/or rectal biopsy made on the basis of the criteria for clinical suspicion of amyloidosis. In two patients the diagnosis of amyloidosis was based on renal biopsy that was performed due to renal insufficiency without proteinuria in one and to progressive proteinuria in the other. In four additional cases, tissue amyloid was documented in screening of mucosal specimens taken in either gastroscopy or colonoscopy from patients without any signs of amyloidosis. The last case of amyloidosis was verified in 2006.

Table 1. Number of tissue specimens taken/positive for amyloid classified according to target tissue in 5-year periods from 1993 to 2007.

| Target tissue | Number of tissue specimens taken/ positive for amyloid per period | | | |
	1993–97	1998–2002	2003–07	Total
ASFA	66/7	11/0	9/1	86/8
Rectal mucosa	57/9	9/2	4/1	70/12
Colonic mucosa	NA/0	NA/1	NA/1	NA/2
Gastric mucosa	NA/1	NA/0	NA/1	NA/2
Renal tissue	0/0	1/0	2/2	3/2
Total number of amyloid-positive patients	11	3	5	19

ASFA, abdominal subcutaneous fat aspiration; NA, not available.

At the end of 2007, according to the data from Statistics of Finland, Kainuu Central Hospital covered a population of 80 203 inhabitants, with 66 763 subjects at the age of ≥ 16. At this time point there were eight subjects [seven (six with RA and one with spondylarthropathy) from the study period 1993–2007 and one (with JIA) diagnosed before 1993] with rheumatic disease-associated amyloidosis at the age of ≥ 16, giving a point prevalence of 12.0/100 000 (95% CI 5.2–23.6). In 1993–2007, the mean number of inhabitants at the age of ≥ 16 in the Kainuu district was 69 600. This gives a mean annual incidence of amyloidosis of 1.8 (95% CI 1.1–2.8)/100 000. The corresponding annual incidence figures for the consecutive 5-year periods from 1993 onwards were 3.2 (1.6–5.7), 0.9 (0.2–2.5), and 1.4 (0.5–3.4), respectively (p=0.29).

Seventeen (89%) of the 19 patients had seropositive RA, one had undifferentiated spondylarthropathy (SpA), and one AS. Table 2 shows the demographic

Table 2. Demographic data and clinical data at diagnosis of amyloidosis in 19 patients with rheumatic disease-associated amyloidosis.

Sex, female, n (%)	14 (74)
Age at diagnosis of rheumatic disease (years), mean (SD)	38 (14)
Age at diagnosis of amyloidosis (years), mean (SD)	64 (8)
Disease duration before diagnosis of amyloidosis (years), mean (SD)	27 (10)
ESR (mm/h), mean (SD)	57 (32)
CRP (mg/L), mean (SD)	49 (38)
Serum creatinine (μmol/L), mean (SD)	143 (151)
Treatment, n (%)	
DMARD combination with prednisolone	5 (26)
DMARD monotherapy with prednisolone	9 (47)
DMARD monotherapy	1 (5)
Prednisolone	2 (11)
NSAID	2 (11)

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug.

RIGHTSLINK)

Table 3. Long-term outcome of 19 patients with rheumatic disease-associated amyloidosis classified according to renal function at the time of verification of amyloidosis.

eGFR (mL/min/1.73 m^2)	≥ 90	60–89	15–59	< 15
N total/N with PU	4/1	7/4	6/2	2/2
Dialysis/RTP (N)	0/0	1/0	2/1	2/2
Deceased (N)/ Survival (years), mean (range)	1/3.5	5/5.4 (2.1–8.9)	4/5.1 (2.4–7.9)	2/9.3 (7.7–8.2)
Cause of death (N)	Lymphoma (1)	CVD (2) RA/amyloidosis (1) RA/infection (1) Sudden death/amyloid cardiomyopathy? (1)	CVD (1) RA/pulmonary fibrosis (1) RA/amyloidosis (2)	CVD (1) AS/amyloidosis (1)
Outcome of patients alive (N)/ Follow-up (years), mean (range)	Normal RF (2)/6.5 (1.3–11.7) Slightly ↓ GFR (1)/1.8	Normal RF (1)/9.5 Slightly ↓ GFR (1)/1.3	Slightly ↓ GFR after RTP (1)/8.9 ↓ GFR (1)/2.5	0

N, number; CVD, cardiovascular disease; RA, rheumatoid arthritis; AS, ankylosing spondylitis; PU, proteinuria > 0.5 g/day; RTP, renal transplantation; eGFR, estimated glomerular filtration rate; RF, renal function: normal RF = eGFR > 90 mL/min/1.73 m^2, Slightly ↓ GFR = eGFR 60–89 mL/min/1.73 m^2; ↓ GFR = 30–59 mL/min/1.73 m^2.

and clinical data for the patients. The median (range) age of the patients at onset of their rheumatoid disease was 35 (22–70) years and the median age of these patients at the time of verification of amyloidosis was 62 (52–80) years. None of the patients were under the age of 50 at the time of diagnosis of amyloidosis. Methotrexate was the most common individual DMARD, which was in use in seven (37%) out of the 19 patients. Four (21%) patients had never used immunosuppressive drugs.

At the time of verification of amyloidosis, four (21%) out of the 19 patients had normal renal function (eGFR ≥ 90 mL/min/1.73 m^2), one of them with proteinuria (Table 3). None of the 19 patients had organomegaly or symptomatic gastrointestinal involvement at the time of verification of amyloidosis.

Eighteen of the 19 patients (95%) had major joint deformities, and at least one total joint replacement surgery had been necessary in 14 patients (74%). Seven (37%) patients had major extra-articular manifestations. Five patients had interstitial lung disease (ILD); fibrosing alveolitis (n = 3) and bronchiolitis obliterans organizing pneumonia (n = 2). One had Felty's syndrome and one pyoderma gangrenosum. RA-associated changes in the cervical spine (atlantoaxial subluxation or atlantoaxial impaction) were documented in nine patients (47%) and three of them were operated on because of progressive damage of the cervical spine.

Follow-up and outcome data

An overall treatment strategy was activated after the diagnosis of amyloidosis. Cyclophosphamide treatment was started for three patients, and combination DMARD therapy for three patients who had had DMARD monotherapy. DMARD therapy was also instituted for the two patients with non-steroidal anti-inflammatory drugs (NSAIDs) alone. Biological therapy was initiated only for one patient.

During the follow-up, five patients underwent haemodialysis because of terminal uraemia and three of them had undergone renal transplantation (Table 3). Four of the five patients (two with a renal transplant) died with a mean (SD) time of 5.9 (4.5) years from the beginning of haemodialysis to death. The causes of death in the two deceased patients with renal transplants were infection complication associated with chronic rejection 7 years after transplantation in one and cardiac failure associated with renal insufficiency after a 5-year period with a well-functioning renal transplant in the other. Overall, 12 (63%) out of the 19 patients died after a median survival time of 6 (95% CI 4–8) years. The 5-year survival rate for the series was 67% (95% CI 41–86) (Figure 1).

The main causes of death are shown in Table 3. Four of the six patients with RA as the main cause of death were considered to die from amyloidosis (two patients
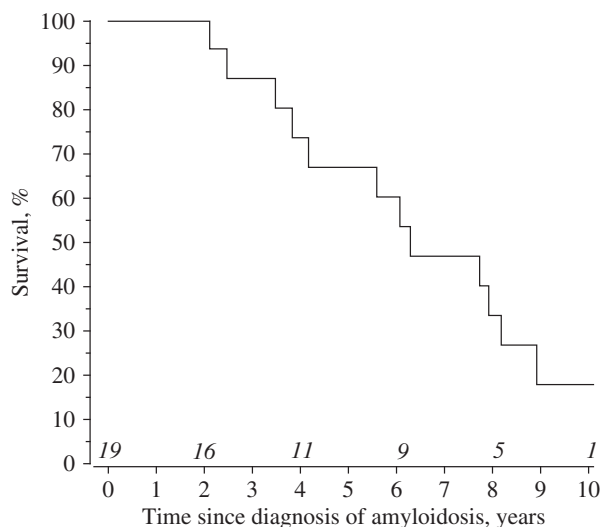

Figure 1. Product-limit survival curve for rheumatic disease-associated amyloidosis after verification of amyloid at biopsy, showing the number of patients at each time point on whom the estimates were based.

had an associated infection, one renal insufficiency, one rejection of the transplanted kidney). Four patients died from a cardiovascular disease, which was cardiac death in two (acute myocardial infarction and cardiac insufficiency of unknown cause one each), cerebral infarction in one, and pulmonary embolism in one. Except for one case, all the other deaths (n = 11) occurred among the patients with impaired renal function (eGFR ≤ 89 mL/min/1.73 m^2) at the time of verification of amyloid.

Data on live patients

At the end of the follow-up, seven patients were alive: six of them had RA and one had undifferentiated SpA. Their mean (SD) follow-up time was 5.3 (4.5) years. Data on their eGFR are shown in Table 3. Two patients had constant proteinuria.

Discussion

The epidemiology of a given disease should be assessed considering the patient population studied. Patients with rheumatic diseases who are prone to clinical amyloidosis are those with an active DMARD-resistant disease. Thus they are often treated in tertiary rheumatology clinics where the patient material does not cover the whole spectrum of the disease. However, our series can be considered a population-based one, because Kainuu Central Hospital is the only hospital in charge of the diagnosis and treatment of rheumatic diseases in the geographical area. The limitations of our study, however, are the observational nature of the series and a selection bias that follows the study design due to the heterogeneous inclusion criteria used, such as combining gastrointestinal biopsy material in the study.

We took both ASFA and rectal biopsy specimens for amyloid testing from patients with a clinical suspicion of amyloidosis (constantly elevated ESR and/or signs of renal disorder) in an outpatient series of patients with different rheumatic diseases. Our results support the view that rectal biopsy is the more sensitive method (11, 12). Hence, we recommend rectal biopsy for identification of amyloid in cases with a high clinical suspicion of amyloidosis without verification of amyloid by the ASFA technique.

Our data from one centre show that the number of patients who met the screening criteria for biopsy decreased considerably during the study period that was initiated in 1993. The number of biopsied patients was 70 in the first 5-year period and only nine in the last one. This is in accordance with the data of a study from another Finnish centre, the Rheumatism Foundation Hospital, which reported a sharp decline in the annual number of ASFA biopsies for detecting amyloidosis due to inflammatory rheumatic diseases (13).

Accordingly, the number of new cases with amyloidosis first decreased from the early 1990s to about the year

2000 and stabilized thereafter. Likewise, a study from a university hospital in Finland showed that new admissions to dialysis due to RA-associated amyloidosis and renal insufficiency decreased towards the end of the 1990s (14). There are also nationwide data from Finland analogous to this trend. First, no new cases of amyloidosis at juvenile age or adolescence have been reported among patients with JIA during the past 15 years (15). Second, the annual number of cases with amyloidosis admitted to the Finnish Registry for Kidney Diseases seems to have been decreasing from the beginning of this millennium (16). The registry has an estimated 97–99% coverage of all patients accepted for renal replacement therapy (RRT; dialysis or renal transplantation) in the country (17).

At the end of 2007, there were eight patients with rheumatic disease-associated amyloidosis, and six of them had RA. The prevalence of RA is 0.8% in Finland (18). Thus, in this population with 66 800 adult inhabitants, there were approximately 530 patients with RA, giving a prevalence of amyloidosis of 1.1% in RA.

When compared to historical controls, it seems that the clinical manifestation of amyloidosis in rheumatic diseases is retarded by several years. In a Norwegian series of AS-associated amyloidosis with cases up to 1980, the mean disease duration of AS at the time of the detection of amyloidosis was 14 years (19). The corresponding figure from a Finnish RA series from the 1980s was 19 years (5), compared to 27 in our series. As to RA, a similar trend was reported from the Netherlands (20). Accordingly, the data from the Finnish Renal Registry show that, from 1987 to 2002, the mean age of admission to RRT increased by over 10 years in patients with RA- and JIA-associated amyloidosis (21).

This dramatic change in the number of patients with a clinical suspicion of amyloidosis and in the number of patients with the confirmed disorder or with its complications, as well as the delay in the appearance of the latter two conditions, can be attributed indirectly to a more active treatment strategy with DMARDs. There has been a marked increase in the annual number of users of DMARDs, and methotrexate in particular, in Finland from 1995 onwards (22). In clinics, the effect of treatment is measured by its ability to lower C-reactive protein (CRP), which is known to be closely associated with serum AA concentrations (23).

Amyloidosis is associated with increased morbidity and mortality. Major joint injuries and extra-articular manifestations were common among our patients. This is compatible with the fact that amyloidosis is associated with long-lasting inflammatory activity and severe disease forms (19, 24). In their study of a population-based Finnish RA series, Sihvonen et al reported that renal amyloidosis in RA is associated with a mortality rate more than twice that of population controls (25). Half of our patients died from a musculoskeletal disorder, amyloidosis being a cause of death in four (33%) of the total number of 12 deaths. That is why cardiovascular diseases, the well-known risk for patients with inflammatory

rheumatic diseases (26, 27), was under-represented as a cause of death in this series. Infection was the immediate cause of death in two cases and the main cause of death in one.

Although rheumatic disease-associated amyloidosis carries a poor prognosis (21), according to the data of the present series, the survival of patients with amyloidosis is improving. In the 1980s, the median survival time of RA patients with clinical amyloidosis was 3 years (5, 28). By contrast, in our series the median survival was 6 years. Data reported in 2007 from a large series of patients with AA amyloidosis showed that the progression of manifest amyloidosis can be retarded by effectively controlling the inflammation (29). It should be noted that during the follow-up of the present series, only one of the 15 patients with eGFR $\geq$ 30 mL/min/ 1.73 m^2 underwent haemodialysis, which can be attributed indirectly to our active policy of anti-rheumatic drug therapy. However, the follow-up period after verification of amyloidosis was too short in some of these patients to draw any firm conclusions.

There may be several reasons for the improved outcome. The use of ASFA biopsy helps us to diagnose amyloidosis in its subclinical phase and enables intensification of therapy thereafter, as was the case in some of our patients. Today, it is realistic to aim at remission of arthritis by means of more effective treatment modalities. In addition, the possibilities of treating associated diseases, such as hypertension and hyperlipidaemia, have improved during the past decades.

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A marked decline in the incidence of renal replacement therapy for amyloidosis associated with inflammatory rheumatic diseases – data from nationwide registries in Finland

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Abstract

Risk for amyloidosis in rheumatic diseases is associated with a long-lasting inflammation. To assess possible changes in the incidence of terminal uraemia due to amyloidosis associated with rheumatic diseases on a nationwide basis, we scrutinised the files of the Finnish Registry for Kidney Diseases for patients suffering from amyloidosis associated with rheumatoid arthritis (RA), ankylosing spondylitis (AS) or juvenile idiopathic arthritis (JIA) over the period 1995–2008. The registry has an estimated 97–99% coverage of all patients accepted for renal replacement therapy (RRT) in the country. Data on the consumption of antirheumatic drugs were collected from two sources: the Social Insurance Institution's Drug Reimbursement Register, and the Sales Register of the National Agency for Medicines from the above period. Altogether 264 cases were identified. Two hundred twenty-nine of them had RA, 15 AS and 20 JIA. When the total annual number of new admissions to RRT varied between 20 and 37 at the end of 1990s, it was under half of that from 2002 onwards. Over this period, the number of users of low-dose methotrexate (MTX) has increased 3.6-fold, the drug being the most frequently used disease modifying anti-rheumatic drug in Finland. The present nationwide series is the first to show that the incidence of end-stage renal disease due to amyloidosis associated with rheumatic diseases is decreasing. An obvious reason for this is intensive anti-rheumatic drug therapy.

Introduction

Amyloidosis; i.e., AA amyloidosis, associated with inflammatory rheumatic diseases has a considerable geographic variation between ethnic groups. It is more common in Europe and Japan than in the US [1–3]. Until now uraemia caused by renal amyloidosis has been a major cause of death in Finnish patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and juvenile idiopathic arthritis (JIA) [4–6]. Lehtinen reported that patients with AS have a mortality rate 1.5 times higher than

expected, which was mostly explained by amyloidosis [6]. In their recent study of a population-based Finnish RA series, Sihvonen et al. reported that renal amyloidosis is associated with a mortality rate more than twice that of population controls [7]. Our previous report of amyloidosis associated with JIA showed that these patients have a poor prognosis with a 10-year survival rate of 75% (95 CI 57–92%) [8]. In a Japanese series 61% of 80 patients with RA died within an average period of 5.6 years after detection of amyloidosis [9]. A very recent Czech

study of renal amyloidosis reported a median survival of 4.5 years in patients with AA amyloidosis [10].

The possibilities to control inflammation and achieve remission in the rheumatic diseases by the use of disease modifying anti-rheumatic drug (DMARD) combinations and biological therapy, such as TNF-α blockers, have improved significantly since the 1990s. However, there is no convincing data to show that this active treatment policy has resulted in a decreased incidence of amyloidosis [11]. We have previously reported data from the Finnish Registry for Kidney Diseases for renal replacement therapy (RRT) (dialysis or kidney transplantation) on patients with amyloidosis associated with inflammatory rheumatic diseases who entered the registry from the late 1980s to 2002 [12]. During that period there was no change in the incidence of new admissions to the registry. The outcome of these patients was extremely poor; after entering RRT median survival times varied from 2 to 3 years irrespective of the underlying rheumatic disease.

We now report a recent trend in the number of new admissions for RRT to the registry from the early 2000 onwards and discuss the role of intensive anti-rheumatic drug therapy on it.

Patients and methods

We scrutinised the files of the Finnish Registry for Kidney Diseases for RRT to search patients suffering from amyloidosis associated with RA, AS or JIA over the period 1995–2008. Patients enter the registry at the same day as their first dialysis treatment for chronic uraemia is provided. From 1965 onwards, this registry has an estimated 97–99% coverage of all patients accepted for RRT [13].

To maximise the identification of patients with rheumatic diseases in the register a search of the files of Statistics of Finland was performed using the personal identification code of subjects without known underlying disease.

The Social Insurance Institution (SII) is responsible for the administration of the national sickness insurance scheme, including drug reimbursements for the entire population. Certain chronic and severe diseases may entitle the patient to a higher than normal reimbursement, and the SII keeps a register on the patients who have been granted the entitlement on the basis of a doctor's certificate. Patients with rheumatic diseases have an opportunity to be entitled to this special reimbursement. The entitlement concerns DMARDs but not non-steroidal anti-inflammatory drugs. TNF-α inhibitors may be reimbursed only in the basic (42%) category. The National Agency for Medicines publishes drug consumption statistics on the basis of sales from

grossists to pharmacies. The unit of measurement is the defined daily dose (DDD), calculated per 1000 inhabitants per day.

The study was approved by the Ethical Committee of the North-Karelia Central Hospital.

Results

Altogether 378 patients were identified, 264 (69.8%) of whom had amyloidosis associated with an underlying rheumatic disease. Two hundred twenty-nine of them had RA, 15 AS and 20 JIA. Since the early 2000s, there has been a progressive decline in the number of new admissions to RRT. When the total annual number of new cases varied between 20 and 37 until 2000, it was approximately 10 from 2002 onwards (Figure 1).

According to data of our national register the number of users of DMARDs has increased steadily since the middle of the 1990s (Figure 2). Low-dose methotrexate (MTX) was the most frequently used DMARD in 2008 with 24,324 recipients of special reimbursement. The corresponding figure was 6800 in 1995, i.e. the growth has in relative terms been 3.6-fold. In 2008, there were 19,082 users of salazosulfapyridine (SASP) (1.7-fold increase), and the respective figure for hydroxychloroquine (HCQ) was 16,737 (2.9-fold increase).

The use of three TNF-α inhibitors (infliximab, etanercept and adalimumab) has also increased since their introduction in the early 2000s. In 2003, DDDs for infliximab and etanercept were 0.21 and 0.05, respectively. The corresponding figures in 2008 for the same agents and adalimumab were 0.42 and 0.33, respectively. These substances can be used for
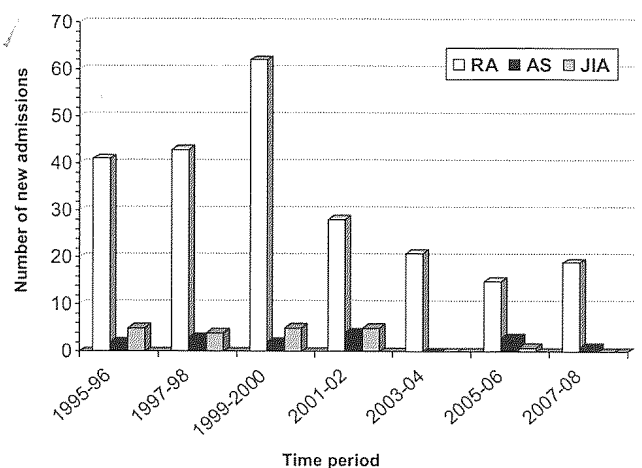

Figure 1. Number of new patients admitted to renal replacement therapy (Finnish Registry for Kidney Diseases) because of amyloidosis associated with rheumatoid arthritis (RA), ankylosing spondylitis (AS) or juvenile idiopathic arthritis (JIA) per 2-year period over the years 1995–2008.
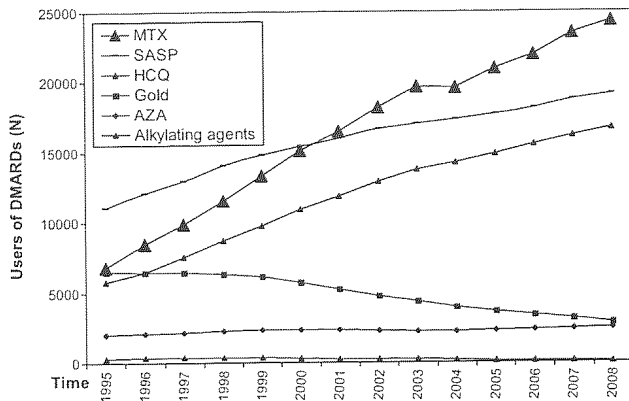
Figure 2. Number of users of disease modifying anti-rheumatic drugs (DMARDs) from 1995 to 2008 in Finland. The most used DMARDs and alkylating agents (cyclophosphamide and chlorambucil) are included. MTX = methotrexate; SASP = salazosulfapyridine;   HCQ = hydroxychloroquine;   AZA = azathioprine; Gold = sodium aurothiomalate.

other indications than rheumatic diseases, too, but the sales register does not reveal the purpose of use.

Discussion

The main message of the present report is that the incidence of end-stage renal disease due to amyloidosis associated with rheumatic diseases has decreased markedly during the recent years. This has occurred despite the fact that today older and older patients are accepted for RRT [14]. At the end of the 1990s, a report from one centre in Finland documented a sharp decline in the annual number of subcutaneous abdominal fat tissue aspiration (ASFA) biopsies for detecting amyloid. One obvious cause of this decline is a decrease in the number of patients with a clinical suspicion of amyloidosis [15]. Thus the decrease in the number of patients with end-stage renal disease due to amyloidosis seems to have been preceded by a decline in the incidence of new cases of amyloidosis by a period of 10 years.

An obvious reason for our result is a change in the treatment strategy of rheumatic diseases. Nowadays, a realistic goal of therapy is to achieve remission or a tight control of the disease by using a combination of DMARDs and biological drugs. After the report of the high remission rate (40%) of the Finnish DMARD combination study (FIN-RACo) [16], the clinical use of MTX, SASP, HCQ and low-dose prednisolone in combination has increased considerably in Finland. That active DMARD policy has prevailed in Finland over the last decade was demonstrated here by national reimbursement statistics, which shows a marked increase in the annual number of users of DMARDs, especially concerning MTX but also when it comes to antimalarials and

SASP, from 1995 onwards. It is to be noted that, according to the results of a multinational QUESTRA-study, Finland is among the countries with the highest remission rates in RA patients [17].

At its best early and active DMARD strategy works as primary prevention of amyloidosis. On the contrary, constantly active disease carries a risk for amyloidosis. Already in the 1980s, ASFA was recommended in the care of patients with continuously active inflammatory rheumatic diseases [18]. Early documentation of tissue amyloid in a subclinical phase of amyloidosis allows secondary prevention of this complication by intensification of DMARD therapy.

About 20% of patients with RA are refractory to traditional DMARDs and for these patients the next option is treatment with biological drugs. Of them, TNF-α blockers have been in clinical use for approximately 10 years in Finland. A preliminary clinical report shows that anti-TNF-α therapy is a promising treatment for refractory amyloidosis secondary to inflammatory joint diseases [19]. However, the increase in the use of these agents is far too recent to have any major influence on the declining trend in number of patients admitted to RRT.

High levels of SAA correlate with the progression of amyloidosis [20] and, *vice versa,* lower levels are associated with its regression [21,22]. Thus, in cases with a histologically confirmed diagnosis of amyloidosis, aggressive immunosuppressive treatment, including biological drugs, should be considered. This is especially important in patients with any signs of renal disease. According to one report, renal biopsy may help in the identification of RA patients with progressive renal damage [23], and should therefore be encouraged.

The diagnosis of amyloid is based on Congo red staining showing green birefringence in polarised light. The clinical correlation is recommended to support the pathological diagnosis but does not in itself make it. The final verification of AA amyloidosis requires immunohistochemical typing with serum amyloid A protein (SAA) antiserum and exclusion of other amyloidoses. In this registry-based material, collected from several different hospitals all around the country over a long study period, typing of amyloid had not been performed systematically. However, the occurrence of other amyloidoses than AA amyloidosis in patients with chronic inflammatory rheumatic disease would be rare and unexpected, but cannot be completely excluded. 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 [24].

In conclusion, the decreasing incidence of end-stage renal disease due to amyloidosis is an indirect

evidence of the effect of better control of inflammation in the rheumatic diseases. Apparently, active drug policy is now, with a lag of 10–15 years, reflected in a lower number of new patients with rheumatic diseases admitted to RRT because of amyloidosis.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Longterm Outcome of Amyloidosis Associated with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To determine the outcome of amyloidosis associated with juvenile idiopathic arthritis (JIA) in a hospital-based series.

Methods. Patient registers and amyloidosis biopsy files of the Department of Pediatrics of Rheumatism Foundation Hospital, the main tertiary center for inflammatory joint disorders in children in Finland, were scrutinized from 1976 to the end of 2003 to look for amyloidosis in patients under age 19 years. Medical records were reviewed and patients were interviewed by telephone. The causes of any deaths were obtained from death certificates.

Results. Twenty-four patients under age 19 years with biopsy-proven amyloidosis were found. As a sign of renal disease at the time of diagnosis of amyloidosis, 16 patients (67%) had proteinuria, but none had renal insufficiency. The 5-year survival rate of the series was 87.5% (95% CI 75% to 100%), and 10-year survival was 75% (54% to 92%). Ten patients (42%) out of the 24 died during a mean followup of 15.4 (range 1.5–27.6) years. The main cause of death was related to JIA in all patients but one. Patients treated with prednisolone alone from the diagnosis of amyloidosis onward had a mortality rate significantly higher than those taking disease modifying antirheumatic drugs and/or cytostatics (p = 0.001). At the end of followup, 14 patients (58%) were alive, 12 with normal renal function (3 of them had undergone renal transplantation), one had renal insufficiency, and one proteinuria. Proteinuria disappeared in 4 patients who were proteinuric (2 with nephrotic syndrome) at baseline, and their renal function remained normal. All the live patients had completed at least the 9 years of compulsory education, and 4 had academic degrees. Two female patients had delivered healthy children.

Conclusion. The outcome of JIA-associated amyloidosis is poor. However, renal disease regressed in some patients under vigorous treatment. Successful treatment makes an active life possible for these patients. (First Release Mar 15 2008; J Rheumatol 2008;35:907–12)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS   AMYLOIDOSIS

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. It is an umbrella concept for a heterogenous group of diseases, with chronic arthritis of unknown cause as the common characteristic. The outcome of the different forms of JIA varies greatly. Until recently, the most common cause of death in Caucasian JIA populations has been amyloidosis[1]. However, data have been published suggesting decreasing incidence and better prognosis of amyloidosis[2-5]. According to data from the Finnish National Renal Registry for Kidney Diseases there was no change in the number of new cases proceeding annually to renal replacement

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therapy [dialysis, renal transplantation (RTP)] due to inflammatory rheumatic disease-associated amyloidosis from 1987 to 2002. Instead, the mean age of patients admitted to the registry has increased significantly (unpublished data).

Amyloidosis is a disorder that occurs as a complication of chronic inflammatory disorders. It occurs primarily in lymphoproliferative disorders, or as a complication of a wide range of chronic inflammatory illnesses such as JIA in susceptible individuals[2,6]. This form is also referred to as AA amyloidosis since the protein subunit of the amyloid fiber is amyloid A (AA). The persistently elevated serum concentration of the fiber precursor protein of amyloid A (SAA) is a prerequisite, but other, mainly unknown, factors are important in amyloidogenesis as well[7]. AA amyloidosis is practically the only amyloidosis type occurring in children with JIA. Amyloidosis is insidious and progressive, leading from an asymptomatic phase to nephrotic syndrome, kidney failure requiring renal replacement therapy, and finally death. Most often the cause of death is renal failure[8], but at times involvement of other organs, e.g., the gut, may be fatal.

Our series represents all subjects among roughly 3500 children with JIA seen at the Rheumatism Foundation Hospital (RFH) in the years 1976–2003 who developed amyloidosis

before the age of 19 years. Altogether, 24 cases were found. Significantly, we noted that since 1991, no new cases of JIA-associated amyloidosis in childhood or in adolescence have been documented in Finland[9]. We will describe the prognosis of the 24 patients and the quality of life of the surviving patients.

MATERIALS AND METHODS

This series comprises patients with JIA according to the ILAR 2001 criteria[10], 24 subjects altogether, who were identified in the patient registers and amyloidosis biopsy files of RFH, with amyloidosis diagnosed before the age of 19 years, from 1976 onwards[9]. The medical histories of most patients (medication, operations, renal function, HLA typing, renal transplants) were checked either in the RFH records, or in those of the treating hospitals.

All surviving subjects were interviewed by telephone by one of the authors (AS) for details of marital status, fertility, number of children, type of residence, schooling, employment, other diseases, and joint prostheses. Patients were followed up until death or until the end of 2003. The data were collected in 2004.

Demographic and clinical characteristics of the 24 patients are shown in Table 1. The oligoarticular disease type in 3 patients at disease onset changed to polyarticular in 2 patients, and to juvenile spondyloarthropathy in one patient. Two patients had refused medication for JIA: one refused disease modifying antirheumatic drugs (DMARD), the other a change from sodium aurothiomalate to cytostatics. At the time of diagnosis of amyloidosis, 19 patients were under 16 years of age, the youngest being 7.5 years old.

The indications for searching for amyloidosis in the 24 patients were proteinuria (n = 15), goiter (n = 2), or continuously high disease activity as assessed by clinical condition and C-reactive protein (CRP) (n = 7). SAA concentrations were not measured. All the 24 cases were biopsy-proven, and the diagnoses were based on the demonstration of green birefringence in polarized light after Congo-red staining. Thirty-seven biopsies were performed altogether. The sites biopsied were subcutaneous fat (n = 8), buccal cavity (n = 10), gastrointestinal tract (n = 8), kidney (n = 9), and thyroidea (n = 2). Two or 3 biopsies at different locations were performed for 9 patients.

Table 1. Characteristics of 24 children with juvenile idiopathic arthritis (JIA) and secondary amyloidosis.

Characteristics	
No. of girls (%)	19 (79)
Age at symptoms, mean (range), yrs	4.7 (1–11)
Age at diagnosis, mean (range), yrs	5.1 (1–12)
Time from onset of JIA to diagnosis of amyloidosis, median (IQR), yrs	8 (4, 12)
Disease onset type, n (%)	
Oligoarthritis	3 (12)
Polyarthritis	10 (42)
Systemic	11 (46)
Disease course, n (%)	
Extended oligoarthritis	2 (8)
Juvenile spondyloarthropathy	1 (4)
Polyarthritis	10 (42)
Systemic	11 (46)
HLA-B27 present, n (%)	13/22* (59)
Rheumatoid factor present, n (%)	1 (4)
Antinuclear antibodies, n (%)	10 (42)
Erythrocyte sedimentation rate at diagnosis of amyloidosis, median (range)	81 (13–147)

* HLA-typing was not performed in 2 of the 24 cases. IQR: interquartile range.

At diagnosis of amyloidosis, 17 patients were taking one DMARD with prednisolone, 2 a combination of DMARD with prednisolone, and 5 patients were taking prednisolone alone (Table 2). Fourteen patients had undergone arthroplasties (2–9 operations per patient) by the end of 2003.

The underlying cause of death was determined from death certificates in accord with the internationally established norm. Autopsy had been performed on all except one.

Statistical analysis. Results were expressed as mean or median, range or interquartile range (IQR). The Kaplan-Meier curve was used to illustrate the information on the cumulative proportions of survival, and the difference between the groups was tested by a permutation-type log-rank test. The 95% confidence intervals of survival rate were obtained by bias-corrected bootstrapping (5000 replications).

RESULTS

At the time of the positive biopsy for amyloid, 18 (75%) of the 24 patients had clinical manifestations of amyloidosis, namely renal disorder (n = 16) and goiter (n = 2).

Renal disorder. At the time of the verification of amyloidosis, none of the 24 patients had renal insufficiency (Figure 1). There were 16 proteinuric patients, of whom proteinuria cleared completely in 4 (2 with nephrotic syndrome at baseline) and almost completely in one with nephrotic syndrome. Four of them were taking chlorambucil and one methotrexate (MTX) after the documentation of amyloidosis. Three of the 5 have been completely free of proteinuria ever since. Eight patients out of the 24 showed no signs of renal disorder in the beginning, but 2 of the 8 developed renal insufficiency later.

Renal biopsy was repeated after 2 to 15 years in 3 proteinuric patients whose proteinuria resolved. Amyloid material was still present in renal tissue in all of them, although initially positive rectal and/or subcutaneous tissue samples had turned negative for amyloid.

Seven patients altogether had undergone RTP — including 2 without signs of renal disease at the time of diagnosis of amyloidosis — after a mean of 12.4 (range 4–21) years from the diagnosis of amyloidosis. Four of them died, one during the operation, and 3 others in the course of the following 7 years. Of the transplanted kidneys of the 3, there was an early rejection in one, and one showed amyloid material in biopsy 6 years after RTP, 2 years before death. In the third case, the family did not consent to autopsy, and the kidney had not been biopsied before death.

At the end of followup, 14 patients were alive, 12 with normal renal function (3 of them with RTP), one had renal insufficiency and one proteinuria (the initial amount of 10 g/day decreased to 1.5–2 g/day). Hypertension needing treatment was documented in 42% of the live patients, in all but one in the post-biopsy period.

Comorbidities. Other disorders among the 24 patients after the diagnosis of amyloidosis were hypertension (n = 12), carditis (n = 2), sarcoidosis (n = 1), diabetes (n = 1), hypothyreosis (n = 2), depression (n = 1), subarachnoidal hemorrhage (n = 1), transient ischemic attack (n = 1), hyperuricemia (n = 1), chronic uveitis (n = 3) leading to blindness in one, glomerulonephritis (n = 1), and leukemia leading to death (n = 1).

Table 2. Treatment of 24 children with JIA and amyloidosis.

Therapy	Initial Therapy for JIA, n (%)	At Diagnosis of Amyloidosis, n (%)	After Diagnosis of Amyloidosis, n (%)
Drugs			
Hydroxychloroquine	21 (87)	3 (12)	1 (4)
Gold sodium thiomalate	14 (58)	6 (25)	2 (8)
Penicillamine	0 (0)	3 (12)	0 (0)
Azathioprine	0 (0)	3 (12)	3 (12)
Sulfasalazine	0 (0)	0 (0)	2 (8)
Methotrexate	0 (0)	2 (8)	3 (12)
Chlorambucil	0 (0)	0 (0)	8 (33)
Prednisolone	11 (46)	24 (100)	24 (100)
Strategy			
No drugs	0 (0)	0 (0)	0 (0)
Single therapy	7 (29)	0 (0)	0 (0)
Single therapy with prednisolone	6 (25)	17 (71)	17 (71)
Prednisolone alone	0 (0)	5 (21)	5 (21)
Combination therapy	6 (25)	0 (0)	0 (0)
Combination therapy with prednisolone	5 (21)	2 (8)	2 (8)
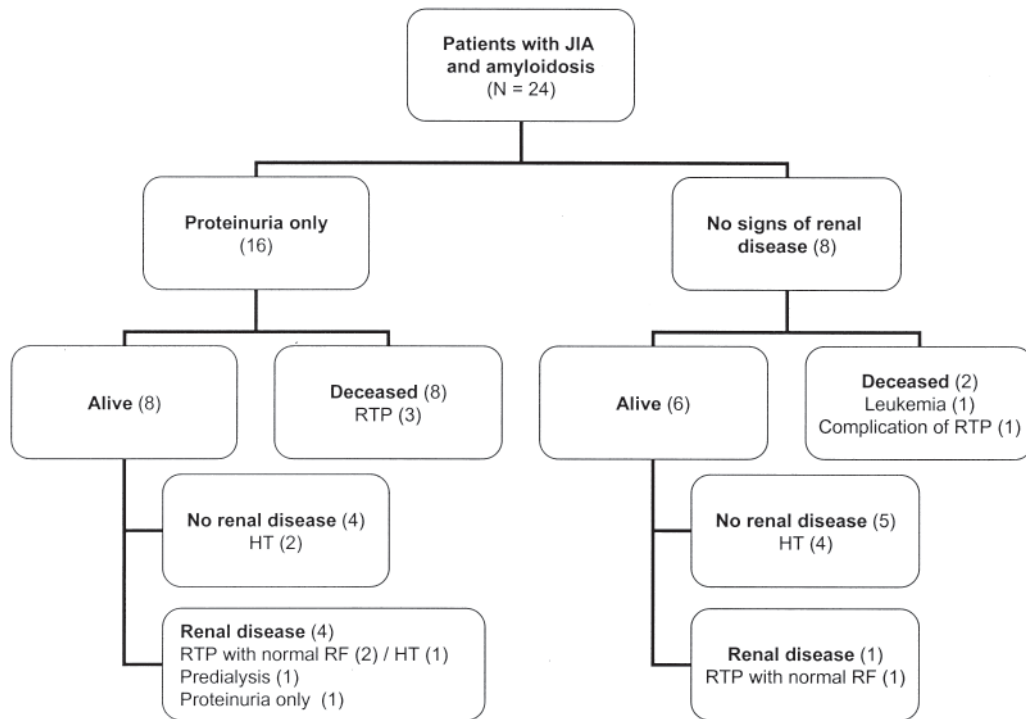
Figure 1. Outcome of 24 patients with juvenile idiopathic arthritis (JIA) and amyloidosis in relation to renal disorder. RTP: renal transplant. RF: renal function, HT: hypertension.

Survival. During a mean followup of 15.4 (range 1.5–27.6) years, 10 patients (42%) out of the 24 died. The 5-year survival rate of the series was 87.5% (95% CI 75% to 100%), and the 10-year survival was 75% (95% CI 54% to 92%) (Figure 2). Gender did not affect the number of deaths: 2 (40%) out of the 5 males and 8 (42%) of the 19 females died.

JIA was the main cause of death in 9 out of 10 deceased patients. The immediate causes of death were amyloidosis in 5 patients [renal insufficiency (n = 4) and hydropericardium (n = 1)] and infection (septicemia) in 3, all the latter with RTP. One death was perioperative. One patient died from leukemia with a 19-month history of chlorambucil treatment (cumulative dose 930 mg).

At some time during the disease course, all patients except

Figure 2. Product-limit survival curves for patients with juvenile idiopathic arthritis after diagnosis of secondary amyloidosis.

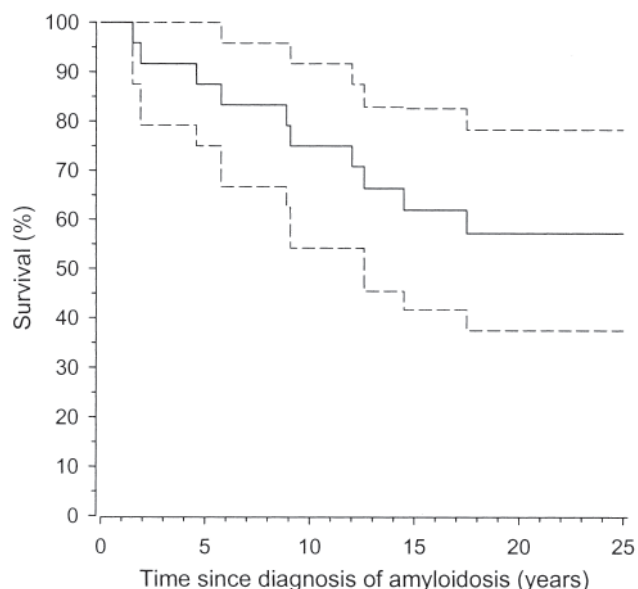one had elevated serum concentrations of immunoglobulin G (IgG) up to 43.4 mg/ml. The one with normal IgG had very high serum IgA, 9.48 mg/ml. Three patients had IgA deficiency. These 3 were alive and free of proteinuria at the end of the followup 12 to 18 years after the diagnosis of amyloidosis. HLA-B27 test was performed in 8 out of the 10 deceased patients, and was positive in 3.

The median timespan from the diagnosis of amyloidosis of the 14 surviving patients was 20 (IQR 18, 23) years.

DMARD therapy and outcome. The overall drug therapy of the patients is shown in Table 2. At the time of verification of amyloidosis, drug treatment was changed in 14 patients. Chlorambucil (+ 6 months from the amyloidosis diagnosis) was started in 8 patients. Two of them died [survival 75% (95% CI 28%–97%)], one of amyloidosis, the other of leukemia, compared to the 8 of 16 [survival 48% (95% CI 20%–70%)] not treated with chlorambucil (p = 0.30). Altogether, 13 patients had some cystostatic therapy during the immediate post-biopsy period: azathioprine (n = 2) 2.5 to 2.9 mg/kg/day; chlorambucil (n = 8), 0.2 mg/kg/day; and MTX (n = 3) 7.8 to 13 mg/m^2/week. All patients who continued prednisolone monotherapy from the first documentation of amyloidosis onwards died, whereas survival was 73% (95% CI 48%–90%) in the patients in whom DMARD and/or cytostatics were continued or changed for another compound (p = 0.001). None of the 24 patients has been treated with biological drugs.

Social data of the patients surviving at the end of followup. Education: Eight patients completed only the compulsory 9-year schooling requirement, 12 earned 1–6 additional years, and 4 completed an academic education of up to 17 years. Working status: At the end of 2003, 9 patients were on a disability annuity due to JIA, 4 worked fulltime, and one was working on a university degree.

Marital status: Five patients were married, one divorced, 2 were engaged to be married, and 6 were single, 2 of them still living with parents.

Fertility: One female patient had delivered one child and another 2 children. The children are healthy and up to 20 years old. The woman with the 2 children had toxemia in both gravidities. She had nephrotic syndrome in the initial phase of amyloidosis; upon treatment with chlorambucil the proteinuria ceased, so she did not require RTP. Fertility was examined in 2 patients, and found to be normal in one female, whereas one male was found to be infertile. The remaining 9 patients were not planning to have children.

DISCUSSION

The Department of Pediatrics of RFH acts as the tertiary center for inflammatory joint disorders for children in Finland. It has traditionally cared for 60%–75% of patients with JIA in the country, i.e., practically all patients with severe disease have been treated here. Thus, most of the patients with a major risk for amyloidosis are probably under our supervision.

The current data show a highest prevalence of amyloidosis in the systemic-onset form of the disease, with incidence in British and German series of JIA-associated amyloidosis of 57% and 77%, respectively[2,11]. This shows a slight difference compared to our series, where the systemic and polyarticular type of disease have an almost equal frequency of amyloidosis, 46% and 42% of the cases, respectively. In 2 of our patients with polyarticular disease, the disease onset was oligoarticular, and one patient with oligoarticular onset developed juvenile spondyloarthropathy. HLA-B27 may act as a factor of chronicity in JIA[12], and so predispose to amyloidosis, as previously reported in Finland[13]. No clear effect of HLA-B27 could be seen on the prognosis of the condition in our current study, however.

The sex distribution (F:M) in JIA-associated amyloidosis varies between different studies, 1.8:1 in the 1970s in Finland[14], 1.6:1 in Germany[11], 1.1:1 in England (the largest one with 79 patients[15]), and our present study, 3.8:1. The general sex distribution among JIA patients in Finland is 2.4:1[16]. Male patients with amyloidosis fared worse than females in both the English[15] and the German[11] series. In our series, with 5 males and 19 females, mortality was of the same level. However, the small number of patients prevents us from drawing any firm conclusions.

There are scant data on the predisposing factors for amyloidosis in rheumatic diseases. In a Polish series with 67 JIA patients with amyloidosis, half the patients had immunoglobulin deficiency, and the phenomenon was associated with an almost 2-fold mortality compared to the rest of the group[17]. In our series, no patient had IgG deficiency. In contrast, the levels of IgG were high, as among the English patients[15]. In our series, all 3 patients with IgA deficiency were alive at the end of the followup.

Elevated blood pressure seems to be a frequent sequela in

JIA-associated amyloidosis. In our series, 42% of the live patients were taking antihypertensive medication. Almost half of the live English patients were hypertonic[2]. More than half the German patients with amyloidosis had elevated blood pressure at some time during the disease[11]. Many of the English and German patients already had hypertension at the diagnosis of amyloidosis[2,11], while all our patients except one developed hypertension during the followup.

The reversibility of amyloidosis has been described[7,15,18]. The disappearance of amyloid can be verified by biopsy, and also radiologically[19]. Our patients have not been systematically followed up in either way. However, the proteinuria disappeared in 4 of the 5 patients in whom it was initially documented. Three of them were taking chlorambucil and one MTX after the first documentation of amyloidosis. Three of the 4 patients have been free of proteinuria since then. However, renal biopsy still showed amyloid in the 3 of those patients in whom the procedure was repeated.

According to the reported 10-year survival rates, amyloidosis has a poor prognosis, which may, however, be influenced by cytostatic treatment (Table 3). None of the patients in the older Finnish series were treated with cytostatics[14], while a combination of azathioprine and glucocorticoids was common in the German series[11], with some patients even having had chlorambucil. David, et al[2] reported a 10-year survival of 80% in 57 patients treated with chlorambucil, but only 24% in 19 patients never treated with cytostatics. In Finland, during 2 consecutive 11-year periods (1969-79 and 1980-90), the percentage of amyloidosis as a direct cause of death diminished from 42 (10 patients) to 17 (4 patients), which could be indirectly attributed to a more active DMARD treatment policy[3]. The respective standardized mortality rates were 2.7 and 2.4.

In our series, chlorambucil was started in 8 patients within 6 months of the amyloidosis diagnosis. Two of them died — one of amyloidosis, with 6 years of proteinuria prior to the biopsy, the other of leukemia that was probably drug-induced — as did half of the 16 patients not treated with chlorambucil. Therapy with conventional DMARD and/or cytostatics was associated with an outcome better than was the case where a glucocorticoid was continued as the only therapy after confirmation of amyloidosis.

During a mean followup of 15 years in our series, 10 patients (42%) out of the 24 died, including 4 of the 7 with RTP. JIA can be considered the main cause of death in 9, amyloidosis being the immediate cause in 6, and septicemia in 3. One patient died of leukemia. At the end of 2003, 14 patients (58%) were alive; 12 had normal renal function, one had renal insufficiency, and one had proteinuria. Renal insufficiency is the most important life-threatening condition in JIA-associated amyloidosis. According to David and Woo[7], 84% of 79 JIA patients with amyloidosis died of renal failure. Infection was the second most common cause of death, usually due to bacterial septicemia.

In our series, half of the 16 originally proteinuric patients died. Among the remaining 8 patients without renal disease at the beginning, 2 developed renal insufficiency and received transplants. One of these 2 died due to a perioperative complication of RTP 9 years after amyloidosis was diagnosed, the other had normal renal function during the entire followup. Only 2 (25%) of the 8 patients originally free of proteinuria died, signifying a better prognosis.

In studies to date, little attention has been paid to the psychosocial aspects and quality of life of patients with amyloidosis, except in the study of David, et al[2], which dealt with their fertility state. In our series, patients did quite well in educational achievement. However, their working state remained poor. Fertility was not systematically assessed in our patients.

Although the mortality rate in our series of patients with JIA-associated amyloidosis was relatively high, our results suggest that vigorous drug therapy may reverse or prevent renal disease, ensuring patients' quality of life. In particular, the finding that the majority of the patients who were free of renal disorder at the time of verification of amyloidosis were still without signs of this manifestation at the end of the followup stresses the importance of early diagnosis of amyloidosis and the role of active antirheumatic therapy. In addition, our results show that in followup of patients with renal amyloidosis, renal biopsy is the only way to accurately confirm the regression of the amyloid accumulation. We look forward to seeing whether the prognosis of JIA-associated amyloidosis improves further with the use of biological drugs.

Table 3. Prognosis of 24 patients with JIA and amyloidosis based on the data of different series.

Country	No. of Patients	Period for Diagnosis of Amyloidosis	Cytostatic Treatment	10-year Survival Rate, %
Finland[14]	48	1950s–1970s	No	42
Germany[11]	60	1950s–1970s	Yes (a few patients)	35
UK[2]	57	1960s–1980s	Yes (chlorambucil)	80
UK[2]	19	1960s–1970s	No	24
Finland (present series)	24	1970s–1980s	Yes (a few patients)*	75

* Active disease modifying antirheumatic drug strategy was common in the post-biopsy period.

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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

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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

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

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.

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.

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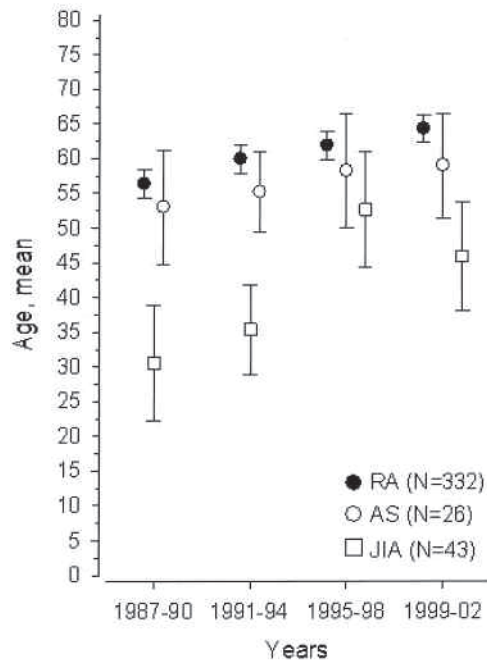
Figure 1. Mean age (95% CI) at acceptance for renal replacement therapy by diagnosis group from 1987 to 2002.

(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,
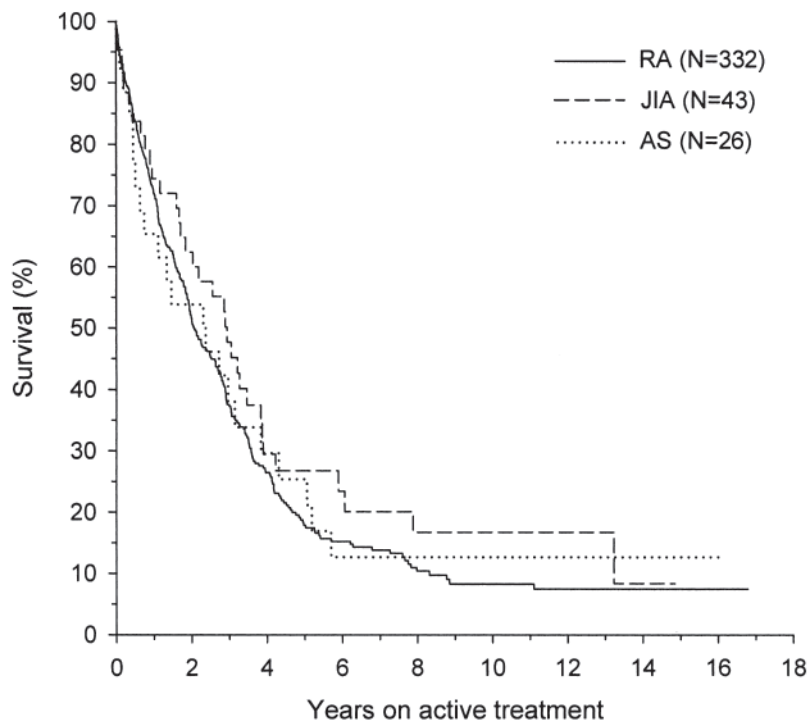

Figure 2. Product-limit survival for patients with amyloidosis associated with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis (AS) after acceptance to renal replacement therapy.

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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LETTERS

The usefulness of subcutaneous fat tissue aspiration biopsy for early confirmation of amyloidosis in patients with active ankylosing spondylitis: comment on the article by van Gameren et al

To the Editor:

We read with interest the report by van Gameren et al on the diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis (1). There are, however, scant data on the prognostic significance of positive fat tissue aspiration in patients with ankylosing spondylitis (AS) without overt clinical signs of AA amyloidosis. Gratacos et al (2) reported that results of a fat tissue aspiration test were positive in 7% of 137 patients in an unselected AS series, and showed that, during a mean followup period of 5 years, the finding was associated with clinical amyloidosis in only half of the patients. One may ask whether this justifies the conclusion that, although amyloidosis is relatively common in AS, its presence is rarely of clinical significance (3) and is not an indication for more active therapy or thorough followup of AS patients who have no signs of overt clinical AA amyloidosis.

To clarify the situation we searched >2,600 records of subcutaneous abdominal fat tissue aspiration biopsies performed at the Rheumatism Foundation Hospital from 1987 to 2000 for files on AS patients (4) with positive amyloid staining but without signs of clinical amyloidosis at the time of biopsy. Five such cases were found among a group of 150 patients with AS who had undergone biopsy. Clinical data were obtained from the patients' medical records. The patients were followed up until death or the end of December 2003, whichever occurred first. The reason for biopsy in all 5 of the patients was persistently elevated C-reactive protein levels (>50 mg/liter). In 2 subjects the first biopsy finding was negative, and the test was repeated after ~18 months. Two of the 5 patients were women. The median disease duration at the time of documentation of AA amyloidosis was 23 years (range 13–26 years). In the postbiopsy period, disease-modifying antirheumatic drugs (DMARDs) had been used in 4 patients, as part of combination therapy in 1 patient and as monotherapy in 3 patients. In addition, long-term cytostatic therapy (chlorambucil and cyclophosphamide) combined with low-dose prednisolone had been used in 2 of the patients. All 5 patients had associated peripheral arthritis, which necessitated ≥1 total joint replacements of large joints in 4 patients.

After >10 years' followup, 2 patients were alive and free of clinical symptoms of amyloidosis. The other 3 patients had all developed proteinuria and renal insufficiency, which had necessitated hemodialysis in 2 patients. Both of these patients died of AS 15 years after the diagnosis of AA amyloidosis. The third patient died of gastrointestinal bleeding 8 years after diagnosis.

There is a marked difference between Europe and the US in the prevalence of AA amyloidosis associated with inflammatory rheumatic diseases. This complication is rare in the US but occurs in ~3–10% of patients living in Europe who have rheumatoid arthritis, juvenile idiopathic arthritis, or AS (5). Clinical AA amyloidosis in AS indicates a poor prognosis. A Finnish hospital-based study of patients with AS with a mean followup time of 25 years demonstrated an overall mortality rate 1.5 times higher than expected, which was explained by a high incidence of deaths from AS, mainly due to AA amyloidosis (6).

We agree with van Gameren et al that fat aspiration is highly useful in clinical practice (1). Our results also support the notion that the procedure should be repeated in patients in whom AA amyloidosis is clinically suspected. The present data, based on long-term followup, show that patients with AS and active inflammatory arthritis in whom amyloid is demonstrated on fat tissue aspiration are at a high risk of developing renal disorder. The progression of subclinical AA amyloidosis to an overt clinical state occurred in 3 patients, despite active DMARD therapy during the postbiopsy period. Although the effect of DMARDs on AS is not well documented, the results of anti–tumor necrosis factor therapy are promising (7). Therefore, we urge that subcutaneous abdominal fat tissue aspiration biopsies be performed in clinical practice in order to confirm a subclinical diagnosis of AA amyloidosis as early as possible.

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Experiences on the use of biological drugs in psoriatic arthritis-associated amyloidosis

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Amyloid A (AA) amyloidosis is a severe complication of inflammatory rheumatic diseases, mainly seen in rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis (AS), and is associated with increased mortality (1, 2). However, with regard to psoriatic arthritis (PsA), the association is with amyloidosis weak and the published data are based mainly on case reports (3). A review by Kagan et al found 39 cases with psoriasis-associated amyloidosis reported by 1998, and 85% of these cases had a concomitant arthropathy (3).

To achieve an early diagnosis of amyloidosis, the use of abdominal subcutaneous fat aspiration (ASFA) biopsy has been recommended in the care of RA patients whenever there is a continuously active disease. However, in cases of PsA, the diagnosis of amyloidosis often seems to be delayed to the stage of renal disorder (3); this may be explained partly by the rarity of this manifestation in PsA. In recent years there have been some case reports of active drug treatment of this manifestation (3–5), but with varying results.

To gain a better knowledge of the outcome of PsA-associated amyloidosis, we examined a large biopsy file for amyloidosis associated with rheumatic diseases (RA, AS, JIA, and PsA) in more than 2600 patients from 1987 to 2000 at the Rheumatism Foundation Hospital (RFH), a nationwide secondary centre for rheumatic diseases in Finland, to find cases with PsA-associated amyloidosis. The biopsy indications were suspicion of amyloidosis due to continuously active inflammation [high C-reactive protein (CRP)] or clinical signs of amyloidosis, such as proteinuria and/or renal insufficiency.

The biopsy file revealed 70 patients with a clinical diagnosis of PsA analysed by Congo red staining of ASFA specimens to show amyloids. The medical records of the patients were reviewed. Forty-one (59%) of the 70 patients met the Caspar criteria for PsA (6), including three cases with a positive biopsy for amyloids; two of these cases were treated with biologicals and are

reported here in a more detail. To assess renal function we used the Cockcroft–Gault formula (7).

One of the patients had oligoarthritis in childhood. After 20 years she developed a psoriatic rash and active polyarthritis simultaneously. Her disease was resistant to disease-modifying anti-rheumatic drugs (DMARDs), and amyloidosis was documented by ASFA biopsy 8 years later. At this stage she had no signs of renal disorder, that is she had normal renal function and no proteinuria. Despite the use of methotrexate (MTX) and low-dose prednisolone, her renal function deteriorated and she was treated with etanercept. However, her renal function was not stabilized until the treatment was changed to tocilizumab (Table 1).

The other patient with active psoriatic spondyloarthropathy also had subclinical amyloidosis. Her disease did not respond to MTX and low-dose prednisolone. Biological therapy with adalimumab was started at a phase when she had moderate renal failure. Later she developed proteinuria but her renal function stabilized. Her treatment was carried out with etanercept for a short period due to suspicion of side-effects of adalimumab. However, adalimumab was later used without problems (Table 1).

Including our patients, there are now seven reported cases of PsA-associated amyloidosis that have been treated with anti-tumour necrosis factor (TNF)α therapy (Table 1). Except for inefficacy in one of our cases and one infection-related death reported (5), the therapy seems to have been beneficial in the rest of the patients. Overall, our results in PsA support the published data on the efficacy of anti-TNFα therapy in other rheumatic conditions associated with amyloidosis (5).

On the basis of case reports, the efficacy of tocilizumab on RA- and JIA-associated amyloidosis seems promising (9, 10). Our experience shows that tocilizumab may be a good alternative for those PsA patients with amyloidosis whose disease is resistant to DMARDs or anti-TNFα therapy.

Table 1. Demographic and clinical data of seven patients with PsA-associated amyloidosis treated with biological drugs according to literature reviews, including the present cases.

Ref. no.	Age at diagnosis of amyloidosis (years)/gender	Duration of arthritis at diagnosis of amyloidosis (years)	Duration of amyloidosis at the onset of biologicals (years)	Site of biopsy	Clinical manifestation at diagnosis of amyloidosis	Treatment for amyloidosis (duration of treatment with biologicals, in months)	Outcome of renal disorder during biological therapy; comments
5	55/M	36	5	Kidney	Severe RF, slight proteinuria	INF (53)	Stable RF, improvement in proteinuria
5	45/F	18	3	Kidney	Severe RF, slight proteinuria, GI disorder	Chlorambucil, INF (52)	Stable RF, improvement in proteinuria; deceased/infection complications
5	67/F	4	3	Kidney	Moderate RF,	INF (53)	Stable RF
5	41/F	6	0.5	Kidney	Severe RF	Glucocorticosteroids, ETA (2)	Stable RF
8	64/F	30	INF was started at diagnosis of amyloidosis	Kidney	Severe RF	Glucocorticosteroids, INF (9)	Stable RF, improvement in proteinuria
Current case 1	36 F	28	17	sc, colon	Subclinical amyloidosis	MTX, glucocorticosteroids, ETA (23), tocilizumab (10)	Stable, moderate RF; subclinical amyloidosis for 13 years
Current case 2	36 F	6	15	sc, gum	Subclinical amyloidosis	MTX, glucocorticosteroids, ETA (14), ADA (67)	Stable, moderate RF, improvement in proteinuria; subclinical amyloidosis for 10 years

PsA, Psoriatic arthritis; M, male; F, female; sc, subcutaneous; RF, renal failure; RF classified as follows: normal = glomerular filtration rate (GFR) > 90, slight RF = GFR 60–89, moderate RF = GFR 30–59, severe RF = GFR 15–29 mL/min/1.73 m^2; MTX, methotrexate; INF, infliximab; GI, gastrointestinal; ETA, etanercept; ADA, adalimumab.

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