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Diagnosis and Treatment of AA Amyloidosis with Rheumatoid Arthritis: State of the Art

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1. Introduction

Amyloidosis is a term applied to a heterogeneous group of rare diseases characterized by extracellular deposition of amyloid, causing target-organ dysfunction and a wide range of clinical symptoms [1]. These symptoms depend on the organ involved, and include nephrotic syndrome, hepatosplenomegaly, congestive heart failure, carpal tunnel syndrome, gastrointestinal (GI) symptoms and macroglossia [2]. Amyloidosis is classified clinically into several types depending on the precursor of the amyloid fibril. The disease involves amyloid fibrils formed in vivo by more than 25 different types of protein [3]. Reactive amyloid A (AA) amyloidosis is the representative systemic condition that develops in patients with chronic inflammatory diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis, inflammatory bowel disease, familial periodic fever syndrome, and chronic infections [4,5,6,7]. In some parts of the world, heredofamilial causes and infections are responsible for a larger proportion of cases of AA amyloidosis. In Turkey, familial Mediterranean fever (FMF) is the cause of more than 60 percent of cases [8]. Other conditions that may be associated with AA amyloidosis include neoplasms, particularly renal cell carcinoma [9], non-Hodgkin lymphoma [10], Castleman's disease [11], and cystic fibrosis [12]. Therapy with biologic agents including anti-tumor necrosis factor (anti-TNF) and anti-interleukin-6 (IL-6) is now employed routinely for the management of RA in patients for whom traditional disease-modifying anti-rheumatic drugs (DMARDs) have failed. In parallel with this shift of treatment strategy, the treatment of amyloidosis has also changed. Recently, we have revealed that the use of biologic agents for these patients can reduce the risk of death [13]. This article discusses current concepts of AA amyloidosis occurring mainly secondarily to RA, and addresses various strategies for prophylaxis, diagnosis, and therapy of this important complication in the light of changes in clinical management, especially hemodialysis (HD).

2. Prevalence

Epidemiological data for AA amyloidosis, extrapolated from autopsy records in Western nations, has indicated that its prevalence varies from about 0.5% to 0.86% according to environmental risk factors and geographic clustering [14,15]. The incidence of AA amyloidosis in RA is still undefined, but is considered to be underestimated. In Europe, 5- 20% of patients with RA develop amyloidosis, the highest incidence being in Finland [16], where reevaluation of autopsy materials for the period 1952-1991 yielded a 30% incidence of AA amyloidosis compared with a figure of 18% detected by routine testing, indicating that a significant proportion of cases may not be detected by standard histologic analysis [17]. Japanese autopsy reports have revealed that about 30% of autopsied RA patients have amyloid deposits [18]. Some Japanese medical centers have reported the incidence of amyloidosis in consecutive patients undergoing GI biopsy. The frequency of amyloidosis in RA has been reported to vary between 5% and 13.3% in cases confirmed by biopsy, and from 14% to 26% in cases confirmed at autopsy [19,20,21,22]. More than 95% of patients with AA amyloidosis are considered to have renal involvement, end-stage kidney disease (ESKD) being found in 10% of cases at the time of diagnosis [23]. Although the subclinical phase of AA amyloidosis is defined by the formation of amyloid deposits in tissue without any clinical manifestation, it is very difficult to distinguish between the clinical and subclinical phases. Obviously, it is difficult to evaluate the natural history of amyloid deposition and to know the length of this phase and its final outcome. In contrast, the prevalence of clinical amyloidosis is likely to be lower; at least half of amyloidosis patients have subclinical disease, and AA amyloidosis is clinically overt in only 25-50%, even after longer periods of follow-up sampling. Considering this discrepancy between the prevalence rates of clinical and subclinical AA amyloidosis, the wide variation in the prevalence of AA amyloidosis secondary to RA may be due partly to marked geographic differences worldwide, possibly including genetic factors, and to the lack of unified statistical studies of AA amyloidosis among races and districts. In view of these factors, the prevalence of AA amyloidosis associated with RA is probably higher than that estimated so far.

3. Pathogenesis of amyloid fibril formation and genetic background

Precise details of the mechanism of amyloid fibril formation are unknown, and may differ among the various types of amyloid [24, 25]. Factors that contribute to fibrillogenesis include a variant or unstable protein structure, extensive beta-conformation of the precursor protein, association with components of the serum or extracellular matrix, and physical properties including the pH of the tissue site. Extracellular matrix components include the amyloid P component, amyloid enhancing factor (AEF), apolipoprotein E (ApoE), and glycosaminoglycans (GAGs). Amyloidosis is classified clinically into several types according to the precursor of the amyloid fibril and the type of amyloid fibril protein. Any complete definition of amyloidosis includes the amyloid fibril protein precursor, the protein type or variant, and the clinical setting at diagnosis [3]. AA amyloidosis complicates many chronic inflammatory diseases and

has been studied most widely in experimental animal models. AA amyloid also occurs spontaneously in various animal species, and can be induced by chronic inflammatory stimuli. The best-known model of this disease is amyloid induction by injection of casein/azocasein in certain genetically susceptible strains of mice. AA fibril formation can be accelerated by an AEF in murine models present at high concentration in the spleen, by basement membrane heparan sulfate proteoglycan, or by seeding with AA or heterologous fibrils [26,27] (AEF has not yet been detected in humans). Therefore, sustained overproduction of SAA is a prerequisite for the development of AA amyloidosis. The mechanism of amyloidosis is initiated by overproduction of SAA as a consequence of acute and chronic inflammation. Next, SAA is internalized by macrophages, followed by intracellular proteolysis, and subsequent release of amyloidogenic peptides into the extracellular space, apparently preceding fibril formation [28]. AA amyloidosis is caused by organ deposition of AA fibrils, which are formed from an N-terminal cleavage fragment of SAA [29]. SAA is a 104-amino-acid protein produced in the liver under transcriptional regulation by proinflammatory cytokines, and transported by a high-density lipoprotein (HDL), HDL3, in plasma [30,31,32,33]. SAA is encoded by a family of SAA genes, which are responsive to proinflammatory cytokines [34,35]. A major factor responsible for the development of AA amyloidosis is increased synthesis and subsequent degeneration of SAA under conditions of chronic inflammation. AA amyloidosis is a rare but serious complication of diseases that stimulate a sustained and substantial acute-phase response, and foremost of which is RA. In RA, there is increased synthesis of SAA accompanied by inflammation, which may be due to elevated levels of proinflammatory cytokines. The increased cytokine levels are correlated with synovitis, which may stimulate synoviocytes to produce SAA [28,36,37] (Figure 1). These mechanisms lead to elevated levels of SAA in joint fluid relative to serum [37], sometimes reaching up to 1,000 times the baseline level [23], thus facilitating the development of AA amyloidosis. However, a high concentration of SAA alone is not sufficient for development of amyloidosis. Several genetic factors have been evaluated, and recent studies have focused on SAA polymorphism as a genetic background factor linked to amyloidogenesis. Allelic variants include acute phase SAAs (SAA1 and SAA2) and SAA4, and post-translational modifications of these gene products. SAA3 is a pseudogene with no product, and the serum concentration of SAA4 does not change during an acute-phase response [31]. The acute-phase proteins SAA1 and SAA2 are apolipoproteins, primarily associated with specific HDL, and are expressed extrahepatically in the absence of HDL [38]. SAA1 and SAA2 are inducible by interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha, lipopolysaccharide (LPS), and several transcription factors, notably SAA activating factor (SAF-1) [39,40]. Both SAA1 and SAA2 are polymorphic proteins, and amyloid fibrils are considered to be formed in tissues from both SAAs1 and 2, but predominantly from SAA1 in humans [41]. Synthesis of amyloid protein from SAAs1 and 2 is strongly induced by inflammatory cytokines such as IL-6 in the liver, in parallel with the disease activity of RA [42]. SAA1 is the most important precursor for tissue AA deposition, because this isotype is predominant in plasma, and AA proteins are derived largely from it. SAA1 has three alleles, designated SAA1.1, SAA1.3, and SAA1.5, defined by amino acid substitutions at positions 52 and 57 of the molecule [3]. SAA2 has two alleles, SAA2.1 and 2.2. The frequency of these alleles varies among populations, and may be associated with the occurrence of AA amyloidosis in diseases such as RA, and also with the level of SAA in blood, efficacy of clear-

ance, susceptibility to proteolytic cleavage by specific metalloproteinases, disease severity, and response to treatment [43]. The SAA1 alleles 1.1 and 1.3 have been proposed as positive risk factors in Caucasian and Japanese patients, respectively [44,45,46,47,48,49,50,51]. While the SAA1.1 allele was found to have a negative association with amyloidosis in Japanese subjects, it showed a positive association in Caucasians. Similarly, SAA1.3 showed an inverse association between Japanese and Caucasians. Recent new data have indicated that the -13T/C single nucleotide polymorphism in the 50-flanking region of SAA1 is a better marker of AA amyloidosis than the exon-3-based haplotype in both Japanese and American Caucasian populations [49,52,53]. Polymorphism of ApoE has been investigated as a potentially relevant genetic background factor, as this molecule is generally involved in the process of amyloid deposition [30]. According to several recent reports, ApoE4 is positively related to the development of AA amyloidosis in patients with RA [54]. Amyloid fibrils associate with other moieties, including GAGs, serum amyloid P component (SAP) and ApoA-II, which are related to the onset of amyloidosis [32, 55]. Recently, aging has also been shown to be a risk factor for AA amyloidosis associated with RA [56]. The fibrils bind Congo red and exhibit green birefringence when viewed by polarization light microscopy, although the deposits can also be recognized in hematoxylin and eosin-stained sections [57, 58]. Electron microscopy demonstrates deposits of amyloid fibril protein in tissues as rigid, non-branching fibrils approximately 8 to 10 nm wide and of varying length, with a 2.5 to 3.5 nm filamentous subunit arranged with a slow twist along the long axis of the fibril [59]. When isolated and analysed by X-ray diffraction, the fibrils exhibit a characteristically abnormal beta-sheet pattern [60]. Typing of amyloid deposits can be done by conventional immunohistochemical staining.
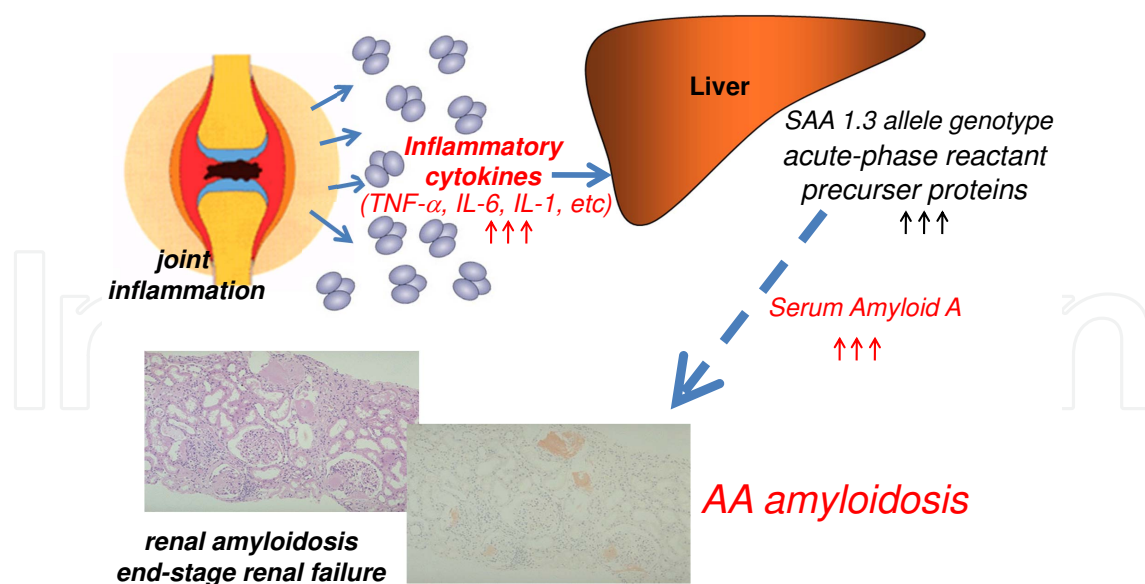

Figure 1. Pathogenesis of AA amyloidosis secondary to RA. RA begins with joint synovitis, and serum amyloid A protein (SAA) is synthesized in the liver chiefly as a result of stimulation with proinflammatory cytokines. Genetic background factors such as the SAA 1.3 allele genotype are a risk factor for amyloidosis. Amyloid fibrils are deposited in tissues of various organs, leading to organ failure. TNF-alpha: tumor necrosis factor-alpha, IL-6: interleukin-6, IL-1: interleukin-1, SAA1.3: one of the SAA1 gene polymorphisms.

4. Diagnosis

A cohort study of patients with RA has shown that deposits of fat AA fibrils are not uncommon (16.3%) [61]. Any patient with long-standing active inflammatory disease, such as RA, who develops proteinuria or intractable diarrhea must first be investigated for AA amyloidosis. No blood test is specially diagnostic for amyloidosis. Results of tests confirming the presence of chronic inflammatory disease, such as an increased erythrocyte sedimentation rate (ESR), or elevated levels of C-reactive protein (CRP) and SAA, are not necessarily discriminatory because most patients with chronic inflammation do not develop amyloidosis. The next step for diagnosis is to perform a biopsy and histopathological examination. In order to begin intensive treatment as early as possible before organ function worsens, it is important to choose a high-sensitivity biopsy site and employ a safe technique. In general, subcutaneous fat, spleen, adrenal gland, liver, labial salivary gland, and sites in the alimentary canal ranging from the tongue and gingiva to the rectum, are frequent sites of AA amyloid deposition [62,63,64,65,66,67,68,69,70,71]. Many non-invasive techniques are useful for assessing organ involvement, but cannot establish whether the findings are related to amyloid. The definitive diagnostic test is biopsy of either an accessible tissue expected to contain amyloid, or a clinically affected organ. GI, rectal and subcutaneous fat biopsies are the procedures of choice, because the methodology is simple [19,72,73,74]. Aspiration biopsy of abdominal fat is recommended for screening in outpatient clinics because it is easy to perform in that setting, requires no specialty consultation or technical experience, has a high yield, and results in only minimal side effects [61]. As experience has shown that the amount of amyloid in fat tissue is low, the operator should aspirate as large a sample as possible. If possible, GI and rectal biopsies are also recommended because their sensitivity is high and they can also be performed at hospitals in an outpatient setting. Generally, the GI is a more sensitive site for biopsy than subcutaneous fat [19,63]. The detection rate is higher in the duodenal bulb and second portion of the small intestine than in the stomach. Additionally, the incidence of amyloidosis in GI biopsies is highly correlated with that in renal biopsies [20]. If GI biopsy reveals amyloid deposition, the presence of renal amyloidosis should be considered [20]. However, a more recent study has revealed that the amounts of amyloid deposition in GI and renal biopsies are not correlated. GI amyloid-positive areas are larger than renal amyloid-positive areas [75]. If a fat biopsy proves negative, biopsy of the clinically involved site is suggested for patients with a limited number of affected organs. More organ-specific biopsies, such as heart, kidney and liver, are recommended. However, such biopsy sites carry a relatively higher risk than GI, rectal or subcutaneous fat biopsies. In such cases, clinicians should weigh the risks and benefits of biopsy. In Japan, however, GI biopsy is commonly performed for screening, rather than fat biopsy. If amyloidosis is strongly suspected clinically in association with marked inflammation, annual screening biopsy is recommended. However, it should be considered that rheumatologist put treatment for inflammation before organ biopsies. The many reports of renal biopsy results for RA patients have suggested that renal amyloidosis is the most serious complication. In RA patients, renal biopsy can sometimes be hazardous because of difficulties in maintaining a fixed body position, osteoporosis, or advanced age [76]. Renal involvement tends to determine the clinical course in such patients. Renal biopsy can also reveal underlying renal disorders such as mesangial prolifera-

tive glomerulonephritis (MesPGN), membranous nephropathy (MN), and thin basement membrane disease (TBMD). Pathological information on such underlying conditions is sometimes very important for the treatment of concomitant amyloidosis. Amyloid cardiomyopathy and autonomic neuropathy have been extremely rare in previously reported series [68], but should be keep in mind when interpreting biopsy results. The third step is histological diagnosis of amyloidosis, which can be established by light microscopy using special staining for amyloid. Alkaline Congo red has long been the standard method of staining for amyloid [57,58, 65]. Deposits of amyloid bind Congo red and exhibit apple-green birefringence when viewed by polarization light microscopy. This provides definitive diagnosis of amyloidosis. However, Dylon stain is more sensitive, and is therefore more useful for the detection of small amounts of amyloid [70, 71]. The use of Dylon stain, also known as direct fast scarlet, has recently become more popular. However, it requires more careful observation because of a tendency for overstaining (Figure 2). Thioflavin T is also more sensitive than Congo red, but less specific [77,78,79]. Although it yields a more intense fluorescent reaction, over-staining often hinders accurate diagnosis. If biopsy samples show a positive reaction, the type of amyloidosis should then be determined. Immunohistochemistry with fluorescent antibodies specific for precursor proteins, such as light chain lambda, kappa, SAA, etc., is a reliable diagnostic complement. Additional testing of serum and urine samples for monoclonal immunoglobulins, and of serum for free light chains, should be performed to exclude AL amyloidosis. Amino acid sequencing and mass spectroscopy of amyloid deposits have been utilitized to identify the precursor protein in some cases, but these techniques are not used routinely. Electron microscopy demonstrates straight, unbranched amyloid fibrils 8 to10 nm in width. Scintigraphy using radiolabeled SAP can identify the distribution of amyloid, and provide an estimate of the total body burden of fibrillar deposits [80]. SAP scintigraphy provides for a good tool for noninvasive diagnosis and for evaluation of the response to therapy over time [23]. The fourth step is to initiate treatment. If AA amyloid is revealed in any organ, the treatment should be focused on systemic amyloidosis, while giving due attention to any underlying chronic inflammatory diseases. If AA amyloidosis is related to tuberculosis or FMF, treatment of these underlying diseases should also be started. It is important to introduce specific therapies for individual diseases in such cases.

5. Quantification of amyloid deposition from biopsy specimens

Amyloidosis is usually diagnosed by histological examination of biopsy samples. However, its quantitative evaluation can be difficult. Some previous studies have tried to clarify the correlation between amyloid load and clinical features, and some trials of image analysis of GI biopsy and/or renal biopsy specimens have been attempted. Amyloid-positive areas in such biopsy specimens were determined on Congo-red-stained sections. One whole-tissue section was photographed, and then the borders of the amyloid-positive areas were traced, excluding any tissue-free spaces. Several studies have examined correlations between amyloid load and clinical parameters, and amyloid load in both GI and renal biopsy specimens were found to be highly correlated with kidney function [75,81,82]. Recently, some studies

have also employed SAA measurements from GI biopsy samples or abdominal fat obtained by needle aspiration to quantify AA [83, 84, 85]. Such quantification of AA from biopsy samples is useful for screening of AA amyloidosis and can be used for follow-up of the disease. Additionally, amyloid load in fat tissue reflects disease severity and can predict the survival of patients with the use of a grading system [86]. These reports have suggested that amyloid load reflects organ damage or disease severity.
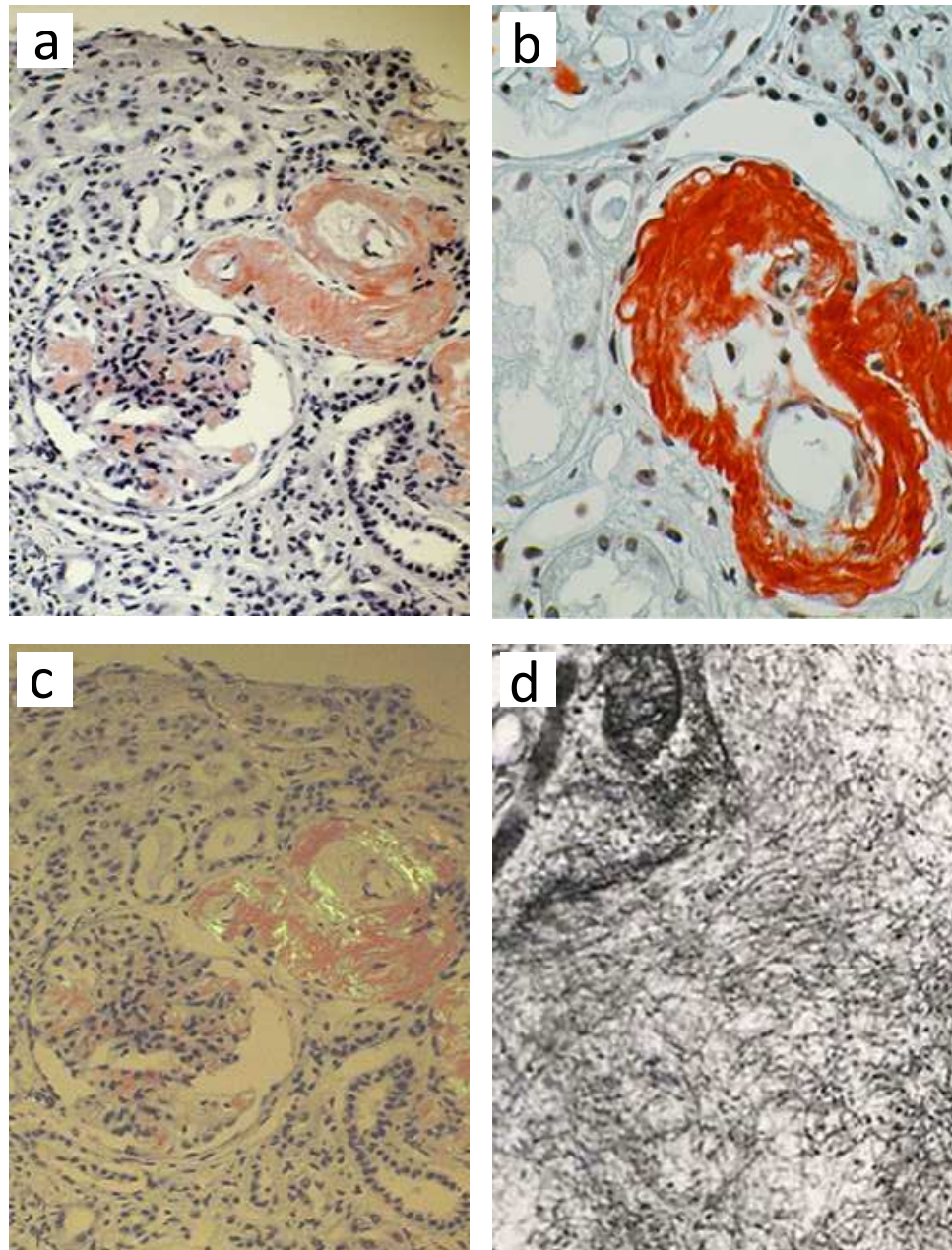

Figure 2. Histological diagnosis of renal amyloidosis. Amyloid substance is reactive with Congo red stain (a) and Dylon stain (b), and shows apple-green fluorescence under a polarizing microscope (c). Electron microscopy shows thin amyloid fibrils with a diameter of about 10 nm in AA and AL amyloidosis

6. Clinical features

The clinical features of amyloidosis are compatible with the infiltration of amyloid deposits. AA amyloidosis is a serious disease with a significant mortality due to ESKD, heart failure, bowel perforation, or GI bleeding [72,85]. Common clinical features of AA amyloidosis include proteinuria, loss of kidney function, and GI disorders. A clinical diagnosis of amyloidosis is usually suspected if proteinuria, renal insufficiency, or intractable diarrhea is present. Attention should also be paid to long-lasting and high inflammatory disease activity. Although AA amyloid can sometimes be detected in patients with arthritis in the absence of other clinical features, the clinical importance of such "silent" deposits remains to be determined. Renal involvement is a well-known complication of amylodiosis with RA. It is usually manifested as proteinuria or nephrotic syndrome with a variable degree of renal impairment that may progress to ESKD. If proteinuria worsens to about 0.5 g/day, amyloidosis should be suspected even if other reasons are plausible. In RA, several underlying renal disorders accompanying renal amyloidosis have been observed [87], including MesPGN, MN, TBMD, and interstitial nephritis [87]. Crescentic glomerulonephritis is a rare underlying disease in RA patients, and can result in rupture of the fragile glomerular basement membrane due to amyloid deposition [88]. Usually, MesPGN and interstitial nephritis are associated with mild to moderate proteinuria, and MN with severe proteinuria. TBMD shows no proteinuria, and usually hematuria alone is evident. Histological investigation frequently demonstrates renal amyloidosis concomitant with these underlying diseases [87]. In renal tissue, primary amyloid deposition may be limited to the blood vessels or tubules. Such patients present with renal failure but little or no proteinuria [89]. These deposits lead to narrowing of the vascular lumina [90]. Glomerular deposits are more common, and are associated with a poor renal outcome in patients with AA amyloidosis associated with RA. One report has described that 27 patients with renal amyloidosis due to RA had glomerular deposits, and that 85% of them showed progression to ESRD during a five-year observation period. However, patients with vascular and tubular amyloid deposits showed no deterioration of kidney function [91]. Such patients with vascular and tubular amyloid deposits usually present with slowly progressive chronic kidney disease with little or no proteinuria, and their prognosis appears to be more favorable [91]. Several studies have demonstrated a relationship between kidney function parameters and histopathological findings in patients with RA. The area of amyloid deposition in renal biopsy specimens was highly correlated with kidney function [81]. Additionally, if amyloid deposits in renal biopsy specimens progressed to some extent, the deterioration of kidney function became irreversible [82]. Because there are currently no methods for correlating the results of renal amyloid biopsy with outcome or therapeutic results, the clinical value of such investigations is still unclear. Standardization of renal amyloid biopsy parameters has been attempted, including biochemical classification, histopathologic classification, scoring of renal amyloid deposition, and association with other histopathologic lesions and grading [92]. The kidneys are usually enlarged slightly when nephrotic, but show a decrease in size as ESKD ensues. GI symptoms, such as alternating periods of constipation and diarrhea or bleeding, may frequently suggest early localization of amyloid deposits and warrant further investigation. Abdominal distention and

appetite loss are also frequently observed. Diminished peristalsis and malabsorption are common results of amyloid deposition, and can lead to nausea, vomiting, diarrhea, or hypo-albuminemia [93]. Endoscopy may demonstrate erosion, ulceration, mucosal weakness, or micro-polyposis, but sometimes no abnormality is evident in patients with mild amyloid deposition [64,94]. Fatal pancreatitis can sometimes occur at the end-stage of renal disease, and this is due to vascular obstruction by amyloid deposits in the pancreas [95]. Liver in-volvement can be manifested as weight loss, fatigue, and abdominal pain. About one-fourth of patients with amyloidosis have hepatic disease. Clinical signs may include only mild hep-atomegaly with elevation of the serum alkaline phosphatase level [96]. In the cardiovascular system, amyloid deposition is limited to the heart. In cases of unexplained heart failure, only small amounts of amyloid deposition are observed around the vascular walls. In contrast, in AL amyloidosis, massive cardiac involvement is invariably evident. In AL amyloidosis, in-tracardiac thrombosis and embolism are frequently observed in those with arterial fibrilla-tion with cardiac amyloidosis [97]. For these patients, anticoagulation therapy should be considered for the protection of left ventricular dysfunction and atrial mechanical dysfunc-tion [98]. Unlike the situation in AL amyloidosis, cardiac involvement in reactive AA amy-loidosis is not so common, affecting only about 10% of patients, and clinically overt heart failure is usually present in the terminal phase of the disease course, in addition to ESKD [99]. Restrictive cardiomyopathy or ischemic heart disease is rarely the cause of death [100]. Hypertension is frequent, and hypotension is rare in such patients, except in those with ESKD. Optimal control of hypertension is necessary for these patients. Hypothyroidism due to amyloid deposition is sometimes observed [101]. In AA amyloidosis, involvement of the musculoskeletal system is rare. Usually, most of the symptoms are due to RA itself, and amyloid deposits do not elicit musculoskeletal symptoms. Central nervous system involve-ment is also unusual. Infiltration of subcutaneous fat is generally asymptomatic, but pro-vides a convenient site for biopsy.

7. Management and treatment

Clinicians should remain vigilant for early signs of amyloidosis. For this purpose, patients with chronic rheumatic disorders, including those with elevated levels of inflammatory markers despite adequate symptom control by specific therapy, should undergo periodic urinalysis or assessments of 24-hour urinary protein excretion. If proteinuria exceeds 1(+) or increases to 0.5 g/day, screening for amyloidosis should be performed to search for amyloid deposits [43]. Occasionally, GI symptoms, such as alternating periods of constipation and di-arrhea or bleeding, may suggest early localization of amyloid deposits and warrant further investigation. If possible, GI endoscopy is recommended, because of its diagnostic yield. If a positive biopsy result is obtained after Congo red staining, accurate immunohistochemical characterization of amyloid as the AA type is mandatory. Although isolated amyloid fibrils are stable *in vitro*, AA amyloid deposits exist in a state of dynamic turnover, which suggests that AA amyloidosis should not be regarded as an end-stage, irreversible process. Once

Control SAA synthesis
1) Tight control of disease activity of RA
a) DMARDs: MTX as the anchor drug
b) Immunosupressant: cyclophosphamide, azathiopurine, tacrolimus, MMF
c) Biologics: anti-TNF, anti-IL-6, rituximab, abatacept
d) Tofacitinib
e) Antifibril drug: eprosidate
Supportive treatment
1) Cardiac
a) Congestive heart failure*: Salt restriction, Diuretics, antihypertensive agent
b) Arrhythmia: Pacemaker, Automatic implantable cardiac defibrillator, antiarrythmics
2) Renal
a) Nephrotic syndrome: Salt restriction, Maintain dietary protein, ACE inhibiter, ARB
b) Renal failure: Dialysis (HD, CAPD): Programmed initiation**
3) Gastrointestinal
a) Diarrhea: Steroid, codeine phosphate, lactate bacteria, octreotide, parenteral nutrition, anti-IL-6
4) Others
a) DMSO: resoluble amyloid deposits (very limited)
b) HB carrier : Etanercept with anti-viral agents is relatively safe.

*If co-existence of renal failure, CHDF (Continuous hemodiafiltration) is effective.

** To avid the trouble for the HD initiation, programmed initiation is recommended.

Table 1. Treatment for AA amyloidosis. SAA serum amyloid A protein, RA rheumatoid arthritis, DMARDs disease-modifying antirheumatic, Drugs, MTX methotrexate, MMF mycophenolate mofetil, TNF tumor necrosis factor, IL-6 interleukin-6, ACE angiotensin converting enzyme, ARB angiotensin receptor blocker, HD hemodialysis, CAPD continuous ambulatory peritoneal dialysis, DMSO dimethyl sulfoxide

amyloidosis has developed, the SAA concentration over the course of the disease represents the main factor affecting renal progression and survival [23,102]. A previous study has revealed a relationship between turnover and regression of amyloid deposits and the corresponding clinical benefit, in terms of both organ function and survival [23]. The natural history of AA amyloidosis is typically progressive, leading to organ failure and death, in patients whose underlying inflammatory disease remains active. By contrast, patients in whom the serum SAA concentration falls to within the reference range as a result of anti-inflammatory therapy show regression of amyloid deposits, stabilisation or recovery of amyloidotic organ function, and excellent long-term survival [103]. The therapeutic approach to AA involves treatment of the RA inflammatory process. It is important to control the level of SAA protein. It appears that reduction of the SAA level to less than 10 mg/L allows resorption of

the deposits and prevents further accumulation [102]. Frequent monitoring of SAA, when available, is therefore recommended in patients with AA amyloidosis as a guide to treatment strategy and follow-up. Alternatively, quantification of CRP may provide a valid marker for monitoring the effective suppression of underlying inflammation in these patients. The therapeutic strategy is shown in Table 1. It may be assumed that tight control of RA with DMARDs such as methotrexate (MTX), or immunosuppressant such as cyclophosphamide, azathioprine, tacrolimus, mycophenolate mofetil, or their combinations would have a similar impact. A small retrospective study has indicated that cyclophosphamide may confer a significant survival benefit in patients with RA and renal AA amyloidosis [104]. In that study, six of 15 patients received monthly pulse cyclophosphamide following confirmation of renal involvement. These treated patients survived longer than those administered non-alkylating drugs. Trends toward decreased proteinuria and maintenance of renal function have also been noted in patients treated with cyclophosphamide. Similar results have been confirmed in a cohort study reported from Japan [105]. Prospective studies are required to properly assess the role and toxicity of this agent in this setting. If treatments for the organ damage, such as immunosuppressive agents or anti-cytokine therapy, are unavailable, medium-dose steroid (prednisolone 10~40 mg daily) is effective. Eprodisate is a glycosaminoglycan (GAG) mimetic that binds to the GAG binding site on serum amyloid A to prevent its interaction with GAG, thus arresting amyloidosis [100]. A recent report has indicated that eprodisate is a useful antifibril compound for treatment of AA amyloidosis, significantly delaying progression to HD or ESKD [107]. When considering supplementary treatment, cardiac amyloidosis is a major therapeutic problem. Loop diuretics are the main therapeutic agents for management of volume overload. However, many patients with cardiac amyloidosis have concomitant renal amyloidosis, making it difficult to maintain a balance between edema and intravascular contraction. Antihypertensive treatment is also important. Rheumatologists should be mindful of hypertension to maintain an optimal blood pressure in treated patients. With regard to renal impairment in patients with RA and amyloidosis, the serum creatinine (Cr) level is relatively low because of reduced muscle volume. Gender, long-lasting inflammation and RA, together with a low level of serum protein, may be associated with a decrease of muscle volume, and these in turn affect the level of serum Cr. This may partly explain why the serum Cr level is not elevated in comparison with creatinine clearance (Ccr) in patients with RA-associated amyloidosis [108]. Measurement of cystatin C and calculation of the estimated glomerular filtration rate (eGFR) are also useful [109]. Even if the serum Cr level is normal, such patients may still have renal damage. If patients are in a nephrotic state, angiotensin converting enzyme (ACE) inhibitor and/or angiotensin II receptor antagonist (ARB) are effective for reducing the level of urinary protein. For patients with renal failure, dialysis is needed. The prognosis of those who require dialysis is not good, although some data suggest a survival benefit among patients with AA amyloidosis [72]. The poor prognosis of these patients is due mainly to a large number of sudden deaths immediately after introduction of HD therapy [110,111]. Additionally, unplanned initiation of HD is significantly associated with poor survival. Therefore, properly planned initiation of HD is highly recommended. To circumvent the problem of HD initiation while ensuring its safety, the procedure for planned introduction is shown in Figure 4.

Programmed initiation of HD will improve the prognosis of patients with ESKD [112]. Continuous ambulatory peritoneal dialysis (CAPD) can also be considered for patients with ESKD, as it has an advantage in preserving the functionality of the kidneys and avoiding hypotension associated with HD. However, in RA patients, disability of the hands due to chronic inflammation, and also the risk of peritonitis, should be considered [113]. Kidney transplantation has been performed successfully for a number of patients with renal failure and AA amyloidosis, but only on a very limited basis [114]. In the near future, kidney transplantation may become a recommended therapy for such patients. For treatment of GI symptoms, mostly intractable diarrhea, medium- to high-dose steroid (prednisolone 10~40 mg daily) is effective. Parenteral nutrition is also effective for this condition. Immunosuppressive therapies may be associated with serious infection in patients with amyloidosis. Advanced age is an important risk factor for infection in patients with RA. Some of the increased risk may be related to steroid usage. Additionally, such patients generally show low protein levels or hypoalbuminemia. These factors may lead to serious infection and/or opportunistic infection. It is possible that infection may exacerbate elevation of the SAA level and lead to additional organ damage. Preventive therapy against infection should always be borne in mind. Dimethyl sulfoxide (DMSO) has been proposed as a therapeutic agent for solubilization of AA deposits, and a number of patients have been treated with DMSO in an uncontrolled trial. There appeared to be salutary effects in some patients, but the accompanying body odor made the treatment unacceptable [115]. Recently, treatment with DMSO has been very limited. Earlier diagnosis of amyloidosis leads to better treatment and an improved chance of recovery.

8. Treatment with biologics

Recent studies have indicated the therapeutic benefit of anti-TNF or anti-IL-6 agents for AA amyloidosis secondary to inflammatory arthritides, including RA [82,103, 116, 117,118,119]. These agents strongly inhibit the production of SAA. If possible, for the treatment of reabsorption of amyloid deposits, and, possibly, recovery of target organ function, treatment with biologics has been recommended. A recent report has indicated that etanercept was effective in a patient with cardiac amyloidosis associated with RA [119]. Biologics are known to be contraindicated for patients with heart failure [120], but may be effective if the heart failure is well controlled. The anti-IL-6 agent tocilizumab has an excellent inhibitory effect on disease activity and joint destruction, and is therapeutically beneficial for the symptoms of AA amyloidosis, especially intractable diarrhea [121]. Recently, we were revealed that treatment of these patients with biologic agents can reduce risk of death. In that study, a total of 133 patients were evaluated and 52 were treated with biologics such as the anti-TNF agents infliximab and etanercept, as well as tocilizumab, with a follow-up of more than 6 years (Figure 3). However, the use of biologics may not significantly influence the HD-free survival rate [13]. Although there are no data for the effect of abatacept on AA amyloidosis, it may be effective in theory. Janus kinase inhibitor also appears to be favorable for the treatment of AA amyloidosis associated with RA [122]. Rituximab therapy also appears effective for reduction of acute-phase protein and stabi-

lization of kidney function and proteinuria in patients with RA-associated amyloidosis [123]. The use of biologics is not part of the conventional treatment approach, and they are chosen according to the conditions in individual patients, such as kidney and pulmonary function. If there is any risk of infection, short-acting biologics are desirable. Especially, in patients receiving tocilizumab, infection may be difficult to find, and rheumatologists therefore need to be vigilant. Treatment with biologic agents is prohibited in certain circumstances, such as severe infections or demyelinating diseases. The treatment of patients with coexisting RA and hepatitis B poses a difficult therapeutic challenge because of the risk that treatment of the RA could aggravate the hepatic disease and increase viremia. In general, the use of biologics such as anti-TNF and anti-IL-6 is contraindicated in patients who are hepatitis B virus (HBV) carriers or have chronic hepatitis B. Reactivation of HBV infection is a well-recognized complication in cancer patients with chronic HBV (hepatitis B surface antigen [HBsAg]-positive) undergoing cytotoxic chemotherapy, and prophylactic antiviral therapy before chemotherapy is recommended in such individuals. Additionally, HBV reactivation in patients with resolved HBV infection (HBsAg-negative and HBs antibody [anti-HBs]-positive and/or hepatitis B core antibody [anti-HBc]-positive) during or after cytotoxic therapy has recently been reported [124,125]. Rheumatologists also need to pay attention to HBV reactivation. However, in clinical practice, it is necessary to use anti-TNF in these patients. The existing data suggest that treatment of such patients with etanercept and tocilizmab co-administered with lamivudine or entecavir is safe [126,127].
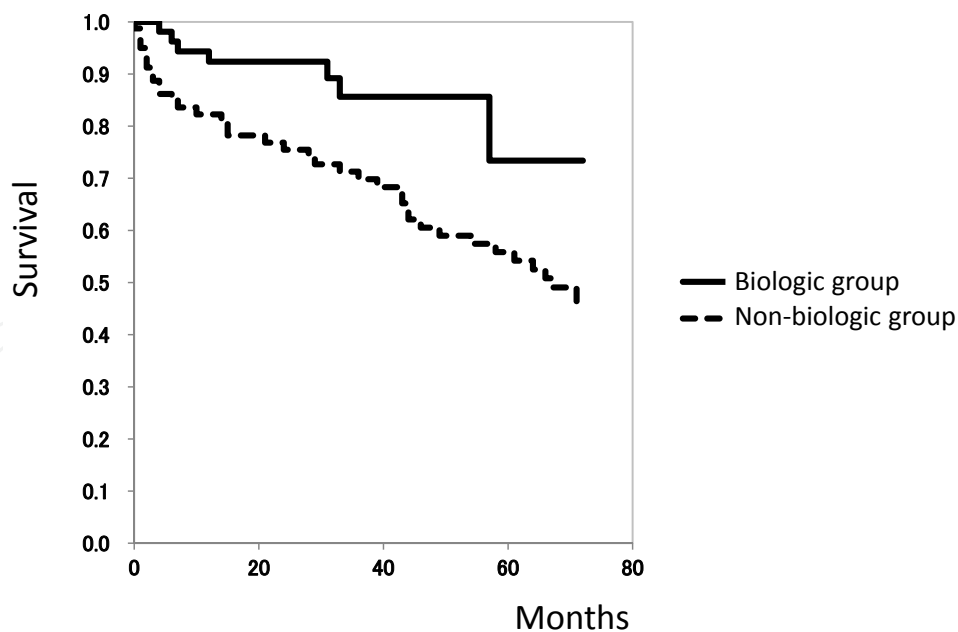

Figure 3. Survival of patients receiving biologic or non-biologic therapy. Fifty-three patients were treated with biologic agents (biologic group) and 80 patients were not (non-biologic group). Survival of patients with and without biologics treatment was assessed using the Kaplan-Meier method. Survival was significantly higher in the biologic group than in the non-biologic group (p=0.012).
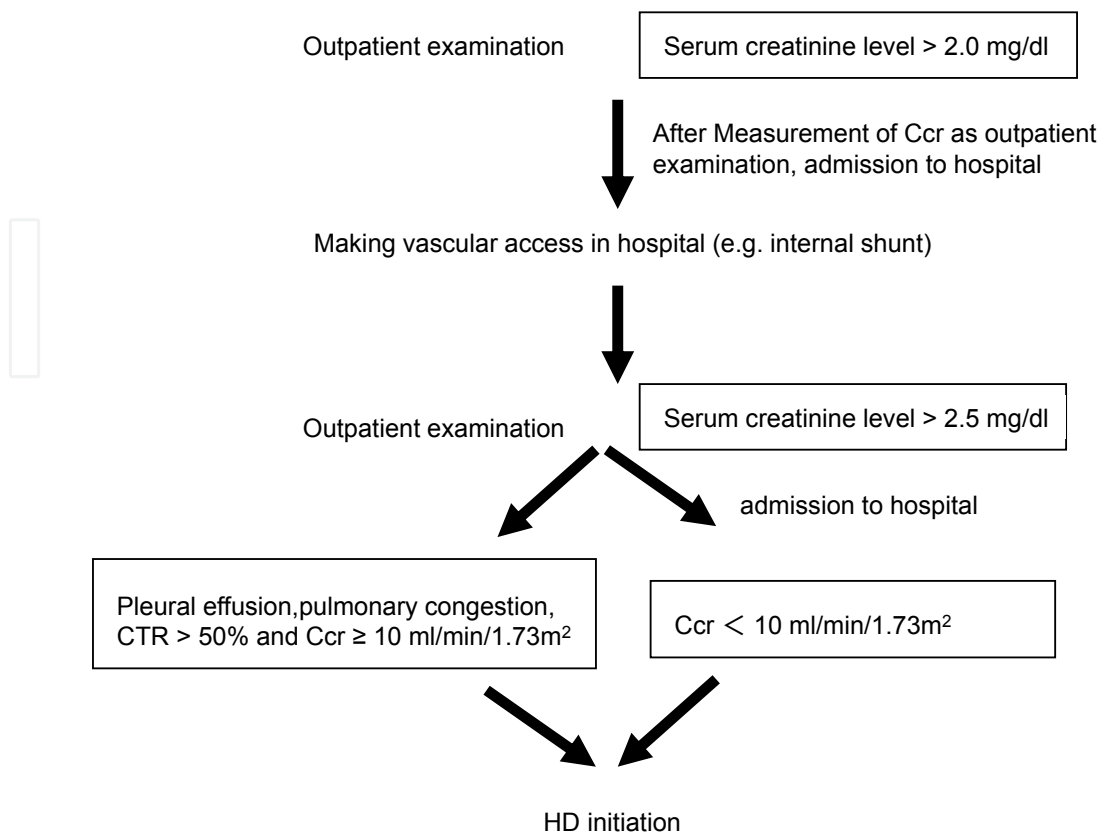
Outpatient examination   Serum creatinine level > 2.0 mg/dl

After Measurement of Ccr as outpatient
examination, admission to hospital

Making vascular access in hospital (e.g. internal shunt)

Outpatient examination   Serum creatinine level > 2.5 mg/dl

admission to hospital

Pleural effusion,pulmonary congestion,
CTR > 50% and Ccr ≥ 10 ml/min/1.73m²

Ccr < 10 ml/min/1.73m²

HD initiation

Figure 4. Program for initiation of hemodialysis. Schematic representation of the program used for our patients with end-stage kidney disease due to reactive amyloidosis associated with rheumatoid arthritis. Ccr: creatinine clearance, CTR: cardiothoracic ratio

9. Outcome

Survival after the diagnosis of AA amyloidosis secondary to RA seems to be 4–5 years [110,128]. Recently, however, a median survival period of more than 10 years after diagnosis has been reported [23]. Survival seems to depend on the timing of diagnosis, and this may partly explain the great individual variation in observed survival time, leading to the notion that an active diagnostic attitude for AA amyloidosis should be adopted in patients with RA. Treatment strategy is also important. Infection and renal failure are generally common causes of death in RA patients with AA amyloidosis [129,130]. A higher risk of severe infection is a substantial problem in the management of such patients. Potent immunosuppressive treatment may sometimes result in infection, and in such cases, prophylactic treatment with an antituberculosis agent is recommended. As for P. jirovecii pneumonia (PCP),prophylactic treatment is less common except for outbrake of PCP [131]. Increased production of SAA is a strong risk factor for ESKD and death, but this may be ameliorated by anti-inflammatory treatment. A relationship between SAA concentration, kidney function and whole-body amyloid burden has been revealed. Outcome has been shown to be favorable in

patients with AA amyloidosis when the SAA concentration is maintained below 10 mg/L [23]. Additionally, the use of biologics is expected improve the prognosis for these patients [13]. Factors associated with poor prognosis are well known to include age at onset of RA and amyloidosis, female gender, a reduced serum albumin concentration, ESKD, the level of disease activity including serum levels of CRP and IgG, and the SAA concentration during follow-up [130]. Steroid dosage, and markers of kidney function that are correlated with kidney disease, such as BUN, Cr, and Ccr, at the time of detection of amyloidosis are also important factors predictive of survival [110]. The results of dialysis for AA amyloidosis are extremely poor, and trouble with the initiation of HD in fact worsens the prognosis, due to a rapid decline of kidney function in the year preceding dialysis. Reported median survival after initiation of HD is more than 1 year [132], or more than 5 years [133]. These reports indicate that strict treatment and care will improve the clinical outcome. It is possible that the use of biologics may improve the HD-free survival rate, but accumulation of further cases is required. Amyloidotic cardiac involvement has been shown to be a poor prognostic factor [134,135]. Heart failure is a severe complication in these patients, who also usually develop concomitant multiple organ failure, as well as renal failure, in the later phase of the RA disease course. To improve the outcome of these patients, frequent examinations for infection and acute inflammatory reactants such as CRP and SAA are necessary.

10. Conclusion

The best approach to treatment of amyloidosis is to prevent progression by controlling the serum level of SAA. In AA amyloidosis, proteinurea, renal dysfunction and GI symptoms are diagnostically informative. It is important not to overlook these symptoms, and to confirm the presence of amyloidosis by organ biopsy. Treatment with biologic agents plays a key role, especially for decreasing the production of SAA, along with prophylactic administration of anti-tuberculosis and anti-fungal agents. Monitoring of adverse events such as infection is an important part of the standard strategy associated with biologics treatment, and checks for chronic inflammatory disorders should be conducted routinely. Rheumatologists should carefully consider the use of biologics in patients with difficult background conditions such as hepatitis B. Such efforts should help to improve the outcome of patients with AA amyloidosis, achieve stabilization or regression of amyloid deposits, and prolong survival.

Acknowledgements

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