Review

Amyloid A amyloidosis secondary to rheumatoid arthritis: pathophysiology and treatment

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ABSTRACT

The introduction of biological therapies targeting specific inflammatory mediators revolutionised the treatment of rheumatoid arthritis (RA). Targeting key components of the immune system allows efficient suppression of the pathological inflammatory cascade that leads to RA symptoms and subsequent joint destruction. Reactive amyloid A (AA) amyloidosis, one of the most severe complications of RA, is a serious, potentially life-threatening disorder caused by deposition of AA amyloid fibrils in multiple organs. These AA amyloid fibrils derive from the circulatory acute-phase reactant serum amyloid A protein (SAA), and may be controlled by treatment. New biologics may permit AA amyloidosis secondary to RA to become a treatable, manageable disease. Rheumatologists, when diagnosing and treating patients with AA amyloidosis secondary to RA, must understand the pathophysiology and clinical factors related to development and progression of the disease, including genetic predisposition and biological versatility of SAA.

Introduction

Amyloidosis is a disorder of protein conformation and metabolism that results in the deposition of insoluble amyloid fibrils in tissues, which causes organ dysfunction; systemic amyloidosis is characterised by failure of various organs and the presence of amyloid precursor protein in the serum (1). Reactive amyloid A (AA) amyloidosis is one of the most severe complications of several chronic disorders, particularly rheumatoid arthritis (RA) (2), and indeed, most patients with reactive AA amyloidosis have an underlying rheumatic disease. An extra-articular complication of RA, AA amyloidosis is a serious, potentially life-threatening disorder caused by deposition in organs of AA amyloid fibrils, which derive from the circulatory acute-phase reactant, serum amyloid A protein (SAA). In fact, AA amyloidosis is the third leading cause of death among patients with RA (3). AA amyloidosis secondary to RA is thus one of the intractable conditions found in patients with collagen vascular diseases and is an uncommon yet important complication of RA (4).

1. Pathophysiology of AA amyloidosis

A sustained high concentration of SAA is a prerequisite for AA amyloidogenesis (Fig. 1). However, AA amyloidosis actually develops in only a minority of patients with active, long-standing inflammatory diseases, which indicate that significant disease-modifying factors may help modulate the occurrence of AA amyloidosis, the rate of AA amyloid fibril deposition in tissues, or induction of tissue damage in this form of amyloidosis. The persistent inflammation caused by chronic diseases, such as rheumatic disorders (*e.g.* RA, juvenile idiopathic arthritis, hereditary autoinflammatory syndromes, and ankylosing spondylitis), chronic infections (*e.g.* tuberculosis, bronchiectasis, acne conglobata, and osteomyelitis), and certain neoplasias (*e.g.* lung adenocarcinoma, hepatocellular carcinoma, renal carcinoma, Hodgkin's lymphoma, and Castleman's disease) is associated with increased release of the proinflammatory cytokines interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF) α. These cytokines induce a markedly increased synthesis of the acute-phase protein SAA, the concentration of which can be 100 to 1000-fold higher than normal (5).

Human AA amyloid fibril deposits consist mostly of *N*-terminal fragments of SAA, which points to proteolytic

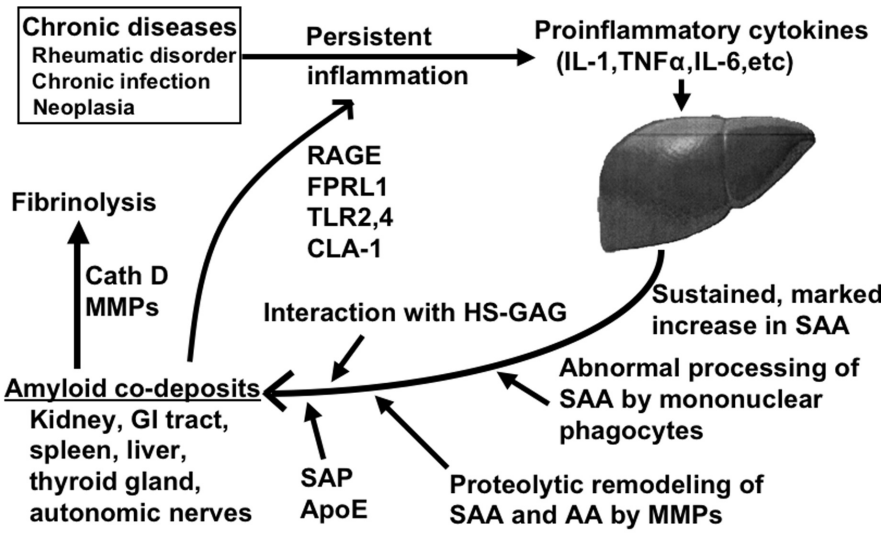

Fig. 1. Pathogenic events involved in amyloid A (AA) amyloidogenesis.
Persistent inflammation caused by chronic diseases is associated with a continuous increase in proinflammatory cytokines (IL-1: interleukin-1, TNF-α: tumour necrosis factor α, IL-6: interleukin-6). These cytokines induce markedly increased synthesis of the acute phase-phase protein serum amyloid A protein (SAA). Abnormal processing of SAA by mononuclear phagocytes is thought to initiate amyloidogenic peptide production and formation of amyloid A (AA) amyloid fibrils in lysosomes. Matrix metalloproteinases (MMPs) and cathepsin D (Cath D) contribute to proteolytic remodelling of SAA, with production of amyloidogenic species. AA amyloid fibrils, plus serum amyloid P component (SAP) and apolipoprotein E (ApoE), and after interaction with haparan sulfate-glycosaminoglycans (HS-GAG), deposit in multiple organs. SAA and AA participate in inflammation through receptors on inflammatory cells. RAGE: receptor for advanced glycation end products; FPRL1: formyl peptide receptor-like 1; TLR2, 4: toll-like receptor 2 and 4; CLA-1: CD36 and LIMPII analogous-1, human orthologue of the scavenger receptor class B type I (SR-BI); GI: gastrointestinal.

cleavage of the precursor being a key event in pathogenesis (6). These amyloid fibril fragments almost exclusively derive from SAA1, which suggests that specific amino acid residues may contribute to a misfolding propensity or that differences in the catabolism exist. The fate of SAA depends largely on its interactions with cellular and extracellular tissue components. Mononuclear phagocytes are involved in SAA catabolism through endocytosis and trafficking to lysosomes (7), where SAA undergoes degradation (8).

A role of mononuclear phagocytes in initiating AA amyloid fibril formation was originally postulated because of the presence of AA amyloid fibrils in intracellular vesicles and close to cell membranes in amyloid-laden tissues (9), and these phenomena were subsequently demonstrated in cell culture models (10). Studies of human monocyte cell lines showed the accumulation of newly formed AA amyloid fibrils in intracellular lysosomal compartments, which indicated that aberrant processing of SAA is relevant for the pathogenesis of AA amyloidosis (11). A role of monocytes in mediating prion-like transmissibility of AA amyoid fibrils acting as seeds was also suggested (12, 13). Furthermore, SAA binds specifically to the heparan sulfate (HS)-glycosaminoglycan complex (14), a common constituent of all kinds of amyloid deposits that was demonstrated to facilitate conformational conversion of a precursor to a β-plated sheet structure. Also, the SAA-HS interaction promotes AA fibrillogenesis by acting as a scaffold for fibril assembly (15). Both SAA and AA were reportedly biosynthesised by blood or tissue matrix metalloproteinases (MMPs) (16) and cathepsin D (17), and this process may in part result in amyloidogenic peptide formation. AA amyloid fibrils would form within lysosomes in macrophages because of disturbed SAA processing. As another factor in amyloid metabolism, mannose-binding lectin (MBL) is a liver-derived protein involved in lectin-mediated complement activation, and lower serum MBL levels are thought to lead to reduced macrophage function. MBL-2 polymorphism determines the blood MBL level and is associated with the role of mononuclear phagocytes in amyloid metabolism (18, 19). Susceptibility to AA amyloidosis has been linked to mononuclear phagocyte function, and SAA processing by monocytes under stimulation with IL-1 or interferon was reportedly disturbed in patients with AA amyloidosis (20), which suggests inflammation-induced abnormalities in monocyte function (21, 22).

Although synthesis of AA amyloid fibrils may be closely related to abnormal processing of SAA and AA in macrophages, the affinity of AA amyloid fibrils for different organs largely accounts for the heterogeneity of such AA amyloid deposits, which still requires explanation (23). In addition, MMPs contribute to proteolytic remodelling of SAA, with production of amyloidogenic species. Tissue glycosaminoglycans facilitate formation and local deposition of AA amyloid fibrils (24), along with other amyloidogenic substances, which may be protected from clearance by interaction with the pentraxin serum amyloid P component (SAP) (25). The main target organ of deposition is the kidney, with resulting significant proteinuria and progression toward renal failure (26). In cases of gastrointestinal (GI) AA amyloidosis, decreased GI motility causes bacterial overgrowth, bile acid deconjugation, and consequently diarrhoea, steatorrhoea, and severe malabsorption (27).

2. SAA and its receptors

SAA is produced primarily in the liver under proinflammatory cytokines stimulation; it is also a central acute-phase protein, like C-reactive protein (CRP). SAA complexes with a carrier protein, being transported into serum by high-density lipoprotein (HDL) in combination with apolipoprotein E (28), and plays an important role in enterohepatic cholesterol circulation. In obese individuals, the frequency of SAA mRNA expression and blood SAA level are both significantly high (29). Thus, the biologically versatile SAA has a significant relationship with lipid metabolism (Fig. 2).

Human SAA composes 104 amino ac-

ids, and the four SAA-encoding genes are on chromosome 11p15.1. SAA contains three subtypes with different primary structures-SAA1, SAA2 and SAA4-which make up two groups. Those in the first group, SAA1 and SAA2, serve as acute-phase proteins. In the second group, SAA4 is expressed constitutively in plasma, is synthesised by different organs and tissues, and is not an acute-phase protein. Inflammation induces *SAA1* and *SAA2* genes and their expression but not expression of *SAA3* (a pseudogene) and *SAA4*. *SAA4* encodes a structural protein of HDL. Because of allele polymorphism, SAA1 has three isoforms (SAA1.1, SAA1.3, and SAA1.5) and SAA2 has two (SAA2.1 and SAA2.2), and the serum level of SAA is affected by SAA1 polymorphism. Expression of the SAA1.5 allele is associated with high blood SAA levels, and SAA1.5 has a high affinity for HDL (30). The primary structures of SAA1 and SAA2 have a 93% amino acid homology. SAA4 shows a 50% homology with the other SAA acute-phase proteins. Thus, acute-phase SAA has multiple patterns of protein polymorphism (31, 32).

Several SAA receptors have been described, including CD36 and LIMPII analogous-1 (CLA-1) (33); lipoxin A1 receptor/formyl peptide receptor-like 1 (FPRL1) (34); tanis, a hepatic receptor activated by glucose (35); and toll-like receptor (TLR) 4 (36) and TLR2 (37). SAA reportedly activated rheumatoid synovial fibroblasts by binding to receptors for advanced glycation end products (RAGE) (38-40). Also, an HDL receptor, the scavenger receptor class B type I (SR-BI), is expressed in RA synovial tissue and is apparently involved in SAA-induced inflammation in arthritis (41), including production of SAA-induced reactive oxygen species (ROS) and proliferation of fibroblasts. Although RAGE is a receptor for signal transduction with biological stimuli, neither SAA nor AA is incorporated into cells via this receptor. SAA serves as a chemoattractant for neutrophils, T cells, and monocytes via FPRL1 and induces production of CCL2, which is a prototype of the CC chemokine subfamily that has the highest chemotactic activity for monocytes (42). Because cytotoxic drugs and cytokine inhibitors affect AA amyloid deposits via their ability to suppress SAA production, anticytokine therapies, by inhibiting expression of RAGE, have been proposed to reduce interactions between AA amyloid fibrils and RAGE and thereby prevent AA-mediated cell toxicity (43).

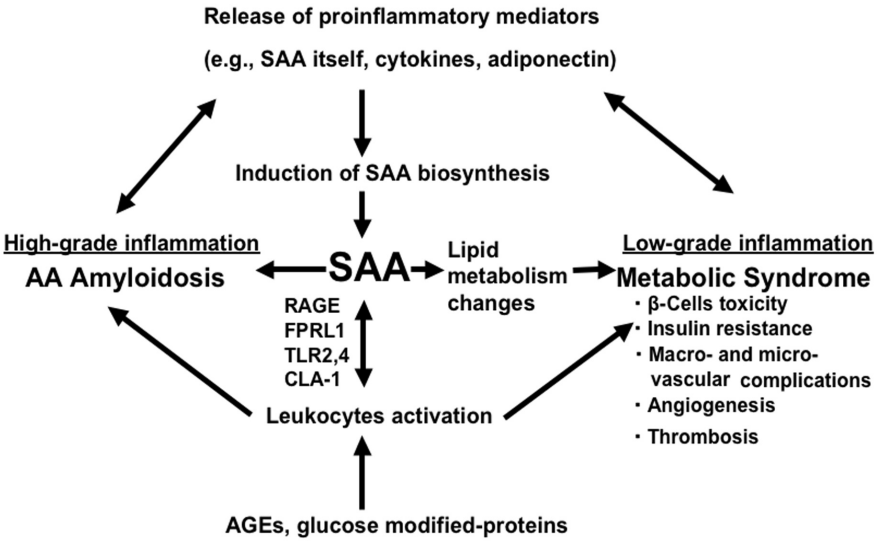

Fig. 2. Biological versatility of serum amyloid A protein (SAA).
SAA plays important roles in both high-grade inflammation and low-grade inflammation. It acts, as cytokines do, via autocrine, endocrine, and paracrine mechanisms. As a precursor protein of amyloid A (AA) amyloid fibrils, SAA induces AA amyloidosis. SAA also affects metabolic syndrome via various modes of action. These humoral and cellular inflammatory events interact, with SAA being a key player. RAGE: receptor for advanced glycation end products; FPRL1: formyl peptide receptor-like 1; TLR2, 4: toll-like receptor 2 and 4; CLA-1: CD36 and LIMPII analogous-1, human orthologue of the scavenger receptor class B type I (SR-BI); AGEs: advanced glycation end products.

SAA reportedly exerts cytokine-like actions (44), stimulates fibroblast differentiation, and elevates ROS production in neutrophils and fibroblasts (45). Furthermore, not only does SAA induce synthesis of MMP-1 and MMP-3 in synoviocytes and chondrocytes and increase production of MMP-9 (46), but it is also involved in innate immunity via TLR4. Additional studies must identify specific receptor(s) involved in SAA-induced biological phenomena in health and disease.

3. SAA1.3 allele and genetic factors related to AA amyloidosis

The frequency of *SAA1* gene polymorphism and that of SAA1 alleles differ among races and regions worldwide. Three main SAA1 alleles-SAA1.1, SAA1.3, and SAA1.5-are defined by two single-nucleotide polymorphisms (SNPs) in exon 3, resulting in two amino acid differences at positions 52 and 57, respectively. In Japanese people, the three alleles occur at approximately the same rate. The association between AA amyloidosis and the SAA1 genotype was first observed in Japanese patients with RA, in whom homozygosity for the SAA1.3 allele proved to be a risk factor (47). The SAA1.3/1.3 genotype in Japanese patients with RA was associated with a shorter latency period before AA amyloidosis onset and more severe AA amyloidosis-related symptoms; it was also a univariate predictor of survival. Thus, the SAA1.3 allele was a risk factor for AA amyloidosis, had an association with clinical severity in this population, and served as an indicator of poor prognosis (48). Among Caucasians, AA amyloidosis was often observed in SAA1.1 homozygous individuals, and the SAA1.1 allele was thought to be a risk factor for AA amyloidosis (49).

With regard to SNPs of the *SAA1* gene promoter region, -13T is a high-risk factor for AA amyloidosis in Japanese patients with RA, with -13T/T and -13T/C being closely associated with AA amyloidosis than is -13C/C (50). Because *SAA1* gene polymorphism affects both

Table I. Selected references to biologics for treatment of AA amyloidosis secondary to RA.

For TNF-α antagonists	E: etanercept/ I: infliximab	Ref. no.
Elkayam O *et al*.: Arthritis Rheum 2002; 46: 2571-3	I	
Gottenberg J-E *et al*.: Arthritis Rheum 2003; 48: 2019-24	E/I	
Ortiz-Santamaria V *et al*.: Rheumatology 2003; 42: 1425-6	E/I	
Smith GR *et al*.: Intern Med J 2004; 34: 570-2	E	
Ravindran J *et al*.: Rheumatology 2004; 43: 669-72	E/I	
Fernandes-Nebro A *et al*.: Am J Med 2005, 118: 552-6	E/I	
Nakamura T *et al*.: Clin Exp Rheumatol 2007; 25: 518-22	E	71
Kuroda T *et al*.: Rheumatol Int 2008; 28: 1155-9	I	
Kuroda T *et al*.: Rheumatol Int 2009; 36: 2409-15	E/I	69
Nakamura T *et al*.: Clin Exp Rheumatol 2010; 29: 1395-401	E	70
Nobre CA *et al*.: Rev Bras Reumatol 2010; 50: 205-10	E	
Ishii W *et al*.: Rheumatol Int 2011; 31: 247-50	E	
For IL-6 receptor antagonist		
Okuda Y, *et al*.: Arthritis Rheum 2006; 54: 2997-3000		72
Sato H, *et al*.: Clin Rheumatol 2009; 28: 1113-6		
Inoue D, *et al*.: Clin Rheumatol 2010; 29: 1195-7		

blood SAA levels and SAA transcriptional activity in hepatocytes, differences in SAA1 proteolysis by MMPs indicate a close association between *SAA1* gene polymorphism and onset of AA amyloidosis (51). However, the mechanism by which *SAA1* gene polymorphism is related to the onset of AA amyloidosis and the reason for ethnic differences in disease-susceptible SNPs are yet unknown.

For *HLA-DRB1* gene polymorphisms, the presence of two shared epitopes including the *04 allele significantly elevates the risk for AA amyloidosis (52).

4. Clinical features and diagnosis of AA amyloidosis secondary to RA

Clinical features of overt AA amyloidosis include long-term psychological distress of RA, markedly high disease activity, and significant inflammatory states. Although a high level of blood SAA is an important factor associated with AA amyloidosis onset, this factor does not always lead to AA amyloidosis in all patients. Several important factors, including the genetic one mentioned above (48), are believed to modify the onset of AA amyloidosis. The actual incidence of AA amyloidosis in RA is still undefined and probably underestimated (53), in that distinguishing clinical and subclinical phase is quite difficult. A cohort study of patients with RA showed that fat AA amyloid deposits were not uncommon-16.3% (54)-so subclinical AA amyloidosis may indeed be common in RA (55). Prevalence values of AA amyloidosis in RA patients in recent series ranged from 7% to 26% (56, 57). The prevalence of clinical amyloidosis is likely to be lower, however, as it probably reflects differences in RA treatments and in genetic backgrounds (58, 59).

AA amyloid deposits primarily target the kidneys, liver, and spleen, and AA amyloidosis becomes clinically overt mainly when renal damage occurs, manifesting as proteinuria, nephrotic syndrome, or impaired renal function (60). Proteinuria is the clinical sign that most often leads to diagnosis of AA amyloidosis in RA patients. Diagnosis must be based on histological examination of tissue specimen, such as from upper GI or rectal biopsy (61). Although mucosal biopsy of the upper GI tract to screen for AA amyloid fibril deposition is an easy, simple diagnostic method, antiulcer drugs may mask amyloidotic signs and symptoms in the GI tract, which may delay diagnosis of AA amyloidosis in RA patients. Positive Congo-red staining, susceptibility to oxidation with potassium permanganate, and green birefringence by polarisation microscopy after Congo-red staining can confirm the presence of AA amyloid fibrils, however (62).

5. Treatment of AA amyloidosis secondary to RA

The principal aim in treating RA patients with AA amyloidosis is to switch off SAA production, by controlling the RA inflammatory process. Anti-inflammatory treatment must be empirical but, as in all patients with AA amyloidosis, should be guided by frequent assessment of SAA concentrations in view of reported correlations between survival and this measure. Estimated survival at 10 years was 90% in AA amyloidosis patients whose median SAA concentration was below 10 μg/ml and was 40% among those whose median SAA exceeded this value, which were statistically significant results (63). Treatment of AA amyloidosis secondary to RA may involve the following strategies.

Suppression of SAA production

For AA amyloidosis in patients with RA, treatment has centered on using cytotoxic agents and biologics. Although case reports and studies of small series of patients showed that these agents can reverse nephrotic syndrome and even lead to complete resolution of proteinuria, anticytokine agents have recently been proposed as therapeutic options (Table I). Anti-proinflammatory cytokine therapy is expected to show efficacy against systemic inflammation and against local inflammation mediated by macrophage differentiation or activation in glomeruli, such as in renal AA amyloidosis secondary to RA (64). The strategy of these treatments focuses on tight control of underlying RA disease activity (65). Requirements include diagnosis of RA as early as possible and treatment with disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX) as the anchor drug. Achieving low disease activity via DMARDs early in the disease course has a strong positive outcome on disease progression. However, although MTX is the most common and effective drug for RA, management of patients with AA amyloidosis secondary to RA and renal involvement is too complex to limit the discussion to MTX.

In RA treatment, tight control of RA is emphasised to obtain clinical remission or lower disease activity; this control is

possible through periodic evaluations of RA disease activity and aggressive pursuit of other more effective treatments (66-68). Together with this strategy, the genetic predisposition allele SAA1.3, which is a known risk factor for AA amyloidosis in Japanese RA patients, should be evaluated when treating both RA and AA amyloidosis (48).
Etanercept and infliximab, both TNFα antagonists, can reduce serum SAA levels in RA patients with AA amyloidosis, which improves rheumatoid inflammation, reduces swollen and tender joint counts, lowers or normalises proteinuria, and ameliorates renal function (69, 70). Despite the small number of series of patients with AA amyloidosis secondary to RA who had etanercept treatment, this drug did benefit both RA inflammation and AA amyloidosis, as measured via the surrogate markers DAS28-ESR, CRP, SAA, and proteinuria, in SAA1.3 allele-carrying RA patients (Table IIa). Also, serum creatinine levels significantly improved in patients with mild RA disease and renal dysfunction (Table IIb). This result suggests that the earlier the intervention with biologics, the better the outcome for patients. Etanercept alone may therefore be efficacious, without MTX (71).
Tocilizumab, an IL-6 receptor antagonist, also demonstrates excellent suppression of SAA levels and may have potential as a therapeutic agent for AA amyloidosis (72). Circulating SAA normally reflects changes in CRP, and levels of both acute-phase reactants usually increase simultaneously, but some differences can occur. SAA and CRP seem to be partly influenced by different cytokines. IL-6-blocking therapy has shown promise in normalising serum SAA levels in RA patients (73). Moreover, blocking IL-6 alone, but not IL-1 or TNFα, completely prevented SAA mRNA expression in human hepatocytes during triple cytokine stimulation (74). For signal transduction, IL-6 binds to membrane-bound IL-6 receptor gp80 (75), and then the IL-6-gp80 dimer interacts with gp130. Formation of gp130-containing complexes leads to activation of Janus kinases (JAKs), which stimulates signal transducers and activators of transcription (STATs) (76). Certain evidence suggests that STAT3 is the key transcription factor responsible for IL-6 activation of SAA gene transcription (77). Therefore, the function of JAK inhibition in the IL-6 signalling pathway will be one target of RA treatments. Suppressing IL-6-mediated proinflammatory signalling pathways via JAK inhibitors may be a novel anti-inflammatory therapeutic strategy for RA and AA amyloidosis. Another agent, tacrolimus, may inhibit T-cell function in pathogenesis of AA amyloidosis (78, 79).

Inhibition of AA amyloid fibril deposits

Eprodisate, a small sulfonated molecule with structural similarity to heparan sulfate, which can cause regression of amyloidosis by destabilising the glycoasaminoglycan backbone of amyloid deposits, delayed progression of renal disease associated with AA amyloidosis (80). In a trial for AA amyloidosis, eprodisate had a beneficial effect on the rate of deterioration of renal function but no effect on urinary protein excretion (80). That eprodisate did not affect SAA levels and preserved kidney function but had no effect on proteinuria raises the interesting possibility that it is the precursors of mature amyloid fibrils are responsible for proteinuria in amyloidosis.

Removal of deposited AA amyloid fibrils

The normal plasma protein SAP binds to all types of amyloid fibrils and contributes to amyloidosis pathogenesis. A pyrrolidine carboxylic acid derivative, which is a competitive inhibitor of SAP binding to amyloid fibrils, can intervere in this process and affect SAP levels. This compound cross-linked and dimerised SAP molecules, which led to extremely rapid clearance by the liver, and thus produced marked depletion of circulating human SAP. This drug action thus removed SAP from human amyloid deposits in tissues and may have a favourable effect on amyloidosis (81).
Another compound, dimethyl sulfoxide (DMSO), is a hydrogen-bond disrupter, cell-differentiating agent, hydroxyl radical scavenger, cryoprotectant, and solubilising agent that is used as a compound for preparation of samples for electron microscopy, as an intracellular low-density lipoprotein-derived cholesterol-mobilising antidote to extravasation of vesicant anticancer agents, and as a topical analgesic. A notable DMSO side effect is garlic-like breath odor and taste in the mouth because of pulmonary excretion of a small amount of DMSO as dimethyl sulfide (82). Oral DMSO was effective against AA amyloidosis, especially GI involvement and early renal dysfunction (83), but using it would not likely be feasible in current clinical practice.

Treatment of organ failure

The predominant feature of AA amyloidosis is proteinuria with or without renal failure. If conservative treatment of renal failure is not sufficient, renal replacement therapy including renal transplantation, continuous ambulatory peritoneal dialysis, or haemodialysis (HD) should be considered. Even in RA patients with AA amyloidosis who undergo HD, anti-TNF-α blockers can demonstrate efficacy (84, 85). HD reportedly had no effect on plasma etanercept concentration, and etanercept pharmacokinetics in patients undergoing HD for chronic renal failure were similar to those with normal renal function (86). Administration of etanercept to HD patients would therefore appear reasonable.

6. Biological diversity and significance of SAA

The life expectancy of patients with RA has been estimated to be 1.2 to 1.7 times worse than that of the general population (87). Complications involving AA amyloidosis may further reduce life expectancy in such patients. Treatment-related clinical remission in RA may lead to structural and functional remissions, which will result in a better quality of life. SAA has biologically diverse and significant roles in health and disease (Fig. 2). Thus, SAA may modify progression of disease – either AA amyloidosis (high-grade inflammation) or metabolic syndrome (low-grade in-

Table IIa. Effect of etanercep on RA inflammation and AA amyloidosis.

Parameter	Initial-visit	Last-visit	*p*-value
RA inflammation (n=14)			
DAS28-ESR	5.99 ± 0.69	2.99 ± 0.15	<0.01
CRP (mg/dl)	4.68 ± 0.87	0.48 ± 0.29	<0.01
AA amyloidosis (n=14)			
SAA (μg/dl)	250 ± 129	26 ± 15	<0.01
Proteinuria (g/day)	2.24 ± 0.81	0.57 ± 0.41	<0.01
Creatinine (mg/dl)*	2.54 ± 1.38	2.50 ± 2.21	0.896

RA: rheumatoid arthritis; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AA: amyloid A; SAA: serum amyloid A protein; *serum levels.

Table IIb. Effect of etanercept on serum creatinine levels in patients with mild RA disease and renal dysfunction*.

Values lower than 2.0 mg/dl (n=6)		Values higher than 2.0 mg/dl (n=8)	
Initial-visit (mg/dl)	Last-visit (mg/dl)	Initial-visit (mg/dl)	Last-visit (mg/dl)
1.37 ± 0.49	1.07 ± 0.59	3.43 ± 1.14	3.56 ± 2.39
a)		b)	

a) p=0.021; b) not significant.
*Although Table IIa shows that the change in serum creatinine value was not statistically significant, using a cutoff value of less than 2.0 mg/dl at the initial-visit demonstrated that the creatinine value improved significantly at the last-visit; for an initial value higher than 2.0 mg/dl, the last-visit value increased.

flammation) – via its biological actions (88, 89). Alleviated inflammation and improved nutritional metabolism would lead to suppression of cardiovascular events and would reduce the incidence of AA amyloidosis in RA. Elucidation of the biological diversity and significance of SAA should enhance understanding of the pathophysiology of AA amyloidosis secondary to RA.

7. Issues that require further perspective

Important issues of future interest that are related to AA amyloidosis secondary to RA include the following: i) tight control of inflammation occurring with underlying RA; ii) factors associated with the risk of AA amyloidosis, such as SAA1.3 allele, which indicates a genetic predisposition to the disease; and iii) screening tools for AA amyloidosis for use even during the subclinical phase. The mechanisms of AA amyloid fibril formation are complicated pathways involving multiple factors, as Figure 1 shows, and elucidation of mechanisms on both deposition and turnover of AA amyloid fibrils should allow development of novel therapeutic options. Reducing the supply of amyloidogenic precursors is usually associated with reabsorption of AA amyloid deposits and perhaps recovery of target organ function. Because AA amyloid fibril shows heterogeneity in organ deposition, clarification of the affinity of AA amyloid fibrils to various organs is needed. Addressing the involvement of various organs and systems – renal, GI, cardiac, thyroid, and autonomic nervous (90) – may permit development of therapeutic countermeasures against complications.

Conclusion

Although significant advances have been made in understanding of the pathology, pathogenesis, and clinical treatment of AA amyloidosis secondary to RA, the disease is still an important complication that warrants investigation. The SAA1.3 allele serves not only as a risk factor for AA amyloidosis but also as a factor related to poor prognosis and shortened survival of Japanese patients with RA, and understanding both disorders would benefit from investigation of the SAA1.3 allele. AA amyloidosis secondary to RA is now clearly influenced by many variables, and clinical pictures differ among patients. The pathological process in RA patients with AA amyloidosis seems to be more complicated and subtle than previously realised. Clarification of the formation and degeneration or turnover of AA amyloid fibrils and elucidation of the biological contributions of SAA in health and disease are indispensable prerequisites to the management of AA amyloidosis secondary to RA.

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