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REVIEW ARTICLE

Clinical strategies for amyloid A amyloidosis secondary to rheumatoid arthritis

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Abstract Secondary amyloid A (AA) amyloidosis is an important complication of rheumatoid arthritis (RA) and has remarkable variation in frequency worldwide. It is a serious, potentially life-threatening disorder caused by deposition in organs of AA fibrils, which are derived from the circulatory, acute-phase-reactant, serum amyloid A protein (SAA). The SAA1.3 allele can serve not only as a risk factor for the association of AA amyloidosis but also as a poor prognostic factor in Japanese RA patients. Both the association of AA amyloidosis arising early in RA disease course and symptomatic variety and severity were found in amyloidotic patients carrying the SAA1.3 allele. Etanercept for patients with AA amyloidosis who carry the SAA1.3 allele showed the amelioration of rheumatoid inflammation, including marked reduction of SAA and improvement of renal function. In light of the SAA1.3 allele significance in Japanese RA patients, both a tight control by disease-modifying antirheumatic drugs and an early intervention of biologics for RA inflammation should be applied to suppress acute-phase response, thus preventing the association of AA amyloidosis. It is suggested that SAA plays not only an important role in the development of AA amyloidosis but also interacts with events closely involved in metabolic syndrome as a high- and low-grade inflammatory modulator, respectively.

Keywords AA amyloidosis · SAA · SAA1.3 allele · Rheumatoid arthritis

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Introduction

Amyloidosis is a disease complex of protein-folding disorders in which normally soluble proteins become abnormal, insoluble amyloid fibrils, leading to deposition in extracellular matrix and damaging the structure and function in tissues and organs [1]. The disease involves amyloid fibrils conformed in vivo by more than 20 different types of protein [2]. Amyloidosis is clinically classified into several types depending on the precursor of amyloid fibril. Amyloid A (AA) fibrils originate from an *N*-terminal cleavage fragment of serum amyloid A protein (SAA), an acute-phase reactant [3]. A major factor responsible for the development of AA amyloidosis is increased synthesis and subsequent degeneration of SAA under chronic inflammatory conditions. Therefore, sustained overproduction of SAA is a prerequisite for the development of AA amyloidosis. AA amyloidosis is a rare but serious complication of diseases that stimulate a sustained and substantial acute-phase response, and foremost is rheumatoid arthritis (RA).

RA generally begins with an inflammatory disease in synovial joints, and it also has marked systemic effects leading to impairment of activities of daily living through joint dysfunction caused by persistence of destructive arthritis. The prevalence of RA is about 0.6% in Japan, and the number of RA patients is estimated to be more than 700,000 including RA-related diseases. The pathophysiology of RA is noninfectious chronic synovitis with autoimmune abnormalities closely involved in the disease condition. Articular lesions are major symptoms in the early course of the disease. However, according to the disease progression, lesions complicate systemic organs, including lungs, kidneys, heart, nervous system, and so on [4–6]. AA amyloidosis is one of the intractable states associated with

RA and as such is a serious, potentially life-threatening disorder with poor prognosis and survival [7].

This review article discusses current concepts in AA amyloidosis secondary to RA, and in the light of clinical management, the strategies on prophylaxis, diagnosis, and therapy of this rare but important complication are addressed.

Pathogenesis of AA amyloidosis secondary to RA

RA is a representative of collagen vascular diseases, a group of systemic chronic progressive inflammatory disorders based on immunological disharmonies. Typically, AA amyloidosis occurs in patients who have sustained, long-standing, active disease [8]. Therefore, AA amyloidosis may not be suspected during the early course of a potential chronic or recurrent inflammatory disease. In rare cases, however, it may occur within a year of a clinically apparent inflammatory disease [9, 10]. AA amyloidosis does not occur in the absence of an acute-phase response or without elevated serum SAA levels. SAA synthesis and secretion by hepatocytes is mediated by cytokines, mainly interleukin (IL)-1, tumor necrosis factor (TNF)-α, and IL-6 [11], and SAA rises up to 1,000 times its baseline level [12]. These cytokines generate a systemic acute-phase response, thereby inducing SAA synthesis and facilitating AA amyloidosis development. The progressive nature of AA amyloidosis largely reflects the persistent nature of the activity of the underlying conditions [13], and due to fluctuations of disease activity, not all patients show evidence of an acute-phase response at the very time of diagnosis [14]. Although it is still unknown exactly how the pathophysiological functions of SAA are associated with the pathogenesis of AA amyloidosis, there appears to be a certain subset of patients in whom SAA is prone to proceed into AA fibrils under different factors, such as proteases, proteoglycans, and serum amyloid P component [15].

Genetic factors in AA amyloidosis secondary to RA

Genetic factors seem to be involved in the prevalence and prognosis, and some factors seem to have an influence on the development and length of the latent period, of AA amyloidosis secondary to RA.

SAA in humans is a family of homologous proteins containing three subtypes of SAA with different primary structures, SAA1, SAA2, and SAA4, which are divided into two groups. The first group comprises well-known acute-phase proteins, SAA1 and SAA2, which are synthesized mainly by hepatocytes in response to inflammatory cytokines and are transported into serum by high-density lipoprotein (HDL) particles [16, 17]. The vast majority of human AA proteins isolated from amyloid deposits are derived from SAA1 [18]. The second group of SAA is expressed constitutively in plasma, and SAA4, which is not an acute-phase protein, is synthesized by different organs and tissues. The SAA genes are clustered, and all map to the short arm of chromosome 11p15.1. Four genes have been identified encoding SAA. Induction of *SAA1* and *SAA2* and their expression are induced by inflammation. *SAA3* is a pseudogene, and *SAA4* encodes the structural protein of HDL; the expression of these latter two genes is not induced by inflammation [14]. Due to allele polymorphism, there are three isoforms of SAA1 (SAA1.1, SAA1.3, and SAA1.5) and two isoforms of SAA2 (SAA2.1 and SAA2.2) [19, 20] (Fig. 1). Serum level is affected by SAA1 polymorphism, but the primary structure has a 90% or more homology between SAA1 and SAA2 [21].

In Japanese RA patients, the SAA1.3 allele has been reported to be associated with increased risk of AA amyloidosis and SAA1.1 with decreased risk [22, 23], whereas SAA1.1 was revealed to be a risk factor for developing AA amyloidosis in a white population [24]. An adequate explanation of the discrepancy has not yet been provided.

More recent reports evaluated another single nucleotide polymorphism in *SAA1*, *T-13C*, and the allele of *SAA-13T* was shown to be a risk factor for AA amyloidosis in both Japanese and white populations [25, 26]. However, little information has been available regarding linkage disequilibrium between these polymorphisms of SAA1, and their impacts on the onset of AA amyloidosis have not been fully investigated. In addition, previous works between SAA1 polymorphism and the prevalence of AA amyloidosis in RA patients have been largely reported in case-control studies [27].

Besides SAA1 polymorphism, the most extensively studied genetic marker in RA is major histocompatibility complex, class II, DRB1 (HLA-DRB1) [28, 29]. Several HLA-DRB1 alleles share a common amino acid sequence, which is commonly called the shared epitope (SE), in the third hypervariable region of the molecule. Recently, it was reported that SE associates with not only disease susceptibility of RA but also with RA chronicity, severity, and extra-articular manifestations, in particular, AA amyloidosis, in RA patients [30, 31]. It is of particular importance that DRB1*04SE has an increased risk of AA amyloidosis in RA [32], and a higher prevalence of double *04SE of HLA-DRB4 is demonstrated in patients with AA amyloidosis secondary to RA [33].

SAA1.3 allele and AA amyloidosis secondary to RA

Abundantly synthesized SAA under chronic inflammatory conditions gives rise to insoluble aggregates of SAA

Isoform	N-terminus	1	2	....	52	..	57	..	60	..	68	69	...	71	72	...	84	...	90	....	104
SAA 1.1		Arg	Ser		**Val**		**Ala**		Asp		Phe	Phe		His	Gly		Glu		Lys		Tyr
1.3		Arg	Ser		**Ala**		**Ala**		Asp		Phe	Phe		His	Gly		Glu		Lys		Tyr
1.5		Arg	Ser		**Ala**		**Val**		Asp		Phe	Phe		His	**Asp**		Glu		Lys		Tyr
SAA 2.1		Arg	Ser		Ala		Ala		Asn		Leu	Thr		**His**	Gly		Lys		Arg		Tyr
2.2		Arg	Ser		Ala		Ala		Asn		Leu	Thr		**Arg**	Gly		Lys		Arg		Tyr
SAA 3		**Absence due to pseudogene**																			
SAA 4		**Constitutional protein of HDL**																			

Fig. 1 Isoforms of SAA subset. SAA1 and SAA2 are acute-phase proteins. Induction of *SAA1* and *SAA2* and their expression are induced by inflammation. *SAA3* is a pseudogene, and *SAA4* encodes the structural protein of HDL, and the expression of these genes is not induced by inflammation. *HDL* high-density lipoprotein. *Bold* amino acid differences

derivatives in multiple organs, resulting in AA amyloidosis—a consequence of RA. The poor prognosis associated with AA amyloidosis is due in part to failure to establish a diagnosis before organ damage has occurred and to the lack of effective means for prevention or cure for AA amyloidosis.

Predictive and prognostic factor of SAA1.3 allele genotype

Whereas there is startling variation in the frequency of AA amyloidosis worldwide, differences also exist for AA amyloidosis complicating RA. The reasons, however, for the marked geographic differences are still unclear [15]. SAA1 gene polymorphism varies greatly among different districts or races. The frequency of SAA1 genotype and the alternative allele differs among Japanese, Chinese, and white Australians, and the frequency of SAA1.1 allele for white Australians is higher than for other races. The frequency of the SAA1.3 allele is about 40% for Japanese, whereas it is much lower for whites [25]. In addition, a closer relationship between the SAA1.3 allele and AA amyloidosis secondary to RA is known [22], which is considered to be one of the factors responsible for the lower incidence of AA amyloidosis among Western patients with RA [15].

The mean life expectancy for RA patients is about 10 years shorter than that for the population in general [34], and it can be further shortened when associated with AA amyloidosis [35]. Though AA amyloidosis usually develops more than 10 years after the onset of RA, one RA patient complicated by severe AA amyloidosis encountered just 1 year after RA onset was proven to be an SAA1.3 homozygote [10]. Subsequent statistical analysis of a large number of RA patients with AA amyloidosis carrying the SAA1.3 allele revealed that the risk for association of AA amyloidosis was about eight times higher for SAA1.3 homozygotes than for the control group and that homozygotes can develop AA amyloidosis very early after RA onset [36]. It was thus shown that the SAA1.3 allele serves not only as a risk factor for the association with AA amyloidosis but also as a poor prognostic factor in Japanese patients with AA amyloidosis secondary to RA [37].

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SAA1.3 homozygosity in RA with AA amyloidosis were 50%, 83%, 61%, and 76%, respectively. Also, sensitivity, specificity, PPV, and NPV of the SAA1.3 allele in RA with AA amyloidosis were 79%, 51%, 45%, and 82%, respectively [37]. Therefore, the generalization of the importance of the SAA1.3 allele as both a risk and a poor prognostic factor may be limited for several reasons: lack of wide-range control studies, ethnic differences in SAA gene polymorphism, relative small number of patients with AA amyloidosis, and heterogeneity in RA and healthy controls. Although a crude agreement of the significance of the SAA1.3 allele in AA amyloidosis in Japanese RA patients is recognized, a careful and discreet attitude is necessary when judging the utility in between the SAA1.3 allele and AA amyloidosis.

Clinical diversity and severity

It is suggested that the SAA1.3 allele genotype could be related to the symptomatic diversity and severity in patients with AA amyloidosis secondary to RA. Amyloidotic involvement of the urinary bladder is very rare but severe, which often reveals massive macroscopic hematuria [38]. Once massive hematuria occurs, it tends to be fatal. Secondary bladder AA amyloidosis should be considered a possible cause of hematuria in patients with long-standing RA, especially those carrying the SAA1.3 allele, and as an important prognostic factor of RA [39].

Clinical features of AA amyloidosis secondary to RA

Prevalence

Though the subclinical phase of AA amyloidosis is defined by the formation of amyloid deposits in tissue without any clinical manifestation, it is very hard to distinguish the clinical from the subclinical phase. 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 a cohort study of patients with RA, it showed that fat AA fibril depositions are not uncommon (16.3%) [40]. It has been estimated that subclinical AA amyloidosis might be common in RA [41, 42]. The prevalence rates of AA amyloidosis in RA patients in recent series to detect amyloid deposits range from 7% to 26% [43–45]. In contrast, the prevalence of clinical amyloidosis is likely to be lower [46–48]. Taking the discordance between prevalence rates of clinical and subclinical AA amyloidosis into consideration, the wide variation in the prevalence of AA amyloidosis secondary to RA is due in part to the frequency for the marked geographic differences worldwide, possibly including genetic factors, and to the lack of unified statistical studies for AA amyloidosis between races and districts. That seems indicate that AA amyloidosis is associated with RA more than so far estimated.

Outcome

Survival after the diagnosis of AA amyloidosis secondary to RA seems to be 4–5 years [49, 50]. This is, of course, dependent on the time at which AA amyloidosis is verified, which may differ considerably [51]. This partly explains the great individual variation in survival time observed, which leads the notion that an active diagnostic attitude toward AA amyloidosis in patients with RA is advisable. Although the relationship among the production of AA precursor protein, the turnover of AA fibrils, and amyloidotic organ function is complex, it has been proved that outcome is favorable in AA amyloidosis when SAA concentration is maintained below 10 μg/ml [52]. The clinical risk factors associated with a poor survival included female gender [53], older age, reduced serum albumin, and increased serum creatinine concentration upon diagnosis of AA amyloidosis [37]. Renal involvement has been considered to be the most critical problem in patients with AA amyloidosis [34, 49], and it dominates the clinical picture in AA amyloidosis [8].

Amyloidotic cardiac involvement has been shown to be a poor prognostic factor [35, 37]. Heart failure is likely to be directly responsible for death in only a minority of patients. However, patients with heart failure may be complicated by multiple organ failure in the later phase of the RA disease course [41]. It seems to be suggested that dysautonomia plays an important role in the etiology of heart failure to some extent in patients with AA amyloidosis in addition to direct amyloid deposits in situ [54]. Although reports published to date concerning AA amyloidosis and autonomic nerve dysfunction in patients with RA are extremely rare, taking into account the importance of cardiovascular symptoms of dysautonomia, which could induce sudden death in AA amyloidosis secondary to RA, autonomic nerve dysfunctions may serve as one of the clinical predictors of poor prognosis in RA. Dysautonomia, such as abnormal gustatory sweating and orthostatic hypotension, seems to be one of the typical symptoms in the end stage of the disease course in RA patients with AA amyloidosis [55].

Causes of death

Infection and renal failure are generally the commonest causes of death in RA patients with AA amyloidosis [34, 41, 49], and they comprise 42.3% and 19.2% of deaths, respectively [37]. A higher risk of severe infections is a substantial problem in the management of RA with AA amyloidosis. Also, the higher causal proportion of renal failure and gastrointestinal (GI) diseases than in RA patients without AA amyloidosis [37] can be attributable to more AA fibril deposition in these organs.

Clinical strategies for AA amyloidosis secondary to RA

Precise definition of the role of the SAA1.3 allele in predicting risk for the onset of AA amyloidosis in RA patients and establishment of a realistic method for clinical utilization of such knowledge will lead to clear perspectives for the treatment of AA amyloidosis. In view of the clinical significance of AA amyloidosis, there is an urgent need to facilitate studies into this complication of RA. Early diagnosis and intervention are essential for RA. However, few specific features are useful to diagnose RA, and its diagnosis is often difficult in daily RA practice. Reducing SAA load is the most rational approach, as it arrests further deposition. Also, amyloid deposits may regress at a low rate over a period of years [56] and exist in a sate of dynamic turnover [52]. Clinical strategies for AA amyloidosis secondary to RA are outlined in Table 1.

Prevention

Preventing AA amyloidosis secondary to RA obviously is the primary aim. The decreasing of AA amyloidosis

Table 1 Clinical strategies in the management of AA amyloidosis secondary to RA

Prevention
(1) Attempt not to stimulate AA amyloidosis
(2) Do not increase the serum levels of SAA
(3) Control fully rheumatoid inflammation
(4) Carefully follow RA patients carrying the SAA1.3 allele
Diagnosis
(1) Do not overlook proteinuria
(2) Evaluate renal function by serum creatinine, cystatin C, and Ccr levels
(3) Watch GI tract symptoms
(4) Strive to detect AA fibrils by GI tract, gingival biopsy, and subcutaneous fat aspiration
(5) Require renal biopsy in cases with proteinuria or renal dysfunction in RA patients
Therapy
(1) Control acute-phase response to suppress SAA synthesis
(2) Control RA disease activity tightly
(i) DMARDs: MTX as the anchor drug
(ii) Immunosuppressants: CYC as the alkylating agent
(iii) Eprodisate: antiamyloid compounds
(iv) Biologics: etanercept, even in patients undergoing HD
(3) Steroid, codeine phosphate, lactate bacteria, and especially octreotide for refractory diarrhea
(4) Stand on the notion of deposited AA fibrils existing in a state of dynamic turnover

AA amyloid A, *RA* rheumatoid arthritis, *SAA* serum amyloid A protein, *Ccr* creatinine clearance, *GI* gastrointestinal, *DMARDs* disease-modifying antirheumatic drugs, *MTX* methotrexate, *CYC* cyclophosphamide, *HD* hemodialysis

incidence clearly indicates the supreme value of prevention by adequately treating inflammatory activity of RA. Further efforts should be directed to find therapies for early and radical recovery from AA amyloidosis. A paradigm shift in RA therapies within the window of therapeutic opportunity would bring about clinical remission of AA amyloidosis [57]. Convalescence will result in abolishing the accompanying acute-phase response and thereby preventing the development of AA amyloidosis [58]. In light of the importance of the SAA1.3 allele in patients with AA amyloidosis secondary to RA [37], it is emphasized that RA patients carrying the SAA1.3 allele should be followed up carefully.

Diagnosis

Proteinuria is the clinical sign that most often leads to the diagnosis of AA amyloidosis in RA patients. The diagnosis must be based on histological examination of tissue specimens, and upper GI or rectal biopsy is helpful [45]. Although the detection sensitivity of AA fibrils is lower compared with the former tools, in RA patients with advanced bone destruction in cervical vertebrates or jaw joints, fine-needle biopsies of subcutaneous fat and gingival specimens are useful and easily obtained [40, 42, 44]. When clinical features raise suspicion for AA amyloidosis, routine screenings by tissue biopsy should be undertaken with informed consent. The presence of AA fibrils should be histochemically confirmed by positive Congo-red staining, susceptibility to oxidation treatment with potassium permanganate, and green birefringence on polarization microscopy after Congo-red staining [59]. The biopsy on screening for deposition of AA fibril in the upper GI mucosa is an easy and simple diagnostic measure. However, it is possible that a multitude of protective administration with antiulcer drugs may mask amyloidotic symptoms in the GI tract, which could delay AA amyloidosis diagnosis in RA patients.

Therapy

The principal aim in treating RA patients with AA amyloidosis is to switch off the production of SAA by controlling the RA inflammatory process. However, whether an effective treatment exists and specific therapies are warranted for AA amyloidosis remains controversial. In recent years, novel antirheumatic drugs, including biologics, have been shown to be highly effective in controlling inflammatory activity and joint destruction [60]. It is important to identify patients with poor prognosis at a stage when it may be possible to alter the disease process and in whom immunosuppressive treatment may be justified. The presence of the SAA1.3 allele in RA patients could be a hallmark for tight control of RA inflammation under vigorous treatment during the early phase of RA disease course [61].

Traditional management of AA amyloidosis has been to target RA disease processes behind the inflammation.

There have been encouraging reports evaluating alkylating agents as beneficial in clinical trials in RA patients with AA amyloidosis [62–64]. It is suggested that the use of immunosuppressive agents can improve prognosis [65–67], and cyclophosphamide (CYC) has proved to be superior to methotrexate (MTX) in treating RA patients with AA amyloidosis [37]. Eprodisate is a new class of antiamyloid compounds for treating AA amyloidosis, which results in a significant delay in progression to hemodialysis (HD) or end-stage renal disease in AA amyloidosis [68, 69].

TNF-α antagonists have emerged as a highly effective approach for inducing rapid and sustained clinical remission in RA [70, 71], and a few cases with favorable outcomes in AA amyloidosis have been reported [72–77]. Recently, it was demonstrated that a humanized anti-IL-6 receptor antibody has an excellent ability to suppress SAA levels [78]. The rationale for using biologics in AA amyloidosis stems from the fact that they lower serum proinflammatory cytokines that regulate SAA synthesis. The efficacy and safety of etanercept have been reported in a retrospective study for patients with AA amyloidosis secondary to RA who carry the SAA1.3 allele [79]. It is possible to use etanercept to treat RA patients with AA amyloidosis, even those undergoing HD. As RA patients with AA amyloidosis carrying the SAA1.3 allele are likely to show poor prognosis and outcome [37], it is desirable to carefully follow-up these patients to diagnose AA amyloidosis as early as possible and thus start etanercept to slow down disease progression.

For RA patients complaining of severe diarrhea due to AA amyloidosis, corticosteroid, codeine phosphate, and lactate bacteria are useful. In remarkable protein losing enteropathy with intractable diarrhea due to AA amyloidosis, a successful treatment that combines somatostatin analogue octreotide and corticosteroids has been reported [80, 81].

Effective control of RA inflammation is expected to suppress its association with AA amyloidosis [82–84]. Taking medicoeconomic factors into consideration, primarily involving MTX as an anchor drug, we can expect that efficacy of biologics reduces the incidence of AA amyloidosis in RA. Under tight control in the management of RA, new strategies will provide the opportunity to aim for low disease activity and even remission [85]. What roles we can expect of the SAA1.3 allele and how we can utilize it for treatment are open questions requiring resolution in order to cultivate a perspective for a bright future in the management of AA amyloidosis secondary to RA (Fig. 2).

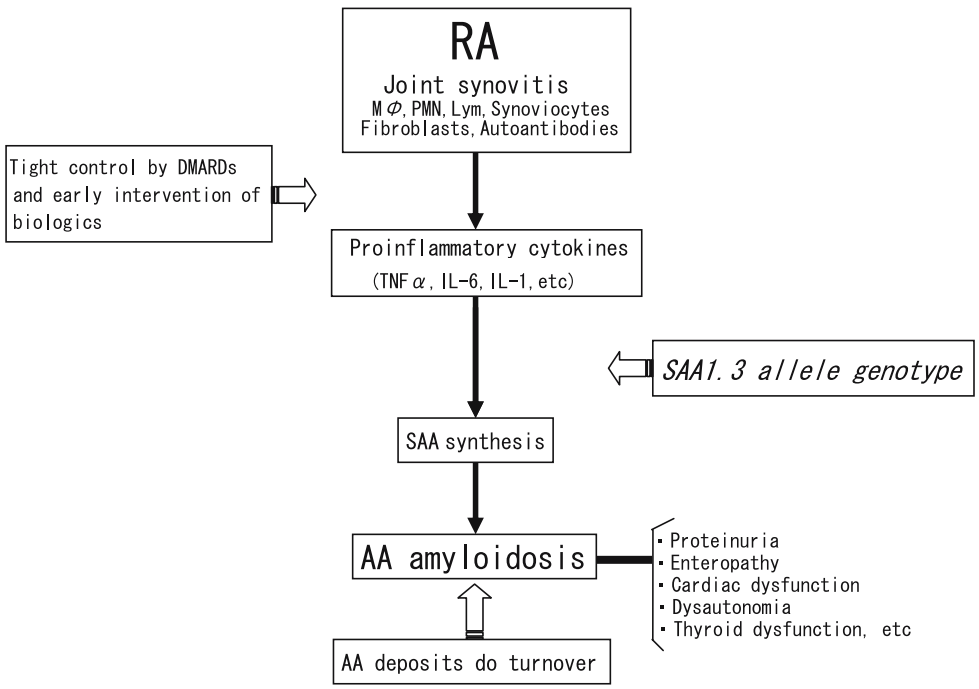

Fig. 2 Management stratagems for amyloid A (AA) amyloidosis secondary to rheumatoid arthritis (RA). RA begins with joint synovitis, and serum amyloid A protein (SAA) is synthesized in the liver chiefly by the stimulus of proinflammatory cytokines. Tight control and early intervention are important to suppress the acute-phase response by controlling RA inflammation. The SAA1.3 allele genotype is a clinical hallmark in practice. Continuous efforts must be applied to slow down rheumatoid activity. It is important to understand the notion that deposited AA fibrils reside within a state of dynamic turnover. *Mϕ* macrophages, *PMN* polymorphonuclear leukocytes, *Lym* lymphocytes, *DMARDs* disease-modifying antirheumatic drugs, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6, *IL-1* interleukin-1, *SAA1.3* one of the SAA1 gene polymorphism

Perspectives of AA amyloidosis through SAA

When arguing AA amyloidosis secondary to RA, the pathophysiological roles of SAA cannot help being discussed as the precursor of AA fibrils. SAA is a type of apoprotein; once released to the circulation, the newly synthesized SAA is incorporated into HDL [86], thus altering HDL metabolism and cholesterol transport [87]. As HDLs play the central role in the back transport of cholesterol from body cells to liver, SAA is closely correlated with lipid metabolism. Also, SAA is likely to be strongly involved in metabolic syndrome characterized by a chain of abnormalities such disturbed glucose metabolism, visceral obesity, hypertension, hypertriglyceridemia, and hypo-HDL-cholesterolemia [88]. The actual role of SAA in relation to metabolic syndrome should be clarified from the point of view of not only the precursor protein in AA amyloidosis, but also of the mediator in atherosclerosis and atherogenesis [89, 90]. Namely, SAA is suggested to play an important role both in the development of AA amyloidosis and in the induction of metabolic syndrome, as a high- and low-grade inflammatory modulator, respectively. Similarly to proinflammatory cytokines, SAA can induce leukocyte synthesis and secretion of some cytokines and attract leukocytes into the inflammatory foci [91]. It is very interesting that SAA binding to human fibroblast-like synoviocytes contributes to destruction of bone and cartilage *via* the promotion of synoviocyte hyperplasia and angiogenesis [92]. As the phenomena of both synovial hyperplasia and endothelial cell proliferation are pathological hallmarks of RA, SAA will provide a potential target for the control of not only RA but also of AA amyloidosis. SAA amyloidogenesis has not been fully elucidated as yet, including the relationship between SAA polymorphism and AA amyloidosis.

Conclusion

Because the SAA1.3 allele serves not only as a risk factor for the association of AA amyloidosis but also as a poor prognostic factor in survival for Japanese patients with RA, it is important to keep the genetic factor in mind when treating RA patients. However, it is now clear that AA amyloidosis secondary to RA is multifactorial and influenced by many variables and that clinical pictures differ among patients. The pathological process of AA amyloidosis in RA patients is likely to be much more complicated and subtle than so far imagined. Although we do not really know yet which clinical variables are indispensable prerequisites for the onset of AA amyloidosis, we have multiple therapeutic options for tight control of RA and AA amyloidosis. Current concepts in recognition and treatment stratagems of AA amyloidosis secondary to RA have been stated from the point of the clinical view of the SAA1.3 allele.

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