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Chapter 9

Developments in the Treatment of Amyloid A Amyloidosis Secondary to Rheumatoid Arthritis

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Abstract

Amyloidosis refers to a heterogeneous group of diseases in which a soluble precursor, misfolded protein, and subsequently aggregates into highly structured protein fibrils with a cross-β-pleated structure. Of these diseases, amyloid A (AA) amyloidosis is a complication of long-standing inflammatory diseases such as rheumatoid arthritis (RA). Treatment of this amyloidosis with RA aims to stop serum AA protein production. Immunosuppressants have reportedly been useful for both RA inflammation and AA amyloidosis. Also, biologics are effective for these specific pathological processes by targeting key players in each inflammation. In addition to the above-mentioned medications, agents both inhibiting AA fibrillogenesis and destabilizing AA fibrils have recently been employed. Phagocytes play important roles in the regression of AA fibrils. Renal involvement is the most common complication in AA amyloidosis. Peritoneal dialysis, hemodialysis, and even renal transplantation are available for patients with end-stage renal disease and AA amyloidosis. This chapter thus discusses current developments in the treatment of AA amyloidosis secondary to RA.

Keywords: AA amyloidosis, rheumatoid arthritis, *SAA1.3* allele, biologics, fibrinolysis

1. Introduction

Amyloidosis is a rare disorder in which extracellular amyloid fibrils are deposited in various tissues. Those fibrils derive from the misfolding of precursor proteins, the result being multiple organs dysfunction. Systemic amyloidosis is thus characterized by failure of all sorts

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of organs and the presence of amyloid precursor protein in the serum. Reactive amyloid A (AA) amyloidosis is one of the most severe complications of a number of chronic disorders, especially rheumatoid arthritis (RA); most patients with this amyloidosis have an underlying rheumatic disease. AA amyloidosis, an extra-articular complication of RA, is a serious disorder, possibly life-threatening, that is caused by deposition in multiple organs of AA amyloid fibrils which originate from the circulatory acute-phase reactant, serum amyloid A protein (SAA) [1–4].

Both treatment and understanding of the roles of cytokines in RA have resulted in considerable progress. Remarkable advances, which not only provide insight into the pathophysiology of the disease but also aid discovery of new therapies to fight the deadly disease, have recently been made [5, 6]. For example, the introduction of biological therapies targeting specific inflammatory mediators revolutionized RA treatment. Focusing on essential components of the immune system allows effective suppression of the pathological inflammatory cascade that produces RA symptoms and the resulting joint destruction [7–10]. Several new biologics may permit AA amyloidosis secondary to RA to become a treatable, even manageable, disease. Furthermore, that the allele *SAA1.3* is not only a univariate predictor of survival but also a risk factor for the association of AA amyloidosis with RA in Japanese patients is very interesting [11].

Patients with RA, who have a less-than-optimal response to or cannot tolerate conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [12], such as methotrexate (MTX) [13, 14], are often prescribed biological DMARDs (bDMARDs). Treatment of AA amyloidosis caused by RA seeks to stop SAA production [15]. This approach to AA amyloidosis treatment is the most common and best-studied therapy; it interferes with synthesis of the precursor protein, with the goal of preventing continued amyloid fibril formation. Similarly, cytotoxic immunosuppressants, such as chlorambucil and cyclophosphamide (CYC), have reportedly been useful for both RA inflammation and AA amyloidosis [16–20].

An alternative approach to therapy involves developing drugs to inhibit amyloid fibrillogenesis. One technique targets AA amyloid deposits directly, by destabilizing AA amyloid fibrils so that they cannot maintain their structural configuration. Treatment with the drug (*R*)-1-[6-[(*R*)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC), a novel hexanoyl bis(D-proline), effectively removes the serum amyloid P component (SAP) from plasma but leaves some SAP in amyloid deposits that can then be specific targets of therapeutic IgG anti-SAP antibodies [21]. Also, eprodisate, which binds to glycosaminoglycan-binding sites on AA amyloid fibrils and in theory would destabilize them in tissues, may thereby cause regression of AA amyloidosis [22]. Although the mechanisms by which amyloid deposits are cleared are not well known, they supposedly involve breakdown of amyloid fibrils and associated molecules by macrophages and/or parenchymal cells [23, 24].

This chapter aims to review the advances in the treatment of AA amyloidosis secondary to RA and to describe the latest therapeutic developments based on our reports and literature reviews.

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2. *SAA1.3* genotype and SAA concentration as predictive and prognostic factors of AA amyloidosis outcome

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, which result in two amino acid differences at positions 52 and 57, respectively, [25]. In Japanese people, the three alleles occur approximately at the same frequency. The association between AA amyloidosis and the *SAA1* genotype was first observed in Japanese patients with RA, in whom *SAA1.3* allele homozygosity proved to be a risk factor [26]. The *SAA1.3/1.3* genotype in Japanese patients with RA was related to a shorter latency before the onset of AA amyloidosis and more severe AA amyloidosis-related symptoms [27, 28]. In addition, it was a univariate predictor of survival (**Figure 1**). Thus, the *SAA1.3* allele was a risk factor for AA amyloidosis, was associated with clinical severity of the disease, and poor prognosis [11]. In Caucasians, AA amyloidosis was often found in *SAA1.1* homozygous individuals, and the *SAA1.1* allele was believed to be a risk factor for AA amyloidosis [29]. As for SNPs of the *SAA1* gene promoter region, –13T was found to be a high-risk factor for AA amyloidosis in Japanese patients with RA, and –13T/T and –13T/C were more closely correlated with AA amyloidosis compared with –13C/C [30]. *SAA1* gene polymorphism affects both SAA transcriptional activity in hepatocytes and blood SAA levels, so differences in enzymatic SAA1 proteolysis have demonstrated a close association between *SAA1* gene polymorphism and the onset of AA amyloidosis [31]. However, the mechanism by which *SAA1* gene polymorphism is associated with of AA amyloidosis onset and the reason for ethnic differences in disease-susceptible SNPs are still unknown.

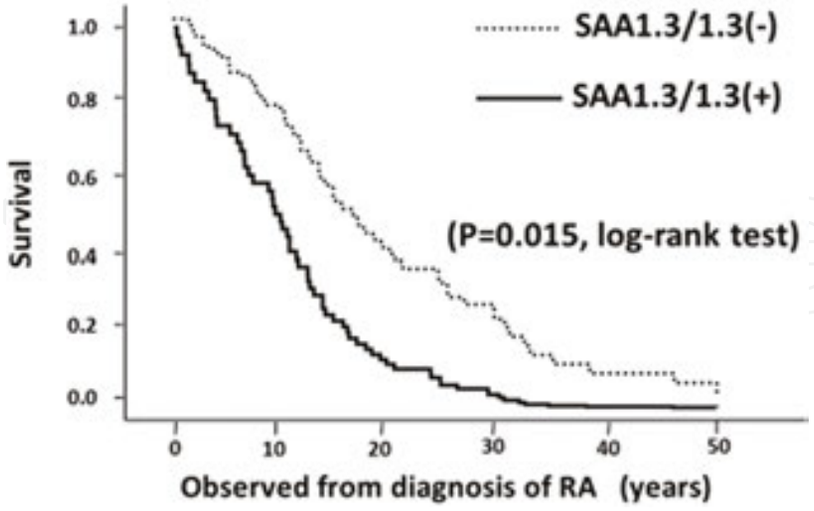


Figure 1. Kaplan-Meier survival curves for RA patients with and without *SAA1.3/1.3*. Statistical analysis of a large number of RA patients with AA amyloidosis who carried the *SAA1.3* allele revealed that the risk for association with AA amyloidosis was about eight times higher for *SAA1.3* homozygotes than for the control group and that homozygotes could develop AA amyloidosis very early after RA onset. Quoted from Nakamura et al. Rheumatology (Oxford) 2006; 45: 43–49.

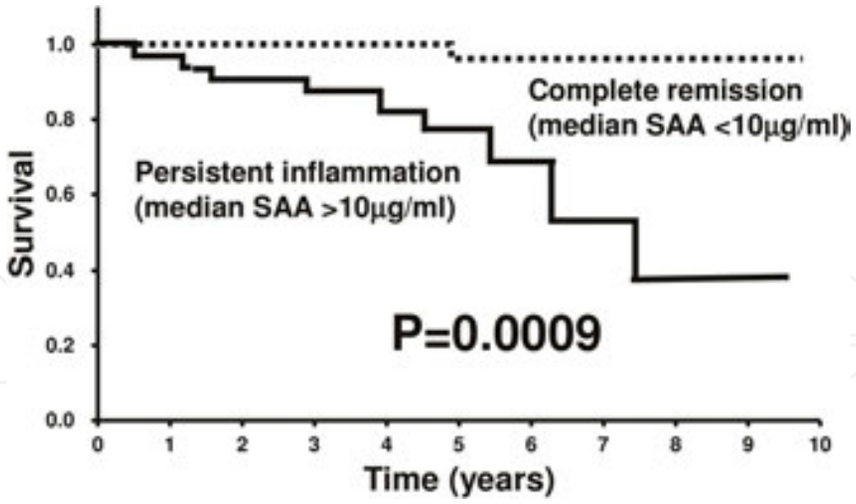


Figure 2. Kaplan-Meier survival curves for patients with systemic AA amyloidosis stratified according to whether the SAA concentration was above or below 10 μg/ml. During follow-up, the proportion of patients with AA amyloidosis who remained alive at 10 years was 90% in the group with median SAA values below 10 μg/ml and 40% in the group with SAA values above that value. Quoted and modified from Gillmore et al. Lancet 2011; 358: 24–29.

The current primary objective of therapy for all forms of amyloidosis was the reduction of the precursor protein supply [32]. In AA amyloidosis, long-term suppression of SAA levels is critical for patient and disease outcomes and for AA amyloidosis in patients with RA. The degree to which SAA concentration increased during follow-up was a strong predictor of outcome [33]. Sustained complete suppression of RA disease activity with the normalization of SAA levels should be the treatment aims in patients with AA amyloidosis, and monitoring the SAA levels is a vital part of patient management (**Figure 2**) [34].

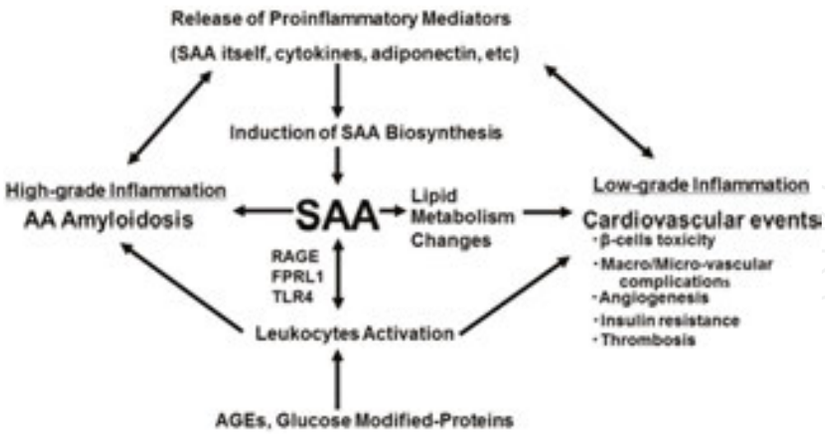


Figure 3. Biological versatility of SAA. SAA has important roles in high-grade and low-grade inflammation. Similar to cytokines, it utilizes autocrine, endocrine, and paracrine mechanisms. SAA, as a precursor protein of AA amyloidosis, induces this amyloidosis. Using different modes of action, SAA also affects metabolic syndrome. These humoral and cellular inflammatory events interact, with SAA as an essential factor. RAGE: receptor for advanced glycation end products; FPRL1: formyl peptide receptor-like 1; TLR2, 4: toll-like receptors 2 and 4; CLA-1: CD36, and LIMPII analogous-1, a human ortholog of the scavenger receptor class B type I (SR-BI); AGEs: advanced glycation end products. Quoted from Nakamura T. Clin Exp Rheumatol 2011; 29: 850–857.

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SAA plays important roles in both high-grade and low-grade inflammation (**Figure 3**) [35]. Similar to cytokines, SAA operates by means of autocrine, endocrine, and paracrine mechanisms. SAA is a precursor protein of AA amyloid fibrils, and it induces AA amyloidosis. SAA also functions in metabolic syndrome by means of different modes of action. As a critical factor in the inflammatory interactions, SAA acts mutually among humoral and cellular events within inflammation.

3. Treatment with conventional synthetic DMARDs for AA amyloidosis secondary to RA

Treatment of patients with RA has focused on using immunosuppressants as conventional synthetic DMARDs (csDMARDs). Although case reports and studies of small series of patients showed that immunosuppressants can reverse nephrotic syndrome [36] and can even lead to complete resolution of proteinuria [37, 38], as **Table 1** shows, management of AA amyloidosis has focused on the RA process causing the inflammation as the underlying disease. We cannot, therefore, determine a clear difference in the effectiveness of therapies for RA and AA amyloidosis.

No. of cases	Diagnosis	Treatment	References
1	RA	CYC	Acta Med Scand 1979; 205: 651
11	RA	CYC/podophyllotoxin/ chlorambucil/ azathioprine	Clin Rheumatol 1987; 6: 27
9	RA	Chlorambucil/CYC	Ann Rheum Dis 1987; 46: 757
1	RA	Chlorambucil	S Afr Med J 1988; 73: 55
4	JIA	Chlorambucil	Pediatr Nephrol 1990; 4: 463
3	RA/JIA	CYC/methotrexate	Medicine (Baltimore) 1991; 70: 246
12	RA/JIA	Chlorambucil/CYC	J Rheumatol 1993; 20: 2051
1	RA	CYC	Clin Nephrol 1994; 42: 30
1	RA	Azathioprine	Arthritis Rheum 1995; 38: 1851
1	RA	CYC	Mod Rheumatol 2000; 10: 160
4	RA	CYC	Arthritis Rheum 2001; 44: 66
15	RA	CYC	Rheumatology (Oxford) 2001; 40: 821
15	RA	CYC	Clin Rheumatol 2003; 22: 371

AA: amyloid A; RA: rheumatoid arthritis; JIA: juvenile idiopathic arthritis; CYC: cyclophosphamide.

Table 1. Reported cases in the treatment for AA amyloidosis secondary to RA/JIA with immunosuppressants.

The efficacy of corticosteroid treatment with regard to AA amyloidosis secondary to RA is still controversial [39]. Corticosteroids can reduce the magnitude of acute phase reactions including synthesis of C-reactive protein (CRP) and SAA. In cultures of human hepatocyte, corticosteroids stimulated SAA production but not CRP production. Although corticosteroids reduced SAA and CRP levels in longitudinal studies of patients with RA, the effect was somewhat greater for CRP than for SAA [40]. Growing evidence suggests that SAA is sensitive to change, achieves much higher levels than CRP, declines rapidly, and may therefore accurately reflect disease activity. The advantages of SAA as a biomarker of disease activity include the rapid production and exceptionally wide dynamic range of the inflammatory response. During acute inflammation, serum SAA levels may rise up to 1000-fold and the biologic half-life of SAA levels are significantly shorter than that of CRP [41]. Monitoring SAA instead of CRP levels would thus be advisable, especially if corticosteroids are used. Treating patients with AA amyloidosis secondary to RA using cytotoxic drugs either alone or together with prednisolone, which is a synthetic glucocorticoid and a cortisol derivative, seems reasonable [42]. Because the effect of immunosuppressants may require weeks or months to be obvious, giving steroids in addition to immunosuppressants is recommended to ensure an immediate reduction in the acute phase response and, in particular, SAA synthesis [43].

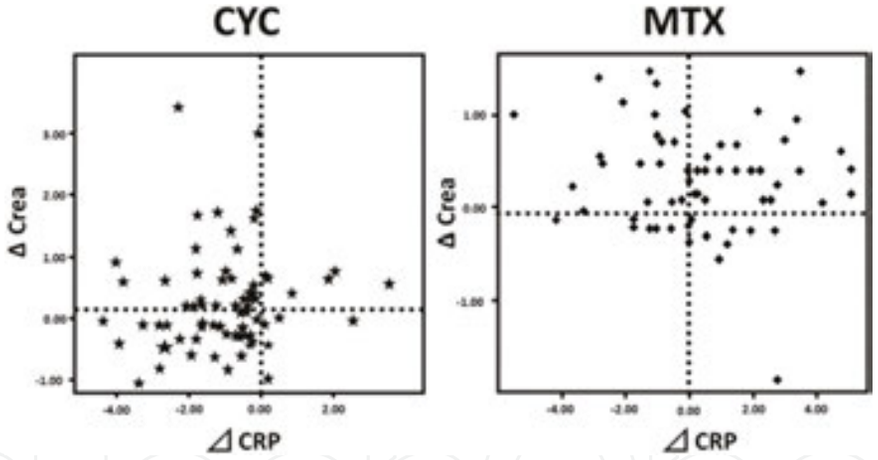


Figure 4. Differences between CYC and methotrexate (MTX) treatments in RA patients with AA amyloidosis. The deducted value (in the figure) was determined by subtracting the starting CRP and serum creatinine values from the corresponding ending values in each treatment. Quoted from Nakamura et al. Rheumatology (Oxford) 2006; 45: 43–49.

Although no evidence is available that csDMARDs have a particular effect on amyloidogenesis and AA amyloidosis in RA, reports provided encouraging description of the beneficial results of alkylating agents in clinical trials in RA patients with AA amyloidosis [44–46]. Using immunosuppressive agents may improve prognosis, and CYC has proved to be superior compared with methotrexate (MTX) for the treatment of RA patients with AA amyloidosis (**Figure 4**) [11]. Because between before and during CYC treatment, the values of Lansbury index, which implies a statistical approach to indices of disease activity, have lowered more; CYC may be more effective mainly in patients with *SAA1.3* homozygosity than in patients

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with *SAA1.3* heterozygosity, which suggests that *SAA1.3* homozygosity is a CYC treatment-susceptible factor (**Figure 5**) [20].

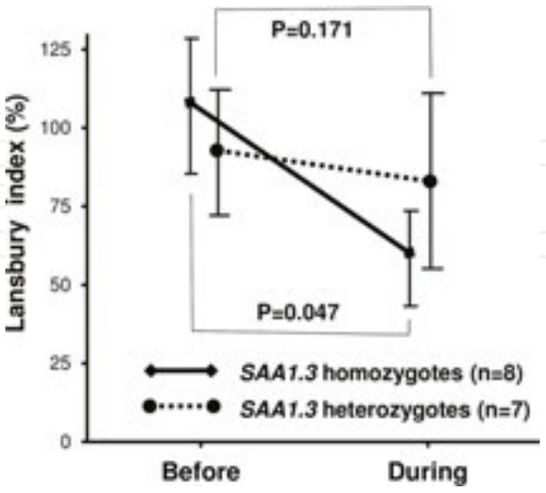


Figure 5. Changes in Lansbury index after CYC or prednisolone treatment in RA patients with AA amyloidosis with *SAA1.3* heterozygosity or homozygosity. In *SAA1.3* homozygous patients, a statistically significant difference occurred between before and during, whereas *SAA1.3* heterozygous patients showed no such significant difference. Quoted from Nakamura et al. Clin Rheumatol 2003; 22: 371–375.

During signal transduction, interleukin-6 (IL-6) binds to the membrane-bound IL-6 receptor gp80 [47], and after which the IL-6-gp80 dimer interacts with gp130. Formation of gp130-containing complexes activates Janus kinases, which stimulates signal transducers and activators of transcription (STATs) [48–50]. Some evidence suggests that STAT3 is the critical transcription factor that is responsible for IL-6 activation of SAA gene transcription [51]. The function of Janus kinase inhibition in the IL-6-signaling pathway will thus be one target of RA treatment. Suppressing IL-6-mediated pro-inflammatory signaling pathways using Janus kinase inhibitors may be a novel anti-inflammatory therapeutic strategy for RA and AA amyloidosis.

Another agent, tacrolimus, may inhibit T-cell function in the pathogenesis of AA amyloidosis. In experimental murine models of AA amyloidosis, blocking the function of T lymphocytes with the calcineurin inhibitor tacrolimus showed that it inhibited deposition of AA amyloid fibril in a dose-dependent manner. Also, the location of $CD4^+$ T lymphocytes in the spleen was identical to that of AA amyloid fibril deposits, which suggests that T lymphocytes have a role in the pathogenesis of AA amyloidosis [52].

4. Treatment with biological DMARDs for AA amyloidosis secondary to RA

Tight control of RA during treatment is important for obtaining clinical remission or for low disease activity [53]. This control is achieved via periodic assessments of RA disease activity

and aggressive investigation of additional more effective treatments [54]. Biological DMARDs (bDMARDs) therapy is expected to be effective against systemic inflammation and local inflammation such as those occurring in RA.

Type of agent	Biologic	References
TNFα antagonist		
	IFX	Arthritis Rheum 2002; 46: 2571
	ETN/IFX	Arthritis Rheum 2003; 48: 2019
	ETN/IFX	Rheumatology (Oxford) 2003; 42:1425
	ETN	Intern Med J 2004; 34: 570
	ETN/IFX	Rheumatology (Oxford) 2004; 43: 669
	ETN/IFX	Am J Med 2005; 118: 552
	ETN	Clin Exp Rheumatol 2007; 25: 518
	IFX	Rheumatol Int 2008; 28: 1155
	ETN/IFX	J Rheumatol 2009; 36: 2409
	ETN	Clin Rheumatol 2010; 29: 1395
	ETN	Rev Bras Reumatol 2010; 50: 205
	ETN	Rheumatol Int 2011; 31: 247
	ETN/ADA	Joint Bone Spine 2013; 80: 223
IL-6 receptor antagonist		
	TCZ	Arthritis Rheum 2006; 54: 2997
	TCZ	Clin Rheumatol 2009; 28: 1113
	TCZ	Clin Rheumatol 2010; 29: 1195
	TCZ	Mod Rheumatol 2014; 24: 405
	TCZ	Amyloid 2015; 22:84
	TCZ	Clin Exp Rheumatol 2015; 33 (Suppl. 94): S46
Selective costimulation modulator of T-cell function		
	ABT	Clin Exp Rheumatol 2014; 32: 501
Anti-CD20 antibody		
	RTX	Joint Bone Spine 2011; 78: 98

DMARDs: disease-modifying antirheumatic drugs; AA: amyloid A; RA: rheumatoid arthritis; TNFα: tumor necrosis factor α; IFX: infliximab; ETN: etanercept; ADA: adalimumab; IL-6: interleukin6; TCZ: tocilizumab; ABT: abatacept; CD: cluster of differentiation; RTX: rituximab.

Table 2. Biological DMARDs for patients with AA amyloidosis secondary to RA.

Etanercept (ETN) and infliximab (IFX), both tumor necrosis factor α (TNFα) antagonists, can lower SAA levels in RA patients with AA amyloidosis [55, 56]. This effect ameliorates both RA

inflammation and AA amyloidosis, reduces the number of swollen and tender joints, lowers or normalizes proteinuria, and improves renal function [57, 58]. Although a small number of patients with AA amyloidosis secondary to RA received ETN, this drug had benefits for both RA inflammation and AA amyloidosis, even in *SAA1.3/1.3* allele-carrying RA patients (**Table 2**) [59–62]. Such benefits were determined by evaluating the surrogate markers disease activity score 28-erythrocyte sedimentation rate, CRP, SAA, and proteinuria (**Table 3**). Also, patients with mild RA disease and renal dysfunction demonstrated significantly improved serum creatinine levels. This result suggests that an earlier intervention with bDMARDs produces a better outcome for RA patients with AA amyloidosis (**Table 4**) [63, 64].

Parameter	Initial visit	Last visit	P-value
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
SAA (μg/ml)	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

ETN: etanercept; AA: amyloid A; RA: rheumatoid arthritis; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SAA: serum amyloid A protein.
*Serum levels.
ETN was significantly effective for RA patients with AA amyloidosis. DAS28-ESR and CRP indicated RA inflammation, and SAA and proteinuria-indicated AA amyloidosis. Quoted and modified from Nakamura et al. Clin Rheumatol 2010; 29: 1395–1401.

Table 3. Effect of ETN on AA amyloidosis secondary to RA.

Creatinine value less than 2.0 (mg/dl) (n = 6)		Creatinine value more 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[a]	1.07 ± 0.59[a]	3.43 ± 1.14[b]	3.56 ± 2.39[b]

ETN: etanercept; AA: amyloid A; RA: rheumatoid arthritis.
Although a statistical significance of serum levels of creatinine was not observed as shown in **Table 3**, when cutting levels of serum creatinine by 2.0 mg/dl, the group with values lower than 2.0 mg/dl revealed to be significant. Regarding with renal dysfunction because of AA amyloidosis secondary to RA, the earlier the intervention, the better the outcome was suggested. Quoted and modified from Nakamura et al. Clin Rheumatol 2010; 29: 1395–1401.
[a] P = 0.021, [b] not significant.

Table 4. Effect of ETN on renal dysfunction in AA amyloidosis secondary to RA.

Tocilizumab, an IL-6 receptor antagonist, also produced excellent SAA suppression and may show promise as a therapeutic agent for AA amyloidosis [65–67]. Circulating SAA levels usually indicate changes in CRP, and levels of these acute phase reactants usually increase at the same time, but certain differences can occur. SAA and CRP seem to be somewhat affected by different cytokines [68, 69]. As mentioned earlier, therapy in which IL-6 is blocked, rather

than therapy utilizing TNF-α blockade, should influence multiple signal transduction systems and may normalize SAA levels in RA patients (**Figure 6**) [70].

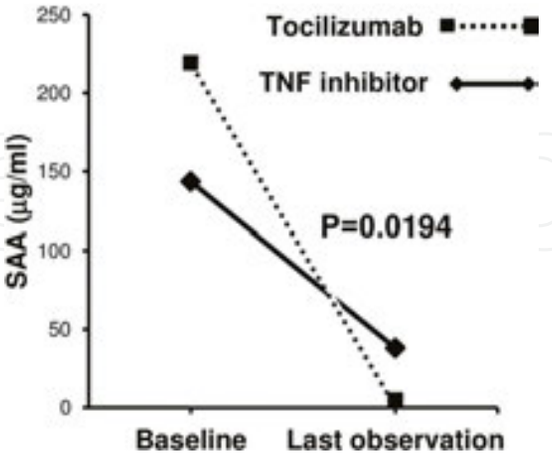


Figure 6. Changes in serum values of SAA between the first and last observations for each biologic. SAA values showed more significant suppression in the tocilizumab group than in the TNF inhibitor group (P = 0.0194, Wilcoxon rank sum test). Quoted and modified from Okuda et al. Mod Rheumatol 2014; 24: 137–143.

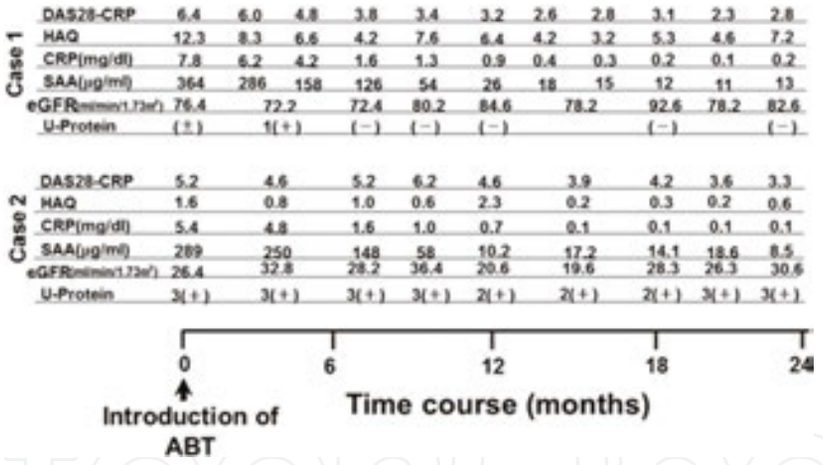


Figure 7. Clinical course of two RA patients with AA amyloidosis who received abatacept treatment. Clinical parameters were related to RA inflammation and AA amyloidosis after treatment. DAS28-CRP: disease activity score in 28 joints based on the CRP level; HAQ: Health Assessment Questionnaire; eGFR: estimated glomerular filtration rate; U-protein: qualitative protein analysis of spot urine. Quoted and modified from Nakamura et al. Clin Exp Rheumatol 2014; 32: 501–508.

Abatacept (ABT) is a soluble fusion protein consisting of the extracellular domain of recombinant human cytotoxic T lymphocyte-associated antigen 4 plus a fragment of the Fc domain human immunoglobulin IgG1 (CTLA-4Ig) [71]. CTLA-4Ig may reduce T lymphocyte responses by competing with CD80/CD86 to access CD28 and thus limit the CD28 signaling that T lymphocyte activation requires [72]. ABT may also affect more than just T lymphocytes [73]. Whether intracellular signaling or other CTLA-4Ig-mediated effects contribute to a favorable

outcome or a poor outcome, especially during the treatment of RA patients, is not entirely clear, and the exact role of CTLA-4Ig in biological systems, including patients with AA amyloidosis secondary to RA, is also unresolved. Although accumulating clinical data on ABT treatment suggest an advantage for ABT in RA management [74, 75], the safety and efficacy of ABT in patients with AA amyloidosis secondary to RA have not yet been studied. **Figure 7** illustrates that in two patients, who had more than 20 years of RA history and who carried the *SAA1.3* allele, which is a risk factor for AA amyloidosis in Japanese RA patients, ABT gradually improved RA disease activities, proteinuria, and various gastrointestinal symptoms and was clinically effective to some degree in one case and completely in the other for both RA inflammation and AA amyloidosis. Study results also suggest that ABT targeting of costimulatory molecules may be useful for treating patients with AA amyloidosis secondary to RA and that ABT may be an alternative to anti-cytokine therapies for AA amyloidosis complicating RA [76].

Rituximab, an anti-CD20 monoclonal antibody, was effective for treating patients with severe active RA who had an inadequate response to TNFα inhibitor (or inhibitors) [77]. The efficacy and safety of rituximab for patients with AA amyloidosis secondary to RA together with substantial clinical improvement in articular symptoms, marked reduction in acute phase reactants, and stabilization of renal function and proteinuria were demonstrated [78].

5. Inhibiting AA amyloid fibrillogenesis in AA amyloidosis secondary to RA

Highly sulfated glycosaminoglycans, especially heparan sulfate and dermatan sulfate proteoglycans, are universal constituents of amyloid deposits and promote fibril assembly and help maintain conformational changes related to amyloidogenesis [79, 80]. Eprodisate is a negatively charged, sulfonated low molecular weight molecule that has a structure which is similar to that of heparan sulfate [81]. It binds to the SAA binding site to prevent interaction of SAA with glycosaminoglycans and thereby inhibits a conformational change required to cause SAA to become amyloidogenic. In in vivo studies with murine models, eprodisate inhibited the development of amyloid deposits [82, 83].

Eprodisate is still the only drug that was tested in a phase II/III multicenter, placebo-controlled, double-blinded study of amyloidosis [84]. Patients were stratified according to the presence of nephrotic syndrome and the treatment center, after of which they were randomized to receive eprodisate or placebo twice daily for up to 2 years. Outcome measures were a composite endpoint of serum creatinine, creatinine clearance, and progression to end-stage renal disease (ESRD) or death. Secondary outcome measures included the creatinine clearance slope, change in proteinuria, improvement in diarrhea, and alteration in amyloid content of abdominal fat. The study demonstrated that eprodisate may have contributed to the failure to achieve the study's primary endpoints, although the eprodisate-treated group did show renal benefits (**Figure 8**). The study, however, did not demonstrate a significant benefit from

active therapy on progression to ESRD or risk of death, although a trend to benefit was seen. A phase III clinical study is currently under way in Japan.

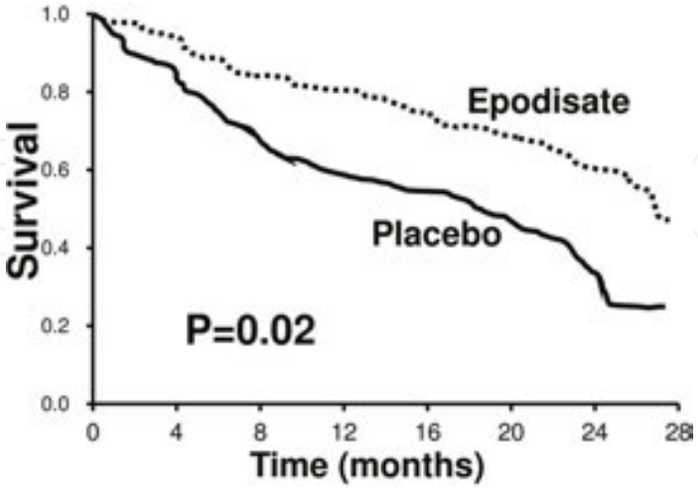


Figure 8. Kaplan-Meier survival curves for patients with AA amyloidosis who were given eprodisate or placebo. In terms of event-free survival, eprodisate demonstrated superior effectiveness compared with placebo, but this effect was not statistically significant. An event was defined as any component of the composite endpoint of worsened disease. Quoted and modified from Dember et al. N Engl J Med 2007; 356: 2349–2360.

6. Immunotherapy for AA amyloidosis secondary to RA

An alternative therapeutic approach was to target other components of amyloid deposits to destabilize amyloid fibrils. SAP is a normal plasma component and is a universal constituent of amyloid deposits. Its presence may therefore mask the presence of amyloid deposits and inhibit effective clearance of amyloid [85]. In fact, SAP knockout mice showed inhibited amyloid formation [86]. SAP was identified as a therapeutic target, which then led to development of CPHPC, a drug that inhibits the binding of SAP to amyloid deposits [87]. The activity of this agent relates to its ability to cross-link SAP molecule pairs face to face, which results in rapid hepatic clearance and completely blocks the binding face of the SAP molecule [88]. A preliminary study demonstrated that regular administration resulted in sustained and profound SAP depletion. Several patients received the drug for many years with no obvious adverse effects, although the degree of potential clinical benefit was not great enough to be determined in this open, non-controlled study (**Table 5**) [89].

Antibodies recognizing a common fibril epitope were raised and given to mice [90] with systemic AA amyloidosis, which resulted in reduced amyloid levels. CPHPC effectively removed SAP from the blood, but only very slowly from amyloid deposits, which allowed the development of an antibody directed at SAP. CPHPC was used to remove the SAP from plasma followed by use of an anti-SAP antibody, which led to rapid clearance by macrophages of experimentally induced amyloid deposits; this method begin developed for use in patients [91].

Patient no.	Amyloid type	Anti-SAP dose (mg)	SAP scan	Change in amyloid load
1	AA	5	Not improved	None detected
2	AApoA1	637	Improved	Liver reduction
3	AA	650	Improved	Kidney reduction

AA: amyloid A; SAP: serum amyloid P component; CPHPC: (*R*)-1-[6-[(*R*)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid; AApoA1: apolipoprotein A1.
Improved SAP scan: an improved scan was defined as a ^{123}I-SAP scintigram revealing a reduction in organ amyloid load at day 42 after SAP-antibody administration.
Combination treatment with CPHPC and anti-SAP antibody was effective to some extent for AA amyloidosis. Quoted and modified from Richards et al. N Engl J Med 2015; 373: 1106–1114.

Table 5. Response of patients with AA amyloidosis to anti-SAP antibody after depletion of plasma SAP with CPHPC.

7. Biomarkers predicting effectiveness of treatment for AA amyloidosis secondary to RA

Because renal dysfunction is the most common symptom in AA amyloidosis secondary to RA, surrogate markers representing the effectiveness of each treatment were investigated, with a focus on kidney function, in RA patients with AA amyloidosis who carried the *SAA 1.3* allele and who were treated with CYC or ETN focusing [92]. Identifying patients with a poor prognosis when it may be possible to modify the disease process and in whom any therapy may be justified is important. The presence of *SAA1.3* allele in Japanese RA patients may be a critical indicator for maintaining tight control of RA inflammation via vigorous treatment during the early phase of the RA disease course [11]. The rationale for using biologics in AA amyloidosis relates to their ability to lower levels of serum pro-inflammatory cytokines, which regulate SAA synthesis [93, 94]. A retrospective study reported the efficacy and safety of ETN for patients with AA amyloidosis secondary to RA who carried *SAA1.3* allele [64]. Using ETN for RA patients with AA amyloidosis may be possible, even for those undergoing dialysis [95, 96]. The efficacy of ETN was compared with that of CYC for treating AA amyloidosis secondary to RA as related to the *SAA1.3* allele, which was not a factor affecting therapeutic susceptibility (**Figure 9**). Demonstrable endpoints included recovery of serum albumin biosynthesis, improvement in the acute phase response, and amelioration of estimated glomerular filtration rate (eGFR). *SAA1.3* allele polymorphism was not affected on these parameters (**Table 6**). Albumin in fact reflects the severity of AA amyloidosis [97]. The changes in CRP and albumin were influenced by the difference between therapies rather than *SAA1.3* allele polymorphism (**Figure 10**). In contrast, the eGFR in patients with end-stage renal damage may reflect diminished urinary flow and may indicate improvement in renal function. Only ETN aided the amelioration of the eGFR, which indicated the greater efficacy of ETN compared with CYC for treating AA amyloidosis secondary to RA.

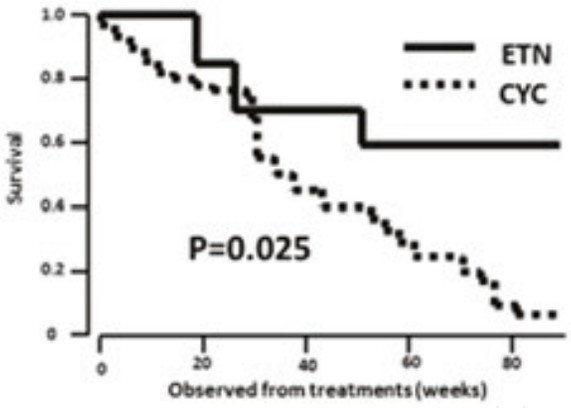


Figure 9. Kaplan-Meier survival curves after the treatment with ETN or CYC. ETN clearly demonstrated more effectiveness for RA patients with AA amyloidosis than did CYC. Quoted and modified from Nakamura et al. Rheumatology (Oxford) 2012; 51: 2064–2069.

Category	CRP	Alb	eGFR	Crea
Within-subject	<0.01	<0.01	0.035	0.085
Interaction with				
SAA1.3 allele polymorphism	0.777	0.715	0.465	0.228
Treatment (ETN/CYC)	<0.01	<0.01	0.032	0.148

ETN: etanercept; CYC: cyclophosphamide; CRP: C-reactive protein; Alb: albumin; eGFR: estimated glomerular filtration rate; Crea: creatinine.
Except creatinine, recovery of serum albumin biosynthesis, improvement in the acute phase response, and amelioration of estimated glomerular filtration rate (eGFR) were valuable parameters to show effectiveness in the treatment with etanercept. *SAA1.3* allele polymorphism was not affected on these parameters. Quoted from Nakamura et al. Rheumatology (Oxford) 2012; 51: 2064–2069.

Table 6. Parameters showing effectiveness of treatment with ETN or CYC.

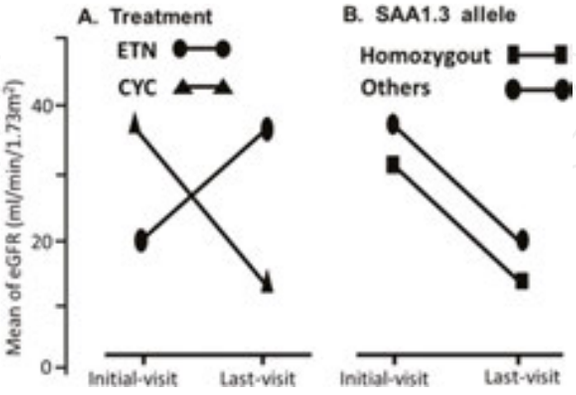


Figure 10. Changes in the eGFR between initial and last visits according to the effectiveness of treatment with ETN or CYC (A) and as a function of the *SAA1.3* allele homozygosity or other polymorphisms (B). ETN increased the eGFR, which improved the reduced renal function caused by AA amyloidosis, more than did CYC, and *SAA1.3* did not affect treatment in both groups of patients. Quoted from Nakamura et al. Rheumatology (Oxford) 2012; 51: 2064–2069.

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8. End-stage renal disease treatment in AA amyloidosis secondary to RA

Kidneys that have extensive AA amyloid deposits are extremely susceptible to intercurrent insults such as hypoperfusion, hypertension, nephrotoxic drug effects, and surgical injuries, which should all be avoided in AA amyloidosis [98, 99]. Renal involvement is the most common problem in AA amyloidosis, and patients with AA amyloidosis frequently progress to end-stage renal disease (ESRD) and poor prognosis (**Figure 11**). When evaluating therapies for renal dysfunction related to AA amyloidosis, renal transplantation has been thought to be a suitable method [100]. However, existing data on patient survival and graft prognosis do not provide conclusive results about whether renal plantation is suitable for patients with AA amyloidosis [101]. An alternative to transplantation is chronic dialysis, but experience with dialysis in patients with AA amyloidosis has not yet as been encouraging [102, 103]. Peritoneal dialysis increases the susceptibility to infection and protein loss [104]. Hypoalbuminemia is well known to predict overall mortality in hemodialysis patients [105]. An elevated CRP value is associated with an increased risk of death in dialysis patients [106], and CRP has been found to be an independent predictor of major adverse cardiac events [107]. Because patients with AA amyloidosis who have progressed to ESRD have already been exposed to significant levels of inflammation, which may be ongoing, they may have an additional cardiovascular risk [108]. Patients with marked proteinuria have an increased risk of thrombosis, and the decision to use anticoagulants must be made on an individual basis [109]. General management principles apply to patients with AA amyloidosis secondary to RA for lowering high lipid levels and modifying diet as other causes of renal dysfunction.

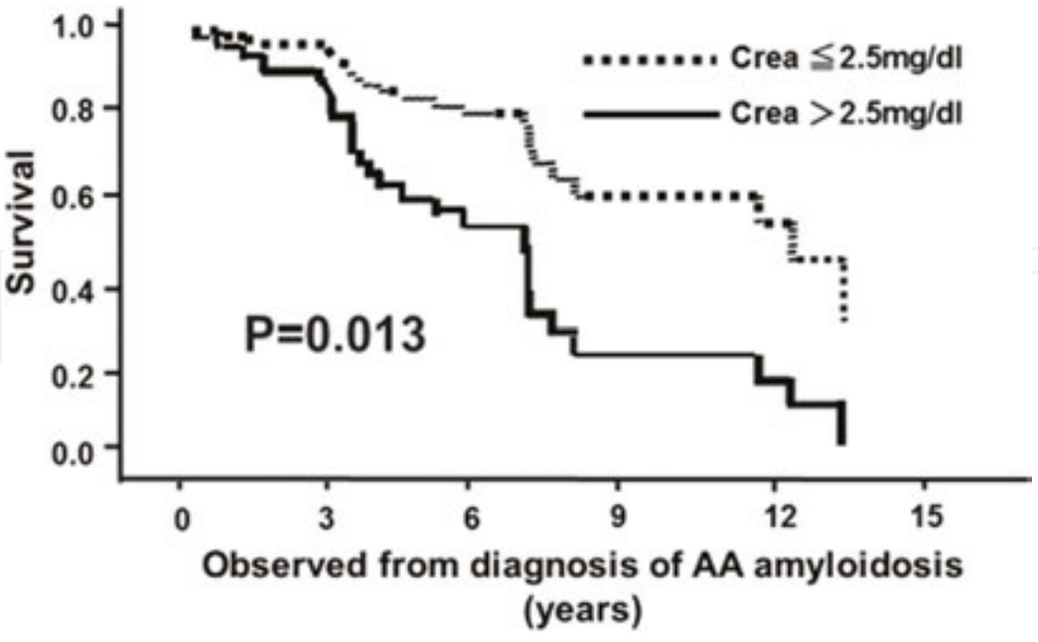


Figure 11. Kaplan-Meier survival curves after diagnosis of AA amyloidosis for patients with serum creatinine values of >2.5 or ≤2.5 mg/dl. Renal dysfunction, the most common symptom in AA amyloidosis secondary to RA, is a factor indicating a poor prognosis for survival. Quoted from Nakamura et al. Rheumatology (Oxford) 2006; 45: 43–49.

9. Possible involvement of phagocytes in degeneration of AA amyloid fibrils

Macrophages participate in SAA processing and deposition [110, 111], and cell surface-expressed heparan sulfate proteoglycans have an essential function in amyloidogenesis through the binding of high-density lipoprotein-associated SAA [112]. In addition, Fc-receptor-positive macrophages have been implicated in the reduction of the amyloid load after inflammation has resolved [113]. Phagocytes such as neutrophils and macrophages will serve an important function for reducing AA amyloid deposits during ABT treatment (**Figure 12**).

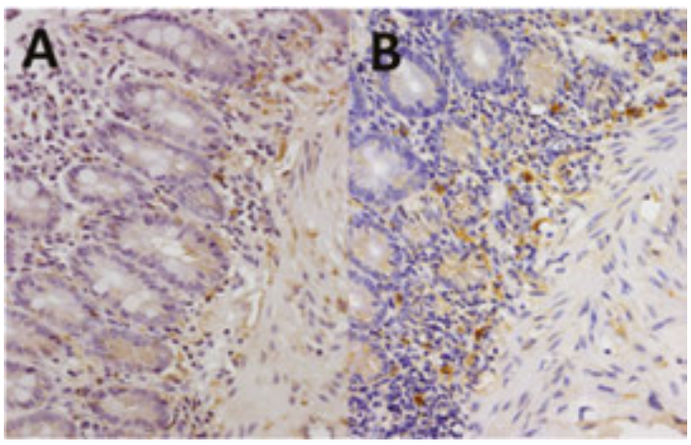


Figure 12. Immunohistochemical analysis of a biopsy specimen from a patient with RA and AA amyloidosis who received abatacept (ABT). (A) Stained with the antibody anti-formyl peptide receptor-like 1 (fPRL-1, the receptor involved in production of reactive oxygen species, degradation, and phagocyte migration) and (B) anti-human CD68 antibody staining. Phagocytes, polymorphonuclear leukocytes, and macrophages stained positively in the upper gastrointestinal mucosa specimen. Quoted and modified from Nakamura et al. Clin Exp Rheumatol 2014; 32: 501–508.

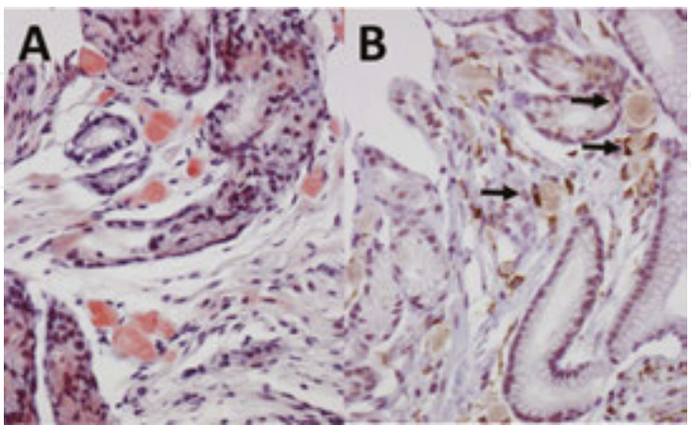


Figure 13. Relation between macrophages and AA amyloid deposits. AA amyloid deposits showed positive Congo-red staining (A), and anti-CD68 antibody-positive macrophages (arrows) surrounded AA amyloid deposits (B). These findings suggest an interaction between macrophages and amyloid deposits for the reduction in AA amyloid deposits. Quoted and modified from Nakamura et al. Clin Exp Rheumatol 2014; 32: 501–508.

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T lymphocytes may influence the formation or metabolism of these amyloid fibrils. These cells colocalized within AA amyloid deposits, which indicates that phagocytes may participate in the metabolism or turnover of these amyloid deposits (**Figure 13**). Involvement of macrophages in AA amyloid reduction was proposed [114], and this hypothesis was supported by observations that macrophage-derived proteases completely degraded AA amyloid [115]. Resolution of AA amyloid deposits appears to start when inflammation subsides and SAA levels normalize. Additional data on the natural clearance of AA amyloid are vital [116], for both a better understanding of the dynamics of amyloidogenesis and the development of effective treatments for patients with AA amyloidosis secondary to RA.

10. Conclusion

AA amyloidosis is an uncommon yet important complication of chronic inflammatory conditions. Significant progress has been made in understanding of pathology, pathogenesis, and clinical treatment of AA amyloidosis secondary to RA, but AA amyloidosis is still a serious problem that deserves continued investigation. The *SAA1.3* allele is both a risk factor for AA amyloidosis and a factor related to poor prognosis and shortened survival in Japanese patients with RA. The incidence of AA amyloidosis secondary to RA will likely decrease because of remarkable advances in RA treatments such as bDMARDs and intracellular signal transduction inhibitors. However, when rheumatologists first meet patients with AA amyloidosis secondary to RA, the patients may be facing a serious, life-threatening disorder such as ESRD and/or cardiac complications, even given the present medical milieu in developed countries. The pathological process in RA patients with AA amyloidosis is likely to be more complicated and subtle than previously realized. Clarification of the formation and degeneration of AA amyloid fibrils induced by not only drugs but also cellular mechanisms and elucidation of the biological significance of SAA in health and disease is indispensable prerequisites to the management of AA amyloidosis secondary to RA. Novel therapies that target AA fibril formation and immunotherapy are currently under investigation and will lead to improved prognosis in the near future.

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Conflict of interest

The author has declared no conflicts of interest.

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