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Therapeutic Strategies in Amyloid A Amyloidosis Secondary to Rheumatoid Arthritis

Tadashi Nakamura

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1. 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 characterized by failure of multiple organs and the presence of amyloid precursor protein in the serum [1-3]. Reactive amyloid A (AA) amyloidosis is one of the most severe complications of several chronic disorders, particularly rheumatoid arthritis (RA) [4], 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) [5]. 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 [6]. However, the actual pathological mechanisms that are responsible for the relationship between SAA and AA amyloidosis have not been fully elucidated.

With new biological therapies, both treatment and understanding of the roles of cytokines and inflammatory cellular events in RA have seen considerable progress. Biologics are recommended for patients with RA who have a suboptimal response or an intolerance to traditional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX). Early diagnosis and rapidly subsequent treatment are essential because patients with advanced disease can't usually undergo intensive therapy. Specific treatment of AA amyloidosis caused by RA aims to stop SAA production. Cytotoxics such as chlorambucil and cyclophosphamide (CYC) and biologics such as anti-tumor necrosis factor (TNF) α inhibitors and anti-interleukin (IL)-6 receptor antibody are reportedly useful for both RA and AA amyloidosis [7, 8]. By the way, the genetic predisposition allele SAA1.3, one of SAA1 gene

polymorphism, 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 [9]. Both the association of AA amyloidosis arising early in the RA disease course and symptomatic variety and severity were found in amyloidotic patients carrying SAA1.3 allele. Etanercept (ETN) for patients with AA amyloidosis secondary to RA, who carry SAA1.3 allele, showed the amelioration of rheumatoid inflammation, including marked reduction of SAA, improvement of proteinuria and creatinine clearance [10], that would demonstrate efficacy and safety even in patients undergone on hemodialysis [11]. These lead us to the notion of clinical significance of SAA1.3 allele in the clinical strategy of Japanese RA patients.

This article will discuss on therapeutic strategies from the point of biologicals view on RA treatment in relation to AA amyloidosis secondary to RA based on our reports and literature reviews.

2. Significance of SAA1.3 allele genotype in Japanese RA patients with AA amyloidosis

It was reported that the frequency of SAA1.3 allele was markedly increased in AA amyloidosis in Japanese RA patients (Fig. 1), suggesting that this allele was a risk factor for AA amyloidosis secondary to RA [12]. That is, SAA1.3 allele has been reported to be associated with increased risk of AA amyloidosis and SAA1.1 with decreased risk [13], while SAA1.1 was revealed to be a risk factor for developing AA amyloidosis in the Caucasian population [14]. We calculated the hazard ratio in the presence or absence of SAA1.3/1.3 homozygosity as a survival parameter after the onset of RA. By means of Cox proportional hazard survival analysis, carrying with SAA1.3/1.3 homozygosity was statistically significant for survival ($P=0.015$) with hazard ratio of 2.101 (95% CI: 1.157 - 3.812). Also, the Kaplan-Meier curve showed a significant difference during observation from diagnosis of RA (Fig. 2). The mean survival period of the all patients with and without SAA 1.3/1.3 was 6.52 ± 6.18 years and 13.8 ± 8.47 years, with 43.8% and 71.6% surviving for 10 years, respectively. The SAA1.3 allele, particularly homozygosity for SAA1.3, was a univariate predictor of survival. The presenting factors which adversely influenced clinical outcome after diagnosis of AA amyloidosis were age ($P=0.001$), raised serum creatinine (Crea) concentration ($P=2.14 \times 10^{-5}$), lowered serum albumin (Alb) concentration ($P=0.001$), and presence of SAA1.3/1.3 ($P=0.035$). While, after diagnosis of RA, age of RA onset ($P=2.95 \times 10^{-4}$) and presence of renal involvement ($P=0.011$) were extracted as survival parameter. The serum Crea value of $>2.5\text{mg/dl}$ upon diagnosis of AA amyloidosis was closely related with poorer survival, when compared with a serum Crea value of $\leq 2.5\text{mg/dl}$ by Kaplan-Meier technique ($P=0.013$ with log-rank statistic) (Fig. 3). The presence of cardiac involvement was likely to be a risk factor to survival ($P=0.062$). These results have revealed the significance of SAA1.3 allele genotype in Japanese RA patients with AA amyloidosis when we follow-up such patients in daily practice [15, 16]. However, we just need more studies about the large prospective trials to prove the usefulness of SAA1.3 allele genotype.

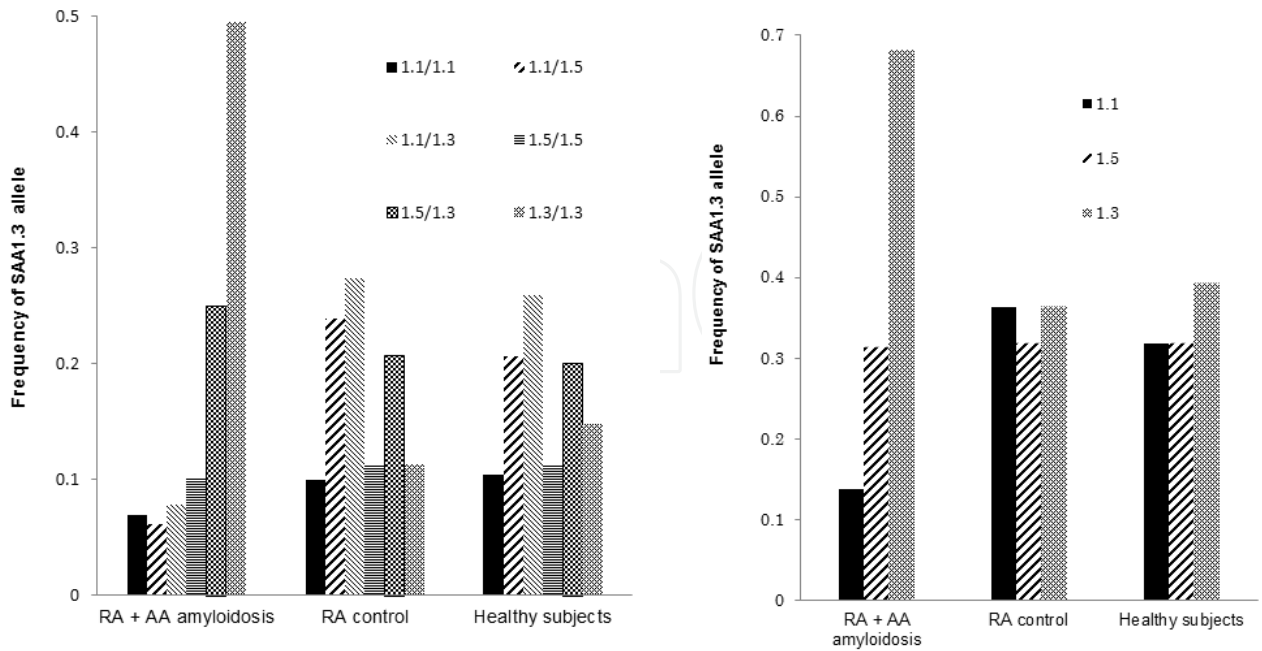


Figure 1. SAA1.3 allele frequency and AA amyloidosis in Japanese RA patients. SAA1.3 allele is associated with increased risk of AA amyloidosis in Japanese RA patients. Figures are courtesy of Satoshi Baba, MD and modified from Reference No. 12.

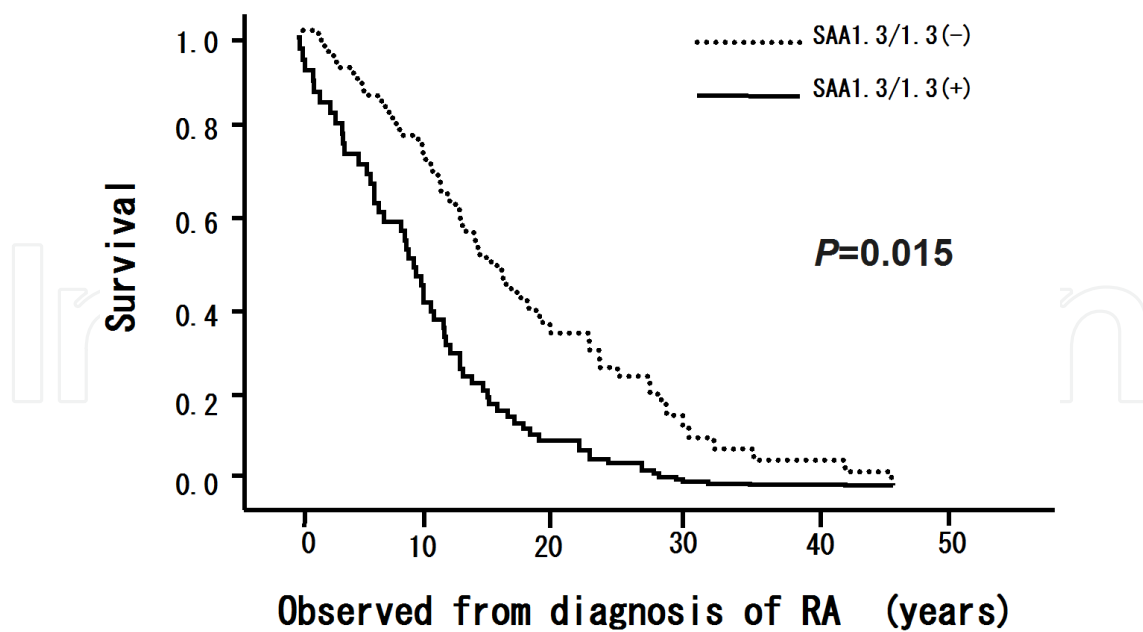


Figure 2. Kaplan-Meier survival curve in RA disease course for RA patients with (continuous line) and without (dotted line) SAA1.3/1.3 ($P=0.015$, log-rank test) from Reference No. 9.

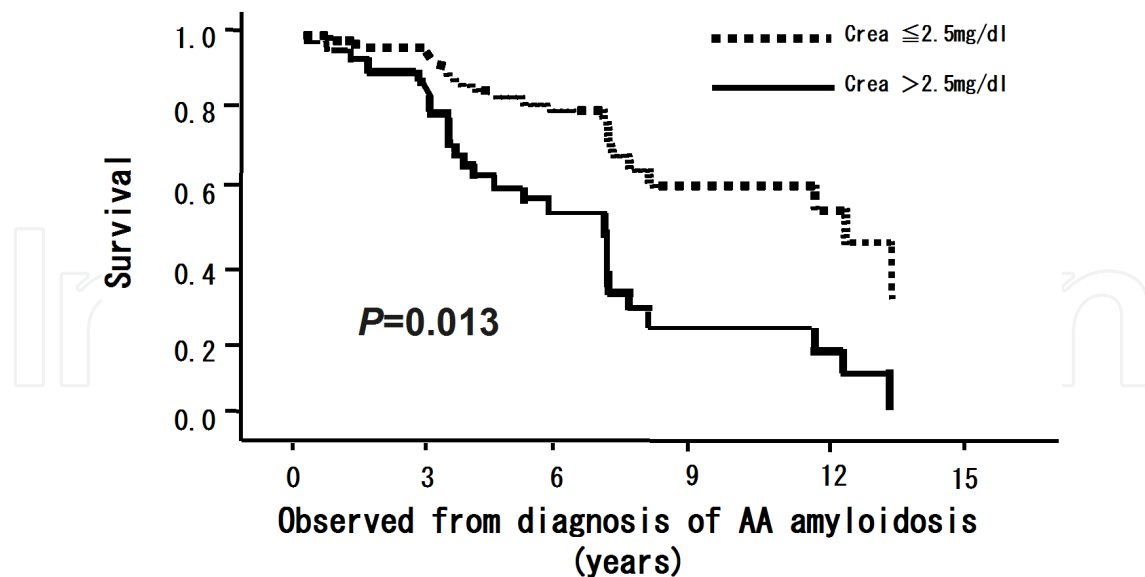


Figure 3. Kaplan-Meier survival curve after diagnosis of AA amyloidosis for patients with serum creatinine $>2.5\text{mg/dl}$ (continuous line) and serum creatinine $\leq 2.5\text{mg/dl}$ (dotted line) ($P=0.013$, log-rank test) from Reference No. 9.

3. Fundamental thoughts for therapies

According to the information on the studies using radiolabelled human serum amyloid component P (SAP) as a specific quantitative *in vivo* scintigraphic tracer for monitoring of systemic AA amyloidosis [17], treatments that effectively suppress production of SAA halt the progressive accumulation of AA amyloid deposits and, in many cases, they are associated with AA amyloid regression, improved organ function and survival [18, 19]. AA amyloid deposits are evidently turning over, their net size reflecting the balance of deposition and regression [20]. Therefore, AA amyloid deposits may regress at a low rate over a period of years and exist in a state of dynamic turnover. The usual clinical impression of inexorable progression of AA amyloidosis actually reflects the progressive and usually incurable nature of the underlying primary condition, which is complicated by AA amyloidosis. However, new and aggressive approaches to therapy, such as cytotoxic anti-inflammatory drugs and biologic agents in chronic rheumatic inflammation, will lead to impressive AA amyloid regression and prolonged survival. Unfortunately these treatments do not always work and there are many difficult cases in those approaches are neither possible now nor likely to become feasible in future. In view of clinical significance of AA amyloidosis, there is an urgent need to facilitate studies into this complication. Early diagnosis and intervention are essential for RA, however, few specific features are useful for diagnosis of RA and its diagnosis is often difficult in daily RA practice. Reduction of SAA load is currently the most rational approach thereby arresting further deposition [21]. It is not exactly known why some patients develop a progressive AA amyloidosis while others do not, although latent deposits may be present. While there is startling variation in the frequency of AA amyloidosis worldwide, differences also exist for AA amyloidosis complicating RA [22]. The reasons, however, for

the marked geographic differences are unclear. The difference in the frequency of AA amyloidosis among different races, and the fact that AA amyloidosis is not consistently related to the length and severity of chronic inflammation suggests that AA amyloidosis may be, at least in part, influenced by genetic factors [23-25].

4. Treatments 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. Treatment of AA amyloidosis secondary to RA may involve the following strategies as outlined in Table 1 [26].

Prevention	<ul style="list-style-type: none"> (1) Be careful not to raise AA amyloidosis (2) Keep the serum levels of SAA³⁾ less than 10 µg/ml (3) Control tightly rheumatoid inflammatory responses (4) Follow-up RA patients carrying SAA1.3 allele carefully
Diagnosis	<ul style="list-style-type: none"> (1) Do not underestimate proteinuria (2) Evaluate renal function by the levels of eGFR⁴⁾, cystatin C, and Ccr⁵⁾ (3) Watch GI⁶⁾ tract symptoms (4) Detect AA amyloid fibrils with organ biopsy like GI tracts, labia, and abdominal subcutaneous fat (5) Require renal biopsy in cases with proteinuria or renal dysfunction in RA patients
Therapy:	<ul style="list-style-type: none"> (1) Control acute-phase responses to suppress the synthesis of SAA (2) Control RA disease activity tightly <ul style="list-style-type: none"> (i) Do not lose window of opportunity (ii) Control RA disease tightly according to T2T⁷⁾ recommendations even in patients undergoing HD⁸⁾ (iii) Choose MTX⁹⁾ plus biologics in cases uncontrollable from early phase (iv) Challenge new biologics and signal transduction inhibitors (3) Steroid, codeine phosphate, lactate bacteriae, and especially octreotide for refractory diarrhea (4) Stand on the notion of deposited AA amyloid fibrils existing in a state of dynamic turnover

¹⁾AA: amyloid A, ²⁾RA: rheumatoid arthritis, ³⁾SAA: serum amyloid A protein, ⁴⁾eGFR: estimated glomerular filtration rate, ⁵⁾Ccr: creatinine clearance, ⁶⁾GI: gastrointestinal, ⁷⁾T2T: treat RA to target, ⁸⁾HD: hemodialysis, ⁹⁾MTX: methotrexate

Table 1. Clinical strategies in the management of AA¹⁾ amyloidosis secondary to RA²⁾

4.1. Suppression of SAA production

For AA amyloidosis in patients with RA, treatment has centered on using cytotoxic agents and is shifting to biologics recently. 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. Traditional management of AA amyloidosis has been to target RA disease to process behind the inflammation. Although there is no evidence that DMARDs have a specific effect on amyloidogenesis and AA amyloidosis in RA [27, 28], there have been encouraging reports evaluating alkylating agents as beneficial in clinical trials in RA patients with AA amyloidosis [29-33]. Treatments in AA amyloidosis secondary to RA including immunosuppressants, biologics, and other supportive therapies will be discussed as follows.

4.1.1. Immunosuppressants

It is suggested that the use of immunosuppressive agents can improve prognosis [34], and CYC was superior to MTX in the management of RA patients with AA amyloidosis [9]. As regards MTX and CYC treatments, we observed differences of both serum C-reactive protein (CRP) and Crea concentrations. That is, we subtracted the CRP- and/or Crea-value at initiation from the CRP- and/or Crea-value at endpoint of corresponding to each treatment. The each deducted value was dotted in Fig. 4. It was clear that more CYC treatments resided within minus area than MTX treatments. CRP improved 1.23 ± 1.67 (mg/dl) in CYC treatments with statistical significance ($P < 0.001$). We reported the possibility that CYC would be more effective predominantly in patients with SAA1.3/1.3 homozygosity than heterozygosity, suggesting of CYC treatment-susceptible factor as SAA1.3/1.3 homozygosity [35]. Concerning immunosuppressants, whether specific therapies were warranted and were superior to previously reported regimens should be elucidated. The strategy of these treatments focuses on tight control of underlying RA disease activity [28]. Requirements include diagnosis of RA as early as possible and treatment with DMARDs, including MTX as the anchor drug. Achieving low disease activity via DMARDs in the early 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 on MTX.

For signal transduction, IL-6 binds to membrane-bound IL-6 receptor gp80 [36], 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) [37]. Certain evidence suggests that STAT3 is the key transcription factor responsible for IL-6 activation of SAA gene transcription [38]. Therefore, the function of JAK inhibition in the IL-6 signaling pathway will be one target of RA treatments. Suppressing IL-6-mediated proinflammatory signaling 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. The function of JAK inhibition in the IL-6 signaling pathway will be one target of RA treatments [39, 40].

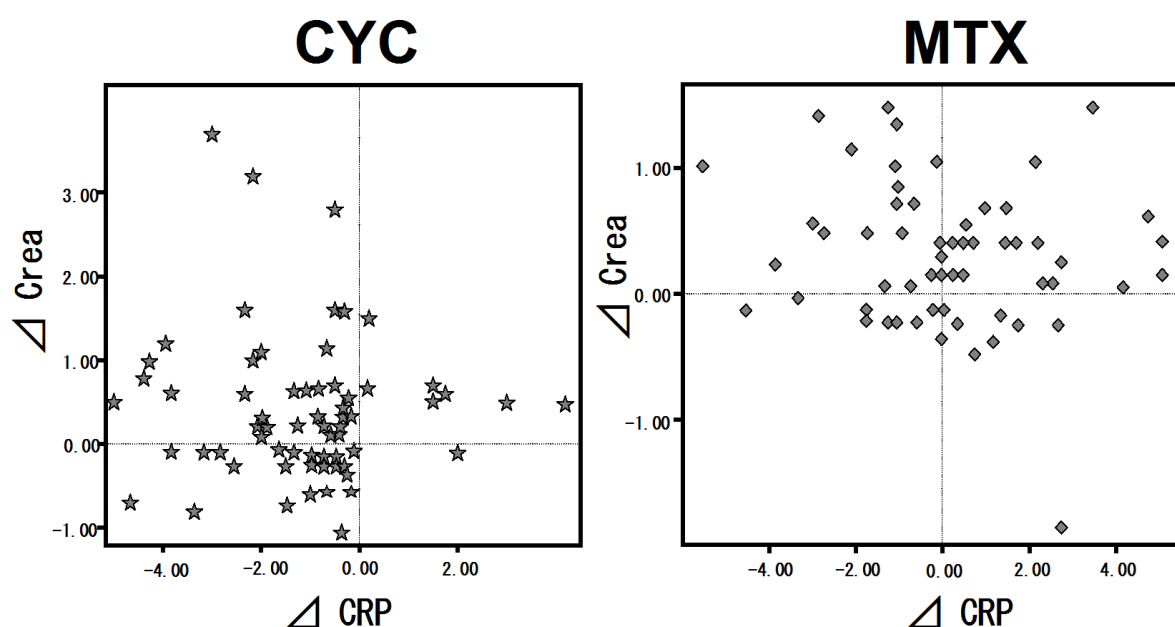


Figure 4. Differences between CYC and MTX treatments for RA patients with AA amyloidosis. The detected value (placed in figures) was calculated by subtracting the starting value of CRP and/or serum creatinine from the endpoint value in each treatment from Reference No. 9.

4.1.2. Biologics

In RA treatment, tight control of RA is emphasized 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 [41-43]. Anti-proinflammatory cytokine therapy is expected to show efficacy against both systemic and local inflammation mediated by macrophage differentiation or activation in glomeruli, such as in renal AA amyloidosis secondary to RA [44].

Infliximab (IFX) and ETN, both TNF α antagonists, can reduce serum SAA levels in RA patients with AA amyloidosis, which improves rheumatoid inflammation, reduces swollen and tender joint counts, lowers or normalizes proteinuria, and ameliorates renal function [45-48]. Also, these agents showed amelioration in renal function for AA amyloidosis secondary to RA (Table 2) [10]. Despite the small number of series of patients with AA amyloidosis secondary to RA who had ETN treatment, this drug did benefit both RA inflammation and AA amyloidosis, as measured via the surrogate markers, disease activity score (DAS)28-erythrocyte sedimentation rate (ESR), CRP, SAA, and proteinuria, in SAA1.3 allele-carrying RA patients (Fig. 5, Table 3). Further, Crea levels significantly improved in patients with mild RA disease and renal dysfunction (Table 4). This result suggests that the earlier the intervention with biologics, the better the outcome for patients. ETN alone may therefore be efficacious, without MTX [49-53].

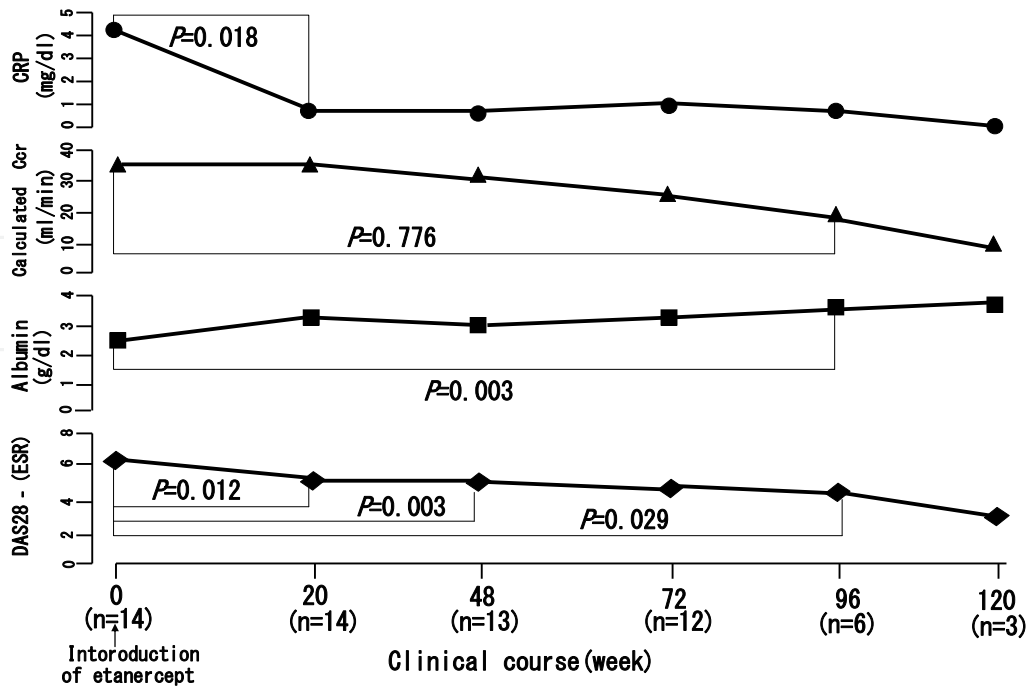


Figure 5. Chronological changes among surrogate markers following etanercept treatment. Ccr: creatinine clearance, CRP: C-reactive protein, DAS: disease activity score, n: number of patients treated with etanercept in the designated observation periods. CRP decreased dramatically by 20 weeks ($P=0.018$) and DAS28-ESR improved to low values significantly following the treatment of etanercept. Although serum and calculated Ccr are coincided to be renal function markers, only serum albumin showed statistical significance between 0 and 96 weeks ($P=0.003$), whereas the calculated creatinine clearance fell gradually 0 and 96 weeks ($P=0.776$).

Case/Age/Sex	Duration (years)		Biologics	Proteinuria (g/day)		Serum Crea (mM/L)		Observation Periods (months)
	RA	AA amyloidosis		Initial	Last	Initial	Last	
1/70/F	18	1	IFX	2	6	93	130	3
2/59/F	13	4	ETN	1.2	0.2	398	425	12
3/59/F	13	4	ETN	1.2	0.72	229	246	7
4/37/M	22	2	IFX	3	0.9	134	145	17

Quoted and modified from Reference No. 47. Data are represented as renal functions between the initial- and last-visit following biologics treatment. RA: rheumatoid arthritis, AA: amyloid A, Crea: levels of creatinine, IFX: infliximab, ETN: etanercept.

Table 2. Effect of TNF alpha blockers on renal AA amyloidosis secondary to RA.

Parameter	Initial-visit	Last-visit	P-value
RA inflammation			
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			
SAA(µg/ml)	250±129	26±15	<0.01
Proteinuria(g/day)	2.24±0.81	0.57±0.41	<0.01
Serum creatinine(mg/dl)	2.54±1.38	2.50±2.21	0.896

The values of DAS28=ESR, CRP, SAA, and proteinuria between the initial visit (before etanercept) and the last treatment (the index time) with etanercept. All improved with statistical significance. In contrast, the serum creatinine did not change statistically. 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. Quoted and modified from Reference No. 10.

Table 3. Surrogate markers between initial- and last-visit following treatment with etanercept

Less than 2.0(mg/dl) (n=6)		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	1.07±0.59	3.43±1.14	3.56±2.39
*		**	

*P=0.021, **not significant

Although Table 3 shows that the change in serum creatinine value was not statistically significant, when using a cutoff value as less than 2.0 mg/dl at the initial-visit, it was demonstrated that the creatinine value improved significantly at the last-visit. Quoted and modified from Reference No. 10.

Table 4. Changes in the values of serum creatinine stratifying by 2.0(mg/dl) at the commencement of etanercept

Tocilizumab (TCZ), an IL-6 receptor antagonist, can demonstrate excellent suppression of SAA levels and may have potential as the first candidate of the therapeutic agent for AA amyloidosis [7]. 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 normalizing serum SAA levels in RA patients. Moreover, blocking IL-6 alone, but not IL-1 or TNF α , completely prevented SAA mRNA expression in human hepatocytes during triple cytokine stimulation [54, 55]. Some reports with promising effect on AA amyloidosis secondary to RA may suggest a possibility of usefulness of this agent [56, 57]. Our case with end-stage renal disease due to AA amyloidosis secondary to RA showed validity of TCZ usage which is reaching to sustain normal SAA levels with successive treatment for 4 years (Fig. 6). In this case due to loss of joint function in advanced RA stage, in spite of lower and limited quality of life, both CRP and SAA are keeping

within normal limits, those may lead to decreasing proteinuria. It is needed to clarify the dissociation between inflammatory rheumatoid activity and destructed articular function under current RA therapeutic strategies using biologics like “disconnect” phenomenon [58].

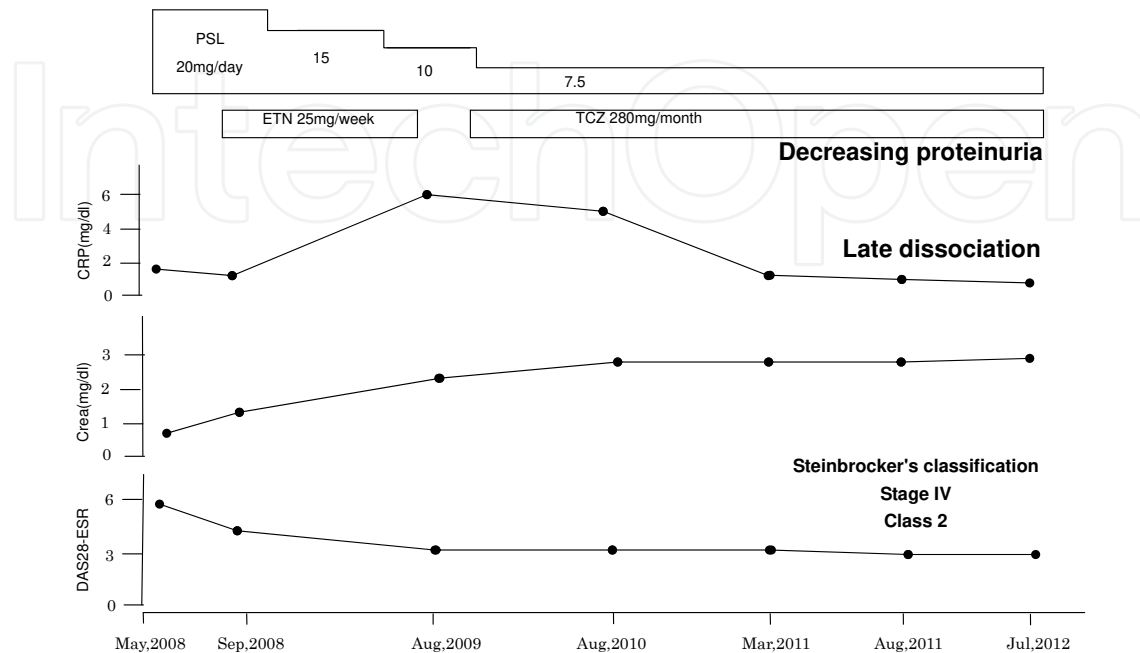


Figure 6. Effect of tocilizumab on AA amyloidosis secondary to RA. DAS28-ESR showed gradually regressed with the association of CRP, however, levels of serum creatinine increased leading to end-stage renal disease. TCZ had an effect on both proteinuria and rheumatoid inflammation, nevertheless, this case showed late dissociation between rheumatoid inflammation and joint functional activity. TCZ: tocilizumab, ETN: etanercept, PSL: prednisolone, Crea: serum creatinine, CRP: C-reactive protein.

T lymphocyte costimulation is a key point in the regulation of immune tolerance, immune response, and autoimmunity. T lymphocyte activation does not take place upon the simple engagement of T cell receptor; a second signal is needed to fully stimulate T lymphocytes. There are a variety of molecules that can act as costimulators, and among these cluster of differentiation (CD)28/CD80 signaling plays a crucial role in modulating T lymphocyte response. Cytotoxic T lymphocyte antigen-4 (CTLA4) is a physiologic antagonist of CD28, and abatacept (ABT), a synthetic analogue of CTLA4, has recently been approved to treat RA. A 70-year-old Japanese woman had been suffering from RA for 28 years with Steinbrocker’s Stage IV and functional Class 2. She was biopsy-confirmed as AA amyloidosis carried with SAA1.3/1.5 allele genotype. ABT was initiated from January 2011 and her clinical course was shown in Fig. 7. The histopathological findings from upper gastrointestinal (GI) biopsy between before and after 1 year from the commencement of ABT revealed a disappearance of AA amyloid fibril deposition (Fig. 8-A, -B). The changes in markers on cytokines and lymphocyte expression might suggest an effect of ABT from the points of immunological aspect in the case (Table 5). These results would show effectiveness of this agent on both RA and AA amyloidosis, with being required further elucidations. In experimental mouse models of AA amyloidosis, blocking T lymphocytes function by the calcinulin inhibitor showed that

tacrolims inhibited AA amyloid fibril deposits in a dose-dependent manner without influencing SAA concentrations. Also, the locality of CD4+ T lymphocytes in the spleen was partially identical to AA amyloid fibril deposits histologically, suggesting the role of T lymphocytes in the pathogenesis of AA amyloidosis [39].

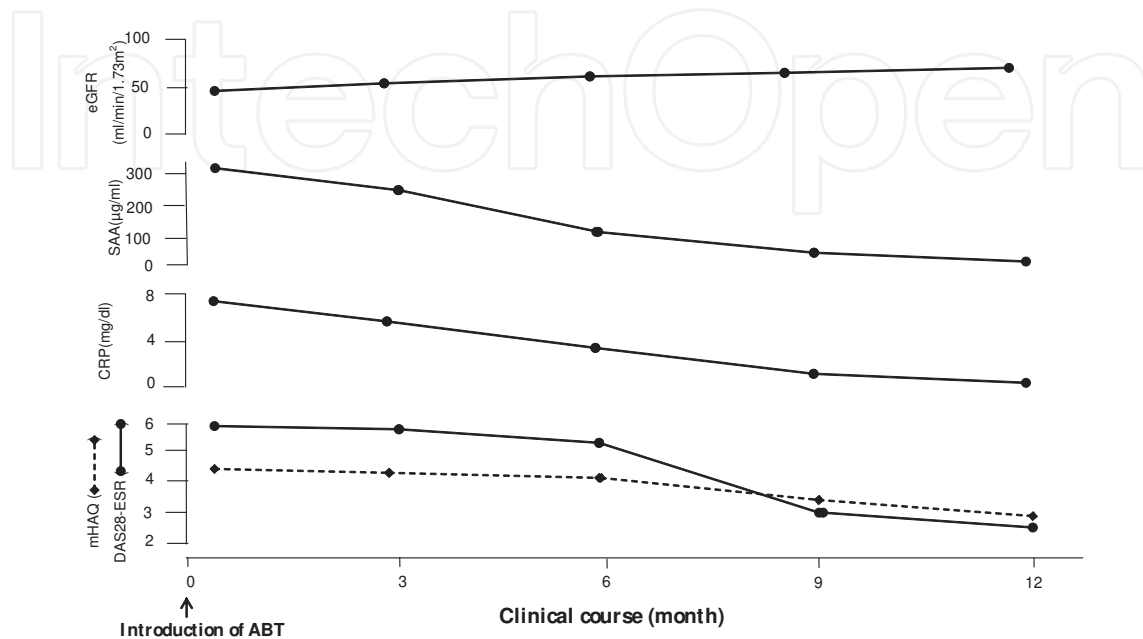


Figure 7. Effect of abatacept on AA amyloidosis secondary to RA. Inflammatory markers, CRP and SAA, decreased gradually, and renal dysfunction ameliorated with the treatment of abatacept. ABT: abatacept, eGFR: estimated glomerular filtration rate, SAA: serum amyloid A protein, CRP: C-reactive protein, mHAQ: modified health assessment questionnaire, DAS: disease activity score, ESR: erythrocyte sedimentation rate.

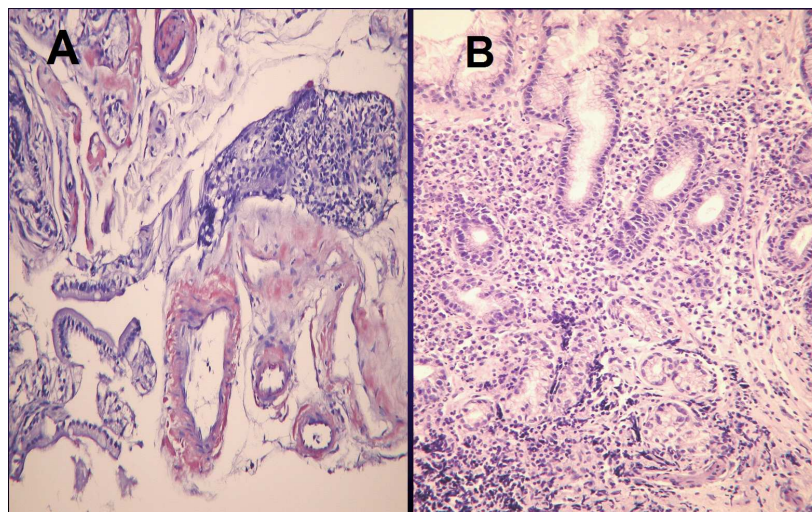


Figure 8. Histological changes before (A) the treatment with abatacept and after (B) one year in the disease course. Amorphous deposits were detected in the specimen from upper gastrointestinal biopsy with Congo Red staining (A). Those disappeared with abatacept treatment after one year (B).

Parameter	Baseline	Clinical course (month)				
	(n=14)	0	3	6	9	12
IL-6 (pg/ml)	11.2±12.9	107	40.4	24.8	7.6	1.7
TNFα (pg/ml)	1.04±0.36	2.2	1.4	1.3	1.1	1.1
IL-2 (U/ml)	<0.8	<0.8	<0.8	<0.8	<0.8	<0.8
CD4+/CD8+	1.30±0.58	2.04	1.63	1.54	1.72	1.77
CD4+CD25++FoxP3+ reg T cells gated on						
Lymphocytes (%)	1.60±0.85	4.8	2.6	2.1	2.4	2.4
CD4+ T lymphocytes (%)	4.79±1.60	9	5.4	4.8	5.2	5.1

Baseline values were determined and expressed by mean ± S.D. of 14 RA patients, matched by disease duration and disease severity to this case. IL-6: interleukin-6, TNFα: tumor necrosis factor alpha, IL-2: interleukin -2, reg T: regulatory T lymphocyte.

Table 5. Changes in cytokines and regulatory T lymphocyte expression after abatacept treatment

Rituximab (RTX), an anti-CD20 monoclonal antibody, was efficacious for patients with severe active RA who have exhibited an inadequate response to one or more TNFα inhibitors [59]. Also, this agent was administered alone in two RA patients and in combination with MTX in other two RA cases with histologic confirmation of AA amyloidosis. The four patients showed a significant clinical improvement of the articular symptoms and marked reduction of the acute phase-reactants. Renal function remained stable in all patients and proteinuria improved in two, worsened in one, and remained stable in the fourth with few adverse effects [60].

Clinical trials are warranted to assess the long-term safety and efficacy of biological treatments and their impacts on the survival of RA patients with AA amyloidosis.

4.1.3. Corticosteroids

The effect of corticosteroid treatment on AA amyloidosis is still controversial. Corticosteroids are capable of reducing the magnitude of the acute phase reaction including the synthesis of CRP and SAA. In human hepatocyte cultures a stimulating effect of corticosteroids was seen on SAA but not on CRP production [61, 62]. Although corticosteroid therapy suppresses both CRP and SAA levels in longitudinal studies of patients with RA, the effect is somewhat more pronounced for CRP than for SAA [63]. Monitoring of SAA instead of CRP levels would be advisable particularly if corticosteroids are being used. It seems reasonable to treat patients with AA amyloidosis secondary to RA using cytostatic drugs either alone or in combination with prednisolone [64-66]. As the effect of cytostatics may take weeks or months to appear, it is recommended to give steroids additionally in order to ensure an immediate reduction of the acute phase response and in particular the synthesis of SAA. Low-

dose prednisolone inclusion in a MTX-based tight control strategy for early RA would be effective, thus could be improved for AA amyloidosis secondary to RA [67].

4.2. Inhibition of AA amyloid fibril deposits

Eprodinate, a small sulfonated molecule with structural similarity to heparan sulfate, which can cause regression of amyloidosis by destabilizing the glycoasaminoglycan backbone of amyloid deposits, delayed progression of renal disease associated with AA amyloidosis. In a trial for AA amyloidosis, eprodinate had a beneficial effect on the rate of deterioration of renal function but no effect on urinary protein excretion [68]. Because eprodinate did not affect SAA levels and preserved kidney function but had no effect on proteinuria, the interesting possibility that it is the precursors of mature amyloid fibrils are responsible for proteinuria in amyloidosis would raise. In the light of higher effects of biologics on AA amyloidosis secondary to RA, the usefulness of eprodinate seems to be inferior to that of biologic under the biologics era.

4.3. Removal of deposited AA amyloid fibrils

The normal plasma protein SAP binds to all types of amyloid fibrils and contributes to amyloidosis pathogenesis [69]. A pyrrolidine carboxylic acid derivative, which is a competitive inhibitor of SAP binding to amyloid fibrils, can intervene in this process and affect SAP levels. This compound cross-linked and dimerized SAP molecules, which led to extremely rapid clearance by the liver, and thus produced marked depletion of circulating human SAP. Therefore, this drug action removed SAP from human amyloid deposits in tissues and may have a favorable effect on amyloidosis [70].

Another compound, dimethyl sulfoxide (DMSO), is a hydrogen-bond disrupter, cell-differentiating agent, hydroxyl radical scavenger, cryoprotectant, and solubilizing agent that is used as a compound for preparation of samples for electron microscopy, as an intracellular low-density lipoprotein-derived cholesterol-mobilizing 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 [71]. Oral DMSO was effective against AA amyloidosis, especially GI involvement and early renal dysfunction [72], but using it would not likely be feasible in current clinical practice.

4.4. 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 hemodialysis (HD) should be considered. Even in RA patients with AA amyloidosis who undergo HD, anti-TNF α blockers can demonstrate efficacy [11, 73]. HD reportedly had no effect on plasma ETN concentration, and ETN pharmacokinetics in patients undergoing HD for chronic renal failure were similar to

those with normal renal function [74]. Administration of ETN to HD patients would therefore appear reasonable. Renal replacement therapy is discussed in Table 6.

Renal transplantation

Immonen K, et al: J Rheumatol 2008; 35: 1334-8

30 cases in 332 RA patients with AA amyloidosis

Median survival: 2.11 years

Peritoneal dialysis/Hemodialysis (HD)

Bergesio F, et al: Nephrol Dial Transplant 2008; 23: 941-51

Prognosis: 17 months

Kuroda T, et al: Reference No. 73

96.9 person-year followup: 42 patients died

50% survival from the initiation of HD: 251 days

Ccr was superior to Crea, Advisable planned initiation of HD

Nakamura T, et al: Reference No. 11

51.8 months Dialysis with ETN 27.8 months Use

Amelioration of DAS28-ESR, CRP, mHAQ, and ESR

RA: rheumatoid arthritis, AA: amyloid A, HD: hemodialysis, Ccr: creatinine clearance, Crea: serum levels of creatinine, ETN: etanercept, DAS: disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, mHAQ: modified health assessment questionnaire.

Table 6. Renal replacement therapy in AA amyloidosis secondary to RA

5. Comparison of effectiveness between biologic and alkylating agent

We previously showed that the genetic predisposition allele SAA1.3 was not only a univariate predictor of survival but also a risk factor for association of AA amyloidosis with RA in Japanese patients [9], and in view of our earlier reports on the efficacy of ETN [10, 48] and CYC [35, 64] given alone for AA amyloidosis secondary to RA, we compared the effectiveness of ETN and CYC, and we assessed biomarkers and analyzed the effect of SAA1.3 allele on these treatments [75].

5.1. Patients and methods

This retrospective cohort study compared effectiveness of CYC and ETN for RA patients with AA amyloidosis who were homozygous for the SAA1.3 allele or other polymorphisms. Sixty-two RA patients received CYC and 24 did ETN; all had biopsy-confirmed AA amyloidosis. The presence of AA amyloid deposits was confirmed histologically via positive Congo Red staining, potassium permanganate susceptibility, and green birefringence seen by polarization microscopy after Congo Red staining, as well as immunohistochemical analysis using anti-AA antibody and anti-immunoglobulin light-chain (AL) antibody to differentiate AL amyloidosis.

Patients with RA had been treated with non-steroidal anti-inflammatory drugs (NSAIDs), prednisolone, DMARDs, and immunosuppressive agents but were often refractory to these agents. Although CYC had been unallowable medico-legally in Japanese governmental health insurance system and we were able to use CYC for RA treatment from August 2010 in Japan, we finally used CYC and investigated its efficacy for enrolled patients until December 2004.

Age, sex, and duration of RA and AA amyloidosis were recorded, as were changes in laboratory indices and clinical evaluations of disease activity included CRP, SAA, ESR, rheumatoid factor (RF), serum Alb, Crea, 24-hour proteinuria, and eGFR. Use of DMARDs, immunosuppressants, or PSL from the time of RA onset to the index time was noted. We chose CRP as an indicator of rheumatoid inflammation and Alb as an indicator of severity of AA amyloidosis [76]. Because renal dysfunction is the most common symptom in AA amyloidosis secondary to RA, we selected Crea and eGFR to assess treatment effectiveness. We calculated eGFRs via the nomogram for modification of diet reported in a Japanese renal disease study (index 0.741) using Crea measured by using an enzymatic method [77]. We also obtained information on drugs including DMARDs, NSAIDs, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. We recorded clinical symptoms and arthritis activity for each time point. We carefully checked adverse effects of immunosuppressants, *e.g.* infection risks, myelosuppression, haemorrhagic cystitis, and carcinogenesis.

We monitored biomarker levels and compared initial (before treatment) and last (after treatment) values. We used statistical analysis to assess effects of the SAA1.3 allele on therapies. We determined the onset of RA by reviewing of charts after AA amyloidosis diagnosis had been confirmed. Clinical symptoms at presentation were the main reason for physicians to obtain tissue biopsies to demonstrate AA amyloid deposits. We estimated survival curves via the Kaplan-Maier technique; we analyzed statistical differences between two curves by the log-rank test. We used Cox proportional hazards models to assess effects of treatments on eGFR and 24-hour proteinuria, with risk of death as the endpoint. We used two-way repeated-measures analysis of ANOVA to simultaneously estimate effects of SAA1.3 or treatments on individual changes in biomarkers. In the model, individual change was defined as within-subjects factors; categorical groups, *i.e.* polymorphisms of the SAA1.3 allele and treatments, were defined as between-subjects factors. To determine the factor affecting individual change, a combined factor (within and between) was defined as interaction. We evaluated significant effects of these factors via ANOVA. We determined significant interaction

of effects of groups (SAA1.3 or treatments) on changes in individual markers. Findings were statistically significant at $P < 0.05$. We used SPSS Statistics 17.0, Base and Advanced (SPSS Inc, Chicago, IL, USA) for statistical analyses.

5.2. Results

Table 7 provides patients' clinical characteristics and laboratory findings. Despite treatments being administered during different periods, clinical and laboratory findings of both groups were quite similar at the start of each treatment, except for the SAA1.3 genotype and duration AA amyloidosis since diagnosis ($P = 0.015$ and $P < 0.001$, respectively). With regard to biomarkers indicating renal dysfunction, ETN had worse kidney damage than did CYC. During the study, patients died in each treatment group at the almost same rate. In the CYC group, congestive heart failure and infectious pneumonia occurred frequently. Patients given ETN had a lower rate of congestive heart failure as cause of death, suggesting of the possibility of an inhibitory effect on progressive heart failure.

Years since RA onset and years since diagnosis of AA amyloidosis were significantly different for SAA1.3 homozygosity *vs* other genotypes (15.6 ± 7.8 *vs* 21.4 ± 9.9 , $P = 0.046$, and 7.44 ± 4.9 *vs* 9.7 ± 4.5 , $P = 0.016$, respectively). Comparison of CRP, Alb, eGFR, and Crea for both groups at initial and final observations, disregarding SAA1.3 allele polymorphisms, showed that ETN reduced serum CRP levels and increased serum Alb levels more than did CYC (ETN *vs* CYC: CRP: from 4.7 ± 0.8 to 0.5 ± 0.3 mg/dl *vs* from 4.0 ± 1.6 to 2.8 ± 1.2 mg/dl, $P < 0.01$; Alb: from 2.6 ± 0.4 to 3.5 ± 0.4 g/dl *vs* from 2.8 ± 0.3 to 2.8 ± 0.5 g/dl, $P < 0.01$, respectively). Thus, ETN significantly improved serum CRP and Alb levels and was clearly more effective than CYC. CRP and Alb interactions with polymorphism (homozygous for SAA1.3 or other polymorphisms) showed no significance ($P = 0.777$ and $P = 0.715$, respectively), but CRP and Alb interactions with treatment (ETN or CYC) demonstrated significant results (both $P < 0.01$). Within-subject analysis showed that treatments improved eGFR: ETN: from 21.8 ± 18.9 to 24.9 ± 18.7 ml/min/ 1.73m^2 *vs* CYC: from 29.3 ± 12.7 to 18.6 ± 9.3 ml/min/ 1.73m^2 , $P = 0.035$, with ETN's effect on eGFR being significant ($P = 0.032$). ETN increased eGFR, thus improving the decreased renal function caused by AA amyloidosis, more than did CYC (Fig. 9A), but this effect was not related to SAA1.3 allele polymorphisms (Fig. 9B). Neither treatment affected Crea levels. SAA1.3 allele did not affect treatment in both groups of patients, as evidenced by interactions of SAA1.3 allele with CRP, Alb, eGFR, and Crea ($P = 0.777$, $P = 0.715$, $P = 0.465$, and $P = 0.228$, respectively).

Because ETN was more effective than CYC, according to CRP, Alb, and eGFR measures, we calculated the hazard ratio between ETN and CYC as a survival parameter. According to Cox proportional hazards survival analysis, ETN significantly improved survival ($P = 0.025$). Also, the Kaplan-Meier curves showed a significant difference between ETN and CYC (Fig. 10). The hazard ratio for ETN evidenced significant results for the risk of death endpoint (eGFR: $P = 0.024$ and 24-hour proteinuria: $P = 0.025$, respectively) but CYC did not (Table 8).

		CYC (n=62) ²⁾	ETN (n=24) ³⁾	P-value ⁴⁾
I.	Sex, Male/Female, n	12/50	4/20	1.000
	SAA1.3 allele, Homozygout/Others, n	22/40	16/8	0.015
	Months since RA onset (mean)	176.0 (111.0)	195.3 (88.3)	0.447
	Months since diagnosis of AA amyloidosis (mean)	22.9(41.7)	67.5 (42.5)	<0.001
	Months of treatment (mean)	38.0 (27.4)	34.0 (23.1)	0.526
	Steinbrocker's classification ⁵⁾			
	Stage II,III,IV, n	5/18/39	3/7/14	
Class 2/3/4, n	38/18/6	14/7/3		
II	MTX therapy (yes/no), n	31/31	15/9	0.297
	PSL dosage (mg/day, mean)	9.91(5.88)	7.97 (4.96)	0.516
III	CRP (mg/dl, mean)	3.99 (1.72)	3.89 (1.97)	0.820
	SAA (µg/ml, mean)	294.8 (166.0)	327.0 (223.4)	0.467
	eGFR (ml/min/1.73 m ² , mean)	29.2 (23.9)	31.2 (20.6)	0.714
	Crea(mg/dl, mean)	2.04 (0.95)	2.23 (1.27)	0.465
	24-Hour urinary protein (g, mean)	1.53 (0.84)	2.09 (1.27)	0.020
	Serum Alb (g/dl, mean)	2.92 (0.32)	3.04 (0.68)	0.128
	RF (U/ml, mean)	237.8 (262.1)	200.8 (154.3)	0.519
IV	Cause of death, n (%)	n=26 (41.9)	n=8 (33.3)	0.464
	Infectious pneumonia	6	3	
	Sepsis	2		
	GI ulcer/bleeding	3		
	Interstitial pneumonia	4	1	
	Myocardial infarction	2		
	Congestive heart failure	7	2	
	Renal failure	1	1	
	Malignancy		1	
Unknown	1			

¹⁾ Baseline data were at the initiation of each treatment. All patients, except those who died, were followed from January 1995 to December 2010. Last observations were made in December 2004 for the CYC group and December 2010 for the ETN group. Values are represented by mean (S.D.) unless otherwise noted. Causes of death of patients who died during the study, and these causes were most closely related to their death. ²⁾CYC was given until December, 2004. Thirty-six alive [8 males, 28 females; mean (S.D.) age = 65.7 (10.8) years] and 26 dead [3 males, 23 females; mean (S.D.) age = 71.9 (8.5) years]. CYC was treated according to the level of 24-h Ccr: Ccr ≥ 80 (ml/min): 100 (mg/day), 60 ≤ Ccr < 80 (ml/min): 75 (mg/day), 40 ≤ Ccr < 60 (ml/min): 40 (mg/day), 10 ≤ Ccr < 20 (ml/min): 25 (mg/day), Ccr < 10 (ml/min): 20 (mg /day). ³⁾ETN was until December, 2010. Sixteen alive [3 males, 13 females; mean (S.D.) age = 64.2 (8.5) years] and 8 dead [1 male, 7 females; mean (S.D.) age = 66.0 (7.8) years]. ⁴⁾Student's-t analysis was performed to compare CYC and ETN, with P < 0.05 indicating a significant result. ⁵⁾Steinbrocher's classification according to JAMA 1949; 140: 659-62. Quoted from Reference No. 75.

Table 7. Clinical characteristics and laboratory findings of patients¹⁾

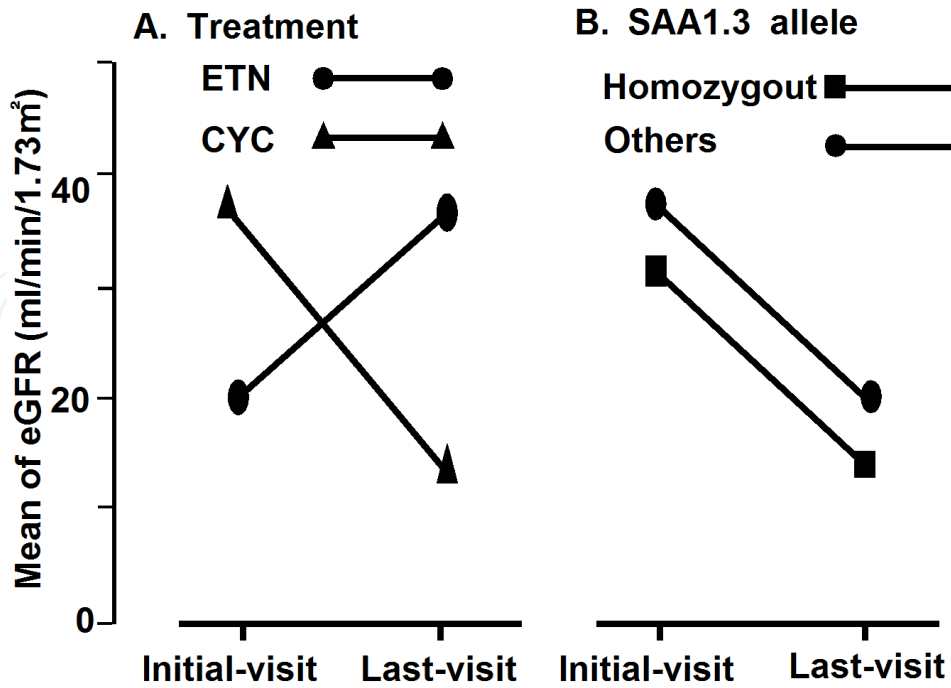


Figure 9. A) Changes in eGFR between initial- and last-visit as an effect of treatment (ETN or CYC). (B) Changes in eGFR between initial- and last-visit as an effect of SAA1.3 allele genotype (homozygosity or other polymorphisms). Quoted and modified from Reference No. 75.

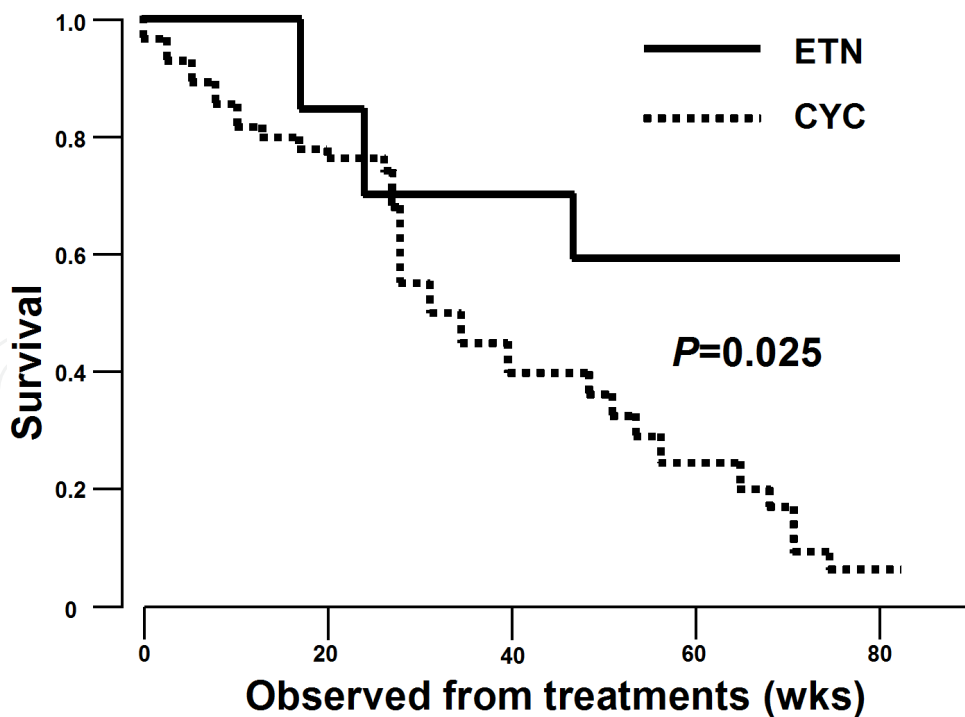


Figure 10. Kaplan-Meier survival curves after treatment with ETN (continuous line) and CYC (dotted line; $P=0.025$, log-rank test). Quoted and modified from Reference No. 75.

	eGFR		24-Hour proteinuria	
	Hazard ratio (95% confidence interval)	P-value	Hazard ratio (95% confidence interval)	P-value
ETN	0.949 (0.907-0.993)	0.024	1.779 (1.074-2.946)	0.025
CYC	0.951 (0.894-1.012)	0.110	1.161 (0.542-2.488)	0.701

Hazard ratio for each treatment using the Cox proportional hazards models to assess effect of treatments on the risk of death as the endpoint, being determined by two variables, eGFR and 24-h proteinuria. Quoted and modified from Reference No. 75. ETN: etanercept, CYC: cyclophosphamide, eGFR: estimated glomerular filtration rate.

Table 8. Hazard ratio for each treatment

5.3. Discussion

The goal of AA amyloidosis therapy is control of the underlying disorder. Treatment suppressing inflammatory activity reduces circulatory levels of SAA, an acute-phase reactant. In AA amyloidosis secondary to RA, treatment has focused on using cytotoxic drugs such as CYC and chlorambucil [29, 32] and more recently on TNF α inhibitors and IL-6 receptor antibody [45,56]. Before the advent of biologics, encouraging reports of alkylating agents as benefiting RA patients with AA amyloidosis were published. The rationale of this treatment seems to be similar to autologous stem cell transplantation, which generates new self-tolerant lymphocytes after alkylating agent treatment by eliminating self-reactive lymphocytes [78]. In the light of the reported superiority of CYC compared with MTX for managing RA patients with AA amyloidosis [9], using alkylating agents may improve AA amyloidosis. Cytotoxic drugs and cytokine inhibitors affect AA amyloid deposits by suppressing SAA production. Also, anti-TNF α therapies, by inhibiting expression of receptors of advanced glycation end-products (RAGE), may reduce interactions between AA amyloid fibrils and RAGE and thereby prevent AA-mediated cell toxicity [79, 80]. Thus, our findings that ETN had greater effects on AA amyloidosis secondary to RA than did CYC was not unexpected, and early therapeutic intervention in RA may avoid the complication of AA amyloidosis by controlling rheumatoid disease activity [26].

In Japan, use of MTX to treat with RA patients was permitted in 1999, the maximum dose being 8 mg/week, until February 2011; use of ETN was allowed in 2005. In our study the time from diagnosis of AA amyloidosis was shorter for the CYC group than the ETN group (Table 8), but treatment strategies and DMARDs used were the same, except for the use of biologics. Although MTX is now considered an anchor drug for RA treatment, it was used infrequently for AA amyloidosis patients because of its renal damage. No significant differences between groups in MTX therapy were found (Table 7). The recovery of Alb biosynthesis, improved acute-phase response, and ameliorated eGFR are all demonstrable endpoints, and we suggest that Alb reflects the severity of AA amyloidosis. We found that the different therapies rather than SAA1.3 allele polymorphism influenced changes in CRP and Alb. Al-

so, eGFR may reflect diminished renal blood flow, and only ETN improved eGFR, thus indicating better renal function and greater efficacy of ETN than CYC (Fig. 9A). We found no evidence linking SAA1.3 allele to treatment efficacy (Fig. 9B).

6. 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 further 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 in 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 realized. 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. By employing with the newly developed therapies, AA amyloidosis secondary to RA will already become both treatable and curable disease. Further, genetic predisposition, SAA1.3 allele genotype, would serve one of personalized medicines to make AA amyloidosis secondary to RA a preventable disease.

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Author details

Tadashi Nakamura

Address all correspondence to: nakamura@k-shinto.or.jp

Section of Clinical Rheumatology, Kumamoto Shinto General Hospital and Graduate School of Medical Sciences, Kumamoto University, Japan

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