Secondary amyloid A (AA) amyloidosis is an uncommon yet important complication of rheumatoid arthritis (RA) and is a serious, potentially life-threatening disorder caused by deposition in organs of AA amyloid fibrils, which are derived from the circulatory acute-phase reactant, serum amyloid A (SAA) [1–3]. This process typically results in organ dysfunction or failure. The natural history of AA amyloidosis secondary to RA is basically progressive, leading to organ failure and death when RA remains active [4]. 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 the prevention or cure for AA amyloidosis. While there is startling variation in the frequency of AA amyloidosis worldwide, differences also exist for AA amyloidosis complicating RA [5]. The reasons, however, for the marked geographic differences are unclear. We found that the frequency of the SAA1.3 allele was markedly increased in AA amyloidosis in Japanese RA patients, suggesting that this allele was a risk factor for AA amyloidosis secondary to RA [6]. Although the actual role of the SAA1.3 allele in the pathogenesis, development and outcome of AA amyloidosis in RA remains obscure, it is important to follow RA patients having the SAA1.3 allele carefully, to diagnose AA amyloidosis as early as possible, and to start suitable treatment to slow progression by controlling the inflammatory aspects of disease activity [7, 8].

The aim of our study was to clarify the role of the SAA1.3 allele as a predictive factor in the development and outcome of AA amyloidosis in Japanese RA patients. Despite the fact that AA amyloidosis secondary to RA is a well-recognized complication, there are few studies evaluating prognostic factors, outcome and natural history. The present study was undertaken to investigate whether mortality in RA patients with AA amyloidosis is increased compared with those without AA amyloidosis and, if so, which clinical variables contribute to the increased mortality in RA patients with AA amyloidosis.

**Objective.** To clarify the clinical significance of the SAA1.3 allele in the development and outcome of AA amyloidosis in Japanese patients with rheumatoid arthritis (RA).

**Methods.** One hundred and twenty RA patients (60 alive and 60 dead) fulfilling the 1987 ACR criteria and 62 RA patients with biopsy-confirmed amyloid A (AA) amyloidosis (36 alive and 26 dead) were enrolled. The SAA1 genotypes were determined by PCR-based restriction fragment length polymorphism. To predict the clinical outcome of AA amyloidosis, we investigated characteristics and survival, focusing on the SAA1.3 allele retrospectively.

**Results.** The SAA1.3 allele genotype was not only a risk factor for the association of AA amyloidosis but also a poor prognostic factor for the development of AA amyloidosis ($P=0.015$). Both the association of AA amyloidosis arising early in the RA disease course and symptomatic variety and severity were found in amyloidotic patients with the SAA1.3 allele. The presenting factors adversely influenced were age ($P=0.001$), lowered serum albumin ($P=0.001$) and creatinine concentration ($P=2.14 \times 10^{-5}$). Renal involvement was associated with poor survival in patients with AA amyloidosis ($P=0.011$) and the presence of cardiac involvement was likely to be a risk factor for survival ($P=0.062$). The rate of the causes of death in respect to the category of infection, gastrointestinal diseases, and renal failure was higher in patients with AA amyloidosis than in those without amyloidosis, gastrointestinal diseases and renal failure. Cyclophosphamide was found to be superior to methotrexate in the management of RA patients with AA amyloidosis.

**Conclusion.** Our data support the fact that homozygosity for the SAA1.3 allele is a univariate predictor of survival in addition to a risk factor for the association of AA amyloidosis adversely influencing the outcome in Japanese RA patients. Renal involvement is a pivotal clinical manifestation in the development of AA amyloidosis, as is likely to be cardiac involvement in AA amyloidosis secondary to RA.

**Key words:** Rheumatoid arthritis, Amyloidosis, SAA1.3 allele.
Patients and methods

Patients and medication

This investigation was designed as a retrospective cohort study comparing RA patients with AA amyloidosis with those without AA amyloidosis. One hundred and twenty RA patients (60 alive (15 males, 45 females; mean age 53.2 ± 15.2 yr) and 60 dead (17 males, 43 females; mean age 51.8 ± 16.9 yr)) fulfilling the 1987 ACR criteria [9] and 62 RA patients with AA amyloidosis [36 alive (7 males, 29 females; mean age 48.1 ± 15.0 yr) and 26 dead (3 males, 23 females; mean age 47.9 ± 11.6 yr)] with biopsy-confirmed AA amyloid were enrolled. The clinical records of these patients, who were followed from January 1995 to December 2004 by the Kumamoto Center for Arthritis and Rheumatology, were reviewed. When clinical features that may raise suspicion of the existence of amyloidosis, such as proteinuria, thyroid dysfunction, weight loss, repeated constipation and diarrhoea, were observed in patients with RA, routine screening that included tissue biopsy (mainly gastric mucosal biopsy) was undertaken with informed consent. The presence of AA amyloid was histologically confirmed by positive Congo red staining, susceptibility to oxidation treatment with potassium permanganate, and green birefringence on polarization microscopy after Congo red staining. Any patient whose clinical chart diagnosis was AA amyloidosis not confirmed by biopsy was excluded from this study.

In Japan both lobenzarit disodium and actarit have been given as inflammatory drugs (NSAIDs), approximately 10 mg/day of glucocorticosteroids (prednisolone [PSL]), and at least one (mean 3.6 ± 2.2) disease-modifying anti-rheumatic drug (DMARD) (intramuscular and oral gold preparations, lobenzarit disodium, d-penicillamine, bucillamine, sulphasalazine and actarit) for their inflammation arthritis, but were often refractory to these therapies. Because DMARD regimens did not induce remission of RA disease activity, the assessment of efficacy of the combination therapy was undertaken with informed consent. The presence of AA amyloid was histologically confirmed by positive Congo red staining, susceptibility to oxidation treatment with potassium permanganate, and green birefringence on polarization microscopy after Congo red staining. Any patient whose clinical chart diagnosis was AA amyloidosis not confirmed by biopsy was excluded from this study.

All RA patients had been treated with non-steroidal anti-inflammatory drugs (NSAIDs), approximately 10 mg/day of glucocorticosteroids (prednisolone [PSL]), and at least one (mean 3.6 ± 2.2) disease-modifying anti-rheumatic drug (DMARD) (intramuscular and oral gold preparations, lobenzarit disodium, d-penicillamine, bucillamine, sulphasalazine and actarit) for their inflammatory arthritis, but were often refractory to these therapies. In Japan both lobenzarit disodium and actarit have been given as inflammatory drugs (NSAIDs), approximately 10 mg/day of glucocorticosteroids (prednisolone [PSL]), and at least one (mean 3.6 ± 2.2) disease-modifying anti-rheumatic drug (DMARD) (intramuscular and oral gold preparations, lobenzarit disodium, d-penicillamine, bucillamine, sulphasalazine and actarit) for their inflammatory arthritis, but were often refractory to these therapies. Because DMARD regimens did not induce remission of RA disease activity, the assessment of efficacy of the combination therapy was undertaken with informed consent. The presence of AA amyloid was histologically confirmed by positive Congo red staining, susceptibility to oxidation treatment with potassium permanganate, and green birefringence on polarization microscopy after Congo red staining. Any patient whose clinical chart diagnosis was AA amyloidosis not confirmed by biopsy was excluded from this study.

Demographic and clinical variables

Demographic and clinical data on the patients were obtained from the medical charts. Sex, age, duration of RA and duration of AA amyloidosis were recorded, and data on changes in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), serum creatinine and serum albumin, comorbidity, and the use of DMARDs, immunosuppressants or PSL from the time of RA onset to the index time were obtained. Comorbidity was classified as infection, cardiovascular disease, respiratory disease, gastrointestinal disease, malignancy, renal failure, cerebrovascular disease, or unknown. Overall clinical symptoms and arthritis activity were also recorded at each time point. The adverse effects of immunosuppressants, such as risk of infection, myelosuppression, haemorrhagic cystitis and carcinogenesis, were checked carefully. These effects have prompted the need for alternative therapies.

Monitoring

The patients were monitored for ESR, CRP, RF, creatinine, albumin, complete blood cell counts and transaminases. In addition to laboratory measurements, Steinbrocker’s functional class [10] and Lansbury’s index [11] were recorded on several occasions. For ethical reasons, repeated visceral biopsies to assess the disease nature of AA amyloidosis were not recommended unless otherwise specified.

Determination of SAA1 genotype

To determine the SAA1 genotype, polymerase chain reaction (PCR)-based restriction fragment length polymorphism analysis was performed using samples from each patient, as described previously [6, 12]. In brief, a SAA1 gene fragment containing the polymorphic site in exon 3 was amplified by PCR. The amplified DNA (530 bp) was digested with restriction enzymes and run on a 10% polyacrylamide gel. The resulting fragments were visualized using silver staining. Homozygous controls for three alleles (1.1/1.1, 1.2/1.2, 1.3/1.3) were also run and stained. With the enzyme BanI, the DNA amplified from the 1.1 allele was digested into three fragments (317, 188 and 25 bp), whereas that from the 1.2 and 1.3 alleles was digested into four fragments (244, 188, 73 and 25 bp). With BciI, the DNA amplified from the 1.2 allele was digested into two fragments (438 and 92 bp), whereas that from the 1.1 and 1.3 alleles was not digested. Written informed consent was obtained from all subjects.

Follow-up

Information on mortality and cause of death were obtained from the Center’s chart and the patient’s general practitioner. Information on mortality could be gathered for all patients. Considering the clinical course or disease state in an individual case, we defined the cause of death as the one that was most closely related to her/his death.

Amyloid-related cardiac involvement

Cardiac amyloidosis was considered based on the following parameters as indicators of the disease, in accordance with previous studies [13, 14]: the lack of other obvious predisposing factors, such as hypertension, valvular disease or ischaemic heart disease, plus one of the following criteria: (i) congestive heart failure; (ii) abnormal electrocardiographic (ECG) findings (findings suggestive of a past myocardial infarction, poor R wave progression, abnormal Q wave, QS pattern or conduction block); and (iii) abnormal echocardiographic findings (thickened right and left ventricular myocardium with normal left ventricular cavity dimensions, diffuse hyper-refractile ‘sparkling granular’ appearance) [15]. An autopsy was performed in seven patients, including needle tissue sampling, who were diagnosed as having amyloid-related cardiac involvement, and amyloid deposits were confirmed in the heart tissue.

Statistical analysis

Mortality was compared between RA patients with and without AA amyloidosis. Survival was depicted graphically with Kaplan–Meier survival curves. Differences between curves were tested with the log-rank statistic. All values were calculated as mean ± s.d. and Bonferroni analysis was performed. The risk of death during follow-up after the beginning of the study was estimated with the Cox proportional hazards model using likelihood backward selection, and is expressed as the hazard ratio and its 95% confidence interval. Findings were considered statistically significant at \( P < 0.05 \). Statistical analyses were performed with SPSS 10.1 software for Windows (SPSS, Chicago, IL, USA).
Effect of SAA1.3 genotype on prognosis in RA

Because we found that the SAA1.3 allele was markedly increased in AA amyloidosis in Japanese RA patients [6, 8], suggesting that this allele was a risk factor for AA amyloidosis secondary to Japanese RA, we calculated the hazard ratio in the presence or absence of SAA1.3/1.3 as a survival parameter after the onset of RA. By means of Cox proportional hazards survival analysis, having SAA1.3/1.3 was statistically significant for survival ($P=0.015$), with a hazard ratio of 2.14 ($2.95 \times 10^{-5}$), lowered serum albumin concentration ($P=0.001$) and the presence of SAA1.3/1.3 ($P=0.035$) (Table 2A). After the diagnosis of RA, the age of RA onset ($P=2.95 \times 10^{-5}$) and the presence of renal involvement ($P=0.011$) were extracted as survival parameters (Table 2B). As shown in Fig. 2, a serum creatinine value of $>2.5$ mg/dl upon diagnosis of AA amyloidosis was closely related to poorer survival, when compared with a serum creatinine value of $\leq2.5$ mg/dl by the Kaplan-Meier technique ($P=0.013$ with log-rank statistic). The presence of cardiac involvement was likely to be a risk factor for survival ($P=0.062$) (Table 2B).

Survival parameters in RA with AA amyloidosis

The presenting factors that adversely influenced clinical outcome after diagnosis of AA amyloidosis were age ($P=0.001$), raised serum creatinine concentration ($P=2.14 \times 10^{-5}$), lowered serum albumin concentration ($P=0.001$) and the presence of SAA1.3/1.3 ($P=0.035$) (Table 2A). After the diagnosis of RA, the age of RA onset ($P=2.95 \times 10^{-5}$) and the presence of renal involvement ($P=0.011$) were extracted as survival parameters (Table 2B). As shown in Fig. 2, a serum creatinine value of $>2.5$ mg/dl upon diagnosis of AA amyloidosis was closely related to poorer survival, when compared with a serum creatinine value of $\leq2.5$ mg/dl by the Kaplan-Meier technique ($P=0.013$ with log-rank statistic). The presence of cardiac involvement was likely to be a risk factor for survival ($P=0.062$) (Table 2B).

Medications in RA with AA amyloidosis

In RA patients with AA amyloidosis, medications used during this study are summarized in Table 3. Two-thirds of both alive and dead patients had previously received NSAIDs. The mean PSL dose received was $8.87 \pm 7.34$ mg/day in alive and $9.67 \pm 8.72$ mg/day in dead patients. There were no differences in medications between alive and dead RA patients with AA amyloidosis. As regards MTX and CYC treatments, we observed differences in both serum CRP and creatinine concentrations. We subtracted the CRP and/or creatinine value at initiation from...
Cox proportional hazards survival analysis (part B of the table).

***TABLE 2. Survival parameters***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) After diagnosis of AA amyloidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.097 (1.039–1.159)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rheumatoid factor (+/-)</td>
<td>1.367 (0.376–4.970)</td>
<td>0.635</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>3.556 (1.777–7.114)</td>
<td>9.83 × 10⁻⁴</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.390 (1.111–1.737)</td>
<td>0.004</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>0.997 (0.977–1.017)</td>
<td>0.758</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.834 (0.555–1.252)</td>
<td>0.382</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>1.004 (0.983–1.025)</td>
<td>0.727</td>
</tr>
<tr>
<td>SAA 1.3/1.3 (+/-)</td>
<td>0.537 (0.794–1.032)</td>
<td>0.035</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.084 (1.034–1.136)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>2.935 (1.723–4.997)</td>
<td>2.14 × 10⁻⁵</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>1.317 (1.112–1.560)</td>
<td>0.001</td>
</tr>
<tr>
<td>SAA 1.3/1.3 (+/-)</td>
<td>0.236 (0.057–0.982)</td>
<td>0.035</td>
</tr>
<tr>
<td>(B) After RA diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of RA onset (yr)</td>
<td>1.081 (1.059–1.104)</td>
<td>2.95 × 10⁻⁴</td>
</tr>
<tr>
<td>Female</td>
<td>0.624 (0.371–1.050)</td>
<td>0.624</td>
</tr>
<tr>
<td>Cardiac involvement (+/-)</td>
<td>1.380 (0.700–2.719)</td>
<td>0.062</td>
</tr>
<tr>
<td>Renal involvement (+/-)</td>
<td>2.151 (1.190–2.890)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Eight variables (first eight rows of part A of the table) were analysed by Cox proportional hazards survival analysis. Four further variables (rows 9–12 of part A) extracted by the regression analysis were statistically significant. Four variables were analysed by time-dependent Cox proportional hazards survival analysis (part B of the table).

**FIG. 2.** Kaplan–Meier survival curve after diagnosis of AA amyloidosis for patients with serum creatinine >2.5 mg/dl (continuous line) and serum creatinine <2.5 mg/dl (dotted line) (P = 0.013, log-rank test).

The CRP and/or creatinine value at the endpoint corresponding to each treatment. Each deducted value was localized in Fig. 3. It was clear that more CYC treatments than MTX treatments were within the minus area. CRP improved by 1.23 ± 1.67 mg/dl in CYC treatments (P < 0.001) (data not shown).

**Causes of death in RA patients with and without AA amyloidosis**

The causes of death in RA with and without AA amyloidosis are shown in Table 3. The majority of deaths was attributed to infection and cardiovascular diseases. In particular, heart diseases were the second leading cause of death in both groups. In patients with AA amyloidosis, gastrointestinal diseases and renal failure accounted for a much greater proportion of deaths than in patients without AA amyloidosis. Malignancy was seen only in patients without AA amyloidosis. The SAA1.3 allele genotype had no statistically significant influence on causes of death in RA patients with AA amyloidosis (data not shown).

**TABLE 3. Medications in RA patients with AA amyloidosis**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Alive (n = 36)</th>
<th>Dead (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Bucillamine</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Aurothiomalate sodium</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Auranofin</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Mizoribine</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>-Penicillamine</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Actarit</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lobenzarit disodium</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion**

There is a startling geographical difference in the frequency of AA amyloidosis among various ethnic groups worldwide, and the reasons for the marked geographic differences are still unclear. One of the most likely explanations of these differences is related to polymorphic heterogeneity of SAA1 genotypes among different ethnic groups, which could result in a different frequency of AA amyloidosis in RA. We have identified a novel polymorphism of serum SAA1.3 and found that the frequency of the SAA1.3 allele was markedly increased in AA amyloidosis in Japanese RA patients, suggesting that this allele was a risk factor for AA amyloidosis secondary to RA [6, 8]. In addition, our data support the notion that the SAA1.3 allele is not only a risk factor for the association of AA amyloidosis with RA, but also a strong predictor of survival in Japanese RA patients with AA amyloidosis (Fig. 1, Table 2A). This suggests an important role of the SAA1.3 allele in the ethnic difference in the prevalence of AA amyloidosis in RA.

It is clear that subclinical amyloidosis may be common in RA [16–18] and other inflammatory rheumatic diseases [19]. The prevalence rates of secondary amyloidosis in RA patients in recent series to detect amyloid deposits range from 7 to 26%; most of these patients have subclinical amyloidosis [5, 20–22]. In contrast, the prevalence of clinical amyloidosis is rather lower; in a Spanish cohort study designed specifically to search for comorbidities and extra-articular complications, clinical amyloidosis was found in only 5 out of 788 registered patients [23–25]. Therefore, in some patients amyloid deposits are truly silent and in others they only reflect preclinical status. Taking the discordance between prevalence rates of clinical and subclinical AA amyloidosis into account, it might be concluded that most RA patients have true silent AA amyloidosis and would not develop clinical visceral involvement. Genetic factors, however, will be involved in the prevalence and prognosis of amyloidosis secondary to RA. Some factors had an influence on the development and length of the latent period of AA amyloidosis secondary to RA [6, 26–28]. Of these, the SAA1.3 allele influenced on susceptibility and prognosis towards AA amyloidosis of RA patients and homozygosity for this allele was a significant risk factor for AA amyloidosis (Fig. 1, Table 2A). This allele was also related with earlier onset of AA amyloidosis, prognosis and symptomatic severity [7, 12, 29]. A similar trend with respect to the frequency of the SAA1.1 allele and homozygosity for this allele was observed in a different ethnic population [30–32]. These results suggest that there is probably differential amyloidogenicity amongst the different SAA1 isoforms.
Identification of patients at risk of developing AA amyloidosis and indicate that homozygosity for SAA1.1 and SAA1.3 in the different populations would be a significant risk factor for the development of AA amyloidosis. One possible reason is the amino acid sequence of the available precursor protein, which is the SAA isoform in the individual at risk. It has been demonstrated that if primary diseases causing AA amyloidosis are appropriately treated, with sustained lowering of SAA levels, amyloid deposits are halted and existing amyloid deposits are often resolved dramatically, leading to improved organ function and prognosis [33]. In recent years, new anti-rheumatic drugs, including biological therapies, have been shown to be highly effective in controlling inflammatory activity and joint destruction [34]. Identification of patients at risk of developing AA amyloidosis in Japanese RA would therefore be an important practical contribution to early diagnosis and suitable therapy, and would also help to elucidate the molecular mechanism of amyloidogenesis. It is of importance 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 homozygosity of SAA1.3 could be a marker for administration of biologicals as a therapeutic candidate during the early phase of the RA disease course (a window of opportunity) [35].

Differences in the frequencies of certain alleles among populations sometimes reflect only markers rather than true risk loci [31]. In some cases, a nearby locus that is in linkage disequilibrium with the first locus turns out to be the real responsible locus. With regard to AA amyloidosis, the SAA2 locus was considered a candidate for this scenario, because SAA2 is also deposited in AA amyloidosis as an acute-phase protein and because this locus is closely linked to the SAA1 locus [36]. When compared among amyloidosis populations, however, the frequencies of individuals with various genotypes at the SAA2 locus did not show significant differences and also did not differ among them [27]. This leads us to exclude the possibility that the SAA2 locus is the locus responsible for amyloidogenesis.

In assessing the prognosis of RA patients with AA amyloidosis, it is important to identify the clinical risk factors affecting the survival of patients. Our study confirmed that age and serum creatinine and albumin concentrations were important predictive factors for survival upon diagnosis of AA amyloidosis (Table 2A). Furthermore, the patients with poorer prognosis were significantly older, had more advanced renal disease, higher creatininaemia and lower albuminaemia at diagnosis of RA (Table 2B). Renal involvement has been considered to be the most critical problem in patients with AA amyloidosis [17, 18, 37] and dominates the clinical picture in AA amyloidosis [38]. We have also reconfirmed the importance of renal involvement as the clinical predictor of survival (Table 2B) [39, 40]. In addition, we have shown that a serum creatinine value of >2.5 mg/dl upon diagnosis of AA amyloidosis was associated with a poorer survival, and the mean survival of patients with a serum creatinine level >2.5 mg/dl was 6.9 yr compared with those with a serum creatinine level ≤2.5 mg/dl, who had a mean survival of 12.2 yr (P = 0.013) (Fig. 2). It is suggested that hypalbuminaemia may be the primary cause of morbidity and mortality in patients with renal failure. Raised serum creatinine and lowered albumin concentration should be recognized as a poor prognostic factor in RA patients with AA amyloidosis.

Renal failure and infection are generally the commonest causes of death in RA patients with AA amyloidosis [37, 38]. Our data showed that infection and renal failure accounted for 42.3 and 19.2% of deaths, respectively (Table 4). The fact that the rate in causes of death in renal failure and gastrointestinal diseases was

![Fig. 3. Differences in CYC and MTX treatments for RA patients with AA amyloidosis. The deducted value (placed in figures) was calculated by subtracting the starting value of CRP and/or creatinine from the endpoint value in each treatment.]
higher in RA patients with AA amyloidosis than in those without AA amyloidosis may be attributable to more amyloid deposition in these organs. It was strongly suggested that renal failure was a characteristic cause of death in RA patients with AA amyloidosis as compared with those without AA amyloidosis.

Unlike AL (amyloid of light chain of immunoglobulin) amyloidosis, AA amyloidosis has attracted very little attention from a neurological point of view, so even basic facts about its evolution are obscure. It is considered that serious cardiac complications and dysautonomia are somewhat infrequent in RA patients with AA amyloidosis at presentation, compared with AL amyloidosis [41–43]. Amyloidotic cardiac involvement estimated by our criteria has shown a trend to be a poor prognostic factor (P = 0.062) (Table 2B). Although the proportion of cardiovascular causes of death in RA patients with AA amyloidosis was the same as in those without AA amyloidosis, heart failure occupied highly more in cardiovascular causes of death of RA patients with AA amyloidosis than those without AA amyloidosis (Table 4). Heart failure is likely to be directly responsible for death in only a minority of patients; however, heart failure may be complicated by multiorgan failure in the later phase of RA disease course. We reported a case of gustatory sweating due to autonomic neuropathy with cardiac amyloid involvement, which dominated the terminal stage of AA amyloidosis secondary to RA [29]. This seems to imply 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. Histological detection of amyloid deposits has not yet been shown in the autonomic nervous system. Autonomic nervous system involvement is uncommon in RA; however, in RA patients with AA amyloidosis it seems likely that autonomic nerve dysfunction is a typical symptom in the end stage of the disease course and gustatory sweating could be useful as a clinical sign. This suggests the importance of gustatory sweating as a hallmark of autonomic nervous system involvement. Of course, renal involvement is a pivotal clinical manifestation in the development of AA amyloidosis, as could be cardiac involvement and dysautonomia in AA amyloidosis secondary to RA.

It is important to identify RA patients with AA amyloidosis, who may have a poor prognosis at a stage when it should be possible to alter the disease process and in whom immunosuppressive treatment may be justified. Traditional management of AA amyloidosis has been to target the underlying disease process behind the inflammation. Although there is no evidence that DMARDs have a specific effect on amyloidogenesis [44, 45] and AA amyloidosis in RA (Table 3), there have been encouraging reports evaluating alkylating agents as beneficial in clinical trials in RA patients with AA amyloidosis [46–49]. It is suggested that the use of immunosuppressive agents can improve prognosis, and we have shown that CYC was superior to MTX in the treatment of RA patients with AA amyloidosis (Fig. 3). We reported the possibility that CYC would be more effective in patients homozygous for SAA1.3/1.3 than in heterozygous patients, suggesting that SAA1.3/1.3 homozygosity is a factor in susceptibility to CYC treatment [8]. The principal aim in treatment of RA patients with AA amyloidosis is to switch off production of the amyloidogenic protein SAA by controlling the rheumatoid inflammatory process. Whether an effective treatment exists for AA amyloidosis remains controversial. Because our study was retrospective and patients were not treated in a uniform fashion, we cannot comment on whether specific therapies are warranted and are superior to previously reported regimens. In recent years, anti-TNF-α therapy has revolutionized the management of RA [50, 51]. As this class of drugs has become more clinically available, there is increasing recognition of their role in inflammatory conditions. Biological therapy suppresses SAA production and it has been shown that, in AA amyloidosis, keeping levels of SAA below 10 μg/ml is associated with the potential for amyloidotic organs to recover [33]. Prospective comparative studies between the combination therapy with CYC plus PSL [8, 52] and anti-TNF-α therapy are now going on in our Center. Whether a response to treatment clearly prolongs survival or whether patients destined to live a long time have more time to respond cannot be answered outside a prospective randomized treatment trial. The efficacy of the therapy to clarify the importance of reduction of disease activity responsible for regression in the process of AA amyloidosis, not only in controlling acute disease activity but also in the prevention of early and late flares, must be considered. A longer follow-up would therefore be required to prove the efficacy of these therapies. Further studies will help to shed light on these all-important points.

Acknowledgements

We would like to thank Professors Laurence A. Boxer and David A. Fox of the University of Michigan Medical Center, Ann Arbor, MI, USA for their editorial advice on the manuscript. This work was supported in part by a Grant-in-Aid for scientific research from the Japanese Ministry of Health, Labour, and Welfare.

The authors have declared no conflicts of interest.

References


