Treatment with Biologic Agents Improves the Prognosis of Patients with Rheumatoid Arthritis and Amyloidosis

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ABSTRACT. ***Objective.*** Reactive amyloid A (AA) amyloidosis is a serious and life-threatening systemic complication of rheumatoid arthritis (RA). We evaluated the safety of therapy with anti-tumor necrosis factor and anti-interleukin 6 biologic agents in RA patients with reactive AA amyloidosis, together with prognosis and hemodialysis (HD)-free survival, in comparison with patients with AA amyloidosis without such therapy.

Methods. One hundred thirty-three patients with an established diagnosis of reactive AA amyloidosis participated in the study. Clinical data were assessed from patient records at the time of amyloid detection and administration of biologics. Survival was calculated from the date when amyloid was first demonstrated histologically or the date when biologic therapy was started until the time of death or to the end of 2010 for surviving patients. Patients who had started HD were selected for inclusion only after the presence of amyloid was demonstrated.

Results. Fifty-three patients were treated with biologic agents (biologic group) and 80 were not (nonbiologic group). Survival rate was significantly higher in the biologic group than in the nonbiologic group. Nine patients in the biologics group and 33 in the nonbiologic group started HD. Biologic therapy had a tendency for reduced risk of initiation of HD without any statistical significance.

Conclusion. Patients with amyloidosis have a higher mortality rate, but the use of biologic agents can reduce risk of death. The use of biologics may not significantly influence the HD-free survival rate.
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Key Indexing Terms:
RHEUMATOID ARTHRITIS REACTIVE AMYLOIDOSIS BIOLOGICS PROGNOSIS

Recently, therapy with biologic agents including anti-tumor necrosis factor (TNF) and anti-interleukin 6 (IL-6) receptor antibodies has developed against a background of increased understanding of the pathogenesis of rheumatoid arthritis (RA), representing a tremendous advance in the management of RA. Such biologic agents produce reliable effects in patients who are resistant to conventional disease-modifying antirheumatic drugs (DMARD). However, these therapies are expensive in comparison with conventional DMARD, and unrestricted use remains unaffordable.

Reactive amyloid A (AA) amyloidosis is a serious and life-threatening systemic complication of RA that arises from chronic, systemic, and longlasting inflammation, with elevated levels of serum AA (SAA) protein[1,2,3]. SAA is an acute-phase 12.5-kDa apolipoprotein associated with high-density lipoprotein, and is the circulating precursor of amyloid A protein. Amyloid A fibrils are insoluble and can be deposited in systemic organs, including the kidneys, heart, or gastrointestinal (GI) tract, because of the overproduction of SAA under inflammatory conditions[2,3,4]. The prevalence of reactive AA amyloidosis in patients with RA is unclear, but is no longer considered rare. The frequency of AA amyloidosis associated with RA ranges from 7% to 26%[5,6,7,8,9], although the prevalence of clinically symptomatic amyloidosis is reportedly lower[10,11]. Common clinical signs of reactive AA amyloidosis in patients with RA can be found by careful observation for the onset of proteinuria, kidney insufficiency, or GI tract symptoms, but amyloid deposition itself can be

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present before clinical signs of AA amyloidosis appear. This subclinical phase might explain the wide variation of disease prevalence.

Treatment with biologics such as anti-TNF and anti-IL-6 receptor antibodies has emerged as a highly effective approach for inducing rapid and sustained clinical remission of RA[12,13]. Further, these biologics dramatically reduce the systemic inflammatory response. Recently, rheumatologists have focused on therapy with biologics, not only for control of RA disease activity, but also as potential agents for the treatment of reactive AA amyloidosis. These biologics show strong suppression of acute-phase reactants such as SAA. A retrospective study and several case reports have indicated that such agents are effective against AA amyloidosis[14,15,16,17]. Clinical experience with anti-TNF and anti-IL-6 therapy in AA amyloidosis has gradually increased, and reports have revealed short-term effects of these treatments. Reduction of urinary protein or improvement of pathological findings in GI series biopsies has been reported[15,16]. We have demonstrated clinical and pathological improvement in 14 patients with amyloidosis who were treated with biologics[17]. The prognosis of amyloid patients treated with biologics has not been thoroughly investigated.

Our purpose was to examine the safety and prognosis of anti-TNF and anti-IL-6 therapy in RA patients with reactive AA amyloidosis by following their clinical course in comparison to patients with AA amyloidosis who did not receive such therapy.

MATERIALS AND METHODS

Patients. One hundred thirty-three patients with an established diagnosis of reactive AA amyloidosis participated in our study between January 1989 and December 2010. Each patient satisfied the 1987 American Rheumatism Association criteria for RA[18]. Our study protocol was approved by the Institutional Review Board of Niigata University Hospital, and the subjects gave informed consent to participate.

Patients diagnosed with amyloidosis before 2003 were treated with methotrexate (MTX), cyclophosphamide, and some other immunosuppressant drugs (conservative therapy). After 2003 some patients were given biologics, while others continued with conventional therapy. Indication for the use of biologics was made by following the official Japanese guidelines[19]. In brief, patients with RA must meet any of the following 3 criteria after treatment with the usual dose of DMARD for 3 months or longer: (1) ≥ 6 tender joints, (2) ≥ 6 swollen joints, and (3) C-reactive protein (CRP) ≥ 2.0 mg/dl or erythrocyte sedimentation rate ≥ 28 mm/h. We recommended that all patients who fulfilled these criteria start biologic therapy. However, some eligible patients chose not to receive biologic therapy because of the high cost. In the nonbiologic group, patients were treated with conventional therapies for amyloidosis, including modulation of dose of steroids or DMARD. In addition, MTX, cyclophosphamide, azathioprine, and tacrolimus were used to treat arthritis.

Fifty-three patients were treated with biologic agents (biologic group) and 80 patients were not (nonbiologic group). From this study population, 5 patients in whom introduction of hemodialysis (HD) preceded initial administration of a biologic agent and 3 patients who started HD at the time of their diagnosis of amyloidosis were excluded from the analysis for HD-free survival. Consequently, the number of subjects for the analysis of HD-free survival was 48 in the biologic group and 77 in the nonbiologic group.

Diagnosis of reactive AA amyloidosis. All patients underwent renal biopsy and GI biopsy, which had confirmed the presence of reactive AA amyloidosis before study entry. Upper GI endoscopy was performed on each patient, regardless of the presence or absence of GI symptoms, to obtain biopsy specimens. Biopsy specimens were obtained from the lesser curvature of the gastric antrum, the bulbus, and the second portion of the duodenum, regardless of the presence or absence of abnormalities on endoscopy. These biopsy specimens were fixed in 10% formalin, embedded in paraffin, and sectioned at 5-μm intervals. Sections were stained with H&E and Congo red. Amyloid deposits detected with Congo red showed green birefringence under polarization microscopy. These deposits were confirmed to be AA-type amyloid using 2 techniques: disappearance of Congo red positivity after incubation with potassium permanganate, and immunohistochemical analysis using anti-amyloid A antibody and anti-immunoglobulin light-chain (AL) antibody to exclude AL amyloidosis.

Assessment. Clinical data were assessed from the patient records at the time of amyloid detection and administration of biologics. Laboratory indices and clinical evaluations of disease activity included serum creatinine (Cr), 24-hour proteinuria, and CRP. Other clinical variables examined were total protein, albumin, blood urea nitrogen (BUN), uric acid (UA), and creatinine clearance (Ccr).

Initiation of hemodialysis. Patients with amyloidosis started HD when Ccr levels were < 10 ml/min/1.73 m^2, or when Ccr levels were > 10 ml/min/1.73 m^2 and pleural effusion, pulmonary congestion, and cardiomegaly were observed.

Statistical analysis. Determination of the onset of the underlying disorder was made retrospectively by review of the patients' charts after the diagnosis of amyloid had been confirmed. The clinical syndrome at presentation was taken as the main reason for the clinician to seek a tissue biopsy to confirm amyloid deposits. All subjects were followed until the end of 2010. The primary endpoint was death and the secondary endpoint was introduction of HD. Of note, no patient received continuous ambulatory peritoneal dialysis. Survival time was counted from the date amyloid was first demonstrated histologically (for the nonbiologic group) or the date when a biologic therapy was started (for the biologic group) up to 72 months, which was the longest followup period observed in the biologic group. For the biologic group, the date of diagnosis of amyloidosis was not used as the starting date for the survival accumulation because all patients were alive from that date until the date of the initial administration of a biologic agent. Inclusion of this period would overestimate the survival time of the biologic group, which should be avoided in this study.

Fisher's exact test for dichotomous variables, chi-square test for multicategorical variables, and Student's t test for continuous variables were used to assess the clinical characteristics of patients with amyloidosis. Survival curves were estimated by the Kaplan–Meier technique and statistical differences between 2 curves were analyzed by log-rank test. Cox proportional hazards models were used to assess the effects of biologic therapy on the risk of each endpoint, i.e., models adjusted for sex and age and multivariable models also adjusted for other possible confounding factors: multivariable model 1 adjusted for sex, age, hematocrit, serum albumin, Cr, and CRP; and multivariable model 2, which included Ccr in the model instead of Cr. Because the difference in the prevalence of severe renal dysfunction may have influenced the difference in the prognosis between the 2 groups, subanalyses were performed excluding subjects with Ccr < 30 ml/min/1.73 m^2. All statistical analyses were performed with SPSS v. 13 for Windows (SPSS Inc., Chicago, IL, USA). Tests were 2-tailed, and differences at $p < 0.05$ were considered significant.

RESULTS

Clinical features of patients with amyloidosis. One hundred thirty-three patients with AA amyloidosis associated with RA were evaluated. Fifty-three patients were treated with biologics (biologic group) and 80 patients were not (nonbiologic group). Table 1 shows the clinical characteristics and laboratory findings in patients. The findings were assessed at the time of diagnosis of amyloidosis in the nonbiologic group and

at the time of biologics administration in the biologic group. MTX was administered to more than one-third of the patients in these 2 groups, but the proportions of patients given MTX did not differ significantly between the groups. However, in Japan, we were restricted to use of MTX not more than 8 mg per week: MTX > 8 mg per week was prohibited by the Health, Labor and Welfare Ministry until 2009. Low levels of serum albumin were frequently observed in both groups. Abnormal Cr and elevated CRP values and mild anemia were significantly more frequent in the nonbiologic group. All patients were treated with nonsteroidal antiinflammatory drugs and DMARD.

History of treatment with biologic agents. Biologic agents had been administered to all patients in the biologic groups and no patients in the nonbiologic group. The profile of biologic usage is shown in Table 2. Etanercept was frequently used. Because many of these patients had renal insufficiency, it was difficult to administer MTX. All patients treated with infliximab received > 6 mg/week, according to drug-use guidelines. Eleven patients were switched to other biologics because of adverse effects or loss of effectiveness.

Survival and causes of death. Survival of patients treated or untreated with biologics, determined according to the Kaplan-Meier method, is illustrated in Figure 1. Of 80 patients in the nonbiologic group, 38 (47.5%) died. Survival was significantly higher in the biologic group than in the nonbiologic group (p = 0.012). In contrast, among the 53 patients in the biologic group, 7 (13.2%) died. Total followup for mortality was 287.6 person-years in the nonbiologic group and 151.3 person-years in the biologic group. The annual rate of mortality due to amyloidosis was 13.2% in the nonbiologic group and 4.6% in the biologic group, the rate in the former being about 3 times that in the latter. In the nonbiologic group, 42 patients died between the time of detection of amyloidosis and up to 72 months afterward. In the biologic group, 7 patients died between the time of administration and up to 72 months thereafter. The causes of death are shown in Table 3. In the

Table 2. History of biologics therapy.

First	Second	Third	No. Patients, Total (%)
INF			6 (11.3)
INF	ETN		1 (1.9)
INF	ETN	TCZ	1 (1.9)
INF	TCZ		5 (9.4)
ETN			24 (45.4)
ETN	TCZ		4 (7.5)
TCZ			12 (22.6)
Total			53 (100)

INF: infliximab; ETN: etanercept; TCZ: tocilizumab.

Table 1. Clinical characteristics and laboratory findings of 153 amyloid-positive patients. Baseline data were at diagnosis of amyloidosis for biologic group and at initial administration of biologics for nonbiologic group. Data are mean (SD) unless otherwise indicated.

Characteristics	No. Patient with Amyloidosis		
	Biologic Group, n (%)	Nonbiologic Group, n (%)	p
Sex, male/female	7/46	2/78	0.03
Mean onset age of RA, years (SD), range	46.9 (13.6), 10–70.5	45.4 (11.1), 20–65	0.6
Mean age of diagnosis of amyloidosis, yrs (SD), range	63.2 (9.6), 31–72	60.9 (9.7), 28–79	0.191
Duration of RA prior to diagnosis of amyloidosis, years (SD), range	16.8 (9.8), 1–42	15.5 (9.0), 2–53	0.4
Stage, n (%)			0.236
II	4 (7.5)	2 (2.5)	
III	11 (20.8)	12 (15.0)	
IV	38 (71.7)	66 (82.5)	
Class, n (%)			0.472
2	25 (47.2)	46 (56.2)	
3	24 (45.3)	28 (36.3)	
4	4 (7.5)	6 (7.5)	
MTX therapy (yes/mo)	21/32	27/53	0.58
Total protein, g/dl	6.6 (1.2)	6.6 (0.9)	0.885
Serum albumin, g/dl	3.3 (0.7)	3.4 (0.7)	0.298
γ globulin, %	22.5 (7.7)	22.1 (6.5)	0.1
BUN, mg/dl	22.0 (10.5)	29.4 (21.6)	0.055
Cr, mg/dl	0.9 (0.5)	1.5 (1.3)	0.012
CRP, mg/dl	2.1 (2.0)	4.7 (3.7)	0.000
ESR Westergren, mm/h	52.0 (33.5)	80.8 (39.8)	0.224
RF, IU/ml	167.4 (264.7)	129.7 (209.9)	0.795
Hemoglobin, g/dl	11.2 (1.8)	10.4 (2.0)	0.06
Hematocrit, %	34.9 (5.2)	32.5 (5.9)	0.057
Creatinine clearance, ml/min/1.73 m^2	76.9 (33.5)	50.9 (35.7)	0.0004
24-hour urinary protein, g/24 h	0.8 (0.9)	1.4 (1.8)	0.12

BUN: blood urea nitrogen; Cr: serum creatinine; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; MTX: methotrexate; RA: rheumatoid arthritis.

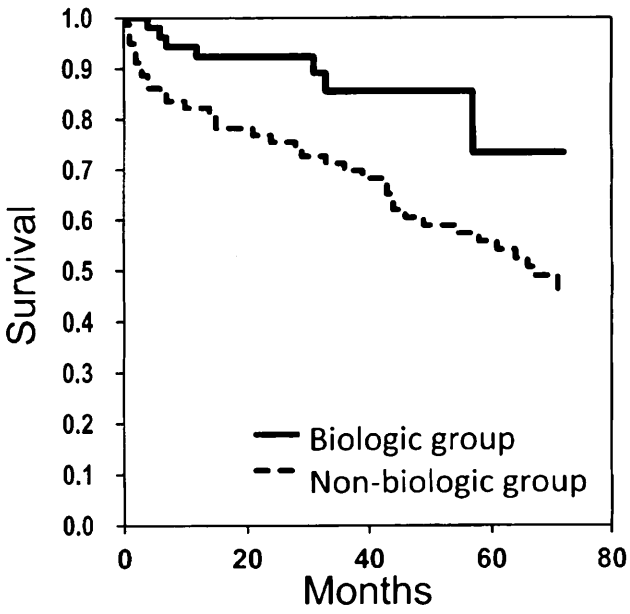

Figure 1. Survival of patients receiving biologic or nonbiologic therapy, Kaplan-Meier method. Total followup periods and annual mortality rates were 287.6 person-years and 13.2% in the nonbiologic group, and 151.3 person-years and 4.6% in the biologic group, respectively. Survival was significantly higher in the biologic group than the nonbiologic group (p = 0.012).

nonbiologic group, congestive heart failure, pneumonia, enteritis, and perforative peritonitis were frequent, as reported[9]. We gained an impression that treatment with biologics inhibited the progression of congestive heart failure. The incidence of other causes of death was low.

Cox proportional hazards models for mortality. Table 4 presents the results of Cox proportional hazards models for mortality. Biologic therapy was significantly associated with reduced risk of death in the sex- and age-adjusted model [hazard ratio (HR) = 0.26, 95% CI 0.11–0.60, p = 0.002]. Biologic therapy was significantly associated with reduced risk of death even after adjustment for possible confounders in multivariable model 1 (HR 0.18, 95% CI 0.05–0.59, p = 0.005). In multivariable model 2, in which Ccr was adjusted instead of Cr, biologic therapy was also associated with a reduced risk. Although the HR in model 2 was not statistically significant, possibly because of decreased number of valid cases caused by missing Ccr data, the absolute value was comparable with that of the sex- and age-adjusted HR. Even if subjects with Ccr < 30 ml/min/1.73 m^2 were excluded from these analyses, HR were not significantly different from those given in Table 4, although multivariable HR became statistically insignificant because of the reduced number of subjects analyzed.

Hemodialysis-free survival. Four of 48 patients in the biologic group and 30 of 77 patients in the nonbiologic group started HD. Total followup for mortality was 234.3 person-years in the nonbiologic group and 137.8 person-years in the biologic group. The annual HD initiation rate for patients with amyloidosis was 12.8% in the former group and 2.9% in the latter, a difference of about 4-fold. The biologic group had a significantly better survival rate (p < 0.001) than the nonbiologic group in terms of the Kaplan-Meier HD-free survival curve (Figure 2).

Cox proportional hazards models for initiation of hemodialysis. Table 5 presents the results of Cox proportional hazards models for initiation of HD. Biologic therapy was significantly associated with reduced risk of HD initiation in the sex- and age-adjusted model (HR 0.34, 95% CI 0.15–0.75, p = 0.007). However, the HR rose to 0.58 (95% CI 0.13–2.47, p = 0.460) and became statistically insignificant in multivariable model 2. When subjects with Ccr < 30 ml/min/1.73 m^2 were excluded, the HR in multivariable model 2 was elevated further and became close to 1.0 (HR 0.74, 95% CI 0.06–8.65, p = 0.814).

DISCUSSION

The frequency of amyloidosis in patients with RA has been reported to range from 5% to 13.3% in cases confirmed by biopsy and from 14% to 26% in cases confirmed by autopsy[8,20]. We have also reported a 7.1% incidence among patients

Table 3. Cause of death in patients with amyloidosis with or without biologic therapy.

Cause of Death	No. Patients with Amyloidosis		
	Biologic Group, n (%)	Nonbiologic Group, n (%)	Total (%)
Congestive heart failure	2 (28.5)	20 (47.5)	22 (45.3)
Pneumonia	0 (0)	6 (14.3)	6 (12.2)
Pulmonary hemorrhage	1 (14.3)	0 (0)	1 (2.0)
Amyloid enteritis	1 (14.3)	7 (16.7)	8 (16.3)
Perforative peritonitis	1 (14.3)	4 (9.5)	5 (10.2)
Gastric ulcer	0 (0)	1 (2.4)	1 (2.0)
Colon cancer	0 (0)	1 (2.4)	1 (2.0)
Ileus	0 (0)	1 (2.4)	1 (2.0)
Arteriosclerosis obliterans	0 (0)	1 (2.4)	1 (2.0)
Septic aortic aneurysm	1 (14.3)	0 (0)	1 (2.0)
Myositis	1 (14.3)	0 (0)	1 (2.0)
Hyperkalemia	0 (0)	1 (2.4)	1 (2.0)
Total	7 (100)	42 (100)	49 (100)

Table 4. Hazard ratio (HR) of death according to treatment status of biologics.

	HR (95% CI)	p
Total subjects		
Sex- and age-adjusted	0.26 (0.11, 0.60)	0.002
Multivariable-adjusted, model 1	0.18 (0.05, 0.59)	0.005
Multivariable-adjusted, model 2	0.28 (0.07, 1.16)	0.080
Subjects with Ccr ≥ 30 ml/min/1.73 m^2*		
Sex- and age-adjusted	0.13 (0.03, 0.69)	0.016
Multivariable-adjusted, model 1	0.18 (0.03, 1.28)	0.088
Multivariable-adjusted, model 2	0.21 (0.03, 1.48)	0.116

Multivariable model adjusted for sex, age, hematocrit (Ht), albumin (Alb), creatinine (Cr), and C-reactive protein (CRP). Numbers of valid cases in the biologic and nonbiologic groups were 53 and 80 for the sex- and age-adjusted model; 36 and 75 for multivariable model 1 adjusted for sex, age, Ht, Alb, Cr, and CRP; and 36 and 68 for multivariable model 2 adjusted for sex, age, Ht, Alb, creatinine clearance (Ccr), and CRP, respectively. * Ccr < 30 ml/min/1.73 m^2 was excluded from the analysis. Multivariable model adjusted for sex, age, Ht, Alb, Cr, Ccr and CRP. Numbers of valid cases in biologic and nonbiologic groups were 31 and 47 for the sex- and age-adjusted model; 31 and 46 for multivariable model 1 adjusted for sex, age, Ht, Alb, Cr, and CRP; and 31 and 46 for multivariable model 2 adjusted for sex, Ht, Alb, Ccr, and CRP, respectively.

Table 5. Hazard ratio (HR) for hemodialysis according to treatment status of biologics.

	HR (95% CI)	p
Sex- and age-adjusted	0.34 (0.15, 0.75)	0.007
Multivariable-adjusted, model 1	0.35 (0.09, 1.32)	0.122
Multivariable-adjusted, model 2	0.58 (0.13, 2.47)	0.46
Subjects with Ccr ≥ 30 ml/min/1.73 m^2*		
Sex- and age-adjusted	0.16 (0.02, 1.32)	0.088
Multivariable-adjusted, model 1	0.42 (0.04, 4.54)	0.477
Multivariable-adjusted, model 2	0.74 (0.06, 8.65)	0.814

Multivariable model adjusted for sex, age, hematocrit (Ht), albumin (Alb), creatinine (Cr), and C-reactive protein (CRP). Numbers of valid cases in the biologic and nonbiologic groups were 52 and 77 for the sex- and age-adjusted model; 35 and 72 for multivariable model 1 adjusted for sex, age, Ht, Alb, Cr, and CRP; and 35 and 65 for multivarable model 2 adjusted for sex, age, Ht, Alb, creatinine clearance (Ccr), and CRP, respectively. * Ccr < 30 ml/min/1.73 m^2 was excluded from this analysis. Multivariable model adjusted for sex, age, Ht, Alb, Cr, and CRP. Numbers of valid cases in biologic and nonbiologic groups were 31 and 47 for the sex- and age-adjusted model; 31 and 46 for multivariable model 1 adjusted for sex, age, Ht, Alb, Cr, and CRP; and 31 and 46 for multivariable model 2 adjusted for sex, Ht, Alb, Ccr, and CRP, respectively.

with a long disease duration, high anatomical class, and high disease activity[9]. In the present retrospective cohort study, we evaluated survival of 133 patients, 53 treated with biologics

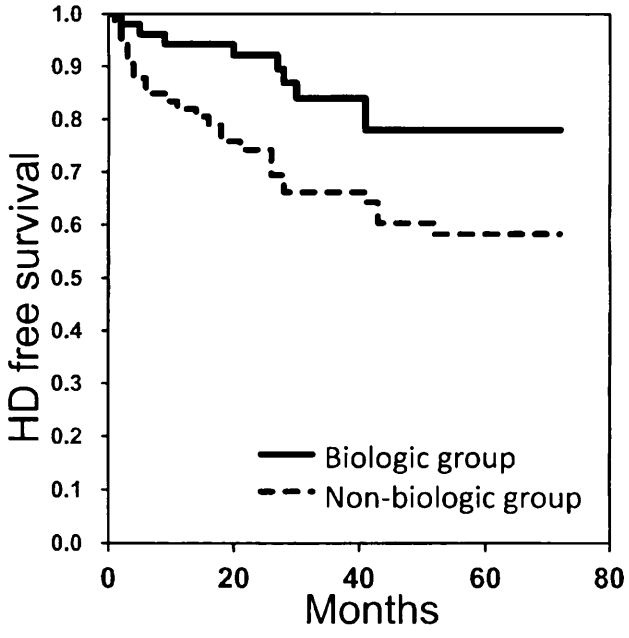

Figure 2. Hemodialysis-free survival in patients receiving biologic or non-biologic therapy, Kaplan-Meier method. HD-free survival was significantly higher in the biologic group than the nonbiologic group ($p < 0.001$). Total followup periods and annual mortality rates were 234.3 person-years and 12.8% in the nonbiologic group, and 137.8 person-years and 2.9% in the biologic group, respectively.

(biologic group) and 80 who were not (nonbiologic group). Characteristics of these patients are shown in Table 1. Renal function in the biologic group was significantly better than that in the nonbiologic group. In Japan, infliximab was introduced in 2003, etanercept in 2005, and tocilizumab in 2008. Diagnosis of amyloidosis was made earlier in the nonbiologic group than in the biologic group. The time background might have been slightly different between the 2 groups, but the treatment strategies and use of DMARD were the same, except for the use of biologics. Our patients were gradually switched to biologics, as shown in Table 3. Recently, the European League Against Rheumatism recommendations for the use of biologics were published[21]. In general, TNF inhibitors are used first, and if this therapy fails, other biologics such as abatacept, rituximab, or tocilizumab are considered. In Japan, we regularly use TNF inhibitors as a first choice of therapy according to the recommendations. However, some studies have demonstrated a dramatic reduction in SAA levels, with subsequent disappearance of the clinical symptoms of AA amyloidosis, with tocilizumab treatment[15,22]. Considering these reports, we have occasionally used tocilizumab as first-line treatment. MTX is now considered an "anchor drug" for treatment of RA. Several studies have indicated that MTX use is associated with reduced risk of cardiovascular disease and atherosclerosis, and reduction of mortality due to myocardial infarction and heart failure[23,24]. Studies have suggested that control of inflammation with MTX may reduce mortality[25,26]. There was no significant difference between our 2 study groups in the frequency of MTX therapy. In Japan, the maximum allowable dosage of MTX was 8 mg per week, until February 2011, but this dosage was not used in amyloidosis patients because of renal damage. For

the use of infliximab, more than 6 mg per week of MTX was required. In our study, because most of the amyloidosis patients showed renal dysfunction, the use of infliximab was limited, and this accounted for the better renal function in the biologics group. Recently, reports have described that biologics can reduce mortality in patients with RA[27,28], but it is difficult to prove this effect statistically. Patients with amyloidosis showed a higher mortality rate than patients with RA without amyloidosis, as we have reported[29,30]. Thus, we found that biologics reduced mortality in patients receiving them. Our multivariate Cox proportional hazards analysis indicated that the use of biologics was significantly correlated with mortality. Renal function is one of the important factors for prognosis. Nevertheless, the magnitude of risk reduction was not significantly changed even after the exclusion of subjects with Ccr < 30 ml/min/1.73 m^2.

In contrast, the effects of biologics in terms of initiation of HD were limited. Our Kaplan-Meier survival curve analysis revealed that HD-free survival was significantly improved (Figure 2). These patients in the biologic group had been diagnosed as having amyloidosis before receiving the drugs. The annual HD initiation rate in patients with amyloidosis was 14.3% in the nonbiologic group and 6.7% in the biologic group. However, diagnosis of amyloidosis was undertaken earlier in the former group than in the latter. The time background might have differed slightly between the groups, but the treatment strategies and DMARD were the same except for the use of biologics, and the guidelines for HD initiation were also the same. The HD initiation rate in the nonbiologic group was about twice that in the biologic group. Our sex- and age-adjusted Cox proportional hazard analysis clearly indicated that the use of biologics was correlated with initiation of HD. However, our multivariate Cox proportional hazards analysis indicated that the use of biologics was not predictive of initiation of HD. These results were confirmed by another analysis in which those subjects with Ccr < 30 ml/min/1.73 m^2 were excluded. Although this lack of significance in the benefit of biologics shown by multivariate Cox proportional hazard analysis is unclear, several possible explanations can be suggested. Our preliminary data indicated that renal insufficiency developed to some extent, which was difficult to ameliorate even when biologics were started (data not shown). We considered that it would be important to introduce biologics earlier, before renal damage became apparent. In addition, it was difficult to determine renal function in patients with amyloidosis. A second possibility is that it was difficult to compare survival from the time of diagnosis of amyloidosis, and therefore we chose to assess survival from the time of administration of biologics up to 72 months. The biologic group had a poorer HD-free survival rate than the nonbiologic group. A third possibility is that the observation period might have been too short. Considering the Kaplan-Meier HD-free survival curve, if we had continued observations for 1 more year, a significant difference might have emerged.

Causes of death in amyloidosis associated with RA have been well documented[30]. Our belief was that treatment with biologics inhibited the progression of congestive heart failure. However, we did not use biologics in patients with chronic renal failure. It is possible to consider that biologics remove amyloid deposits from the heart and vessels, and this may inhibit the onset of congestive heart failure. One study demonstrated that anti-TNF therapy with etanercept did not have a beneficial effect on the rate of hospitalization death due to chronic heart failure (CHF)[31]. The authors considered that proinflammatory cytokines did not have a deleterious role in the pathophysiology of CHF. However, none of our patients had CHF upon initiation of biologics.

There have been several attempts to establish an effective protocol for treatment of reactive AA amyloidosis associated with RA, including the use of corticosteroids, immunosuppressants, and biologics such as TNF-α and IL-6 receptor antagonists to control RA disease activity and improve kidney function and overall patient survival[32,33]. Some reports have suggested that patients with AA amyloidosis have laboratory signs of an inflammatory process, with significantly increased plasma levels of acute-phase proteins such as CRP[9,33]. Our patients showed high disease activity during the clinical course of RA. Mild azotemia and elevated Cr were frequent, indicating renal insufficiency. Proteinuria was also common in these patients.

We recently reported the effect of anti-TNF therapy for rapid and sustained removal of amyloid deposits in gastric mucosal tissue with amelioration of renal function[17]. Thus, we speculate that rapid removal of amyloid deposits from renal tissue might have resulted in amelioration of renal function. In patients with amyloidosis, it has not been fully investigated whether biologics reduce mortality. Our data clearly suggested that biologic therapy can reduce mortality and risk of HD in these patients. Additionally, we recently reported a program for safe initiation of HD in amyloidosis patients with RA[34]. Some patients with amyloidosis will progress to endstage renal disease (ESRD) even if they receive biologic therapy. Additionally, the prognosis of amyloidosis patients receiving HD is poor, because of a large number of sudden deaths immediately following HD. Programmed initiation of HD improves the prognosis of patients with ESRD. Use of biologics combined with this program is expected to reduce mortality, even when these patients might require HD.

We have demonstrated that patients with amyloidosis have a higher mortality rate, but that the use of biologics can reduce mortality, although it may not influence the HD-free survival rate. Therapy with biologic agents is now considered the standard method of care for DMARD-resistant patients with RA, and might also become an accepted strategy for amyloidosis patients with RA.

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