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Treatment responses and their predictors in patients with rheumatoid arthritis treated with biological agents

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Abstract : Biological agents represent an important advancement in for the treatment of rheumatoid arthritis (RA), but there is a subset of patients who do not improve despite therapy. This study aimed to determine the efficacy of biological agents for RA and to identify clinical factors that are associated with their response. We studied 98 patients with RA who started an initiating biological agent which was selected from infliximab, etanercept, adalimumab and tociliximab at 4 medical institutions. Etanercept was the most frequently used biological agent followed by infliximab although there was a difference in the selection of the biological agents among medical institutions. We found that etanercept achieved the highest treatment response, remission rate and drug survival rate. A high disease activity in the baseline disease activity score-c-reactive protein (CRP) was shown to be a negative predictor of the treatment response, and high patient global assessment was significantly less likely to achieve a good response. At week 4, decreases in 28 swollen joint counts and CRP were useful as predictors for sustaining the efficacy up to week 48. These data demonstrate that assessments of the disease activity at baseline and the early treatment response may be useful in predicting the efficacy and drug survival rate of biological agents. J. Med. Invest. 60 : 77-90, February, 2013

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INTRODUCTION

Rheumatoid arthritis (RA) is a disease characterized by destructive synovial joint inflammation leading to substantial joint damage, deformity, and functional disability (1). The affected joints exhibit hyperplasia of inflamed synovium infiltrated with a range of immune cells, which induce the production of various cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 (2-4). The treatment of RA has advanced substantially in the past two decades because of the development of aggressive therapies for the early stages of the disease and the advent of molecular targeted therapies (5, 6).

TNF-α is a key cytokine driving synovial inflammation in RA (7). The introduction of anti-TNF-α therapies has dramatically improved the treatment

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of patients with severe RA (8, 9). Three such agents are currently available in Japan ; infliximab, etanercept, and adalimumab. Infliximab is a chimeric anti-human TNF-α monoclonal antibody, and, in terms of its antigenicity, the use of methotrexate is mandatory when infliximab is used (10). Etanercept is a fully human soluble TNF receptor fusion protein, with a relatively short half-life in blood (11). Adalimumab is a fully human monoclonal antibody with a high specificity for TNF-α (12). On the other hand, IL-6 is a multifunctional cytokine produced by various cell types and binds to the membrane-expressed IL-6 receptors (13). In patients with active RA, high levels of IL-6 are present in the synovial fluid and IL-6 is expressed in the synovial membrane ; in addition, the levels of IL-6 correlate with the degree of radiological joint damage (14, 15). Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor that was developed in Japan, and it has been shown to dramatically improve the treatment of patients with RA (16).

With the advent of biological agents, the ultimate goal for the treatment of patients with RA is remission or low disease activity in the early stage of the disease (17). These agents induce a rapid therapeutic response and play an essential role in therapies for treating RA (18). However, not all patients respond to biological agents (19), and a considerable number of patients fail to go into remission. A recent study showed that approximately 30% of patients with RA fail to respond or do not tolerate a first anti-TNF biological agent, and approximately 50% of these patients discontinue the therapy within 2 years (20). On the other hand, Nishimoto *et al.* showed that only 59.7% of patients treated with tocilizumab achieved the remission (21), thus suggesting that a significant proportion of patients do not respond to this type of treatment. Moreover, some patients experienced adverse effects such as serious infusion reactions and severe infections, and biologic agents are substantially more expensive than conventional disease-modified anti-rheumatic drugs (DMARDs) (22, 23). Therefore, although it is important to identify predictors of efficacy before or in the early stages after the therapy, only minimal data related to the factors that can identify the patients who are most likely to respond to these therapies have been published (24-27).

The aim of this study was to identify the clinical factors which dictate response to biological agents. In Japan, the clinical use of infliximab and etanercept started in 2003 and 2005, respectively. In 2008, two biological agents, adalimumab and tocilizumab, were approved in Japan. Therefore, during April 1, 2009 and March 31, 2011, these four biological agents were available for the treatment of patients with RA. In the present study, we compared the treatment responses and drug survival rates of the individual biological agents, and examined the predictors present at baseline and at 4 weeks after the treatment that were associated with the treatment responses.

MATERIALS AND METHODS

Patients

The present study was conducted at Tokushima University Hospital (Univ) and its related three medical institutions : Toyo Hospital (Toyo), Miyoshi Municipal Mino Hospital (Mino), and Hanoura Hospital of Orthopedics and Internal Medicine (Hanoura). RA was diagnosed according to the 1987 American College of Rheumatology classification criteria for RA (28). We enrolled patients with RA who started one of four biological agents as an initiating biological agent, ie., infliximab, etanercept, adalimumab or tocilizumab.

Ninety-eight patients with RA who had started to receive an initiating biological agent between April 1, 2009 and March 31, 2011 were included in the present study. All patients failed to respond satisfactorily to treatment with at least one DMARD, including methotrexate. Infliximab was administered as intravenous drip infusions at a dose of 3 mg/kg at weeks 0, 2, 6, and doses up to 10 mg/kg were administered every 8 weeks thereafter (29). It was recommended that infliximab must be administered with methotrexate. Etanercept was administered subcutaneously at a dose of either 25 mg/week or 50 mg/week (one 50 mg dose or two 25 mg doses) (30). Adalimumab was administered subcutaneously at a dose of 40 mg once biweekly (31). Tocilizumab was administered as intravenous drip infusions every 4 weeks at a dose of 8 mg/kg (32).

Assessments

At baseline and at 4, 12, 24 and 48 weeks of follow-up, we recorded various clinical data. Clinical responses to therapy were evaluated using the disease activity score (DAS) 28-C-reactive protein (CRP) (high disease activity, >4.1 ; moderate disease activity, ≥ 2.7 to <4.1 ; low disease activity, ≥ 2.3 to <2.7 ; remission, <2.3) (33). The patient outcomes

were assessed at week 48. The predictors of efficacy at week 48 were examined at baseline. Patients who discontinued the biological agent prior to the end of the 48-week follow-up because of lack of efficacy were labelled as non-responders.

Statistical analysis

Data were expressed as the mean± standard deviation (SD). Categorical variables were expressed as number and percentages. All tests were 2-tailed, with differences reported as significant if p values were less than 0.05. DAS28-CRP was analyzed using corrections for multiple comparisons according to Steel test. Kaplan-Meier estimates of the probability for drug survival were used. When significant interactions were detected, post hoc multiple comparisons were made with the use of the Bonferroni's correction in which $p<0.008$ was considered statistically significant (34).

RESULTS

Baseline characteristics

Table 1 shows the patients' baseline characteristics according to the biological agents they received. Ninety-eight patients were initially enrolled in this study. Etanercept was the most frequently administered biological agent (46.9%) followed by infliximab (22.4%), adalimumab (21.4%), and tocilizumab (9.2%). The mean age was 56.2 years, and 77.6% of the patients were female. The mean disease duration was 6.9 years. There was no significant difference in age, gender, disease duration, stage, or class among the biological agents. The mean baseline DAS28-CRP score showed high disease activity (>4.1) for all the biological agents, and was not significantly different among them. In addition, there was no significant difference in the components of DAS28-CRP among the biological agents. Seventy patients (71.4%) received methotrexate concurrently, and 64 patients (65.3%) were currently taking corticosteroids at baseline. Methotrexate was concomitantly administered to all patients treated with infliximab (p=0.0042), in approximately two-thirds of those treated with etanercept or adalimumab, and one-third of those treated with tocilizumab. There was no significant difference in the percentage of patients receiving corticosteroids among the biological agents. The baseline characteristics are presented according to the medical institutions in Table 2. Univ had the most patients (57 patients, 58.2%). The number of patients in Toyo, Hanoura, and Mino was 21 (21.4%), 10 (10.2%), and 10 (10.2%), respectively. Among the institutions, the patients in Toyo were significantly younger (p=0.0267) and of higher class (p=0.0275) than the value of all institutions. The disease duration tended to be shorter in Univ versus the other institutions, but there was no significance. Patients in Hanoura had significantly (p=

Table 1 Baseline characteristics according to biological agents

Biological agents	infliximab	etanercept	adalimumab	tocilizumab	total
n	22 (22.4)	46 (46.9)	21 (21.4)	9 (9.2)	98 (100)
Age (yrs)	52.5± 13.3	55.6± 14.8	59.8± 11.5	59.6± 14.7	56.2± 13.8
Female (%)	77.3	87.0	52.4	87.5	77.6
Disease duration (years)	4.8± 6.2	6.3± 8.5	9.3± 10.0	9.5± 9.5	6.9± 8.5
Interstitial pneumonia	0	7 (15)	2 (10)	2 (22)	11 (11)
Stage	2.0± 1.0	2.3± 1.0	2.4± 0.9	2.2± 1.1	2.2± 1.0
Class	2.0± 0.6	2.2± 0.7	2.1± 0.7	2.1± 0.6	2.1± 0.7
DAS28-CRP	4.2± 1.3	4.7± 1.0	4.6± 0.9	4.7± 1.4	4.6± 1.1
28 SJC	5.2± 4.5	8.5± 5.9	6.3± 3.3	7.3± 4.1	7.1± 5.1
28 TJC	3.3± 4.8	6.7± 5.1	4.6± 4.7	3.4± 3.8	5.2± 5.0
Patient global assessment	48.0± 27.5	61.2± 24.5	73.8± 18.2	73.3± 26.0	62.6± 25.3
CRP (mg/dl)	2.4± 2.3	2.3± 2.3	3.4± 3.3	3.6± 3.0	2.7± 2.6
Concurrent methotrexate use Dose, mg/week	22 (100.0)* 7.6± 1.1	31 (67.4) 7.3± 1.4	14 (66.7) 6.5± 1.6	3 (33.3) 6.5± 2.5	70 (71.4) 7.2± 1.4
Concurrent corticosteroid use Dose, mg/day	14 (63.6) 5.6± 2.3	31 (67.4) 5.3± 2.0	11 (52.4) 5.3± 2.5	8 (88.9) 5.1± 1.8	64 (65.3) 5.4± 2.3

Numbers in parentheses show percentage. Values express as mean± SD. *p=0.0042 in comparison with the value of total.

Table 2 Baseline characteristics according to institutions

Hospitals	Hanoura	Mino	Toyo	Univ	total
n	10	10	21	57	98
Age (years)	58.9±14.2	63.5±6.9	46.6±15.2*	57.9±12.6	56.2±13.8
Female (%)	50.0	70.0	90.5	78.2	77.6
Disease duration (years)	6.1±3.5	6.0±2.5	5.9±3.1	4.6±3.7	6.9±3.5
Interstitial pneumonia	1 (10)	0	3 (14)	7 (12)	11 (11)
Stage	2.7±0.5	2.9±0.7	2.6±0.8	1.9±1.0	2.2±1.0
Class	2.1±0.3	2.3±0.5	2.6±0.6**	2.0±0.7	2.1±0.7
DAS28-CRP	4.6±1.0	4.3±1.4	4.6±1.0	4.7±1.1	4.6±1.0
28 SJC	3.1±1.5***	6.5±3.1	9.8±7.4	7.0±4.1	7.1±5.1
28 TJC	6.0±4.2	3.8±4.8	7.1±5.4	4.5±4.9	5.2±5.0
Patient global assessment	65.8±24.6	63.5±20.8	58.7±18.7	63.6±29.4	62.6±25.3
CRP, mg/dl	3.0±2.3	3.3±3.0	1.7±2.2	3.0±2.7	2.7±2.6
Concurrent methotrexate use Dose, mg/week	8 (80.0) 7.6±1.5	9 (90.0) 6.7±1.4	17 (81.0) 7.3±1.2	37 (64.9) 7.1±1.9	70 (71.4) 7.2±1.4
Concurrent corticosteroid use Dose, mg/day	6 (60.0) 5.1±2.0	7 (70.0) 5.7±2.0	11 (52.4) 4.5±1.9	40 (70.2) 5.6±2.5	64 (65.3) 5.4±2.3

Numbers in parentheses show percentage. Values express as mean±SD. *p=0.0267, **p=0.0275 and ***p=0.008 in comparison with the value of total.

0.008) less 28 swollen joint count (SJC), but there was no significant difference in the value of DAS28-CRP, 28 tender joint count (TJC), patient global assessment, or CRP among the institutions. There was no significant difference in the percentage of patients receiving methotrexate or corticosteroids among the institutions. The numbers and percentages of the biological agents used in the 4 institutions are compared in Table 3. Etanercept was the most frequently used biological agent in all the institutions. In Mino and Toyo, over half of the patients were treated with etanercept. Infliximab was the second most frequently used biological agent in Hanoura and Univ. Subcutaneous drugs (etanercept and adalimumab) were mostly administered to patients from Toyo (90.5% of patients) and Mino (90%).

Follow-up

Kaplan-Meier drug survival time was estimated for all patients treated with biological agents (Figure 1). At week 48, 86.1%, 71.4%, 52.9% and 33.3% of patients continued the initiating etanercept, tocilizumab, adalimumab, and infliximab, respectively. There was a significant difference in drug survival times between etanercept and infliximab at week 48 (p=0.0004). Table 4 shows the time course for

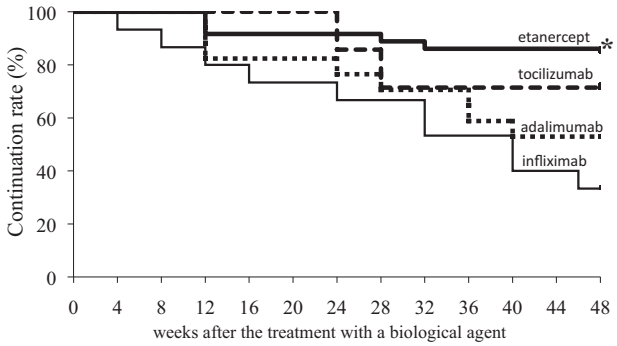

Figure 1. Kaplan-Meier drug survival time for the biological agents which were discontinued due to a lack of efficacy. *p=0.0004 vs. infliximab.

Table 3 Selection of biological agents among institutions

	infliximab	etanercept	adalimumab	tocilizumab	total
Hanoura	3 (30.0)	4 (40.0)	2 (20.0)	1 (10.0)	10 (10.2)
Mino	0	6 (60.0)	3 (30.0)	1 (10.0)	10 (10.2)
Toyo	2 (9.5)	16 (76.2)	3 (14.3)	0	21 (21.4)
Univ	17 (29.8)	20 (35.1)	13 (22.8)	7 (12.3)	57 (58.2)
Total	22 (22.4)	46 (46.9)	21 (21.4)	9 (9.2)	98 (100)

Numbers in parentheses show percentage.

Table 4 Time course of clinical assessments

weeks	0	4	12	24	48
discontinued					
IE	0	0	1	1	
AE	0	1	2	6	
	⇧	⇧	⇧	⇧	
Remission & low disease activity	5	37	37	39	30
Moderate & high disease activities	93	60	54	35	20
discontinued	⇩	⇩	⇩	⇩	
IE	0	2	7	10	
AE	1	2	5	6	

IE ; inefficacy, AE ; adverse event

the clinical data. Four patients with missing data were excluded. Of 94 patients, 23 patients (24.5%) discontinued treatment with the biological agents due to adverse events, and 21 patients (22.3%) discontinued due to a lack of efficacy. Therefore, at week 48, 50 patients (53.2%) continued to receive the initiating biological agents ; of these, 30 patients were in remission or low disease activity, and 20 patients were in moderate or high disease activity. Table 5 shows continuation and treatment responses according to the biological agents at week 48. The percentage of patients who had discontinued for lack of efficacy until week 48 were high in those treated with infliximab (64.3%) and adalimumab (43.8%), and were low in those treated with etanercept (8.8%). Of the 50 patients who continued treatment with the initiating biological agents up to week 48, 24 patients (48.0%) were in remission, 6 patients (12.0%) had low disease activity, and 20 patients (40.0%) had moderate or high disease activity. There was no significant difference in the remission rates in the patients who continued the initiating biological agents up to week 48 among biological agents, but a moderate or high disease activity was more prevalent in patients treated with etanercept and adalimumab versus those treated with infliximab and tocilizumab.

Twenty-seven patients who discontinued the initiating biological agents due to adverse events (23 patients) or missing data (4 patients) were excluded from the efficacy analysis. Therefore, 71 patients were included for the final efficacy analysis. The clinical efficacy for the biological agents at 48 weeks is shown in Figure 2. In total, 30 patients (42.2%) were in remission or had low disease activity, and

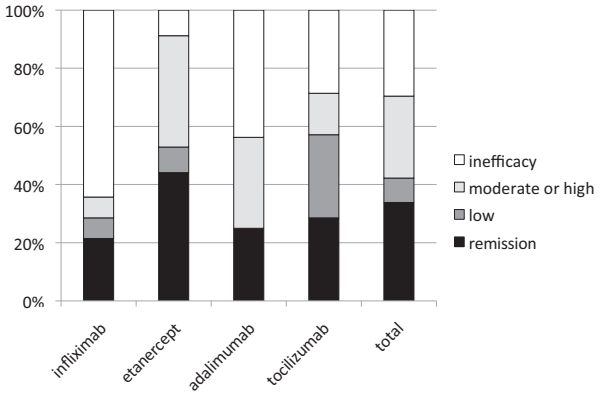

Figure 2. Clinical assessments of therapy with biological agents at week 48.

Table 5 Continuation and treatment responses of biological agents at week 48

	n	discontinued by inefficacy	continued			
			total	DAS28-CRP		
				remission	low	moderate or high
infliximab	14	9 (64.3)	5 (35.7)	3 (60.0)	1 (20.0)	1 (20.0)
etanercept	34	3 (8.8)	31 (91.2)	15 (48.4)	3 (9.7)	13 (41.9)
adalimumab	16	7 (43.8)	9 (56.3)	4 (44.4)	0	5 (55.6)
tocilizumab	7	2 (28.6)	5 (71.4)	2 (40.0)	2 (40.0)	1 (20.0)
Total	71	21 (29.5)	50 (70.4)	24 (48.0)	6 (12.0)	20 (40.0)

Numbers in parentheses show percentage.

41 patients (57.7%) had moderate or high disease activity or discontinued due to lack of efficacy. Over 50% of the patients were in remission or had low disease activity after receiving etanercept (52.9%) or tocilizumab (57.1%). The percentage of patients in remission or low disease activity was low in those treated with infliximab (28.6%) or adalimumab (25.0%).

Thereafter, we evaluated the efficacy of combination therapy with biological agents plus methotrexate. Patients treated with infliximab were not included in this analysis because all of them were combined with methotrexate. As shown in Figure 3, there was no significant difference in the efficacy of etanercept and tocilizumab between monotherapy and combination therapy. Adalimumab in combination with methotrexate tended to be superior to adalimumab monotherapy but the difference was not statistically significant.

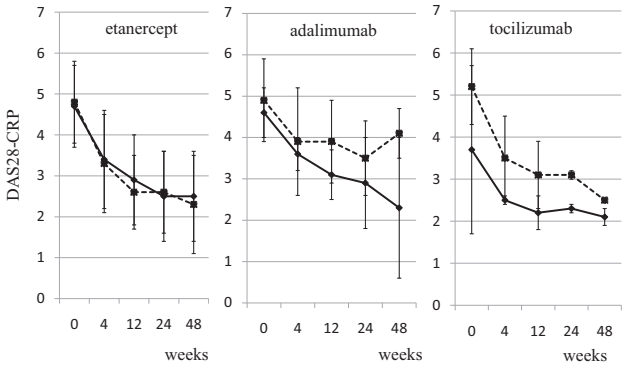

Figure 3. Comparison of DAS-CRP between patients with or without concomitant methotrexate. The solid lines indicate those with methotrexate, and dotted lines show those without methotrexate.

Predictors of response

Achieving a low disease activity and remission is now a realistic objective in RA management (35). In the present study, in order to identify predictors for a beneficial outcome, predictors of remission and low disease activity in DAS28-CRP at week 48 were examined. Of 98 patients, 27 patients (27.6%) who discontinued an initiating biological agent for a reason other than lack of efficacy were excluded from this analysis, thus leaving 71 patients in the final analysis. The patients treated with biological agents were divided into 2 groups according to the efficacy data at week 48. Group 1 (named the "RL group") comprised patients in remission or low disease activity and Group 2 (named the "MHD group") comprised patients with moderate or high disease activity, or those who discontinued treatment due to lack of efficacy. To determine the clinical factors at baseline to predict the efficacy at week 48, the baseline characteristics were compared between the RL and MHD groups (Table 6). Patients

Table 6 Comparison of baseline characteristics between RL and MHD groups

	RL group	MHD group	P value
n	30	41	
Age (years)	52.4 ± 14.2	58.2 ± 12.5	0.1270
Female (%)	76.7	75.6	0.9179
Disease duration, years	8.0 ± 11.1	7.7 ± 7.6	0.6732
Disease duration, < 2 years (%)	33.3	32.5	0.9414
Stage	2.3 ± 1.0	2.5 ± 1.0	0.4897
Class	2.1 ± 0.7	2.2 ± 0.6	0.3262
DAS28-CRP	4.3 ± 1.1	4.8 ± 1.0	0.0676
High (%)	50.0	74.4	0.0069
Moderate (%)	43.3	23.1	0.5065
28 SJC	7.9 ± 6.6	7.1 ± 4.0	0.6638
28 TJC	4.8 ± 5.3	5.9 ± 5.0	0.2255
Patient global assessment	53.8 ± 25.1	67.7 ± 21.7	0.0308
CRP, mg/dl	2.2 ± 2.4	3.1 ± 2.9	0.1365
Concurrent methotrexate use Dose, mg/week	24 (80.0) 7.5 ± 1.2	30 (73.2) 6.9 ± 1.7	0.7697 0.2126
Concurrent corticosteroid use Dose, mg/day	18 (60.0) 5.4 ± 2.0	30 (63.4) 5.0 ± 1.9	0.5054 0.1184

Numbers in parentheses show percentage. Values express as mean± SD. RL ; remission and low disease activity, MHD ; moderate activity, high activity, and discontinued by inefficacy, SJC ; swollen joint counts, TJC ; tender joint counts

with a high disease activity in the DAS28-CRP scores at baseline were significantly (p=0.0069) more frequent in the MHD group versus the RL group, and higher DAS28-CRP scores at baseline were likely to be seen in patients in the MHD group versus the RL group, although statistical significance was not observed. The baseline patient global assessments were significantly (p=0.0308) lower in the RL group than in the MHD group. Age, gender, disease duration, stage, class, 28 SJC, 28 TJC, CRP, concurrent methotrexate use, or concurrent corticosteroid use were not significantly different between the two groups. To examine whether the disease activity and response assessment to the biological agent at week 4 were related to those at week 48, DAS28-CRP and its components at week 4 were compared between the RL and MHD groups (Table 7). DAS28-CRP at week 4 was significantly lower in the RL group than the MHD group. Of the DAS28 components, 28 TJC, patient global assessment, and CRP but not 28 SJC at week 4 were significantly lower in the RL group versus the MHD group. When the results between the baseline and week 4 were compared in each group, DAS28-CRP, 28 TJC, and patient global assessment were significantly decreased in both the RL and MHD groups. On the other hand, a significant decrease in 28 SJC and CRP at week 4 compared with baseline was seen in the RL group but not in the MHD group.

Drug safety

Adverse events which resulted in discontinuation of the biological agents were analyzed. Twenty-three patients (23.5%) discontinued the biological agents due to adverse events. The most common adverse events were skin eruptions (9 cases) followed by abnormalities in liver function (7 cases), worsening of interstitial pneumonia (3 cases), pneumonia (2 cases), malignancy (one case), and hemorrhage from digestive tract (one case). The percentage of patients who discontinued due to adverse events was 7 patients (31.9%) in infliximab, 10 patients (21.7%) in etanercept, 4 patients (19.0%) in adalimumab, and 2 patients (22.2%) in tocilizumab. No significant difference was seen in the rate of adverse events among the biological agents.

DISCUSSION

In order to identify the predictors of a beneficial outcome for the administration of biological agents to patients with RA, the present study assessed efficacy, drug survival and safety of four biological agents. When the disease activity was examined by DAS28-CRP at week 48, 42.3% of patients had a low DAS score (remission or low disease activity ; RL group), and 33.8% of patients were considered to be in remission. The results showed that 57.7% of patients did not improve despite therapy, having a high DAS score (moderate disease activity or high disease activity, or discontinued by lack of efficacy ; MHD group). These findings pertaining to the response rate are in agreement with other reports (36-38). The present study showed that the efficacy at week 48 was not different among the biological agents in the patients who continued the biological agents up to week 48 ; however, a difference was observed when the patients who discontinued the biological agents due to lack of efficacy were included in the analysis. The proportion of patients who discontinued the biological agents due to a lack of efficacy was higher in the patients treated with infliximab or adalimumab and was lower in those treated with etanercept. Etanercept achieved

Table 7 Disease activity at weeks 0 and 4 in RL and MHD groups

	RL group n=30			MHD group n=41			p*
	baseline	week 4	p	baseline	week 4	p	
DAS28-CRP	4.3±1.1	2.7±1.1	<0.0001	4.8±1.0	3.9±1.1	0.0003	0.0002
28 SJC	7.9±6.6	5.0±5.5	0.0079	7.1±4.0	5.6±4.0	0.1239	0.1645
28 TJC	4.8±5.3	1.8±3.0	0.0111	5.9±5.0	3.6±3.8	0.0208	0.0133
Patient global assessment	53.8±25.1	27.6±23.1	0.0001	67.7±21.7	47.7±25.9	0.0013	0.0033
CRP, mg/dl	2.2±2.4	0.4±0.7	0.0004	3.1±2.9	2.1±2.9	0.1243	0.0031

Values express as mean± SD. *p value between RL group and MHD group at week 4. RL ; remission and low disease activity, MHD ; moderate activity, high activity, and discontinued by inefficacy, SJC ; swollen joint counts, TJC ; tender joint counts, CRP ; c-reactive protein

a higher 48-week remission rate than the other biological agents. The proportion of patients in the RL group was higher in the patients treated with etanercept or tocilizumab versus those treated with infliximab or adalimumab. The drug survival rate was also shown to be higher for etanercept and tocilizumab. These results in which etanercept and tocilizumab showed superior efficacy are in agreement with those in other reports (39-41). The drug survival and the proportion of patients achieving DAS28 remission were significantly better for etanercept in comparison to infliximab or adalimumab (42), and etanercept had a longer drug survival rate than infliximab or adalimumab (37). On the other hand, a high proportion (59.7%) of patients treated with tocilizumab was shown to achieve DAS-defined remission (21). Patients who received tocilizumab showed similar drug survival rates when compared with TNF inhibitor, but DAS remission rates at 6 months were higher for tocilizumab (66.7%) versus TNF inhibitors, including infliximab, etanercept and adalimumab (25.8%) (43).

Cytokine-blocking agents have been shown to result in a significant decrease in acute phase reactions such as CRP. In particular, tocilizumab led to a normal CRP level in almost all patients (44), thus indicating that CRP in the DAS score might lead to an overestimation in the efficacy of tocilizumab. Therefore, when the efficacy of biological agents including tocilizumab is assessed, more stringent remission criteria such as Clinical Disease Activity Index in which CRP is excluded should be used, in light of the absence of acute phase reactions (17). A problem associated with the use of infliximab is that its efficacy often decreases during prolonged treatment (45, 46), thus supporting the present data that infliximab had the lowest drug survival rate. In the case of infiximab treatment, depending on the primary or secondary failure, the dosage of infliximab could be increased to a maximum of 10 mg/kg administered at 4- to 8-week intervals (29). Therefore, in instances when infliximab dosage is insufficient, higher dosages will improve the treatment response. We cannot rule out that the dosage of infliximab was insufficient in some patients throughout the survey.

Although therapies with biological agents represent an important advancement in the treatment of patients with RA, there is a proportion of patients who do not improve despite therapy and these drugs have some serious toxicities and are expensive (47). Therefore, it would be ideal to predict the patients who will respond to these agents. In this study, we aimed to identify specific clinical factors that predict the response to biological agents in patients with RA. In this observational study of response to biological agents, certain factors emerged as independent predictors of response. Patients were divided into 2 groups, RL and MHD groups, according to the DAS score at week 48. The RL group comprised patients in remission or low disease activity, and the MHD group comprised those with a moderate or high disease activity, or those who discontinued due to lack of efficacy. With respect to the DAS28 response, the patients with a high disease activity in baseline DAS28-CRP were significantly less likely to be in the RL group. Baseline DAS28-CRP itself was likely to be lower in the RL group than in the MHD group. These results suggest that the low level of baseline disease activity is a strong predictor of the efficacy at week 48. Of the DAS28-CRP components, only high patient global assessments were significantly less likely to achieve remission or low disease activity for therapies with the biological agents. Previous reports showed that patients with moderate disease activity at baseline were significantly likely to be in remission at 6 months after treatment with etanercept compared with those with high disease activity (48), and that the disease activity at baseline was inversely associated with the response to anti-TNF inhibitors (infliximab, etanercept, and adalimumab) (49) . The data presented here indicate that low DAS28-CRP and patient global assessments at baseline are useful predictors of the efficacy of four biological agents (infliximab, etanercept, adalimumab, and tocilizumab) in the treatment of RA.

There was no significant difference in other baseline characteristics, including age, gender, disease duration, stage, class, and the concurrent use of methotrexate or corticosteroid between the RL and MHD groups. Whether the disease duration and concurrent use of methotrexate could predict the treatment response still remains controversial. Some clinical trial reports have demonstrated that disease duration may influence the treatment response to biological agents in patients with RA (18, 50, 51). At 6 months after first-line tocilizumab treatment, the remission rate according to DAS28 was 49.6% in recent-onset patients compared with 21% in patients with the disease for > 10 years (21), and disease duration before starting anti-TNF-α agents in patients with RA predicted drug retention (48). This result might be expected, as an increasing

disease duration would be associated with a more irreversible disease. On the other hand, other reports showed that the disease duration did not predict the response to infliximab and etanercept (36) and to infliximab, etanercept and adalimumab (52), which is a finding that is consistent with the present study. Previous reports showed that a low health assessment questionnaire (HAQ) at baseline predicted a good clinical outcome (36, 49, 53), but we did not examine HAQ in this study. To determine whether the degree of disability rather than disease duration in itself may be responsible for DAS response, the role of functional capacity such as HAQ as the predictor for the treatment response may need to be examined. The concurrent use of methotrexate was shown to be a good predictor of the response for etanercept (48, 54), for infliximab and etanercept (36), and for infliximab, etanercept and adalimumab (36, 42, 49). On the other hand, a recent report showed that concomitant methotrexate use was not a predictor of treatment response to TNF inhibitors (37). Although the difference was suggested to be due to the response criteria chosen, such as the European League against Rheumatism (EULAR) responses using DAS28 and ACR response criteria (37), the reason for the controversial results is unknown. Further studies are needed to clarify the validity of predictors for the response of biological agents.

The RL group showed a significantly lower DAS 28-CRP at week 4 versus the MHD group. Of the DAS components, 28 TJC, patient global assessment, and CRP at week 4 was significantly lower in the RL group than in the MHD group. To determine the predictors of a 48-week response at week 4, the change in DAS28 response from baseline to week 4 was compared between the RL and MHD groups. DAS28-CRP, 28 TJC, and patient global assessment were all found to significantly decrease at week 4 in both groups when compared with those at baseline. However, 28 SJC and CRP significantly decreased in the RL group, but not in the MHD group. These data indicate that decreases in 28 SJC and CRP at week 4 were therefore useful predictors for sustaining the efficacy up to week 48.

The decision to select an initiating biologic agent is highly dependent on various factors such as disease severity, comorbidities, patient choice and compliance, and overall cost (55). There is no reason to prefer one particular biological agent due to efficacy because there is strong evidence that all the evaluated biological agents were able to reduce synovitis and erosive damage, which thus resulted in an improved disability and quality of life (17, 56). The present study showed that the disease severity was not responsible for the selection of an initiating biological agent because there was no significant difference in the baseline DAS28-CRP score among the biologic agents. The preference due to physicians may be another important factor. In the present study, etanercept was the most used biological agent (46.9%) followed by infliximab, adalimumab, and tocilizumab. Since infliximab and etanercept were approved early in Japan in 2003 and 2005, respectively, they have since been widely used to treat RA patients, thus resulting in the physicians' familiarity with these products. On the other hand, adalimumab and tocilizumab were approved in 2008, just before the start of this study. In this 2-year study, the number of patients treated with adalimumab or tocilizumab was low in the first year, but increased in the second year (data not shown), thus suggesting that the physician's familiarity with adalimumab and tocilizumab had been increased by usage. Both the route and frequency of administration may influence the preference. To assess the variation in the usage of biological agents, this study compared an initiating biological agent among the medical institutions, and showed that there were certain differences among the institutions in the selection of biological agents. Since etanercept and adalimumab were administered subcutaneously, efforts to effectively teach the method of self-injection to patients were therefore needed. These efforts were not needed in patients treated with infliximab or tocilizumab which were administered as intravenous drip infusions, but careful observation by the medical staffs was needed during the infusions. These differences may influence the selection of biological agents in medical institutions because the number of medical staffs working in patient care is different among them. Chilton F *et al.* examined the treatment preferences and choices which RA patients would make when faced with anti-TNF-α therapy options, and showed that 41% of the RA patients wanted their rheumatologist to make treatment decisions for anti-TNF-α treatments, 33% wanted to make the decision themselves, and 7% preferred a joint decision (57). The present study showed that subcutaneous drugs were preferred at some institutions rather than intravenous drugs, and they were likely to be continued up to week 48 for patients even with a moderate or high disease activity. This result suggests that medical

institutions should improve both their equipment and staff training to be able to select the biological agent that is most suitable for each patient.

In conclusion, we compared the efficacy of biological agents in RA patients, and found that etanercept achieved the highest treatment responses and remission rate, while it also had the longest drug survival rates. Furthermore, we showed that patients with a high disease activity at the baseline DAS28-CRP were predictors of the treatment response to biological agents, and of DAS28-CRP components, high patient global assessments were significantly less likely to achieve good response. Moreover, decreases in 28 SJC and CRP at week 4 were found to be useful predictors for sustaining the efficacy up to week 48.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

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