pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 24, No. 4, August, 2017
https://doi.org/10.4078/jrd.2017.24.4.227

Original Article

Comparing Effectiveness Rituximab (Mabthera®) to Other Second-line Biologics for Rheumatoid Arthritis Treatment in Patients Refractory to or Intolerant of First-line Anti-tumor Necrosis Factor Agent: An Observational Study

Yong-Wook Park[1], Ki-Jo Kim[2], Hyung-In Yang[3], Bo Young Yoon[4], Sang Hyon Kim[5], Seong-Ho Kim[6], Jinseok Kim[7], Ji Seon Oh[8], Wan-Uk Kim[9], Yeon-Ah Lee[10], Jung-Yoon Choe[11], Min-Chan Park[12], Sang-Heon Lee[13]

[1]Department of Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, [2]Division of Rheumatology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, [3]Division of Rheumatology, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, [4]Department of Rheumatology, Inje University Ilsan Paik Hospital, Goyang, [5]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, [6]Division of Rheumatology, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan, [7]Department of Internal Medicine, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, [8]Division of Rheumatology, Department of Internal Medicine, National Medical Center, Seoul, [9]Department of Internal Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, [10]Division of Rheumatology, Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, [11]Division of Rheumatology, Department of Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, [12]Division of Rheumatology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, [13]Division of Rheumatology, Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea

Objective. Failure of first-line anti-tumor necrosis factor (TNF) agents in in rheumatoid arthritis patients leads to decisions among second-line biologic agents. To better inform these decisions, the therapeutic effectiveness of rituximab is compared with other second-line biologic agents in this observational study. **Methods.** Between November 2011 and December 2014, study subjects were observed for 12 month periods. Patients with an inadequate response to initial anti-TNF agent received either rituximab or alternative anti-TNF agents (adalimumab/etanercept/infliximab) based on the preference of patients and physicians. The efficacy end point of this study was the change in 28-joint count Disease Activity Score (DAS28) at six and 12 months from baseline. Safety data were also collected. **Results.** Ninety patients were enrolled in the study. DAS28 at six months did not change significantly whether the patients were treated with rituximab or alternative anti-TNF agents in intention-to-treat analysis (n=34, -1.63 ± 0.30 vs. n=31, -2.05 ± 0.34) and standard population set analysis (n=31, -1.51 ± 0.29 vs. n=24, -2.21 ± 0.34). Similarly, the change in DAS28 at 12 months did not reach statistical significance (-1.82 ± 0.35 in the rituximab vs. -2.34 ± 0.44 in the alternative anti-TNF agents, p=0.2390). Furthermore, the incidences of adverse events were similar between two groups (23.5% for rituximab group vs. 25.8% for alternative anti-TNF agents group, p=0.7851). **Conclusion.** Despite the limitations of our study, switching to rituximab or alternative anti-TNF agents after failure of the initial TNF antagonist showed no significant therapeutic difference in DAS28 reduction. **(J Rheum Dis 2017;24:227-235)**

Key Words. Rheumatoid arthritis, Rituximab, Anti-tumor necrosis factor agent, DAS28 score

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by the progressive and irreversible destruction of joints [1]. According to the 2009 National Health and Nutrition Survey in Korea, the prevalence of RA was 1.9% in subjects aged ≥30 years and 4.3% in ≥65 [2]. While RA is less prevalent compared to other chronic diseases, it develops in relatively younger ages, causes severe disability and seriously inter-

Received : January 12, 2017, **Revised :** (1st) March 23, 2017, (2nd) May 25, 2017, **Accepted :** June 13, 2017

Corresponding to : Sang-Heon Lee, Division of Rheumatology, Department of Internal Medicine, Konkuk University School of Medicine, 120 Neungdong-ro, Gwangjin-gu, Seoul 05029, Korea. E-mail : shlee@kuh.ac.kr

feres with daily activities [3,4]. According to the 2009 National Health Insurance Statistical Yearbook, approximately 280 thousand patients were treated for RA yearly in Korea, incurring more than Korean Won 300 billion as direct treatment expenses [5].

The treatment goal for RA is to control pain with a minimum of side effects, delay disease progression, postpone development of joint damage and dysfunction as much as possible, and thereby preserve the quality of life [6]. During the past decades, great improvements have been achieved in the field of RA treatment with the emergence of biologic disease-modifying antirheumatic drugs including anti-tumor necrosis factor (anti-TNF) agents and their establishment in clinical practice [7]. Nonetheless, approximately one third of patients treated with first-line anti-TNF drugs failed to meet the American College of Rheumatology 20% response criteria, the minimum index for the effects of RA medication [8-12]. In addition, some patients experienced a gradual decrease in efficacy with long-term use or early discontinuation of TNF antagonists due to side effects [13].

In case of treatment failure after the first-line anti-TNF agents, the second-line biologics including alternative anti-TNF agents or biologics with a different mechanism of action (e.g. interleukin-6 inhibitors [tocilizumab], B-cell depleting antibodies [rituximab], or inhibitors of T-cell co-stimulation [abatacept]) are commonly used [14]. To date, however, no study has been conducted comparing the efficacy among the second-line biologics in Korea. Thus, the objective of this observational study was to investigate and compare the therapeutic effectiveness of rituximab (Mabthera®) and second-line biologic agents in RA patients after failure of the first-line TNF antagonists in the real clinical practice in Korea.

MATERIALS AND METHODS

This was a non-interventional, prospective and observational study. Between November 2011 and December 2014, patients using second-line biological agents for RA treatment were enrolled in 13 University Hospitals. The decision making related to the treatment strategy was made on the preference of patients and physicians without arbitrations. The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients and local Institutional Review Boards approved the protocol.

The inclusion criteria for this study were: (i) RA subjects aged over 20 years who were discontinued the first-line anti-TNF treatment owing to inadequate response or intolerance and (ii) initiated second-line biologics including either rituximab or alternative anti-TNF agents, different from the first anti-TNF one, within 6 weeks before participation of the study. The only exclusion criterion was subjects who participated in other clinical trials related to RA and received investigational products accord-

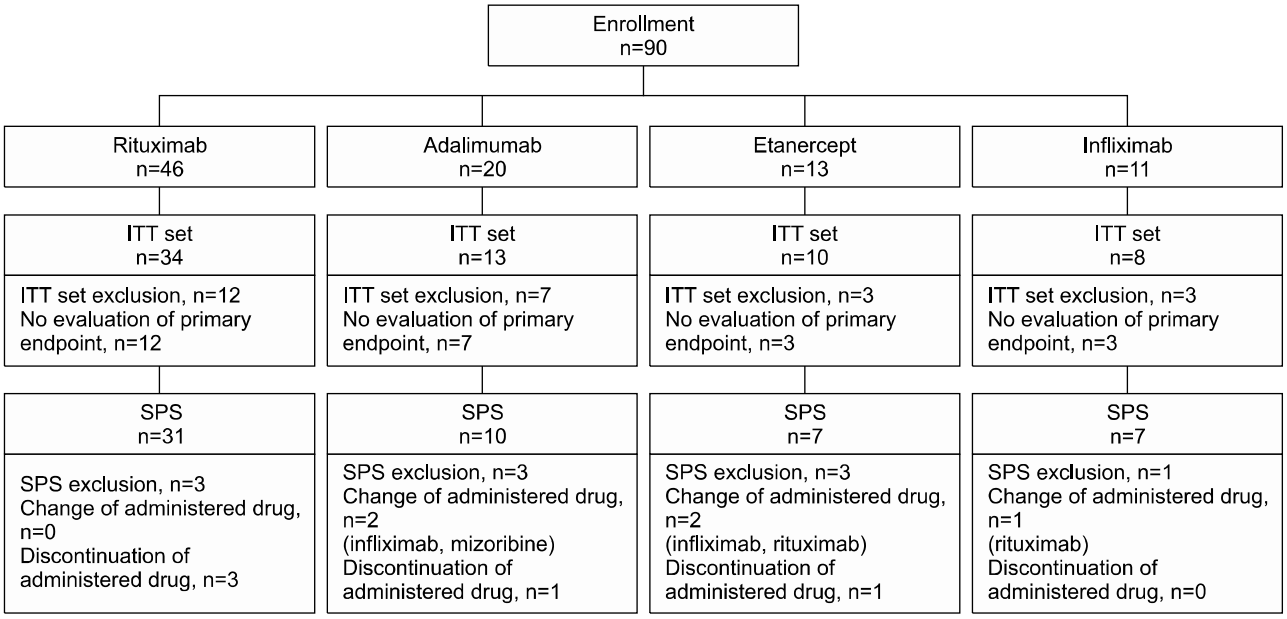

Figure 1. Study participation diagram. ITT: intention-to-treat, SPS: standard population set.

ing to the protocol while being treated with the first or second-line biological agents.

Patients were classified into two groups according to the prescribed second-line biologic agents: rituximab vs. alternative anti-TNF agents (adalimumab, etanercept, infliximab). Demographic and clinical data were collected at the baseline and follow-ups were performed at 6 and 12 months. The primary endpoint of this study was the change in 28-joint count Disease Activity Score (DAS28) calculated with 3 variables including tender joint count, swollen joint count, and erythrocyte sedimentation rate (ESR) after 6 months.

The secondary endpoint was the change in DAS28 after 12 months. Safety data including adverse events (AEs), adverse drug reactions (ADRs), and serious adverse events (SAEs) were also collected. ADRs were defined as AEs related to the medication and the relationship of AEs to each drug was assessed by the physicians. SAEs were defined as AEs presenting a significant hazard or side effect (e.g. any event that was fatal, life-threatening, required hospitalization, or resulted in persistent or significant disability) [15,16].

Statistical analyses were performed using a commercially available software package (SAS version 9.3 system; SAS Institute Inc., Cary, NC, USA). The intention-to-treat set (ITT set) included subjects who received at least one

Table 1. Demographic and disease information (intention-to-treat set)

Variable			Rituximab group (n = 34)	Other anti-TNF agents group (n = 31)	p-value
Age (yr)	Mean ± SD		55.62 ± 11.92	52.74 ± 14.36	0.3815§
	Median		60.00	55.00	
	20 ~ 29		0 (0.0)	2 (6.5)	0.2226†
	30 ~ 39		4 (11.8)	4 (12.9)	
	40 ~ 49		7 (20.6)	7 (22.6)	
	50 ~ 59		6 (17.7)	7 (22.6)	
	60 ~ 69		15 (44.1)	6 (19.4)	
	70 ~ 79		2 (5.9)	5 (16.1)	
Gender	Male		9 (26.5)	5 (16.1)	0.3111†
	Female		25 (73.5)	26 (83.9)	
Smoking status	Smoker		5 (14.7)	0 (0.0)	0.1040‡
	Non smoker		26 (76.5)	27 (87.1)	
	UK		3 (8.8)	4 (12.9)	
RF status at baseline	Positive		18 (52.9)	19 (61.3)	0.7599‡
	Negative		4 (11.8)	2 (6.5)	
	ND or UK		12 (35.3)	10 (32.3)	
Anti-CCP status at baseline	Positive		15 (44.1)	15 (48.4)	1.0000‡
	Negative		3 (8.8)	2 (6.5)	
	ND or UK		16 (47.1)	14 (45.2)	
Arthroplasty history*	Hip	Yes	3 (8.8)	1 (3.2)	0.1496‡
		No	30 (88.2)	25 (80.7)	
		UK	1 (2.9)	5 (16.1)	
	Knee	Yes	1 (2.9)	4 (12.9)	0.3619‡
		No	30 (88.2)	25 (80.7)	
		UK	3 (8.8)	2 (6.5)	
	Elbow	Yes	0 (0.0)	2 (6.5)	0.5467‡
		No	30 (88.2)	25 (80.7)	
		UK	4 (11.8)	4 (12.9)	
	Shoulder	Yes	0 (0.0)	0 (0.0)	0.4995‡
		No	30 (88.2)	25 (80.7)	
		UK	4 (11.8)	6 (19.4)	

Values are presented as number (%). TNF: tumor necrosis factor, SD: standard deviation, RF: rheumatoid factor, CCP: citrullinated protein, ND: not done, UK: unknown. *The total number of patients is counted by duplication. †Pearson's chi-square test. ‡Fisher's exact test. §Two sample t-test.

dose of the second-line biologics and had the primary endpoint results. The standard population set (SPS) consisted of subjects who maintained the second-line biological agents which were initially selected for 6 months among the ITT set. Two sample t-test was conducted to compare continuous variables between groups. Pearson's chi-square or Fisher's exact test was used to compare categorical variables. Analysis of covariance (ANCOVA) models was performed to compare the change of DAS28 at 6 and 12 months between groups. The DAS28 and rheumatoid factor (RF) status at baseline were included in the models as covariances. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 90 patients were ultimately enrolled in the study. Among them, 46 (51.1%) patients received rituximab; 44 (48.9%) were treated by the second-line TNF antagonists including adalimumab (20 subjects), etanercept (13 subjects), and infliximab (11 subjects) after failure of the first-line anti-TNF treatment. After excluding 25 patients who failed to assess the primary outcome at 6 months, 34 were in the rituximab group, and 31 were in the alternative anti-TNF agents group in the ITT set. Three patients in the rituximab and 7 patients in the alternative anti-TNF agents were further excluded owing to change or discontinuation of the initial medication in the SPS set. Details of patient enrollment and study flow are shown in Figure 1.

The mean age of the rituximab group was 55.62±11.92 and the alternative anti-TNF agents group was 52.74±14.36 years. Majority of patients were female and non-smoker in both groups (73.5% and 76.5% in the rituximab group and 83.9% and 87.1% in the alternative anti-TNF agents, respectively). The baseline characteristics did not differ significantly between two groups (Table 1).

Table 2 demonstrates the pattern of prescription and the

Table 2. Prescription status at 12 months from second-line biological agents started for each treatment group (intention-to-treat set)

Prescription status		Rituximab group (n=34)	Other anti-TNF agents group (n=31)	p-value
Initial anti-TNF agents	n	34	31	
	Adalimumab	17 (50.0)	15 (48.4)	1.0000†
	Etanercept	14 (41.2)	13 (41.9)	
	Infliximab	3 (8.8)	3 (9.7)	
Reason for discontinuation of initial anti-TNF agents	n	34	31	
	No response	9 (26.5)	7 (22.6)	0.8529†
	Loss of response	23 (67.7)	21 (67.7)	
	Side effects	2 (5.9)	3 (9.7)	
Status of second-line biologics at 6 months	n	34	31	
	Maintain	31 (91.2)	24 (77.4)	0.0620†
	Change	0 (0.0)	5 (16.1)	
	Discontinuation	3 (8.8)	2 (6.5)	
Reason for discontinuation of second-line biologics	n	3	7	
	No response	3 (100.0)	2 (28.6)	0.2083†
	Loss of response	0 (0.0)	3 (42.9)	
	Side effects	0 (0.0)	2 (28.6)	
Status of second-line biologics at 12 months	n*	29	21	
	Maintain	24 (82.8)	17 (81.0)	0.3389†
	Change	4 (13.8)	1 (4.8)	
	Discontinuation	1 (3.5)	3 (14.3)	
Reason for discontinuation of second-line biologics	n	5	4	
	No response	1 (20.0)	1 (25.0)	1.0000†
	Loss of response	3 (60.0)	2 (50.0)	
	Side effects	1 (20.0)	0 (0.0)	
	Other	0 (0.0)	1 (25.0)	

Values are presented as number (%). TNF: tumor necrosis factor. *In the rituximab and other anti-TNF agents groups, 5 patients who failed to follow up at 12 months are excluded. †Fisher's exact test.

reason of medication change over the study period. Most of the patients received either adalimumab or eternacept as the initial anti-TNF treatment. The most common reason of discontinuation of the first treatment was loss of response over the time. After change of medication, 3 patients were discontinued their treatment due to no response in the rituximab group, while 5 were changed and 2 were suspended their medication in the alternative anti-TNF agents group at 6 months of follow-up. On the other hand, 24 out of 29 subjects (82.8%) in the rituximab group and 17 out of 21 (81.0%) in the alternative anti-TNF agents group maintained the second-line medications at 12 months of follow-up.

Changes in DAS28 at 6 and 12 months after using secondary biological agents treatment for each treatment group are presented in Tables 3 and 4. After adjusting for DAS28 and RF status at baseline, changes in DAS28 at 6 months were −1.63±0.30 in the rituximab group and −2.05±0.34 in the alternative anti-TNF agents group in the ITT analysis which did not reach statistical significance (p=0.3037). The SPS analysis also showed no statistical difference (−1.51±0.29 in the rituximab vs. −2.21±0.34 in the alternative anti-TNF agents, p=0.0951). Similarly, change in DAS28 at 12 months did not significantly differ between two groups (−1.82±0.35 in the rituximab vs. −2.34±0.44 in the alternative anti-TNF agents, p=0.2390).

Since most of enrolled patients showed DAS28 high disease activity (>5.1) at baseline, all patients can be classified as moderate response or no response according to European League Against Rheumatism (EULAR) response criteria based on DAS28 score. Moderate EULAR response after 6 months was noted in 64.7% and 77.4% in the rituximab group and the alternative anti-TNF group, respectively. Similarly, the EULAR moderate response

Table 3. Change in DAS28 at 6 months comparing to baseline for each treatment group

DAS28		Rituximab	Other TNF inhibitors	p-value
ITT		n=34	n=31	
Baseline	n	34	31	
	Mean±SD	6.35±1.14	5.54±1.14	0.0056*
	Median	6.35	5.65	
	Min, Max	3.47, 8.35	3.37, 7.95	
6 months	n	34	31	
	Mean±SD	4.46±1.63	3.74±1.40	
	Median	4.13	3.59	
	Min, Max	0.68, 7.54	1.21, 7.17	
Change	n	34	31	
	Mean±SD	−1.89±1.73	−1.80±1.53	0.3037†
	LS Mean±SE	−1.63±0.30	−2.05±0.34	
	Median	−1.91	−1.83	
	Min, Max	−6.09, 1.31	−5.09, 1.13	
SPS		n=31	n=24	
Baseline	n	31	24	
	Mean±SD	6.30±1.18	5.47±1.04	0.0089*
	Median	6.10	5.49	
	Min, Max	3.47, 8.35	3.37, 7.95	
6 months	n	31	24	
	Mean±SD	4.56±1.51	3.56±1.33	
	Median	4.13	3.37	
	Min, Max	1.59, 7.54	1.21, 6.98	
Change	n	31	24	
	Mean±SD	−1.74±1.59	−1.91±1.53	0.0951†
	LS Mean±SE	−1.51±0.29	−2.21±0.34	
	Median	−1.86	−1.97	
	Min, Max	−4.76, 1.31	−5.09, 1.13	

Change is difference between baseline and 6 months. DAS28: disease activity score in 28 joints, TNF: tumor necrosis factor, ITT: intention-to-treat, SPS: standard population set, SD: standard deviation, LS: least squares, SE: standard error. *Two sample t-test. †The p-values are based on analysis of covariance models with control for DAS28 and rheumatoid factor of baseline.

Table 4. Change in DAS28 at 12 months comparing to baseline for each treatment group

DAS28		Rituximab group (n=24)	Other anti-TNF agents group (n=17)	p-value
Baseline	n	24	17	
	Mean±SD	6.28±1.27	5.49±0.92	0.0341†
	Median	6.13	5.65	
	Min, Max	3.47, 8.35	3.37, 6.98	
12 months	n*	22	16	
	Mean±SD	3.85±1.37	3.10±1.07	
	Median	3.92	3.20	
	Min, Max	0.01, 6.99	1.21, 5.25	
Change	n*	22	16	
	Mean±SD	−2.30±1.52	−2.29±1.36	0.2390‡
	LS Mean±SE	−1.82±0.35	−2.34±0.44	
	Median	−2.34	−2.39	
	Min, Max	−5.28, −0.04	−4.70, 0.61	

Change is difference between baseline and 12 months. DAS2: disease activity score in 28 joints, TNF: tumor necrosis factor, SD: standard deviation, LS: least squares, SE: standard error. *In the rituximab and other anti-TNF agents groups, 2 patients and 1 patient who have missing data at 12 months are excluded from analysis. †Two sample t-test. ‡The p-values are based on analysis of covariance models with control for DAS28 and rheumatoid factor of baseline.

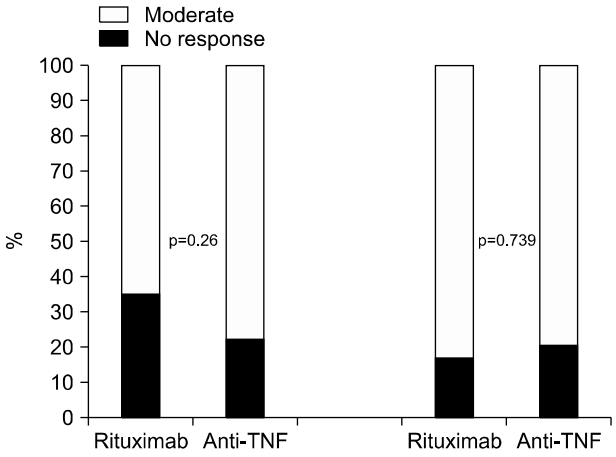

Figure 2. European League Against Rheumatism response after 6 months and 12 months of treatment with rituximab and alternative anti-tumor necrosis factor (TNF) agents.

rate was not different between the rituximab group and the alternative anti-TNF agents (82.8% and 79.2%, respectively) at 12 months (Figure 2).

Table 5 summarizes the AEs during the study period. In the rituximab group, a total of 12 AEs (8/34 patients, 23.5%) were reported, while 15 AEs (8/31 patients, 25.8%) were observed in the alternative TNF antagonists group. Among all AEs, 5 AEs (4/34 patients, 11.8%) and 3 AEs (3/34 patients, 8.8%) in the rituximab group were classified as ADRs and SAEs, whereas 7 AEs (5/31 patients, 16.1%) were categorized into ADRs in the alternative anti-TNF agents group. The incidence of AEs, ADRs, and SAEs did not differ between two groups (p=0.7851 for AEs; p=0.8205 for ADRs; p=0.8330 for SAEs, respectively). The detail of AEs are presented in Table 5.

DISCUSSION

For RA patients with deficient effects of or inadequate response to the first-line anti-TNF agent, the Korea Health Insurance Review & Assessment Service recommended changing the medication to another anti-TNF agents, rituximab, or abatacept. According to the UK National Institute for Health and Clinical Excellence guidelines, rituximab was preferentially recommended for these patients, mainly due to its excellent cost-effectiveness compared to other second-line biologics [17]. In addition, small observational studies conducted in Swiss reported a greater reduction in DAS28 by rituximab than other drugs [18,19]. In this study, however, we found that the change in DAS28-ESR at 6, 12 months was similar, regardless of medications chosen. And Standard Population Set interim analysis also showed no statistical difference at 6 months.

There are several reasons for the conflicting results between the studies. The composition of the study population differ in each study. Although demographic profiles of the current study including age and gender dis-

Table 5. Adverse events on organ systems (intention-to-treat set)

System Organ Class (preferred term)	Rituximab group (n = 34)		Other anti-TNF agents group (n = 31)	
	n* (%)	Event	n* (%)	Event
Number of subjects with adverse event (0.7851†)	**8 (23.5)**	**12**	**8 (25.8)**	**15**
Gastrointestinal disorders	**1 (2.9)**	**1**	**4 (12.9)**	**5**
Diarrhea	0 (0.0)	0	2 (6.5)	2
Abdominal discomfort	1 (2.9)	1	0 (0.0)	0
Abdominal pain upper	0 (0.0)	0	1 (3.2)	1
Mouth ulceration	0 (0.0)	0	1 (3.2)	1
Nausea	0 (0.0)	0	1 (3.2)	1
Infections and infestations	**2 (5.9)**	**2**	**3 (9.7)**	**4**
Upper respiratory tract infection	1 (2.9)	1	1 (3.2)	2
Pneumonia	1 (2.9)	1	0 (0.0)	0
Tuberculosis	0 (0.0)	0	1 (3.2)	1
Urethritis	0 (0.0)	0	1 (3.2)	1
Skin and subcutaneous tissue disorders	**2 (5.9)**	**4**	**2 (6.5)**	**2**
Erythema	1 (2.9)	1	0 (0.0)	0
Pruritus	1 (2.9)	1	0 (0.0)	0
Rash	0 (0.0)	0	1 (3.2)	1
Skin lesion	1 (2.9)	1	0 (0.0)	0
Skin ulcer	0 (0.0)	0	1 (3.2)	1
Urticaria	1 (2.9)	1	0 (0.0)	0
General disorders and administration site conditions	**0 (0.0)**	**0**	**2 (6.5)**	**2**
Oedema	0 (0.0)	0	1 (3.2)	1
Pyrexia	0 (0.0)	0	1 (3.2)	1
Respiratory, thoracic and mediastinal disorders	**1 (2.9)**	**1**	**1 (3.2)**	**1**
Cough	0 (0.0)	0	1 (3.2)	1
Dyspnea	1 (2.9)	1	0 (0.0)	0
Eye disorders	**2 (5.9)**	**2**	**0 (0.0)**	**0**
Dry eye	1 (2.9)	1	0 (0.0)	0
Iritis	1 (2.9)	1	0 (0.0)	0
Immune system disorders	**1 (2.9)**	**1**	**0 (0.0)**	**0**
Anaphylactoid reaction	1 (2.9)	1	0 (0.0)	0
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0**	**1 (3.2)**	**1**
Back pain	0 (0.0)	0	1 (3.2)	1
Psychiatric disorders	**1 (2.9)**	**1**	**0 (0.0)**	**0**
Delirium	1 (2.9)	1	0 (0.0)	0
Number of subjects with adverse drug reaction (0.8205†)	**4 (11.8)**	**5**	**5 (16.1)**	**7**
Skin and subcutaneous tissue disorders	**2 (5.9)**	**3**	**2 (6.5)**	**2**
Erythema	1 (2.9)	1	0 (0.0)	0
Pruritus	1 (2.9)	1	0 (0.0)	0
Rash	0 (0.0)	0	1 (3.2)	1
Skin ulcer	0 (0.0)	0	1 (3.2)	1
Urticaria	1 (2.9)	1	0 (0.0)	0
Infections and infestations	**1 (2.9)**	**1**	**2 (6.5)**	**2**
Pneumonia	1 (2.9)	1	0 (0.0)	0
Tuberculosis	0 (0.0)	0	1 (3.2)	1
Urethritis	0 (0.0)	0	1 (3.2)	1
Gastrointestinal disorders	**0 (0.0)**	**0**	**2 (6.5)**	**2**
Diarrhea	0 (0.0)	0	1 (3.2)	1
Nausea	0 (0.0)	0	1 (3.2)	1
Immune system disorders	**1 (2.9)**	**1**	**0 (0.0)**	**0**
Anaphylactoid reaction	1 (2.9)	1	0 (0.0)	0
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0**	**1 (3.2)**	**1**
Cough	0 (0.0)	0	1 (3.2)	1
Number of subjects with serious adverse reaction (0.8330†)	**3 (8.8)**	**3**	**0 (0.0)**	**0**
Immune system disorders	**1 (2.9)**	**1**	**0 (0.0)**	**0**
Anaphylactoid reaction	1 (2.9)	1	0 (0.0)	0
Infections and infestations	**1 (2.9)**	**1**	**0 (0.0)**	**0**
Pneumonia	1 (2.9)	1	0 (0.0)	0
Respiratory, thoracic and mediastinal disorders	**1 (2.9)**	**1**	**0 (0.0)**	**0**
Dyspnea	1 (2.9)	1	0 (0.0)	0

Dictionary: MedDRA v17.0. TNF: tumor necrosis factor. *The total number of patients is counted by duplication. †The p-values are based on Fisher's exact test.

tribution were similar to previous studies as well as general epidemiologic data for RA [14,20], it is well known that the response to the medication is different depending on the race [21]. The number of previously administered anti-TNF agents also impacts the effects of later administered biologics in treating RA [22-24]. It is hard to draw a firm conclusion from the previous and current studies, due to their non-interventional design and relatively small number of patients.

In regard to the safety of the medications, the incidence of AEs, ADRs, and SAEs were not different between groups which was comparable to the results of previous studies [18,19]. Except previously known anaphylactoid reaction or infection due to immunosuppression, additional unexpected serious adverse drug reactions were not observed [25].

As our study was a non-interventional observational study, there were several intrinsic limitations. First, unlike randomized controlled trials, the choice of the biologic agent was dependent on the preference of the patients and their attending physicians which meant that selection bias was inevitable. However, the baseline characteristics did not differ between two groups. Second, owing to the small number of patients enrolled, this study did not reach statistical power to detect the difference of efficacy between rituximab and alternative anti-TNF agents. Therefore, our study has some limitation to get the significant power to determine the effect size. Because there was more percentage of patients that dropped out in the anti-TNF agents group, it might have a bias to analyze the change of DAS28 only in the remaining group. There is a high probability that rituximab was shown to be more effective than the anti-TNF agents. Considering the baseline DAS28 was higher in rituximab group, the analysis of change in DAS28 at 12 months was conducted with ANCOVA with control for DAS28 and RF of baseline. Regard to baseline characteristics, there are limitation due to missing values of rheumatoid factor status and anti-citrullinated protein antibody status because of multicenter trial in character.

CONCLUSION

This 12 months follow-up observational study, which compared effectiveness in reducing disease activity of rituximab and alternative anti-TNF agents, shows no significant difference between two treatments. However, the findings of our study are expected to be utilized as basis of future clinical trials and development of treatment guidelines for RA patients in Korea.

ACKNOWLEDGMENTS

All authors read and approved the final consents of the manuscript. Taeyeon Kwon and Sungeun Kim at Roche Korea contributed to the study. Medical writing for this manuscript was provided by Soo-hyun Lew at DreamCIS. This study is a Roche-sponsored study (NCT01592292).

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Maciejewska Rodrigues H, Jüngel A, Gay RE, Gay S. Innate immunity, epigenetics and autoimmunity in rheumatoid arthritis. Mol Immunol 2009;47:12-8.
2. Korea Ministry of Health and Welfare and Korea Centers for Disease Control & Prevention. Korea Health Statistics 2009: Korea National Health and Nutrition Examination Survey (KNHANESIV-3). 2009, p. 557.
3. Bae SC. Rheumatoid arthritis: past, present and future. J Korean Med Assoc 2010;53:842.
4. Kim YJ, Choi CB, Sung YK, Lee H, Bae SC. Characteristics of Korean patients with RA: a single center cohort study. J Korean Rheum Assoc 2009;16:204-12.
5. 2009 National Health Insurance Statistical Yearbook. Seoul, Korea National Health Insurance Corporation, Health Insurance Review & Assessment Service, 2010, p. 472.
6. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum 2002;46:328-46.
7. Kahlenberg JM, Fox DA. Advances in the medical treatment of rheumatoid arthritis. Hand Clin 2011;27:11-20.
8. Redlich K, Schett G, Steiner G, Hayer S, Wagner EF, Smolen JS. Rheumatoid arthritis therapy after tumor necrosis factor and interleukin-1 blockade. Arthritis Rheum 2003;48: 3308-19.
9. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000; 343:1594-602.
10. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.
11. Weinblatt ME, Keystone EC, Furst DE, Moreland LW,

Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.
12. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 2008;67:547-54.
13. Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis 2006;65:746-52.
14. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
15. Emery P, Gottenberg JE, Rubbert-Roth A, Sarzi-Puttini P, Choquette D, Taboada VM, et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis 2015;74:979-84.
16. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res 2012;26:1719-25.
17. NICE technology appraisal guidance 195. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: Part review of NICE technology appraisal guidance 36. Review of NICE technology appraisal guidance 126 and 141. August 2010. London, National Institute for Health and Clinical Excellence, 2010.
18. Finckh A, Ciurea A, Brulhart L, Kyburz D, Möller B, Dehler S, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007; 56:1417-23.
19. Finckh A, Ciurea A, Brulhart L, Möller B, Walker UA, Courvoisier D, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis 2010;69:387-93.
20. Sung YK, Cho SK, Choi CB, Bae SC. Prevalence and incidence of rheumatoid arthritis in South Korea. Rheumatol Int 2013;33:1525-32.
21. Burroughs VJ, Maxey RW, Levy RA. Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. J Natl Med Assoc 2002;94(10 Suppl):1-26.
22. Furst DE, Gaylis N, Bray V, Olech E, Yocum D, Ritter J, et al. Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. Ann Rheum Dis 2007;66:893-9.
23. Gomez-Reino JJ, Carmona L. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther 2006;8:R29.
24. Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. Arthritis Res Ther 2009;11 Suppl 1:S1.
25. van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann RM, Furst DE, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 2013; 72:1496-502.