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Research Article

Study of Patients who Switched to Biosimilars after Low Disease Activity was Achieved by Preceding Originator Etanercept

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Received: October 05, 2020; **Published:** November 28, 2020

Abstract

Objectives: Biosimilars were developed as therapeutic drugs for rheumatoid arthritis (RA) in terms of medical economics. We focused on the outcomes of continuous therapy in patients who chose to switch to Etanercept (ETN)- Biosimilar (BS) after low disease activity was achieved by Originator ETN.

Methods: Forty Japanese patients with RA were asked whether they would choose to switch to ETN-BS after the disease activity was decreased and stabilized by Originator ETN.

Results: Of these, 27 (67.5%) patients switched to the BS. The effect was maintained in 25 of these patients, whereas the remaining 2 patients dropped out due to adverse reactions. Spacing was possible in 24 (96%) of the 25 patients. They could also maintain remission and low disease activity.

Conclusion: This study is the first report to show the clinical usefulness of switching to BS after the disease activity was decreased and stabilized by Originator ETN in Japanese.

Keywords: *Etanercept; Biosimilar; Switching; Rheumatoid Arthritis; Japanese*

Abbreviations

RA: Rheumatoid Arthritis; BS: Biosimilar; IFX: Infliximab; ETN: Etanercept; DAS-28-ESR: Disease Activity Score 28 Erythrocyte Sedimentation Rate; BMI: Bone Mass Index; LEF: Leflunomide; BUC: Bucillamine

Introduction

Biosimilars (BSs) were developed as therapeutic drugs for rheumatoid arthritis (RA) in terms of medical economics: in Japan, a BS of infliximab (IFX:Remicade; originator, Mitsubishi Tanabe, IFX-BS: Infliximab BS, Nippon Kayaku) was launched in November 2014 and a BS of etanercept (ETN:Enbrel; originator Pfizer; ETN-BS: Etanercept BS [MA], AYUMI Pharmaceutical and Mochida Pharmaceutical) was launched in May 2018 [1]. Although BSs are not same to the preceding drugs, they demonstrate efficacy and safety equivalent to these, and their drug prices have decreased as of April 2020 (Table 1). Therefore, many patients with RA and insurance mechanisms benefit from BSs [2]. The present study focused on the outcomes of continuous therapy in patients who chose to switch to ETN-BS after low disease activity was achieved by ETN.

Price of a preceding product (standard dose)	Price of the BS (standard dose)
Infliximab (200 mg/8 weeks) 150,018 yen	Infliximab-BS (200 mg/8 weeks) 86,458 yen (57.6%)
Etanercept 50 mg Pen (50 mg/week) 25,171 yen	Etanercept-BS (50 mg Pen) 17,025 yen (67.6%)

Table 1: *Comparison of drug prices as of April 2020.*

Methods

We recommended all patients with RA who were receiving ETN to switch to ETN-BS. This also included patients whose RA disease activity was stable enough for successful spacing in the Department of Orthopedics, Sakai Sakibana Hospital, and the affiliated Hara Hospital. In principle, we specifically explained the study to patients with RA who had maintained a disease activity score 28 erythrocyte sedimentation rate (DAS-28-ESR) of less than 3.2 for 3 months or longer or those whose satisfaction was very high; responsible people and other family members were also included in this explanation. They were then asked whether they would be willing to switch. For comparison, we also investigated the background of patients who started ETN-BS as the first biological product during the same period.

Results

Forty patients enrolled in this study from May 2018 to December 2019 (Table 2); among these, 13 (32.5%) did not wish to switch. In patients who did not wish to switch, the cost of ETN was lower than when it was initially administered because of spacing. Therefore, switching to BS to solve the cost problem was not their priority. The biggest reason why these patients or their families did not wish to switch was because they did not want to disturb the currently stabilized RA disease activity. Regarding background factors, 9 (69.2%) of the 13 patients who did not want to switch had a history of orthopedic surgery (among the total 40 patients, 16 (40.0%) had a history of surgery; among 27 patients who wished to switch, 7 (25.9%) had a history of surgery. Of the 27 patients who switched to ETN-BS, 2 dropped out during the course of the study: 1. A 79-year-old woman with a disease duration of 20 years, at stage 4 and class 2, with a history of surgery of joints, vertebrae, etc. and a body mass index (BMI) of 21.8. She had received ETN for 8 years and her DAS-28-ESR was 2.18 at the time of switching. At the third dose of BS, she felt a sense of discomfort, and the BS was discontinued at her request. 2. A 53-year-old woman a disease duration of 33 years, at stage 4 and class 2, and with a BMI of 20.5. She had received ETN for 11 years and her DAS-28-ESR was 2.74 at the time of switching. Rashes appeared immediately after the administration of BS, and the BS was discontinued. None of the symptoms were serious. These 2 patients again administered the previous ETN and the disease activity also returned to the previous level.

Change in DAS-28-ESR in 25 patients who continued BS was 2.60 ± 0.61 before switching and 2.43 ± 0.49 3 months after switching, showing that the effect of BS was maintained (Figure 1). Moreover, spacing was possible in 24 (96%) of the 25 patients. One patient in whom spacing was not done continued receiving 50 mg of ETN-BS once a week (a 78-year-old woman with a disease duration of 17 years, at stage 2 and class 2, and with a BMI of 24.9. She had been receiving ETN for 12 years. Immediately before switching to the BS, her DAS-28-ESR worsened to 4.39; therefore, the BS was increased from 25 mg/week to 50 mg/week. The DAS-28- ESR was decreased to 2.8 at 1 month after administration, and her satisfaction was also stabilized. However, the BS was maintained at this dose without spacing.

Although different from the main theme of this report, 13 (76.5%) of the 17 patients with RA who started ETN-BS as the first biological product during the same period (Table 3) was able to continue ETN-BS; however, 4 patients dropped out (insufficient effect in 2 patients, injection site pruritus in 1 patient, and no visit in 1 patient). In 7 (53.8%) of the 13 patients, disease activity was decreased, which enabled spacing. The proportion of patients with a history of orthopedic surgery in this series was 47.1%, which showed no difference compared to that of patients who switched treatments (40.0%). Only 1 year has passed, and further follow-up is necessary in the future.

			Etanercept (ETN)	Switching to BS	No switching
			All patients who used ETN		
Patients	Total		40	27 (67.5%)	13 (32.5%)
	Men		7	5	2
	Women		33	22	11
Mean age		Years	65.3	65.7	64.4
Mean disease duration		Years	16.9	16.1	18.5
Stage	I		2	2	0
	II		17	12	5
	III		2	2	0
	IV		19	11	8
Class	1		3	2	1
	2		34	23	11
	3		3	2	1
	4		0	0	0
RA activity	DAS28ESR		2.51	2.60	2.37
BMI			22.4	22.4	23.4
Concomitant drugs					
	MTX		27	18	9
	Mean dose	mg/week	7.19	6.48	8.6
	LEF		5	4	1
	Bc		4	1	3
	Others		4	4	
PSL			15	10	5
	Mean dose	mg/day	3.5	3.5	3.5
History of orthopedic surgery			16	7	9

Table 2: *Background of patients who used etanercept (all, switching to BS, no switching).*

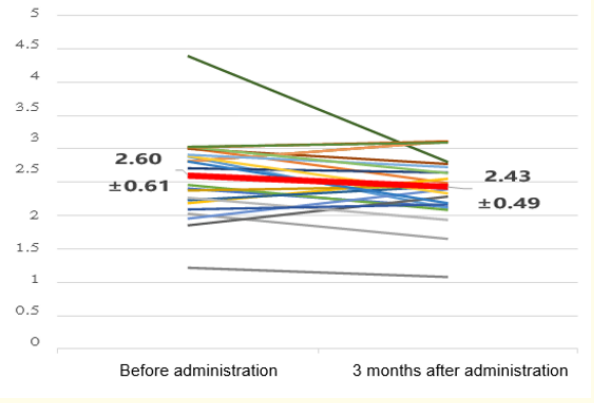

Figure 1: *Patients who switched to BS Change in DAS-28-ESR.*

Patients with RA	17 patients (8 men and 9 women)
Age	Mean, 69.2 years (46 - 86 years)
Disease duration	Mean, 10.8 years (1 - 30 years)
Stage	I: 0 patient; II: 6 patients; III: 2 patients; IV: 9 patients
Class	1: 2 patients; 2: 13 patients; 3: 2 patients; 4: 0 patient
BMI	24.6 (17.1 - 29.4)
Concomitant drugs	MTX: 6 patients (mean dose: 7.7 mg/week) SASP: 4 patients LEF: 1 patient Bc: 1 patient Others: 5 patients Concomitant use of PSL: 8 patients (mean dose: 4.7 mg/day)
History of orthopedic surgery	8 patients (47.1%)
After treatment (3 months)	DAS28 ESR 2.03
Patients for whom spacing was done	8 patients 1w ⇒ 2w: 4 patients 1w ⇒ 3w: 4 patients

Table 3: *Background of patients who used etanercept biosimilar as the first biological product.*

Discussion

Because of the advanced aging population in Japan, the treatment of RA in the elderly has become an important problem [3]. According to a report of actual clinical practice from our affiliated hospital, more than 40% of elderly patients with RA aged 70 years or older have a history of orthopedic surgery, and the number of patients with early RA based on the stage and class distribution is small [4]. ETN is a drug that can be continued for a long time, and a study in which the dose was reduced to half once the disease activity was stabilized has been published [5]. Our hospital has been demonstrating that even a small amount of biological product is effective in maintaining low disease activity in elderly Japanese with low BMIs [6]. Advantages of receptor antibodies such as ETN and abatacept have been reported; they do not necessarily require methotrexate (MTX), the use of which is limited in the elderly and patients with renal dysfunction, and are easier to administer to patients with infections and complications [7,8]. When a BS product was launched for the first time in Japan in 2016 and 10 patients who were stable on IFX were asked whether they would choose to switch to the BS, 6 (60%) of them did not wish to switch. However, when the second BS product was launched in 2018, the proportion of patients who were stable on ETN and did not switch to ETN-BS decreased to 32.5%, indicating that the efficacy and safety of BSs themselves had been socially recognized.

According to the results of a previous phase III extension study of ETN-BS (South Korea), which investigated the effect of the drug after switching from a preceding product, the effect was maintained during the observation period. No major problem was reported. However, the administration method had not been changed [9].

Most importantly, when the disease activity is stabilized, the dose of biological product can be reduced. After ETN was replaced with ETN-BS, the anti-RA effect was maintained. The administration method was then reviewed and spacing was performed. Almost 1 year after switching, no patient relapsed, which we consider a significant finding.

Conclusion

Forty Japanese patients with RA, including the elderly, were asked whether they would choose to switch to ETN-BS after the disease activity was decreased and stabilized by ETN. Of these, 27 (67.5%) patients switched to the BS.

The effect was maintained in 25 of these patients, whereas the remaining 2 patients dropped out due to adverse reactions. Spacing was possible in 24 (96%) of the 25 patients. They could also maintain remission and low disease activity.

Acknowledgement

Special thanks for the director general Dr. Keiji Inoue (Keijin group).

Conflict of Interest

No potential conflict to this article was reported.

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Volume 11 Issue 12 December 2020