Biological Retention Rates, the Reasons of Switching, and Prognostic Factors in Patients with Psoriasis Treated Biologics

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Objective: To review patients who were treated at Tokai University Hospital with biologic agents for psoriasis vulgaris and psoriatic arthritis and analyze the biological retention rate, reasons for switching biologics, and investigate possible clinical prognostic factor which may affect whether a patient preferred one biologic to another.
Methods: Clinical courses of 63 patients who received biologic agents between September of 2010 to June of 2019 were investigated. Biological retention rate of each biologic agents, reasons of switching to another biologic agent, and prognostic factors, if any, between switched and non-switched patients were examined.
Results: The biological retention rate of ustekinumab (UST) was significantly longer than that of infliximab (IFX) or adalimumab (ADA). The major reason of switching was due to secondary loss of efficacy. Patients being treated with UST were more likely to switch to another biologic when they exhibited nail lesions.
Conclusion: These results suggested that biological retention rate of UST was superior than that of IFX or ADA. Furthermore, with patients administered UST, nail symptom suggested possible clinical prognostic factor for switching to other biologic agents.

Key words: psoriasis, biologics, switching, biological retention rate, prognostic factor

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that impairs patients' quality of life worldwide [1]. Not only limited to the skin, this disease also affects nails and joints. More than half of patients with psoriasis complain of itching [1], as well as interference of sleep, causing mental of disorders [2]. Interleukin (IL)23-IL17 pathway and tumor necrosis factor (TNF)-α is a key mediator in the development and maintenance of psoriasis [3]. With the arrival of biologic agents, patients with moderate to severe symptoms improved drastically [2]. Moreover, these biologic agents show high efficacy with low rates of severe adverse events.

In Japan, biologics have been approved since 2010, and now 7 agents, (TNF)α inhibitors (infliximab, adalimumab), IL23 inhibitors (ustekinumab, guselkumab), and IL17 inhibitors (secukinumab, ixekizumab, brodalumab) [4–10], can be used as of April 2019.

However, in real world, some patients have to switch to other biologics due to inefficacy or adverse events. With psoriasis, previous studies have reported that biological retention rate of UST has been superior than TNF-αblocker [11, 12]. Bayaraa *et al.* reported that reasons for switching biologics were mainly secondary loss of efficacy or primary ineffectiveness [12]. Honda *et al.* reported that for those receiving ADA, discontinuation was associated with high baseline psoriasis area, severity index (PASI) score and older age, and noted that all of the switched cases were associated with high baseline PASI score [13]. However, with previous reports, possible prognostic clinical factors that may imply the discontinuation of one biologic are not confirmed to be consistent [13–15].

In this study, we reviewed patients treated with biologic agents who visited our outpatient clinic, analyzed biological retention rate, reasons for switching biologics, and investigated possible clinical prognostic factors which may affect whether a patient will switch to another biologic treatment.

MATERIAL AND METHODS

Patients

Among 63 patients (46 males, 17 females), who visited the Department of Dermatology, Tokai University Hospital from September 2010 to June 2019 with symptoms of psoriasis vulgaris and psoriatic arthritis, clinical information was extracted from the medical records for all patients who received first biologics. The extracted information included the following: sex, age, age of onset, height, body weight, body mass index (BMI), comorbidities, PASI, life history (smoking, drinking), nail symptoms, and itching.

This study was approved by the Institutional Review Board for Clinical Research, Tokai University Hospital (reference number: 19R-219), on December 11, 2019.

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Table 1 Patient background and comorbidities

	Male	Female	Total
Number of patients	46	17	63
Age, years (mean ± SD)	52.4 ± 13.7	54.9 ± 10.4	53.1 ± 12.8
Onset age, years (mean ± SD)	36.3 ± 13.9	37.3 ± 16.9	36.7 ± 14.6
Ht, cm (mean ± SD)	170 ± 6.5	158 ± 5.0	167 ± 8.3
BW, kg (mean ± SD)	74.8 ± 16.8	62.5 ± 18.7	71.5 ± 18
BMI (mean ± SD)	25.8 ± 5.0	25.5 ± 7.6	25.7 ± 5.7
PASI (mean ± SD)	8.3 ± 6.5	6.0 ± 7.7	7.7 ± 6.8
PsA, n (%)	11 (17.5%)	10 (15.9%)	21 (33.3%)
Smoking, n (%)	20 (31.7%)	3 (4.8%)	23 (36.6%)
Alcohol, n (%)	19 (30.2%)	8 (12.7%)	27 (42.9%)
Nail, n (%)	23 (36.6%)	9 (14.3%)	32 (50.8%)
Itch, n (%)	18 (28.6%)	11 (17.5%)	29 (46.0%)

Ht: height; BW: body weight; BMI: body mass index;
PASI: Psoriasis Area and Severity Index; SD: standard deviation;
PsA: psoriatic arthritis; n: number of patients

Comorbidities	Number of patiens	%
Hypertension	14	22.2
Hypercholesterolaemia	14	22.2
Hyperuricemia	4	6.3
Fatty liver	9	14.3
Diabetes	8	12.7
Depression	3	4.8
HBV(+), or HCV(+)	10	15.9
Ulcerative colitis	2	3.2
gallstones	1	1.6
Chronic kidney disease	1	1.6
Cardiovascular disease	3	4.8
Cerebral infarction	2	3.2
Tuberculosis	2	3.2
T-spot (+)*	2	3.2
Malignant tumor	2	3.2
Gillan barre syndrome	1	1.6

*seroconversion negative to positive during biologic treatment

Biological retention rate

The beginning and final dates of biologic administration were recorded. In patients with multiple biologics, all biologics were also recorded accordingly. Retention time analysis was used to calculate the biological retention rates for each biologic agent. Termination due to primary inefficacy, secondary loss of efficacy, or adverse events was tagged "event", while termination resulting from economic burden or remission was tagged "censored".

Reasons for switching

When a biologic agent was discontinued (either terminated or switched to another biologic agent), the reason was examined and classified into the following five categories: (i) primary inefficacy; (ii) secondary loss of efficacy; (iii) adverse events; (iv) economic burden; or (v) remission.

Clinical factors

Clinical factors such as age, onset age, sex, initial PASI score, smoking habit, alcoholic habit, height, weight, BMI, nail symptom, and itching were compared between non-switched and switched cases in IFX and UST treatment.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [16].

Fisher's exact test and student's t-test were performed to compare the average value and the ratio between the two groups in age, onset age, sex, baseline PASI, smoking habit, alcohol habit, nail symptom, and itching, respectively. For comparison of drug survival curves, the log–rank test was performed. $P < 0.05$ was regarded as a significant difference in all analyses.

RESULTS

Patients

Table 1 shows the baseline demographics and background characteristics of patients. With 46 males and 17 females, the average age was 53.1 ± 12.8 years old, with onset age at 36.7 ± 14.6 years old. The average height and body weight were 167 ± 8.3 cm, 71.5 ± 18 kg respectively. The average BMI and PASI were 25.7 ± 5.7 and 7.7 ± 6.8, respectively. The percentage of patients who had PsA, smoking, alcohol, nail symptoms and skin itch were 33.3%, 36.6%, 42.9%, 50.8%, and 46.0% respectively.

Clinical course

Figs. 1 and 2 shows clinical course of these patients. Of the 63 patients, 37 were classified as continuing, two terminated due to economic burden, one terminated due to remission, and 23 as switched. Of the 23 switched patients, 5 patients switched again to a third biologic agent.

Reasons for switching to a different biologic

Fig. 2 shows the number of patients switching for different reasons. With the first-line drugs, the main reason for switching was secondary loss of efficacy with 14 patients, followed by adverse events with 5 patients, and primary inefficacy with 4 patients.

With the second-line drugs, the main reason for switching was primary inefficacy with 3 patients, followed by secondary loss of efficacy with 2 patients, and adverse events with one patient.

Retention time of biologic products

The continued duration of first-line biologics was examined using retention time analysis. Among the 63 patients, the most used first-line drug was UST, which was administrated to 24 patients. The second most frequently used first-line drug was IFX, which was administrated to 17 patients. ADA, IXE, BRO, GUS, and SEC were administrated to 6, 5, 4, 4, and 3, respectively (Table 2). The retention curves for these first-line drugs are shown in Fig. 3. The median reten-

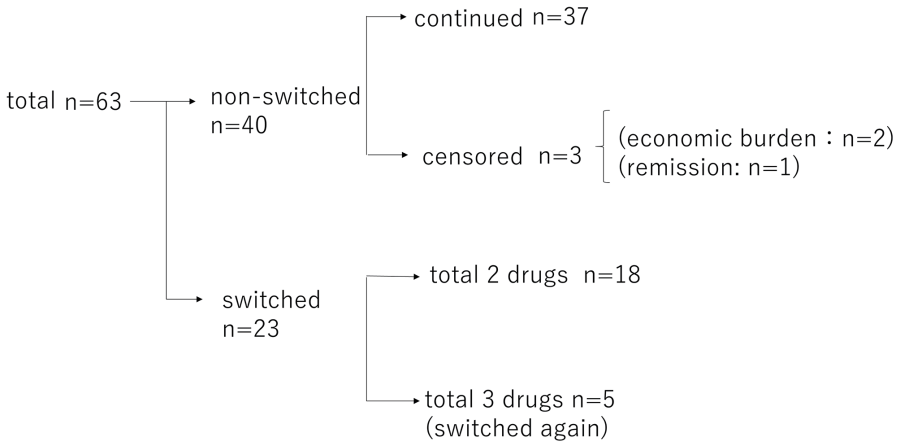

Fig. 1 Flow chart of biologic agents used in all psoriatic patients.

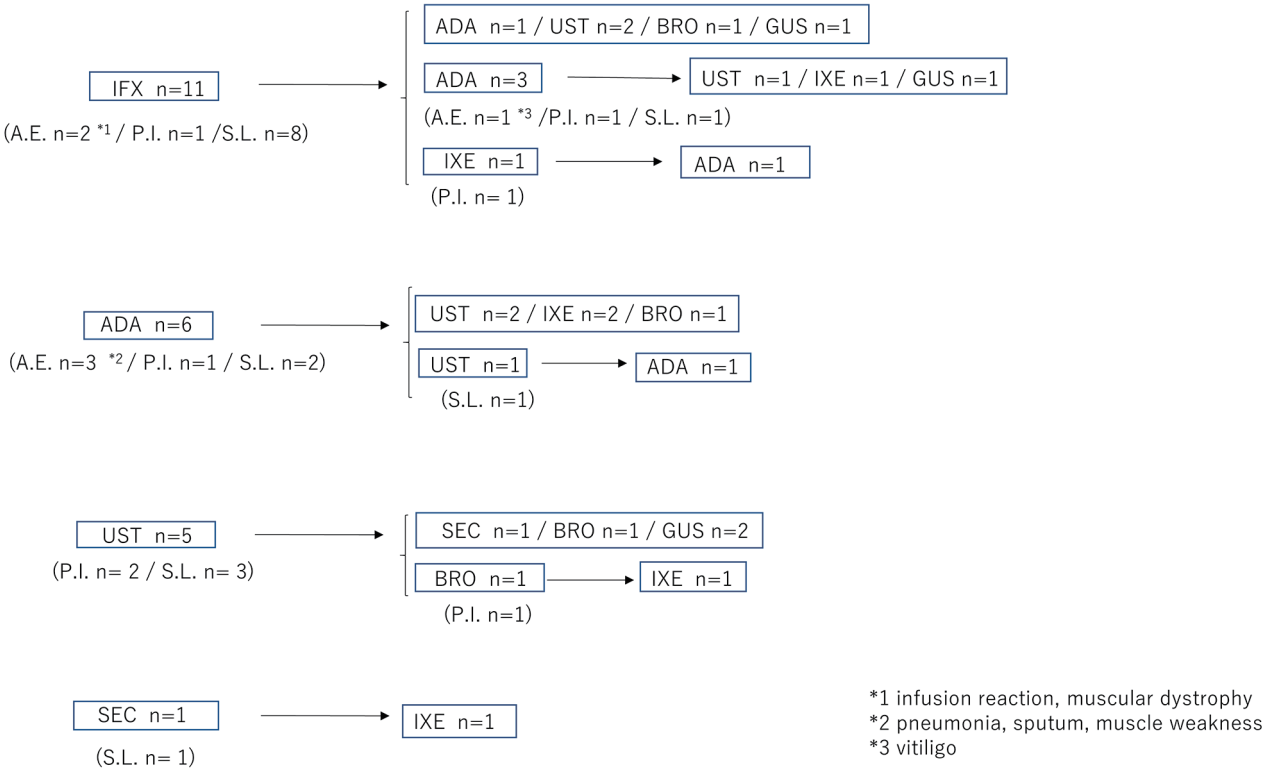

Fig. 2 Flow chart of switched cases and reasons.
A.E, adverse events; P.I., Primary inefficacy; S.L., Secondary loss of efficacy

tion curves of patients taking UST were significantly larger than those of patients taking IFX and ADA (P = 0.0023 and 0.0121, respectively).

Clinical factors relating to non-switched and switched cases in IFX and UST

Clinical factors of age, onset age, baseline PASI, height, body weight, BMI, sex, smoking habit, alcohol intake habit, nail symptom, itching between non-switched and switched cases in IFX and UST were compared in Table 3.

There were no significance between the two groups on age, onset age, baseline PASI, height, body weight, BMI, sex, smoking habit, alcohol intake habit, nail symptom, and itching, with either IFX or UST. However, for patients being treated with UST, a significant number of patients who switched to another biologics showed nail symptoms (p = 0.047).

DISCUSSION

In this study, the biological retention of UST was superior than that of IFX and ADA, which is similar to previous studies [11, 12]. Our results conformed superiority of UST over TNF-α inhibitors. As shown in Fig. 3, SEC, IXE, BRO, and GUS presented no significant difference between other biologics such as IFX, ADA, and UST on biological retention.

The reason for switching from the first-line biologic in our hospital was mainly secondary loss of efficacy. One of the major reasons for high frequency due to secondary loss of efficacy is considered that anti-biologic agent antibodies [12]. In Japan, It is reported that

Table 2 Demographic characteristics of psoriatic patients used each biologics

	IFX	ADA	UST	SEC	IXE	BRO	GUS	Total
Number of patients	17	6	24	3	5	4	4	63
Male/Female	11/6	5/1	20/4	2/1	3/2	4/0	1/3	46/17
Age, years (mean ± SD)	55.1 ± 13.1	50.3 ± 8.0	48.6 ± 13.9	58.7 ± 20.3	58.2 ± 5.5	55 ± 11.3	63.5 ± 6.8	53.1 ± 12.8
Onset age, years (mean ± SD)	39.8 ± 14	37.8 ± 9.8	31.7 ± 15.4	34 ± 10.5	35.6 ± 16.6	41 ± 19.6	51.3 ± 2.9	36.7 ± 14.6
Ht, cm (mean ± SD)	164 ± 8.4	172 ± 6.7	170 ± 7.8	165 ± 9.9	164 ± 5.5	172 ± 5.9	158 ± 7.1	167 ± 8.3
BW, kg (mean ± SD)	72.4 ± 24.8	76.8 ± 12.7	70.7 ± 15	88 ± 18.2	64.2 ± 9.0	76.5 ± 14.2	55.5 ± 10.5	71.5 ± 18
BMI (mean ± SD)	26.7 ± 6.9	26.0 ± 3.9	24.7 ± 5.0	33.3 ± 11.1	24.0 ± 3.4	25.9 ± 3.6	22.6 ± 2.6	25.7 ± 5.7
PASI (mean ± SD)	7.5 ± 7.5	9.9 ± 5.3	7.9 ± 5.9	2.2 ± 2.3	8.9 ± 13.3	9.8 ± 3.8	5.0 ± 6.2	7.7 ± 6.8
PsA, n	14	1	0	2	3	0	1	21
Smoking, n	3	2	12	0	3	1	2	23
Alcohol, n	4	2	13	1	4	2	1	27
Nail, n	9	3	9	2	4	3	2	32
Itch, n	7	2	13	1	3	2	1	29
Duration, days (mean ± SD)	786.4 ± 732.3	941.2 ± 1092	1229 ± 659.8	1137 ± 326.3	351.4 ± 242	326.5 ± 374.6	152.3 ± 54	882.4 ± 734.7
Switch, n	11	6	5	1	0	0	0	23

Ht: height; BW: body weight; BMI: body mass index; PASI: Psoriasis Area and Severity Index; SD: standard deviation; PsA: psoriatic arthritis; n: number of patients

Table 3 Demographic characteristics of non-switched and switched cases in IFX and UST

		Switch(-)	Switch(+)	P			Switch(-)	Switch(+)	P
IFX	No. of patients	6	11		UST	No. of patients	19	5	
	Sex (male/female) n, %	3(50%)/3(50%)	8(72.7%)/3(27.3%)	0.600		Sex (male/female) n, %	15(78.9%)/4(21.1%)	5(100%)/0(0%)	0.544
	Age, years (mean ± SD)	58.2 ± 9.9	53.3 ± 14.7	0.487		Age, years (mean ± SD)	46.3 ± 13.4	57.4 ± 13.4	0.113
	Onset age, years (mean ± SD)	47.2 ± 11.1	35.7 ± 14.2	0.110		Onset age, years (mean ± SD)	31.6 ± 16.4	32.0 ± 12.3	0.958
	Ht, cm (mean ± SD)	162.0 ± 9.3	164.9 ± 8.0	0.508		Ht, cm (mean ± SD)	168.5 ± 7.6	174.0 ± 7.8	0.166
	BW, kg (mean ± SD)	68.2 ± 11.8	74.6 ± 30.0	0.627		BW, kg (mean ± SD)	69.2 ± 16.3	76.6 ± 6.2	0.333
	BMI (mean ± SD)	26.1 ± 3.6	27.0 ± 8.3	0.794		BMI (mean ± SD)	24.4 ± 5.4	25.5 ± 3.4	0.665
	PASI (mean ± SD)	3.1 ± 1.7	9.9 ± 8.4	0.076		PASI (mean ± SD)	7.1 ± 6.1	10.8 ± 4.0	0.219
	Smoking n %	1 (16.7%)	2 (18.2%)	1.000		Smoking n %	8 (42.1%)	4 (80%)	0.317
	Alcohol n %	2 (33.3%)	2 (18.2%)	0.584		Alcohol n %	10 (52.6%)	3 (60%)	1.000
	Nail n %	3 (50%)	6 (54.5%)	1.000		Nail n %	5 (26.3%)	4 (80%)*	0.047 *
	Itch n %	2 (33.3%)	5 (45.5%)	1.000		Itch n %	11 (57.9%)	2 (40%)	0.630

Ht: height; BW: body weight; BMI: body mass index; PASI: Psoriasis Area and Severity Index; SD: standard deviation; PsA: psoriatic arthritis; n: number of patients. Fisher's exact test and student's t-test were performed to compare the average value and the ratio between the two groups in age, onset age, sex, baseline PASI, smoking habit, alcohol habit, nail symptom, and itching, respectively.
$P < 0.05$ was regarded as a significant difference in all analyses. For patients being treated with UST, a significant number of patients who switched to another biologics showed nail symptoms ($p = 0.047$) *

anti-adalimumab antibody was detected in 15.6% cases in ADA, and anti-infliximab antibody was detected in 30% in IFX [17]. Since the presence of anti-biologic agent antibodies may influence the levels and function of the agent in the body, this immune response can alter the efficacy of the biologic treatment [18].

As for adverse events, one patient experienced muscle weakness and one patient experienced vitiligo during ADA treatment. There have been a number of reports of neurological adverse events in patients receiving anti-TNFα therapy, however, the relation of these events with the use of TNF-α inhibitors remains to be elucidated [19]. It is reported that a significantly increased risk of newly developed vitiligo was observed in the anti-TNF group compared to the unexposed group [20]. The mechanism is still unknown, but they concluded that TNF inhibition may give rise to cytokine shifts and the subsequent recruitment of autoreactive T cells to the epidermis, leading to the destruction of melanocytes [20]. During UST treatment, two cases turned out to be positive for tuberculosis with the Enzyme Linked Immunospot-test (ELISPOT). They received prophylactic isoniazid and pyridoxal without reactivation of tuberculosis. Although UST

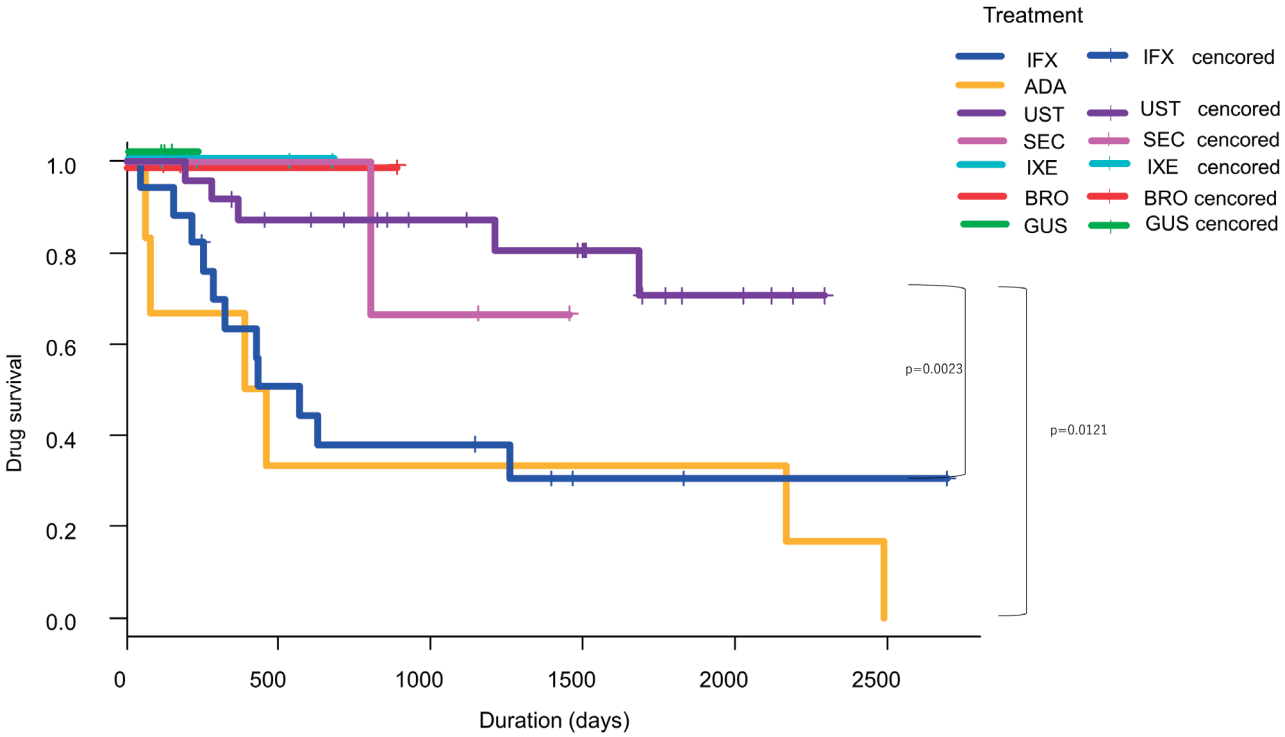

Fig. 3 Survival curve of biologic treatment in psoriatic patients. First line drug used in all psoriatic patients. For comparison of drug survival curves, the log–rank test was performed. $P < 0.05$ was regarded as a significant difference in all analyses. The P value of median survival curves of patients taking IFX and other drugs (ADA, UST, SEC, IXE, BRO, and GUS) are 0.522, 0.0023, 0.251, 0.164, 0.283, and 0.547, respectively. The P value of median survival curves of patients taking ADA and other drugs (UST, SEC, IXE, BRO, and GUS) are 0.0121, 0.257, 0.085, 0.156, and 0.226, respectively. The P value of median survival curves of patients taking SEC and other drugs (IXE, BRO, and GUS) are 1, 0.564, and 1, respectively. The P value of median survival curves of patients taking IXE and other drugs (BRO and GUS) are 1, and 1, respectively. The P value of median survival curves of patients taking BRO and GUS is 1. The P value of median survival curves of patients taking UST and other drugs (SEC, IXE, BRO, and GUS) are 0.547, 0.555, 0.716, and 0.838, respectively.
The median survival curves of patients taking UST were significantly larger than those of patients taking IFX and ADA (P = 0.0023 and 0.0121, respectively).

treatment had a low frequency of seroconversion rate for tuberculosis than TNF-α inhibitors [21], we should pay attention to reactivation of tuberculosis.

We compared between switched and non-switched cases with IFX and UST treatment to detect possible prognostic factors in Table 3. The only significant difference between switch and non-switch group was nail lesion of UST group. This suggested that the presence of nail lesion may act as a predictor of whether a patient will switch to another biologic in UST treatment. Previous studies investigated age, sex, PASI, body weight, BMI, and smoking as a predictive factor [13, 14], but there were no studies which investigated nail symptom as a predictive factor. Further studies will be needed to clarify that nail lesion may act as a predictor.

In conclusion, we examined biological retention rate of several biologics, reasons of switching to another biologic agents, and looked for possible prognostic factors. There were several limitations to this study. This study was retrospective, had only a small sample size, and was single centered. New biologic agents such as SEC, IXE, BRO and GUS has not been on the market long enough to be assessed. However, what we can say from this study is that the biological retention rate of UST was significantly longer than that of IFX and ADA. The main reason for changing the biologic agent was secondary loss of efficacy. Lastly the only significant difference between switch and non-switch group was nail lesion of UST group.

Further studies including multicenter study will be needed to evaluate optimal use of biologic agents for psoriasis.

CONFLICT OF INTEREST

T. Mabuchi has received lecture fees from Maruho and Kyowa Kirin. M. Tokuyama, M. Ota, R. Saitoh, M. Sawamura, N. Okitsu, T. Shimizu, A. Kondoh and H. Yamaoka have no conflict of interest to declare.

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