**Switching of biologics in psoriasis: reasons and results**

*Hiromi Honda, MD; Yoshinori Umezawa, MD, PhD; Sota Kikuchi, MD; Koichi Yanaba, MD, PhD; Osamu Fukuchi, MD; Toshihiro Ito, MD, PhD; Yoshimasa Nobeyama, MD, PhD; Akihiko Asahina, MD, PhD; Hidemi Nakagawa, MD, PhD*

All authors: Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan

**Address for Correspondence**: Hiromi Honda, MD

Department of Dermatology

The Jikei University School of Medicine

3-25-8 Nishishimbashi

Minato-ku, Tokyo, 105-8461, Japan

Tel: +81-3-3433-1111 Ext: 3341

E-mail: babahiromi@jikei.ac.jp

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**Running head:** Switching of biologics in psoriasis

**ABSTRACT**

**Background:** Efficacy and safety profiles of biologics have been established for moderate-to-severe psoriasis. However, inefficacy or adverse events sometimes require changing the treatment to other biologics. Here, we examined the effectiveness of this strategy.

**Methods:** We retrospectively investigated cases requiring switching biologics. We enrolled 275 psoriatic patients treated with biologics between January 2010 and December 2014 in our hospital. Of these, 51 required a switch to another biologic. First-line therapies were infliximab (IFX, *n* = 26), adalimumab (ADA, *n* = 18), and ustekinumab (UST, *n* = 7), and second-line therapies were IFX (*n* = 5), ADA (*n* = 21), and UST (*n* = 25). Reasons for switching were inefficacy (*n*= 38), adverse events (*n* = 11), and others (*n* = 2). The details were primary failure (*n = 15*), secondary failure (*n* = 23), and infusion reactions (*n* = 8).

**Results:** In 49 patients who switched biologics due to inefficacy and adverse events, the mean Psoriasis Area and Severity Index (PASI) score at Week 16 was 4.3 for first-line therapies and 2.9 for second-line therapies ($P < 0.05$).

**Conclusions:** Switching to a second biologic therapy to address the first's inefficacy or adverse events often results in significant improvement in moderate-to-severe psoriasis.

## Introduction

Psoriasis is a chronic inflammatory skin disorder which affects approximately 1%–3% of the general population.[1] Patients with severe psoriasis that impairs their quality of life require aggressive treatment. Use of conventional treatments such as retinoids, methotrexate, or cyclosporine is often limited by organ toxicity. For this reason, the advent of biologic treatment was revolutionary in psoriasis therapy. However, although biologic agents are effective in treating psoriasis without severe adverse events (AEs), approximately 30% of patients show an insufficient response to this therapy.[2–7] In addition, some patients still encounter AEs, such as infusion reactions, drug eruption, or infections. Patients with suboptimal response or AEs are usually switched to other biologics; however, relatively few studies have examined the efficacy of changing biologics in these situations.[8-11] Identifying prognostic factors associated with treatment discontinuation would greatly aid in predicting the efficacy of the first agent and in assessing the risk of adverse events.

Three biologic agents—infliximab (IFX), adalimumab (ADA), and ustekinumab (UST)—were available for psoriasis treatment in Japan as of 2014. To clarify the efficacy of agents before and after switching and factors related to discontinuation of the initial biologic therapy, we retrospectively investigated the clinical course in cases requiring switching by examining the records of patients treated with biologics between January 2010 and December 2014 in our hospital.

## Materials and Methods

*Patients*

This retrospective cohort study was conducted in patients aged 20 years or older who were diagnosed with psoriasis vulgaris (PsV) or psoriatic arthritis (PsA). Patients treated with biologics between January 2010 and December 2014 in the Jikei University School of Medicine, and those who were observed for more than 52 weeks were enrolled in this study.

*Treatments*

IFX was intravenously administered (5 mg/kg) at Weeks 0, 2, and 6, and every 8 weeks thereafter. ADA was subcutaneously administered at 80 mg at Week 0 and 40 mg every 2 weeks thereafter; the dose could be increased up to 80 mg every two weeks for patients showing inefficacy. UST was administered via subcutaneous injection of 45 mg at Weeks 0 and 4 and every 12 weeks thereafter; the dose could be increased up to 90 mg for patients showing inefficacy.

When a patient showed inefficacy, encountered AEs, or experienced other problems, such as economic or injection interval issues, subsequent treatments were determined on the basis of discussions with patients regarding incremental increases in dosage of their current treatment or changing to a different agent.

***Reasons for alterations in biologics treatment***

Reasons for changing treatment regimen were categorized as follows: (i) inefficacy, including primary failure (not achieving a ≥ 50% PASI score improvement at 24 weeks), secondary failure (losing initial efficacy during treatment), (ii) AEs, including infusion reactions, interstitial pneumonia, and temporal arteritis, and (iii) other reasons, including cost, or frequency of hospital visits.

***Efficacy assessment***

Psoriasis Area and Severity Index (PASI) was measured at the first biologic treatment (week 0) and Weeks 14–16, and at the same time points in patients who were switched to a second biologic.

Clinical efficacy was evaluated in cases with inefficacy and AEs using the following measurements taken at Week 0 and Weeks 14–16 for both the initial and second biologic treatment protocols: the reduction rate in the PASI score, and achievement of a 75% reduction in PASI score (PASI-75). In addition, the ratio of patients who underwent dose escalation was noted.

***Clinical factors***

Clinical factors of age, initial PASI score, smoking habit, and body mass index (BMI) were compared between non-switched and switched cases with inefficacy and/or AEs.

***Statistical analysis***

Statistical analysis was performed using commercial software (SPSS Inc., Chicago, IL, USA). The two-sample *t*-test and Test for Equal Variance were performed to assess differences between the two groups in age, BMI, PASI at Week 0 and 14–16, PASI improvement rate, and PASI-75. The logistic regression analysis were performed to assess differences between the two groups in age, baseline PASI, BMI, gender, and smoking habit. A value of $P < 0.05$ was considered significant.

***IRB status***

This study was approved by Institutional review board, the Ethics committee of The Jikei University School of Medicine for Biomedical Research (No. 28-266(8509)).

## RESULTS

*Patients*

314 patients initiated treatment with biologics between January 2010 and December 2014 in the Jikei University School of Medicine. Of these 314 patients, 39 patients were excluded because of the observation period of less than 52 weeks, and 275 cases were enrolled in this study, They consisted of the subgroups treated with IFX (*n*=59), ADA (*n*=91), and UST (*n*=125). A total of 51 patients subsequently required switching to another biologic. The length of the whole observation period in all patients ranged 12-71 months (median value, 39.4 months). Table 1 shows their baseline demographics and background characteristics. No significant differences were noted between patients treated with any biologic in terms of PASI at baseline, disease duration, body weight, or BMI. However, the mean age and distribution of psoriasis types among UST cases differed significantly from values in other treatment groups. Table 1 shows the first-line therapies in the switched cases and the percentage of patients switching from each drug.

### *Reasons for switching to a different biologic*

Table 2 shows the number of patients switching for different reasons. There were no switches due to the development of infection. The major reason for switching was inefficacy. The total number of patients who switched due to inefficacy, AEs and others reasons was 38, 11 and 2, respectively. The other reasons were the frequency of hospital visits ($n$ = 1) and the cost of treatment ($n$ = 1).

The characteristics of patients experiencing primary or secondary failure or AEs with IFX, ADA, and UST are shown in Table 3. Most adverse events occurred with IFX.

### *Efficacy in patients who switched biologic treatment*

The PASI scores in patients who switched biologics are shown in Figure 1 a, b, c.

The PASI-75 response for the first and second treatment was 59.1% and 43.7%, respectively, and the overall PASI-75 response from the beginning of the first treatment to the evaluation period of the second treatment was calculated to be 69.0%. Switching to a second biologic therapy to address the first's inefficacy or adverse events resulted in significant improvement.

***The ration dose escalation***

The proportion of the patients who underwent dose escalation in continuation cases were 13 out of 73 (17.8%) for adalimumab, and 21 out of 118 (17.8%) for ustekinumab. On the other hand, the proportion of those who underwent dose escalation before bio switch was 9 out of 18 (50.0%) for adalimumab, and 3 out of 7 (42.9%) for ustekinumab. The reasons for bio switch in those cases were inefficacy in 10 cases and adverse events in 2 cases.

***Clinical factors relating to continuous and switched cases***

Clinical factors of age, baseline PASI, smoking habit, and BMI between continuously treated and switched cases are compared in Table 3. When comparing all patients (including IFX, ADA, and UST), a significant difference in baseline PASI was noted between the two groups. However, when examining only those patients initially treated with IFX, no significant differences in baseline PASI were noted. Among patients initially treated with ADA, significant differences in age, baseline PASI, and smoking habit were noted between the two groups; and in those initially treated with UST, a significant difference in mean BMI was noted between the switched and non-switched groups.

## DISCUSSION

The mean PASI score at Week 14-16 was 4.3 for all first-line patients and 2.9 for those receiving second-line treatment, suggesting that switching to a different biologic therapy after experiencing inefficacy or AEs with the first treatment often resulted in a significant improvement. In these cases, PASI score on the second drug at Week 0 and Week 14-16 was 8.3 and 2.9 in patients with inefficacy, and 8.0 and 2.8 in patients with AEs, respectively. Significant improvement in PASI scores was noted on the second drug in patients switching for both inefficacy and AEs.

We identified several clinical factors associated with discontinuing the first treatment agent: for those receiving ADA, discontinuation was associated with high baseline PASI score, and elder age, There was no prognostic indicator for switching from IFX and UST. All of the switching cases were associated with high baseline PASI score.

Treatment with biologics is now standard treatment for moderate-to-severe cases of psoriasis due to the high efficacy and promising safety profile. Efficacy is particularly notable in patients who do not respond to conventional treatments, such as retinoids, cyclosporine, or phototherapy. Further, biologics are extremely effective in treating cases with nail, scalp, and joint involvement, which often fail to improve with conventional treatments. Despite these advantages, however, 10%–30% of patients are insufficient or non-responders, or experience adverse events, leading to treatment discontinuation. For example, IFX is associated with infusion reactions and secondary failure, and ADA and UST are associated with primary failure.[12,13] Such patients are therefore often switched to other biologics.

However, several reports have stated that patients previously treated with biologics show a lower PASI-75[14–16] than those treated with nonbiologics, suggesting that previously-treated patients may fail subsequent biologics as well. While switching insufficiently- or non-responding patients to a different biologic is a relatively common practice, few studies have examined the efficacy of secondary biologic treatment in such patients.[17–22] We therefore retrospectively investigated these cases using patient records.

In our study, the PASI-75 response for the first and second treatment was 59.1% and 43.7%, respectively. This lower PASI-75 in 2nd bio treatment than 1st one caused due to lower baseline PASI scores of starting of 2nd-biologics. However, patients who switched to a different biologic

exhibited a substantial reduction in PASI score after switching ($P < 0.05$).This result suggests that switching to a different biologic may indeed improve psoriasis in patients who do not sufficiently respond to the first treatment. Of note, comparing Week 14–16 PASI scores between first and second biologics may be a more accurate way of assessing disease progress than comparing drug efficacy using PASI-75, as PASI score directly reflects the present patient condition.

In Japan, dose escalation was admitted as a treatment option only for adalimumab (40 mg→80 mg) and ustekinumab (45 mg→90 mg) in our study period. Our study showed that among those who underwent dose escalation, some patients (40.9% (9/22) for adalimumab and 12.5% (3/24) for ustekinumab) subsequently switched to other biologics, mainly because of inefficacy. Thus, almost half of the bio-switched cases (50.0% (9/18) for adalimumab and 42.9% (3/7) for ustekinumab) had been dose escalated prior to switching. Our study highlights the presence of refractory cases who required bio switch even after dose escalation.

We observed a number of differences in clinical factors between continuously treated and switched cases. Among patients treated with ADA, significant differences were noted in age, and baseline PASI score, between the two groups. Elderly patients on ADA tended to switch to UST. The efficacy of anti-TNFα agents is known to be reduced in patients with elevated BMI, and elderly patients. [23-25] Given this, a reduced ADA response in patients with high BMI, older age, or high PASI-resulted in their switching to other biologics due to inefficacy. In the present study, the most commonly reported reason for switching biologics was related to inefficacy of treatment. Therefore, associated factors which may reduce response such as BMI, age and PASI baseline should be considered before starting treatment.

Several limitations to the present study warrant mention. First, the study was retrospective in nature. Second, Weeks 14–16 might be somewhat too early to quantify the efficacy of a treatment, as most patients required treatment with biologics for longer than this before they show improvement. Confirming the validity of this study will require a larger sample size and longer study period.

Discontinuation of treatment was most commonly due to inefficacy. Careful consideration of the potential effects of age on treatment efficacy may lead to the selection of biologics less affected by these factors. In addition, our results suggest that switching to a different biologic may

indeed improve psoriasis in patients who do not sufficiently respond to the first treatment.

**Legends**

Figure 1 **PASI score, Reduction rate of PASI and PASI-75 at Weeks 0 and 14–16 for the first and second biologic treatments.**

(a) Mean ± SD PASI score for the first treatment was 15.8 ± 13.2 at Week 0 and 4.3 ± 6.1 at Weeks 14–16 for all first-line patients. Mean ± SD PASI score for the second treatment was 8.1 ± 6.7 at Week 0 and 2.9 ± 3.1 for Weeks 14–16. In cases with inefficacy, mean ± SD PASI score at Week 0 to Weeks 14-16 was 15.7 ± 12.3 to 4.9 ± 6.8, and for second treatment was 8.3 ± 6.9 to 2.9 ± 3.3. In cases with AEs , for Weeks 0 to 14–16 for the first and second biologic treatments were (mean ± SD) 16.3 ± 16.5 to 2.6 ± 1.7 and 8.0 ± 6.2 to 2.8 ± 1.9, respectively.

(b) The reduction rate with the first treatment in all switched patients from Week 0 to Weeks 14–16 was 70.1% (1st Bio W-0→W-14-016), from second treatment Week 0 to second treatment Weeks 14–16 was 53.3% (2nd Bio W-0→W-14-16), and from first treatment Week 0 to second treatment Weeks 14–16 was 72.7% (1st Bio W-0→2ndW-14-16). No statistical significance was noted.

(c) PASI-75 with the first treatment from Week 0 to Weeks 14–16 was 59.1% (1st Bio W-0→ W-14-16); from second treatment Week 0 to second treatment Weeks 14–16 was 43.7% (2nd Bio W-0→W-14-16); and from first treatment Week 0 to second treatment Weeks 14–16 was 69.0% (1stBio W-0→2ndW-14~16). No statistical significance was noted.

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Table 1. Demographic characteristics of the study population

| | **1st treatment** | | |
|---|---|---|---|
| | *infliximab* | *adalimumab* | *ustekinumab* |
| **Number of patients** | 59 | 91 | 125 |
| **Age, years (mean ± SD)** | 50.8 ± 12.5 | 50.2 ± 12.7 | 57.1 ± 16.6 |
| **Male: female (Male %)** | 46:13 (78.0%) | 65:26 (71.4%) | 90:35 (72%) |
| **Type of psoriasis (PsV: PsA)** | 38 : 21 | 63 : 28 | 118 : 6 |
| **PASI baseline (mean ± SD)** | 17.2 ± 13.6 | 11.6 ± 9.2 | 11.4 ± 6.5 |
| **Number of continuously treated patients** | 33 | 73 | 118 |
| **Number of switched patients (%)** | 26(44.1%) | 18 (19.8%) | 7 (5.6%) |
| **Duration of 1st bio treatment (mean ± SD months)** | 14.0 ± 9.9 | 14.0 ± 5.4 | 9.4 ± 5.8 |
| **2nd treatment (*n*)** | | | |
| *infliximab* | - | 4 | 1 |
| *adalimumab* | 15 | - | 6 |
| *ustekinumab* | 11 | 14 | - |

PsV, psoriasis vulgaris; PsA, psoriatic arthritis; SD, standard deviation; BMI, body mass index

Table 2. Reasons for switching to different biologics

| | Infliximab | Adalimumab | Ustekinumab | Total |
|---|---|---|---|---|
| **Number of patients** | 26 | 18 | 7 | 51 |
| **Inefficacy** | | | | |
| *primary failure* | 4 | 7 | 4 | 15 |
| *secondary failure* | 11 | 9 | 3 | 23 |
| **Adverse event*** | 10 | 1 | 0 | 11 |
| **Patient's request** | 1 | 1 | 0 | 2 |

*Adverse events: eight infusion reactions, two cases of interstitial pneumonia (infliximab), one case of temporal arteritis (adalimumab)

Table 3. Demographic characteristics of continuously treated and switched cases

| 1st Bio | | Switch(-) | Switch(+) | *P*-value | Odds ratio |
|---|---|---|---|---|---|
| *infliximab* | **Number of patients** | 33 | 26 | | |
| | **Age (mean ± SD)** | 50.5 ± 11.2 | 50.2 ± 12.4 | 0.838 | 1.004 |
| | **Sex (Male%)** | 75.0 | 80.6 | 0.809 | 1.183 |
| | **PASI baseline (mean ± SD)** | 17.2 ± 12.0 | 17.1 ± 15.0 | 0.970 | 0.999 |
| | **% smokers** | 25.0 | 29.0 | 0.794 | 1.179 |
| | **BMI (mean ± SD)** | 24.2 ± 4.1 | 23.9 ± 3.7 | 0.585 | 0.962 |
| *adalimumab* | **Number of patients** | 73 | 18 | | |
| | **Age (mean ± SD)** | 48.3 ± 12.9 | 56.4 ± 11.6 | 0.010 | 1.062 |
| | **Sex (Male%)** | 69.8 | 77.8 | 0.342 | 2.013 |
| | **PASI baseline (mean ± SD)** | 10.8 ± 9.0 | 14.8 ± 9.6 | 0.049 | 1.057 |
| | **% smokers** | 27.0 | 37.0 | 0.097 | 2.733 |
| | **BMI (mean ± SD)** | 24.3 ± 4.7 | 24.1 ± 2.2 | 0.421 | 0.941 |
| *ustekinumab* | **Number of patients** | 118 | 7 | | |
| | **Age (mean ± SD)** | 56.9 ± 16.7 | 62.3 ± 15.1 | 0.211 | 1.038 |
| | **Sex (Male%)** | 70.3 | 100 | 0.998 | $1.34 \times 10^{8}$ |
| | **PASI baseline (mean ± SD)** | 11.2 ± 6.4 | 15.2 ± 6.0 | 0.278 | 1.066 |
| | **% smokers** | 31.4 | 42.9 | 0.764 | 1.301 |
| | **BMI (mean ± SD)** | 23.3 ± 3.2 | 25.1 ± 2.2 | 0.376 | 1.153 |
| **Total** | **Number of patients** | 224 | 51 | | |
| | **Age (mean ± SD)** | 53.3 ± 15.2 | 54.3 ± 13.6 | 0.593 | 1.006 |
| | **Sex (Male%)** | 70.8 | 82.1 | 0.131 | 1.834 |
| | **PASI baseline (mean ± SD)** | 11.8 ± 8.4 | 16.1 ± 12.4 | 0.005 | 1.043 |
| | **% smokers** | 32.0 | 39.3 | 0.358 | 1.345 |
| | **BMI (mean ± SD)** | 23.8± 3.9 | 24.0 ± 3.2 | 0.742 | 0.986 |

PASI, psoriasis area and severity index; SD, standard deviation; BMI, body mass index;
*1,*2 and *3 indicate $p<0.05$, respectively, versus continuously treated cases

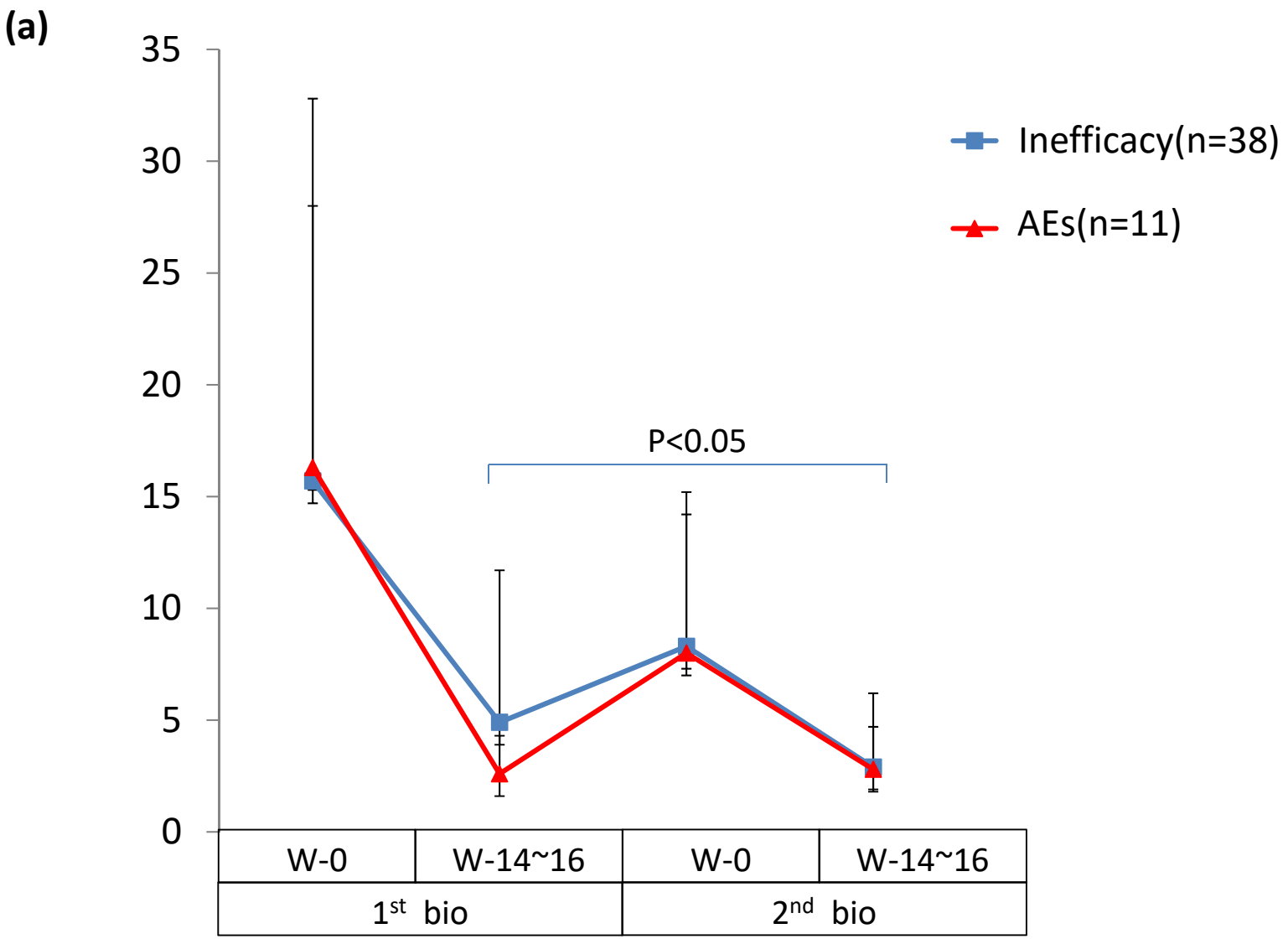


Figure 1a. PASI score at Weeks 0 and 14-16 for 1st biologic treatment and 2nd biologic treatment.

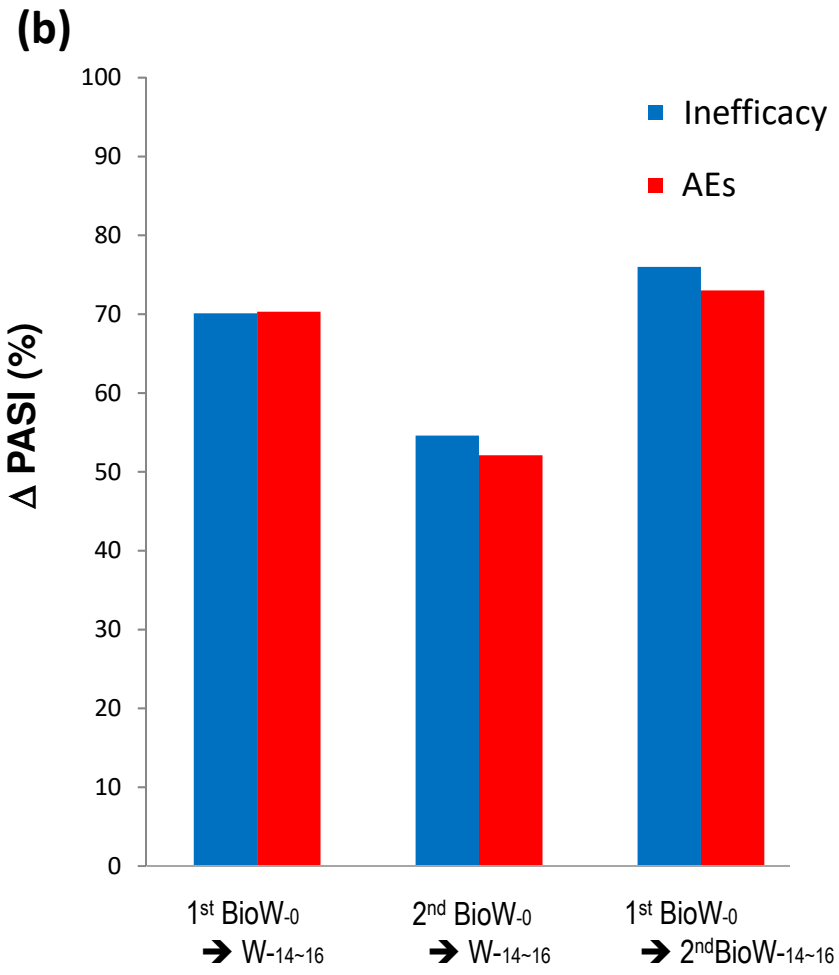


Figure 1b. Reduction rate in PASI

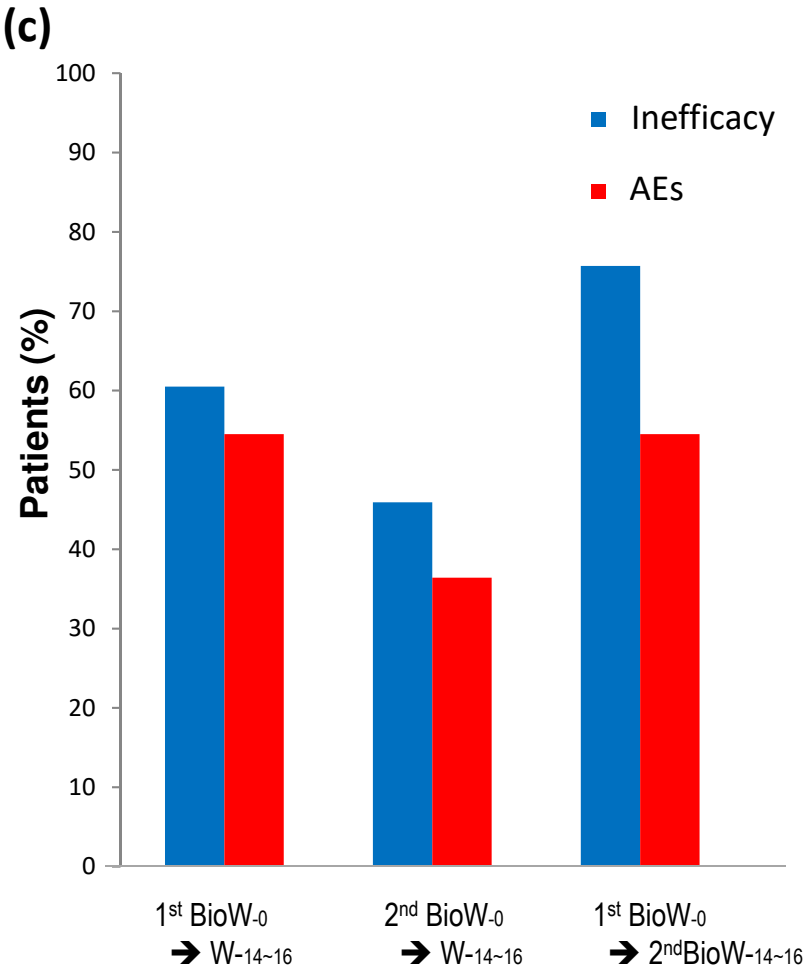


Figure 1c. Proportion of patients achieving a PASI-75 response